

Theofilos Karachalios
Editor

Bone-Implant Interface in Orthopedic Surgery

Basic Science to
Clinical Applications

 Springer

Bone-Implant Interface in Orthopedic Surgery

Theofilos Karachalios
Editor

Bone-Implant Interface in Orthopedic Surgery

Basic Science to Clinical Applications

 Springer

Editor

Theofilos Karachalios, MD, DSc
Orthopaedic Department
Faculty of Medicine
School of Health Sciences
University of Thessalia
CERETETH
University General Hospital of Larissa
Larissa
Greece

ISBN 978-1-4471-5408-2 ISBN 978-1-4471-5409-9 (eBook)

DOI 10.1007/978-1-4471-5409-9

Springer London Heidelberg New York Dordrecht

© Springer-Verlag London 2014

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. Exempted from this legal reservation are brief excerpts in connection with reviews or scholarly analysis or material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work. Duplication of this publication or parts thereof is permitted only under the provisions of the Copyright Law of the Publisher's location, in its current version, and permission for use must always be obtained from Springer. Permissions for use may be obtained through RightsLink at the Copyright Clearance Center. Violations are liable to prosecution under the respective Copyright Law.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

While the advice and information in this book are believed to be true and accurate at the date of publication, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

In the 1960s and early 1970s, it was customary to see crippled women and men, with hip and knee joint deformities and serious restriction of movement, tottering very short distances using various walking aids and describing how agonizingly painful their arthritic joints were. In November 1962, just over 50 years ago, the pioneer (Sir John Charnley) in hip reconstruction surgery made the modern breakthrough. Thanks to basic scientists, engineers, the industry, and dedicated orthopedic surgeons who have invested their scientific and professional lives in adult reconstructive surgery, we can now provide arthritic patients with painless joint movement and restoration of function. Total joint arthroplasty has progressively become a major aspect of surgery in the twentieth century [1]. However, the road to success for arthroplasty has been neither easy nor without obstacles. Problems of surgical technique arose, low-quality implants were used, patterns of failure were recognized, surgeons had to learn from devastating clinical failures, and patients were often “fashion victims” [2]. In parallel, spinal surgery, fracture surgery, and sport injuries surgery evolved; the use of implants became increasingly common; mistakes were made; failure patterns were recognized; and solutions found.

During the early decades when arthroplasty was developing, we learned from expert opinions and from the studies undertaken by the designers of materials and were sometimes biased. Industry-influenced data was not filtered and thoroughly assessed. We were led to believe that the implant is to blame for failures, and due to the lack of strong evidence to support the principles of our surgical techniques, we familiarized ourselves with both good and bad arthroplasty stratagems. Fortunately, we now have reliable educational and training programs, we critically review high-quality literature, we have evidence-based studies (Levels I and II RCTs, meta-analysis, and national registry data), and continental regulatory bodies inform and scrutinize industrial proposals. We also carefully record the complications that arise in our procedures and take preventive measures. It is now accepted that the long-term survival of a TJA is a multifactorial issue, since, other than the implant, factors related to diagnosis, the patient, the surgeon, and the surgical technique are also important.

Yet, notwithstanding the above improvements it seems that we are still liable to create new patterns of failure and disaster. Clear examples of this lie in the recent overuse of minimally invasive surgical techniques and the problems which occur with metal on metal bearings of all types and, more

alarmingly, with the modular interfaces of the big femoral heads and the modular necks. Added to these problems, there is the matter of finance. Health providers question the cost-effectiveness of arthroplasty procedures and especially the need for the introduction of the newer, more expensive techniques and implants.

Can we reply to the questions, “What is the optimal design and fixation of the implants we use for orthopedic reconstructions? What are the gold standards? and Can we do better?” In an attempt to throw light on these questions, the present authors critically evaluate data from basic science, experimental *in vivo* and *in vitro* biological and mechanical models, autopsy specimens, and long-term clinical studies. It is obvious that a huge effort has been put in both by individual research centers and the implant industry without considering the cost-effectiveness of the research. It has also become apparent that theoretical and laboratory studies do not always hold up in the cold morning light of long-term clinical studies and that there are few quality Levels I and II clinical outcome studies.

In this book we focus on the bone orthopedic implant interface in general, and we hope it will be useful both for the novice who seeks a quick introduction to this specific topic and for more experienced surgeons who seek an in-depth critical review of current practices.

References

1. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. *Lancet*. 2007;370(0597):1508–19.
2. Muirhead-Allwood SK. Lessons of a hip failure. *BMJ*. 1998;316(7132):644.

Contents

1	Current Evidence in Designs and Fixation Surfaces in Total Hip Arthroplasty	1
	Theofilos Karachalios, George Komnos, and Konstantina Kolonia	
2	Early and Late Mechanical Stability of the Cementless Bone-Implant Interface in Total Joint Arthroplasty	13
	Elise C. Pegg, Stephen J. Mellon, and Harinderjit S. Gill	
3	Bone-Cement Interface in Total Joint Arthroplasty	27
	Dionysios-Alexandros Verettas	
4	The Implant-Cement Interface in Total Hip Arthroplasty	35
	Georgios Digas and Johan Kärrholm	
5	Cobalt–Chrome Porous-Coated Implant-Bone Interface in Total Joint Arthroplasty	55
	George C. Babis and Andreas F. Mavrogenis	
6	Titanium Porous-Coated Implant-Bone Interface in Total Joint Arthroplasty	67
	Emilios E. Pakos and Theodoros Xenakis	
7	Grit-Blasted Implant Bone Interface in Total Joint Arthroplasty	83
	Eduardo García-Rey and Eduardo García-Cimbrelo	
8	HA-Coated Implant: Bone Interface in Total Joint Arthroplasty	91
	Henrik Daugaard, Joan E. Bechtold, and Kjeld Soballe	
9	Trabecular Metal: Bone Interface in Total Joint Arthroplasty	121
	Konstantinos A. Bargiotas	
10	Assessment of a Failed (Painful?) Total Joint Arthroplasty	127
	Theofilos Karachalios, Sotirios Michalitsis, and Aikaterini Veloni	

11	The Biology of Aseptic Loosening	139
	Theofilos Karachalios and Antonios Koutalos	
12	Cement-Bone Interface in Revision Arthroplasty	159
	Theofilos Karachalios and Konstantinos G. Makridis	
13	Cementless Fully Porous-Coated Implant-Bone Interface in Revision Total Hip Arthroplasty	169
	George A. Macheras, Stefanos D. Koutsostathis, and Spyridon P. Galanakis	
14	Cementless Tapered Fluted Implant-Bone Interface in Revision Total Joint Arthroplasty	183
	Panagiotis Megas and Christos S. Georgiou	
15	Bone-Graft and Implant-Graft Interface in Total Hip Arthroplasty	197
	Nikolaos Roidis and Athanasios Pollalis	
16	The Effect of Pharmacological Agents on the Bone-Implant Interface	221
	Ioannis K. Triantafillopoulos and Nikolaos A. Papaioannou	
17	Bone-Implant Interface in Biofilm-Associated Bone and Joint Infections	239
	Konstantinos N. Malizos and Maria Ioannou	
18	Modular Interfaces	255
	George C. Babis and Vasileios I. Sakellariou	
19	Local and Distant Reaction to Metallic Wear Debris	269
	Panagiotis Megas and Christos S. Georgiou	
20	Bone-Implant Interface in Spine Surgery	295
	Pavlos G. Katonis and Kalliopi I. Alpantaki	
21	Bone-Tendon and Bone-Ligament Interface	307
	Alexander Tsarouhas and Michael E. Hantes	
22	Bone-Implant Interface in Patients with Neoplastic Disease	327
	Vasileios Kontogeorgakos	
	Index	335

Contributors

Kalliopi I. Alpantaki, MD, DSc Faculty of Medicine, University of Crete, Iraklion, Crete, Greece

George C. Babis, MD, DSc First Department of Orthopaedic Surgery, University of Athens, Attikon University General Hospital, Chaidari, Attica, Greece

Konstantinos A. Bargiotas, MD Orthopaedic Department, University General Hospital of Larissa, Larissa, Greece

Joan E. Bechtold Orthopaedic Biomechanics Laboratory, Excelen Center for Bone and Joint Research and Minneapolis Medical Research Foundation, Minneapolis, MN, USA

Henrik Dugaard, MD, PhD Department of Orthopaedic Surgery, Frederiksberg Hospital, Frederiksberg

Georgios Digas, MD, DSc, PhD Department of Orthopaedics, General Hospital Xanthi, Xanthi, Greece

Spyridon P. Galanakos, MD, DSc Fourth Orthopedic Department, KAT Hospital, Athens, Greece

Eduardo García-Cimbrelo, MD, PhD Orthopaedics Department, Hospital La Paz-Idi Paz, Madrid, Spain

Eduardo García-Rey, MD, PhD, EBOT Orthopaedics Department, Hospital La Paz-Idi Paz, Madrid, Spain

Christos S. Georgiou, MD Department of Orthopaedics and Traumatology, University Hospital of Patras, Rion, Greece

Harinderjit S. Gill Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

Department of Mechanical Engineering, University of Bath, Bath, UK

Michael E. Hantes, MD, DSc Orthopaedic Department, Faculty of Medicine, School of Health Sciences, University of Thessalia, University General Hospital of Larissa, Larissa, Hellenic Republic, Greece

Maria Ioannou, MD, DSc Pathology Department, Faculty of Medicine, School of Health Sciences, University of Thessalia, Biopolis, Larissa, Greece

Theofilos Karachalios, MD, DSc Orthopaedic Department, Faculty of Medicine, School of Health Sciences, University of Thessalia, CERETETH, University General Hospital of Larissa, Larissa, Hellenic Republic, Greece

Johan Kärrholm, MD Department of Orthopaedics, Sahlgrenska University Hospital, Mölndal, Sweden

Pavlos G. Katonis, MD, DSc Faculty of Medicine, University of Crete, Iraklion, Crete, Greece

Konstantina Kolonia Orthopaedic Department, Faculty of Medicine, School of Health Sciences, University of Thessalia, University General Hospital of Larissa, Larissa, Hellenic Republic, Greece

George Komnos, MD Orthopaedic Department, General Hospital of Karditsa, Karditsa, Greece

Vasileios Kontogeorgakos, MD, DSc Department of Orthopaedic Surgery, University General Hospital of Larissa, Larissa, Greece

Antonios Koutalos, MD Orthopaedic Department, University General Hospital of Larissa, Larissa, Greece

Stefanos D. Koutsostathis, MD Second Orthopedic Department, Mitera General Hospital, Athens, Greece

George A. Macheras, MD, DSc Fourth Orthopedic Department, KAT Hospital, Athens, Greece

Konstantinos G. Makridis, MD, MSc Academic Unit, Leeds Teaching Hospitals, Leeds, UK

Konstantinos N. Malizos, MD, PhD, DSc Department of Orthopaedic Surgery and Musculoskeletal Trauma, Faculty of Medicine, School of Health Sciences, University of Thessalia, Biopolis, Larissa, Greece

Andreas F. Mavrogenis, MD First Department of Orthopaedics, Attikon University Hospital, Athens University Medical School, Athens, Greece

Panagiotis Megas, MD, PhD, DSc Department of Orthopaedics and Traumatology, University Hospital of Patras, Rion, Greece

Stephen J. Mellon Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

Sotirios Michalitsis, MD, DSc Orthopaedic Department, University General Hospital of Larissa, Larissa, Greece

Emilios E. Pakos Laboratory of Orthopaedics and Biomechanics, School of Medicine, University of Ioannina, Ioannina, Greece

Nikolaos A. Papaioannou, MD, DSc Laboratory for the Research of Musculoskeletal System, Medical School, University of Athens, Athens, Greece

Elise C. Pegg Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

Athanasios Pollalis, MD Third Orthopaedic Department, KAT Hospital, Athens, Greece

Nikolaos Roidis, MD, DSc Third Orthopaedic Department, KAT Hospital, Athens, Greece

Vasileios I. Sakellariou, MD, DSc First Department of Orthopaedic Surgery, University of Athens, Attikon University General Hospital, Chaidari, Attica, Greece

Kjeld Soballe Department of Orthopaedic Surgery, Aarhus University Hospital, Aarhus C, Denmark

Ioannis K. Triantafillopoulos, MD, MSc, DSc, FEBOT Laboratory for the Research of Musculoskeletal System, Medical School, University of Athens, Athens, Greece

Alexander Tsarouhas, MD, DSc Department of Orthopaedic Surgery, University Hospital of Larissa, Larissa, Greece

Aikaterini Veloni, MD Orthopaedic Department, University General Hospital of Larissa, Larissa, Greece

Dionysios-Alexandros Verettas, MD, PhD, MSc(Orth) Orthopaedic Department, University General Hospital of Alexandroupolis, Alexandroupolis, Greece

Theodoros Xenakis Laboratory of Orthopaedics and Biomechanics, School of Medicine, University of Ioannina, Ioannina, Greece

Current Evidence in Designs and Fixation Surfaces in Total Hip Arthroplasty

Theofilos Karachalios, George Komnos, and Konstantina Kolonia

Introduction

Since its introduction in the 1960s, total hip arthroplasty (THA) has proved to be an excellent and reliable mode of treatment for the end stages of hip pathology, with satisfactory clinical outcomes at 15–20 years [1–4]. Following the initial problems which the pioneers accounted in the 1960s and 1970s (such as surgical technique, structural design failures, and infection), in the 1980s, orthopaedic surgeons faced problems of choice of both acetabular and femoral components and the selection of cemented or cementless implant fixation. Soon afterwards, it was proved that the above

dilemmas had been misleading since the long-term survival of a THA is a multifactorial issue, since, other than the implant, factors related to the diagnosis, the patient, the surgeon, and surgical technique are also important (Fig. 1.1). However, until now, the implant has been easy to blame for failures. A possible explanation is the fact that we do not have strong evidence supporting implant design and fixation principles. Instead, we have evidence of good and bad recipes, surgeons having learned from devastating clinical failures and patients having often been “fashion victims” [5].

In the modern era of THA, it seems that bearing surfaces (a whole chapter by itself) are the crucial issue for the long-term survival of the artificial joint, and in all international hip forums, implant

T. Karachalios, MD, DSc (✉)
Orthopaedic Department, Faculty of Medicine,
School of Health Sciences, University of Thessalia,
CERETETH, University General Hospital of Larissa,
Mezourlo Region, Larissa 41110,
Hellenic Republic, Greece
e-mail: kar@med.uth.gr

G. Komnos, MD
Orthopaedic Department, General
Hospital of Karditsa, Karditsa, Greece

K. Kolonia
Orthopaedic Department, Faculty of Medicine,
School of Health Sciences, University of Thessalia,
University General Hospital of Larissa,
Mezourlo Region, Larissa 41110,
Hellenic Republic, Greece

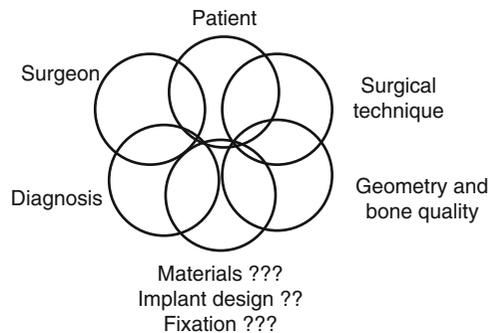


Fig. 1.1 Parameters affecting the long-term survival of a THA

design and implant fixation issues are considered to have been solved. Can we therefore reply to the question, "What is the optimal design and fixation of the implant?" This question is of importance especially nowadays when Economic Health Providers are asking challenging questions.

In an attempt to throw light on the latter question, data from basic science, experimental *in vivo* and *in vitro* biological and mechanical models, autopsy specimens, and long-term clinical studies have been critically evaluated. It is obvious that a huge effort has been put in both by individual research centers and the implant industry without considering the cost-effectiveness of this research. It has also become apparent that theoretical and laboratory studies do not always hold up in the cold morning light of long-term clinical studies and there are few quality level I and II clinical studies. In contrast, there are numerous level III studies in which the factors, mid-term follow-up, patient selection criteria, one center or one surgeon experience, implant modifications, and a high rate of dropout after 15 years, reveal serious defects.

Achieving Implant Incorporation

The lifetime of a THA can be divided into three phases: the initial months during which the implant must become rigidly fixed (early stable phase) and the remainder of the implant's life, during which fixation may be either maintained (late stable phase) or lost (late unstable phase). An early unstable phase may also be seen, although infrequently these days, due mainly to surgical technique errors. The qualities of the arthroplasty that facilitate short-term fixation (such as cement mantle and implant surface texture) may not be the ones most important for long-term fixation (such as implant geometry and stiffness). Three methods are now routinely used to achieve initial fixation: (1) cementing the implant in the bone using polymethylmethacrylate (PMMA), (2) creating a porous or rough implant surface into which bone can grow, and (3) stimulating bone apposition by covering the implant surface with a bioactive substance such as hydroxyapatite (HA) [6] (Fig. 1.2).

Bone-Cement Interface

PPMA that has been utilized since the early 1960s has stood the test of time. Cement is not glue and there is no adhesion between cement and bone; it merely forms a micromechanical interlock with bone (Fig. 1.3). If the bone surface is smooth, the mechanical interlock is poor. To achieve fixation, therefore, the bony surfaces must be rough and irregular. Intimate contact between cement and bone can only be achieved when the bone surface is clean (removal of bone debris and blood clots is an advantage) and the trabecular space is open. Thus, cleaning of the bone bed with pressure lavage and pressurization of the cement are very important. The initial bone reaction can be described as an infarct with necrosis of the bone marrow. The dead marrow tissue is replaced with fibrous tissue, and repair of the fractured trabeculae is accomplished via removal by osteoclastic resorption and new bone formation within the fibrous tissue. Osteoid and later mineralized bone may fill the irregular surface of the bone. In other areas, foreign-body giant cells can be seen together with connective tissue membrane. Bone or an intact hematopoietic marrow can be found beyond this membrane. Bone remodeling of the underlying bone occurs due to an alteration in the stress pattern occasioned by use of an implant [7–11]. Willert has categorized the response of bone to the insertion of cement into three phases [12]. In phase I, the first 2–3 weeks after surgery, tissue necrosis is the dominant finding; in phase II, there is a reparative stage (fibrous, cartilaginous, and osseous tissue) which lasts up to 2 years; and during phase III, a stable bed forms. Direct contact between cement and bone can occur, but the usual interface at the mid-term stages is a fibrohistiocytic membrane [7–12]. With old generations of cement techniques (thumb and finger insertion), only 20 % of cement was in direct contact with the bone, while with second generation (medullary canal plug) and third generation (plug, pulsative lavage, and pressure device), an estimated 40–60 % of direct contact can be expected (Fig. 1.4). Cemented femoral components are well tolerated by the skeleton over a long period of use, and fibrous tissue is sparsely formed at the femoral cement-bone interface of those well fixed and

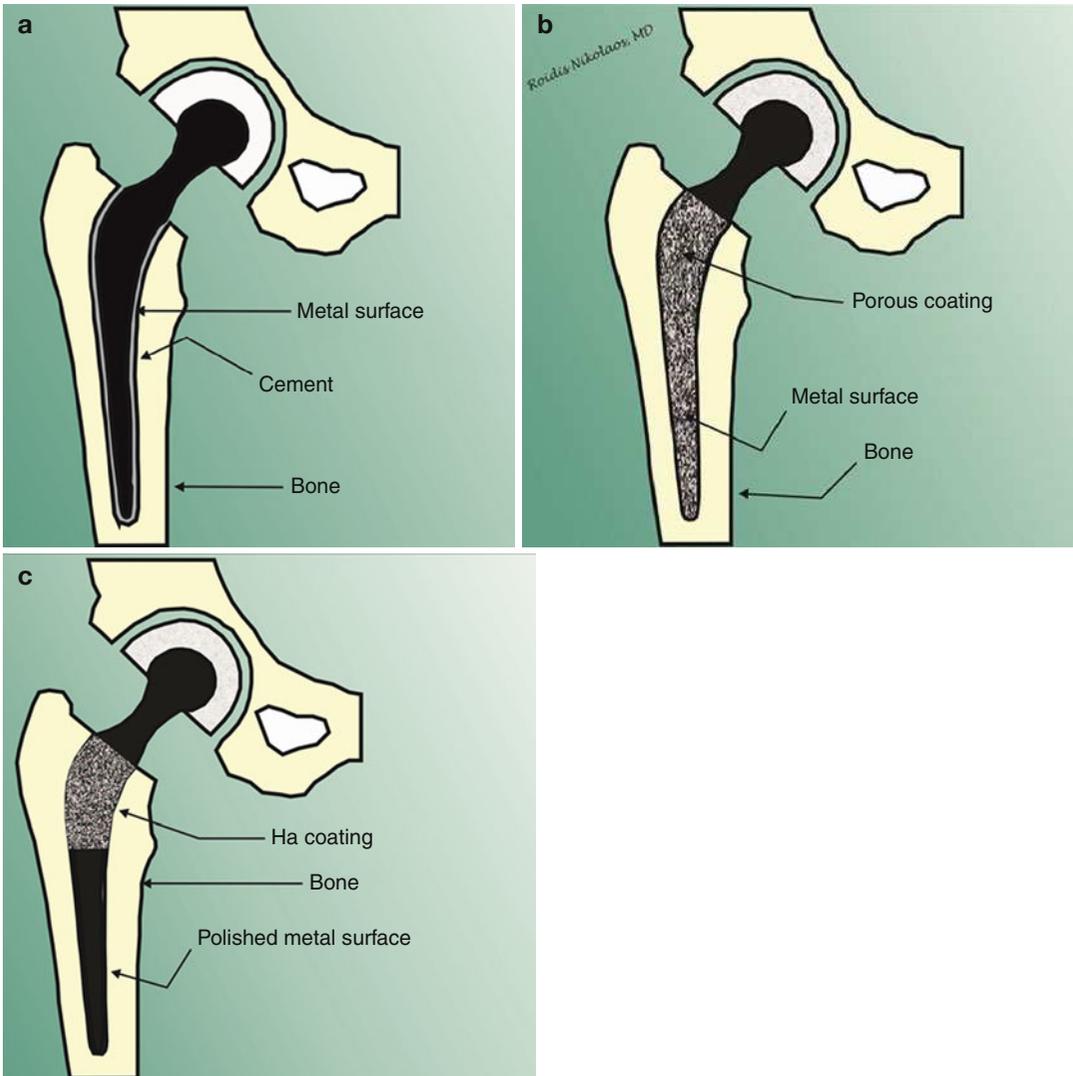


Fig. 1.2 Line drawings showing: (a) cemented THA, (b) cementless THA, and (c) HA-coated cementless THA

clinically successful prostheses. The cement mantle can be well supported by extensive medullary bone remodeling, and the formation of a dense shell of new bone that resembles a new cortex is attached to the outer cortex by new trabecular struts [13].

Cement-Femoral Stem Interface

It has been shown that the optimal shape of a stem should transmit torsional as well as axial load to the cement and to the bone without creating damaging peak stresses and without

excessive micro-movement. Mechanical factors, cement type and creep, implant type, alloy material, hip stem design, cross-section geometry, stem surface finish, and heat generation during the exothermic polymerization of cement can all affect the interface (Fig. 1.5). The stem should remain mechanically stable in the long term despite being subjected to repetitive loading. Two methods have been adopted to achieve these goals: “loaded-taper” or “force-closed” fixation and “composite-beam” or “shaped-closed” fixation [14, 15]. In the loaded-taper model epitomized by the Exeter implant and its

Fig. 1.3 Cement-bone microinterlock

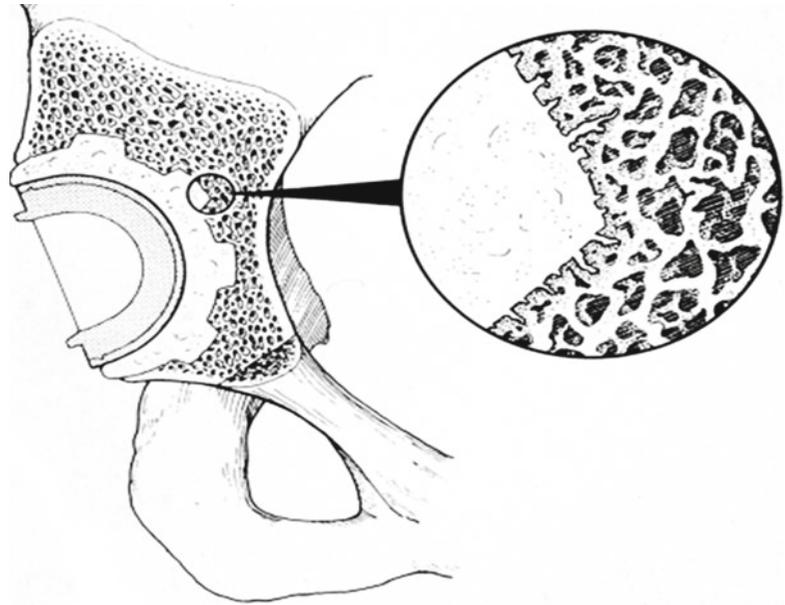


Fig. 1.4 Third generation of cementing technique. Satisfactory clinical and radiological outcome at 18 years follow-up

modern counterparts, the stem is tapered in two or three planes and becomes lodged as a wedge in the cement mantle during axial loading, reducing

peak stresses in the proximal and distal cement mantle. The stem is allowed to subside at early stages without compromising long-term clinical outcome. Polished stems with a loaded-taper design are preferred since they allow stepwise subsidence to a stable position, with the associated micro-movement producing less metal and cement debris at the cement-stem interface. They are very sensitive to a rough surface finish and are incompatible with the use of a collar as a positioning device, an anatomical shape or canal-filling design of the stem, since these features prevent subsidence within the cement mantle. In the composite-beam concept, the stem needs to be rigidly bound to the cement since subsidence or impairment of the stem-cement interface may result in damage to the cement, with the generation of PMMA and/or metal debris, and ultimately failure of the implant. These implants are not intended to subside at the early stages, and in order to optimize stability, roughening or cement pre-coating of the surface has been shown to increase cement-stem bonding. Implants with a strong cement-stem bond are more sensitive to the presence of incomplete and thin cement mantles with a poor cement-bone interface than are polished stems. Discussion about the behavior of the cement-stem interface was initiated by Harris

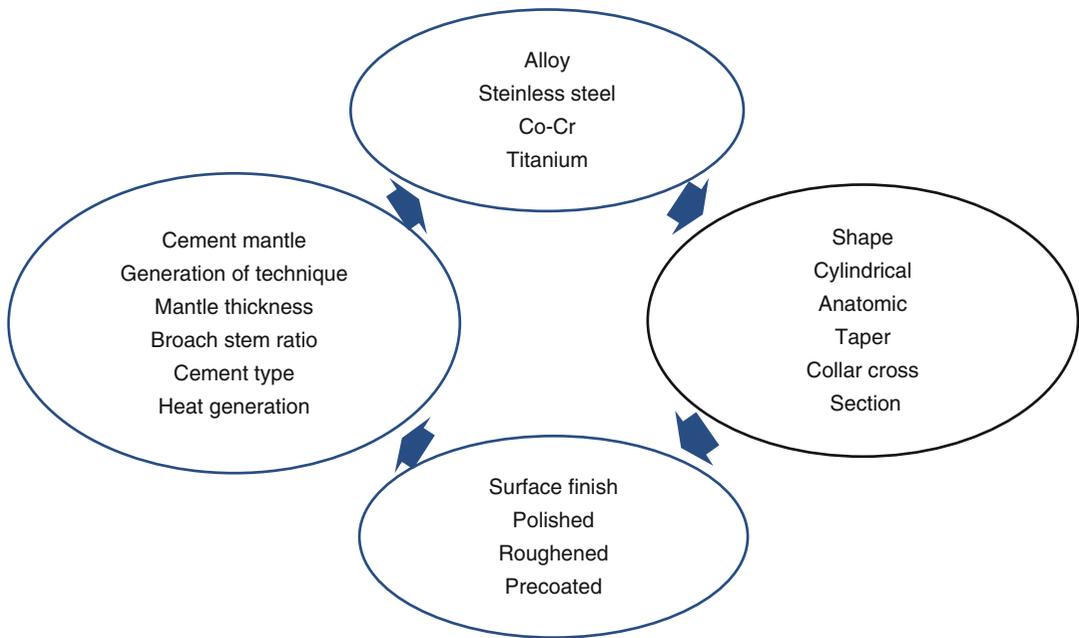


Fig. 1.5 Implant-related parameters affecting the long-term survival of cemented THA

who observed that cement failure begins at the stem-cement interface [16]. In his opinion, the cement-stem interface can be made stronger by fixing the cement to the stem. Rough stems need a thick, continuous cement mantle of good quality with a strong cement-bone interface and should be made of wear-resistant materials, whereas polished stems may be more tolerant to suboptimal cementing and manufactured from less wear-resistant materials. It has been recommended that a cement mantle which is subjected to high stresses should be between 2 and 5 mm thick, especially in the proximal-medial part of the implant and around the tip of the distal stem [17]. Several features of the shape of the stem influence the *in vivo* behavior of femoral components, including the overall shape (straight or anatomical), the cross section (oval or square), the presence of a collar, the shape of the tip of the stem, the length of the stem, and whether the edges are rounded to a greater or lesser degree [14, 15]. A stem relying on the composite-beam principle can be either straight or anatomical. Composite beams can be achieved with the interposition of a thick or a thin layer of cement, depending on whether the implant is undersized

compared with the broach or not. A canal-filling stem (stems related to the “French paradox” principle) is cemented line to line with the size of the last broach used, and stem cortex contact points as well as areas of thin cement supported by cortical bone help to stabilize the implant.

The Test of Time

Cemented surgical techniques and the design of implants have evolved dramatically. Some of these changes have resulted in improved survival rates (good recipes) while others have not (bad recipes), and registry data have shown that not all cemented cups and stems are the same [18]. It should be understood that satisfactory cemented designs are at least 15–20 years ahead of cementless designs, lessons have been learned, and reliable long-term data exists. Cement has been implicated as a major cause of failure responsible for large lytic and foreign-body reactions around both acetabular and femoral implants [19]. Later it was understood that these reactions were the result of a biological response to wear debris.

Cemented Cups

We have learned that cemented cups require exposure to cancellous bone, the bone bed must be clean and dry, and adequate bony coverage of the cup is necessary. Wear and aseptic loosening appear late after the 10th postoperative year and survival rates are inferior in younger patients. We are still not able to fully control radiolucent lines at the bone-cement interface, and cemented cups still produce inconsistent results [20]. Cemented cups have shown a 97 % survival rate at 10 years and 85 % at 20 years [21, 22]. A survival rate of 98 % at 10 years and 90 % at 16 years (based mainly on the Charnley and Exeter cup) has been reported in the 2007 annual report of the Swedish Registry. However, survival rates of 78 % at 10 years and 68 % at 20 years were reported in younger patients [23–25].

Cemented Stems

It has been reported (long-term studies and registry data) that improved cementing techniques have resulted in improved clinical outcomes [26, 27]. However, even a small change in a satisfactory design can have a substantial effect on long-term outcome. Young age does not affect femoral long-term survival (Swedish, Norwegian and Danish Registries, 2007 annual reports). Third-generation cementing techniques are affected by stem pre-coating problems. Survival rates vary, at a high level, but satisfactory designs tend to produce a constant 1–1.5 % aseptic loosening rate of the femoral stem at 15 years. Good loaded-taper recipes are the Charnley stem with survival rates of over 90 % at 10 years with losses of 10 % per decade and a final 77–81 % at 20–30 years [25, 28, 29] and the Exeter stem with an exceptional survival rate of 93.5 % at 33 years [30, 31]. Good composite-beam recipes are the Lubinus SP II stem [32–34] and the original Muller straight stem with a 94 % survival rate at 15 years [35, 36]. The French paradox recipe (by far the most inexperienced user-friendly technique) including different polished rectangular canal-filling stems cemented line to line has produced excellent long-term

results [37–40]. Although in vivo both concepts of stem fixation have proved to be effective, they cannot work together. It is important to understand on which principle a particular stem relies.

Bone-Implant Interface

Despite unsatisfactory early attempts at cementless fixation, in the early 1980s, it became evident that lamellar bone can be attached to specific implant surfaces without intervening fibrous tissue, a phenomenon called osseointegration [41]. Since osseointegration was considered to be a more biological mode of implant fixation, numerous biological, biomechanical, and human retrieval studies were performed in order to throw light on this biological process. We now know that this is a fracture healing-like process which occurs approximately 4–12 weeks after implantation and may continue for up to 3 years [42, 43]. During the stages of this “interface healing” process, cartilaginous, fibrous, and osseous tissue are formed (primary stable membrane, 4–6 weeks), and at the end, the surface of the prosthesis is covered, to a varying degree, by bone (stable interface, 4 months). The initial stages of this process are direct contact and micromotion sensitive, and early stability (press-fit technique) of the interface is mandatory [44, 45]. Several factors affect the osseointegration of implants, with their relative importance being unknown (Fig. 1.6). Ingrowth occurs when bone grows inside a porous surface, a phenomenon which depends on the surface characteristics of the implant. Surfaces for ingrowth include sintered beads, fiber mesh, and porous metals (Fig. 1.7). Sintered beads are microspheres of either cobalt chromium or titanium alloy attached by the use of high temperatures (excellent bond strength, high resistance to abrasion) [46]. Fiber mesh coatings are titanium metal pads attached by diffusion bonding [46]. Porous metals (a recent development) have a uniform three-dimensional network, with high interconnectivity of the voids and high porosity (75–85 %) compared with that of sintered beads and fiber metal coatings (30–50 %) [47]. Ingrowth requires a pore size between 50 and 400 μm , and the percentage of voids within the coating should be between

Fig. 1.6 Implant-related parameters affecting the long-term survival of cementless THA

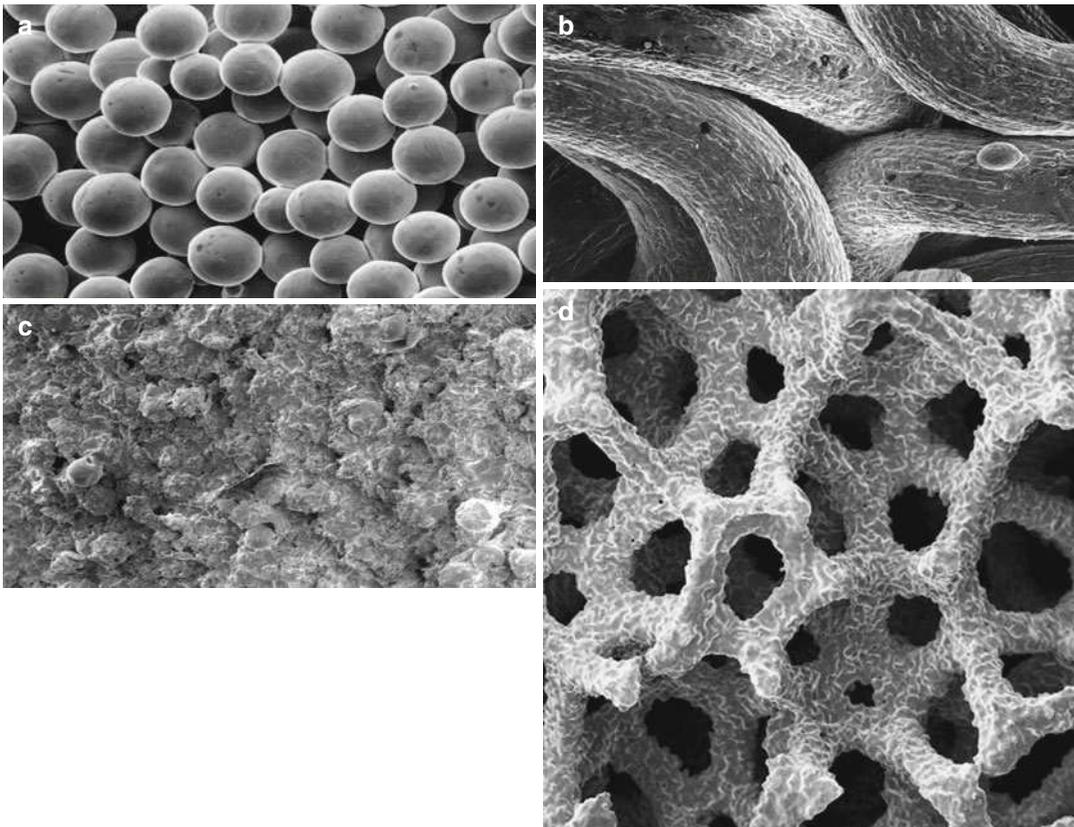
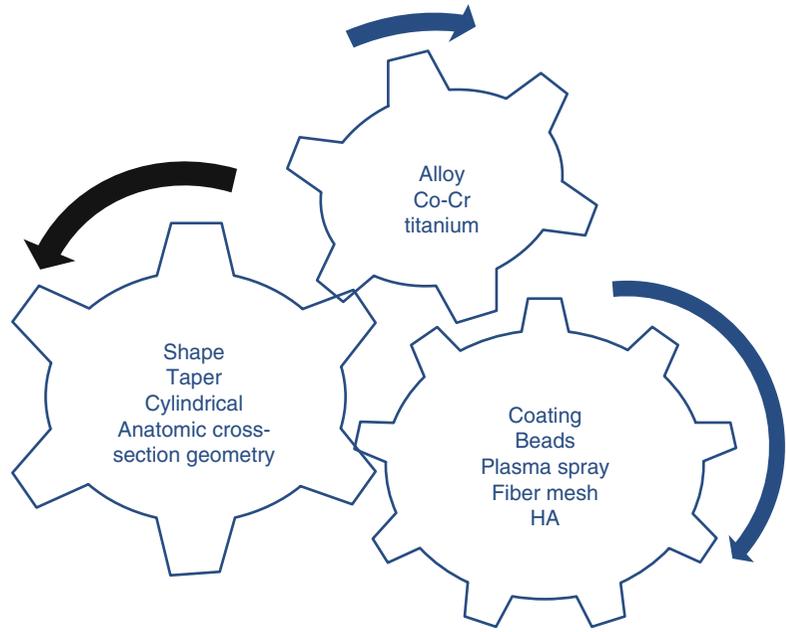
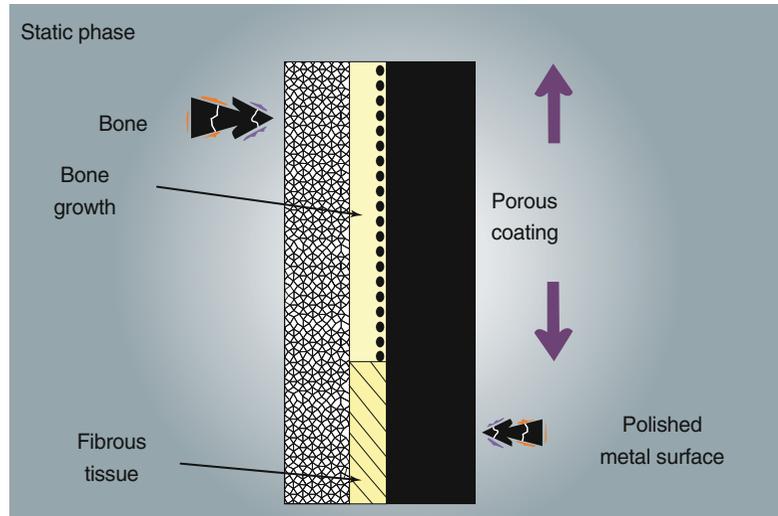


Fig. 1.7 (a) Sintered beads coating. (b) Fiber mesh coating. (c) Plasma spray coating. (d) Porous metal surface

Fig. 1.8 Line drawing of the bone-implant interface of a modern cementless design



30 and 40 % to maintain mechanical strength [48]. Ongrowth occurs when bone grows onto a roughened surface. Ongrowth surfaces are created by grit blasting or plasma spraying (Fig. 1.7). Grit blasting creates a textured surface by bombarding the implant with small abrasive particles. The surface roughness ranges from 3 to 5 mm [43, 49]. Plasma spraying involves mixing metal powders with an inert gas that is pressurized and ionized, forming a high-energy flame. The molten material is sprayed onto the implant, creating a textured surface (weaker mechanical bond, abrasion, and wear). There is less interconnecting porosity than with the ingrowth surfaces; however, 90 % of implant fatigue strength is retained, whereas only 50 % is retained after diffusion bonding and sintering [50]. Hydroxyapatite is a calcium phosphate compound that is plasma sprayed directly on the implant alone or over a porous coating. It is osteoconductive and enhances the growth of mineralized bone onto the implant [51, 52]. HA bone interface is more tolerant to interface gaps and micromotion. Interface strength, interface degradation, and HA particle third-body wear are of concern [53, 54]. The good “recipe” for HA-coated implants is titanium alloy substrate, plasma spray technique, high crystallinity HA of 50–75 μm thickness, which does not compromise its strength or biological behavior [54, 55]. It is generally accepted that fixation surfaces need to be circumferential and continuous. Metaphyseal osseointegration and proximal stress transfer are

enhanced, and coating provides a seal which stops wear particle migration preventing interface osteolysis [56, 57]. Cobalt-chromium-molybdenum alloys and titanium-aluminum-vanadium alloys are most commonly used for cementless femoral stem designs. The modulus of elasticity of titanium alloys is closer to that of bone than is that of cobalt-chromium alloys. Theoretically, this should produce less thigh pain and stress shielding [58]. Thigh pain, however, is believed to be a result of not only the stiffness of the metal but also the stem geometry, and recent long-term clinical data have shown that proximal stress shielding phenomenon has been overestimated from the clinical point of view [59, 60]. In a modern cementless implant direct bone formation can be seen on 70–80 % of porous surfaces, fibrous tissue (with well-organized dense collagen network) on 20 % of porous surfaces, and amorphous fibrous tissue on smooth surfaces (Fig. 1.8). Improved direct bone formation is seen in HA-coated prostheses. Proximal femoral morphology and bone quality also seem to affect fixation [61]. Early cementless stems were classified as straight or curved. Current stems are referred to as proximally porous-coated tapered or fully coated cylindrical. While these simplifications are acceptable in general terms, they miss important design characteristics and make comparisons misleading. A comprehensive classification system is needed, with that proposed by Khanuja being useful for comparisons, although not complete [62].

The Test of Time

Cementless surgical techniques and the design of implants have also evolved dramatically. Some of these changes have also resulted in improved survival rates (good recipes), while others have not (bad recipes), and mid-term and long-term clinical and registry data have also shown that not all cementless cups and stems are the same. No data exist to support the idea that the use of super alloys and improved surfaces, as a single factor, affects clinical results at 15 years. Despite improvements in manufacturing, structural failures of implants still appear [63]. The long-term results of the first generation of cementless cups are heavily affected by problems of the locking mechanism, backside wear, and osteolysis. Cups made of porous materials, approaching the 10-year time interval, present promising clinical data [64, 65]. Additionally, high failure rates were observed with the use of HA-coated hemispherical cups [66]. There is also evidence that femoral stem geometry is more important than alloy and surface characteristics [59, 67–69].

There are several good “recipes” which combine different alloy, geometry, and surface finish principles [62]. Numerous reports of the CLS Spotorno femoral stem, which is a grit-blasted single wedge for tapered proximal fixation, show a 98.8 % survival rate at 15–20 years [70]. Taper-Lock and Tri-Lock, two versions (plasma spray and porous coated) of a single wedge for proximal tapered fixation, showed a 99 % survival rate at 22 years [71]. Two versions of the Omnifit stem, a double wedge for metaphyseal filling and proximal HA fixation, showed a 99 % survival rate at 17–24 years [66, 69, 72]. Another similar design, the Corail HA-coated stem, showed a 97 % survival rate at 20 years [73]. In the same category, the HA-coated Furlong stem showed 97–99 % survival at 15–20 years [74]. The Mallory tapered round stem, for tapered proximal fixation, showed a 95.5 % survival rate at 20 years [75]. The small Wagner stem, a tapered spline cone for distal fixation, showed a 95–98 % survival rate at 15 years [76]. The Zweymuller grit-blasted tapered rectangular stem, for tapered distal fixation, showed a 96–98 % survival rate at 20 years [77]. The anatomic cylindrical fully coated stem for distal

fixation showed a 92 % survival rate at 22 years [78, 79]. Generally, all the above designs and several modern 3° taper stems (with follow-up observation just above 15 years) present an average 1.5 % revision rate for aseptic loosening at 15 years.

Evidence-Based Data

In a systematic review and meta-analysis of cemented versus cementless cups, it was found that using contemporary techniques, both cemented and uncemented sockets, can yield good long-term results, but the overall/all cause reoperation risk is lower for cemented fixation. It is suggested until and unless cross-linked polyethylene (PE) liners or alternative bearings can prove to yield a superior outcome in the future, the cemented PE cup remains the gold standard, for all age groups, and by which every acetabular component should be compared [4, 80]. There are two systematic reviews comparing cemented and cementless femoral stems. In the first one, no difference was found [3]. In the second, cemented stems showed superior clinical and functional results in the short term, but cemented stems showed less clear superiority in the long term, and radiological results did not correlate with the clinical outcome [81]. In a RCT (level I) study with a 20-year follow-up cemented THA showed lower survival rates compared to cementless; the cementless tapered stem was associated with a survival rate of 99 % [82]. Age younger than 65 years and male gender were predictors of revision surgery [82]. Finally, in a recent report from the Swedish Register, it was found that the survival of uncemented THA is inferior to that of cemented, mainly related to poorer performance of uncemented cups, uncemented stems perform better than cemented stems, and unrecognized intraoperative femoral fractures may be an important reason for early failure of uncemented stems [83].

Conclusion

Long-term survival of THA is multifactorial. The patient, diagnosis, and surgeon factors are perhaps more important than the implant per se. There are several good and bad recipes for

both cemented and cementless arthroplasty. It seems that a 1.5 % revision rate (for both cemented and cementless stem fixation) for aseptic loosening at 15 years follow-up is a target for future comparisons. Financial investment in the development of new materials and designs has not been translated in improved survival rates at 15 years follow-up. The weak link of contemporary THA remains bearing surfaces.

References

1. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. *Lancet*. 2007;370(0597):1508–19.
2. Laupacis A, Bourne R, Rorabeck C, Feeny D, Wong C, Tugwell P, Leslie K, Bullas R. The effect of elective total hip replacement on health-related quality of life. *J Bone Joint Surg Am*. 1993;75:1619–26.
3. Morshed S, Bozic KJ, Ries MD, Maclau H, Colford Jr JM. Comparison of cemented and uncemented fixation total hip replacement: a metaanalysis. *Acta Orthop Scand*. 2007;78(3):315–26.
4. Pakvis D, van Hellemond G, de Visser E, Jacobs W, Spruit M. Is there evidence for a superior method of socket fixation in hip arthroplasty? A systematic review. *Int Orthop*. 2011;35:1109–18.
5. Muirhead-Allwood SK. Lessons of a hip failure. *BMJ*. 1998;316(7132):644.
6. Bauer TW, Schils J. The pathology of total joint arthroplasty. I. Mechanisms of implant fixation. *Skeletal Radiol*. 1999;28:423–32.
7. Charnley J. The reaction of bone to self-curing acrylic cement. A long-term histological study in man. *J Bone Joint Surg Br*. 1970;52B:340–53.
8. Lindwer J, Van Den Hooff A. The influence of acrylic cement on the femur of the dog: a histological study. *Acta Orthop Scand*. 1975;46:657–71.
9. Petty W. The effect of methylmethacrylate on bacterial phagocytosis and killing by human polymorphonuclear leukocytes. *J Bone Joint Surg Am*. 1978;60A:752–7.
10. Rhinelander FW, Nelson CL, Stewart RD, Stewart CL. Experimental reaming of the proximal femur and acrylic cement implantation: Vascular and histologic effects. *Clin Orthop*. 1979;141:74–89.
11. Slooff TJ. The influence of acrylic cement. *Acta Orthop Scand*. 1971;42:465–81.
12. Willert HG, Ludwig J, Semlitsch M. Reaction of bone to polymethacrylate after hip arthroplasty: a long term gross, light microscopic and scanning electron microscopic study. *J Bone Joint Surg Am*. 1974;56A:1368–82.
13. Jasty M, Maloney WJ, Bragdon CR, Haire T, Harris WH. Histomorphological studies of the long term skeletal responses to well fixed cemented femoral components. *J Bone Joint Surg Am*. 1990;72A:1220–9.
14. Scheerlinck T, Casteleyn PP. The design features of cemented femoral hip implants. *J Bone Joint Surg Br*. 2006;88B:1409–18.
15. Shah N, Porter M. Evolution of cemented stems. *Orthopedics*. 2005;28(8S):819–25.
16. Harris WH. Long-term results of cemented femoral stems with roughened precoated surfaces. *Clin Orthop*. 1998;355:137–43.
17. Ramaniraka NA, Rakotomanana LR, Leyvraz PF. The fixation of the cemented femoral component: effects of stem stiffness, cement thickness and roughness of the cement-bone interface. *J Bone Joint Surg Br*. 2000;82B:297–303.
18. Espehaug B, Furnes O, Engesaeter LB, Havelin LI. 18 years of results with cemented primary hip prostheses in the Norwegian Arthroplasty Register: concerns about some newer implants. *Acta Orthop Scand*. 2009;80:402–12.
19. Jones LC, Hungerford MA. Cement disease. *Clin Orthop*. 1990;225:192–5.
20. Ritter MA, Thong AE. The role of cemented sockets in 2004: is there one? *J Arthroplasty*. 2004;19(4S):92–4.
21. Garcia-Cimberelo E, Munuera L. Late loosening of the acetabular cup after low friction arthroplasty. *J Bone Joint Surg Am*. 1992;74A:1119–29.
22. Berry DJ, Harmsen WS, Cabanela ME, Morrey BF. Twenty five year survivorship of two thousand consecutive primary Charnley total hip replacements: factors affecting survivorship of acetabular and femoral components. *J Bone Joint Surg Am*. 2002;84A:171–7.
23. Georgiades G, Babis GC, Hartofilakidis G. Charnley low friction arthroplasty in young patients with osteoarthritis: outcomes at minimum of twenty-two years. *J Bone Joint Surg Am*. 2009;91A:2846–51.
24. Hartofilakidis G, Karachalios T, Zacharakis N. Charnley low friction arthroplasty in young patients with osteoarthritis. A 12 to 24 year clinical and radiographic follow up study of 84 cases. *Clin Orthop*. 1997;341:51–4.
25. Hartofilakidis G, Karachalios T, Karachalios G. The 20 year outcome of the Charnley arthroplasty in younger and older patients. *Clin Orthop*. 2005;434:177–82.
26. Herberts P, Malchau H. Long term registration has improved the quality of hip replacement: a review of the Swedish THR Register comparing 160.000 cases. *Acta Orthop Scand*. 2000;71:111–21.
27. Halley DK, Glassman AH. Twenty to twenty six year radiographic review in patients 50 years of age or younger with cemented Charnley low friction arthroplasty. *J Arthroplasty*. 2003;18(7S):79–85.
28. Wroblewski BM, Siney PD, Fleming PA. Charnley low-frictional torque arthroplasty in patients under the age of 51 years: follow-up to 33 years. *J Bone Joint Surg Br*. 2002;84B:540–3.
29. Wroblewski BM, Fleming PA, Siney PD. Charnley low-frictional torque arthroplasty of the hip: 20-to-30 years results. *J Bone Joint Surg Br*. 2009;81B:427–30.
30. Williams HD, Browne G, Gie GA. The Exeter universal cemented femoral component at 8 to 12 years: a study of the first 325 hips. *J Bone Joint Surg Br*. 2002;84B:324–34.

31. Ling RS, Charity J, Lee AJ, Whitehouse SL, Timperley AJ, Gie GA. The long term results of the original Exeter polished cemented femoral component: a follow up report. *J Arthroplasty*. 2009;24:511–7.
32. Savilahti S, Myllyneva I, Pajamaki KJ, Lindholm TS. Survival of Lubinus straight (IP) and curved (SP) total hip prosthesis in 543 patients after 4–13 years. *Arch Orthop Trauma Surg*. 1997;116:10–3.
33. Partio E, von Bonsdorff H, Wirta J, Avikainen V. Survival of the Lubinus hip prosthesis: an eight- to 12-year follow-up evaluation of 444 cases. *Clin Orthop*. 1994;303:140–6.
34. Soballe K, Christensen F, Luxhoj T. Total hip replacement ad modum Lubinus: five- to seven-year follow-up. *Arch Orthop Trauma Surg*. 1987;106:108–12.
35. Riede U, Luem M, Ilchmann T, Eucker M, Ochsner PE. The ME Muller straight stem prosthesis: 15 year follow-up. Survivorship and clinical results. *Arch Orthop Trauma Surg*. 2007;127:587–92.
36. Müller ME. Lessons of 30 years of total hip arthroplasty. *Clin Orthop*. 1992;274:12–21.
37. Langlais F, Kerboul M, Sedel L, Ling RSM. The 'French paradox'. *J Bone Joint Surg Br*. 2003;85B:17–20.
38. Langlais F, Howell JR, Lee AJC, Ling RSM. The "French paradox". *Hip Int*. 2002;12:166–8.
39. Kerboul L, Hamadouche M, Courpied JP, Kerboul M. Long-term results of Charnley-Kerboul hip arthroplasty in patients younger than 50 years. *Clin Orthop*. 2004;418:112–8.
40. Hamadouche M, Boutin P, Daussange J, Bolander ME, Sedel L. Alumina -on- alumina total hip arthroplasty: a minimum 18.5-year follow-up study. *J Bone Joint Surg Am*. 2002;84A:69–77.
41. Albrektsson T, Branemark PI, Hansson HA, Lindstrom J. Osseointegrated titanium implants. Requirements for ensuring a long lasting, direct bone to implant anchorage in man. *Acta Orthop Scand*. 1981;52:155–70.
42. Galante J, Rostoker W, Lueck R, Ray RD. Sintered fiber metal composites as a basis for attachment of implants to bone. *J Bone Joint Surg Am*. 1971;53A:101–14.
43. Zweymuller KA, Lintner FK, Semitsch MF. Biologic fixation of a press fit titanium hip joint endoprosthesis. *Clin Orthop*. 1988;235:195–206.
44. Engh CA, O'Connor D, Jasty M, McGovern TF, Bobyn JD, Harris WH. Quantification of implant micromotion, strain shielding, and bone resorption with porous coated anatomic medullary locking femoral prostheses. *Clin Orthop*. 1992;285:13–29.
45. Jasty M, Bragdon C, Burke D, O'Connor D, Lowenstein J, Harris WH. In vivo skeletal responses to porous surfaced implants subjected to small induced motions. *J Bone Joint Surg Am*. 1997;79A:707–14.
46. Bourne RB, Rorabeck CH, Burkart BC, Kirk PG. Ingrowth surfaces. Plasma spray coating to titanium alloy hip replacements. *Clin Orthop*. 1994;298:37–46.
47. Bobyn JD, Stackpool GJ, Hacking SA, Tanzer M, Krygier JJ. Characteristics of bone ingrowth and interface mechanics of a new porous tantalum biomaterial. *J Bone Joint Surg Br*. 1999;81B:907–14.
48. Haddad Jr RJ, Cook SD, Thomas KA. Biological fixation of porous-coated implants. *J Bone Joint Surg Am*. 1987;69A:1459–66.
49. Hacking SA, Bobyn JD, Tanzer M, Krygier JJ. The osseous response to corundum blasted implant surfaces in a canine hip model. *Clin Orthop*. 1999;364:240–53.
50. Callaghan JJ. The clinical results and basic science of total hip arthroplasty with porous-coated prostheses. *J Bone Joint Surg Am*. 1999;75A:299–310.
51. Søballe K, Gotfredsen K, Brockstedt-Rasmussen H, Nielsen PT, Rechnagel K. Histologic analysis of a retrieved hydroxyapatite-coated femoral prosthesis. *Clin Orthop*. 1991;272:255–8.
52. Nakashima Y, Hayashi K, Inadome T, Uenoyama K, Hara T, Kanemaru T, Sugioka Y, Noda I. Hydroxyapatite-coating on titanium arc sprayed titanium implants. *J Biomed Mater Res*. 1997;35:287–98.
53. Bloebaum RD, Zou L, Bachus KN, Shea KG, Hofmann AA, Dunn HK. Analysis of particles in acetabular components from patients with osteolysis. *Clin Orthop*. 1997;338:109–18.
54. Søballe K, Overgaard S. The current status of hydroxyapatite coating of prostheses. *J Bone Joint Surg Br*. 1996;78B:689–91.
55. Søballe K, Hansen ES, Brockstedt-Rasmussen H, Bunker C. Hydroxyapatite coating converts fibrous tissue to bone around loaded implants. *J Bone Joint Surg Br*. 1993;75B:270–8.
56. Emerson Jr RH, Sanders SB, Head WC, Higgins L. Effect of circumferential plasma-spray porous coating on the rate of femoral osteolysis after total hip arthroplasty. *J Bone Joint Surg Am*. 1999;81A:1291–8.
57. Bobyn JD, Jacobs JJ, Tanzer M, Urban RM, Aribindi R, Sumner DR, Turner TM, Brooks CE. The susceptibility of smooth implant surfaces to periimplant fibrosis and migration of polyethylene wear debris. *Clin Orthop*. 1995;311:21–39.
58. Healy WL, Tilzey JF, Iorio R, Specht LM, Sharma S. Prospective, randomized comparison of cobalt-chrome and titanium Trilock femoral stems. *J Arthroplasty*. 2009;24:831–6.
59. Lavernia C, D'Apuzzo M, Hernandez V, Lee D. Thigh pain in primary total hip arthroplasty: the effects of elastic moduli. *J Arthroplasty*. 2004;19(7S2):10–6.
60. Karachalios T, Tsatsaronis C, Efraimis G, Papadelis P, Lyritis G, Diakomopoulos G. The long-term clinical relevance of calcar atrophy caused by stress shielding in total hip arthroplasty: a 10-year, prospective, randomized study. *J Arthroplasty*. 2004;19:469–75.
61. Dorr LD, Faugere MC, Mackel AM, Gruen TA, Bogner B, Malluche HH. Structural and cellular assessment of bone quality of proximal femur. *Bone*. 1993;14(3):231–42.
62. Khanuja HS, Vakil JJ, Goddard MS, Mont MA. Cementless femoral fixation in total hip arthroplasty. *J Bone Joint Surg Am*. 2011;93-A:500–9.
63. Magnissalis EA, Zinelis S, Karachalios T, Hartofilakidis G. Failure analysis of two Ti-alloy total

- hip arthroplasty femoral stems fractured in vivo. *J Biom Mat Res.* 2003;15:299–305.
64. Macheras GA, Papagelopoulos PJ, Kateros K, Kostakos AT, Baltas D, Karachalios T. Radiological evaluation of the metal bone interface of a porous tantalum monoblock acetabular component. *J Bone Joint Surg Br.* 2006;88B:304–9.
 65. Malizos KN, Bargiotas K, Papatheodorou L, Hantes M, Karachalios T. Survivorship of monoblock trabecular metal cups in primary THA: midterm results. *Clin Orthop.* 2008;466:159–66.
 66. Capello WN, D'Antonio JA, Jaffe WL, Geesink RG, Manley MT, Feinberg JR. Hydroxyapatite-coated femoral components: 15-year minimum followup. *Clin Orthop.* 2006;453:75–80.
 67. Kim YH. Titanium and cobalt-chrome cementless femoral stems of identical shape produce equal results. *Clin Orthop.* 2004;427:148–56.
 68. Camazzola D, Hammond T, Gandhi R, Davey JR. A randomized trial of hydroxyapatite-coated femoral stems in total hip arthroplasty: a 13-year follow-up. *J Arthroplasty.* 2009;24:33–7.
 69. Incavo SJ, Beynon BD, Coughlin KM. Total hip arthroplasty with the Secur-Fit and Secur-Fit Plus femoral stem design a brief follow-up report at 5 to 10 years. *J Arthroplasty.* 2008;23:670–6.
 70. Muller LA, Wenger N, Schramm M, Hohmann D, Forst R, Carl HD. Seventeen year survival of the cementless CLS Spotorno stem. *Arch Orthop Trauma Surg.* 2009;130:269–75.
 71. McLaughlin JR, Lee KR. Total hip arthroplasty with an uncemented tapered femoral component. *J Bone Joint Surg Am.* 2008;90A:1290–6.
 72. Epinette JA, Manley MT. Uncemented stems in hip replacement, hydroxyapatite or plain porous: does it matter? Based on a prospective study of HA Omnifit stems at 15-years minimum followup. *Hip Int.* 2008;18:69–74.
 73. Vidalain JP. Twenty-year results of the cementless Corail stem. *Int Orthop.* 2011;35:189–94.
 74. Valera Pertegàs M, Vergara-Valladolid P, Crusi-Sererols X, Sancho-Navarro R. Fully hydroxyapatite-coated total hip replacement: ten-year results. *Hip Int.* 2010;20(7S):79–85.
 75. Lombardi Jr AV, Berend KR, Mallory TH, Skeels MD, Adams JB. Survivorship of 2000 tapered titanium porous plasma-sprayed femoral components. *Clin Orthop.* 2009;467:146–54.
 76. Schuh A, Schraml A, Hohenberger G. Long-term results of the Wagner cone prosthesis. *Int Orthop.* 2009;33:53–8.
 77. Suckel A, Geiger F, Kinzl L, Wulker N, Garbrecht M. Long-term results for the uncemented Zweymuller/Alloclassic hip endoprosthesis. A 15-year minimum followup of 320 hip operations. *J Arthroplasty.* 2009;24:846–53.
 78. Engh Jr CA, Claus AM, Hopper Jr RH, Engh CA. Long-term results using the anatomic medullary locking hip prosthesis. *Clin Orthop.* 2001;393:137–46.
 79. Belmont Jr PJ, Powers CC, Beykirch SE, Hopper Jr RH, Engh Jr CA, Engh CA. Results of the anatomic medullary locking total hip arthroplasty at a minimum of twenty years. A concise follow-up of previous reports. *J Bone Joint Surg Am.* 2008;90A:1524–30.
 80. Clement ND, Biant LC, Breusch SJ. Total hip arthroplasty: to cement or not to cement the acetabular socket? A critical review of the literature. *Arch Orthop Trauma Surg.* 2012;132:411–27.
 81. Ni GX, Lu WW, Chiu KY, Fong DY. Cemented or uncemented femoral component in primary total hip replacement? A review from a clinical and radiological perspective. *J Orthop Surg.* 2005;13:96–105.
 82. Corten K, Bourne RB, Charron KD, Au K, Rorabeck CH. Comparison of total hip arthroplasty performed with and without cement: a randomized trial. A concise follow-up, at twenty years, of previous reports. *J Bone Joint Surg Am.* 2011;93A:1335–42.
 83. Hailer NP, Garellick G, Kärrholm J. Uncemented and cemented primary total hip arthroplasty in the Swedish Hip Arthroplasty Register. *Acta Orthop Scand.* 2010;81:34–41.

Early and Late Mechanical Stability of the Cementless Bone-Implant Interface in Total Joint Arthroplasty

2

Elise C. Pegg, Stephen J. Mellon,
and Harinderjit S. Gill

Introduction

The mechanical stability of an orthopedic implant is essential for optimal function and outcome. Implant design and theories about fixation have changed greatly over the years, but what does remain is a belief in the importance of achieving both primary stability and secondary stability.

Primary stability: Mechanical fixation of an implant achieved at surgery
Secondary stability: Bone growth directly onto the implant surface, enabling long-term fixation

The purpose of this chapter is to examine our current understanding of how these two stages can be achieved and the various influencing factors.

There are two main techniques used to achieve fixation of orthopedic components: application of polymethylmethacrylate (PMMA) to “cement”

the implant into the bone and “cementless” fixation where bone ingrowth directly onto the implant is encouraged using bioactive implant coatings and a rough surface texture. Much of our understanding of primary and secondary stability stems from the early studies of these techniques; therefore, we will begin by discussing the history behind cementless fixation. We will then examine the current theories behind the mechanism by which primary and secondary stability is achieved and finally we will focus on how implant design can affect stability.

Development of Cementless Components

Fixation of early components for joint replacement was largely unsatisfactory; many components were press-fit into the bone and some experimented with screw fixation [1], but loosening remained a common complication [2]. In 1962, Sir John Charnley decided to employ PMMA cement for his low-friction arthroplasty hip [3], and following the success of the procedure, PMMA cement use in orthopedics became common. However, some issues were associated with PMMA cement. One of these was the high temperature resulting from the exothermic polymerization reaction; this could lead to necrosis of the bone in some cases [4]. In addition to this, in 1976, Harris et al. published a paper reporting osteolysis following hip arthroplasty with an unusually high number of macrophages

E.C. Pegg • S.J. Mellon
Nuffield Department of Orthopaedics,
Rheumatology and Musculoskeletal Sciences,
University of Oxford, Oxford, UK

H.S. Gill (✉)
Nuffield Department of Orthopaedics,
Rheumatology and Musculoskeletal Sciences,
University of Oxford, Oxford, UK

Department of Mechanical Engineering,
University of Bath, Bath, UK
e-mail: richie.gill@ndorms.ox.ac.uk

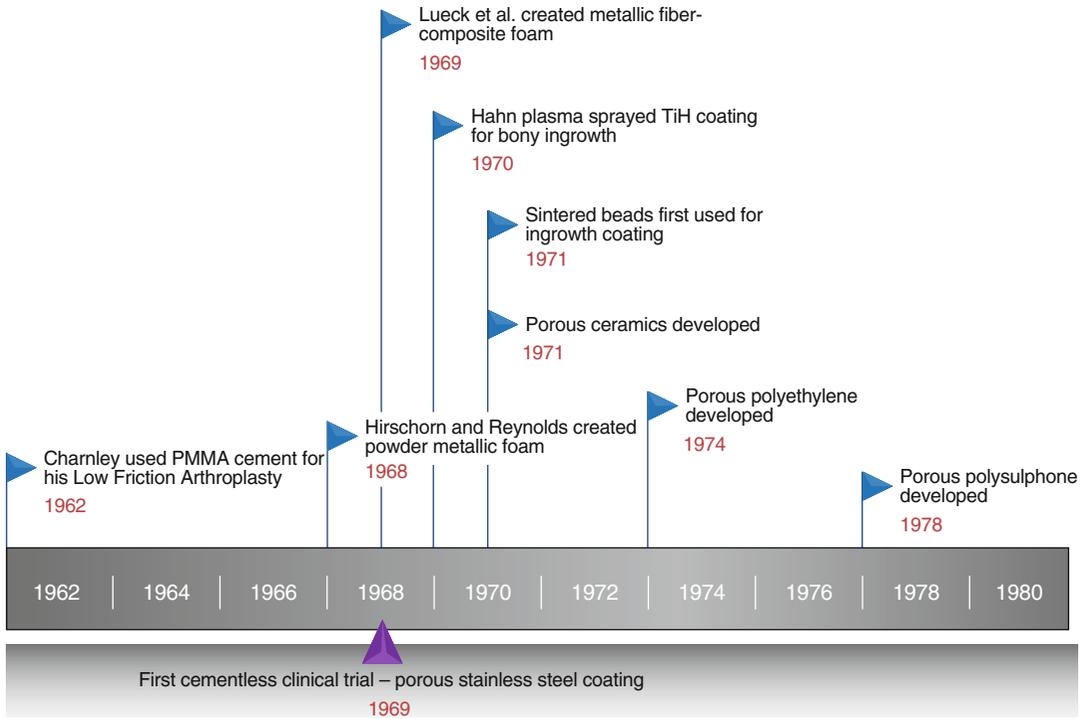


Fig. 2.1 Timeline of significant events in cementless fixation research

and voids in the surrounding tissue [5]. The tissue response was deemed to be an adverse reaction to the PMMA cement and the term “cement disease” was coined to describe this phenomenon. However, it was found later that UHMWPE wear debris was the culprit [6].

Nevertheless, as a result of these findings, attempts to produce coatings for orthopedic implants that remove the requirement of PMMA cements began in 1968 [7]. Hirschorn and Reynolds developed a porous cobalt-chrome alloy material [7]; the foam was produced using powder metallurgy techniques and demonstrated good tissue ingrowth into the open pores after 28 days of implantation in dogs. Despite these promising fixation characteristics, the authors expressed a concern regarding the mechanical strength of the material [8]. In 1969, Lueck et al. suggested that fiber-metal composites could provide a metallic foam which had both the strength and porosity adequate for orthopedic applications [9]. The materials developed by both Hirschorn [10] and Lueck [11] were not used commercially as solid implants,

but did become used as coatings on metallic components. Throughout the 1970s, a variety of porous materials and coatings were produced and investigated for cementless applications. These included sintered beads [12], plasma-sprayed coatings of different metallic alloys [13, 14], porous ceramic materials [15], porous polyethylene [16], and porous polysulfone [17], to name but a few (Fig. 2.1). The cementless coatings used today are largely based upon this body of work, and it has also aided our current understanding of the mechanisms behind implant fixation.

For an orthopedic component to become well fixed within the bone, it is necessary for there to be no barrier between the implant and the bone; this barrier may take the form of fibrous tissue. Whether or not fibrous tissue or a fibrocartilage layer develops depends upon the conditions at the bone-implant interface [18]. If lamellar bone is successfully attached to implants without intervening fibrous tissue, this is often termed osseointegration [19]. The mechanism by which osseointegration occurs is generally split into two

Table 2.1 Techniques for measuring micromotion at the bone/stem interface for femoral stems implanted in cadaveric femora [48]

Authors	Year	Method	Precision
Whiteside and Easley [26]	1989	Dial gauges touching implant through holes in femur	5 μm
Walker et al. [27]	1987	Noncontact eddy current displacement transducers measured steel rod touching implant	
Nunn et al. [28]	1989	Cantilever attached to bone with pointer on implant surface	
Schneider et al. [29]	1989	5 transducers on an x-y table measuring both rotation and micromotion	
Burke et al. [30]	1991	Extensometer attached to a pin within a metal cylinder. The pin was attached to the bone. Measured variation in the position of the pin within the cylinder	1 μm
Callaghan et al. [31]	1992		
Engh et al. [32]	1992		
McKellop et al. [33]	1991	Rigid frame attached to bone. Strain gauges measured frame movement	2 μm
Gilbert et al. [34]	1992	LVDTs attached to aluminum cubes on implant	
Berzins et al. [35]	1993	LVDTs attached to three steel spheres in contact with implant	
Hua and Walker [36]	1994	LVDTs attached to plastic targets inserted into femoral component	
Harman et al. [37]	1995	Linear extensometer measured rotational displacement	
Monti et al. [38]	1999	Method used by Harman et al. plus four LVDTs measuring shear micromotion at various locations	2.3–5 μm
Baleani et al. [39]	2000		
Viceconti et al. [40]	2001		
Cristofolini et al. [41]	2003		

stages: primary stability and secondary stability. Primary stability can be achieved without secondary stability; however, secondary stability cannot be achieved without primary stability. Both primary stability and secondary stability are necessary for complete osseointegration of an implant.

Primary Stability

In this section we will examine the following questions:

- How can the primary stability of a component be experimentally assessed?
- How unstable can an implant be without it affecting the function?
- What might a patient do to reduce the stability of their joint replacement?

Four main techniques have been used to examine the primary stability of implants: animal studies, cadaveric tests, computational modelling, and in vivo measurements. The majority of early studies were animal based. A common method employed was the “pull out” method; this is where, after a defined period of implantation

time, a tensile force is applied to the implant to remove it and the resistance to that force is related to its fixation [20–22]. A different approach was necessary to examine the effect of instability on the implant region. Pilliar et al. performed a series of studies in dogs, where implants were oscillated to different distances, thus simulating varying degrees of motion [23, 24]; the implantation site was then examined histologically. Another method for assessing the primary stability of cementless components is to implant them into cadaveric bones and measure the movement of the implant within the bone (also called “micromotion”) induced by physiological loading; retrieved bones with implants already in situ have also been tested [25] (Table 2.1). Experimental studies of cementless tibial components implanted into cadaveric tibiae showed micromovements in the range of 200–500 μm [42, 43]. It has also been possible to study micromotion using computational modelling. The finite element (FE) method simulates the behavior of a system based upon basic mechanical laws. Several studies have validated such models against experimental data [44]. These simulations

can provide information that is difficult to obtain experimentally. For instance, it is possible to create a complete map of the implant micromotion across the whole bone interface [45, 46], experimentally; this information is limited to where the gauges are positioned. Pancanti et al. used anatomical data from four different patients and simulated implant micromotion while performing nine different tasks; the position and force data were taken from an instrumented hip prostheses [44]. A recent statistical FE analysis demonstrated, over a simulated population of 1,000 cases, that a mismatch of up to 1 mm between the stem and the host bone at random locations of the interface is sufficient to produce a grossly loosened stem in 2 % of the patients, while for another 3–5 %, the high level of predicted micromotion is likely to prevent any substantial osseointegration [47]. These combinations of both experimental and simulation methods can be a powerful tool for examining primary stability.

In vivo assessment of implant stability is also possible through the use of radiostereometric analysis (RSA). Through taking radiographs at a variety of angles, the three-dimensional position of the implant within the bone can be determined; if this is performed over a period of time, the migration of the implant within the bone can be found [48]. According to Kärrholm et al. [49], when used in total hip arthroplasty, RSA has a precision of 0.15 mm in translation and 0.3° in rotation at the 99 % significance level. The four main methods outlined here, which examine primary stability, can help us answer many questions. One of the questions examined early on was how much stability is necessary for an implant to be successful. Several studies have clearly shown that excessive motion at the bone-implant interface has a detrimental effect on the amount of bone growth [23, 24, 50]. Pilliar et al. were the first group to suggest that there might be a micromotion threshold, whereby loosening would occur if this threshold were exceeded [23]. The authors performed a study that dynamically loaded intermedullary implants in dogs by varying degrees of oscillatory motion; when micromotion was beyond 150 μm , fibrous tissue was found surrounding the implant. This threshold

value has been supported by several different studies [51–53]. Similar values have been found even on porous surfaces which (sintered beads [23] or plasma-sprayed titanium alloy [30, 51, 54, 55]) promote bone ingrowth.

The micromotion value at which bone formation changes to a combination of bone and fibrocartilage is less clear; but studies have shown it to be in the range of 20–40 μm (Fig. 2.2). In the situation where a fibrous membrane is formed, although this interface may be stable for a certain amount of time, factors such as relative motions or wear particulate can provoke inflammatory reactions causing interface bone resorption and implant loosening [56]. Patient activity shortly after surgery is thought to have a detrimental effect on primary stability of cementless components. In an animal study, dogs implanted with a smooth cementless stem that were allowed to walk early postsurgery showed a higher loosening rate than those that were protected from loading for some time [57]. Several papers have also stated the importance of rotational stability of the femoral stem for the osseointegration process of the prosthesis [58–63]. In vitro studies on cementless femoral stems have shown that the highest values of relative micromotion are recorded when the implanted femur is subjected to high torque components [59–62, 64–69] which induce shear forces at the bone-implant interface [70]. An analysis of 70 failed implants revealed that failure most commonly occurs because of high torques [71]. In vivo investigations based on instrumented hip prostheses found that stair climbing and stand to sit/sit to stand activities generated the highest torsion moments [72–74].

Secondary Stability

In this section, we will examine the following questions:

- What is osteoinduction and how does it occur?
- By what mechanism do cells attach to the implant surface?
- How is bone formed?

Once primary stability has been achieved, biological processes are stimulated which enable bone

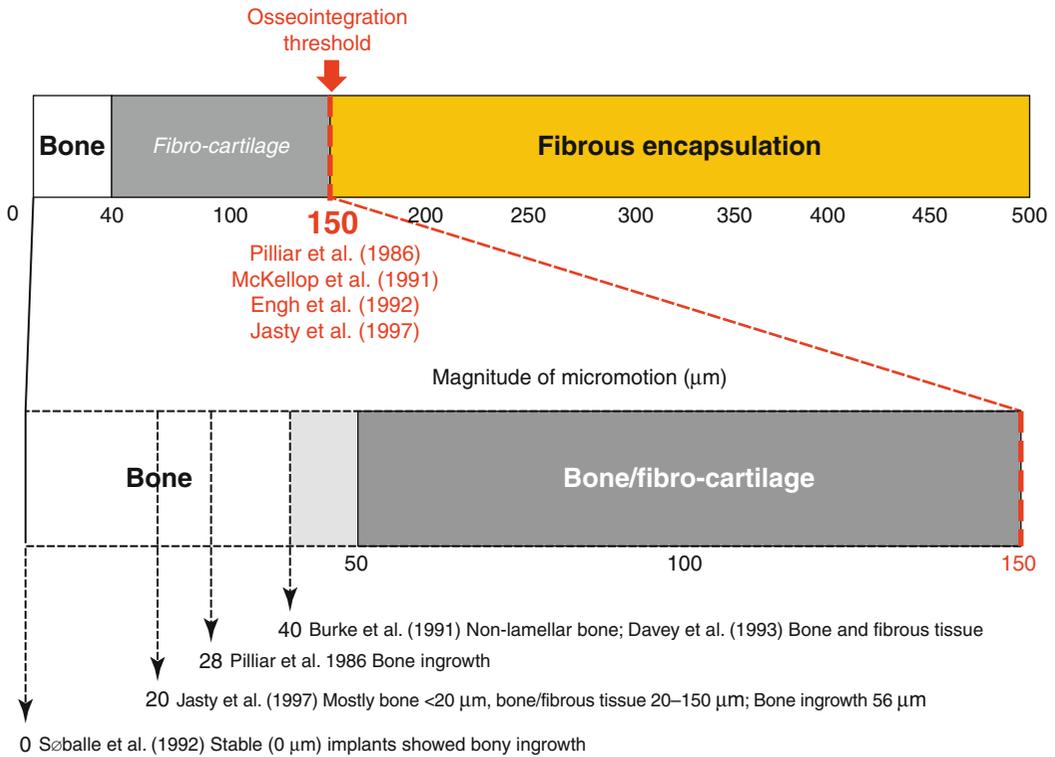


Fig. 2.2 Illustration of the tissue formation resulting from different magnitudes of micromotion

growth to fill the gap between the bone and the implant surface to achieve secondary stability. This process can be split into three parts; osteoinduction, osteoconduction, and osseointegration [75]. Within bone there are four fully differentiated cell types: osteoblasts (bone forming), osteoclasts (bone resorbing), bone-lining cells, and osteocytes (can form or resorb bone) (Fig. 2.3). Osteoclasts are produced from the fusion of mononuclear precursors from the blood, whereas all other cells are differentiated from the local mesenchymal cells (osteoprogenitor cells) [76]. Osteoinduction is the process whereby the osteoprogenitor cells within the bone are stimulated to differentiate into osteoblasts. This process occurs naturally in situations where bone healing is required; injury to the bone causes the release of mediators such as growth factors which simulate osteoinduction [77]. However, in the case of cementless implants coated in hydroxyapatite, which does not release growth factors or other known osteoinductive agents, the mechanism is less clear.

Osteoinduction: stimulation of osteoprogenitor cells to differentiate

Osteoinduction resulting from biomaterials has primarily been reported on calcium phosphate-based material. For this reason it has been hypothesized that the induction results from the dissolution of calcium and phosphate ions [78, 79]. However, there have been some reports of osteoinduction occurring on surfaces which do not contain calcium and phosphate; one theory is that the surface chemistry promotes the calcium and phosphate in solution surrounding the material to precipitate onto the surface [80, 81]. Another possibility is that the injury to the surrounding tissue as a result of the surgery stimulates osteoinduction [75]. Once osteoinduction has occurred and the population of osteoblast cells at the implantation site have increased sufficiently, it is likely that one or more of the cells will make direct contact with

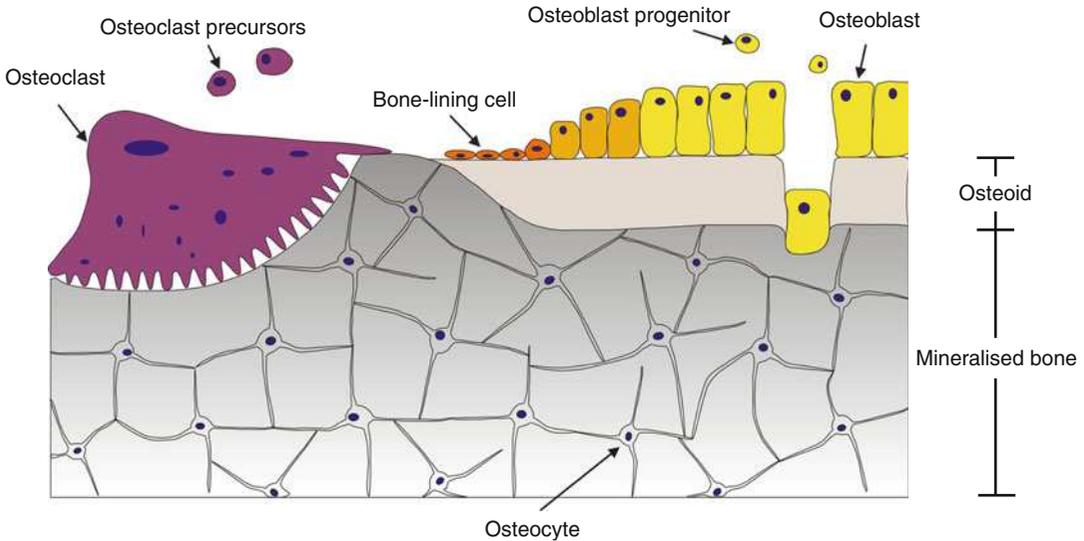


Fig.2.3 Schematic illustration of the cells within bone [57]

the implant. The osteoconductivity of the surface is a measure of how quickly these cells attach and proliferate across the surface. The interaction of the cells with the surface occurs through trans-membrane proteins called “integrins.”

Osteoconduction: the attachment and proliferation of cells on the implant

Integrins are situated within the cell membrane and consist of two units (Fig. 2.4). A variety of integrins can be found within the membrane, and they have many different roles in cellular functions, one of which is adhesion. During cell adhesion, the integrins bind to a specific motif found on most extracellular matrix (ECM) proteins. This is the sequence arginine-glycine-aspartic acid (also called RGD) [82]. The bound integrins then cluster together into focal contacts triggering a flow of signalling molecules to and from the cell which cause, amongst other responses, cell adhesion. In the case of a cementless implant, the surface normally does not contain the RGD motif, unless it is artificially added [83], but integrin binding can still occur. This is because after implantation of any material into the body, proteins will quickly be absorbed onto the surface of

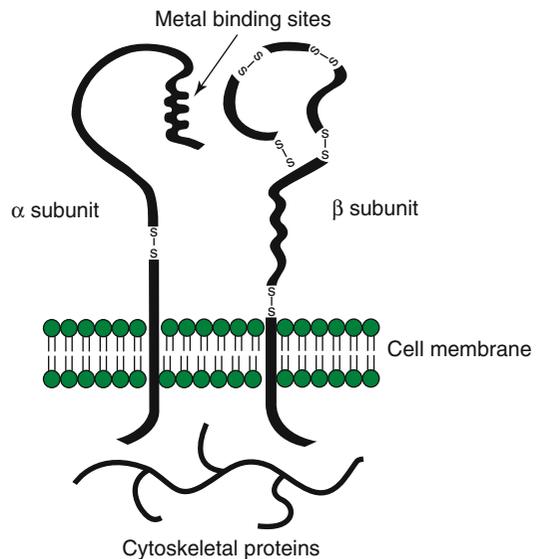


Fig.2.4 Illustration of the structure of an integrin [118]

the implant; the integrins can therefore bind to these absorbed proteins. It has been shown that the content of the protein layer varies over time; very mobile proteins are observed to adhere early on, and these are later replaced by proteins with a greater affinity to the surface. This is referred to as the “Vroman effect” [84]. The proteins which will adhere to the surface and their final orientation are largely dependent on the surface chemistry,

roughness, and surface energy [85]. The nature of the resultant layer of proteins is thought to affect the response of the osteoblasts to the surface [86].

Osteointegration is the long-term attachment of the bone to the implant; this is the aim of the coating on a cementless implant. After the osteoblast progenitor cells have differentiated into osteoblast cells, and these have adhered to the surface of the implant, bone growth can begin. The osteoblasts proliferate on the surface of the material and the surface of the bone, while proliferating they also secrete a mixture of bone matrix proteins, known as osteoid. Ninety percent of osteoid is Type I collagen, and this provides the structure on which bone mineral is deposited; also released are proteoglycans, glycoproteins, and γ -carboxylated proteins, which regulate cell adhesion, migration, proliferation, and mineralization [87].

Osseointegration: bone formation between the bone and the implant surface

The events leading up to full osseointegration of an implant can take in some cases up to 3 years and often do not begin until 4–12 weeks after implantation [88, 89]. The processes outlined in this section involve many stages, and each stage is very sensitive to the environment surrounding the implant-bone interface. An understanding of these processes and the factors that influence them is vital for ensuring complete fixation of a cementless component.

Design Factors

Research into optimizing the design of cementless components has focussed on two main factors: the morphology of the implant and the surface properties of the implant. These properties affect both primary stability and secondary stability of the implant.

Implant Morphology

The geometrical shape of a cementless hip can vary widely, and there is much dispute as to the optimal design. Khanuja et al. categorized current cementless hips into six different types based upon their design [90]; examination of the outcome of the different designs demonstrated that there was little difference between the survival rates of the different stems (Table 2.2). Nevertheless, there is a clear philosophy behind each design, and the stem type can be tailored for a specific scenario.

Early designs of cementless hip aimed to fix the stem strongly in the distal region of the femur; this meant that many designs had increased stem lengths and large diameters distally. It soon became apparent that this resulted in distal loosening due to stress shielding [91] and designs were modified accordingly. Later designs promoted proximal fixation, and consequently, many cementless hip designs apply coating to just the proximal region [91].

Table 2.2 Summary of clinical studies examining the survivorship of different cementless hip stem designs

Stem type	Description	Total no. of hips	Mean duration of follow-up (range) (year)	Mean stem survivorship (%)	References
1	Single wedge	737	14.1 (6–22.6)	95.1	[1–9]
2	Double wedge	872	11.3 (5–20)	98.7	[10–13]
3A	Tapered, round	1,942	10.1 (2–23)	97.1	[14, 15]
3B	Tapered, spline/curve	94	11.5 (10–14)	91.5	[16]
3C	Tapered, rectangle	196	13.4 (10–17.25)	100.0	[17, 18]
4	Cylindrical fully coated	2,557	12.2 (0–29)	97.8	[19–24]
5	Modular	1,065	9.6 (2–17)	99.5	[25–44]
6	Anatomic	714	12.9 (8–17.2)	97.0	[29–51]

Results from each study have been summed together

The design of a hip stem is often based upon the desired loading region [90]. For instance, tapering of the proximal region can be used to ensure proximal loading (Types 1–3 in Table 2.2). Type 4 hip stems aim for even loading throughout the length of the stem, and thus the entire stem is coated. Type 6 anatomic stems aim to match the endosteal geometry, and thus careful preparation of the bone is required to ensure the patient bone shape matches that of the stem [92]. Reaming of the bone in preparation for implantation is an important factor in both the primary stability of the implant and the resultant stem design. In order to achieve good primary stability, it is necessary to have a close fit between the bone and the implant surface. This is often achieved by rasping a hole in the bone which is slightly smaller than the implant enabling press-fit fixation. Often the distal region of the femur is not reamed; this minimizes the risk of damage to the endosteal blood supply. The shape of the hip stem is also limited to shapes that can be reamed out from above.

One feature of hip stem design for which there has been much debate is the function of a collar and whether the presence of a collar affects the outcome and stability of a cementless hip (Fig. 2.5). Collars were introduced to ensure the stem does not subside into the femur and to distribute load more evenly onto the medial cortex to prevent stress shielding [93]. Broadly speaking, collar designs were split into two categories: large and small. In 1990 Kwong et al. reported bone resorption at the collar-calcar interface [94]; a later clinical study also indicated calcar resorption after 5 years of implantation of large collared stems [95]. The proposed causes for bone resorption primarily relate to the quality of contact between the collar and the calcar [96]; it was suggested that uneven loading could result from poorly cut bone which does not match the collar angle or poor cementing. The small collared stems, however, demonstrated good clinical results, and several studies showed little difference between small collared and collarless stems [97, 98]. Both designs are still used in current practice.

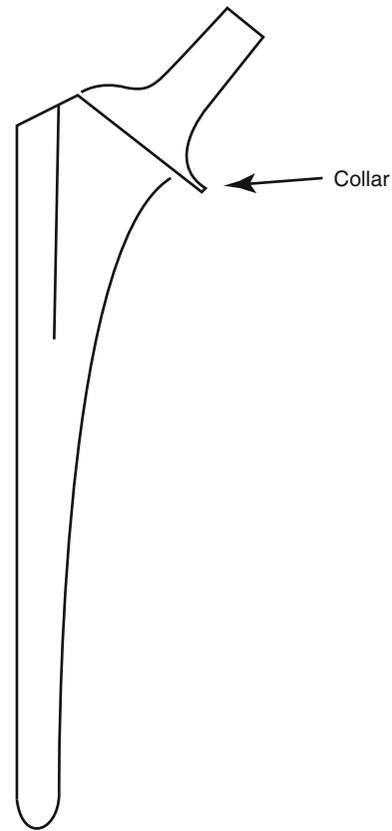


Fig. 2.5 Illustration of a collared hip stem

Coating Design

Cementless implants are designed to promote osteointegration; commercially the surfaces are normally roughened and coated with hydroxyapatite (Table 2.3). Surfaces can be roughened chemically [99] or mechanically [100]; another approach is to apply a rough coating to the implant either by plasma-spraying metallic particles [101] (Fig. 2.6) or bonding metallic “beads” to the surface [100]; alternatively, the whole implant might be a porous metallic mesh manufactured from tantalum or titanium alloys [102]. These surface coatings are both rough and porous. The pore size of surfaces has been shown to affect osteointegration. Studies have shown that if the pore size is too small, the quality of bone ingrowth is poor [103, 104], whereas very large pores can cause fibrous tissue formation [105]. Good osteointegration is observed with pore sizes of 100–400 μm [106].

Table 2.3 Summary of the different commercial cementless fixation products currently available

Manufacturer	Product	Roughening technique	HA coating method
Smith & Nephew	StikTite	Sintered pure titanium powder	
	RoughCoat	Sintered pure titanium beads	
	Porous Plus	Sintered pure titanium beads	Plasma sprayed
DePuy	Porocoat	Sintered pure titanium beads	
	Duofix	Sintered pure titanium beads	Plasma sprayed
Biomet	Regenerex	Porous titanium alloy foam	
	PPS+OsteoCoat	Plasma-sprayed titanium alloy	Plasma sprayed
	PPS+BoneMaster	Plasma-sprayed titanium alloy	Electrochemical deposition
Zimmer	Trabecular metal	Porous tantalum alloy foam	
	CSTi	Sintered pure titanium powder	Plasma sprayed
	Fiber metal	Titanium fiber mesh	Plasma sprayed
Stryker	Tritanium	Arc-deposited pure titanium onto polyurethane foam	
	PS	Plasma-sprayed pure titanium	
	PureFix	Chemically roughened	Plasma sprayed
	Secur-Fit HA	Arc-deposited pure titanium	Plasma sprayed
	Peri-Apatite	Plasma-sprayed pure titanium	Solution precipitated

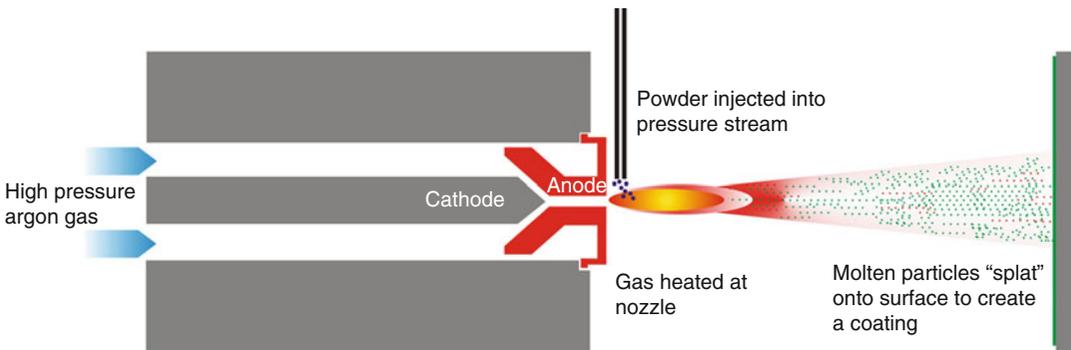


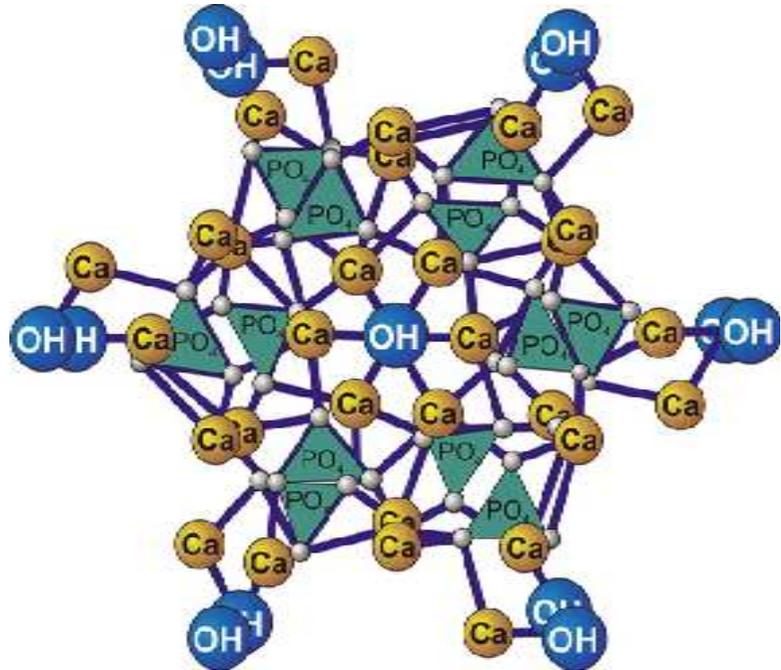
Fig. 2.6 Schematic of the plasma-spraying process used to create porous coatings

Plasma spraying: thermal spraying technique where the coating material is passed into a plasma jet at 10,000 K where it partially melts and is then projected at 300 m/s onto the surface

The adherence of the coating to the substrate is crucial; factors affecting the strength of the coating are the coating thickness, the content and crystallinity of the coating, and parameters involved in the plasma-spraying process such as the heat and the pressure of the jet. All commercial

coatings have to be regularly tested, in accordance with international standards [107] to minimize the risk of coating delamination. Hydroxyapatite (HA) has approximately the same chemical composition as the mineral phase of bone and can be synthetically produced or harvested from natural sources (Fig. 2.7). For commercial orthopedic components, HA tends to be plasma sprayed onto implants as a coating to promote osteointegration [108]; however, it can also be deposited electrochemically onto surfaces [109] or by solution precipitated onto a surface [110]. In some cases the entire component can be made from HA where biodegradation is desired [111].

Fig. 2.7 Structure of hydroxyapatite



With the aim of further improving the bioactivity of HA coatings, some researchers have included silicon into the composition [112]. Silicon is known to play a role in the formation of bone [113], and in vitro results have shown increased osteoblastic growth on silicon-doped HA coatings [114, 115]; some in vivo testing has been performed on animals [116, 117]. However, further work is required before the coatings may be used commercially.

Summary

Successful cementless implant fixation is essential for the survivorship and good function of a joint replacement. Fixation is often split into two events: stability of the joint in the initial stages (primary stability) and biological growth towards the surface of the implant resulting in full fixation (secondary stability). Good primary stability of the joint can be achieved by ensuring a press fit between the bone and the implant surface. For this to be possible, it is important that there is a good match between the shape of the implant and the reamed bone. The roughness of the implant

surface can also aid primary stability by causing a “scratch fit” into the bone. Many authors support the theory that a certain amount of micromotion of the implant within the bone is acceptable but that if this exceeds the threshold of 150 μm , then fibrous tissue will surround the implant and primary stability will not be possible. The patient activity immediately after surgery is also of great importance and should be minimized to ensure the implant remains fixed. As has been outlined, achieving primary stability is only part of the story. For full fixation of an implant within the bone, bone growth needs to occur to fill the gap between the bone and the implant surface. This secondary fixation relies upon the correct biological signals to be produced to stimulate the osteoblasts to produce mineralized bone. These signals can be influenced by many factors including surface chemistry and roughness. Most commercially available coatings incorporate a rough metallic coating underlayer and a hydroxyapatite top coating; these are applied to the surfaces of implants in the region where bone fixation is desired. More recently, metallic foams manufactured from titanium and tantalum alloys have been introduced which provide a highly porous surface for bone ingrowth

and can be applied as coatings or used as solid materials. These innovations in cementless component design have enabled current cementless components to be a viable alternative to cemented components, with comparable survivorship and outcome. New designs are constantly helping to increase our understanding of what causes an implant to become well fixed and how we can improve the function of these components further.

References

1. Ring P. Complete replacement arthroplasty of the hip by the Ring prosthesis. *J Bone Joint Surg Br.* 1968; 50B(4):720.
2. Alsen S, Olsson O. Loosening and fracture of Judet's hip prosthesis. *Acta Chir Scand.* 1956;111(2):158–64.
3. Charnley J. The bonding of prostheses to bone by cement. *J Bone Joint Surg Br.* 1964;46B:518–29.
4. DePisa J, Sih G, Berman A. The temperature problem at the bone-acrylic cement interface of the total hip replacement. *Clin Orthop.* 1976;121:95–8.
5. Harris WH, et al. Extensive localized bone resorption in the femur following total hip replacement. *J Bone Joint Surg Am.* 1976;58A:612–8.
6. Kadoya Y, Kobayashi A, Ohashi A. Wear and osteolysis in total joint replacements. *Acta Orthop Scand.* 1998;278(S):1–16.
7. Hirschhorn J, Reynolds J. Powder metallurgy fabrication of surgical implant materials. *J Metal.* 1968;20(8):A36–7.
8. Hirschhorn JS, McBeath AA, Dustoor MR. Porous titanium surgical implant materials. *J Biomed Mater Res.* 1971;5(6):49–67.
9. Lueck RA, et al. Development of an open pore metallic implant to permit attachment to bone. *Surg Forum.* 1969;20:456–7.
10. Young FA, Spector M, Kresch CH. Porous titanium endosseous dental implants in rhesus monkeys: micro-radiography and histological evaluation. *J Biomed Mater Res.* 1979;13(6):843–56.
11. Turner TM, et al. Bone ingrowth into the tibial component of a canine total condylar knee replacement prosthesis. *J Orthop Res.* 1989;7(6):893–901.
12. Welsh RP. Surgical implants: the role of surface porosity in fixation to bone and acrylic. *J Bone Joint Surg Am.* 1971;53A(5):963.
13. Bortz SA, Onesto EJ. Flame and plasma sprayed ceramics for uses in biomedical applications. *Composites.* 1974;5(4):151–6.
14. Hahn H, Palich W. Preliminary evaluation of porous metal surfaced titanium for orthopedic implants. *J Biomed Mater Res.* 1970;4(4):571–7.
15. Klawitter JJ, Hulbert SF. Application of porous ceramics for the attachment of load bearing internal orthopedic applications. *J Biomed Mater Res.* 1971; 5(6):161–229.
16. Sauer BW, et al. The role of porous polymeric materials in prosthesis attachment. *J Biomed Mater Res.* 1974;8(3):145–53.
17. Spector M, et al. A high-modulus polymer for porous orthopedic implants: biomechanical compatibility of porous implants. *J Biomed Mater Res.* 1978;12(5): 665–77.
18. Prendergast PJ, Huiskes R, Soballe K. Biophysical stimuli on cells during tissue differentiation at implant interfaces. *J Biomech.* 1997;30(6):539–48.
19. Albrektsson T, Albrektsson B. Osseointegration of bone implants – a review of an alternative mode of fixation. *Acta Orthop Scand.* 1987;58(5):567–77.
20. D'Lima DD, et al. Bone response to implant surface morphology. *J Arthroplasty.* 1998;13(8):928–34.
21. Basarir K, et al. Osseointegration in arthroplasty: can simvastatin promote bone response to implants? *Int Orthop.* 2009;33(3):855–9.
22. Bereiter H, Burgi M, Rahn BA. Behaviour of the anchorage of a cement-free cup component of a hip-prosthesis over time in animal-experiments. *Orthopade.* 1992;21(1):63–70.
23. Pilliar RM, Lee JM, Maniopoulos C. Observations on the effect of movement on bone ingrowth into porous-surfaced implants. *Clin Orthop.* 1986;208: 108–13.
24. Cameron HU, Pilliar RM, Macnab I. Effect of movement on bonding of porous metal to bone. *J Biomed Mater Res.* 1973;7(4):301–11.
25. Monti L, Cristofolini L, Viceconti M. Methods for quantitative analysis of the primary stability in uncemented hip prostheses. *Artif Organs.* 1999;23(9): 851–9.
26. Whiteside LA, Easley JC. The effect of collar and distal stem fixation on micromotion of the femoral stem in uncemented total hip arthroplasty. *Clin Orthop Relat Res.* 1989;239:145–53.
27. Walker PS, Schneeweis D, Murphy S, Nelson P. Strains and micromotions of press-fit femoral stem prostheses. *J Biomech.* 1987;20(7):693–702.
28. Nunn D, Freeman MA, Tanner KE, Bonfield W. Torsional stability of the femoral component of hip arthroplasty. Response to an anteriorly applied load. *J Bone Joint Surg Br.* 1989;71B:452–5.
29. Schneider E, Eulenberger J, Steiner W, Wyder D, Friedman RJ, Perren SM. Experimental method for the in vitro testing of the initial stability of cementless hip prostheses. *J Biomech.* 1989;22(6–7):735–44.
30. Burke DW, O'Connor DO, Zalenski EB, Jasty M, Harris WH. Micromotion of cemented and uncemented femoral components. *J Bone Joint Surg Br.* 1991;73B:33–7.
31. Callaghan JJ, Fulghum CS, Glisson RR, Stranne SK. The effect of femoral stem geometry on interface motion in uncemented porous-coated total hip prostheses. Comparison of straight-stem and curved-stem designs. *J Bone Joint Surg Am.* 1992;74A: 839–48.
32. Engh CA, O'Connor D, Jasty M, McGovern TF, Bobyn JD, Harris WH. Quantification of implant

- micromotion, strain shielding, and bone resorption with porous-coated anatomic medullary locking femoral prostheses. *Clin Orthop*. 1992;285:13–29.
33. McKellop H, Ebramzadeh E, Niederer PG, Sarmiento A. Comparison of the stability of press-fit hip prosthesis femoral stems using a synthetic model femur. *J Orthop Res*. 1991;9(2):297–305.
 34. Gilbert JL, Bloomfeld RS, Lautenschlager EP, Wixson RL. A computer-based biomechanical analysis of the three-dimensional motion of cementless hip prostheses. *J Biomech*. 1992;25(4):329–40.
 35. Berzins A, Sumner DR, Andriacchi TP, Galante JO. Stem curvature and load angle influence the initial relative bone-implant motion of cementless femoral stems. *J Orthop Res*. 1993;11(5):758–69.
 36. Hua J, Walker PS. Relative motion of hip stems under load. An in vitro study of symmetrical, asymmetrical, and custom asymmetrical designs. *J Bone Joint Surg Am*. 1994;76A:95–103.
 37. Harman MK, Toni A, Cristofolini L, Viceconti M. Initial stability of uncemented hip stems: an in-vitro protocol to measure torsional interface motion. *Med Eng Phys*. 1995;17(3):163–71.
 38. Monti L, Cristofolini L, Viceconti M. Methods for quantitative analysis of the primary stability in uncemented hip prostheses. *Artif Organs*. 1999; 23(9): 851–9.
 39. Baleani M, Cristofolini L, Toni A. Initial stability of a new hybrid fixation hip stem: experimental measurement of implant-bone micromotion under torsional load in comparison with cemented and cementless stems. *J Biomed Mater Res*. 2000;50(4): 605–15.
 40. Viceconti M, Cristofolini L, Baleani M, Toni A. Pre-clinical validation of a new partially cemented femoral prosthesis by synergetic use of numerical and experimental methods. *J Biomech*. 2001;34(6): 723–31.
 41. Cristofolini L, Teutonico AS, Monti L, Cappello A, Toni A. Comparative in vitro study on the long term performance of cemented hip stems: validation of a protocol to discriminate between “good” and “bad” designs. *J Biomech*. 2003;36(11):1603–15.
 42. Branson PJ, et al. Rigidity of initial fixation with uncemented tibial knee implants. *J Arthroplasty*. 1989; 4(1):21–6.
 43. Volz RG, et al. The mechanical stability of various non-cemented tibial components. *Clin Orthop*. 1988;226:38–42.
 44. Pancanti A, Bernakiewicz M, Viceconti M. The primary stability of a cementless stem varies between subjects as much as between activities. *J Biomech*. 2003;36(6):777–85.
 45. Tissakht M, Eskandari H, Ahmed AM. Micromotion analysis of the fixation of total knee tibial component. *Comput Struct*. 1995;56:365–75.
 46. Dammak M, Shirazi-Adl A, Zukor DJ. Analysis of cementless implants using interface nonlinear friction. Experimental and finite element studies. *J Biomech*. 1997;30(2):121–9.
 47. Viceconti M, et al. Primary stability of an anatomical cementless hip stem: a statistical analysis. *J Biomech*. 2006;39(7):1169–79.
 48. Britton C, Lyons G, Prendergast PJ. Measurement of the relative motion between an implant and bone under cyclic loading. *Strain*. 2004;40(4): 193–202.
 49. Karrholm J, et al. Radiostereometry of hip prostheses – review of methodology and clinical results. *Clin Orthop*. 1997;344:94–110.
 50. Cook SD, Thomas KA, Haddad RJ. Histologic analysis of retrieved human porous-coated total joint components. *Clin Orthop*. 1998;234:90–101.
 51. Jasty M, et al. In vivo skeletal responses to porous-surfaced implants subjected to small induced motions. *J Bone Joint Surg Am*. 1997;79A:707–14.
 52. McKellop H, et al. Comparison of the stability of press-fit hip-prosthesis femoral stems using a synthetic model femur. *J Orthop Res*. 1991;9(2):297–305.
 53. Engh CA, et al. Quantification of implant micromotion, strain shielding, and bone-resorption with porous-coated anatomic medullary locking femoral prostheses. *Clin Orthop*. 1992;285:13–29.
 54. Søballe K, et al. Tissue ingrowth into titanium and hydroxyapatite-coated implants during stable and unstable mechanical conditions. *J Orthop Res*. 1992; 10(2):285–99.
 55. Davey JR, O’Connor DO, Burke DW, Harris WH. Femoral component offset. Its effect on strain in bone-cement. *J Arthroplasty*. 1993;8(1):23–6.
 56. Spector M, et al. Tissue changes around loose prostheses – a canine model to investigate the effects of an anti-inflammatory agent. *Clin Orthop*. 1990;261:140–52.
 57. Massin P, et al. Cementless fixation of hip prostheses in dogs. *Int Orthop*. 1991;15(4):299–303.
 58. Karrholm J, Snorrason F. Subsidence, tip, and hump micromovements of noncoated ribbed femoral prostheses. *Clin Orthop*. 1993;287:50–60.
 59. Phillips TW, Nguyen LT, Munro SD. Loosening of cementless femoral stems – a biomechanical analysis of immediate fixation with lading vertical, femur horizontal. *J Biomech*. 1991;24(1):37–48.
 60. Nunn D, et al. Torsional stability of the femoral component of hip arthroplasty. Response to an anteriorly applied load. *J Bone Joint Surg Br*. 1989;71B:452–5.
 61. Sugiyama H, Whiteside LA, Kaiser AD. Examination of rotational fixation of the femoral component in total hip-arthroplasty – a mechanical study of micromovement and acoustic-emission. *Clin Orthop*. 1989;249:122–8.
 62. Schneider E, et al. A comparative-study of the initial stability of cementless hip prostheses. *Clin Orthop*. 1989;248:200–9.
 63. Hua J, Walker PS. Relative motion of hip stems under load. An in vitro study of symmetrical, asymmetrical, and custom asymmetrical designs. *J Bone Joint Surg Am*. 1994;76A:95–103.
 64. Callaghan JJ, et al. The effect of femoral stem geometry on the interface motion in uncemented porous-coated total hip prostheses – comparison of

- straight-stem and curved-stem designs. *J Bone Joint Surg Am.* 1992;74A:839–48.
65. Gustilo RB, et al. Rationale, experience, and results of long-stem femoral prosthesis. *Clin Orthop.* 1989;249:159–68.
 66. Harman MK, et al. Initial stability of uncemented hip stems – an in-vitro protocol to measure torsional interface motion. *Med Eng Phys.* 1995;17(3):163–71.
 67. Ishiguro N, et al. Macrophage activation and migration in interface tissue around loosening total hip arthroplasty components. *J Biomed Mater Res.* 1997;35(3):399–406.
 68. Maloney WJ, et al. Biomechanical and histologic investigation of cemented total hip arthroplasties – a study of autopsy-retrieved femurs after in-vivo cycling. *Clin Orthop.* 1989;249:129–40.
 69. Martens M, et al. The mechanical characteristics of the long bones of the lower-extremity in torsional loading. *J Biomech.* 1980;13(8):667–76.
 70. Alfaro-Adrián J, Gill HS, Murray DW. Should total hip arthroplasty femoral components be designed to subside? A radiostereometric analysis study of the Charnley Elite and Exeter stems. *J Arthroplasty.* 2001;16(5):598–606.
 71. Wroblewski BM. Mechanism of fracture of the femoral prosthesis in total hip-replacement. *Int Orthop.* 1979;3(2):137–9.
 72. Bergmann G, Graichen F, Rohlmann A. Is staircase walking a risk for the fixation of hip implants. *J Biomech.* 1995;28(5):535–53.
 73. Hodge WA, et al. Contact pressures from an instrumented hip endoprosthesis. *J Bone Joint Surg Am.* 1989;71A:1378–86.
 74. Kotzar GM, et al. Telemeterized in-vivo hip-joint force data – a report on 2 patients after total hip-surgery. *J Orthop Res.* 1991;9(5):621–33.
 75. Albrektsson TA, Johansson CJ. Osteoinduction, osteoconduction and osseointegration. *Eur Spine J.* 2001;10:S96–101.
 76. Marks SC, Popoff SN. Bone cell biology: the regulation of development, structure, and function in the skeleton. *Am J Anatomy.* 1988;183(1):1–44.
 77. Frost HM. The biology of fracture healing: an overview for clinicians. Part I. *Clin Orthop.* 1989;248:283–93.
 78. Yuan H, et al. Bone formation induced by calcium phosphate ceramics in soft tissue of dogs: a comparative study between porous α -TCP and β -TCP. *J Mater Sci Mater Med.* 2001;12(1):7–13.
 79. Barrère F, Blitterswijk CAV, Groot KD. Bone regeneration: molecular and cellular interactions with calcium phosphate ceramics. *Int J Nanomed.* 2006;1:317–32.
 80. Fujibayashi S, et al. Osteoinduction of porous bioactive titanium metal. *Biomaterials.* 2004;25(3):443–50.
 81. Takemoto M, et al. Mechanical properties and osteoconductivity of porous bioactive titanium. *Biomaterials.* 2005;26(30):6014–23.
 82. Ruoslahti E, Pierschbacher M. New perspectives in cell adhesion: RGD and integrins. *Science.* 1987;238(4826):491–7.
 83. Massia SP, Hubbell JA. Covalent surface immobilization of Arg-Gly-Asp- and Tyr-Ile-Gly-Ser-Arg-containing peptides to obtain well-defined cell-adhesive substrates. *Anal Biochem.* 1990;187(2):292–301.
 84. Vroman L, et al. Interaction of high molecular weight kininogen, factor XII, and fibrinogen in plasma at interfaces. *Blood.* 1980;55(1):156–9.
 85. Boyan BD, et al. Role of material surfaces in regulating bone and cartilage cell response. *Biomaterials.* 1996;17(2):137–46.
 86. Anselme K. Osteoblast adhesion on biomaterials. *Biomaterials.* 2000;21(7):667–81.
 87. Mackie EJ. Osteoblasts: novel roles in orchestration of skeletal architecture. *Int J Biochem Amp Cell Biol.* 2003;35(9):1301–5.
 88. Galante J, et al. Sintered fiber metal composites as a basis for attachment of implants to bone. *J Bone Joint Surg Am.* 1971;53-A(1):101–4.
 89. Zweynuller K, Lintner K, Semlitsch M. Biologic fixation of a press-fit titanium hip joint endoprosthesis. *Clin Orthop.* 1988;235:195–206.
 90. Khanuja H, et al. Cementless femoral fixation in total hip arthroplasty. *J Bone Joint Surg Am.* 2011;93-A(5):500–9.
 91. Engh CA, Bobyn JD, Gorski JM. Biological fixation of a modified Moore prosthesis. *Orthopedics.* 1984;7(2):285–98.
 92. Goldberg VM. Anatomic cementless total hip replacement: design considerations and early clinical experience. *Acta Orthop Belg.* 1993;59(S1):183–9.
 93. Fagan MJ, Lee AJC. Role of the collar on the femoral stem of cemented total hip replacements. *J Biomed Eng.* 1986;8(4):295–304.
 94. Kwong KS. The biomechanical role of the collar of the femoral component of a hip replacement. *J Bone Joint Surg Br.* 1990;72B:664–5.
 95. Carlsson AS, et al. A large collar increases neck resorption in total hip replacement. 204 hips evaluated for 5 years. *Acta Orthop Scand.* 1995;66(4):339–42.
 96. Jeon I, et al. The biomechanical effect of the collar of a femoral stem on total hip arthroplasty. *Comp Meth Biomech Biomed Eng.* 2011;14(1):103–12.
 97. Meding JB, et al. Comparison of collared and collarless femoral components in primary uncemented total hip arthroplasty. *J Arthroplasty.* 1997;12(3):273–80.
 98. Meding JB, et al. A comparison of collared and collarless femoral components in primary cemented total hip arthroplasty: a randomized clinical trial. *J Arthroplasty.* 1999;14(2):123–30.
 99. Azzam KA, Austin MS, Sharkey PF. Early failure of a nonmodular titanium femoral stem after primary hip arthroplasty. *J Arthroplasty.* 2010;25(2):333.e1–5.
 100. Svehla M. Morphometric and mechanical evaluation of titanium implant integration: comparison of five surface structures. *J Biomed Mater Res A.* 2000;51(1):15.
 101. Park MS, et al. Plasma spray-coated Ti femoral component for cementless total hip arthroplasty. *J Arthroplasty.* 2003;18(5):626–30.

102. Levine B. A new era in porous metals: applications in orthopaedics. *Adv Eng Mater.* 2008;10(9):788–92.
103. Bobyn JD, et al. The optimum pore size for the fixation of porous-surfaced metal implants by the ingrowth of bone. *Clin Orthop.* 1980;150:263.
104. Hulbert SF, et al. Potential of ceramic materials as permanently implantable skeletal prostheses. *J Biomed Mater Res.* 1970;4(3):433–56.
105. Kent JN, Homsy CA, Hinds EC. Proplast in dental facial reconstruction. *Oral Surg Oral Med Oral Path.* 1975;39(3):347–55.
106. Itälä AI, et al. Pore diameter of more than 100 μm is not requisite for bone ingrowth in rabbits. *J Biomed Mater Res.* 2001;58(6):679–83.
107. ISO 13779-1:2008 Implants for surgery – Hydroxyapatite, in part I: ceramic hydroxyapatite.
108. de Groot K, Geesink R, Klein CP, Serekian P. Plasma sprayed coatings of hydroxylapatite. *J Biomed Mater Res.* 1987;21(12):1375–81.
109. Rößler S. Electrochemically assisted deposition of thin calcium phosphate coatings at near-physiological pH and temperature. *J Biomed Mater Res A.* 2003; 64(4):655.
110. Hansson U, Ryd L, Toksvig-Larsen S. A randomised RSA study of Peri-Apatite™ HA coating of a total knee prosthesis. *Knee.* 2008;15(3):211–6.
111. Veis A, et al. Osseointegration of Osseotite and machined titanium implants in autogenous bone graft. A histologic and histomorphometric study in dogs. *Clin Oral Implants Res.* 2004;15(1):54–61.
112. Gibson IR, Best SM, Bonfield W. Chemical characterization of silicon-substituted hydroxyapatite. *J Biomed Mater Res A.* 1999;44(4):422.
113. Carlisle EM. Silicon: a possible factor in bone calcification. *Science.* 1970;167(3916):279.
114. Thian ES, et al. The response of osteoblasts to nanocrystalline silicon-substituted hydroxyapatite thin films. *Biomaterials.* 2006;27(13):2692–8.
115. Thian ES, et al. Magnetron co-sputtered silicon-containing hydroxyapatite thin films. An in vitro study. *Biomaterials.* 2005;26(16):2947–56.
116. Porter AE, et al. Comparison of in vivo dissolution processes in hydroxyapatite and silicon-substituted hydroxyapatite bioceramics. *Biomaterials.* 2003;24(25): 4609–20.
117. Patel N, et al. A comparative study on the in vivo behavior of hydroxyapatite and silicon substituted hydroxyapatite granules. *J Mater Sci Mater Med.* 2001;13(12):1199–206.
118. Hynes RO. Integrins: versatility, modulation, and signaling in cell adhesion. *Cell.* 1992;69(1):11–25.

Bone-Cement Interface in Total Joint Arthroplasty

3

Dionysios-Alexandros Verettas

The bone-cement interface represents a complex structure of acrylic bone cement interdigitating with and filling up trabecular marrow spaces, creating in this way an interlock between cement and bone. This interface thus provides the fixation of the whole cement mantle into the femur or the acetabulum. Obviously, the stability of the cement mantle and the longevity of the implants are directly dependent on the mechanical behavior of the bone-cement interface. Polymethylmethacrylate (PMMA) or otherwise “acrylic cement” was used in the industry for the first time in 1843. The first report on its use in humans was in dentistry in 1941 [1] and in orthopedic surgery in 1945 [2, 3]. However, the first report of its use in hip arthroplasty surgery was by Habouche in 1953 [4].

Although cement fixation of implants is common in a variety of joint arthroplasties, such as total knee, shoulder, and elbow arthroplasty, and in specific cases of fracture and tumor surgery, most of the principles of cementation (both experimental and clinical data) have been studied in total hip arthroplasty, because of its unique biomechanical characteristics and patterns of load transfer on the implants and on the bone-cement interface.

The use of PMMA for the fixation of implants in total hip arthroplasties was popularized by the pioneer work of Sir John Charnley in the early

1960s and has lasted up to now [5] (Fig. 3.1). Charnley believed that acrylic cement was necessary not only for the stabilization of the implants but also for the smoother transmission of the loads to the bone. Although the use of cementless implants has grown significantly over the years, a number of meta-analyses and reports of national joint registries [6, 7] have suggested that the long-term cemented fixation of hip replacement components is durable and successful.

Charnley rightly believed that the fixation of the implant to the bone by means of acrylic cement is obtained not through adhesion (glue) of the cement onto the bone but through interdigitation of the cement into trabecular bone. If the amount of acrylic cement penetration into bone is increased, the mechanical bond will improve, leading to a higher interface shear strength and fracture toughness [8]. Thus, successful long-term fixation requires stability on both interfaces, the implant-cement interface and the bone-cement interface. The stability of the one can directly affect the stability of the other [9]. The long-term survival of the bone-cement interface has been the subject of many studies. Experiments with specimens from the bone-cement interface have suggested that the interface degrades over time by fatigue loading [10].

Many parameters can influence the biomechanical properties of bone cement and affect the stability of the bone-cement interface: (1) cementing technique, (2) thickness of the cement mantle, (3) surface texture of the femoral component, (4) shape of the femoral component, and 5. manufacturing-metallurgy (Fig. 3.2).

D.-A. Verettas, MD, PhD, MSc(Orth)
Orthopaedic Department, University General
Hospital of Alexandroupolis, Alexandroupolis
68100, Greece
e-mail: dveretta@med.duth.gr



Fig. 3.1 Satisfactory radiological results at 32 years follow-up of a very early example of Charnley THA

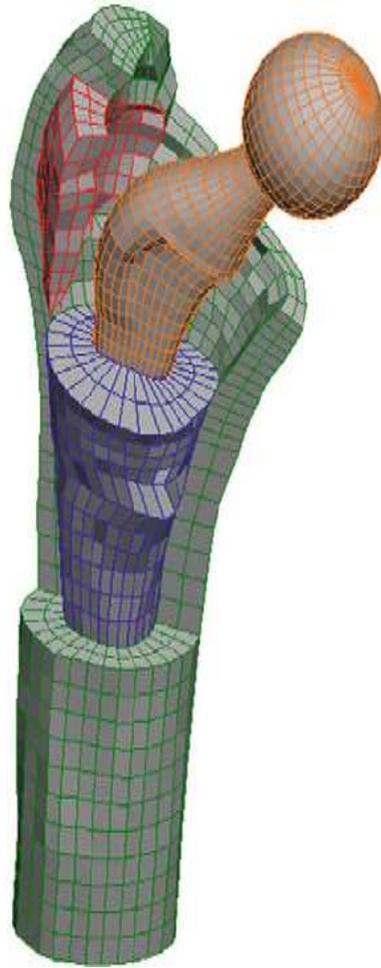


Fig. 3.2 FEA model which incorporates all variables influencing the initial mechanical behavior of the implant-bone-cement interfaces

Cementing Technique

Cementing technique is pivotal for the survival of a stable bone-cement interface. Over the years, a number of cementing techniques have been tried before universal agreement had been reached on the current “third-generation” technique (Fig. 3.3). In the early stages of its use, Sir John Charnley believed that the cement should be introduced by finger pressure. Since then the technique has evolved through three generations and now it is universally accepted that the femoral canal should be plugged to avoid distal migration of the cement and increase the interdigitation pressure and consequently the interface surface area and strength.

The bone should be meticulously prepared; washed, preferably with pulsating lavage; and kept dry with specially designed instruments. The cement should be inserted in the “nonsticky” phase, by means of a special cement gun, which in certain preparation sets can be used for mixing the cement also, without the need for a mixing bowl. The insertion of the cement into the bone should start certain minutes after the commencement of mixing, according to the brand of the cement. Following the introduction of the cement, proximal seals (Fig. 3.4) are used to keep the cement under pressure and the implant is inserted when the cement is in a much less viscous state. Horne et al. studied the histology



Fig. 3.3 Satisfactory radiological results at 20 years using third generation of cementing technique

of the bone-cement interface in a canine total hip arthroplasty model after using two different cementing techniques [11]. He noticed a marked increase in the radiographic appearance of the amount of cement influx into the cancellous bone when canal plugging, lavage, and pressurization of the cement were used. Similarly the histological examination of their specimen showed that the cement had reached far into the endosteal cortex and that the cancellous bone had remained viable when the above mentioned technique was used. The Swedish Hip Arthroplasty Register has shown a survivorship of 95 % at 10 years using this modern cementing technique [12, 13].

Mixing the cement has been the subject of considerable controversy. It seems that the mixing technique plays a role regarding the formation of voids inside the cement. These voids can adversely affect the mechanical behavior of the cement. Macaulay W et al. studied three mixing techniques, vacuum mixing, centrifugation, and hand mixing, and concluded that the best result with the least number of voids was in the method of vacuum mixing [14]. Mau et al. reached similar conclusions in their study of various vacuum mixing systems with different brands of cement regarding porosity, reliability, and bending strength [15]. Contrary to these findings, the Swedish Arthroplasty Register 2000 report noticed that at 5-year follow-up there was a higher risk of revision after vacuum mixing as



Fig. 3.4 Maintenance of cement pressurization using a proximal seal

opposed to manual mixing of the cement [12]. However, after 5 years the risk of revision after vacuum mixing became considerably less. It seems that a consensus exists that mixing the cement in vacuum produces a far more homogeneous dough with extremely few voids.

Jafri et al. described an experimental model to investigate the effect of preheating the femoral component on the porosity of the cement at the bone-cement and cement-implant interface [16]. They concluded that heating the femoral stem to 40 °C before insertion reduces the porosity of the cement significantly. Similarly, Baleani et al. showed experimentally that both vacuum mixing and preheating the stem increased the static mechanical strength of bone cement and additionally improved its fatigue life [17]. This is based on the theory that the curing of the cement is initiated at the bone-cement interface because this area is warmer. As a result of curing, shrinkage away from the cement-stem interface will follow causing this interface to weaken. Preheating the stem could reverse the direction of polymerization and hence protect the integrity of both interfaces. Curing of the cement takes place through an exothermic reaction during which polymerization is completed in temperatures ranging from 66 to 82 °C [18]. These temperatures can be detrimental for the integrity of collagen in the surrounding tissues, because collagen cannot withstand temperatures in excess of 56 °C. In the clinical situation, however, the curing temperature rarely rises over 48–56 °C, because the local blood circulation, the metallic surface of the implants, and the large surface area of the bone-cement interface dissipate the heat and enhance the cooling of the area, so that intraoperatively the temperature of the cement is 32.3 °C. The addition of antibiotics in the cement has been a major advantage in the attempts to provide antibiotic prophylaxis around the implant and, thus, to decrease the rate of infection [19, 20]. However, the amount of antibiotic which is impregnated in the cement can equally affect its mechanical properties. The flexural strength of antibiotic-loaded cement is inferior to that of cement without antibiotics. In addition the cement toughness decreases with excessive amounts of mixed antibiotics. It has

been shown that the maximum of 2 g of antibiotic can be safely added to 40 g of cement powder without detrimental effects on its biomechanical properties [21, 22]. However, the addition of antibiotics to the cement and their slow elution in the surrounding tissues in very small quantities can raise other issues, such as toxicity, the development of resistance by the microorganisms, and the development of allergic reactions to the antibiotic, which may be manifested in the form of loosening, in cases of revision with cement loading with the same antibiotics. Furthermore, the choice of antibiotics that can be loaded in the cement is limited since they should not be affected by the heat of polymerization; they should be water soluble and heat stable.

Thickness of the Cement Mantle

The thickness of the cement mantle has been traditionally accepted to be approximately 2–5 mm, especially in the proximal and medial area of the femur and at the tip of the distal end of the implant areas in which the cement is prone to damage after initial loading [23]. This amount of thickness of the cement mantle assures a very satisfactory result both clinically and biomechanically [24]. On the other hand, certain investigators have shown that the “French paradox,” according to which the thickness of the cement mantle can be as small as 1 mm, could give equally good results [25] (Fig. 3.5). Skinner et al. compared the clinical and radiological 10-year survival of two groups of patients with cemented total hip prostheses. One group had the femoral canal over reamed by 2 mm and the other group had their canal reamed to the same size as the prosthesis. The survival was slightly better in the group of line-to-line reaming. There were significantly more lytic lesions and radiolucent lines in the group of 2 mm-thick cement mantle [26]. In such cases, these canal filling stems, being polished and either taper shaped or rectangular, transfer their loads directly to bone through close cortical contact. Obviously, they are not meant to subside but they offer certain theoretical advantages. By removing most of the weak cancellous



Fig. 3.5 Satisfactory radiological result at 25 years with the “French paradox” principle

bone, they transfer the loads almost directly to the much stronger cortical bone, thus improving the stability of the implant. During insertion of these stems, the orientation and the insertion depth are more accurately obtained. Additionally, these canal filling stems can produce a high intramedullary pressure during insertion, a fact that increases the amount of interdigitation of the cement into the bone, providing a high-quality bone-cement interface [27]. Although certain retrieval studies have suggested that thin mantles are more susceptible to the production of cement cracks, biomechanical studies have shown that the rate of the propagation of fatigue cracks in the cement are independent of the thickness of the cement mantle [28, 29]. These findings are of considerable clinical significance because,

through these cracks, wear particles may transverse the interface and enter the bone, initiating the development of osteolysis. Interestingly, Ramaniraka et al. in a study of the fixation of cemented femoral components showed that considerably thicker cement mantles of 5–10 mm could increase micromovement and have a detrimental effect on the implant survival [30].

Surface Texture of the Femoral Component

The influence of the surface texture of the femoral component on the stability of the bone-cement interface cannot be better illustrated than in the case of the Exeter hip arthroplasty. In an attempt to improve the rate of survival of the femoral components, the designers changed the surface texture from polished to matt. However, in a midterm follow-up period, they noticed that, contrary to their expectations, the rate of loosening increased [31]. Having to revert to the original design, they explained that the failure of the matt surfaced implant was due to the fact that the matt surface can wear more easily through abrasion and lead to the development of defects in the cement mantle through which joint fluid with wear particles can lead to destabilization of the cement-implant bond. Massin et al. in a finite element analysis has shown that stresses in a strong implant-cement bond, such as in the cases of femoral stems with a rough surface finish, are predominantly tensile and shear and less of a compression type [32]. Bone cement is tolerant of compression loads but not in tension and shear [33]. Consequently, these types of stresses will, in time, result in damage to the cement-stem interface. Once the cement-implant bond has been destabilized, loosening of the bone-cement interface will follow [34]. Waandres et al. in finite element interface models showed that the majority of plastic displacement was caused by fatigue damage and that this fatigue damage considerably increases the stress levels in the bone [35]. Della Valle et al. has reported that such a rough surface finish adversely affects the survivorship of cemented implants because of loosening and metallic shedding in the bone-cement interface

[36, 37]. On the other hand, in the case of polished texture of the femoral component, the initial micromovement and subsidence of approximately 2 mm takes place gradually over the first 2 years after implantation at the cement-implant interface, finally reaching a stable position, thus protecting the bone-cement interface and avoiding loosening [38]. Numerous attempts to improve the stability of the cement-stem bond have been made by roughening the surface of the implant or by pre-coating it. A rough surface finish of a femoral stem has consistently produced inferior results. Due to the differences in elasticity between metal, cement, and bone, the repetitive loads which are applied to this construct by the patient's body weight and the contraction of the muscles of the proximal femur make the chances of absolute stability improbable. RSA studies both *in vitro* and *in vivo* have shown that perfect stability of the stem does not exist [39].

Shape of the Femoral Component and Metallurgy

The shape of the femoral stem plays an equally important role in the long-term survival of the bone-cement interface. Ideally, a femoral stem should be able to transmit all type of stresses to the surrounding cement and bone, without creating peak forces and excessive micromovement. In the cases of the double taper (Exeter) or triple taper (C stem) collarless design, the axial loading of the implant will convert the axial forces into radial compressive forces at the bone-cement interface. This shape of stem, if combined with a smooth polished surface, will allow for a gradual subsidence and consequent stabilization over the first 2 years after implantation. In a radiostereometric analysis Alfaro-Adrian and Stefansdottir showed that these stems can subside axially from 0.9 to 1.4 mm and into retroversion from 0.4 to 0.5 mm in the first year, followed by stability for the next years [40, 41]. This migration seems to be independent of the thickness of the cement mantle and of the viscosity and type of cement used [42, 43]. There are, in addition, femoral stems designed in such a way that are not intended to subside and, consequently, are extremely dependent on a perfect cementing

technique which should provide a cement mantle with no voids (composite beam concept). Alfaro-Adrian and Catani et al. [44] have used radiostereometric methods to study the rate of migration of these stems and concluded that the longitudinal migration is less than in the taper design, ranging from 0.1 to 0.5 mm during the first year, but their movement into retroversion is considerably higher, ranging from 1.0 mm to even 2 mm. These stems initially provide good stability, but their tolerance to long-term migration is not known [45]. Certain non-taper-designed femoral stems are provided with a collar. The collar could be useful in transferring loads from the implant to the femoral calcar and the medial cement mantle, in addition to reducing tensile stresses to the stem and preventing migration [46]. The disadvantage of the collar, however, is exactly this prevention of migration and the settling of the femoral stem in a final stable position. Additionally, in the long term it does not seem to prevent absorption of the calcar. The anatomical shaped stems are designed to fit the overall shape of the femur in a better way, thus allowing for a better centralization of the stem and providing a more symmetrical thickness of the cement mantle. Their anatomical shape and the presence of a collar prevent the subsidence of these stems, but numerous reports, as well as the Swedish Arthroplasty Registry, have shown that excellent and long lasting clinical results can be obtained [47]. Thien and Karholm in an analysis of three different cemented stems have suggested that in cases of femoral stems with rough surface finish, a small-size stem could be a risk factor for debonding and loosening of the bone-cement interface. Similarly, an increased offset and long femoral neck would have the same deleterious effect [48].

The choice of metallurgical construction of the femoral components is equally important for the long-term survival of the bone-cement interface. Titanium alloys, being less tolerant to wear, should not be used for stems with rough surface finish. As described, these stems are prone to creating tensile stresses that can readily lead to wear, of the abrasion type, and the production of wear particles. This is illustrated by a number of reports of the inferior performance of unpolished cemented titanium stems [49, 50].

Cemented Fixation of the Acetabulum

Cemented fixation of the acetabular component in total hip arthroplasty is a widely accepted method. The principles of correct cementation technique apply for the acetabulum as well as for the femoral stem. Despite the increased tendency over the last few years to prefer cementless fixation of acetabular components, recent reports from the Swedish National Hip Arthroplasty Register and the National Joint Registry for England and Wales showed that cemented fixation produces better and longer lasting survival with intact bone-cement interfaces compared to cementless fixation [7, 50].

References

- Charnley J. Acrylic cement in orthopaedic surgery. Baltimore: Williams and Wilkins; 1970.
- Judet R, Judet J. Essais de reconstruction prothetique de la hanche après resection de la tete femoral. *J Chir.* 1949;65:17–24.
- Haboush EJ. A new operation for arthroplasty of the hip based on biomechanics, photoelasticity, fast setting dental acrylic and other considerations. *Bull Hosp Joint Dis.* 1953;14:242–77.
- Charnley J. Anchorage of the femoral head prosthesis to the shaft of the femur. *J Bone Joint Surg Br.* 1960; 42B:28–30.
- Morshed S, Bozic KJ, Ries MD, Malchau H, Colford Jr JM. Comparison of cemented and uncemented fixation in total hip replacement: a meta-analysis. *Acta Orthop Scand.* 2007;78(3):315.
- Hailer NP, Garellick G, Karrholm J. Uncemented and cemented primary total hip arthroplasty in the Swedish Hip Arthroplasty Register. *Acta Orthop Scand.* 2010; 81:34–44.
- Funk MJ, Litsky AS. Effect of cement modulus on the shear properties of the bone-cement interface. *Biomaterials.* 1998;19:1561–7.
- Gardiner RC, Hozack WJ. Failure of the cement bone interface. A consequence of strengthening the cement-prosthesis interface? *J Bone Joint Surg Br.* 1994;76B(1):49–56.
- Mann KA, Miller MA, Race A, Verdonschot N. Shear fatigue micromechanics of the cement bone interface: an in vivo study using digital image correlation techniques. *J Orthop Res.* 2009;27:340–6.
- Horne JG, Bruce W, Devane PA, Teoh HH. The effect of different cement insertion techniques on the bone-cement interface. *J Arthroplasty.* 2002;17(5):579–83.
- Swedish Arthroplasty Register. 2000 Annual Report. Gotteborg: Swedish Arthroplasty Register.
- Malchau H, Herberts P, Eisler T, Garellick G, Soderman P. The Swedish total hip replacement register. *J Bone Joint Surg Am.* 2002;84A:S2–20.
- MacAulay W, DiGiovanni CW, Restrepo A, Saleh KJ, Walsh H, Crosssett LS, et al. Differences in bone-cement porosity by vacuum mixing, centrifugation, and hand mixing. *J Arthroplasty.* 2002;17:569–75.
- Mau H, Schelling K, Heizel C, Wang JS, Breusch JS. Comparison of various vacuum mixing systems and bone cements as regards reliability, porosity and bending strength. *Acta Orthop Scand.* 2004;75: 160–72.
- Jafri AA, Green SM, Partington PF, McCascie AW, Muller SD. Pre-heating of components in cemented total hip arthroplasty. *J Bone Joint Surg Br.* 2004; 86B:1214–9.
- Baleani M, Bialblocka-Juszczak E, Engels GE, Viceconti M. The effect of vacuum mixing and pre-heating the femoral component on the mechanical properties of the cement mantle. *J Bone Joint Surg Br.* 2010;92B:454–60.
- Hansen D, Jensen JS. Prechilling and vacuum mixing not suitable for all bone cements: handling characteristics and exotherms of bone cements. *J Arthroplasty.* 1990;5:287–90.
- Buchholz HW, Engelbrecht H. Uber die depotwirkung einiger antibiotic bei vermischung dem kunstharz Palacos. *Chirurg.* 1970;41:511–5.
- Elson RA, Jephcott AE, McGeachie DB, Verettas D. Antibiotic-loaded acrylic cement. *J Bone Joint Surg Br.* 1977;59B:200–5.
- Davies JP, Harris WH. Effect of hand mixing tobramycin on the fatigue strength of Simplex P. *J Biomed Mater Res.* 1991;25:1409–14.
- Lautenschlager EP, Marshall GW, Marks KE, et al. Mechanical strength of acrylic bone cements impregnated with antibiotics. *J Biomed Mater Res.* 1976;10: 837–45.
- Stolk J, Maher SA, Verdonschot N, Prendergast PJ, Huiskes R. Can finite element models detect clinically inferior cemented hip implants? *Clin Orthop.* 2003; 409:138–50.
- Ebramzadeh E, Sarmiento A, McKellop HA, Llinas A, Gogan W. The cement mantle in total hip arthroplasty: analysis of long term radiographic results. *J Bone Joint Surg Am.* 1994;76A:77–87.
- Langlais F, Kerboull M, Sedel L, Ling RSM. Annotation: the “French Paradox”. *J Bone Joint Surg Br.* 2003;85B:17–20.
- Skinner JA, Todo S, Taylor M, Wang JS, Pinskerova V, Scott G. Should the cement mantle around the femoral component be thick or thin? *J Bone Joint Surg Br.* 2003;85B:45–52.
- Scheerlinck T, Casteleyn PP. The design features of cemented femoral hip implants. *J Bone Joint Surg Br.* 2006;88B:1409–18.
- Hertzler J, Miller MA, Mann K. Fatigue crack growth rate does not depend on mantle thickness: an idealized cemented stem construct under torsional loading. *J Orthop Res.* 2002;20:676–82.

28. Mann KA, Gupta S, Race A, Miller MA, Cleary RJ, Ayers DC. Cement microcracks in thin mantle regions after in vitro fatigue loading. *J Arthroplasty*. 2004;19:605–12.
29. Ramaniraka NA, Rakotomanana LR, Leyvraz PF. The fixation of the cemented femoral component: effects of stem stiffness, cement thickness and roughness of the bone-cement interface. *J Bone Joint Surg Br*. 2000;82B:297–303.
30. Howie DW, Middleton RG, Costi K. Loosening of matt and polished cemented femoral stems. *J Bone Joint Surg Br*. 1998;80B:573–6.
31. Massin P, Astoin E, Lavaste F. Influence of proximal stem geometry and stem-cement interface characteristics on bone and cement stresses in femoral hip arthroplasty: finite element analysis. *Rev Chir Orthop Reparatrice Appar Mot*. 2003;89:134–43.
32. Kuehn KD, Ege W, Gopp U. Acrylic bone cements: mechanical and physical properties. *Orthop Clin North Am*. 2005;36:29–39.
33. Murray DW. Cemented femoral fixation: the North Atlantic divide. *Orthopaedics*. 2011;34(9):462–4.
34. Waanders D, Janssen D, Mann KA, Verdonshot N. The effect of cement creep and cement fatigue damage on the micromechanics of the bone-cement interface. *J Biomech*. 2010;43(15):3028–34.
35. Della Valle AG, Zoppi A, Petersen MG, Salvati EA. A rough surface finish adversely affects the survivorship of a cemented femoral stem. *Clin Orthop*. 2005;436:158–63.
36. Della Valle AG, Rana A, Nestor B, Bostrom M, Westrich G, Salvati EA. Metallic shedding, surface finish changes and extensive femoral osteolysis in the loose Spectron EF stem. *Clin Orthop*. 2006;442:165–7.
37. Middleton RG, Howie DW, Costi K, Sharpe P. Effects of design changes on cemented tapered femoral stem fixation. *Clin Orthop*. 1998;355:47–56.
38. Nivbrant B, Karrholm J, Soderlund P. Increased migration of the SHP prosthesis: radiostereometric comparison of the Lubinus SP2 design in 40 cases. *Acta Orthop Scand*. 1999;70:569–70.
39. Alfaro-Adrian J, Gill HS, Murray DW. Should total hip arthroplasty femoral components be designed to subside: a radiostereometric analysis study of the Charnley Elite and Exeter stems. *J Arthroplasty*. 2001;16:598–606.
40. Stefansdottir A, Franzen H, Johnsson R, Ornstein E, Sundberg M. Movement pattern of the Exeter femoral stem: a radiostereometric analysis of 22 primary hip arthroplasties followed for 5 years. *Acta Orthop Scand*. 2004;75:408–14.
41. Glyn-Jones S, Hicks J, Alfaro-Adrian J, Gill HS, McLardy-Smith P, Murray DW. The influence of cement viscosity on the early migration of a tapered polished femoral stem. *Int Orthop*. 2003;27:362–5.
42. Nelissen RG, Garling EH, Valstar ER. Influence of cement viscosity and cement mantle thickness on migration of the Exeter total hip prosthesis. *J Arthroplasty*. 2005;20:521–8.
43. Catani F, Ensini A, Leardini A, Bragonzoni L, Toksvig-Larsen S, Giannini S. Migration of cemented stem and restrictor after total hip arthroplasty: a radiostereometry study of 25 patients with Lubinus SP II stem. *J Arthroplasty*. 2005;20:244–9.
44. Hauptfleisch J, Glyn-Jones S, Beard DJ, Gill HS, Murray DW. The premature failure of the Charnley Elite-Plus stem: a confirmation of RSA predictions. *J Bone Joint Surg Br*. 2006;88B:179–83.
45. Ebramzadeh E, Sangiorgio SN, Longjohn DB, Buhari CF, Dorr LD. Initial stability of cemented femoral stems as a function of surface finish, collar and stem size. *J Bone Joint Surg*. 2004;86A:106–15.
46. Savilahti S, Myllyneva I, Pajamaki KJ, Lindholm TS. Survival of Lubinus straight (IP) and curved (SP) total hip prosthesis in 543 patients after 4–13 years. *Arch Orthop Trauma Surg*. 1997;116:10–3.
47. Thien TM, Karrholm J. Design related risk factors for revision of primary cemented stems. *Acta Orthop Scand*. 2010;81:407–12.
48. Witt JD, Swann M. Metal wear and tissue response in failed titanium alloy total hip replacements. *J Bone Joint Surg Br*. 1991;73B:559–63.
49. McGrath LR, Shardlow DL, Ingham E, Andrews A, Ivory J, Stone MH, et al. A retrieval study of capital hip prostheses with titanium alloy femoral stems. *J Bone Joint Surg Br*. 2001;83B:1195–201.
50. National Joint Registry for England and Wales. 6th Annual Report 2009. Hemel Hempstead: NJR.

The Implant-Cement Interface in Total Hip Arthroplasty

4

Georgios Digas and Johan Kärrholm

Introduction

Despite being in clinical use for more than 40 years, the detailed function of cemented femoral stems is still not completely understood. After insertion into the femur, the behavior of the bone/cement/stem construct can be expected to depend on a number of factors. A fundamental function performed by the bone cement is the transfer and distribution of the stress between the prosthesis and the bone. The success of cemented systems, in the long term, depends on many factors. The prosthesis itself can, depending on its material composition, shape, size, and surface finish, have a complex influence on its surroundings. Bone cement and its structural and mechanical characteristics in particular have a similar influence when combined with different stem designs. Thus, the quality and shape of the materials and interaction at the stem-cement interfaces are of great importance for long-term performance.

The development of clinical loosening has been attributed to micromovements, abrasive wear, leakage, and even the pumping of joint fluid

out into the cement-bone interface. The initiation of this process may vary. There is, however, substantial evidence that debonding occurs between the cement and the stem, which may initiate loosening [1, 2]. Consequently, many stem designs are made to obtain firm fixation to the cement by the use of a collar, macrotecture, rough surface, or pre-coating with polymethylmethacrylate. A diametrically different opinion is that debonding of the stem is unavoidable and that the stem should therefore be designed to adapt to such an event. The polished double-tapered uncollared stem is an example of this [3].

Effect of Prosthetic Design and Choice of Material on Stem-Cement Interface

Stem Material

There are three types of materials that are commonly used for cemented femoral stems. These are cobalt–chromium alloys, stainless steel, and titanium alloys. The use of a titanium alloy (usually Ti-6Al-4V or Ti-5Al-2.5Fe, Ti-6Al-7Nb) was attractive because its stiffness is closer to that of bone and bone cement than the other two alloys. The clinical performance of stems made of titanium alloy seems to be closely related to stem design and especially to the choice of surface designs. Those with rougher surface have shown high failure rates [4, 5]. Some smooth and polished stems [6, 7] seem to perform well,

G. Digas, MD, DSc, PhD (✉)
Department of Orthopaedics,
General Hospital Xanthi,
Xanthi 67100, Greece
e-mail: georgios.digas@gmail.com

J. Kärrholm, MD
Department of Orthopaedics,
Sahlgrenska University Hospital,
Mölndal SE-431 80, Sweden

Fig. 4.1 This photograph shows an Exeter stem extracted 10 years postoperative. Note the severe crevice corrosion at the medial surface of the stem



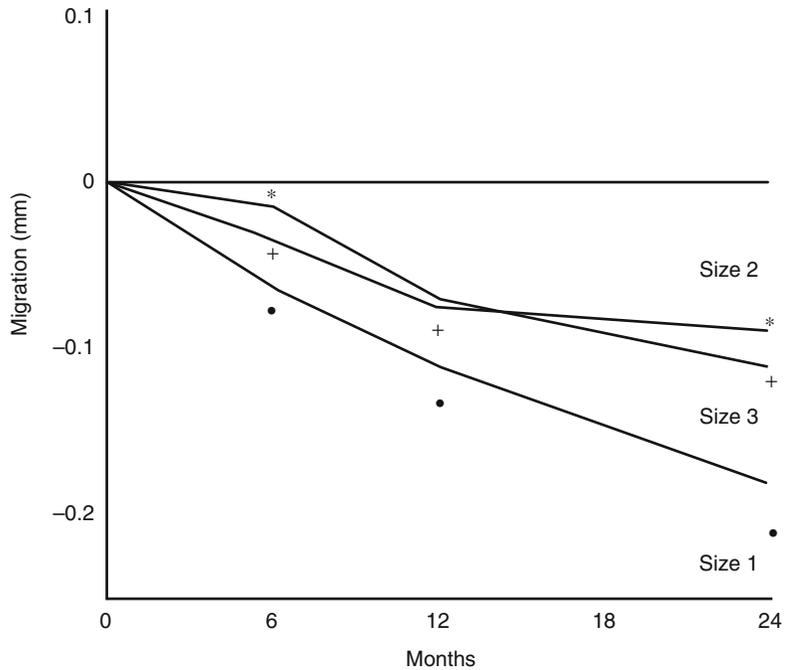
but these are also sensitive to changes of design, especially if used with high offset or in small sizes [8]. Titanium–alumina–vanadium alloy has a stiffness of about 50 % relative to CoCr or stainless steel (elastic modulus $E=230$ GPa for CoCr and 110 GPa for titanium). It is therefore more flexible, but it is uncertain whether this feature influences the frequency of stem–cement bonding in vivo. The higher flexibility of the stem will increase proximal cement stresses. For designs with small proximal dimensions, particularly in the M-L direction, cement stresses may become too high in the stem–cement interface resulting in debonding and cement failure. Titanium alloys have a high resistance against corrosion [9]. They are, however, comparatively soft and susceptible to abrasive wear of the oxide film as well as fretting and crevice corrosion. This type of corrosion is driven by the generation of a gap (the crevice) between the stem and the cement. It has often been reported to occur at the taper of modular implants. There are some reports of early failure of cemented titanium stems showing severe crevice corrosion at the stem–cement interface [10–12], but only a few studies show this type of corrosion for designs made of stainless steel [13], whereas reports of crevice corrosion of CoCr seem to be restricted to the head taper junction (Fig. 4.1). Even if it is not completely clear to what

extent crevice corrosion between the stem and the cement has an influence on clinical failure rates, it seems to be evident that this phenomenon is of clinical relevance for some designs of cemented titanium implants. Taking this into consideration, titanium stems should not be advised when very small section shafts are required, particularly in heavy patients. If they are used they should have a polished or very smooth surface to avoid abrasive wear, fretting corrosion, and increased particle load in the joint space.

Cross-Sectional Shape

Femoral stems should be able to withstand axial, bending, and rotational forces. During activities such as rising from a chair or stair climbing, rotational forces increase [14]. The ability of a stem to withstand these forces is design dependent. The cross-sectional area (geometry, size) and shape (rounded, squared), the CCD angle, and offset should be considered, in addition to patient-related factors, as factors related to the stresses transferred to the interfaces. Several radiostereometric studies have demonstrated that well-functioning stems may also slowly displace into retroversion and varus and in most cases subside inside the cement mantle as an effect of these forces [15–18].

Fig. 4.2 Proximal (+)/distal (–) migration of the gravitational stem center related to stem size. Data are shown mean \pm SE (Adapted from Olofsson et al. [17])



Thus, rotational resistance has become an important parameter of the design. Stems with a circular cross-sectional shape have smaller rotational stability at the stem-cement interface. The cross-sectional shape should therefore be rectangular or irregular to improve rotational stability. Stems with proximal–distal profiles along the surface also have an improved rotational stability. A potential disadvantage of a stem with a rectangular cross section is that great stresses are generated at its edges, resulting in debonding and even fracture of the cement. Most of these stems are polished and wedge shaped which reduces the risk of clinical complications due to abrasive wear. Rotational stability also depends on the cross-sectional size of the implant, which does not really explain why certain stem designs show deteriorating results with decreasing stem size.

In a retrospective study by Sylavain and coworkers, a rough-surfaced pre-coated stem was analyzed with an average of follow-up 36 months. These authors found a trend towards failure in smaller prosthesis sizes [19]. Kalairajah et al. [20] reported the clinical and radiographic outcomes of Taperloc arthroplasties. Patients who had smaller stems (7.5 mm or 10 mm) had a 27 % failure rate, whereas

those patients who were implanted with stems equal to or greater than 12.5 mm had a 12 % failure rate. Thien et al. [21] studied design-related risk factors of 21,008 Exeter polished stems, 43,036 Lubinus SPII stems, and 7,140 Spectron EF primary stems in the Swedish Hip Arthroplasty Register inserted from 1999 through 2006. They found an increased failure rate due to loosening of the smallest version (extra-narrow) of the Lubinus stem and of the two smallest sizes of the Spectron EF primary stem. The crude revision rate of the Exeter stem was slightly higher than for the Lubinus stem, but with the Exeter the choice of stem size had no influence on the risk of revision due to loosening. Bourne et al. [22] reported that bone cement pressure during stem insertion increased when progressing from a small to a large stem, which could be expected to influence fixation at the stem-cement interface. The current authors have evaluated design variations on early migration measured with RSA of Spectron primary cemented stems [17]. Our results showed a higher but insignificant increase of stem migration in the cement mantle for the smallest stem size (Fig. 4.2) corresponding to findings by Thien et al [21]. This suggests that for at least for non-polished stem designs,

Fig. 4.3 This photograph shows a Spectron stem size one revised 8 years postoperative. The subsidence and rotation in the cement mantle had abrasive polishing effect on the matt surface on this particular stem leading to loosening and revision surgery



there is a certain lower limit for downsizing. If a matte or grit-blasted cemented stem becomes too small, it cannot withstand external forces sufficiently, resulting in abrasive wear, loosening, and osteolysis (Fig. 4.3). This limit probably varies depending on the activity of the patient and the time frame of the observation period. This means that special consideration should be given to active and heavy patients with a narrow femoral canal, especially if a large offset is required. For these cases, alternatives other than a small-sized non-polished cemented stem should be considered.

Stem Design Different Philosophies

The number of design variations of cemented femoral stems available today is partly a result of different design philosophies in combination with experience obtained from clinical studies and observations made in National Registers. It has become more and more obvious that it is the combination of shape and surface finish of the stem that is of importance for long-term results. The detailed interaction between these factors is, however, still not completely understood. Based largely on the surface finish of the stem, and also on the way the stem interacts with the cement mantle, two main philosophies of fixation have

evolved, one based around a polished stem surface and the other based on a rough stem surface, with or without adjuvant fixation features. Huiskes et al. [23] have reintroduced the concept of shape-closed fixation versus force-closed modes of fixation for cemented femoral stems.

A shape-closed fixation design (Fig. 4.4) is one in which the stem achieves fixation at the stem-cement interface through a match in the shape of the surfaces of the stem and the cement with the cement gripping the surface of the stem. The aim is to achieve a rigid interlock between the stem and cement and thereby nullify movement at this interface. These designs have matte, grit-blasted, and beaded or porous surfaces into which the cement is intended to penetrate, thus achieving a solid bond between the stem and the cement. Attempts have been made to improve bonding between stem and cement by pre-coating the stem surface with cement applied onto the surface during manufacture of the stem [24]. This pre-coated stem is then inserted into the cement in the femoral canal, which binds with the pre-coated surface. Early clinical trials have suggested that the use of pre-coated stems is associated with favorable short- to medium-term survival in some studies [25, 26]. However, Callaghan et al. [27] have found that the use of a pre-coated stem is associated with poor survival,



Fig. 4.4 The Spectron EF and Exeter stems are examples for shape-closed and force-closed fixation system, respectively

with a loosening rate of 24 % at an average of only 8 years follow-up. These results of pre-coated femoral stems have been confirmed by several other clinical studies [28–30]. Therefore, it appears that, despite theoretical advantages, the use of pre-coating is detrimental to the long-term survival of femoral implants. The reason for this remains unclear. Debonding of the pre-coating from a comparatively rough undersurface over time, followed by abrasive wear and corrosion might be one explanation.

A force-closed system (Fig. 4.4) is one in which the fixation of the stem within the cement is achieved through the balance of forces without the need for the existence of a bond between the stem and the cement. A stem may act as a taper within the cement, in which case fixation is achieved through the balance of forces across the stem-cement interface and bonding between the stem and cement is neither necessary nor desirable. The balance of forces arises from the ability of a polished tapered stem to subside over short distances within the cement mantle. Retrieval

analysis and laboratory experiments have shown that this subsidence is accommodated by cement creep. The subsidence of the polished taper within the cement means that this type of stem can maintain satisfactory fixation despite changes in the cement mantle over time. This ability to subside may allow the loading of the stem to be distributed evenly, especially in the proximal femur where remarkable preservation of calcar bone has been seen with this type of stem [31].

Milles [32] has investigated the effect of stem surface finish on cement stresses. He has shown that for polished stems the major load component is radial compression but for rough stems there is significant shear (Fig. 4.5). Studies evaluating the physical properties of acrylic cement [33, 34] have shown that cement is significantly stronger when loaded in compression compared to loading in tension or shear.

Surface Roughness

In attempts to improve the bonding between stem and cement, several authors have, in the laboratory, investigated the relationship between stem surface roughness and the shear strength achieved at the interface [35–37]. These studies have shown that increasing stem roughness leads to increased strength of the stem-cement interface, although in many cases the testing methods have been unrealistic and have disregarded the effects of cyclical loading [36]. Such experimental data have led to the belief that a rough surface finish is beneficial [24] and to the development of a number of femoral prostheses with roughened surfaces. Kärrholm et al. [15] used RSA to measure the migration of different femoral stem designs inside the cement mantle. They found that stem migration inside the mantle occurred with variable frequency for all designs studied, including two with comparatively rough surfaces. If these findings can be generalized, such stems should be used cautiously and probably only in sizes with a sufficiently large surface area to be able to counteract debonding and inducible displacements during activity as previously discussed. Verdonshot and coworkers [38] implanted

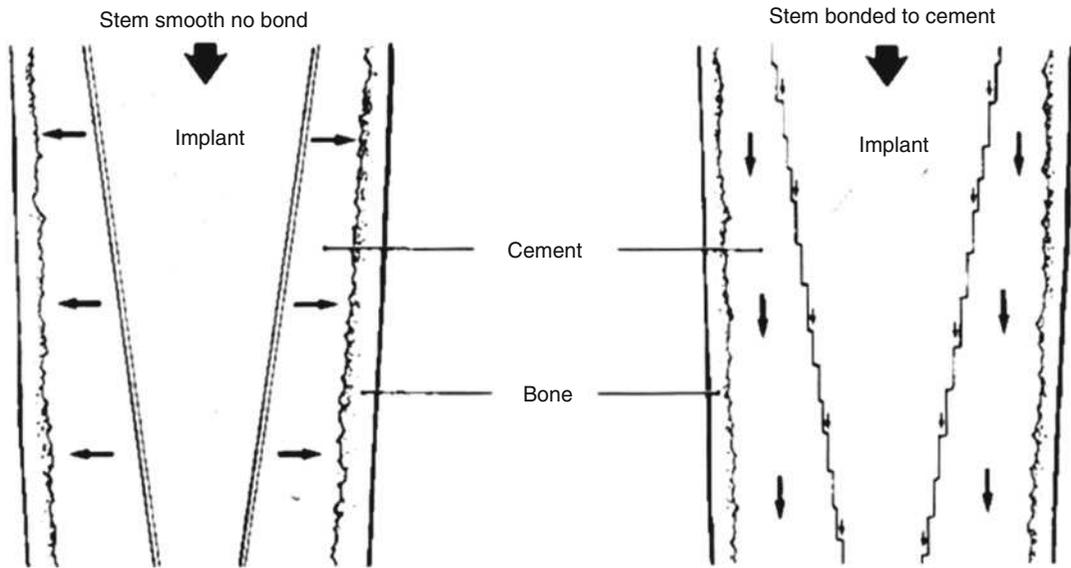


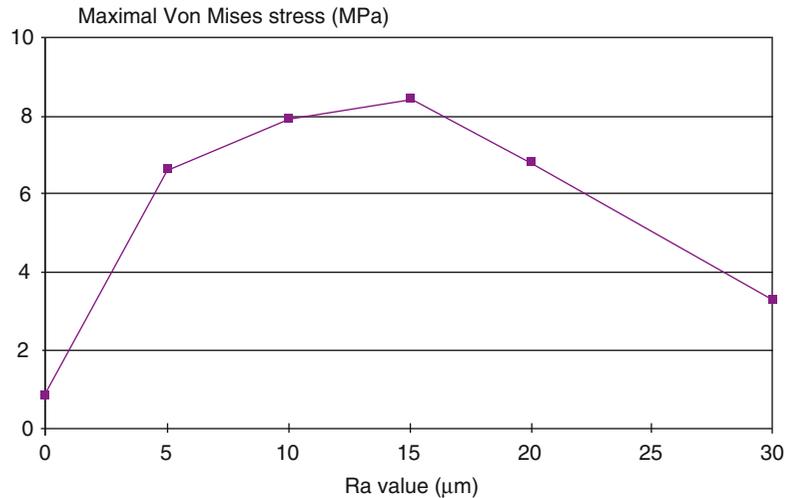
Fig. 4.5 In polished stems there is no bond to the cement, the load at the cement-bone interface is radial compression. If the stem is bonded to the cement, the loads at the cement-bone junction are shear loads

metal tapers into cement with three different surface roughness values (R_a 's were 0.02, 1.1 and 11 μm) and exposed the tapers to a cyclic load. They measured migration and determined the amount of damage at the interface (abrasion) and in the cement (cracks) in sections using scanning electron microscopy (SEM). Although migration was less for the rough tapers, the amount of (abrasive) damage was larger for these components. The experimental study by Crowninshield et al. [37], who applied a cyclic displacement onto a rough piece of metal that was compressed against bone cement, is in agreement with these findings. Verdonschot and coworkers evaluated the relationship of surface roughness, cyclic micromotions, and stresses in the cement around the asperities of the roughness profile using finite element micromodels [39]. Micromotions reduced with increasing surface roughness. Despite the fact that cyclic micromotions were maximal for a surface roughness of 0 μm (theoretical case), the local cement stresses remained low due to the absence of asperities on the metal surface. At a roughness value of $R_a=15 \mu\text{m}$, local cement stresses were very high, indicating a high abrasive mechanism. Interestingly, when the surface roughness was further increased, local cement

stresses reduced again because of reduced cyclic motions caused by the better "grip" of the metal surface on the cement (Fig. 4.6). These studies by Verdonschot show the complexity of stem-cement interface mechanics and cement abrasion. The surface roughness beyond which the abrasive potential diminishes depends on many other factors such as prosthetic design, offset, loading conditions, location, cement characteristics, and other patient-related factors.

There are well-documented instances when roughened stems have been found to fail earlier than polished versions of the same implant. According to the Swedish Register, the Exeter matt stem with a surface finish of about $R_a=1.0 \mu\text{m}$ produced significantly worse results than the polished version (with a roughness of $R_a=0.02 \mu\text{m}$). The Iowa stem is another example [40]. Race et al. [41] reported more gaps at the stem-cement interface with a grit-blasted cemented Charnley femoral stem ($R_a 5.3 \mu\text{m}$) than with a similar design with a satin surface ($R_a 0.75 \mu\text{m}$). On the other hand, Von Knoch et al. [42] evaluated the surface roughness of 11 femoral components ($R_a=1 \mu\text{m}$) that were retrieved after 2–15 years. They found no abrasion or corrosion phenomena suggesting that the stem had been very stable. Spectron EF

Fig. 4.6 Results from a finite element micro-analysis of the surface roughness of a straight-tapered unbonded stem. The local stresses around the asperities of the stem surface did show a maximum at 15 μm ; beyond that value the local stresses were reduced (Adapted from Verdonschot et al. [39])



prosthesis which is a straight cobalt–chromium stem, proximally grit-blasted with an average surface roughness of 2.8 μm and distally smoother with an average roughness of 0.7 μm , has shown 97.5 % survival at 15 years in the Swedish hip registry [43].

There have been studies reporting good results using femoral stems with either smooth [40–49] or rough surfaces [50–54]. The optimum balance between these two factors still remains uncertain. Failure of THAs is of multifactorial origin (cementing, patient characteristics, component design); thus, valid comparisons cannot be made unless most of the factors are similar between the studies being compared.

Stem Migration and Wear

Perfect bonding between the stem and cement must be achieved and this bond must be durable to produce long-term success of rough stems. Poor adherence of the cement to the stem and inclusion of gas (air mixed with evaporation from the cement), shrinkage of the cement during curing, and creep may cause early debonding and gaps at the interfaces [55–57]. Additionally, both experimental [58] and in vivo [59, 60] studies have shown that during the lifetime of a hip replacement, the stem further debonds from the cement, opening up a gap between the stem and

cement [38, 61]. Howell et al. [62] have reported an analysis of stem wear on the surface of 172 femoral stems of 23 different designs. They demonstrated that wear changes affected 93 % of stems in the study and this included 74 stems that were reported as being well fixed by the revising surgeon. The wear was often localized and was concentrated along the anterolateral and postero-medial borders of the stems. They found a fundamental difference in wear morphology on matt and polished stems. Matt stems were found to wear through abrasive polishing of the surface. Removal of debris was probably brought about by fluid in the stem-cement interface, and they found evidence of slurry wear of the matt stem surfaces caused by high-pressure fluid containing hard particles (Fig. 4.7). In contrast, the wear morphology of polished stems was typical of fretting wear and the stem surface surrounding the areas of wear was unaffected by the wear process.

Our group evaluated 97 hips that were randomized to receive Spectron primary stems fixed with either fluoride-containing cement or conventional cement [63]. Subsidence was measured with radiostereometric analysis. Two patients (three hips) underwent revision surgeries. Subsidence in the cement mantle of these hips was between 0.4 and 1.35 mm at revision surgery (Fig. 4.8).

When a rough stem subsides in the cement mantle over the acceptable level for this particular stem design, a high probability of abrasive polishing of

Fig. 4.7 Scanning electron micrograph of erosion or “slurry wear” seen on the surface of a matt stem. A comet tail appearance is seen on one side of each surface depression, a typical appearance of slurry wear caused by high-pressure fluid containing hard particles (Adapted from Howell et al. [62])

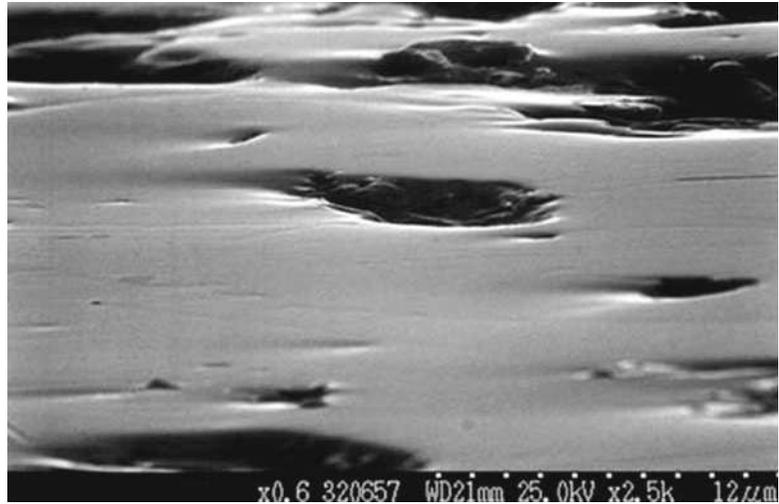
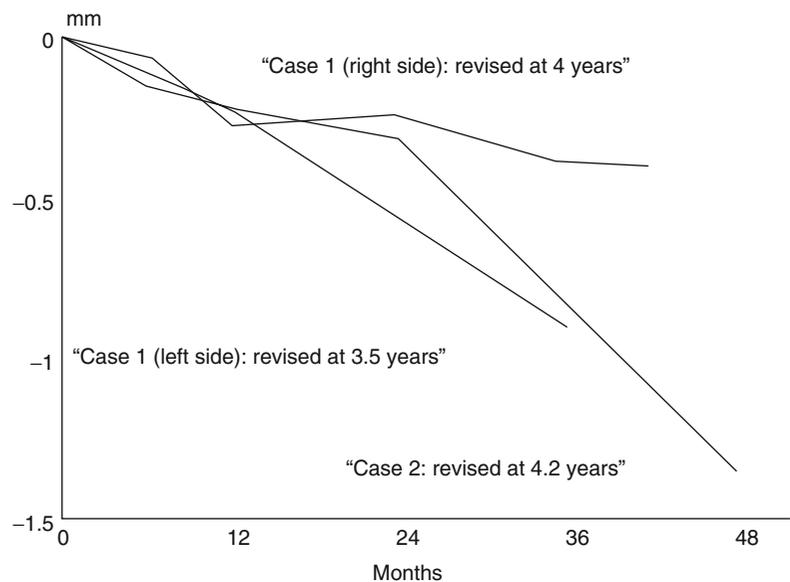


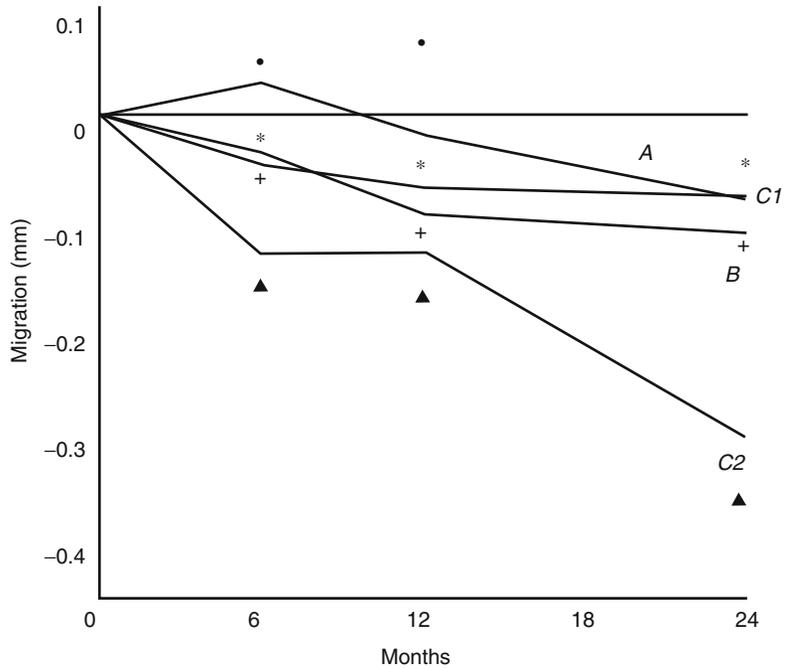
Fig. 4.8 This graph shows the distal migration in three stems (two patients) that had been revised (Adapted from Digas et al. [63])



the matt surface is indicated as well as abrasive wear of the cement mantle. This may have several important effects. It generates large numbers of particles that may contribute to third-body wear, both at the stem-cement interface and at the articulation. Another important effect of abrasive wear of the cement mantle is enlargement of the gap at the stem-cement interface, which leads to cyclical movements of the stem and further cement wear. The result is destabilization of the stem within its cement mantle and a slow but probably continuous enlargement of the space between the stem and the

cement. On the other hand, the fretting wear of polished stems as shown by Howell et al. [62] occurs below the level of the original stem surface, leaving the surrounding stem unaffected. It is therefore likely that polished stem wear represents a more benign process. Furthermore, a stem with a polished surface and the correct geometry may function as a taper within the cement [31, 64, 65], allowing subsidence of the stem within the cement mantle, thus closing the stem-cement interface, preventing fluid migration and the dispersal of particulate debris. As a consequence, polished stems,

Fig. 4.9 Proximal (+)/distal (−) stem migration related to cement mantle quality is shown. Data are shown mean \pm SE for Barrack groups A to C2 (Adapted from Olofsson et al. [17])



at least in theory, are less prone to the resultant third-body wear or the effects of debris and fluid flow. Stems with matt surface, such as the Lubinus SPII, have excellent survival rates in the Swedish hip registry (94.3 % at 19 years). Other stems with matt surface, such as the Müller CoCrNiMo straight stem [66] and MS-30 [67], have also shown good long-term performance (92.7 % at 15 years and 100 % at 10 years, respectively). The reason why these designs rarely seem to fail because of abrasive wear is not known but could perhaps be related to good fixation inside the mantle and reduced sensitivity to wear in cases where debonding occurs. A firmer fixation of the stem to the mantle might have other beneficial effects such as reducing the risk of periprosthetic fractures [68].

The Cement Mantle

The quality of the cement mantle is important for stem fixation [69–71]. Ramaniraka et al. [72] have evaluated micromovements at the bone-cement and stem-cement interfaces. They found that movements at the bone-cement interfaces were minimal if the cement mantle had a thickness of 3–4 mm but

increased if it became wider. Abnormally high micromovements occurred when the cement was thinner than 2 mm. With use of contemporary cementing technique, initiation of loosening at the bone-cement interface is probably very rare. The production of an intact and durable cement mantle during an operation is, however, of fundamental importance.

As early as 1983 Carlsson et al. [73] observed scalloping around stems with broken cement mantles. They suggested the use of a centering device to avoid this complication. The present authors have evaluated the influence of design variation on the early migration of cemented stems with RSA [17]. We found that cases classified as C2 (presence of stem–cortex contact according to Barrack’s classification) subsided more than those with a better quality of cement mantle (A–C1, Fig. 4.9). This observation suggests that patients with cortex–stem contact more easily debond from the mantle, which facilitates transport of joint fluid and debris from the joint to the interface. An inadequate cement mantle, with implant contact with the inner and distal femoral cortex, has been correlated with long-term loosening and femoral osteolysis [74].

Creep

Fatigue failure and creep are two critical factors in the endurance of bone cement. The bone cement creeps under dynamic and static loading conditions. As a result, stems which are debonded from the cement may gradually subside, depending on their shape and surface roughness followed by expansion of the cement mantle around the shaft. This phenomenon produces a redistribution of the stresses in the cement, which may have favorable or damaging effects on the entire prosthetic system. According to Verdonshot and Huiskes [58], the amount of stem subsidence which can be explained by creep is only around 0.05 mm. Kärrholm et al. [15] have shown that stems which subside less than 0.1 mm during the first 2 years have a low revision rate in the Swedish National Hip Arthroplasty Registry. Lee et al. [75] claim that the cement can tolerate a considerable amount of deformation if subjected to continuous pressure at body temperature over weeks or months. Two phenomena have been described which are correlated with creep in cement. The first is the debonding of the stem from the cement, which can induce locally increased stress resulting in fractures inside the mantle. The other is the plastic flow of the cement. It has been shown that cement creep relaxes cement stresses and creates a more favorable stress distribution at the interface [76]. Delayed injection time of acrylic bone cement increases creep compared with bone cement prepared according to standard injection procedures [77]. Creep therefore depends not only on the material properties but also on the handling of the cement by the surgeon. Waanders et al. [78] investigate how fatigue damage and cement creep separately affect the mechanical response of cement at various load levels in terms of plastic displacement and crack formation in FEA studies. They conclude that when cement is subjected to low stresses, plastic interface displacement is mostly caused by cement creep, while at higher loads cement fatigue cracking is the dominant factor. They conclude that cement creep can decrease crack formation in cement by up to 20 %. Cement creep does not decrease the stress levels in the bone with respect to its initial state, and cement

fatigue damage only results in an increase in bone stresses. Vacuum mixing reduces the porosity of the cement and as a consequence volumetric creeping may increase from 3–5 % to 5–7 % in different cements [79]. Creeping at the cement-bone interface can be regarded as beneficial as some interface gaps allow for revascularization [80] and no studies have shown any detrimental effect on the stem-cement interface when cement with reduced porosity due to vacuum mixing is used [57]. The exact consequences of creeping are, however, still unknown, especially concerning its relation to aseptic failure and its effects when used with polished versus matte or rough surface finishes.

The Influence of Porosity at the Stem-Cement Interface

Extensive porosity at the stem-cement interface has been found in retrieved cement mantles and in laboratory-prepared specimens [81]. This interface porosity is caused by entrapment of air at the stem surface during stem insertion and by residual porosity in the cement. A further cause is the cement's shrinkage away from the colder stem surface which produces pores [81]. Although cement curing is chemically initiated, polymerization is thermally activated. Thus, cement curing starts at the warmer bone surface and progresses towards the cooler stem. Resultant pores as well as residual pores in the cement are driven towards the last polymerizing region of the stem. To counteract this effect, Jafri et al. [82] evaluated the effect of preheating the stem. They observed a dramatic reduction of porosity at the stem-cement interface. This effect was observed at a temperature difference between the bone and the stem of 3° and was most pronounced at a difference of 7°. They recommended preheating of the stem to 40° in clinical practice. Iesaka et al. [83] have shown that stems preheated to 37° had greater interface shear strength at stem-cement interface than stems at room temperature both initially (53 % greater strength) and after simulated aging (155 % greater strength). Fatigue lifetimes were also improved and there was a >99 % decrease in interface porosity. When

Table 4.1 The different stem design and patient materials

Group	Name	Material	Surface finish (μm)		Male/fem	Mean age
			Prox.	Dist.		
1	Lubinus SP II	CoCr alloy	1.5	1.5	8/12	67(52–78)
2	Lubinus SP II	TiALV alloy	1.0	1.0	9/14	65(51–76)
3a	Spectron EF	CoCr alloy	2.8	0.7	6/10	70(65–76)
3b	Spectron EF	CoCr alloy	2.8	0.7	10/11	58(42–70)
3c	Spectron EF	CoCr alloy	2.8	0.7	4/13	71(61–81)
4	Anatomic-Option	CoCr alloy	1.5	1.5	15/29	58(32–69)
5	Tifit	TiALV alloy	1.3	1.3	12/8	52(38–66)
6	SHP	CoCr alloy	3.8	2.0	8/12	67(55–78)
7	Exeter	Stainless steel	<0.5	<0.5	11/5	71(63–81)

cement is mixed under vacuum, cement porosity is significantly reduced, producing less porosity at the stem-cement interface [57, 81]. Various studies have shown that interface porosity affects the debonding energy of the interface [84], weakens the resistance of the cement to torsional load [85], and decreases fatigue life of the stem-cement interface [83]. Interface porosity has also been linked to the initiation of cement cracks [59, 86]. The evidence that reduction of interface porosity improves the strength of the interface, thereby increasing the longevity of cemented implants, is convincing.

Migration Pattern of Cemented Femoral Stems

Several studies [87–89] have shown that early migration precedes clinical loosening. Micro-movements open up interfaces, increase abrasive wear, and may be an indirect indication of asymmetrical loading of the cement mantle, subsequently resulting in fracture.

Today, there are a number of studies which have measured the migration of different designs of cemented femoral stems using RSA [2, 89–95]. In these studies migration has always been measured in relation to the bone and sometimes also in relation to cement. These materials represent stems of different shapes, materials, and surface finishes. The main purpose of many of these studies has been to evaluate total migration (stem vs bone) and to what extent this migration occurs at the stem-cement interface. Kärrholm and coworkers have evaluated the micromotion of the most

common stems used in Sweden [15]. The materials are presented in Table 4.1. Lubinus SP II is anatomic, double curved with anterior and posterior ridges and a wide collar. Lubinus SP II stems of CoCr alloy constitute the references in this study because of their thorough documentation in the Swedish National Registry. This stem design showed a small early subsidence with only minimal increase after 6 months (Fig. 4.10). Spectron EF is straight and has a medial collar. The first version had a stem length of 135 mm (3a). In the following version (3b-c), the stem length increases with increasing size. These stems showed no or almost no subsidence until after 6 month follow-up. There was a levelling of the curve after 2 years, suggesting a period of deformation of the cement or debonding in only a few of the cases followed by secondary stabilization (Fig. 4.10). The Tifit stem is straight and has a small medial collar. It has anterior and posterior longitudinal indentations. Its length increases with increasing size. Anatomic-Option is anatomic, double curved with proximal indentations. The stem length increases with increasing size. Both designs tended to show increasing subsidence after 6 month follow-up. The Tifit stems, followed for 5 years, migrated more slowly after the 2-year follow-up (Fig. 4.11). Scientific hip (SHP) has no collar and a teardrop-like appearance proximally but becomes more cylindrical and tapered distally. The stem has four proximal PMMA spacers. The tip is sharp. All have a CCD angle of 120°. The length of the SHP stem increases with increasing size. The Exeter stem is a polished straight, double-tapered, flat, collarless stem with a centralizer fixed

Fig. 4.10 Subsidence of the Lubinus SP II and Spectron EF stems

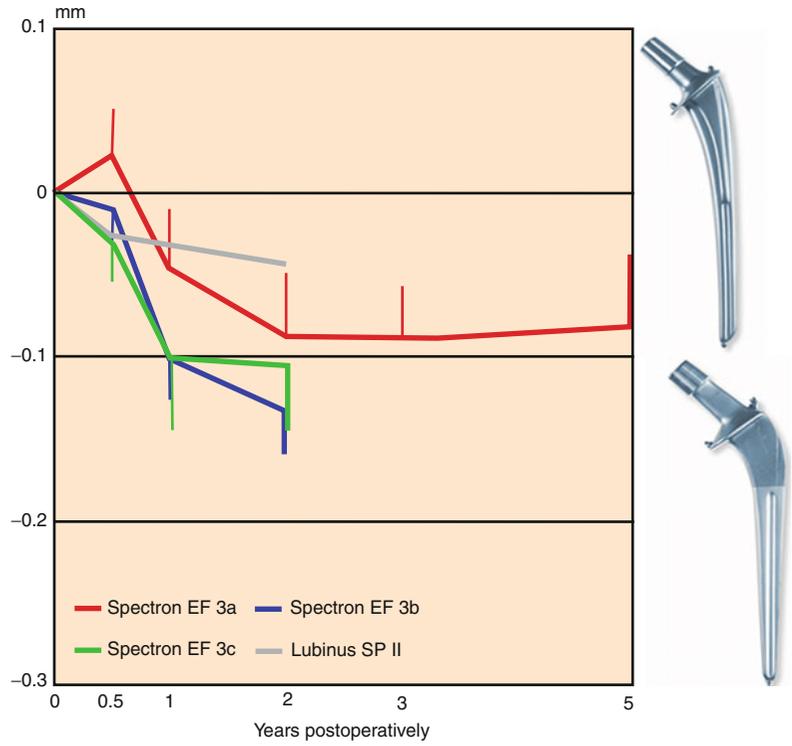


Fig. 4.11 Subsidence of the Tifit and Anatomic-Option stems

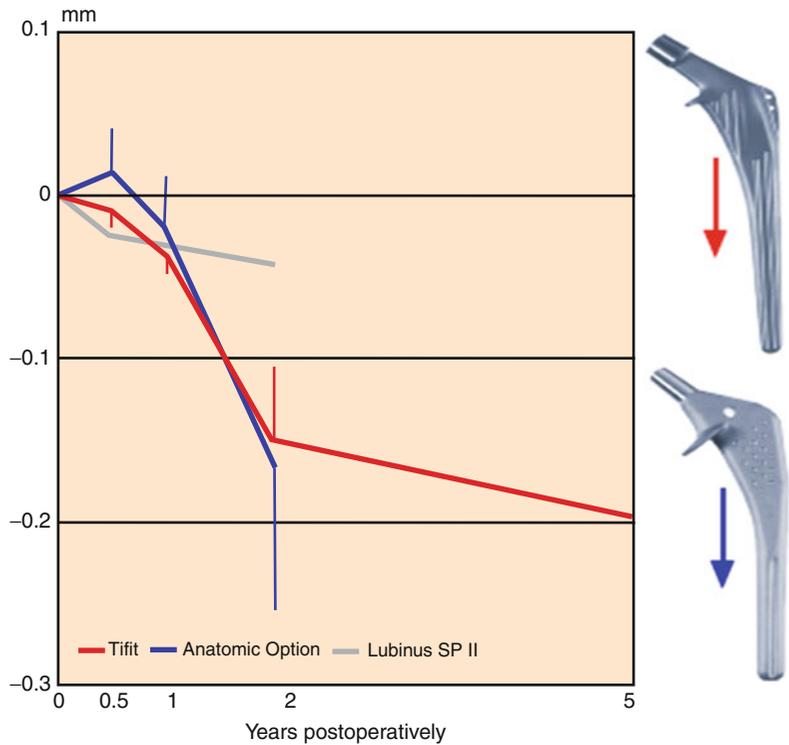
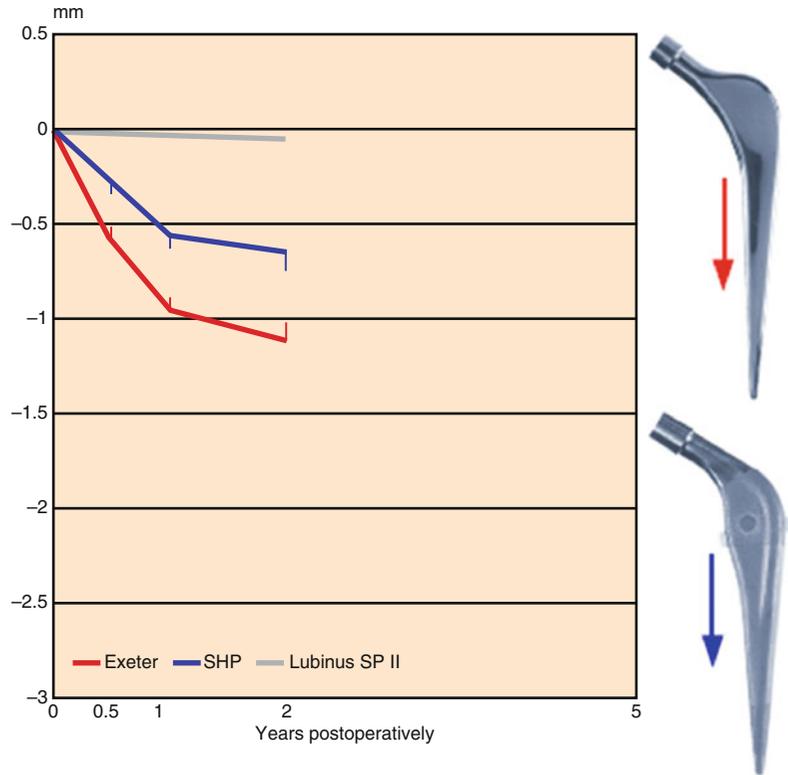


Fig. 4.12 Subsidence of the SHP and Exeter stems



to the tip. The collarless stems and especially the Exeter designs showed early and fast subsidence. The migration rate tended to decrease somewhat after 1 year (Fig. 4.12).

At 2 years control most stem designs showed retroversion. Median values exceeding 1° were noted for the Exeter (1.7) and SHP design (2.5). There was also a slight tendency to posterior tilt. The median varus/valgus tilt was close to zero. In all series stem subsidence was more common in the cement mantle (Table 4.2). Four stems that had been revised before the 5-year control showed more subsidence and retroversion than the remaining cases in each group up to 2-year follow-up. According to this study there is a close connection between stem geometry and recorded micromotion. Although subsidence of the stem and posterior displacement of the head are believed to be the most important predictors of early failure in cemented total hip arthroplasty [89], it has become generally accepted that early clinical migration values must be related to stem shape and surface finish. Thien et al. [96] used RSA in a prospective

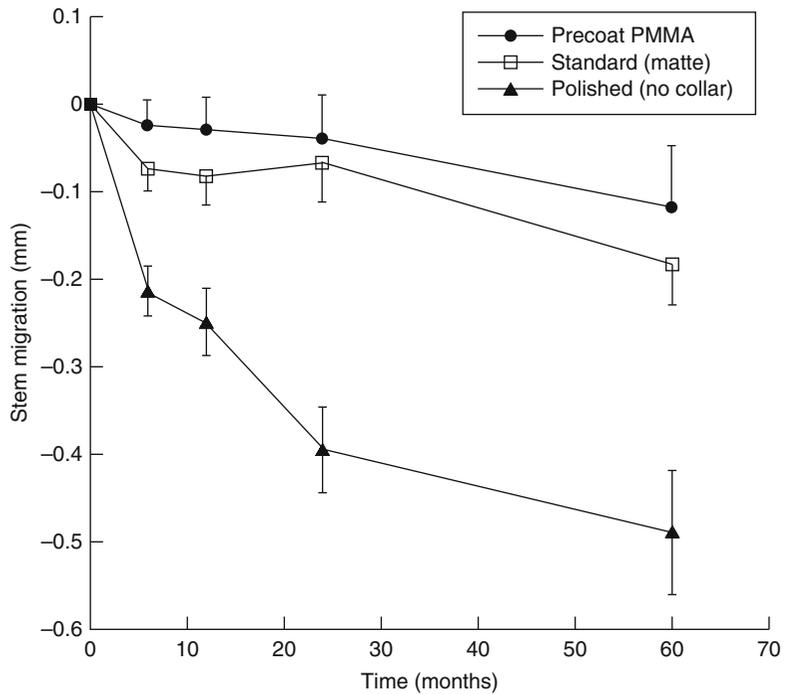
randomized study to evaluate fixation of 3 modifications of the Lubinus SP2 stem. These stems were 27 matte (standard design), 28 polymethylmethacrylate (PMMA) coated, and 29 collarless and polished. They have identical stem design, shape, and alloy. The only difference was the surface finish and the presence of a collar or not. The mean subsidence for the polished stem was 0.4 mm at 2 years, while for the other two groups the respective values were below 0.1 mm. Between 2 and 5 years, subsidence for the three groups was nearly equal (Fig. 4.13). This study shows the effect of surface finish on stem migration. Other RSA studies have shown similar behavior for the standard matte Lubinus design with low mean values regarding both subsidence and rotation [91, 97]. Twenty-two Exeter stems have been evaluated with RSA up to 5 years by Stefansdottir et al [94]. The median migration at 2 years was 1.34 mm and at 5 years 1.77 mm. A major part of the migration occurred within the first 4 months after surgery. There were no reoperations during the 5-year follow-up in the two studies mentioned above.

Table 4.2 Stem subsidence inside the cement mantle in mm

Group	Implant	Total	Significant subsidence ($p < 0.01$) ^a	Cement mantle		Stem inside mantle	
				Subsiding >significant value	Value ranges	Subsiding >significant value	Value ranges
1	Lubinus SP II	4	0.11	0		4	-0.20 to -0.12
2	Lubinus SP II	13	0.18	2	-0.32 to -0.20	10	-0.46 to -0.18
3a	Spectron EF	11	0.18	0		4	-0.25 to -0.19
3b	Spectron EF	16	0.20	3	-0.30 to -0.23	4	-0.46 to -0.21
3c	Spectron EF	12	0.11	4	-0.25 to -0.17	5	-0.28 to -0.13
6	SHP	14	0.11	2	-0.42 to -0.32	14	-1.10 to -0.17
7	Exeter	16	0.20	0		16	-1.94 to -0.71

^aSignificant level ($p < 0.01$) for individual cases in each study varies depending on technique related factors

Fig. 4.13 This graph shows the proximal (+)/distal (-) migration of all 3 stem types vs the femoral bone in all cases. Mean and SEM (Adapted from Thien et al. [96])



According to the Swedish arthroplasty hip registry, the survival rate for Lubinus SPII stem is 94.3 % at 19 years, while for the Exeter stem 96.9 % at 12 years. From these RSA studies and the Swedish arthroplasty hip registry, it is evident

that the amount of tolerable migration of the stem until clinical failure varies depending on the design and surface finish of the stem. Even if the magnitude of migration is design related, the pattern of motion in cases with impending clinical failures

seems to be similar. The stem subsidence and rotation into retroversion are higher in failures than clinical successful uses of the same type. These implants with later clinical failure can be identified within first years of follow-up. One example is the Spectron stem which was introduced in the early 1980s. In 1995 a new version was introduced (Spectron EF Primary). The stem became narrower and shorter in the smallest sizes. In addition, a version with an increased offset, a polished neck, and a narrower cone was introduced. In the previously mentioned study [15], the older version of Spectron stem had a mean subsidence lower than 0.1 mm at 5-year follow-up (Fig. 4.10). A previous study of ours evaluating the new version of Spectron stem with RSA showed subsidence of 0.28 mm in the cement mantle at 5 years when Palacos cement had been used [63]. The higher early subsidence rate of the new Spectron design is mirrored in the annual report of the Swedish Hip Arthroplasty Register 2010 [43] which shows lower survival rate for this particular stem compared with the older design (new design 95 % at 12 year vs older design 97.5 % at 15 year, Fig. 4.14). The higher subsidence rate of this stem, which has a rough surface finish, may increase particle production due to abrasive wear. In some cases, and after a variable time period, osteolysis may develop and the mantle may fracture leading to clinical loosening and revision surgery.

RSA Studies Evaluating the Stem-Cement Interface

Accurate measurements of the cement mantle migration are more difficult than the corresponding measurements of the femoral stem because of problems of visualizing cement markers and obtaining sufficient marker scatter. This often means that reliable data can only be obtained for migration in the proximal/distal direction. Few RSA studies have evaluated micromotion in the stem-cement interface as part of total stem migration related to bone up to 5 years. In a prospective randomized study, Nivbrant et al. [6] evaluated two types of bone cement (bone cement with reduced amount of monomer Cemex Rx and Palacos R)

that were used to fixate 47 Lubinus SP2 prostheses with 5 years of follow-up. All stems in this study were made of titanium alloy, and their surface was slightly smoother than the cobalt-chrome alloy version. In 28 cases subsidence of the cement mantle could be studied. In 14 of 16 cases where stem subsidence relative to bone exceeded 0.18 mm (the 99 % confidence limit of precision for this study), more than 50 % of this motion occurred inside the mantle. Stefandottir et al. [94] followed the migration of the Exeter stems in 22 primary hip arthroplasties for 5 years. The median migration at 5 years was 1.77 mm. The cement mantle could be evaluated in 12 cases. Five cement mantles migrated above the detection level (0.2 mm) between 0.20 and 0.64 mm. A correlation between distal migration and retroversion was found. They concluded that distal migration and rotations occur mainly inside the cement mantle. In a prospective study 97 hips were randomized to receive a Spectron EF stem fixed with fluoride-containing acrylic bone cement (Cemex F) or conventional bone cement (Palacos) [63]. Evaluation at 5 years revealed no differences in stem migration. In 61 cases (27 Cemex F, 34 Palacos) where proximal/distal migration between stem and cement could be studied, subsidence increased similarly in both groups. Subsidence between stem and bone exceeding 0.15 mm (the 99 % confidence limit of precision in this study) was observed in 35 cases (17 Cemex F, 18 Palacos). In 23 hips at least 50 % of this subsidence occurred inside the cement mantle. Four of the 28 cases (2C, 2P) showed distal migration of the cement mantle exceeding the detection limit for individual cases (0.16 mm; range, 0.17–0.37 mm). Eighty-four hips randomly received Lubinus SP2 stem with matte (M), polymethylmethacrylate coated (PG), or polished surface (uncollared) (P) [96]. The polished stems subsided more than the matte and PMMA-coated stems at 6 months and after 5 years (Fig. 4.14). Stem subsidence in relation to the cement could be evaluated in 37 cases (12 P, 12 M, 13 PC) at 5 years. In 11 of the 12 polished stems, more than 50 % of this subsidence occurred inside the cement mantle (Fig. 4.15). In 10 of 12 matte stems and 8 of 13 PMMA-coated stems, less than 50 % of subsidence occurred in stem-cement interface.

Fig. 4.14 Implant survival regarding stem revision for loosening/osteolysis with or without simultaneous cup revision

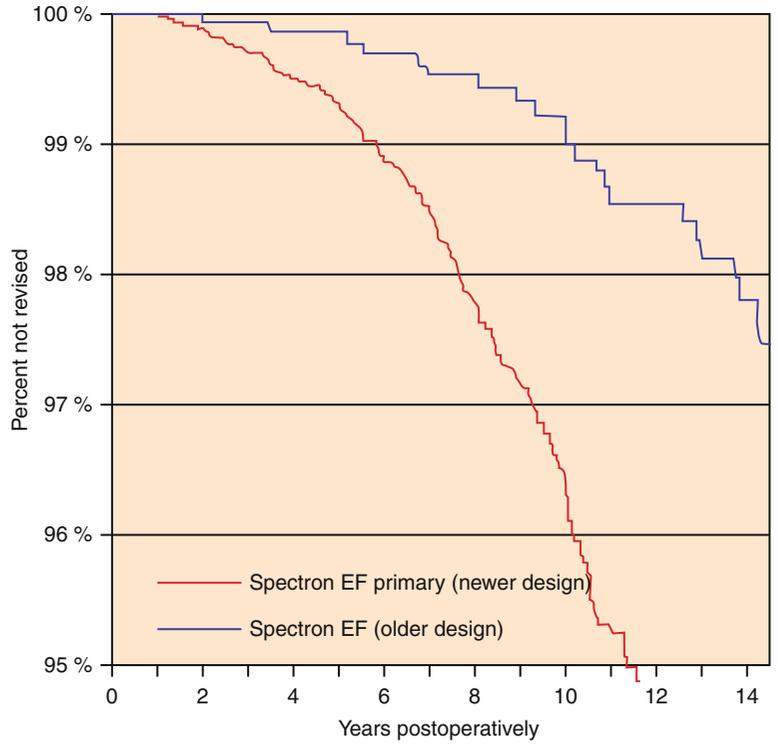
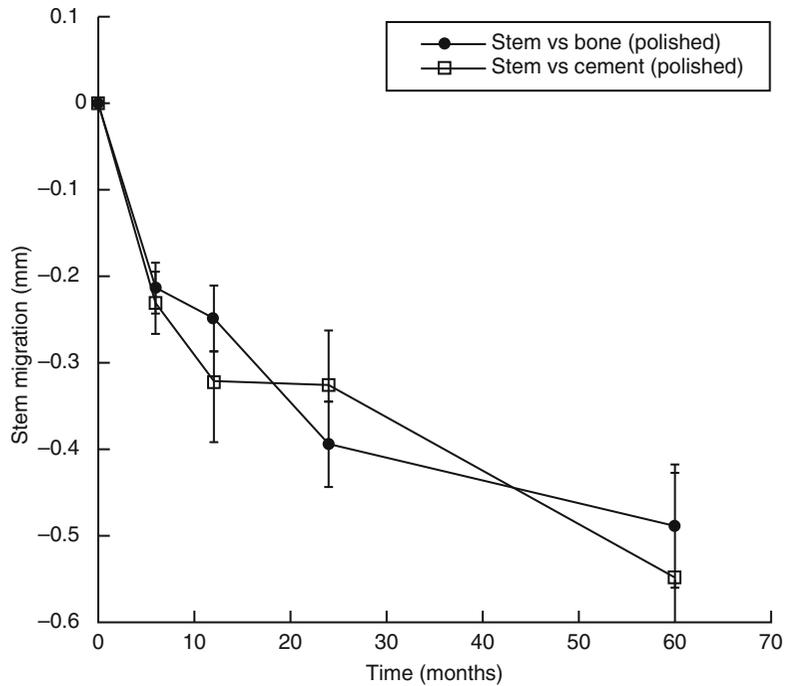


Fig. 4.15 This graph shows the proximal (+)/distal (-) migration over time of the polished stems vs the bone ($n=25$ stems) and vs the cement ($n=12$). Mean values and SEM (Adapted from Thien et al. [96])



In summary, RSA data have revealed that stem subsidence inside the mantle occurs with variable frequency and magnitude in almost all designs of

THA regardless of the presence of a rough surface finish. Subsidence for polished stems is higher than for matt or rough stems and occurs mainly in

the cement mantle, while stems with a matte or rough surface finish subside at both interfaces. The stem-cement interface might be stronger with a rough surface and may postpone debonding, but when they debond, rough stems may produce more cement debris than polished ones [38]. Some matt stems, for example, the Lubinus SP, seem to be comparatively resistant to abrasive wear. There seems, however, to be a lower size limit for this design, since the introduction of the smallest version (extra-narrow) resulted in an increased failure rate, mainly due to loosening. This particular size has, however, been used in small numbers and has, according to our knowledge, not been studied with RSA.

The increased subsidence of the polished stems in the cement mantle may be advantageous in the reduction of stresses at the bone-cement interface by facilitation of more even distribution of load at the interfaces. In the study by Thien et al. [96] mentioned above, the polished version showed significantly less loss of proximal bone mineral density, suggesting a more physiological loading of the bone. This effect, however, seemed to be temporary and mainly lasted for 2 years, whereas continued stem subsidence could be measured during the entire period of 5 years of observation. Subsidence below the acceptable limit for each stem may be advantageous if it increases stem-cement contact and stability, provided that this is not necessarily associated with inducible displacements during activity. Another effect of subsidence may be the maintenance of proximal load distribution [96]. As previously mentioned, polished stems have the disadvantage of being associated with increased risk of periprosthetic fracture. This has been well documented for the Exeter design but concerns may exist for many other designs of polished stems [98, 99]. The reason for this is unclear. It could be important to consider this in patient groups with increased risk of these complications, such as cases with previous femoral neck fractures, idiopathic femoral head necrosis, or an osteoporotic femur due to other causes.

The choice of optimum stem design may thus vary depending on patient characteristics. For the majority of patients, the choice between a well-documented matt or polished stem is not

controversial. The experience of the surgeon with a particular design is probably the most important factor for the result. In active patients with a narrow femur, a polished design is probably preferable. In older patients, and especially those with the diagnoses mentioned above, a well-documented matt stem is preferable. Many stem designs used with cement have very good clinical records in the long term [43, 100, 101]. For older patients room for improvement is limited. It should, however, be emphasized that some of these stems have undergone modifications one or more times during the last 10–15 years. Furthermore, the indications for THA have tended to embrace more patients of younger age, and the demands on the implants might have increased with increasing general health and activity levels of the patient population in the older age groups. Further improvements could include minimization of particle production at the stem-cement interface to minimize third-body wear and the development of stems and fixation principles which are associated with less proximal bone loss. A still more reproducible fixation of the mantle might also be beneficial in young patients.

References

1. Verdonchot N, Huiskes R. Cement debonding process of total hip arthroplasty stems. *Clin Orthop*. 1997;336:297–307.
2. Thanner J, Freij-Larsson C, Kärrholm J, et al. Evaluation of Boneloc. Chemical and mechanical properties, and a randomized clinical study of 30 total hip arthroplasties. *Acta Orthop Scand*. 1995;66:207–14.
3. Anthony PP, Gie GA, Howie CR, Ling RS. Localised endosteal lysis in relation to the femoral component of cemented total hip replacements. *J Bone Joint Surg Br*. 1997;79B:675–9.
4. Ebramzadeh E, Normand PL, Sangiorgio SN, et al. Long-term radiographic changes in cemented total hip arthroplasty with six designs of femoral components. *Biomaterials*. 2000;24:3351–63.
5. Jergesen HE, Karlen JW. Clinical outcome in total hip arthroplasty using a cemented titanium femoral prosthesis. *J Arthroplasty*. 2002;17:592–9.
6. Nivbrant B, Kärrholm J, Röhrli S, et al. Bone cement with reduced proportion of monomer in total hip arthroplasty. Preclinical evaluation and randomized study of 47 cases with 5 years' follow-up. *Acta Orthop Scand*. 2001;72:572–84.

7. Espehaug B, Furnes O, Engesaeter LB, Havelin LI. 18 years of results with cemented primary hip prostheses in the Norwegian Arthroplasty Register. Concerns about some newer implants. *Acta Orthop Scand*. 2009;80:402–12.
8. Hallan H, Espehaug B, Furnes O, et al. Is there still a place for the cemented titanium femoral stem? 10,108 cases from the Norwegian Arthroplasty Register. *Acta Orthop Scand*. 2012;83:1–6.
9. Semlitsch M. Titanium alloys for hip joint replacements. *Clin Mater*. 1987;2:1–13.
10. Willert HG, Broback LG, Buchhorn GH, et al. Crevice corrosion of cemented titanium alloy stems in total hip replacements. *Clin Orthop*. 1996;333:51–75.
11. Hallam P, Haddad F, Cobb J. Pain in the well-fixed, aseptic titanium hip replacement. The role of corrosion. *J Bone Joint Surg Br*. 2004;86B:27–30.
12. Thomas SR, Shukla D, Latham PD. Corrosion of cemented titanium femoral stems. *J Bone Joint Surg Br*. 2004;86B:974–8.
13. Walczak J, Shahgaldi F, Heatley F. In vivo corrosion of 316L stainless-steel hip implants: morphology and elemental compositions of corrosion products. *Biomaterials*. 1998;19:229–37.
14. Bergmann G, Deuretzbacher G, Heller M, et al. Hip contact forces and gait patterns from routine activities. *J Biomech*. 2001;34:859–71.
15. Kärrholm J, Nivbrant B, Thanner J, et al. Radiostereometric evaluation of hip implant design and surface finish. Scientific Exhibition, AAOS, Orlando; 2000.
16. Gill HS, Alfaro-Adrian J, Alfaro-Adrian C, et al. The effect of anteversion on femoral component stability assessed by radiostereometric analysis. *J Arthroplasty*. 2002;17:997–1005.
17. Olofsson K, Digas G, Kärrholm J. Influence of design variations on early migration of a cemented stem in THA. *Clin Orthop*. 2006;448:67–72.
18. Kadar T, Hallan G, Aamodt A, et al. A randomized study on migration of the Spectron EF and the Charnley flanged 40 cemented femoral components using radiostereometric analysis at 2 years. *Acta Orthop Scand*. 2011;82:538–44.
19. Sylvain GM, Kassab S, Coutts R, Santore R. Early failure of a roughened surface, precoated femoral component in total hip arthroplasty. *J Arthroplasty*. 2001;16:141–8.
20. Kalairajah Y, Molloy S, Patterson M. The effect of femoral stem size on failure rates in total hip replacement cemented with Boneloc. *Acta Orthop Belg*. 2002;68:33–6.
21. Thien TM, Kärrholm J. Design-related risk factors for revision of primary cemented stems. Analysis of 3 common stems in the Swedish Hip Arthroplasty Register. *Acta Orthop Scand*. 2010;81:407–12.
22. Bourne RB, Oh I, Harris WH. Femoral cement pressurization during total hip arthroplasty: the role of different femoral stems with reference to stem size and shape. *Clin Orthop*. 1984;183:12–6.
23. Huiskes R, Verdonschot N, Nivbrant B. Migration, stem shape, and surface finish in cemented total hip arthroplasty. *Clin Orthop*. 1998;355:103–12.
24. Harris WH. Is it advantageous to strengthen the cement metal interface and use a collar for cemented femoral components of total hip replacements? *Clin Orthop*. 1992;285:67–72.
25. Schmalzried TP, Harris WH. Hybrid total hip replacement: a 6.5 year follow-up study. *J Bone Joint Surg Br*. 1993;75B:608–15.
26. Goldberg VM, Ninomiya J, Kelly G, Kraay M. Hybrid total hip arthroplasty: a 7- to 11-year follow-up. *Clin Orthop*. 1996;333:147–54.
27. Callaghan JJ, Tooma GS, Olejniczak JP, et al. Primary hybrid total hip arthroplasty: an interim follow-up. *Clin Orthop*. 1996;333:118–25.
28. Collis DK, Mohler CG. Loosening rates and bone lysis with rough finished and polished stems. *Clin Orthop*. 1998;355:113–22.
29. Dowd JE, Cha CW, Trakru S, et al. Failure of total hip arthroplasty with a precoated prosthesis: 4-toll-year results. *Clin Orthop*. 1998;355:123–36.
30. Ong A, Wong KL, Lai M, et al. Early failure of precoated femoral components in primary total hip arthroplasty. *J Bone Joint Surg Am*. 2002;84A:786–92.
31. Fowler J, Gie GA, Lee AJ, Ling RS. Experience with Exeter Hip since 1970. *Orthop Clin N Am*. 1998;19:477–89.
32. Milles AW. A preliminary report on stem/cement interface and its influence on bone/cement interface. In: Older J, editor. *Implant bone interface*. Berlin: Springer; 1990.
33. Lewis G. Properties of acrylic bone cement: state of the art review. *J Biomed Mater Res*. 1997;38:155–82.
34. Yoon YS, Oxland TR, Hodgson AJ, et al. Mechanical aspects of degree of cement bonding and implant wedge effect. *Clin Biomech*. 2008;23:1141–7.
35. Bundy KJ, Penn RW. The effect of surface preparation on metal/bone cement interfacial strength. *J Biomed Mater Res*. 1987;21:773–805.
36. Chen CQ, Scott W, Barker TM. Effect of metal surface topography on mechanical bonding at simulated total hip stem-cement interfaces. *J Biomed Mater Res*. 1999;48(4):440–6.
37. Crowninshield RD, Jennings JD, Laurent ML, Maloney WJ. Cemented femoral component surface finish mechanics. *Clin Orthop*. 1998;355:90–102.
38. Verdonschot N, Huiskes R. Surface roughness of debonded straight-tapered stems in cemented THA reduces subsidence but not cement damage. *Biomaterials*. 1998;19:1773–9.
39. Verdonschot N, Tanck E, Huiskes R. Effects of prosthesis surface roughness on the failure process of cemented hip implants after stem-cement debonding. *J Biomed Mater Res*. 1998;42:554–9.
40. Collis DK, Mohler CG. Comparison of clinical outcomes in total hip arthroplasty using rough and polished cemented stems with essentially the same geometry. *J Bone Joint Surg Am*. 2002;84A:586–92.

41. Race A, Miller MA, Ayers DC, et al. The influence of surface roughness on stem-cement gaps. *J Bone Joint Surg Br.* 2002;84B:1199–204.
42. von Knoch M, Bluhm A, Morlock M, von Foerster G. Absence of surface roughness changes after insertion of one type of matte cemented femoral component during 2 to 15 years. *J Arthroplasty.* 2003;18:471–7.
43. Garellick G, Kärrholm J, Rogmark C. Annual report 2010. Swedish Hip Arthroplasty Register. 2011; <http://www.shpr.se/Libraries/Documents/AnnualReport-2010-3.sffb.ashx>.
44. Howie DW, Middleton RG, Costi K. Loosening of matt and polished cemented femoral stems. *J Bone Joint Surg Br.* 1998;80B:573–6.
45. Hinrichs F, Kuhl M, Boudriot U, Griss P. A comparative clinical outcome evaluation of smooth (10–13 year results) versus rough surface finish (5–8 year results) in an otherwise identically designed cemented titanium alloy stem. *Arch Orthop Trauma Surg.* 2003;123:268–72.
46. Della Valle AG, Zoppi A, Peterson MG, Salvati EA. A rough surface finish adversely affects the survivorship of a cemented femoral stem. *Clin Orthop.* 2005;436:158–63.
47. Ritter MA, Harty LD, Lorenzo RA, Lutgring JD. Total hip arthroplasty with satin finish, tapered stems. *Orthopedics.* 2005;28:1454–6.
48. Dattir SP, Kurta IC, Wynn-Jones CH. Ten-year survivorship of rough-surfaced femoral stem with geometry similar to Charnley femoral stem. *J Arthroplasty.* 2006;21:392–7.
49. Firestone DE, Callaghan JJ, Liu SS, et al. Total hip arthroplasty with a cemented, polished, collared femoral stem and a cementless acetabular component. A follow-up study at a minimum of ten years. *J Bone Joint Surg Am.* 2007;89A:126–32.
50. Malchau H, Herberts P, Ahnfelt L. Prognosis of total hip replacement in Sweden. Follow-up of 92,675 operations performed 1978–1990. *Acta Orthop Scand.* 1993;64:497–506.
51. Sanchez-Sotelo J, Berry DJ, Harmsen S. Long-term results of use of a collared matte-finished femoral component fixed with second-generation cementing techniques. A fifteen-year-median follow-up study. *J Bone Joint Surg Am.* 2002;84A:1636–41.
52. Meneghini RM, Feinberg JR, Capello WN. Primary hybrid total hip arthroplasty with a roughened femoral stem: integrity of the stem-cement interface. *J Arthroplasty.* 2003;18:299–307.
53. Kärrholm J, Herberts P. Annual report 2006 Swedish total hip arthroplasty register. www.shpr.se.
54. Callaghan JJ, Liu SS, Firestone DE, et al. Total hip arthroplasty with cement and use of a collared matte-finish femoral component: nineteen to twenty-year follow-up. *J Bone Joint Surg Am.* 2008;90A:299–306.
55. Crawford RW, Evans M, Ling RS, Murray DW. Fluid flow around model femoral components of differing surface finishes – In vitro investigations. *Acta Orthop Scand.* 1999;70:589–95.
56. Ling RS, Lee AJ. Porosity reduction in acrylic cement is clinically irrelevant. *Clin Orthop.* 1998;355:249–53.
57. Wang JS, Franzin H, Lidgren L. Interface gap implantation of a cemented femoral stem in pigs. *Acta Orthop Scand.* 1999;70:229–33.
58. Verdonschot N, Huiskes R. Acrylic cement creeps but does not allow much subsidence of femoral stems. *J Bone Joint Surg Br.* 1997;79B:665–9.
59. Jasty M, Maloney WJ, Bragdon CR, et al. The initiation of failure in cemented femoral components of hip arthroplasties. *J Bone Joint Surg Br.* 1991;73B:551–8.
60. Mohler CG, Callaghan JJ, Collis DK, et al. Early loosening of the femoral component at the cement-prosthesis interface after total hip replacement. *J Bone Joint Surg Am.* 1995;77A:1315–22.
61. Callaghan JJ, Forest EE, Sporer SM, et al. Total hip arthroplasty in the young adult. *Clin Orthop.* 1997;344:257–62.
62. Howell JR, Blunt LA, Doyle C, et al. In vivo surface wear mechanisms of femoral components of cemented total hip arthroplasties: the influence of wear mechanism on clinical outcome. *J Arthroplasty.* 2004;19:88–101.
63. Digas G, Kärrholm J, Thanner J. Addition of fluoride to acrylic bone cement does not improve fixation of a total hip arthroplasty stem. *Clin Orthop.* 2006;448:58–66.
64. Norman TL, Saligrama VC, Hustosky KT, et al. Axisymmetric finite element analysis of a debonded total hip stem with an unsupported distal tip. *J Biomech Eng.* 1996;118:399–404.
65. Shen G. Femoral stem fixation: an engineering interpretation of the long-term outcome of Charnley and Exeter stems. *J Bone Joint Surgery Br.* 1998;80B:754–6.
66. Räder DA, Czaja S, Morscher EW. Fifteen-year results of the Müller CoCrNiMo Straight Stem. *Arch Orthop Trauma Surg.* 2001;121:38–42.
67. Berli BJ, Schäfer D, Morscher EW. Ten-year survival of the MS-30 matt-surfaced cemented stem. *J Bone Joint Surg Br.* 2005;87B:928–33.
68. Lindahl H, Malchau H, Herberts P, Garellick G. Periprosthetic femoral fractures classification and demographics of 1049 periprosthetic femoral fractures from the Swedish National Hip Arthroplasty Register. *J Arthroplasty.* 2005;20:857–65.
69. Breusch SJ, Lukoschek M, Kreuzer J, et al. Dependency of cement mantle thickness on femoral stem design and centralizer. *J Arthroplasty.* 2001;16:648–57.
70. Ebramzadeh E, Sangiorgio SN, Longjohn DB, et al. Initial stability of cemented femoral stems as a function of surface finish, collar, and stem size. *J Bone Joint Surg Am.* 2004;86A:106–15.
71. Maloney WJ, Keeney JA. Leg length discrepancy after total hip arthroplasty. *J Arthroplasty.* 2004;19:108–10.
72. Ramaniraka NA, Rakotomanana LR, Leyvraz PF. The fixation of the cemented femoral component. Effects of stem stiffness, cement thickness and roughness of the cement-bone surface. *J Bone Joint Surg Br.* 2000;82B:297–303.

73. Carlsson AS, Gentz CF, Linder L. Localized bone resorption in the femur in mechanical failure of cemented total hip arthroplasties. *Acta Orthop Scand.* 1983;54:396–402.
74. Garellick G, Malchau H, Regner H, et al. The Charnley versus the Spectron hip prosthesis: radiographic evaluation of a randomized prospective study of 2 different hip implants. *J Arthroplasty.* 1999;14:414–25.
75. Lee AJC, Ling RSM, Vangala SS. Some clinically relevant variables affecting the mechanical behaviour of bone cement. *Arch Orthop Traumat Surg.* 1978;92:1–18.
76. Verdonschot N, Huiskes R. Creep, properties of three low temperature-curing bone cements: a preclinical assessment. *J Biomed Mater Res.* 2000;53:498–504.
77. Norman TL, Williams M, Gruen TA, Blaha JD. Influence of delayed injection time on the creep behaviour of acrylic bone cement. *J Biomed Mater Res.* 1997;37:151–4.
78. Waanders D, Janssen D, Mann KA, Verdonschot N. The effect of cement creep and cement fatigue damage on the micromechanics of the cement-bone interface. *J Biomech.* 2010;16(43):3028–34.
79. Muller SD, Green SM, McCaskie AW. The dynamic volume changes of polymerising polymethyl methacrylate bone cement. *Acta Orthop Scand.* 2002;73:684–7.
80. Draenert K, Draenert Y, Garde U, Ulrich C. Manual of cementing technique. Berlin/Heidelberg/New York/Tokyo: Springer; 1999. p. 26–8.
81. Bishop NE, Ferguson S, Tepic S. Porosity reduction in bone cement at the cement-stem interface. *J Bone Joint Surg Br.* 1996;78B:349–56.
82. Jafri AA, Green SM, Partington PF, et al. Pre-heating of components in cemented total hip arthroplasty. *J Bone Joint Surg Br.* 2004;86B:1214–9.
83. Iesaka K, Jaffe WL, Kummer FJ. Effects of preheating of hip prostheses on the stem-cement interface. *J Bone Joint Surg Am.* 2003;85A:421–7.
84. Mau H, Schelling K, Heisel C, et al. Comparison of different vacuum mixing systems and bone cements with respect to reliability, porosity and bending strength. *Acta Orthop Scand.* 2004;75:160–72.
85. Davies JP, Kawate K, Harris WH. Effect of interfacial porosity on the torsional strength of the cement-metal interface. 41st annual meeting orthopedic research society, Orlando; 1999. p. 713.
86. Verdonschot N. Biomechanical failure scenarios for cemented total hip replacement. 1995. Thesis. Ph.D.
87. Freeman MA, Plante-Bordeneuve P. Early migration and late aseptic failure of proximal femoral prostheses. *J Bone Joint Surg Br.* 1994;76B:432–8.
88. Krismser M, Stöckl B, Fischer M, et al. Early migration predicts late aseptic failure of hip sockets. *J Bone Joint Surg Br.* 1996;78B:422–6.
89. Kärrholm J, Borssén B, Löwenhielm G, Snorrason F. Does early micromotion of femoral stem prostheses matter? 4-7-year stereoradiographic follow-up of 84 cemented prostheses. *J Bone Joint Surg Br.* 1994;76B:912–7.
90. Kärrholm J, Malchau H, Snorrason F, Herberts P. Micromotion of femoral stems in total hip arthroplasty. A randomized study of cemented, hydroxyapatite-coated, and porous-coated stems with roentgen stereophotogrammetric analysis. *J Bone Joint Surg Am.* 1994;76A:1692–705.
91. Nivbrant B, Kärrholm J, Soderlund P. Increased migration of the SHP prosthesis: radiostereometric comparison with the Lubinus SP2 design in 40 cases. *Acta Orthop Scand.* 1999;70:569–77.
92. Derbyshire B, Porter ML. A study of the Elite Plus femoral component using radiostereometric analysis. *J Bone Joint Surg Br.* 2007;89B:730–5.
93. Glyn-Jones S, Polgár K, Hicks J, et al. RSA-measured inducible micromotion and interface modeling with finite element methods. *Clin Orthop.* 2006;448:98–104.
94. Stefánsdóttir A, Franzén H, Johnsson R, et al. Movement pattern of the Exeter femoral stem A radiostereometric analysis of 22 primary hip arthroplasties followed for 5 years. *Acta Orthop Scand.* 2004;75:408–14.
95. Sundberg M, Besjakov J, von Schewelov T, Carlsson A. Movement patterns of the C-stem femoral component: an RSA study of 33 primary total hip arthroplasties followed for two years. *J Bone Joint Surg Br.* 2005;87B:1352–6.
96. Thien TM, Thanner J, Kärrholm J. Randomized comparison between 3 surface treatments of a single anteverted stem design: 84 hips followed for 5 years. *J Arthroplasty.* 2010;25:437–44.
97. Catani F, Ensini A, Leardini A, et al. Migration of cemented stem and restrictor after total hip arthroplasty: a radiostereometry study of 25 patients with Lubinus SP II stem. *J Arthroplasty.* 2005;20:244–9.
98. Lindahl H, Garellick G, Regner H, et al. Three hundred and twenty-one periprosthetic femoral fractures. *J Bone Joint Surg Am.* 2006;88A:1215–22.
99. Leonardsson O, Kärrholm J, Åkesson K, et al. Higher risk of re-operation for bipolar and uncemented hemiarthroplasty. *Acta Orthop.* 2012;83:459–66.
100. Graves S, Davidson D, de Steiger R. Annual report 2011. AOA National Joint Replacement Registry. 2011. <http://www.dmac.adelaide.edu.au/aoanjrr/documents/AnnualReports2011/AnnualReport-2011-WebVersion.pdf>.
101. Furnes O, Gjertsen J E. Annual report 2011. Norwegian Arthroplasty Register/Norwegian Hip Fracture Register. <http://nrlweb.ihelse.net/Rapporter/Rapport2011.pdf>.

Cobalt–Chrome Porous-Coated Implant–Bone Interface in Total Joint Arthroplasty

5

George C. Babis and Andreas F. Mavrogenis

Cobalt–Chrome Alloys

Cobalt–chrome (Co–Cr) is a metal alloy of cobalt and chromium with a very high specific strength. For as long as investment casting has been available as an industrial process, cobalt-based alloys have been used in demanding applications including dental and orthopedic implants [1]. The alloy composition used in orthopedic implants, described in industry standard ASTM-F75, is composed of cobalt with (1) chromium (27–30 %) and (2) molybdenum (5–7 %) and (3) limits on other important elements such as manganese and silicon (<1 %), iron (<0.75 %), nickel (<0.5 %), and carbon, nitrogen, tungsten, phosphorus, sulfur, boron, etc. [1]. Besides cobalt–chrome–molybdenum (Co–Cr–Mo), cobalt–nickel–chromium–molybdenum (Co–Ni–Cr–Mo) is also used for implants (Table 5.1) [2, 3].

The possible toxicity of released Ni ions from Co–Ni–Cr alloys and their limited frictional properties have been a matter of concern in using these alloys as articulating components. Thus, Co–Cr–Mo is usually the dominant alloy for total joint arthroplasty [3]. Co–Cr–Mo alloys can withstand high temperatures and have a high wear resistance. The alloy is especially used where high stiffness or a highly polished and extremely wear-resistant material is required. It can be used in gas turbines, valve seats, nuclear power plants, automotive engines, aerospace fuel nozzles, engine vanes, and other components, most importantly in a variety of medical prosthetic implant devices, such as knee implants, metal-to-metal hip joints, and dental prosthetics due to its high biocompatibility [1]. The increased stability and excellent material properties of Co–Cr alloys are advantageous for long-term durability and thus are a promising advance for younger patients in need of total joints.

Porous Metallic Coatings

For a number of years there has been increasing interest in surface treating orthopedic implants in an attempt to improve implant fixation. Various coatings have been manufactured. Porous metallic and ceramic coatings deposited on implants facilitate implant fixation and bone ingrowth. Implant surfaces modified by ion implantation or physical vapor deposition exhibit superior hardness and wear resistance. Polymeric coating

G.C. Babis, MD, DSc (✉)
First Department of Orthopaedic Surgery,
University of Athens, Attikon
University General Hospital,
Chaidari, Attica, Greece

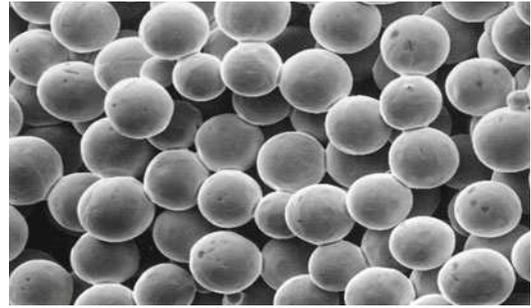
A.F. Mavrogenis, MD
First Department of Orthopaedics,
Attikon University Hospital, Athens
University Medical School,
Chaidari, Attica 12462, Greece

Table 5.1 Properties of stainless steel, cobalt–chrome, and titanium metallic biomaterials

Properties	Stainless steel	Cobalt–chrome	Titanium
Stiffness	High	Medium	Low
Strength	Medium	Medium	High
Corrosion resistance	Low	Medium	High
Biocompatibility	Low	Medium	High

formulations are used to enhance biocompatibility and biostability, thrombo-resistance, antimicrobial action, dielectric strength, and lubricity make medical devices used within the body more visible to ultrasound and for delivery of drugs [4]. It is well known in the medical arts for providing a metallic bone prosthesis with a porous metallic coating to enhance the fixation of the prosthesis to the patient's bone. Such fixation is generally achieved by either cementation or bone tissue ingrowth. Bone cement or freshly grown bone tissue occupies pore volume in the porous coating and thereby serves to lock the prosthesis in place. Until the 1970s, polymethyl methacrylate bone cement was the predominant means to fix a joint replacement implant to bone. This fixation is primarily mechanical. Cement penetrates the cancellous bone and locks onto small surface irregularities on the implant. In contrast, fixation by bone ingrowth has been recommended by many orthopedic researchers as a means of eliminating or alleviating several disadvantages associated with fixation by bone cement (such as premature loosening of the prosthesis, tissue reaction with the bone cement, the need to remove a substantial amount of bone to provide space for the cement mantle). However, failure of a bone tissue ingrowth fixation of cementless implants, which would lead to premature loosening of the implant, remains a matter of concern. In a metallic prosthesis comprising a porous coating extending over a nonporous substrate, such failure can occur at the substrate–porous coating interface, within the porous coating or within the patient's bone outside the coating.

A variety of different porous metallic coatings have been proposed for enhancing the fixation of a metallic prosthesis by bone ingrowth. Three types of porous metallic coatings are currently available: (1) beaded, sintered Co–Cr coatings on a Co–Cr substrate (Fig. 5.1); (2) beaded, vacuum-sintered

**Fig. 5.1** Beaded, sintered Co–Cr coating on a Co–Cr substrate is shown under magnification

titanium coatings on a titanium substrate; and (3) vacuum-sintered titanium fiber mesh pads on a titanium substrate. Three items adequately characterize these types of porous coatings: (1) the materials used and any standards to which they conform; (2) the static shear strength of the coating to the substrate (ASTM F1044); and (3) the average bead and pore size, overall pore volume, the number of bead layers, and the thickness of the coating [4].

Forms and Fabrication Techniques

The porous coatings can take various forms and require different technologies. Co–Cr porous coatings can be produced from the following: (1) Spherical metal powders made by gas atomization. The tiny spheres, or beads as they are frequently referred to in the medical field, are 175–250 μm in diameter. Porous coatings produced from spherical powders are most frequently used on cobalt–chrome implant materials. (2) Wires or fibers that are formed into porous pads [4]. Sintering involves heating the implant to about one-half or more of the melting temperature of the alloy to enable diffusion mechanisms to form necks that join the beads to one another



Fig. 5.2 Proximal beaded, sintered Co–Cr coating on a second-generation cementless Co–Cr stem

and to the surface of the implant. In the case of alloy beads, the manufacturer applies the coating material using binders over specific regions of the implant (Fig. 5.2) surface and then attaches the coating to the substrate by various high-temperature sintering stages. The porous coatings so formed (35–50 vol % porosity) are typically 500–1,000 μm thick and consist of a regular three-dimensional interconnected porous structure [5]. Tissue ingrowth into this three-dimensional porous coating results in resistance to shear, compressive, and tensile forces at the bone-implant interface (Fig. 5.3) [6].

Bond Failure of Sintered Porous Coatings

The metallurgical process for adhering the coating to the implant is a complex high-temperature process that requires a series of steps. The challenge is to provide strong bonds between each of the powder spheres (beads) and between the coating and the implant without significantly degrading the strength and corrosion resistance of the component. Proper processing prior to applying the porous coating is also critical for adequate bonding [4, 7].

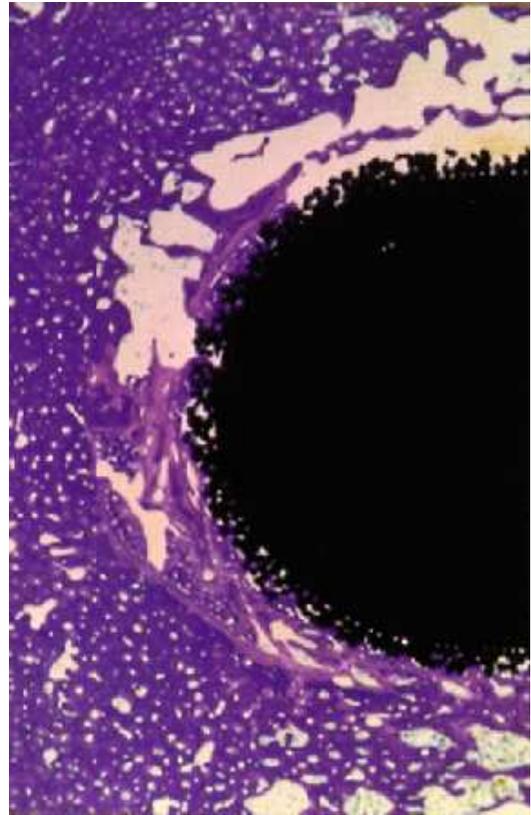


Fig. 5.3 Bone ingrowth into a beaded, sintered Co–Cr coating

Ion Implantation

Ion implantation is an approach for modifying the surface properties of materials. It is similar to a coating process, but it does not involve the addition of a layer on the surface. Ion implantation uses a highly energetic beam of ions (positively charged atoms) to modify the surface structure and the chemistry of materials at low temperature. The process does not adversely affect component dimensions or bulk material properties [4, 8]. The ion implantation process is conducted in a vacuum chamber at very low pressure (10^{-4} to 10^{-5} torr, or 0.13–0.013 Pa). Large numbers of ions (typically 10^{16} – 10^{17} ions/ cm^2) bombard and penetrate a surface interacting with the substrate atoms immediately beneath the surface. Typical depth of penetration is a fraction of a micrometer [4, 8]. Titanium and Co–Cr alloy

orthopedic prostheses for hips and knees are among the most successful commercial applications of ion implanted components for wear resistance. In use, these components articulate against an ultrahigh molecular weight polyethylene mating surface (acetabular cup). Wear reduction may be further reduced by implantation of nitrogen ions into the alloy [8].

Hydroxyapatite-Coated Co–Cr Porous-Coated Implants

Friedman et al. compared hydroxyapatite (HA)-coated titanium and HA-coated Co–Cr implants in the distal femur of a rabbit model and evaluated bone apposition and interfacial shear strength [9]. The implants were press-fit into the metaphyseal cancellous bone of the lateral femoral condyle in a transverse fashion. The mechanical strength of the interface between HA and bone was measured using the push-out method. No differences were found in the shear strength and the amount of bone apposition between the titanium and Co–Cr implants. The HA-coated Co–Cr implants performed in a similar manner to the HA-coated titanium implants, both mechanically and histologically, suggesting that HA-coated Co–Cr implants deserve further study as a viable alternative to titanium for the biological fixation of total joint components in orthopedic surgery [9].

Biocompatibility of Co–Cr Porous-Coated Implants

The use of Co–Cr–Mo in orthopedic surgery is well tolerated [10]. Nevertheless, the alloy is still considered less biocompatible than titanium [11]. A recent study explored the biocompatibility of Co–Cr–Mo by investigating the biomechanical implant fixation and implant osseointegration of Co–Cr–Mo (ASTM F-75) porous bead-coated and titanium (ASTM F-136) porous bead-coated implants in an animal model. In ten dogs, the two implant types were inserted into the proximal part of the humerus. Implant sites were over drilled, leaving an empty 0.75-mm gap between

implant and surrounding bone. The implants were observed for 6 weeks and were evaluated by the biomechanical push-out test and histomorphometry. The authors found a statistically significant 40 % decrease in the biomechanical fixation of Co–Cr–Mo porous bead-coated implants compared with titanium porous bead-coated implants that could be critical for long-term performance. Implant osseointegration was comparable between the two implants; however, a slight decrease in bone volume density around Co–Cr–Mo implants was observed [12].

Outcome of Co–Cr Porous-Coated Implants

Metal-on-metal hip bearings made of Co–Cr–Mo alloy possess excellent wear properties and are a tempting choice for young and active patients [13, 14]. Previous experience suggested that cementless cobalt alloy porous-coated femoral components can achieve durable biological fixation by bone ingrowth for active patients less than 70 years old who have no metabolic bone disease (Fig. 5.4) [15]. Engh and Bobyn have shown that circumferential coating of more than half the femoral stem results in proximal bone atrophy [16]. Other authors reported the outcome of a porous-coated Co–Cr femoral component (Tri-lock; DePuy, Warsaw, IN) with a straight collarless stem of cast Co–Cr–Mo alloy (Muller type; DePuy, Warsaw, IN). The proximal five-eighths of the stem was coated circumferentially with sintered beads of average diameter 150 μm (100–250) to form an irregular porous surface with empty spaces ranging from 150 to 400 μm . The design allowed an interference fit with the medial and lateral endosteal cortices as viewed in the frontal plane. The thin flat lateral profile gave rotational stability and three-point fixation for the stem in the curved upper femur [15]. At 5- to 8-year follow-up, good or excellent results were recorded in 70 % by the Mayo Clinic hip evaluation and in 84 % by the Harris hip score. Revision for aseptic loosening of the femoral stem was necessary in only one hip. Thigh pain diminished with time and was present in only two hips at the



Fig. 5.4 Satisfactory long-term clinical and radiological outcome of a AML stem

last follow-up. Endosteal bone formation was seen at the junction of the smooth and the porous segments of the stem in 94 % of hips; in 60 % of them it continued after 3 years. No focal endosteal bone resorption was observed. In 90 % of hips, proximal femoral atrophy did not progress after 3 years. Discontinuous radiolucent lines were seen around 30 % of stems, most commonly in zones I, IV, and VII. They were not progressive in 94 % and their presence did not correlate with the clinical outcome [15]. Recently, encouraging long-term results have been reported for cylindrical and tapered cementless cobalt–chromium stems [17–23]. Extensively porous-coated cementless implants made from Co–Cr alloys have achieved good results. The most commonly used was the anatomical medullary locking stem (AML[®], DePuy Orthopaedics, Inc., Warsaw, IN) (Fig. 5.5). Engh et al. followed up 196 of these stems implanted in patients with an average age of 55 years for 11 years and found a mechanical failure rate of only 2.6 % [17, 18]. Kronick et al. reported on 174 hips in 154 patients younger than 50 years of age using the AML[®] and Prodigy[®] (both DePuy Orthopaedics, Inc., Warsaw, IN) extensively porous-coated stems. At an average follow-up of 8.3 years, 99.4 % of the stems showed stable fixation, 96 % had bone ingrowth, 3.4 % were fibrous stable, and 1.1 % were revised. The rate of

osteolysis in the femur was 14 % and was limited to zones 1 and 7 [24]. Engh and Hopper retrospectively reviewed the outcome of 3,314 total hip arthroplasties performed with AML[®], Prodigy[®], and Solution[®] stems (all DePuy Orthopaedics, Inc., Warsaw, IN) [25]. These hips included 460 proximally coated stems and 2,854 extensively coated stems. The survival rates for proximally and extensively coated stems were >95 % at 15 years, using revision for any reason as an endpoint. Slight differences in thigh pain, stress shielding, and patient satisfaction were not significant. The 2.8 % rate of component loosening among proximally coated stems was significantly higher than the 1.1 % rate observed with extensively coated stems [25]. Kim compared proximal porous-coated stems of identical shape, but with two types of stem materials (Ti alloy or Co–Cr alloy) to determine the differences in these stems in clinical and functional outcomes, prevalence of thigh pain, stem alignment and canal fill, cup position, degree of periprosthetic bone loss, prevalence of polyethylene liner wear and osteolysis, incidence of aseptic loosening of acetabular and femoral components, and complications. The clinical and radiographic results of this study were similar (no significant differences) between the titanium and Co–Cr alloy femoral components; however, the titanium alloy femoral

Fig. 5.5 Different versions of the AML stem which was widely used in North America with satisfactory long-term results



component retained greater periprosthetic bone as compared with the Co–Cr alloy femoral component [26]. Yoon et al. reported long-term stability of the tapered fully porous-coated cobalt–chrome Autophor 900S stems (Osteo AG, Selzach, Switzerland). The survival rate of the stems at 17 years was 94.5 %. A stable stem with bone ingrowth was identified in all 120 hips, excluding femoral revision cases (seven hips). The causes of the seven femoral revisions were aseptic loosening in four, infection in two, and stem fracture in one. No surgical intervention was performed for osteolysis or stress shielding [23].

Metallic Ions Release from Co–Cr Porous-Coated Implants

Porous-coated technology has several inherent problems, one of which is the potential for the increased release of metallic ions due to more corrosion associated with the large surface area of

the porous metal. The long-term effects of hyperphysiological concentrations of metallic ions are largely unknown, but many studies have indicated that the potential for toxicity or even carcinogenicity exists [27–30]. In addition to simple corrosion, there is the release of metal debris due to wear or fretting and fretting-corrosion mechanisms. Experience with metal-on-metal articulations showed that the rate or quantity of release of metal due to wear can be far more significant than that due to corrosion [30–32]. Material released by wear or fretting is more susceptible to corrosion because the protective effect of the passive oxide film is reduced. Furthermore, corrosion is enhanced in the presence of fretting and by differences in electrochemical potential between passivated and non-passivated regions on the surface of the metal [30–33].

Metallic ions release from metallic porous-coated prostheses raises important questions as to the fixation of porous-coated hip prostheses and the mechanical integrity of the metallic porous coating.

While it has been occasionally observed that a few sintered particles become loose from a femoral prosthesis as it is impacted into the intramedullary canal, in the vast majority of patients the implant remains well fixed in the canal and no progressive loosening of particles is observed. If there is no motion at the bone-implant interface, constituents of the alloy are released primarily by corrosion (excluding wear debris from the ball-and-socket articulation). If on the other hand, the implant is not fixed or it becomes loose, cyclic motion at the bone-implant interface during loading and unloading can cause increased loosening of particles, fretting wear of particles, fretting corrosion, metallosis, and reactive changes in tissue. The metallic debris that is released in this manner resembles that observed with metal-on-metal joint replacements [30]. High local (tissue) levels of metal can develop and there may be problems related to sensitivity, inflammatory response, or systemic toxicity [31, 32]. When a cementless porous-coated femoral component is used, the stem is usually impacted with considerable force into a close-fitting channel. This may be the major cause of initial loosening of particles. Loosening of particles occurs in approximately 2 % of patients. Using sintering techniques and new methods for manufacturing textured or porous surfaces other than sintering, loosening of particles has been diminished [33]. It also seems reasonable to assume that loosening of particles would be most likely to develop after revision using a cementless porous-coated prosthesis [30].

Corrosion Behavior of Co–Cr Porous Coatings

Particle release due to sloughing of the coating is a potential concern with Co–Cr alloys. The heightened release of particles can lead to severe wear and damage of the implant, enhanced inflammatory response, and decreased stability of the fixation [30, 34]. Clinical evidence suggests that bead sloughing can be attributed to either shear stresses at initial implantation or micromotion at the porous coating-bone interface [30, 35–39]. However, it has been hypothesized that this sloughing of beads from porous coatings may be due in part to corrosion at the fusion zones in the coatings, as opposed to a solely

mechanical failure [34]. In addition, the tendency for the beads to slough may be related to the microstructure of the coating. The neck regions of the beads may have a different chemical composition from the rest of the surface due to melting and resolidification, and there are distinct compositional differences among the carbides in the fusion zones [40–43]. These local inhomogeneities can lead to preferential attack of the grain boundaries and regions of carbide precipitation as well as favoring galvanic corrosion [43]. According to Georgette and Davidson, the corrosion behavior of Co–Cr alloys depends on the microstructure [44]. A more stable, uniform oxide layer would be expected with a more homogeneous matrix (annealed alloy) than with a highly dendritic (as cast) structure [44]. Jacobs et al. stated that changes in the microstructure resulting from incipient melting of carbides during the porous coating sintering process may cause an increase in corrosion potential for porous-coated alloys as compared to conventional alloys [43]. In addition, this carbide melting may predispose these alloys to accelerated intergranular corrosion. Preferential or localized corrosion of the porous coating can lead to cracking and increase the susceptibility to failure [43]. Sintering heat treatments cause changes in the microstructure that result in changes in the corrosion behavior of the porous coatings. An *in vitro* study using SEM analysis examined the effects of microstructure on the corrosion of Co–Cr porous coatings [34]. The results showed a progressive generalized dissolution of the cobalt-rich matrix, with preferential attack of the grain boundaries and areas surrounding the carbides due to sensitization. This behavior was independent of microstructure; however, the severity of the attack was microstructure dependent. The degree and extent of sensitization is related to the alloy composition, porous coating procedures, and subsequent thermal treatments [34].

Metallic Failures of Co–Cr Porous-Coated Implants

Although metallic failure is relatively uncommon with many of the high-strength alloys currently used in implant applications, there continues to be concern about the reduced fatigue strength

associated with porous-coated Co–Cr–Mo alloys in weight-bearing applications [37, 45–52]. Failures were fatigue related; low ductility and low fatigue strength have been implicated [53, 54]. The mechanical properties of porous-coated Co–Cr implants may be compromised because of the sintering heat treatment [44, 55]. Metallurgical defects and poor microstructure, owing to suboptimal processing, have been associated with mechanical failures [45, 54, 56]. In total knee arthroplasty, many tibial tray fractures and femoral component fractures have been reported for Co–Cr–Mo alloy [37, 46–52].

Influence of Co–Cr Porous Coating on Infection

Porous-coated implants, particularly those made of Co–Cr alloys, may carry a higher risk of infection than do smooth-surfaced alternatives. An experimental study in a rabbit model showed that the Co–Cr implants were easier to infect compared to titanium [57]. The researchers implanted cylinders of Co–Cr or titanium, with smooth or porous surfaces, into rabbit bones which had been inoculated with suspensions of *Staphylococcus aureus* in various doses. Results showed that the bacterial concentration required to produce infection of porous-coated titanium implants was 2.5 times smaller than that necessary to infect implants with polished surfaces; probably, the bacteria colonize the porous surface faster than did the tissue cells. Moreover, porous-coated Co–Cr implants required bacterial concentrations that were 40 times smaller than those needed to infect implants with polished surfaces and 15 times smaller than those required to infect porous-coated titanium implants; this may reflect the better osseointegration of titanium compared to Co–Cr [57].

Titanium is one of the best materials for implantation in bone, because of its biocompatibility; once a glycoprotein film has formed on a titanium-oxide surface, osteoblasts rapidly colonize it and this may protect the surface against colonization by bacterial pathogens. Co–Cr alloy is less readily colonized by the cells of the host and is consequently colonized more easily by

bacteria [58]. Therefore, the advantages and disadvantages of an implant, such as improved osseointegration, larger ion-release surfaces, surface wear, and relative stiffness, must be weighed against the higher infection rates in the porous-coated implants, and particularly in the Co–Cr porous-coated implants [57].

Influence of Sex and Estrogens on Co–Cr Porous Coating Ingrowth

Sex hormones are an established variable in the studies of bone density and mineral metabolism [59, 60]. The sex-related differences in bone physiology may correspond to differences in bone ingrowth into the porous surface. Many total hip or knee arthroplasties have been performed in aged patients. At least some of these patients are in osteoporotic status due to menopause and/or aging. Most orthopedists would use cemented prostheses for severely osteoporotic patients based on the belief that bone ingrowth into the porous surface of a cementless prosthesis may not be achievable in these patients [61]. High-dose estrogen has been shown to stimulate the differentiation and activity of osteoblasts in vitro and increase bone formation and bone mass in animal models as well as in postmenopausal women [62–66]. Shih et al. evaluated the effects of sex and estrogen therapy on bone ingrowth into porous-coated implant in an animal model [67]. Three months after implantation, histological examination showed significantly more bone ingrowth in areas with cortical bone contact than in areas with cancellous bone contact. Bone ingrowth was essentially the same in male and female control dogs. Ovariectomized dogs showed less overall bone ingrowth than male and female controls. Bone ingrowth in areas with cortical bone contact did not decrease significantly, whereas bone ingrowth in areas with cancellous bone contact was significantly impaired in ovariectomized dogs compared with female controls. Short-term high-dose estradiol treatment did not increase bone ingrowth volume fraction. Mechanical tests did not show any statistical differences among groups [67]. The authors concluded that the type

of bone contact is the key factor affecting the amount and pattern of bone ingrowth into the porous surface and recommended extensively or full-coated porous prostheses to achieve enough cortical bone contact and ingrowth for postmenopausal patients.

Novel Techniques for Micro-structural Metal Surface Texture

Long-term success of porous-coated prostheses is often impaired by the loss of fixation between the prosthesis and bone. To overcome the potential disadvantages of porous-coated prostheses, including metal debris from porous coatings (third-body wear particles) and irregular micro-texture of metal surfaces, a recent study presented a precisely controllable porous texture technique based on material removal by the yttrium–aluminum–garnet (YAG) laser for controlling application of micro-structural metal surface texture (tartan check shape) [68]. Using this technique, free shapes can be applied to complex, three-dimensional hard metal surfaces such as Co–Cr. In this study, tartan check shapes made by crossing grooves and dot shapes made by forming holes were produced on titanium (Ti6Al4V) or cobalt–chrome (Co–Cr) and evaluated with computer-assisted histological analysis and the measurement of bone–metal interface shear strength. The width of grooves or holes ranged from 100 to 800 μm (100, 200, 500, and 800 μm), with a depth of 500 μm . Results showed superior osteoconduction (especially in the 500- μm grooves) with the tartan check shape compared to commercial porous coating and superior shear strength between the bone and implant interface. Additionally, titanium provided faster osteoconduction than cobalt–chrome in tartan check shape samples [68].

References

1. ARCAM.ASTM F75 CoCr Alloy. Arcam EB system. Available at: <http://www.arcam.com/CommonResources/Files/www.arcam.com/Documents/EBM%20Materials/Arcam-ASTM-F75-Cobalt-Chrome.pdf>. Accessed on March 1, 2012.

2. Browne M, Gregson PJ. Metal ion release from wear particles produced by Ti-6Al4V and Co-Cr alloy surfaces articulating against bone. *Mater Lett.* 1995; 24:1–6.
3. Nouri A, Hodgson PD, Wen CE. In: Biomimetic porous titanium scaffolds for orthopedic and dental applications, Mukherjee A. (Ed). *Biomimetics, Learning from Nature*, chapter 21, InTech Open Access Publisher, 2010:415-50
4. ASM International. Coatings. In: Davis JR, editor. *Handbook of materials for medical devices*. 03rd ed. Materials Park: ASM International; 2003. p. 179–95.
5. Pilliar RM. Porous biomaterials. In: Williams D, editor. *Concise encyclopedia of medical & dental materials*. Oxford/New York/Cambridge, MA: Pergamon Press and The MIT Press; 1990. p. 312–9.
6. Bobynd JD, Cameron HU, Abdulla D, Pilliar RM, Weatherly GC. Biologic fixation and bone modeling with an unconstrained canine total knee prosthesis. *Clin Orthop.* 1982;166:301–12.
7. Lisin M, Peterson RR. Failure of the bond between a cobalt alloy prosthetic casting and a sintered porous coating. In: Esaklul KA, editor. *Handbook of case histories in failure analysis*. 1st ed. Materials Park: ASM International; 1992. p. 449–51.
8. Hirvonen JK, Sartwell BD. Ion implantation. In: *Surface engineering, ASM handbook*. 5th ed. Materials Park: ASM International; 1994. p. 604–10.
9. Friedman RJ, Bauer TW, Garg K, Jiang M, An YH, Draughn RA. Histological and mechanical comparison of hydroxyapatite-coated cobalt-chrome and titanium implants in the rabbit femur. *J Appl Biomater.* 1995;6(4):231–5.
10. Jakobsen SS, Larsen A, Stoltenberg M, Bruun JM, Soballe K. Effects of as-cast and wrought cobalt-chrome-molybdenum and titanium-aluminum-vanadium alloys on cytokine gene expression and protein secretion in J774A.1 macrophages. *Eur Cell Mater.* 2007;14:45–54.
11. Baldwin L, Hunt JA. Host inflammatory response to NiCr, CoCr, and Ti in a soft tissue implantation model. *J Biomed Mater Res A.* 2006;79:574–81.
12. Jakobsen SS, Baas J, Jakobsen T, Soballe K. Biomechanical implant fixation of CoCrMo coating inferior to titanium coating in a canine implant model. *J Biomed Mater Res A.* 2010;94(1):180–6.
13. Firkins PJ, Tipper JL, Saadatzadeh MR, Ingham E, Stone MH, Farrar R, Fisher J. Quantitative analysis of wear and wear debris from metal-on-metal hip prostheses tested in a physiological hip joint simulator. *Biomed Mater Eng.* 2001;11:143–57.
14. Rieker C, Kottig P. In vivo tribological performance of 231 metal-on-metal hip articulations. *Hip Int.* 2002;12: 73–6.
15. Pellegrini Jr VD, Hughes SS, Evarts CM. A collarless cobalt-chrome femoral component in uncemented total hip arthroplasty. Five- to eight-year follow-up. *J Bone Joint Surg Br.* 1992;74B:814–21.
16. Engh CA, Bobynd JD. The influence of stem size and extent of porous coating on femoral bone resorption

- after primary cementless hip arthroplasty. *Clin Orthop.* 1998;231:7–28.
17. Sotereanos NG, Engh CA, Glassman AH, Macalino GE, Engh Jr CA. Cementless femoral components should be made from cobalt chrome. *Clin Orthop.* 1995;313:146–53.
 18. Engh Jr CA, Culpepper 2nd WJ, Engh CA. Long-term results of use of the anatomic medullary locking prosthesis in total hip arthroplasty. *J Bone Joint Surg Am.* 1997;79A:177–84.
 19. Grant P, Grøgaard B, Nordsletten L. Ultralok uncemented femoral prostheses: 12 to 15 year follow-up evaluation. *J Arthroplasty.* 2004;19(3):274–80.
 20. Mallory TH, Lombardi Jr AV, Leith JR, Fujita H, Hartman JF, Capps SG, Kefauver CA, Adams JB, Vorys GC. Minimal 10-year results of a tapered cementless femoral component in total hip arthroplasty. *J Arthroplasty.* 2001;16(8 S1):49–54.
 21. Parvizi J, Keisu KS, Hozack WJ, Sharkey PF, Rothman RH. Primary total hip arthroplasty with an uncemented femoral component: a long-term study of the Taperloc stem. *J Arthroplasty.* 2004;19(2):151–6.
 22. Teloken MA, Bissett G, Hozack WJ, Sharkey PF, Rothman RH. Ten to fifteen-year follow-up after total hip arthroplasty with a tapered cobalt-chromium femoral component (tri-lock) inserted without cement. *J Bone Joint Surg Am.* 2002;84A:2140–4.
 23. Yoon TR, Rowe SM, Kim MS, Cho SG, Seon JK. Fifteen- to 20-year results of uncemented tapered fully porous-coated cobalt-chrome stems. *Int Orthop.* 2008;32(3):317–23.
 24. Kronick JL, Barba ML, Paprosky WG. Extensively coated femoral components in young patients. *Clin Orthop.* 1997;344:263–74.
 25. Engh CA, Hopper Jr RH. The odyssey of porous-coated fixation. *J Arthroplasty.* 2002;17(4 S1):102–7.
 26. Kim YH. Titanium and cobalt-chrome cementless femoral stems of identical shape produce equal results. *Clin Orthop.* 2004;427:148–56.
 27. Heath JC, Freeman MA, Swanson SA. Carcinogenic properties of wear particles from prostheses made in cobalt-chromium alloy. *Lancet.* 1971;1(7699):564–6.
 28. Sunderman Jr FW. Metal carcinogenesis in experimental animals. *Food Cosmet Toxicol.* 1971;9(1):105–20.
 29. Woodman JL, Black J, Jimenez SA. Isolation of serum protein organometallic corrosion products from 316LSS and HS-21 in vitro and in vivo. *J Biomed Mater Res.* 1984;18(1):99–114.
 30. Buchert PK, Vaughn BK, Mallory TH, Engh CA, Boby JD. Excessive metal release due to loosening and fretting of sintered particles on porous-coated hip prostheses. Report of two cases. *J Bone Joint Surg Am.* 1986;68A:606–9.
 31. Evans EM, Freeman MA, Miller AJ, Vernon-Roberts B. Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement. *J Bone Joint Surg Br.* 1974;56B:626–42.
 32. Dobbs HS, Minski MJ. Metal ion release after total hip replacement. *Biomaterials.* 1980;1(4):193–8.
 33. Cohen J, Lindenbaum B. Fretting corrosion in orthopedic implants. *Clin Orthop.* 1968;61:167–75.
 34. Placko HE, Brown SA, Payer JH. Effects of microstructure on the corrosion behavior of CoCr porous coatings on orthopedic implants. *J Biomed Mater Res.* 1998;39(2):292–9.
 35. Hamblen DL, Paul JP. The integrity of porous coatings for cementless implants. *J Bone Joint Surg Br.* 1988;70B:521–3.
 36. Callaghan JJ, Dysart SH, Savory CG. The uncemented porous-coated anatomic total hip prosthesis. Two-year results of a prospective consecutive series. *J Bone Joint Surg Am.* 1988;70A:337–46.
 37. Morrey BF, Chao EY. Fracture of the porous-coated metal tray of a biologically fixed knee prosthesis. Report of a case. *Clin Orthop.* 1988;228:182–9.
 38. Davey JR, Harris WH. Loosening of cobalt chrome beads from a porous-coated acetabular component. A report of ten cases. *Clin Orthop.* 1988;231:97–102.
 39. Cameron HU. Six-year results with a microporous-coated metal hip prosthesis. *Clin Orthop.* 1986;208:81–3.
 40. Clemow AJ, Daniell BL. Solution treatment behavior of Co-Cr-Mo alloy. *J Biomed Mater Res.* 1979;13(2):265–79.
 41. Kilner T, Pilliar RM, Weatherly GC, Allibert C. Phase identification and incipient melting in a cast Co-Cr surgical implant alloy. *J Biomed Mater Res.* 1982;16(1):63–79.
 42. Pilliar RM. Powder metal-made orthopedic implants with porous surface for fixation by tissue ingrowth. *Clin Orthop.* 1983;176:42–51.
 43. Jacobs JJ, Latanision RM, Rose RM, Veeck SJ. The effect of porous coating processing on the corrosion behavior of cast Co-Cr-Mo surgical implant alloys. *J Orthop Res.* 1990;8(6):874–82.
 44. Georgette FS, Davidson JA. The effect of HIPing on the fatigue and tensile strength of a case, porous-coated Co-Cr-Mo alloy. *J Biomed Mater Res.* 1986;20(8):1229–48.
 45. Kohn DH, Duchyene P, Cuckler JM, et al. Fractographic analysis of failed porous and surface-coated cobalt-chromium alloy total joint replacements. *Med Prog Technol.* 1994;20:169.
 46. Ranawit CS, Johanson NA, Rimnac CM, et al. Retrieval analysis of porous-coated components of total knee arthroplasty. *Clin Orthop.* 1986;209:244.
 47. Scott RD, Ewald FC, Walker PS. Fracture of the metallic tibial tray following total knee replacement. *J Bone Joint Surg Am.* 1984;66A:780.
 48. Flivik G, Ljung P, Rydholm U. Fracture of the tibial tray of the PCA knee. *Acta Orthop Scand.* 1990;61:26.
 49. Huang CH, Yang CY, Cheng CK. Fracture of the femoral component associated with polyethylene wear and osteolysis after total knee arthroplasty. *J Arthroplasty.* 1999;14:375.
 50. Wada M, Imura S, Bo A, et al. Stress fracture of the femoral component in total knee replacement: a report of 3 cases. *Int Orthop.* 1997;21:54.

51. Whiteside LA, Fosco DR, Brooks JG. Fracture of the femoral component in cementless total knee arthroplasty. *Clin Orthop*. 1993;286:71.
52. Swarts E, Miller SJ, Keogh CV, Lim G, Beaver RJ. Fractured Whiteside Ortholoc II knee components. *J Arthroplasty*. 2001;16(7):927–34.
53. Ducheyne P, De Meester P, Aernoudt E. Fatigue fractures of the femoral component of Charnley and Charnley-Muller type total hip prostheses. *J Biomed Mater Res*. 1975;6:199.
54. Galante JO, Rostoker W, Doyle JM. Failed femoral stems in total hip prostheses. *J Bone Joint Surg Am*. 1975;57A:230.
55. Pilliar RM. Porous-surfaced metallic implants for orthopaedic applications. *J Biomed Mater Res*. 1987; 21:1.
56. Rostoker W, Chao EYS, Galante JO. Defects in failed stems of hip prostheses. *J Biomed Mater Res*. 1978; 12:635.
57. Cordero J, Munuera L, Folgueira MD. Influence of metal implants on infection. An experimental study in rabbits. *J Bone Joint Surg Br*. 1994;76B:717–20.
58. Gristina AG, Naylor PT, Myrvik QN. Mechanisms of musculoskeletal sepsis. *Orthop Clin North Am*. 1991; 22:363–71.
59. Compston JE. Sex steroids and bone. *Physiol Rev*. 2001;81:419–77.
60. Raisz LG, Wiita B, Artis A, et al. Comparison of the effect of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. *J Clin Endocrinol Metab*. 1996;81:3743.
61. Harris WH, Davies JP. Modern use of modern cement for total hip replacement. *Orthop Clin North Am*. 1988;19: 581–9.
62. Ernst M, Schmid C, Froesch ER. Enhanced osteoblastic proliferation and collagen gene expression by estradiol. *Proc Natl Acad Sci U S A*. 1988;85: 2307–20.
63. Tobias JH, Compston JE. Does estrogen stimulate osteoblasts function in postmenopausal women? *Bone*. 1999;24:121–4.
64. Edwards MW, Bain SD, Bailey MC, et al. 17 p-estradiol stimulation of endosteal bone formation in the ovariectomized mouse: an animal model for the evaluation of bone-targeted estrogens. *Bone*. 1992;13: 29–34.
65. Bord S, Beavan S, Ireland D, et al. Mechanisms by which high-dose estrogen therapy produces anabolic skeletal effects in postmenopausal women: role of locally produced growth factor. *Bone*. 2001;29: 216–22.
66. Khastgir G, Studd J, Holland N, et al. Anabolic effect of long-term estrogen replacement on bone collagen in elderly postmenopausal women with osteoporosis. *Osteop Int*. 2001;12:465–70.
67. Shih LY, Shih HN, Chen TH. The effects of sex and estrogen therapy on bone ingrowth into porous coated implant. *J Orthop Res*. 2003;21(6):1033–40.
68. Hirao M, Sugamoto K, Tamai N, Oka K, Yoshikawa H, Mori Y, Sasaki T. Macro-structural effect of metal surfaces treated using computer-assisted yttrium-aluminum-garnet laser scanning on bone-implant fixation. *J Biomed Mater Res A*. 2005;73(2):213–22.

Titanium Porous-Coated Implant-Bone Interface in Total Joint Arthroplasty

Emilios E. Pakos and Theodoros Xenakis

Introduction

Cementless fixation has been a principal method for fixation of orthopedic implants for decades. Accordingly, different rough and porous surfaces have been developed and applied in clinical use. A variety of these coatings are continuously investigated in order to improve bone–implant integration and enhance osteogenesis at the implant surface. One of the most important elements used in joint arthroplasty is titanium.

History

Titanium is the fourth most common abundant structural metal on earth after iron, aluminum, and magnesium. It does not occur as a pure metal in nature, and it forms compounds with other chemical elements. The most common mineral sources are ilmenite (FeTiO_3) and rutile (TiO_2), which are widely distributed in the Earth's crust and lithosphere. Titanium was discovered in 1791 by the English clergyman and mineralogist Reverend William Gregor in the village of Manaccan, England. Gregor accidentally discovered a black sand that contained a previous unknown metal and named the metal

as manaccanite after the place of the discovery. He reported his findings to the Royal Geological Society of Cornwall and in the German science journal Crell's *Annalen* [1]. A few years later in 1795 the German Martin Heinrich Klaproth also discovered the same metal in rutile from Hungary and named it as titanium after the Titans of Greek mythology. Initially unaware of Gregor's discovery, when he heard about it he compared manaccanite with his discovery and found that they had discovered the same metal. Gregor was eventually credited the discovery of the metal, though the name of titanium was the one that was used all over the years.

Throughout the years several attempts were made to isolate titanium from its ores. However, this was firstly achieved in the twentieth century with a process developed by Kroll in Luxemburg [2, 3]. This process named as Kroll process involved the reduction of titanium tetrachloride with magnesium and remains the dominant process for titanium production till today.

Titanium Properties

The material properties are of crucial importance not only for the formation of bone around the inserted implant but for the maintenance of this bone as well. The main physical properties of titanium are the high corrosion resistance and the highest strength-to-weight ratio. It is a strong metal with low density that is quite ductile (especially in an oxygen-free environment), lustrous,

E.E. Pakos • T. Xenakis (✉)
Laboratory of Orthopaedics and Biomechanics,
School of Medicine, University of Ioannina,
Ioannina 45110, Greece
e-mail: xebiolab@cc.uoi.gr

and metallic white in color [4]. The relatively high melting point (more than 1,650 °C or 3,000 °F) makes it useful as a refractory metal. It is paramagnetic and has fairly low electrical and thermal conductivity [4, 5].

One of the most substantial properties of titanium is osseointegration. This phenomenon refers to the formation of a direct interface between an implant and bone, without intervening soft tissue due to the migration of osteoblasts and connective tissue into the pores. The Swedish bioengineer Per-Ingvar Brånemark in 1952 [6] was the first one who used the term “osseointegration” to describe the direct structural and functional connection between living bone and the surface of an implant. Brånemark realized that after implanting titanium cylinders into the femurs of rabbits, he could not extract the titanium without destroying the surrounding bone. The discovery that bone will integrate with titanium components, not rejecting the element as it does with other materials, was the beginning of the study of osseointegration. Due to these properties, titanium materials (both unalloyed and alloyed) have become important materials initially in the aerospace industry in the 1950s and currently not only in industrial applications, but in dental and medical fields as well. Commercially there are four different grades of pure titanium used in clinical practice, but also various alloys. In pure titanium, the concentration of oxygen and iron is gradually increasing in the four different grades, with a consequent change in alloy strength (ultimate tensile strength to failure) ranging from 250 MPa in grade 1 to 680 in grade 4B. Titanium alloys may be classified as either α , near- α , $\alpha+\beta$, metastable β , or stable β depending upon their room temperature microstructure [7, 8]. Based on this classification, alloying elements for titanium fall into three categories: α -stabilizers, such as Al, O, N, and C; β -stabilizers, such as Mo, V, Nb, Ta (isomorphous), Fe, W, Cr, Si, Ni, Co, Mn, and H (eutectoid); and neutral, such as Zr [9]. The most common titanium alloy used from the beginning in orthopedic implants is Ti-6Al-4V. This was further developed over the next years and new alloys such as Ti-6Al-7Nb. The permanent application of these alloys has been suggested that may be toxic for the tissues, due to the release

of vanadium and aluminum. Therefore, newer implants known as beta titanium alloys that are free of these elements were developed [10, 11]. This new generation of alloys exhibits superior mechanical properties such as lower elasticity, but with adequate strength.

Coating Methods and Types of Titanium Coatings

The biological behavior of a material is influenced to a great extent by its surface properties. The coating of an implant aims to improve implant performance regarding implant fixation, wear, and corrosion, given that it is affecting bone tissue remodeling. Biocompatibility and mechanical stability of the implant are the main factors associated with a successful implantation of an implant in joint arthroplasty. The preparation of titanium surface involves various mechanical, thermal, chemical, electrochemical, and vacuum-based treatments either alone or in combinations [12–17]. At a second stage, the process utilizes the deposition or the addition of foreign materials characterized by the presence of pores to promote the apposition of bone on the implant surface. The pore size seems to play a substantial role for bone ingrowth into the pores [18]. The minimum pore size that is required for weight-bearing implants such as hip and knee prostheses should be approximately 100–150 μm , while most orthopedic implants have coatings with pores measuring from 100 to 400 μm [19]. Several methods have been reported to add bioactivity to titanium implants [20]. Different processes vary in complexity of preparation and also in the type of porous material that they produce. Plasma spraying is the most popular technique widely applied since nowadays, that produces highly porous surfaces with open and interconnected pores, which can vastly improve bone ingrowth characteristics [17, 18, 21, 22]. Moreover, with the plasma spraying method, the compressive modulus of the porous substrate can be produced to match that of cancellous bone, in order to eliminate the problems resulting from stress shielding [18, 23]. Alternative methods include the immersion of titanium into simulated body fluids (SBF) [24], chemical methods [25], laser methods [26], and

sputtering methods [27]. Several types of coatings have been applied to titanium surfaces. Among the large variety of titanium coatings, calcium phosphates mainly hydroxyapatite [28], titanium oxide [29] and nitride [30], zirconium oxide [31], and diamond-like carbon coatings [32] have been used in orthopedic implants. Hydroxyapatite displayed the most promising results and has been extensively studied for over than 20 years. The biological advantages of HA are the enhancement of bone formation, the accelerated bonding between the implant surface and surrounding tissues, and the reduction of potentially harmful metallic ion release [33, 34].

Animal Studies

The period around 1970 was an exceptionally productive period regarding the fabrication and use of porous-coated titanium for orthopedic implants. Hirschhorn et al. in 1971 were the first who described the fabrication and testing of commercially pure (CP) porous titanium as an implant material [35]. They turned from cobalt–chromium alloy to titanium, because of the lower density and modulus of elasticity of the latter. Two years earlier, Lueck et al reported the fabrication and implantation of a porous CP titanium fiber composite material [36]. They proposed the use of fiber–metal composites, which combine strength with porosity, are not brittle, and have a large range of elastic strain, and tear, in contrary to the porous metallic materials fabricated by powder metallurgy techniques that exhibit poor strength characteristics when the degree of porosity is sufficient to permit bone ingrowth [36, 37]. At the same period, Galante et al. [38] and Lambert et al. [39] proposed the use of fiber–titanium composites as a method of fixation of prosthetic implants. Through studies that were conducted in rabbits and dogs, they suggest the use of fiber–metal composites in the form of a thin sleeve surrounding and bonded to a central solid metal core that could provide fixation to bone and uniform stress distribution at the implant-bone interface [38]. Finally, the same period Hahn et al reported favorable outcomes of plasma-sprayed porous titanium hydride coating [40].

In the following years, the main investigations were directed towards the understanding of structural, morphological, and mechanical properties of different types of coatings in titanium porous-coated implants and the comparison of different coating types and the clarification of parameters that play important role in order to establish a successful implantation and an adequate bone ingrowth for implant survival. Turner et al aimed to compare ingrowth of bone into three types of porous-coated titanium prostheses, and to determine the effect of the type of porous coating and the degree of coverage of the stem on the remodeling of bone on the femoral side in cementless canine total hip arthroplasty [41]. Four types of Ti porous-coated femoral prostheses were used: sintered fiber–metal prostheses, prostheses with sintered beads, prostheses with plasma flame spray coating, and femoral components circumferentially coated with plasma-sprayed commercially pure titanium. No significant difference in ingrowth of bone was observed at 1 month, whereas at 6 months there was significantly less ingrowth into the beaded surface than into the fiber–metal surface. In all groups, a proximal-to-distal gradient of loss of cortical bone was observed by 6 months, and the magnitude of bone loss was dependent on the extent (severe loss in circumferential coating) rather than on type of coating. Drastic thinning of the anterior part of the cortex surrounding the titanium fiber–metal-coated intramedullary part of a canine prosthetic replacement of the proximal end of the femur also has been reported [42]. An increase in intracortical porosity throughout the proximal end of the femur and a decrease in the average width of the cortical bone compared with the contralateral femur, which was not operated on, were observed in a canine total hip replacement model of fixation with a femoral component that was coated with titanium fiber metal [43].

During the last 20 years, the vast majority of experimental studies were directed towards hydroxyapatite coatings in titanium implants. The results of these studies have suggested that the coating of hydroxyapatite applied to titanium porous-coated prostheses might have desirable properties for weight-bearing orthopedic implants. Thomas KA et al. in 1987 showed that hydroxyapatite-

coated implants exhibited significantly greater values of maximum interface shear strength and stiffness than the uncoated implants after all time periods [44]. Histologically, all areas coated with the hydroxyapatite material were covered with an osteoid layer after 3 weeks, which was mineralized after 10 weeks. In all cases, longer-term implants demonstrated mineralization of interface bone directly onto the hydroxyapatite coating, and in no case was a fibrous layer observed between the coating and the interface bone. Similar results in animal studies were reported by Cook et al. [45–47], Søballe K et al. [48], Maistrelli GL et al. [49], and Karabatsos et al. [50] in later periods. The benefits of hydroxyapatite coating based on the animal studies include accelerated response of bone to the implant, increased interfacial strength, enhanced filling of the gap, and the lack of a fibrous tissue membrane development. Limited animal studies reported on the effectiveness of hydroxyapatite titanium porous-coated acetabular implants. These results demonstrated that hydroxyapatite porous-coated acetabular components significantly enhanced bone ingrowth in the presence of wear particles, preventing their migration and reducing osteolysis [51]. Different hydroxyapatite coating methods have also been examined in order to improve ingrowth of bone onto the implant surface and increase of mechanical anchoring strength to bone such as surface-induced mineralization techniques [52] or arc-sprayed techniques [53]. Finally, recent experimental studies in animals have been focalized on the enhancement of fixation of titanium porous-coated implants with the use of local bisphosphonate treatment [54, 55], growth factors [56], and bone morphogenetic proteins [57], with encouraging results.

Despite the large amount of experimental studies regarding titanium porous-coated implants in orthopedic surgery, several processes involving the material-bone interface stages are not well understood. The response to titanium implantation seems to be similar to other materials and involves the formation of hematoma, the adhesion of inflammatory cells, the persistence of multinuclear cells, the bone formation, and finally the bone remodeling.

Human Studies

Since the idea of bone ingrowth around synthetic materials was generated in 1909 [58] and since the first experimental application of porous materials 40 years later, it was only in 1970 where the application of porous surface in titanium was described [40, 59]. The introduction and acceptance of titanium as implant was facilitated by reports of poor adaptation and increased erosion over time with the implants used to that point, line stainless steel. The exceptional material compatibility with the human organism as well as the decreased elasticity and density of titanium made it an excellent choice as implant material. Implants inserted in the human body are causing various tissue responses mainly involving the bone tissue around the implant [60]. This reaction to the bone-implant interface is related basically to the material properties and the architecture design of the implant [61]. Implants that are corroded are reported having a severe tissue response compared to those being stable. The most common material used alloys are cobalt–chromium and titanium alloy metals. Titanium seems to minimize the stress shielding in comparison with the stiffer cobalt–chromium alloy implants by having a lower modulus of elasticity and better biocompatibility [62]. Even from the early experience of titanium implants, it was suggested that the tissue response to the implant was not confined to the osseous tissue, but it was expanded to the non-osseous surrounding tissue [61]. Comparing titanium with other metals used in the past as implants, like steel and cobalt, titanium demonstrated lower modulus of elasticity and reduced incidence of stem fracture with no incidence of abnormal wear in the joints [60].

There are several factors that are affecting bone fixation: micromotion of the bone-implant interface, poor biocompatibility, and inadequate contact. Taking into consideration the fact that bone ingrowth does not occur when the distance of the bone is more than 50 μm and that the rate of bone advanced apposition is approximately 1 $\mu\text{m}/\text{day}$, it is easy to realize the precision needed during the operation [63]. In several cases the most common response



Fig. 6.1 Bone ingrowth within the porous-coated surface of a titanium femoral component

finding at the site of the implantation was initially the formation of slender trabeculae of intramembranous bone at the bone-implant interface [64]. The bone ingrowth within the porous coating and the adjacent bone formed a continuum usually at 1 month after the operation, meaning that the femoral component exhibited certain degree of stability relatively early after the implantation that promoted early rehabilitation of these patients [64]. In order for the implant to achieve its initial bone ingrowth, it usually takes up to 3–6 months, while during the next period of the next 1 or 2 years bone ingrowth is progressing appositionally towards the porous coating depth (Fig. 6.1).

Total Hip Arthroplasty

Femoral Component

The use of orthopedic implants from titanium and its alloys started in the United Kingdom in 1970s. At that time, the problems encountered with the use of cobalt–chromium prostheses, mainly their early fatigue and failure as well as atrophy and reaction of the surrounding bone, facilitated the search for a new material with improved structural properties. The first used alloy was the Ti-6Al4V, which apart of the excellent biocompatibility demonstrated significant strength and fatigue resistance [65]. The replacement of vanadium by iron formed the Ti-5Al-2.5Fe that was used for implants that they were able to bend. The biocompatibility of the titanium is related etiologically to its ability to cause chemisorption of superoxide due to its effective passivation. Passivation is the process of forming a titanium oxide at the surface of the implant when titanium or its alloys are exposed to the body tissue [65, 66].

Nowadays, there are two widely accepted methods of implant fixation, cemented and uncemented. The cemented fixation provides a static result, meaning that it does not allow remodeling of microfractures that can occur at the interface of bone implant [67, 68]. On the other hand, cementless fixation has the advantage to be biological that allows bone ingrowth to the implant surface [67, 68]. However, the use of cemented implants was proven problematic especially in young patients where there was observed a high number of loosening cases [69]. Cementless arthroplasty proved to be a feasible alternative to cemented implantation for total hip replacement. The aseptic loosening as well as the difficulties in stem revision when cement was used was bypassed by the use of cementless arthroplasty [70, 71]. The first results of the use of uncemented fixation were discouraging with patients suffering from thigh pain, aseptic loosening, and proximal osteolysis [72, 73].

Over time, the design of the femoral component was continually changing in order to address problems reported and to improve the features of the fixation. It was suggested that the osteolysis

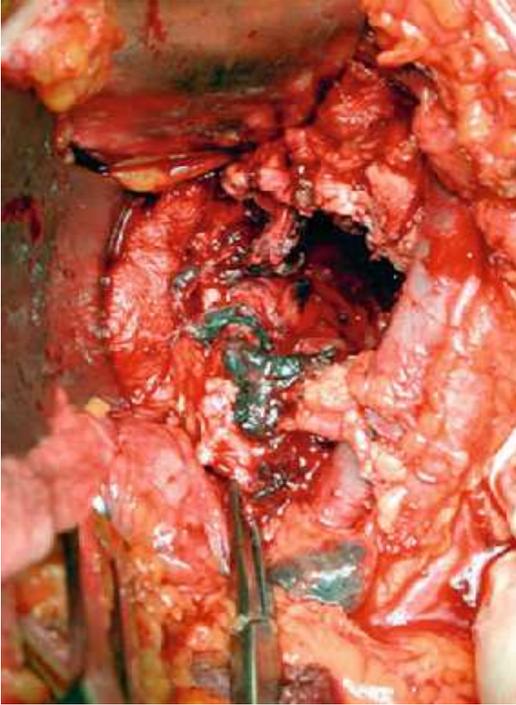


Fig. 6.2 Black deposits in the periprosthetic tissue from the wear of a titanium porous-coated THA implant

found in several cases was related to the stem design that involved stress-shielding effect at the component [74]. The results of THA using titanium alloys continued to be very good at an intermediate follow-up period. This is probably the result of the excellent adaptation performed at the bone-implant interface [75]. One problem noted with the use of titanium, is the extensive osteolysis and polyethylene wear, when metal on polyethylene articulation was the configuration used. These considerations led to the development and study of designs as ceramic-on-ceramic, metal-on-metal, and crossed-linked polyethylene. The behavior of Ti-6Al-4V when used against polyethylene in a cemented prosthesis was catastrophic. Early reports suggested the presence of black deposits and significant wear of the polyethylene and titanium damage when titanium alloys were used as a bearing surface (Fig. 6.2). Thus, the use of a ball head from CoCrMo or Al₂O₃ that could be the bearing surface replacing titanium in this area was proposed [76].

The introduction of porous-coated implants that was localized only to the proximal part of the femoral stem improved significantly the outcome (Fig. 6.3). Midterm results of porous-coated femoral stems showed minor loosening, and subsequently very few revisions were performed [75]. Although the coating should be limited to the proximal portion of the stem, at the same time it must be extended enough in order to provide adequate support and resistance to the load sustained. This is crucial especially in young and active patients [77]. The use of a plasma-sprayed porous-coated titanium alloy femoral stem showed very good results even at 10 years after primary arthroplasty, with minor loosening and revision rates reported [78].

The development of hydroxyapatite-coated implant improved the survival of the implants in clinical setting due to the proposed extremely strong bond to the host bone (Fig. 6.4). Remarkable bone apposition around the component with more rigid fixation and at the same time its ability to allow gradual replacement of the coating with living bone at an acceptable rate are the proposed advantages of the hydroxyapatite. Questions have risen from the potential strength of the bonding at the bone-implant interface and the brittleness of the material [79]. Gradually, new bone grows into the prosthesis at a rate comparable to the healing rate of a fracture [79]. Randomized trials proved the superiority of the hydroxyapatite-tricalcium phosphate-coated stems confirming that they had significantly less femoral bone loss [80, 81]. Primary reports suggested that the addition of hydroxyapatite coating dramatically improved the relatively poor results of earlier cementless press-fit stems facilitating initial and long-lasting mechanical stability [82] and led to a more rapid clinical improvement after THA [83]. However, these findings were not confirmed in several randomized controlled studies that showed comparable outcome with and without the use of hydroxyapatite coating [84, 85] with a survival rate being 100 % for the stem and 89 % for the cup after 16 years regardless the use of hydroxyapatite coating or not [85].

There are two different ways of hydroxyapatite coatings, plasma sprayed and electrochemically deposited (EDHA). Although plasma sprayed



Fig. 6.3 Pre- and postoperative x-ray of a cementless THA with the use of a proximally porous-coated titanium femoral stem (Synergy stem, Smith & Nephew)

exhibits good results regarding prosthesis survival, the EDHA allows various biological substances like antibiotics or adhesives without considerable increase in implant thickness. Both groups showed similar clinical results and no difference in stem migration. However, there is evidence of less bone resorption in zone Gruen 1 with EDHA [86]. Despite the fact that titanium implants coated with hydroxyapatite have shown a survival rate of nearly 98 % in 10 years, other metals may exhibit an enhanced antimicrobial activity and a favored response to osteoprotegerin/receptor activator of nuclear factor K ligand (RANKL) ratio in cellular level studies [87]. However, the addition of other metals to hydroxyapatite coating needs to demonstrate its potential effect in clinical trials. Alterations in taper design have showed comparable results to cemented implants, in patients younger than 75 years old with funnel-shaped proximal femoral

medullary canals [88]. Other advances in femoral stem design aimed to reduce stress shielding and proximal bone loss [89], with the use of circumferential porous-coated design and the use of titanium, which is more biocompatible being the most important [77, 90]. Further studies provided adequate data in order to improve anatomic orientation of the hip joint and more completely seal the proximal femoral canal to reduce particle-related osteolysis [91–94]. Advances in our knowledge about biological reaction and the confirmation of the pathogenetic mechanism of wear in total hip replacement by the acceptance of stem migration within the effective joint space have also led to improvements in implant design [92]. New implant designs with extensive porous titanium fiber–metal fixation surface, a mixture of CoCrMo in the core, and a layer from polymer have found to achieve stable fixation and reduced stress shielding at 10 year follow-up



Fig. 6.4 Custom-made cementless THA with a titanium porous-coated femoral implant covered with hydroxyapatite at the proximal part (pre- and postoperative x-ray)

[95]. In this level I therapeutic study, the 10-year survival of the implant was 100 %, with cortical bone apposition along the distal stem that was judged complete in 92 % of the cases. No revision was performed, and there was no radiographic evidence of loosening or failure [95]. The adaption of a circumferential coating was found to have favored outcome and decreased the possibility of osteolysis and loosening possibly due to its ability to prevent the access and migration of particles wear [75]. Recently, long-term survival of titanium porous plasma-sprayed femoral implants was found to be extremely high [96]. Specifically, the cumulative survival was 98.6 % at 5 years, 98.4 % at 10 years, 97.1 % at 15 years, and 95.5 % at 20 years when any stem revision was used as the end point [96]. Interestingly, this outcome was not influenced by factors such as

age or femoral anatomy or pathology, and it could be used with similar results in older patients or patients suffering from osteoporosis [96]. When aseptic revision for failure of ingrowth was determined as the end point, then stem survival was reported to be as high as 99 % [96]. In an attempt to produce a hip replacement system that could reduce stress shielding and minimize other complications such as thigh pain, systems like Buechel–Pappas THA have developed [97]. Its improvements include a 30°-angled loading collar without porous coating at the medial part of the proximal component and a thin-film ceramic surface coating. The clinical and radiographic evaluation demonstrated very good survival of these prostheses [97]. A recent study evaluating osseointegration in stem revision with actual radiographic signs has shown that although

reduced, there is still an increased incidence of stress shielding due to the higher stiffness that the stem demonstrates beyond 18 mm of diameter [98]. A new design that combines cementless, metal-backed alumina bearings showed promising early clinical and radiographic results with regard to wear-related problems [99].

Acetabulum

Titanium implants of acetabular component of the hip joint replacement were compared with the recently developed tantalum cups for revision surgery. Early findings suggest that bone deficiency can determine the implant of choice. Tantalum exhibited better results with fewer failures in major deficiency grades. In cases where there was no bone deficiency both titanium and tantalum implants demonstrated comparable outcome [100]. In the condition of acetabular bone defects in total hip replacement, the use of cemented polyethylene cup together with impaction of allograft bone has considered for years a successful technique. On the contrary, the usage of uncemented cup stabilized with screws has proven unsafe and problematic. There are promising results with the use of press-fit tri-spike cup, which is composed of a porous surface from titanium alloy that allows secure fixation without the use of screws. Recently, there are reports that favored the use of a porous acetabular component which may allow a greater number of surgical options for reconstruction [101, 102]. The survivorship for the tri-spike acetabular component was 100 % for cup loosening/revision and 97.8 % for radiolucency at 9 years follow-up [102]. The presence of osteoporotic bone may impair the bone ingrowth in prostheses that are inserted using uncemented technique. Therefore it is common to use cement for these patients. However, titanium alloy stems implanted cementless in patients with osteoporotic bone demonstrated similar results compared to non-osteoporotic bone [103]. Stem survival was found 100 % at 5, 10, and 15 years for aseptic loosening in all types of bone classes (A, B, C) [103]. The reliability demonstrated by cementless fixation of a tapered femoral component in total hip arthroplasty has been questioned

by the fact that the patients introduced first were young with good bone quality. However, studies conducted in patients with low bone quality confirmed the satisfactory results of this fixation even in these patients [104].

The failure mode of the acetabular component varies among the different cup designs. In a study comparing the different cup fixation methods in relation to revision, it was suggested that all methods provide comparable fixation. However, when the results were analyzed separately depending on the cause of the revision, it was found that aseptic loosening among the spiked cups was increased, while recurrent dislocation revision cases were equal among the different groups [105]. Hemispheric titanium acetabular components that have the advantage of not using screws for fixation, have demonstrated comparable results to other implants [106].

Cemented Fixation

The usage of cemented titanium implants is infrequent. Several studies suggested that the cemented fixation of titanium alloys resulted in poor outcome [107, 108]. Recently, the clinical and radiographic outcome of the use of cemented double-tapered femoral stem made from titanium was reported to be excellent [109]. A minor vertical subsiding, radiolucency without osteolysis at the bone-cement interface and a cortical hypertrophy were found in a small number of hips at 5 years, with no clinical effect [110]. The role of cemented fixation when titanium alloys implants are used remains controversial [110, 111].

In summary, the evolution of cementless total joint replacement was based on the late failure of the prostheses that use cement, involving particularly the acetabular component of hip replacements. The porous-coated prostheses were introduced as a need to alter the features of the bone-metal interface and increase strength against shearing forces that produced implant failure. The porous-coated surface allows adequate bone ingrowth, meaning that pores are created in order to allow the growth of bone into the metal surface. Certain characteristics of the pores

are affecting the properties of the bone-metal interface and therefore are related to loosening or failure of the implant device. Several properties of the pores have been proposed to alter bone-implant interface mechanics like porosity, pore depth, and pore gaps. Porous coating is nowadays usually constricted to the proximal part of the prostheses. This allows more homogeneous bone loading and minor stress shielding.

Total Knee Arthroplasty

Overall, a small number of components for total knee arthroplasty (TKA) are made from titanium alloys (Fig. 6.5). Their introduction started because of the mechanical advantages of titanium that potentially could improve outcome in cementless implants. One of the major problems in knee replacement is migration of the implant and consequent aseptic loosening of the components. The use of titanium alloys was introduced because of the advantages of titanium regarding its biocompatibility, its strength, and elasticity. However, the concern about excess wear of the polyethylene against titanium implants has risen early [112]. In vitro there was no any additional wear of the polyethylene because of the use of titanium [113]. Furthermore, early results from the use of titanium alloys in TKA have shown comparable results in short-term survival of these implants [114]. Titanium implants used for TKA have demonstrated an increased rate of wear debris production compared to cobalt–chromium metallic components. Also, TKA using titanium failed earlier and was associated with a prompt failure at the patellofemoral region [115]. The excessive wear debris with titanium implants have led to elevated serum titanium levels. These could serve as a marker of component failure in total knee replacements with titanium alloy bearings, especially if this is localized to the patellar component [116].

In uncemented total knee replacement, porous coating is used in order to achieve biological fixation of bone-implant interface. The superiority of the uncemented fixation is questionable. Regarding fixation, it seems that



Fig. 6.5 Titanium porous-coated TKA

hydroxyapatite augmentation offers better outcome compared to simple coated implants but with no obvious advantage compared to cemented fixation. Radiostereometric analysis (RSA) provides a very good predictive value for TKA migration [117]. Several studies have highlighted the poor bone ingrowth in to porous coating surfaces, especially in the tibia. For this reason, iliac grafting has been used to promote bone growth with promising results [118, 119].

Other Joint Arthroplasties

Apart from the use of cementless prostheses in the hip and knee joint, titanium alloy implants have been used in elbow total replacement

surgeries with relative success [120]. Though, the problems of tissue metallosis and wear are present also in the elbow, despite the fact it is considered a non-weight-bearing joint [120].

References

1. vom Hrn William Gregor. Beobachtungen und Versuche über den Menakanite, einen in Cornwall gefundenen mangetischen Sand; (Observations and experiments in a magnetic sand found in Cornwall). *Crell's Chemische Annalen*. 1971;15:40–54, 103–19.
2. Kroll W. "Verformbares Titan und Zirkon" (Eng: Ductile Titanium and Zirconium) *Zeitschrift für anorganische und allgemeine. Chemie*. 1937;234:42–5.
3. Kroll WJ. The production of ductile titanium. *Trans Electrochem Soc*. 1940;78:35–47.
4. Donachie Jr MJ. *TITANIUM: a technical guide*. Metals Park: ASM International; 1988. p. 11.
5. Stwertka A. Titanium. In: *Guide to the elements* (Revised ed.). New York: Oxford University Press; 1998. p. 81–2.
6. Brånemark PI, Hansson BO, Adell R, Breine U, Lindström J, Hallén O, Ohman A. Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. *Scand J Plast Reconstr Surg*. 1997;16S:1–132.
7. Collings EW. The physical metallurgy of titanium alloys. In: Gegel HL, editor. *ASM series in metal processing*. Cleveland/Metals Park: American Society for Metals; 1984.
8. Polmear JJ. Chapter6. Titanium alloys. In: *Light alloys*. London: Edward Arnold Publ; 1981.
9. Long M, Rack HJ. Titanium alloys in total joint replacement—a materials science perspective. *Biomaterials*. 1998;19:1621–39.
10. Samuel S, Nag S, Nasrazadani S, Ukirde V, El Bouanani M, Mohandas A, Nguyen K, Banerjee R. Corrosion resistance and in vitro response of laser-deposited Ti-Nb-Zr-Ta alloys for orthopedic implant applications. *J Biomed Mater Res A*. 2010;94:1251–6.
11. Guillemot F. Recent advances in the design of titanium alloys for orthopedic applications. *Expert Rev Med Devices*. 2005;2:741–8.
12. Larsson C, Thomsen P, Lausmaa J, Rodahl M, Kasemo B, Ericson LE. Bone response to surface modified titanium implants: studies on electropolished implants with different oxide thicknesses and morphology. *Biomaterials*. 1994;15:1062–74.
13. Larsson C, Thomsen P, Aronsson BO, Rodahl M, Lausmaa J, Kasemo B, Ericson LE. Bone response to surface-modified titanium implants: studies on the early tissue response to machined and electropolished implants with different oxide thicknesses. *Biomaterials*. 1996;17:605–16.
14. Nishiguchi S, Nakamura T, Kobayashi M, Kim HM, Miyaji F, Kokubo T. The effect of heat treatment on bone-bonding ability of alkali-treated titanium. *Biomaterials*. 1999;20:491–500.
15. Baleani M, Viceconti M, Toni A. The effect of sand-blasting treatment on endurance properties of titanium alloy hip prostheses. *Artif Organs*. 2000;24:296–9.
16. Degasne I, Baslé MF, Demais V, Huré G, Lesourd M, Grolleau B, Mercier L, Chappard D. Effects of roughness, fibronectin and vitronectin on attachment, spreading, and proliferation of human osteoblast-like cells (Saos-2) on titanium surfaces. *Calcif Tissue Int*. 1999;64:499–507.
17. Ryan G, Pandit A, Apatsidis DP. Fabrication methods of porous metals for use in orthopaedic applications. *Biomaterials*. 2006;27:2651–70.
18. Otsuki B, Takemoto M, Fujibayashi S, Neo M, Kokubo T, Nakamura T. Pore throat size and connectivity determine bone and tissue ingrowth into porous implants: three-dimensional micro-CT based structural analyses of porous bioactive titanium implants. *Biomaterials*. 2006;27:5892–900.
19. Pilliar RM. Porous biomaterials. In: Williams D, editor. *Concise encyclopedia of medical & dental materials*. Oxford/New York/Cambridge, MA: Pergamon Press and the MIT Press; 1990. p. 312–9.
20. Jasty M, Rubash HE, Paiement GD, Bragdon CR, Parr J, Harris WH. Porous-coated uncemented components in experimental total hip arthroplasty in dogs. Effect of plasma-sprayed calcium phosphate coatings on bone ingrowth. *Clin Orthop*. 1992;280:300–9.
21. Zhang C, Leng Y, Chen J. Elastic and plastic behavior of plasma-sprayed hydroxyapatite coatings on a Ti-6Al-4V substrate. *Biomaterials*. 2001;22:1357–63.
22. Massaro C, Baker MA, Cosentino F, Ramires PA, Klose S, Milella E. Surface and biological evaluation of hydroxyapatite-based coatings on titanium deposited by different techniques. *J Biomed Mater Res*. 2001;58:651–7.
23. Chen D, Bertollo N, Lau A, Taki N, Nishino T, Mishima H, Kawamura H, Walsh WR. Osseointegration of porous titanium implants with and without electrochemically deposited DCPD coating in an ovine model. *J Orthop Surg Res*. 2011;6:56.
24. Bigi A, Boanini E, Bracci B, Facchini A, Panzavolta S, Segatti F, Sturba L. Nanocrystalline hydroxyapatite coatings on titanium: a new fast biomimetic method. *Biomaterials*. 2005;26:4085–9.
25. Liu Y, Layrolle P, de Bruijn J, van Blitterswijk C, de Groot K. Biomimetic coprecipitation of calcium phosphate and bovine serum albumin on titanium alloy. *J Biomed Mater Res*. 2001;57:327–35.
26. Fernandez-Pradas JM, Clèries L, Martinez E, Sardin G, Esteve J, Morenza JL. Influence of thickness on the properties of hydroxyapatite coatings deposited by KrF laser ablation. *Biomaterials*. 2001;22:2171–5.
27. Yang Y, Kim KH, Ong JL. A review on calcium phosphate coatings produced using a sputtering process—an alternative to plasma spraying. *Biomaterials*. 2005;26:327–37.

28. Froimson MI, Garino J, Machenaud A, Vidalain JP. Minimum 10-year results of a tapered, titanium, hydroxyapatite-coated hip stem: an independent review. *J Arthroplasty*. 2007;22:1–7.
29. Haenle M, Fritsche A, Zietz C, Bader R, Heidenau F, Mittelmeier W, Gollwitzer H. An extended spectrum bactericidal titanium dioxide (TiO₂) coating for metallic implants: in vitro effectiveness against MRSA and mechanical properties. *J Mater Sci Mater Med*. 2011;22:381–7.
30. Harman MK, Banks SA, Hodge WA. Wear analysis of a retrieved hip implant with titanium nitride coating. *J Arthroplasty*. 1997;12:938–45.
31. Balla VK, Xue W, Bose S, Bandyopadhyay A. Laser-assisted Zr/ZrO₂ coating on Ti for load-bearing implants. *Acta Biomater*. 2009;5:2800–9.
32. Kornu R, Maloney WJ, Kelly MA, Smith RL. Osteoblast adhesion to orthopaedic implant alloys: effects of cell adhesion molecules and diamond-like carbon coating. *J Orthop Res*. 1996;14:871–7.
33. Scott DF, Jaffe WL. Host-bone response to porous-coated cobalt-chrome and hydroxyapatite-coated titanium femoral components in hip arthroplasty: dual-energy X-ray absorptiometry analysis of paired bilateral cases at 5 to 7 years. *J Arthroplasty*. 1996;11:429–37.
34. Røkkum M, Reigstad A. Total hip replacement with an entirely hydroxyapatite-coated prosthesis: 5 years' follow-up of 94 consecutive hips. *J Arthroplasty*. 1999;14:689–700.
35. Hirshhom HS, McBeath AA, Dustoor MR. Porous titanium surgical implant materials. *J Biomed Mater Res Syrup* 1971;2:49–67.
36. Lueck RA, Galante J, Rostoker W, Ray RD. Development of an open pore metallic implant to permit attachment to bone. *Surg Forum*. 1969;20:456–7.
37. Spector M. Historical review of porous-coated implants. *J Arthroplasty*. 1987;2:163–77.
38. Galante J, Rostoker W, Lueck R, Ray RD. Sintered fiber metal composites as a basis for attachment of implants to bone. *J Bone Joint Surg Am*. 1971;53A:101–4.
39. Lembert E, Galante J, Rostoker W. Fixation of skeletal replacement by fiber metal composites. *Clin Orthop*. 1972;87:303–10.
40. Hahn H, Palich W. Preliminary evaluation of porous metal surfaced titanium for orthopedic implants. *J Biomed Mater Res*. 1970;4:571–7.
41. Turner TM, Sumner DR, Urban RM, Rivero DP, Galante JO. A comparative study of porous coatings in a weight-bearing total hip-arthroplasty model. *J Bone Joint Surg Am*. 1986;68A:1396–409.
42. Chao EYS, Galante JO. Animal study of titanium fiber metal prostheses for segmental bone and joint replacement. In: Kotz R, editor. *Proceedings of the second International workshop of the design and application of tumor prostheses for bone and joint reconstruction*, Vienna; 1983. p. 123–8.
43. Chen PQ, Turner TM, Ronnigen H, Galante J, Urban R, Rostoker W. A canine cementless total hip prosthesis model. *Clin Orthop*. 1983;176:24–33.
44. Thomas KA, Kay JF, Cook SD, Jarcho M. The effect of surface macrotexture and hydroxylapatite coating on the mechanical strengths and histologic profiles of titanium implant materials. *J Biomed Mater Res*. 1987;21:1395–414.
45. Cook SD, Thomas KA, Kay JF, Jarcho M. Hydroxyapatite-coated titanium for orthopedic implant applications. *Clin Orthop*. 1988;232:225–43.
46. Cook SD, Thomas KA, Kay JF, Jarcho M. Hydroxyapatite-coated porous titanium for use as an orthopedic biologic attachment system. *Clin Orthop*. 1988;230:303–12.
47. Cook SD, Thomas KA, Kay J. Experimental coating defects in hydroxylapatite-coated implants. *Clin Orthop*. 1991;265:280–90.
48. Søballe K, Hansen ES, Brockstedt-Rasmussen H, Pedersen CM, Bünger C. Hydroxyapatite coating enhances fixation of porous coated implants. A comparison in dogs between press fit and noninterference fit. *Acta Orthop Scand*. 1990;61:299–306.
49. Maistrelli GL, Mahomed N, Garbuz D, Fornasier V, Harrington IJ, Binnington A. Hydroxyapatite coating on carbon composite hip implants in dogs. *J Bone Joint Surg Br*. 1992;74B:452–6.
50. Karabatsos B, Myerthall SL, Fornasier VL, Binnington A, Maistrelli GL. Osseointegration of hydroxyapatite porous-coated femoral implants in a canine model. *Clin Orthop*. 2001;392:442–9.
51. Coathup MJ, Blackburn J, Goodship AE, Cunningham JL, Smith T, Blunn GW. Role of hydroxyapatite coating in resisting wear particle migration and osteolysis around acetabular components. *Biomaterials*. 2005;26:4161–9.
52. Wheeler DL, Campbell AA, Graff GL, Miller GJ. Histological and biomechanical evaluation of calcium phosphate coatings applied through surface-induced mineralization to porous titanium implants. *J Biomed Mater Res*. 1997;34:539–43.
53. Nakashima Y, Hayashi K, Inadome T, Uenoyama K, Hara T, Kanemaru T, Sugioka Y, Noda I. Hydroxyapatite-coating on titanium arc sprayed titanium implants. *J Biomed Mater Res*. 1997;35:287–98.
54. Jakobsen T, Baas J, Kold S, Bechtold JE, Elmengaard B, Søballe K. Local bisphosphonate treatment increases fixation of hydroxyapatite-coated implants inserted with bone compaction. *J Orthop Res*. 2009;27:189–94.
55. Jakobsen T, Kold S, Bechtold JE, Elmengaard B, Søballe K. Local alendronate increases fixation of implants inserted with bone compaction: 12-week canine study. *J Orthop Res*. 2007;25:432–41.
56. Lamberg A, Bechtold JE, Baas J, Søballe K, Elmengaard B. Effect of local TGF-beta1 and IGF-1 release on implant fixation: comparison with hydroxyapatite coating: a paired study in dogs. *Acta Orthop Scand*. 2009;80:499–504.
57. Sumner DR, Turner TM, Urban RM, Viridi AS, Inoue N. Additive enhancement of implant fixation following combined treatment with rhTGF-beta2 and rhBMP-2 in a canine model. *J Bone Joint Surg Am*. 2006;88A:806–17.

58. Greenfield EJ. Mounting for artificial teeth, U.S. Patent Office, Serial No. 478360, Patented Dec 14, 1909.
59. Grindlay JH, Clagett OT. A plastic sponge prosthesis for use after pneumonectomy; preliminary report of an experimental study. *Proc Staff Meet Mayo Clin.* 1949;24:538.
60. Agins HJ, Alcock NW, Bansal M, Salvati EA, Wilson PD, Pellicci PM, Bullough PG. Metallic wear in failed titanium-alloy total hip replacements. A histological and quantitative analysis. *J Bone Joint Surg Am.* 1998;70A:347–56.
61. Head WC, Bauk DJ, Emerson RH. Titanium as the material of choice for cementless femoral components in total hip arthroplasty. *Clin Orthop.* 1995;70:85–90.
62. Meachim G, Williams DF. Changes in nonosseous tissue adjacent to titanium implants. *J Biomed Mater Res.* 1973;7:555–72.
63. Ni GX, Lu WW, Chiu KY, Fong DY. Cemented or uncemented femoral component in primary total hip replacement? A review from a clinical and radiological perspective. *J Orthop Surg.* 2005;13:96–105.
64. Urban RM, Jacobs JJ, Sumner DR, Peters CL, Voss FR, Galante JO. The bone-implant interface of femoral stems with non-circumferential porous coating. *J Bone Joint Surg Am.* 1996;78A:1068–81.
65. Sun L, Berndt CC, Gross KA, Kucuk A. Material fundamentals and clinical performance of plasma-sprayed hydroxyapatite coatings: A review. *J Biomed Mater Res.* 2001;58:570–92.
66. Semlitsch M. Titanium alloys for hip joint replacements. *Clin Mater.* 1987;2:1–13.
67. Rothman RH, Cohn JC. Cemented versus cementless total hip arthroplasty. A critical review. *Clin Orthop.* 1990;254:153–69.
68. Bloebaum RD, Bachus KN, Momberger NG, Hofmann AA. Mineral apposition rates of human cancellous bone at the interface of porous coated implants. *J Biomed Mater Res.* 1994;28:537–44.
69. Dorr LD, Luckett M, Conaty JP. Total hip arthroplasties in patients younger than 45 years. A nine- to ten-year follow-up study. *Clin Orthop.* 1990;260:215–9.
70. Callaghan JJ. Results of primary total hip arthroplasty in young patients. *Instr Course Lect.* 1994;43:315–21.
71. Smith SE, Garvin KL, Jardon OM, Kaplan PA. Uncemented total hip arthroplasty. Prospective analysis of the tri-lock femoral component. *Clin Orthop.* 1991;269:43–50.
72. Bourne RB, Rorabeck CH, Ghazal ME, Lee MH. Pain in the thigh following total hip replacement with a porous-coated anatomic prosthesis for osteoarthritis. A five-year follow-up study. *J Bone Joint Surg Am.* 1994;76A:1464–70.
73. Maric Z, Karpman RR. Early failure of noncemented porous coated anatomic total hip arthroplasty. *Clin Orthop.* 1992;278:116–20.
74. Engh CA, Hooten JP, Zettl-Schaffer KF, Ghaffarpour M, McGovern TF, Macalino GE, Zicat BA. Porous-coated total hip replacement. *Clin Orthop.* 1994;298:89–96.
75. Mallory TH, Head WC, Lombardi AV, Emerson RH, Eberle RW, Mitchell MB. Clinical and radiographic outcome of a cementless, titanium, plasma spray-coated total hip arthroplasty femoral component. Justification for continuance of use. *J Arthroplasty.* 1996;11:653–60.
76. Manley MT, Capello WN, D'Antonio JA, Edidin AA, Geesink RG. Fixation of acetabular cups without cement in total hip arthroplasty. A comparison of three different implant surfaces at a minimum duration of follow-up of five years. *J Bone Joint Surg Am.* 1998;80A:1175–85.
77. Hofmann AA, Feign ME, Klauser W, VanGorp CC, Camargo MP. Cementless primary total hip arthroplasty with a tapered, proximally porous-coated titanium prosthesis: a 4- to 8-year retrospective review. *J Arthroplasty.* 2000;15:833–9.
78. Meding JB, Keating EM, Ritter MA, Faris PM, Berend ME. Minimum ten-year follow-up of a straight-stemmed, plasma-sprayed, titanium-alloy, uncemented femoral component in primary total hip arthroplasty. *J Bone Joint Surg Am.* 2004;86A:92–7.
79. Geesink RG, de Groot K, Klein CP. Bonding of bone to apatite-coated implants. *J Bone Joint Surg Br.* 1988;70B:17–22.
80. Tanzer M, Kantor S, Rosenthal L, Bobyn JD. Femoral remodeling after porous coated total hip arthroplasty with and without hydroxyapatite-tricalcium phosphate coating: a prospective randomized trial. *J Arthroplasty.* 2001;16:552–8.
81. Yee AJ, Kreder HK, Bookman I, Davey JR. A randomized trial of hydroxyapatite coated prostheses in total hip arthroplasty. *Clin Orthop.* 1999;366:120–32.
82. Miyakawa S, Kawamura H, Mishima H, Yasumoto J. Grit-blasted and hydroxyapatite-coated total hip arthroplasty: an 11- to 14-year follow-up study. *J Orthop Sci.* 2004;9:462–7.
83. Vaughn BK, Lombardi AV, Mallory TH. Clinical and radiographic experience with a hydroxyapatite-coated titanium plasma-sprayed porous implant. *Semin Arthroplasty.* 1991;2:309–16.
84. Kim YH, Kim JS, Oh SH, Kim JM. Comparison of porous-coated titanium femoral stems with and without hydroxyapatite coating. *J Bone Joint Surg Am.* 2003;85A:1682–8.
85. Kim YH, Kim JS, Joo JH, Park JW. Is hydroxyapatite coating necessary to improve survivorship of porous-coated titanium femoral stem? *J Arthroplasty.* 2012;27:559–63.
86. Bøe BG, Röhrh SM, Heier T, Snorrason F, Nordsletten L. A prospective randomized study comparing electrochemically deposited hydroxyapatite and plasma-sprayed hydroxyapatite on titanium stems. *Acta Orthop Scand.* 2011;82:13–9.
87. Fielding GA, Roy M, Bandyopadhyay A, Bose S. Antibacterial and biological characteristics of plasma sprayed silver and strontium doped hydroxyapatite coatings. *Acta Biomater.* 2012. doi:10.1016/j.actbio.2012.04.004.

88. Bourne RB, Rorabeck CH. A critical look at cementless stems. Taper designs and when to use alternatives. *Clin Orthop.* 1998;355:212–23.
89. Bugbee WD, Culpepper WJ, Engh CA, Engh CA. Long-term clinical consequences of stress-shielding after total hip arthroplasty without cement. *J Bone Joint Surg Am.* 1997;79A:1007–12.
90. Haddad RJ, Cook SD, Thomas KA. Biological fixation of porous-coated implants. *J Bone Joint Surg Am.* 1987;69A:1459–66.
91. Sarmiento A, Turner TM, Latta LL, Tarr RR. Factors contributing to lysis of the femoral neck in total hip arthroplasty. *Clin Orthop.* 1976;145:208–12.
92. Emerson RH, Sanders SB, Head WC, Higgins L. Effect of circumferential plasma-spray porous coating on the rate of femoral osteolysis after total hip arthroplasty. *J Bone Joint Surg Am.* 1999;81A:1291–8.
93. Kitamura S, Hasegawa Y, Iwasada S, Yamauchi K, Kawamoto K, Kanamono T, Iwata H. Catastrophic failure of cementless total hip arthroplasty using a femoral component without surface coating. *J Arthroplasty.* 1999;14:918–24.
94. Butler JB, Lansky D, Duwelius PJ. Prospective evaluation of total hip arthroplasty with a cementless, anatomically designed, porous-coated femoral implant: mean 11-year follow-up. *J Arthroplasty.* 2005;20:709–16.
95. Hartzband MA, Glassman AH, Goldberg VM, Jordan LR, Crowninshield RD, Fricka KB, Jordan LC. Survivorship of a low-stiffness extensively porous-coated femoral stem at 10 years. *Clin Orthop.* 2010;468:433–40.
96. Lombardi AV, Berend KR, Mallory TH, Skeels MD, Adams JB. Survivorship of 2000 tapered titanium porous plasma-sprayed femoral components. *Clin Orthop.* 2009;467:146–54.
97. Buechel FF, Buechel FF, Helbig TE, D'Alessio J, Pappas MJ. Two- to 12-year evaluation of cementless Buechel-Pappas total hip arthroplasty. *J Arthroplasty.* 2004;19:1017–27.
98. Rodriguez JA, Deshmukh AJ, Klauser WU, Rasquinha VJ, Lubinus P, Ranawat CS. Patterns of osseointegration and remodeling in femoral revision with bone loss using modular, tapered, fluted, titanium stems. *J Arthroplasty.* 2011;26:1409–17.
99. Hwang BH, Lee WS, Park KK, Yang IH, Han CD. Straight tapered titanium stem with alumina bearing in cementless primary total hip arthroplasty: a minimum 5-year follow-up. *J Arthroplasty.* 2011;26:1310–7.
100. Jafari SM, Bender B, Coyle C, Parvizi J, Sharkey PF, Hozack WJ. Do tantalum and titanium cups show similar results in revision hip arthroplasty? *Clin Orthop.* 2010;468:459–65.
101. Yue EJ, Duffy GP. Impaction grafting using a cemented porous-coated modular acetabular component. *J Arthroplasty.* 2008;23:466–9.
102. Klaassen MA, Martínez-Villalobos M, Pietrzak WS, Mangino GP, Guzman DC. Midterm survivorship of a press-fit, plasma-sprayed, tri-spike acetabular component. *J Arthroplasty.* 2009;24:391–9.
103. Meding JB, Galley MR, Ritter MA. High survival of uncemented proximally porous-coated titanium alloy femoral stems in osteoporotic bone. *Clin Orthop.* 2010;468:441–7.
104. Reitman RD, Emerson R, Higgins L, Head W. Thirteen year results of total hip arthroplasty using a tapered titanium femoral component inserted without cement in patients with type C bone. *J Arthroplasty.* 2003;18:116–21.
105. Engh CA, Hopper RH, Engh CA. Long-term porous-coated cup survivorship using spikes, screws, and press-fitting for initial fixation. *J Arthroplasty.* 2004;19:54–60.
106. Dorr LD, Wan Z, Cohen J. Hemispheric titanium porous coated acetabular component without screw fixation. *Clin Orthop.* 1998;351:158–68.
107. Sarmiento A, Gruen TA. Radiographic analysis of a low-modulus titanium-alloy femoral total hip component. Two to six-year follow-up. *J Bone Joint Surg Am.* 1985;67A:48–56.
108. Jergesen HE, Karlen JW. Clinical outcome in total hip arthroplasty using a cemented titanium femoral prosthesis. *J Arthroplasty.* 2002;17:592–9.
109. Akiyama H, Kawanabe K, Yamamoto K, So K, Kuroda Y, Nakamura T. Clinical outcomes of cemented double-tapered titanium femoral stems: a minimum 5-year follow-up. *J Orthop Sci.* 2011;16:689–97.
110. Bowditch M, Villar R. Is titanium so bad? Medium-term outcome of cemented titanium stems. *J Bone Joint Surg Br.* 2001;83B:680–5.
111. Boyer P, Lazennec JY, Poupon J, Rousseau MA, Ravaut P, Catonné Y. Clinical and biological assessment of cemented titanium femoral stems: an 11-year experience. *Int Orthop.* 2009;33:1209–15.
112. Rostoker W, Galante JO. Some new studies of the wear behavior of ultrahigh molecular weight polyethylene. *J Biomed Mater Res.* 1976;10:303–10.
113. Peterson CD, Hillberry BM, Heck DA. Component wear of total knee prostheses using Ti-6Al-4V, titanium nitride coated Ti-6Al-4V, and cobalt-chromium-molybdenum femoral components. *J Biomed Mater Res.* 1998;22:887–903.
114. Baldwin JL, El-Saied MR, Rubinstein RA. Uncemented total knee arthroplasty: report of 109 titanium knees with cancellous-structured porous coating. *Orthopedics.* 1996;19:123–30.
115. La Budde JK, Orosz JF, Bonfiglio TA, Pellegrini VD. Particulate titanium and cobalt-chrome metallic debris in failed total knee arthroplasty. A quantitative histologic analysis. *J Arthroplasty.* 1994;9:291–304.
116. Jacobs JJ, Silverton C, Hallab NJ, Skipor AK, Patterson L, Black J, Galante JO. Metal release and excretion from cementless titanium alloy total knee replacements. *Clin Orthop.* 1999;358:173–80.

117. Onsten I, Nordqvist A, Carlsson AS, Besjakov J, Shott S. Hydroxyapatite augmentation of the porous coating improves fixation of tibial components. A randomised RSA study in 116 patients. *J Bone Joint Surg Br.* 1998;80B:417–25.
118. Bloebaum RD, Bachus KN, Jensen JW, Hofmann AA. Postmortem analysis of consecutively retrieved asymmetric porous-coated tibial components. *J Arthroplasty.* 1997;12:920–9.
119. Kim KJ, Iwase M, Kotake S, Itoh T. Effect of bone marrow grafting on the titanium porous-coated implant in bilateral total knee arthroplasty. *Acta Orthop Scand.* 2007;78:116–22.
120. Kudo H, Iwano K, Nishino J. Cementless or hybrid total elbow arthroplasty with titanium-alloy implants. A study of interim clinical results and specific complications. *J Arthroplasty.* 1994;9:269–78.

Grit-Blasted Implant Bone Interface in Total Joint Arthroplasty

7

Eduardo García-Rey and Eduardo García-Cimbreló

Introduction

Different types of cementless fixation provide excellent long-term results in total joint arthroplasty. Scandinavian Registers report that although cemented prostheses are the implants that offer the best survivorship at 10 and 15 years of follow-up, when the five most common cementless total hip arthroplasties (THA) are analyzed, the risk of revision in terms of aseptic loosening is lower for the latter [1]. Although the follow-up for assessing these comparisons is different, mainly due to the probability of cup revision being due to the higher wear rate of cementless sockets, the cementless stems offer a better outcome than cemented do when bone fixation is evaluated. These clinical findings show us that early cementless fixation models were failing in the attempt to achieve implant osseointegration in the early and late time periods [2–4]. Fortunately, other types of cementless fixation have achieved better results [5–8]. In the knee, although cemented fixation is the preferred option, some designs are reported to have had good rates of osseointegration [9, 10]. One of the most successful types of cementless bone fixation is the grit-blasted interface.

E. García-Rey, MD, PhD, EBOT (✉)
E. García-Cimbreló, MD, PhD
Orthopaedics Department,
Hospital La Paz-Idi Paz, Pº Castellana 261,
Madrid 28046, Spain
e-mail: edugrey@yahoo.es

Data from Basic Sciences and Experimental Studies

The fundamental principles for a successful and durable bone fixation after surgical implantation are primary stability, osseointegration, and bone remodeling. Once primary stability is achieved, the micromotion of the implant must be minimal in order to obtain bone apposition and to sustain this situation for remodeling according to Wolff's law and to avoid fibrous fixation.

Biological bone fixation is achieved secondary to the so-called ingrowth or ongrowth of the implant. Ingrowth fixation is provided by a porous-coated metallic surface which allows bone ingrowth to invade the pores, but the size, depth, and gaps between the parts of the prosthesis are critical to achieving this goal. The grit-blasting technique provides an ongrowth fixation. The metallic surface is roughened with an abrasive spray of particles that pit the metallic surface, creating peaks and valleys that offer the areas for the bone to grow. Contrary to porous coated, osseointegration is related to surface roughness, that is, the average distance from peak to valley on the roughened area. The greater the roughness is increased, the higher the interface shear strength. While the porous-coating area can be limited to some sections of the design of the implant, such as the metaphyseal area in the femur, grit blasting must cover the whole implant.

When an implant is inserted, compressive forces perpendicular to the interface and parallel shear forces are transmitted, and this transmission

Table 7.1 High survival of cementless total hip arthroplasty made of titanium alloys

	Number of hips	Implant	Follow-up	Survival Aseptic loosening % cup/stem	Related failures/radiological analysis
Delaunay and Kapandji [20]	200	Alloclassic	2–11	99.1	
Pospischill and Knahr [19]	103	Alloclassic	10–17	98.3/100	Radiolucent lines (RL) proximal femur
Grubl et al. [21]	133	Alloclassic	10	93/99	Proximal RL, cortical thickening
García Cimbreló et al. [22]	104	Alloclassic	10–13	94.2/100	Wear, 32 femoral head
Zweymüller et al. [28]	118	Bicon/SL-Plus	10	100	Proximal RL
Aldinger et al. [23]	186	CLS Spotorno	15–20	94	Proximal osteolysis

depends on the coefficient of friction, as well as the compression between the components. The surface roughness achieves sufficient frictional resistance to decrease micromotion. Thus, during insertion, the bone is expanded, and this elastic deformation of the bone results in a force that fixes the prosthesis. Since this deformation could also weaken the bone and affect the fixation with the passing of time, the shape of the implants is designed to leave a space before total contact with the implant or with a tapered geometry to convert the axial loads to compressive forces that will augment fixation [11].

The grit-blasted technique uses titanium alloys. The first studies were done with Ti6Al4V alloys and found extensive direct bone growth onto the surface with a roughness of 1 μm ($R_a 1.23 \pm 0.3 \mu\text{m}$) being seen in autopsies [12]. The Ti6Al7Nb alloy and a change of surface roughness to 4 micra ($R_a 4.14 \pm 0.36 \mu\text{m}$) improved the surface characteristics, and more bone growth was observed even in elderly patients [13]. Further investigations reported that other titanium implants, with a R_a value of 6 micra, also induced some bone formation; that, however, was usually separated by a thin layer of fibroblasts, and, in some regions, the bone was remodeling and forming adjacent to the surface of the implant [14]. Thus, other implants made of a Ti6Al7Nb, with a microporous surface treatment ($R_a = 4.4 \mu\text{m}$) and combined with a triple taper when used in the femur, allow integration of the alloy, although the radiological analysis does not show distal fit and fill [15]. Feighan et al. observed that blasting the

titanium alloy implants had a significant effect on the bone apposition to the implant and on the bone-implant interfacial pullout bone strength. They also suggested that this type of surface offered substrate on which bone matrix can directly form, and according to Wolff's law, with bone growth on to the surface-blasted implants, loads are transferred from the implant to the bone and stability is provided [16]. Goldberg et al. found that, in young rabbits, grit-blasted titanium alloy implants have appreciably more bone intimately in contact with the implant surface than the titanium fiber metal or solid polished implants [17]. However, surgical technique and the geometry of the implants also play an important role in the biological effects that the titanium grit-blasted implants offer.

Data from Clinical Human Studies

There are many authors who report the high survival of cementless total hip arthroplasty made of titanium alloys (Table 7.1). The surgical press-fit technique for primary stability of the implant and the implant shape determine the outcome of the prosthesis, but the surface that contacts to the cancellous bone can be porous coated or grit blasted and promotes either osseous ingrowth or ongrowth, respectively. On the acetabular side, both threaded and hemispherical cups provide very low rates of aseptic loosening. Although most threaded cups provide poor results [18], the introduction of the titanium grit-blasted surface

could improve these results. The conical self-cutting threaded cup made of pure titanium cuts the acetabular bone providing primary stability and allows the osseointegration onto the rough titanium surface [19]. Delanauy and Kapandji observed that the 10-year survival of the Alloclassic cementless total hip arthroplasty (Centerpulse-Zimmer, Warsaw, IN, USA) was similar to the best cemented implants analyzed in the Swedish Register; they reported only one cup needing revision due to aseptic loosening at 5 years [20]. Other authors also report the excellent long-term outcome for this design with a very low rate of thigh pain and loosening for either acetabular and femoral components [21, 22]. Aldinger et al also observed excellent long-term results for the CLS Spotorno (Zimmer) stem with a survival for aseptic loosening at 17 years of 94 %; however, they emphasized that late loosening can be observed in the undersized components. They also observed that radiological osteolysis was not frequent and had only been observed in the proximal area of the femur [23].

The radiological analysis of the acetabulum shows an immediate postoperative radiographic gap between the cup and the bone in one third of the hips. At the end of the follow-up, the gap was only visible in a few hips and was located in DeLee and Charnley zone 1 or zone 2 (two hips); none of these patients had had any clinical symptom [22]. Acetabular osteolysis is not frequent (less than 20 % of the hips) and is focal, mild, and without clinical relevance in any case. When aseptic radiographic loosening is observed, it is usually related to the presence of a vertical acetabular angle, acetabular wear equal to or greater than 1 mm and a 32-mm femoral head. Although all of the loosened cups had 32-mm femoral heads, the polyethylene liners, except in one hip, were at least 8-mm thick. Garcia Cimbrello et al. showed that, according to the Cox multivariate regression analysis, the risk of cup loosening increased with the use of a 32-mm femoral head (hazard risk=0.1391, 95 % confidence interval, 0.0163–1.1911 ($p=0.0352$)) [22].

Thigh pain is infrequent using a straight tapered grit-blasted stem, and although the cause of this clinical problem is still not clear, it has been reported that it can appear in well-fixed porous-coated stems [24]. The radiological analysis of the

femur shows that, although a varus position of the stem may be observed in many cases, the component fixation is the rule, and there are no signs of loosening. According to the different series, ten percent of the hips had more than 5 mm of nonprogressive subsidence of femoral stem, with an average interval from operation to stem subsidence of 2 years, but it was nonprogressive in all hips. All the hips with stem subsidence showed radiographic evidence of stable fixation, and none of the patients reported pain. Another radiological finding that may be seen is a complete bone pedestal at the tip of the stem. Femoral cortical thickening is usually more frequent, the mean time of appearance is at 4 years, and it can be seen in around a third of hips. Cortical thickening is probably due to the concentration of focal stress in the transient zone between the stiff area around the stem and the elastic area below the implant: fortunately, cortical thickening is not related to stem loosening [25]. Proximal femoral osteopenia due to stress shielding is common in the Engh et al. grade 1 hips. The average interval from operation to appearance of femoral osteopenia grade 2 was 4 years, and when osteopenia is more severe, although this is less frequent, it appears later, at around 7 years. The risk of appearance of proximal femoral osteopenia (grades 2 and 3) increased with the degree of acetabular wear and physical activity. Korovesis et al., using dual energy x-ray absorptiometry (DEXA), concluded that the Zweymüller stem did not induce substantial stress shielding and its subsequent bone remodeling [26]. In another DEXA study, Karachalios et al. assessed the evolution of four different cementless stems at 10 years, and they reported early bone loss in the calcar region at 2 years after surgery, with, however, a progressive recovery of bone loss up to the tenth postoperative year. Thus, patients presented satisfactory clinical results [27]. Regarding femoral osteolysis, this is proximal, focal, and mild and is frequently observed 6 years after the surgery.

Surgery and Different Application

Since titanium grit-blasted implants provide excellent long term clinical and radiological results, as mentioned above, the proper surgical



Fig. 7.1 Anteroposterior view radiograph of a grit-blasted THA with a threaded cup and a straight tapered femoral stem at 21 years of follow-up

technique and the design of the components are critical for the success of the surgery. In both the acetabular and the femoral sides, the surgical technique must try to avoid reaming excessive amounts of bone to enhance ongrowth in these implants. In the acetabulum, a press-fit with the hemispherical components should not be either over or underreamed, the central osteophyte must be excised and the subchondral bone spared. Although most authors report excellent long-term fixation with threaded grit-blasted cups and most hemispherical cups are porous coated, there are some designs that also provide excellent biological bone fixation [7]. If dense subchondral bone is preserved and the roughened surface engages with a press-fit, adequate fixation is usually achieved. Zenz et al assessed 82 hips for 10 years and observed that there was no aseptic



Fig. 7.2 Anteroposterior view radiograph of a biradial cup and a grit-blasted tapered stem at ten years of follow-up

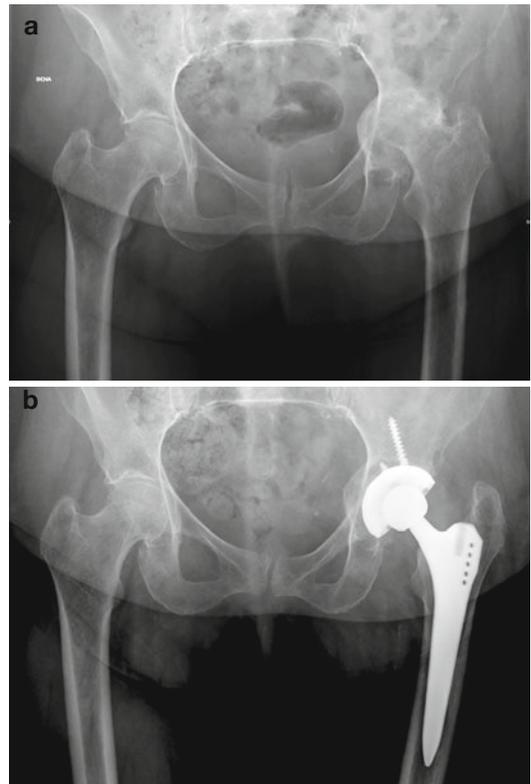


Fig. 7.3 (a) Preoperative radiograph of a female patient of 76 years old. (b) Postoperative radiograph with a grit-blasted hemispherical cup and autograft from the femoral head and a second-generation Zweymüller stem at 2 years

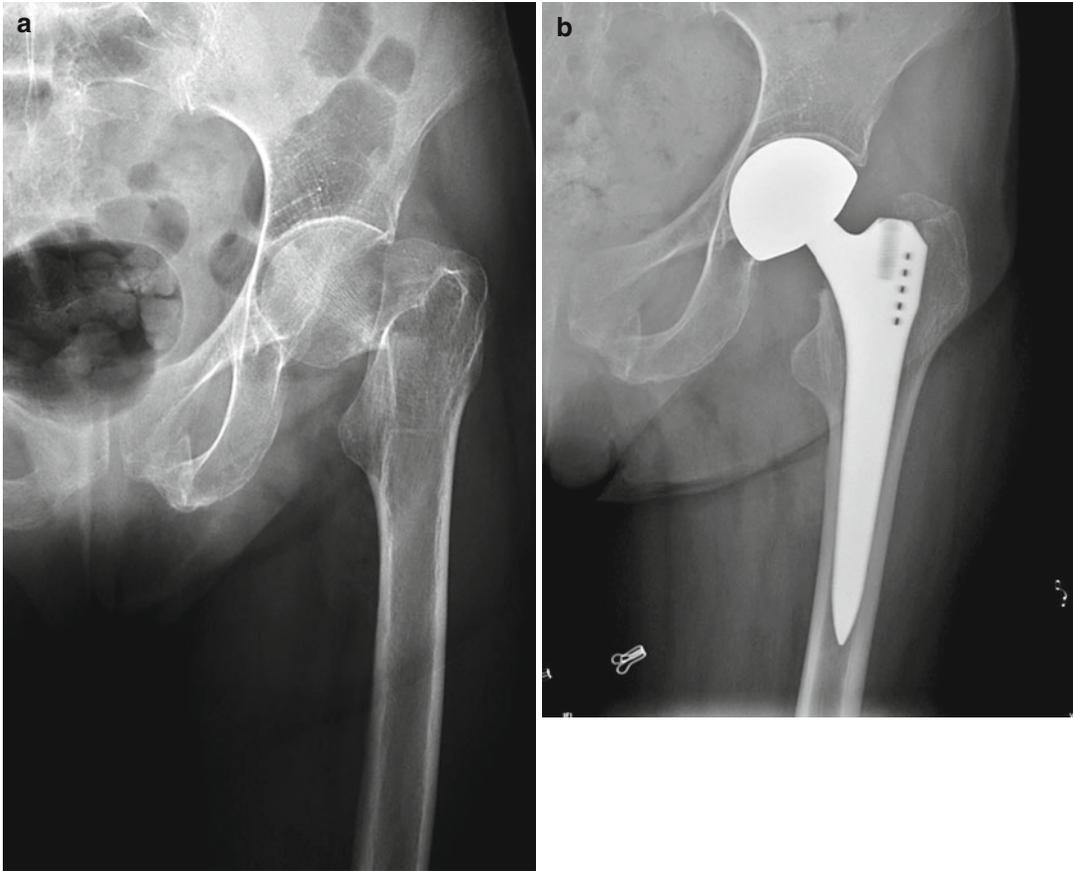


Fig. 7.4 (a) Radiograph of a femoral neck fracture in an 88-year-old female patient with an osteoporotic femur. (b) Postoperative radiograph at 2 years follow-up

loosening using the Allofit (Zimmer) cup. This implant is biradial with a hemispherical periphery and a flattened polar region; the surface is a titanium alloy grit-blasted with corundum and prepared with a macrostructure of grooves and ridges with a dimension of 400 to 600 micra. They emphasized that both the biradial design, which that concentrates the forces on the periphery, and the surface of the cup provided enough biological fixation for long term implant survival (Figure 2). In femurs the cylindrical reamers are currently less use as they can produce radiological changes such as femoral osteopenia and cortical hypertrophy more frequently [6]; these problems can be decreased with the so-called tapered implants and almost all current cementless stems in primary surgery use this design. This tapered shape maintains enough proximal

cancellous bone to enhance stability, decreases the incidence of intraoperative fractures and promote good long term results even in malposition of the component, thus, the conservative bone preparation of these stems reduces damage to endosteal circulation [22].

Zweymuller made small changes in the design of the threaded cup and developed a biconical design, the Bicon cup (PlusOrthopaedics AG, Rotkreuz, Switzerland), in order to avoid excessive acetabular resection with the same titanium grit-blasted principles and also provide excellent results in terms of biologic fixation [26]. They also modified the stem, the SL-Plus stem (PlusOrthopaedics), and although more radiolucent lines have been reported by others, acceptable long term results in terms of fixation have also been achieved [28]. Zweymuller et al also

showed that radiolucent lines represent a steady state in most of cases without progression and without affecting the outcome of the prosthesis [29] (Figure 3). They also suggested that the possible explanation for the appearance of these proximal radiolucent lines in the femur could be explained by more cancellous bone being removed by rasping the bone at the level of the neck resection so a gap may be appear between the bone and the implant at the time of surgery, and, this gap was not obliterated by newly formed bone. These implants are even successful in osteoporotic bone and are now indicated in more situations: they are currently used for hemiarthroplasty when treating displaced femoral neck fractures in the elderly [30]. Klestil et al observed that despite a certain degree of migration measured by the EBRA-FCA methods in more active patients, good results could be achieved in patients with a low degree of physical activity [31] (Figure 4). However, although fixation is not a problem with these types of grit-blasted stems, the functional results are better and the rate of complications are still usually lower with cemented stems [32]. Other femoral designs with a proximal porous-coated area added a grit-blasted area on the dyaphyseal zone of the stem. Kang et al observed that a grit-blasted area on the diaphysis of the stem instead of a smooth area in a metaphyseal porous-coated femoral stem, improved the clinical and radiological results [33]. Currently, many femoral stems are similar to his design and follow these principles.

All basic, experimental, clinical, and radiological outcomes of the grit-blasted surface made of titanium show us that is a successful biomaterial when used in total joint arthroplasty (Figs. 7.1, 7.2, 7.3, and 7.4). It is a safe procedure, and it can be defined as one of the gold standard techniques for cementless prostheses. To date, all different topics regarding arthroplasty must be taken into account such as the designs of the implants and the pathology of the patient before using any implant. Thus, this surface has provided excellent results, and other designs incorporating a smooth interface instead of a roughened one have been abandoned due to their poor results. During the last four decades we have learned that an

orthopedic surgeon must keep in mind grit-blasted cementless implants when using a total joint arthroplasty.

References

1. Hailer NP, Garellick G, Kärrholm J. Uncemented and cemented primary total hip arthroplasty in the Swedish Hip Arthroplasty Register: evaluation of 170,413 operations. *Acta Orthop Scand.* 2010;81:34–41.
2. Niimäki T, Puranen J, Jalovaara P. Total hip arthroplasty using isoelastic femoral stems. A seven to nine year follow-up in 108 patients. *J Bone Joint Surg Am.* 1994;76A:413–8.
3. Cruz-Pardos A, García-Cimbrello E, Cordero-Ampuero J. Porous-coated anatomic uncemented total hip arthroplasty. A 10–17 year follow-up. *Hip Int.* 2005;15:78–84.
4. Kim SY, Kim DH, Kim YG, Oh CW, Ihn JC. Early failure of hemispheric hydroxyapatite-coated acetabular cups. *Clin Orthop.* 2006;446:233–8.
5. Clohisy JC, Harris WH. The Harris-Galante porous-coated acetabular component with screw fixation: an average ten-year follow-up study. *J Bone Joint Surg Am.* 1999;81A:66–73.
6. García-Rey E, García-Cimbrello E, Cordero-Ampuero J. Outcome of hemispherical porous-coated acetabular component with a proximally hydroxyapatite-coated anatomical femoral component: a 12- to 15-year follow-up study. *J Bone Joint Surg Br.* 2009;91B:327–32.
7. Zenz P, Stiehl JB, Knechtel H, Titzler-Hochmaier G, Schwagerl W. Ten-year follow-up of the non-porous Allofit cementless acetabular component. *J Bone Joint Surg Br.* 2009;91:1443–7.
8. Macheras GA, Papagelopoulos PJ, Kateros K, Kostakos AT, Baltas D, Karachalios TS. Radiological evaluation of the metal-bone interface of a porous tantalum monoblock acetabular component. *J Bone Joint Surg Br.* 2006;88B:304–9.
9. Ritter MA, Meneghini RM. Twenty-year survivorship of cementless anatomic graduated component total knee arthroplasty. *J Arthroplasty.* 2010;25:507–13.
10. Baker PN, Khaw FM, Kirk LM, Esler CN, Gregg PJ. A randomised controlled trial of cemented versus cementless press-fit condylar total knee replacement: 15-year survival analysis. *J Bone Joint Surg Br.* 2007;89B:1608–14.
11. Brown CU, Norman TL, Kish 3rd VL, Gruen TA, Blaha JD. Time-dependent circumferential deformation of cortical bone upon internal radial loading. *J Biomech Eng.* 2002;124:456–61.
12. Lintner F, Zweymüller K, Brand G. Tissue reactions to titanium endoprostheses. Autopsy studies in four cases. *J Arthroplasty.* 1986;1:183–95.
13. Bohm G, Lintner F, Auterith A, Lester DK, Zweymüller KA. Morphometric examination of

- straight, tapered titanium stems: a retrieval study. *Clin Orthop.* 2001;393:13–24.
14. Coathup MJ, Blunn GW, Flynn N, Williams C, Thomas NP. A comparison of bone remodelling around hydroxyapatite-coated, porous-coated and grit-blasted hip replacements retrieved at post-mortem. *J Bone Joint Surg Br.* 2000;82B:118–23.
 15. Spotorno L, Romagnoli S, Ivaldo N, et al. The CLS system. Theoretical concept and results. *Acta Orthop Belg.* 1993;59(S1):144–8.
 16. Feighan JE, Goldberg WM, Davy D, Parr JA, Stevenson S. The influence of surface-blasting on the incorporation of titanium-alloy implants in a rabbit intramedullary model. *J Bone Joint Surg Am.* 1995;77A:1380–95.
 17. Goldberg VM, Stevenson S, Feighan J, Davy D. Biology of grit-blasted titanium alloy implants. *Clin Orthop.* 1995;319:122–9.
 18. Snorrason F, Karrholm J. Primary migration of fully threaded acetabular cup. *J Bone Joint Surg Br.* 1990;72B:647–52.
 19. Pospischill M, Knahr K. Cementless total hip arthroplasty using a threaded cup and a rectangular tapered stem. Follow-up for ten to 17 years. *J Bone Joint Surg Br.* 2005;87B:1210–5.
 20. Delanaux C, Kapandji AI. Survival analysis of cementless grit-blasted titanium total hip arthroplasties. *J Bone Joint Surg Br.* 2001;83B:408–13.
 21. Gröbl A, Chiari C, Gruber M, Kaider A, Gottsauner-Wolf F. Cementless total hip arthroplasty with a tapered, rectangular titanium stem and a threaded cup: a minimum ten-year follow-up. *J Bone Joint Surg Am.* 2002;84A:425–31.
 22. Garcia Cimbrello E, Cruz Pardos A, Madero R, Ortega Andreu M. Total hip arthroplasty with use of the cementless Zweymuller Alloclassic system. A ten to thirteen-year follow-up study. *J Bone Joint Surg Am.* 2003;85A:296–303.
 23. Aldinger PR, Jung AW, Breusch SJ, Ewerbeck V, Parsch D. Survival of the cementless Spotorno stem in the second decade. *Clin Orthop.* 2009;467:2297–304.
 24. Barrack RL, Jasty M, Bragdon C, Haire T, Harris WH. Thigh pain despite bone ingrowth into uncemented femoral stems. *J Bone Joint Surg Br.* 1992;74B:507–10.
 25. Köster G, Leib S, Willert HG. Noncemented hip replacement using a conical screw-in cup and a straight press-fit stem. A six to eight-year clinical and radiological follow-up study. *Hip Inter.* 1998;8:208–18.
 26. Korovessis P, Piperos G, Michael A, Baikousis A, Stamatakis M. Bone mineral density changes around stable uncemented Zweymuller total hip arthroplasty. *Int Orthop.* 1997;5:389–96.
 27. Karachalios T, Tsatsaronis C, Efraimis G, Papadelis P, Lyritis G, Diakoumopoulos G. The long-term clinical relevance of calca atrophy by stress shielding in total hip arthroplasty. *J Arthroplasty.* 2004;19:469–75.
 28. Zweymuller KA, Steindl M, Schwarzingler U. Good stability and minimal osteolysis with a biconical threaded cup at 10 years. *Clin Orthop.* 2007;463:128–37.
 29. Wick M, Lester DK. Radiological changes in second- and third generation Zweymuller stems. *J Bone Joint Surg Br.* 2004;86B:1108–14.
 30. Zweymuller KA, Schwarzingler U, Steindl M. Radiolucent lines and osteolysis along tapered straight cementless titanium hip stems: a comparison of 6-year and 10-year follow-up results in 95 patients. *Acta Orthop Scand.* 2006;77:871–6.
 31. Bezwada HP, Shah AR, Harding SH, et al. Cementless bipolar hemiarthroplasty for displaced femoral neck fractures in the elderly. *J Arthroplasty.* 2004;19:73–7.
 32. Klestil T, Biedermann R, Krueger A, et al. Cementless hemiarthroplasty in femoral neck fractures: evaluation of clinical results and measurement of migration by EBRA-FCA. *Arch Orthop Trauma Surg.* 2006;20:380–6.
 33. Taylor F, Wright M, Zhu M. Hemiarthroplasty of the hip with and without cement. A randomized clinical trial. *J Bone Joint Surg Am.* 2012;94A:577–83.
 34. Kang JS, Dorr LD, Wan Z. The effect of diaphyseal biological fixation on clinical results and fixation of the APR-II stem. *J Arthroplasty.* 2000;15:730–5.

HA-Coated Implant: Bone Interface in Total Joint Arthroplasty

8

Henrik Daugaard, Joan E. Bechtold, and Kjeld Soballe

Introduction

The goal of osseointegration of orthopedic and dental implants is the rapid achievement of a mechanically stable and long lasting fixation between living bone and the implant surface. In total joint replacements of cementless designs, coatings of calcium phosphates were introduced as a means of improving the fixation of implants. Of these, hydroxyapatite (HA) is the most widely used and most extensively investigated. HA is highly osteoconductive, and the positive effect is well documented in both basic and long-term clinical research [1–6]. This chapter describes experimental and clinical studies evaluating bone-implant fixation with HA coatings.

HA stimulates formation of bone so that the bone trabeculae and implant surface porosity interact in a mechanical interlock and through a direct chemical bond to the bone tissue [7, 8].

H. Daugaard, MD, PhD (✉)
Department of Orthopaedic Surgery,
Frederiksberg Hospital, Nordre Fasanvej 57,
2000, Frederiksberg, Denmark
e-mail: h.daugaard@dadlnet.dk

J.E. Bechtold
Orthopaedic Biomechanics Laboratory,
Excelen Center for Bone and Joint Research
and Minneapolis Medical Research Foundation,
914 South Eighth Street, Minneapolis, MN 55404, USA

K. Soballe
Department of Orthopaedic Surgery,
Aarhus University Hospital, Tage Hansens Gade 2,
Aarhus C DK-8000, Denmark
e-mail: kjeld@soballe.com

Implant retrievals in humans have shown consistent evidence of osseointegration [9–14]. Furthermore, the HA-promoted circumferential osseointegration could reduce periprosthetic osteolysis by establishing a biological seal of the peri-implant space. Sealing can prevent potential migration of the polyethylene wear debris by third-body wear from the surface of the joint prosthesis [15–31].

Several hydroxyapatite application techniques on metallic substrates have been described. Traditionally, bioactive osteoconductive coatings are done by the plasma-spray technique. Newer pyroprocessing and hydrocoating techniques include ion beam sputtering, electron beam sputtering, plasma sputtering, radiofrequency sputtering, electrostatic spray deposition, pulsed laser deposition, hot isostatic pressing, sol-gel, biomimetic deposition, precipitation, electrophoretic deposition, and electrochemical deposition [15, 16, 19, 32–72]. Of these, only the electrochemical-deposited HA coating has shown a potential beyond basic research in vivo [15–22, 48, 57, 58, 73–80], and this is the only alternative HA coating used so far clinically [81–86]. For this reason, the application technique of electrochemical-deposited HA (EDHA) is elaborated in more detail further in this chapter. Likewise, the plasma-sprayed and the EDHA coating in relation to experimental and clinical studies is described.

The osteoconductive property of hydroxyapatite coatings depends on coating thickness, on crystallinity, solubility and stability [19, 87, 88],

on composition, purity and trace elements, and electrical polarization of the hydroxyapatite surface [89–94]. All these conditions vary with the method of application. The mechanism of bone formation on HA-coated implants is as follows: HA releases calcium and phosphate ions into the peri-implant space. Reprecipitation of carbonated apatite then occurs on the coating surface [95]. The HA binds serum proteins and cellular integrin receptors attracting osteoblastic cells to the surface [86, 96]. Bone is then formed on the coating surface and on the bone [97]. Bone ongrowth develops more rapidly on coatings with low crystallinity because the initial dissolution and release of calcium ions is faster than those associated with a coating of high crystallinity [88, 98]. Porter [88] established that the earliest-stage bone formation (3 h to 14 days) on HA plasma-sprayed implants is influenced by the solubility of the HA. Coatings with high crystallinity exhibit delayed new bone formation. In a study by Overgaard et al. [98], implant coatings with low crystallinity revealed increased mechanical fixation, bone ingrowth, and resorption of the coating. Low-crystalline coating releases more calcium and phosphate ions due to dissolution. Although stable coatings may reinforce bonding for longer, they are intrinsically less bioactive. Coatings that deliver a high local source of calcium and phosphate ions for rapid-contact osteogenesis are more bioactive coatings and tend to disintegrate faster.

Electrochemical HA (EDHA) Application Technique

Plasma-sprayed hydroxyapatite is a successful coating for osseointegration and long-term survival of uncemented implants. The HA coating consists of a layer of spray-dried HA deposited by plasma-spraying through a heated plasma arc at high temperatures. The technique is well established and applied on the majority of HA-coated implants for joint replacements in use today. In the following, the newer alternative electrochemical-deposited HA method is described in more detail. Developments with electrodeposition of HA will be summarized in detail below.

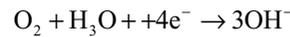
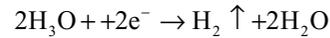
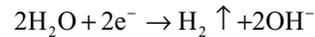
Compared to HA plasma-spray, electrochemically deposited HA coating is simpler and less expensive in manufacturing [99]. The process is characterized by ease of process control; by ability to control the thickness, composition, and microstructure of the deposit [34, 35, 40, 99–106]; and by the suitability for coating of complex implant geometries. The coatings are much thinner (1–20 μm) [15, 17, 81, 99, 100, 105] compared to a plasma-sprayed HA coating (50 μm) and may improve the substrate/coating bond strength. This may reduce the residual stresses and thereby the potential risk of coating failure by fracture and delamination at the implant interface [15, 26, 27, 76, 107, 108]. The lower temperature processing in the electrodeposition may counter the heterogeneities that are seen with the plasma-spray HA coating process in which high temperatures cause decomposition of HA into various undesirable heterogeneous phosphate phases with heterogeneous properties [8, 109–119]. Since it is not a line-of-sight method, the coating is more uniform and even on an implant with a non-line-of-sight porous surface and on an implant with a geometrically complex shape. It reserves the implant roughness and achieves full three-dimensional coverage of the entire porous coating of an implant [15, 73, 99]. This results in a deeper bioactive layer into implant porosities, which evokes a complete topographical stimulus over the entire implant surface and provides a larger surface area for osseointegration. This could provide less periprosthetic osteolysis with the establishment of a biological seal of the peri-implant space in which bone defects exist and where sealing ensures against a potential migration of the polyethylene wear debris by third-body wear from the surface of the joint prosthesis [15–31]. The application technique allows potential incorporation of biological matter in the coating during its processing [18, 21, 22, 100].

Titanium implant surfaces are known to spontaneously nucleate apatite layers when in contact with simulated body fluids [34–36, 72, 120]. The principle of the electrochemical deposition of calcium phosphate is based on the solubility of calcium phosphate using aqueous electrolytes containing Ca- and P-bearing ions. The coatings

can be regulated in morphology, composition, purity, crystallinity, and hence resorbability because of better control of the physiochemical conditions under which they are produced (electrolyte pH and temperature, calcium phosphate composition of electrolyte, the current density, current loading time, and the composition of the substrate metal) [15, 34, 35, 40, 76, 99–106, 121–123]. At electrophoresis deposition, growth of microcrystalline calcium phosphate molecules occur on implants from supersaturated calcifying solutions (Figs. 8.1, 8.2, and 8.3) as carbonated apatite [124], octacalcium phosphate [40, 125], brushite [73, 77, 126–128], and HA [15, 17–19, 21, 22, 57, 58, 73, 74, 76, 78, 79, 81, 82, 102].

In the technique described by Rossler et al. [99, 105] and Shirkhazadeh et al. [40], calcium phosphate deposition is based on the pH-dependent solubility of calcium phosphates, which decreases with increasing pH. During cathodic polarization of the metal implant, hydrolysis of water takes place close to the implant. This increases the pH at the surface such that the solubility threshold is reached in the calcium phosphate solution and calcium phosphate precipitates [99, 105]. During cathodic polarization of a metal, the following reactions occur at the

surface of the cathode (reduction of water, proton discharge, reduction of dissolved oxygen):



which results in the formation of hydroxyl ions and hence alkalization close to the surface. Using this electrochemical process, the pH at the cathode-electrolyte interface can be controlled and therefore so can the calcium phosphate deposition through nucleation and growth of the coating.

Deposition of an HA coating on an implant by an anodizing process has to a lesser degree been investigated. Ishizawa et al. [15, 103, 104] formed an anodic titanium oxide film containing Ca and P (AOFCP) on commercially pure titanium which was anodized in an electrolytic solution of dissolved β -glycerophosphate and calcium acetate. HA crystals were subsequently precipitated on the AOFCP by hydrothermally heating of the coating at 300 °C. The HA coating was thin (1 μm) and showed osteoconductive property [15, 76].

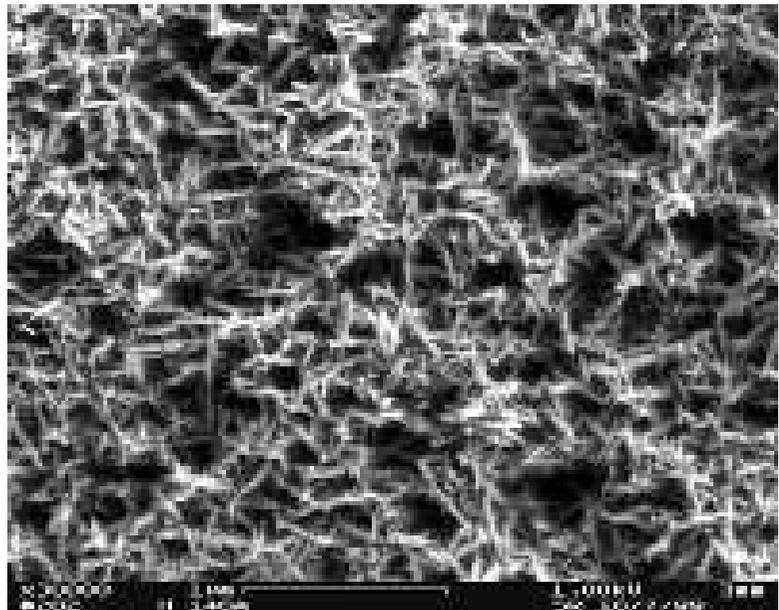


Fig. 8.1 Electrochemically deposited hydroxyapatite (BoneMaster®). Scanning electron microscope (SEM) photograph showing hydroxyapatite needles (This material is reproduced with permission of John Wiley & Sons, Inc. from Rößler et al. [99])

Fig. 8.2 Electrochemically deposited hydroxyapatite (BoneMaster®). Scanning electron microscope (SEM) photograph showing amorphous calcium phosphate with starting crystallization into hydroxyapatite needles on titanium (This material is reproduced with permission of John Wiley & Sons, Inc. from Rößler et al. [99])



Fig. 8.3 Electrochemically deposited hydroxyapatite (Bonit). Scanning electron microscope (SEM) photograph showing the typical efflorescent needle-like structure of HA crystals (This material is reproduced with permission of John Wiley & Sons, Inc. from Registad et al. [74])



Improvement of the EDHA coating adhesion to the implant is obtained by roughening of the implant. Hydroxyapatite adhesion to metallic substrates can be unsatisfactory without the previous blasting of the titanium surface [15, 129–131].

Some electrochemical coatings have been experimentally applied under conditions far from physiological. These include temperatures

during the process in the range of 60–800 °C and acid or alkalized solutions [15–17, 19, 40, 48, 57, 58, 73, 74, 76–82, 102, 124–126, 132, 133]. These additional procedures have been applied in order to convert CaP precursors into hydroxyapatite and other biomimetic coatings. One of these is the cathodic deposition of octacalcium phosphate [125] or of brushite [126] which can then be transformed into hydroxyapatite by

subsequent heat treatment [80, 124] or alkalinization [73–75, 81, 125, 133]. The advantage of a low-temperature and more physiological processing [54, 60, 69] is a more predictable and controlled environment for the deposition of the coating, and more crystallographically consistent coatings without creating undesired calcium phosphates. Also, application under more physiological conditions in temperature and acidity may show potential advantages in applying carrier coatings which are able to transport substrates such as bone-active substances and antibiotics [18, 21, 22, 100].

Electrochemical deposition of HA, in conditions close to physiological, have shown promise clinically in the technique of BoneMaster® [83] and Bonit [81, 82, 84, 86]. BoneMaster's technique [20, 21, 83, 99, 100, 105, 134] is hydroxyapatite deposited electrochemically. It results in an implant coating of hydroxyapatite of 5 μm , 1/10 of the plasma-sprayed hydroxyapatite, and a porous needle-like structure [99, 100] (Fig. 8.1). It is evenly distributed along the implant surface and resorbed readily [21]. Deposition is performed in a CaP-electrolyte ($\text{Ca}^{2+}/\text{H}_x\text{PO}_4^{(3-x)-}$) near physiological conditions (pH 6.4, temperature 36 °C). Cathodic alkalization leads first to the formation of a thin homogeneous calcium phosphate pre-layer with a nanoscale surface topography of alternating wall-like elevations and channels. These channels in the pre-layer are formed as pathways by hydroxyl ions and hydrogen. Small CaP islands are formed that coalesce and form a homogeneous layer on the implant surface. Upon this homogeneous CaP pre-layer, spheres of amorphous calcium phosphate form (Fig. 8.2). These spheres are small clusters of calcium phosphate (30 nm) and can grow up to 300 nm. The amorphous calcium phosphate is then transformed into crystalline hydroxyapatite as a function of electrophoretic current density. The hydroxyapatite crystals are needles with dimensions of <500-nm length and <60-nm width. By varying the electrochemical parameters, a homogeneous coating of either amorphous calcium phosphate, crystalline hydroxyapatite, or the intermediate phase can be achieved. This allows the formation of coatings with different proper-

ties in solubility and morphology [99, 100, 105]. The EDHA coatings evaluated experimentally and clinically consisted of 70–72 % crystalline HA and a Ca/P ratio of 2.0 [21, 83, 99, 100, 105]. Bonit's technique [73–75, 77, 81, 82, 84, 86, 133, 135] is hydroxyapatite deposited electrochemically. The initial coating, which is deposited electrochemically at room temperature, is a composite of brushite ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) converted to HA by NaOH treatment [75]. The Ca/P ratio is 1.6 (SD 0.1) [135] and the coating thickness 10 μm [81]. It is described as “nanocrystalline” HA [135] as demonstrated by X-ray diffraction and infrared spectroscopy [75]. Scanning electron microscope photographs reveal a fine crystalline structure, where CaP crystals are fixed on the titanium implant surface in the shape of platelets and pins of 15–20 μm in length (Fig. 8.3) [133]. A high porosity of 60 % creates a capillary effect, which enables early adhesion and proliferation of osteoblast-like cells [75].

Experimental Studies on Plasma-Sprayed HA-Coated Implants

In an experimental series of studies, Soballe et al. [136–141] has evaluated the osseointegration and mechanical fixation of plasma-sprayed HA-coated implants.

Clinical Motivation for Experimental Studies

In the clinical situation, initial direct apposition of implant to bone (press fit) is often limited to relatively small areas [142], and most of the porous-coated area of femoral components has been demonstrated to lack osseous contact (gaps). Anatomic variations in the bone, deficient implant design, and poor surgical technique are factors responsible for gaps between the implant surface and surrounding bone. The first step in the series of studies on implant fixation therefore focused on enhancement of bone ingrowth across a *gap* between bone and implant

by HA coating, compared with implants inserted in *press fit*. The use of bone bank allografts in joint replacement surgery has gained increasing importance, particularly in cementless reconstruction of failed arthroplasties in which direct fit to host bone cannot be obtained because of loss of bone stock around the loose implant. A new model was created to study *bone graft* incorporation into porous-coated implants and analyze the incorporation of allogeneic bone graft into Ti- and HA-coated implants as compared with implants without bone graft [140]. An important cause of inferior bone-implant fixation might be the presence of relative *motion* between implant and bone. Experimental studies of cementless hip and knee prosthetic components implanted into cadaver bone have shown micromotion ranging between 100 and 500 μm [143–151].

Basic Experimental Design Studies Establishing Plasma-Sprayed HA as an Implant Coating

The experimental series of plasma-sprayed HA studies [136–141] are based on the following study design

Animals

An animal model is required because it is possible to separate the more complex clinical situation into different well-defined elements that can be controlled, enabling us to study isolated problems. Furthermore, the animal provides a full physiologic response to mechanical and biological stimuli, not possible in an *in vitro* setting

Implants and Surface Coatings

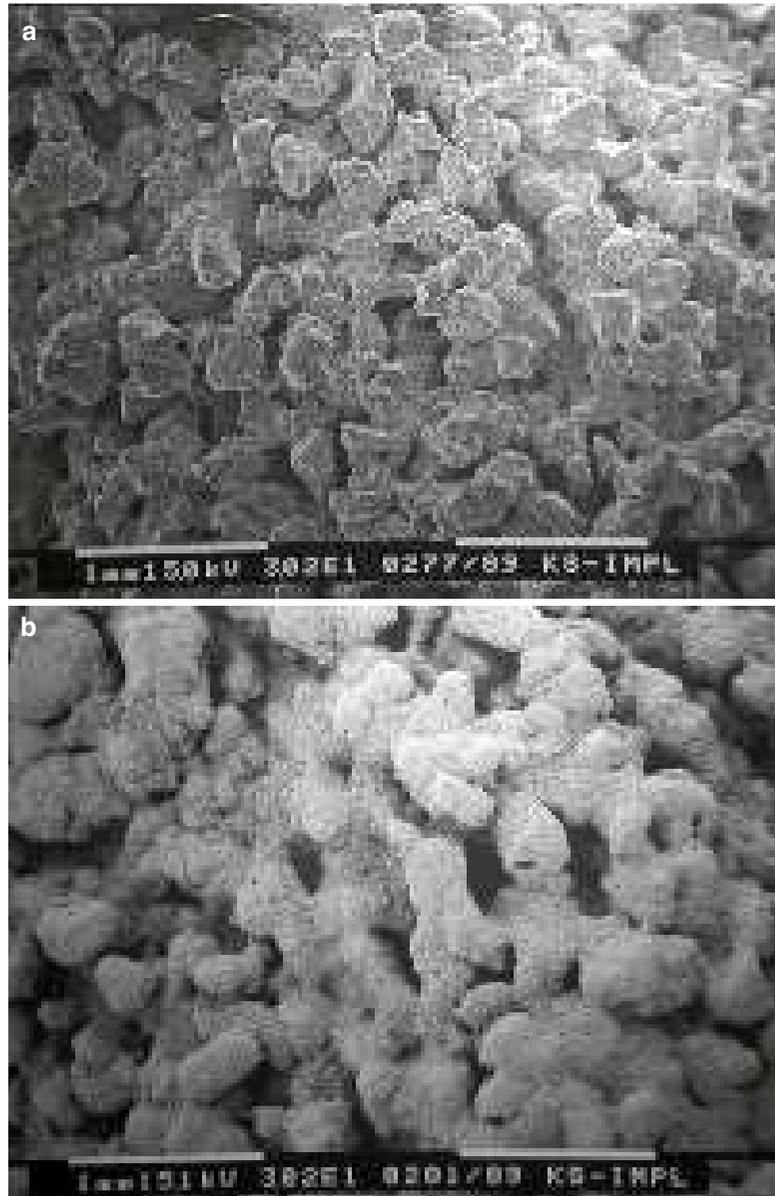
The types of implant coatings were Ti (plasma-sprayed) and HA (plasma-sprayed). The cylindrical Ti- and HA-coated plugs were 6 mm in diameter with an overall length of 10 mm, fabricated with a precision of ± 0.05 mm. Ti implants consisted of a solid Ti-6Al-4V alloy core with a coating of Ti6Al-4V deposited by plasma-spray technique resulting in a mean pore size of 300 μm

(Fig. 8.4a). The HA-coated implants consisted of analogous Ti porous-coated implants on which a layer of spray-dried synthetic HA was deposited by plasma-spraying (Fig. 8.4b). According to the manufacturer, the strength of attachment between the HA and the substrate, as determined by ASTM standard C-633 for cohesive strength of coatings to metal, revealed minimum tensile strength of 34.5 MPa and a minimum shear strength of 20.7 MPa. Results from X-ray diffraction analysis of the ceramic coating are given in including the crystallinity, Ca/P ratio, and coating thickness.

Models for Implantation

The site for implantation was selected to mimic the clinical patient findings, including presence of a cancellous bone bed. The distal femoral epiphysis was therefore chosen as the implantation site because it contains cancellous bone and is affected by arthritic joint changes. Two basically different models were used. In the first five studies in the series, an *unloaded* model was used, and in the last three studies, a *loaded* model was used [136–141]. The unloaded model was employed to study the amount of bone apposition onto HA and Ti implant surfaces under standardized conditions without possible variations in load pattern of the implant. A *gap* model was developed in which the holes were drilled 2 mm larger in diameter than the diameter of the implant, permitting a 1 mm gap surrounding the implants (Fig. 8.5a). The implants were centralized by two titanium spacers fixed at each end of the implant. In addition, a *bone graft* model was developed in which 2 mm over reaming was conducted to study incorporation of bone graft around implants. The graft was added until the canal was filled, and a Ti washer was mounted to keep the graft in place and to superficially centralize the implant. Finally, a *micromotion* device was constructed. This model consisted of an implantable dynamic device (Fig. 8.6) that was inserted into the knee joint as illustrated in Fig. 8.7. The system was adjusted preoperatively to a stiffness of approximately 14 N/mm with a preload of 0.5N, the total

Fig. 8.4 (a) Scanning electron microscopy of titanium (a) and hydroxyapatite (b) coating. Note the porous structure of titanium coating (a) and the preservation of pores after coating with HA. $\times 50$. Bar = 1 mm (From Soballe et al. [137])



displacement force being 10 N. The maximal movements in the axial direction could be predetermined and limited to the desired amount owing to the design of the device. Movements of 500 *mi* and 150 J.tn were used.

Evaluation

After termination, the distal femora were prepared. Standardized sections were cut at a right

angle to the long axis of the implant. One section was used for UV fluorescence microscopy, another for histomorphometric and morphologic evaluation on ground-stained specimens and one for mechanical testing. In addition, some results were evaluated by polarized light microscopy, collagen analysis, and transmission electron microscopy with microanalysis (EDAX).

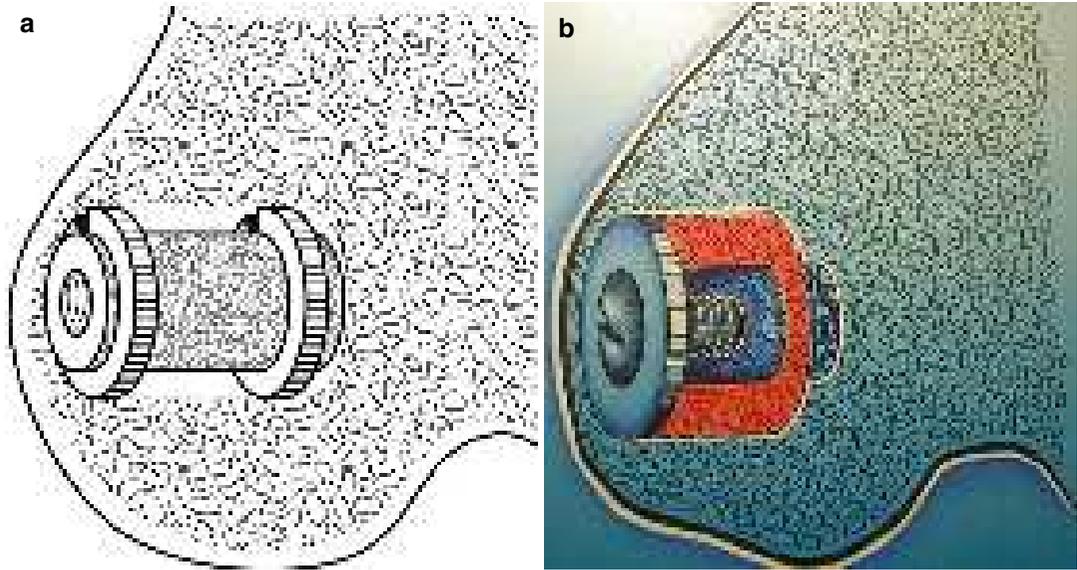


Fig. 8.5 (a) Schematic drawing showing an implant centralized in a drill hole by two Ti washers. This provides a 1 mm gap around the implant. (b) Schematic drawing showing an implant centralized in the overreamed canal, surrounded by a 2 mm gap that allows bone graft to be

packed around the implant. The deep part of the implant is fixed in the bone by press fit. A Ti washer keeps the graft in place and centralizes the implant superficially. Dotted area illustrates bone graft (From Soballe et al. [140])

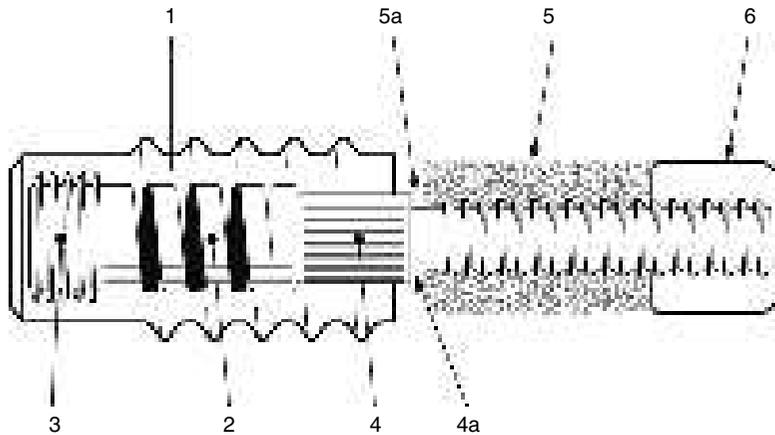


Fig. 8.6 The unstable device consists of seven components all manufactured from titanium alloy (Ti-6Al-4V) as the porous-coated Ti implant. A hollow Ti cylinder (1) with self-tapping threads ensures firm fixation in the bone. A spring (2) is placed inside the cylinder and held in place by a screw (3) at one end. In the other end a Ti piston (4) can move freely in the axial direction. When mounted, the platform (4a) on the piston projects exactly 500 m over the end of the Ti cylinder. When the implant (5) is screwed onto the threads of the piston and axial bar is applied on the polyethylene plug (6), the implant will move until it is

stopped by reaching the Ti cylinder, and the movement is limited to 500 μm . To prevent rotation of the piston, one end of the spring is fixed to the piston (4) and the other to the screw (3), which is locked into the Ti cylinder by a small polyethylene plug inserted into the threads of the screw. A hole through the piston and the polyethylene plug connects the compartment in the Ti cylinder with the knee joint. The coating is removed at the distal end of the implant (5a) to prevent bony ingrowth in this area (From Soballe et al. [138])

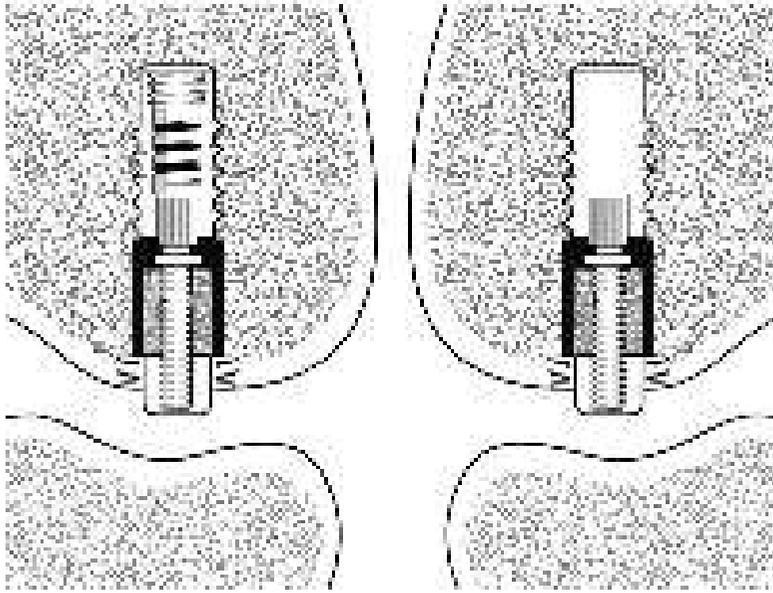


Fig. 8.7 The dynamic system consists of an implantable device manufactured from titanium alloy (Ti-6Al-4V) which is inserted into the weight-bearing part of the medial femoral condyle (see Fig. 8.5). Details of the dynamic device are shown in Fig. 8.7. The polyethylene plug projects above the femoral articular cartilage. A Ti ring is mounted subchondrally and serves as a bearing and centralizer for the polyethylene plug. When the knee is

loaded during gait, load transfer from the tibial part of the knee will displace the polyethylene and the implant in axial direction and tighten the spring. When the leg later is unloaded, the tightened spring will move the implant back to the initial position. Thus, a controlled movement (pre-determined to 500 μm or 150 μm) will occur during each gait cycle (From Soballe et al. [138] and [139])

Findings of Experimental HA Plasma-Sprayed Implant Studies

Effect of a Gap Between Bone and Implant

The effect of HA was investigated when implants were surrounded by a gap compared with press-fit implants [136]. The observation period was 4 weeks and six mature dogs comprised the material. The initial 1 mm gaps surrounding the Ti implants were bridged by very limited amounts of immature woven bone, whereas a great amount of newly formed bone filled the gap around the HA-coated implants. Bone tissue was observed on the HA implant surface, with no interposed fibrous tissue layer present. In some areas a thin fibrous layer separated the Ti implant surfaces from the ingrown bone, but in other areas direct apposition of bone was noted. The gap around the Ti-coated implants led to a 65 % reduction in fixation as compared with the

press-fit implants. In contrast, no differences were found between the “gap” and press-fit implants when an HA coating was used. Surrounded by a gap, the fixation of HA-coated implants was 120 % increased as compared with Ti implants. The corresponding value for shear stiffness was 425 %. No effect of HA coating was obtained when implants were inserted in press fit. The greatest amount of bone ingrowth was found with the press-fit, HA-coated implants. This was increased compared with HA-coated implants surrounded by a gap which, again, was greater than Ti implants in press fit. The smallest amount of bone ingrowth was found in Ti implants surrounded by an initial gap.

Effect of Bone Grafting on Implant Fixation

A model was created (Fig. 8.5b) to study cancellous allogeneic bone graft incorporation into Ti- and HA-coated implants with and without

bone graft. The observation time was 6 weeks, and 12 mature dogs were used. The cancellous bone graft was taken from the proximal humerus from 12 other dogs, stored in sterile containers at -80°C , and milled into a homogeneous graft. This study demonstrated a 400 % enhanced fixation of grafted Ti-coated implants compared with that of the overreamed controls (Fig. 8.8). However, HA coating used without bone graft was capable of enhancing the fixation to nearly the same degree. Only minor improvement was obtained when bone graft was used together with HA. Since both components are known to increase bony ingrowth when used separately, this lack of a measurable additive effect of adding bone graft to HA-coated implants might be explained by the presence of bone graft packed around the implant, which could have eliminated the osteoconductive effect of HA.

Effect of Micromotion on Implant Fixation

Obtaining rigid initial stability appears to be one of the major problems in noncemented joint replacement surgery and is initially dependent on the strength of the mechanical interlock achieved between implant and bone during implantation. Several studies have investigated the stability of hip and knee prostheses immediately after implantation, and there is agreement that relative movement between implant and bone occurs in the range of 100–600 μm [143, 145].

500 μm Movements

Seven mature dogs were used. Push-out test showed that the shear strength of unstable Ti and HA implants was significantly reduced as compared with the corresponding mechanically stable implants ($p < 0.01$). However, shear strength values of unstable HA-coated implants were significantly greater than those of unstable Ti implants ($p < 0.01$) and were comparable to those of stable Ti implants. The greatest shear strength was obtained with stable HA-coated implants, which was increased threefold as compared with the stable Ti implants ($p < 0.001$). Quantitative determination of bony ingrowth confirmed the mechanical test, except for the stronger anchorage of unstable HA implants as

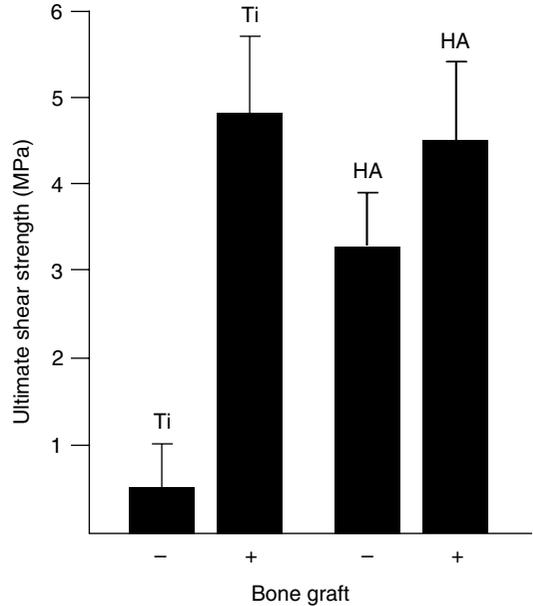


Fig. 8.8 Results from push-out test. Use of bone graft filled in the defect is illustrated by -/-, - indicates that bone graft was not used, leaving the implant surrounded by a 2 mm gap. Mean \pm SEM, $n = 7$

compared with unstable Ti implants, in which no difference in bony ingrowth was found. Collagen concentration was significantly higher in membranes around HA-coated implants as compared with membranes around Ti implants.

150 μm Movements

This study comprised 14 mature dogs. Results from the 500 μm study were reproduced in this study regarding the presence of fibrocartilage around unstable HA-coated implants, whereas fibrous connective tissue characterized the membrane around unstable Ti implants. In addition, this study revealed a thinner membrane around unstable HA implants compared with unstable Ti implants. A radial orientation of collagen fibers was found in the membrane around unstable HA-coated implants, whereas a more random orientation was found in most membranes around Ti implants. The shear strength of unstable HA-coated implants was significantly greater than that of unstable Ti implants ($p < 0.001$) but also greater than that of stable Ti implants ($p < 0.05$). The greatest shear strength obtained by stable HA-coated implants was tenfold higher than that of stable Ti

implants. No significant difference was demonstrated between the amount of bone apposition on the unstable HA and stable Ti implants. The gap-healing capacity around stable HA-coated implants increased toward the HA surface and was significantly greater than that of Ti implants.

In conclusion, initial stability of the implant was shown to be a prerequisite for achieving bone ingrowth [137–139]. However, HA coating seemed to be capable of modifying the fibrous membrane, resulting in a stronger fibrous anchorage when subjected to relative motion between bone and implant.

Magnitude of Motion

The threshold of implant motion that allows bone ingrowth is still unknown. There appears to be a relationship between the magnitude of bone-implant motion and the type of interfacial tissue developed. It is therefore interesting to look at the effect of different amounts of movement on implant fixation. An increased fixation strength was obtained with decreased range of motion (500–150 μm) by both HA and Ti implants and a further increase in fixation when the observation time was extended from 4 to 16 weeks [137–139]. Comparing the fixation strength of continuously loaded Ti implants with 16 weeks of observation time (1.8 MPa) with those from the 4 weeks study with HA coating (1.85 MPa) indicates that the fixation of fibrous-anchored HA implants is obtained in one-quarter of the time required for the equal fixation of implants without HA coating.

Effect of HA Coating on Implant Fixation

In experimental studies on plasma-sprayed HA implant coating [139–141], the gap-healing capacity of bone was increased by HA coating compared with Ti coating, even at a relatively great distance from the HA surface. This indicates that the osteoconductive effect of HA is not limited to the bone-forming capacity on the surface of the implant. HA also activates bone formation at some distance from the surface. The positive gradient of bone demonstrated toward the HA surface indicates that the osteoconductive effect of HA is more pronounced close to the surface under stable conditions [139]. In conclusion, early experi-

mental studies establishing performance of HA showed strong bonding of HA-coated implants.

Summary of Experimental HA Plasma-Sprayed Implant Studies

The success of bone ingrowth into porous-coated implants depends on several factors which can be separated into four main groups: status of host bone bed, implant-related factors, mechanical stabilization and loading conditions applied on the implant, and adjuvant therapies. The present series of studies was performed to investigate the effect of HA coating on bone ingrowth into porous-coated implants subjected to pathologic and mechanical conditions mimicking the clinical situation. Host bone-related factors were studied in the first four experiments. First, the significance of a gap between bone and implant was studied and compared with press-fit insertion. The HA coating yielded a superior effect on bone ingrowth compared with Ti in situations where the implant was surrounded by a gap. No effect was found in the press-fit situation. Gaps of 1 and 2 mm around the implant were bridged by bone around HA implants, whereas significantly smaller amounts of bone filled the gap around Ti implants. To study the effect of adjuvant therapies, a bone graft model was developed to investigate bone graft material in combination with Ti- and HA-coated implants. Allogeneic bone graft packed around the implant enhanced the anchorage of Ti implants, but HA coating alone without bone graft offered almost the same improvement in anchorage in 2 mm defects. Only minor improvement was obtained when bone graft was used together with HA. The last three experiments focused on the significance of mechanical stabilization and loading conditions of the implant immediately after surgery. Micromotion between bone and implant prevented bony ingrowth and resulted in development of a fibrous membrane. HA coating was shown to modify this fibrous membrane, as evidenced by presence of fibrocartilage, higher collagen concentration, radiating orientation of collagen fibers, and a thinner membrane as compared with Ti-coated implants. In a long-term study (16 weeks), the membrane around HA implants was demonstrated to be replaced by

bone even when subjected to continuous load, whereas the membrane around Ti implants persisted after 16 weeks. Great amounts of bone ingrowth into loaded but stable HA-coated implants were demonstrated even in the presence of an initial gap around the implant. Dynamic load was even demonstrated to increase the amount of bone ingrowth into HA-coated implants, which was threefold greater compared with completely unloaded implants. This effect of dynamic load was not demonstrated on Ti implants. The best anchorage and the greatest amount of bone ingrowth were obtained in the loaded stable situation when the implant was coated with HA. Increased fibrous fixation was obtained with decreased range of motion (from 500 to 150 μm) by both HA and Ti implants, and a further increase in fixation was obtained when the observation time was extended from 4 to 16 weeks. From these studies it could also be demonstrated that the fixation of fibrous-anchored HA implants was obtained in one-quarter of the time required for the equal fixation of implants without HA coating. The consequence of immobilization of a motion-induced fibrous-anchored implant was complete replacement of the membrane by bone, irrespective of the type of coating.

Experimental Studies on Electrochemical-Deposited HA (EDHA) Coated Implants

Electrochemically deposited HA coatings (EDHA) have been introduced in the dental [15, 17, 18, 22, 73, 74, 78, 80] and orthopedic field [16, 19–21, 48, 57, 58, 76, 77, 79] in experimental studies with various animal models. The osteoconductive effect of EDHA has shown potential with regard to implant integration in bone as to *mechanical fixation* [16, 20, 21, 58, 73, 74, 76–78] and *osseointegration* [15, 17–20, 22, 48, 73, 76, 77, 79, 80].

EDHA Versus Titanium

Electrochemical deposition of a HA coating on titanium-aluminum-vanadium (Ti-6Al-4V)

implants significantly improved the *osseointegration* after 1 month in a study by Schliephake et al. [18], while no significant differences in bone in contact were found after 3 months. In a subsequent study from the same group, similar differences were seen at reversed time points [22]. Schmidmaier et al. [20] demonstrated better bone ingrowth of the EDHA-treated implants, with significantly more direct bone in contact compared to a control group of titanium implants after 2 months. Similar results are seen by Yang et al. at 4 and 8 weeks [48], by the same research group at 6 and 12 weeks [57], and in studies by Costa [17] and Badr [80].

Yang et al. [58] evaluated the *implant fixation* with bone tissue of EDHA-coated implants compared to non-coated implants. At time point 2, 4, and 8 weeks, the fixation evaluated by removal torque was increased significantly in the EDHA group. Ban et al. [16] report similar results on the early-stage fixation between bone and implant [16] at 3 and 6 weeks with no remarkable difference at 9 weeks. The research group by He et al. [78] evaluated EDHA coated and uncoated sand-blasted/dual acid etched implants after 2, 4, 6, 8, and 12 weeks of bone healing, and found that removal torque testing fixation improved of the EDHA-coated implants after 2 weeks of healing with similar values after 6, 8, or 12 weeks of healing implying a beneficial effect on interfacial shear strength during the early stages of bone healing.

Schwarz [77] and Reigstad [73] evaluated both the short-term *osseointegration and implant fixation*. Schwarz et al. [77] showed at 12 weeks the implant anchorage measured by the pullout test was not improved. The EDHA enhanced significantly bone-implant contact but not the level of anchorage. Reigstad et al. [73] compared EDHA (Bonit) and non-coated implants in tibia and femur after 6 and 12 weeks of insertion. The biomechanical removal torque test showed significantly increased values for the coated implants after 12 weeks but not after 6 weeks of integration. Higher bone-implant contact was found for the coated implants in the tibia after 6 weeks and for both tibial and femoral screws after 12 weeks. There was no difference in the inflammatory reaction around the implants, and possible grains

of the coating could be detected after 6 weeks, but not after 12 weeks of follow-up. Schmidmaier et al. [20] found at 2 months a higher fixation and bone ongrowth of the EDHA-coated implants compared to the uncoated controls.

EDHA Versus HA Plasma-Spray

Osseointegration of EDHA-coated implants compared to HA plasma-spray was investigated by Wang et al. [19]. They demonstrated improved initial bone formation of plasma-sprayed HA coatings with higher bone apposition ratios than those exhibited by bare Ti-6Al-4V and EDHA coatings after 7 days. However, at 14 days after implantation, EDHA and plasma-sprayed HA coatings exhibited similar bone apposition ratios that were much higher than that of the uncoated Ti-6Al-4V.

Reigstad et al. [74] compared the *mechanical fixation* of EDHA-coated implants (Bonit) to HA plasma-spray as a subsequent study of EDHA-coated to non-coated implants [73]. The removal torque demonstrated stronger bone-to-implant fixation for the HA- than EDHA-coated screws at 6 and 12 weeks with no significant difference after 52 weeks.

Daugaard et al. [21] evaluated the *osseointegration and mechanical fixation* of implants coated with plasma-sprayed hydroxyapatite coating and a thinner coating of electrochemical-assisted deposition of hydroxyapatite during the early stages of implant fixation and bone regeneration. The electrochemical-assisted deposition was performed near physiological conditions, and uncoated plasma-sprayed titanium alloy (Ti-6Al-4V) served as negative control. The hydroxyapatite plasma-spray implants were prepared using the same standard hydroxyapatite

plasma-spraying technique as for clinical applications, with specifications: 50- μm -thick HA coating (Ca/P ratio 1.67), a mean surface roughness (R_a) of 41 μm , a maximum roughness depth (R_y) of 445 μm , and 62 % hydroxyapatite. The electrochemical-assisted hydroxyapatite deposition was done by a time (75 min)-, temperature (36 °C)-, and pH (6.4)-controlled process in an electrolyte solution consisting of 1.67 mM CaCl_2 and 1 mM $\text{NH}_4\text{H}_2\text{PO}_4$ in equal volumes with the sample polarized in cathode galvanostatic mode (-75 A/m^2). The layer consisted of 70 % crystalline hydroxyapatite and a thickness of 5 μm (Ca/P ratio 2.0) [24, 25]. A canine experimental 1 mm model was used, and observation time was 4 weeks. Hydroxyapatite coatings deposited by plasma-spray technique or electrochemically had a significantly improved mechanical fixation compared to the titanium controls with no difference between the two hydroxyapatite coatings (Table 8.1). At 4 weeks, implants displayed bone formation expanding the gap. All hydroxyapatite coatings showed significantly increased bone ongrowth compared to the titanium control with no statistical difference between the individual hydroxyapatite applications (Table 8.2). The HA coating was not visible for the electrochemical HA coating but still apparent of the plasma-sprayed HA with a thickness of 30–50 μm .

Similar findings on osseointegration and implant fixation are described by Ishizawa et al. [15, 76] and osseointegration by Lakstein et al. [79].

Clinical Results of HA Coatings

In the decades since the early experimental evidence for the role of HA in improving implant fixation, numerous prospective clinical studies

Table 8.1 Mechanical testing

	Ultimate shear strength (MPa)	Apparent shear stiffness (MPa/mm)	Total energy absorption (J/m^2)
P-Ti	0.0 (0.0–0.3)	0.0 (0.0–1.3)	0 (0–45)
P-HA	2.1 (1.5–3.2) ^a	7.8 (4.2–17.9) ^a	535 (213–574) ^a
E-HA	2.0 (0.7–3.4) ^a	9.0 (2.7–16.6) ^a	339 (92–618) ^a

Data presented as median and interquartile ranges. $n=7$

P-Ti plasma-spray titanium alloy, *P-HA* plasma-spray hydroxyapatite coating, *E-HA* electrochemical-assisted hydroxyapatite coating

^a $p < 0.05$ compared to P-Ti [152]

Table 8.2 Histomorphometry

Ongrowth	Bone	Marrow	Fibrous tissue
P-Ti	3 (0–3)	33 (21–50)	56 (45–76)
P-HA	51 (20–62) ^a	33 (10–35)	15 (2–71)
E-HA	18 (5–25) ^a	54 (32–68) ^b	21 (17–64) ^a
0–500 µm	Bone	Marrow	Fibrous tissue
P-Ti	11 (10–16)	71 (52–77)	13 (12–17)
P-HA	18 (11–27)	65 (61–69)	9 (0,7–27)
E-HA	24 (11–28) ^a	67 (51–75)	11 (4–16)
500–1,000 µm	Bone	Marrow	Fibrous tissue
P-Ti	11 (6–18)	80 (72–88)	0,1 (0–0.7)
P-HA	13 (10–29)	81 (69–85)	0 (0–0.2)
E-HA	19 (14–22) ^a	75 (72–83)	0 (0–0.5)

Density (percentage) of bone, marrow-like and fibrous tissue at the implant surface, concentric zone 0–500 µm, and 500–1,000 µm

Median, interquartile ranges. $n=7$

P-Ti plasma-spray titanium alloy, *P-HA* plasma-spray hydroxyapatite coating, *E-HA* electrochemical-assisted hydroxyapatite coating

^a $p<0.05$ compared with titanium

^b $p<0.05$ compared with HA plasma-sprayed [152]

have been undertaken. Tables 8.3 and 8.4 summarize recent literature (2009–2012) for studies on plasma-sprayed and electrochemically deposited HA that are prospectively randomized, with long-term follow-up, or using RSA methodology. The clinical studies on electrochemically deposited HA implant coatings are further described in detail in the next paragraph of this chapter.

The preponderance of evidence indicates that HA coating either improves or does not change the clinical durability and survival of an implant and that function is either unchanged or improved. In other words, HA does not appear to have deleterious effects in clinical use, and with specific conditions it enhances fixation, extends implant survival, and improves patient function. While HA is most often used in the femoral component of THA, several studies evaluate its use in the acetabular component of THA and in the tibial component of TKA.

Acetabular loosening is more common than femoral component loosening, but the literature on the topic is sparse and conflicting. Gottlieb

et al. [166] demonstrated less osteolysis and loosening with HA-coated acetabular cups, despite increased wear with HA. In a Swedish Registry study of 8,043 acetabular cups, Lazarinis [167] demonstrated an adjusted RR of 1.7 for HA coating compared to non-HA porous-coated cups, questioning the use of HA in primary components. Stilling [168], in a 15-year follow-up on a prospective randomized study, showed inferior survival of first-generation plasma-spray cups compared to non-HA porous-coated cups. Specific attributes of HA that are noted in recent clinical studies are that it can effectively seal the femoral bone-implant interface from migration of polyethylene wear debris [164]. RSA studies generally demonstrate moderate initial migration (3–6 months postoperatively), which then stabilizes. Importantly, a recent long-term (11–16 years) RSA study of HA- and non-HA-coated tibial components demonstrated that the reduced migration with HA is durable for this extended period. This supports the premise also for HA, of secure early fixation being indicative of long-term durability.

Clinical Studies on Electrochemical-Deposited HA

Clinical proven HA alternatives to the plasma-spray HA is the electrochemical-deposited HA coating [81–86].

The *osseointegration* of electrochemically deposited HA on implants has been studied in *case reports* by ten Broeke [81] and Malchiodi [86]. ten Broeke et al. [81] analyzed four retrieved Symax femur stems at 3, 9, 13, and 32 months, respectively, due to infection, recurrent dislocation, and acetabular fracture. The Symax stem (Stryker, Montreux, Switzerland) is a straight tapered stem forged of titanium alloy (Ti-6Al-4V) with a proximal electrochemically deposited HA (EDHA) (Bonit, DOT GmBH, Rostock, Germany) on a plasma-sprayed, commercially pure titanium coating [75]. Distally the stem is anionic oxidized (Dotize, DOT GmBH, Rostock, Germany) [81], which reduces protein adsorption and consequently distal bone apposition and

Table 8.3 Clinical primary implant studies on plasma-sprayed and electrochemically deposited implants

Author, year	Type of study	Joint, patient demographics, and number	Follow-up	Revision or failure rate/subsidence	Functional measures	Author conclusions
Femoral component						
YH Kim, 2012 [153]	Prospective study of bilateral simultaneous primary THA; component identical geometry (with or without hydroxyapatite coating), by one surgeon	55 patients (110 hips) Age at surgery: 46.3 years (27–63 years)	15.6 years (15–16 years)	Cumulative survival for the stem was 100 % in both groups, and for the cup was 89 % in both groups	The mean Harris hip score in both groups improved from 39 points and 41 points, respectively, to 93 and 91 points	After long-term follow-up, the porous surfaces did not improve or diminish the results of total hip arthroplasty
Bercovy M et al., 2012 [154]	Prospective study comparing HA vs. cemented tibial components	157 (HA)-coated tibial components with 164 cemented components in 291 patients (ROCC rotating platform total knee)	7.6 years (5.2–11)	1 HA revised, 1 cemented revised, revision as endpoint, survival at 9 years was 99.1 %	Radiological assessment of the tibial interface HA was more stable ($p < 0.01$). Operating time was shorter ($p < 0.006$) for HA	HA-coated components perform at least as well as the same design with cemented fixation of both components
von Schewelov, T, 2012 [155]	Prospective RSA measure of fixation of dislocated femoral neck fracture fixed with fully HA-coated Coral total or hemiarthroplasty	38 patients achieved follow-up. Mean age 81 (70–96) years	24-month follow-up	31 of the 38 implants migrated distally and rotated (retroversion), until 3 months, then stabilized. There was more distal migration with undersized stem and no correlation with BMD	Migration did not result in clinical complications	Migration occurred up to 3 months and then stabilized and was not correlated with bone BMD. Clinical results were favorable
Pijls BG, 2012 [156]	Prospective randomized controlled trial of RSA migration of HA-coated, uncemented, and cemented tibial components in TKA	68 knees: 24 HA-coated, 20 uncemented, 24 cemented	11–16 years (or death or revision)	10-year mean migration: HA – 1.66 mm, uncemented – 2.25 mm, 0.79 mm – cemented TKA ($p < 0.001$). Seven revisions occurred: aseptic loosening (2 uncemented and 1 cemented), septic (2 uncemented and 1 cemented), instability (1 HA coated)	Clinical (KSS) and radiographic scores were not statistically significantly different. KSS was not different between the fixation types ($p = 0.9$, GLMM adjusted for age, sex, diagnosis, revisions, and BMI)	HA reduces migration of uncemented tibial components, most notably in first years after surgery. The positive HA effect is durable to 10 years, and delamination of HA layer did not occur. Cement had lowest migration overall and is safe choice for TKA

(continued)

Table 8.3 (continued)

Author, year	Type of study	Joint, patient demographics, and number	Follow-up	Revision or failure rate/subsidence	Functional measures	Author conclusions
Bjoe B et al., 2011 [83]	Prospective RSA measure of fixation of BoneMaster® (BM; electrodeposit) and plasma-sprayed hydroxyapatite (HA) on identical stem geometry	50 patients (55 hips). Taperloc (Biomet) stem is tapered and porous coated proximally, with either HA or BM coating	2 years (postoperatively 3, 6, 12, and 24 months). 1 patient did not have follow-up	Subsidence at 2 years: 0.25 (HA) and 0.28 (BM) mm. No statistically significant differences between the groups for both migration and rotation. The BM group retained significantly more bone than the HA group in Gruen zone 1 during the first 2 years	Harris hip score at 2 years: BM increased from 55 (pain score 20) to 95 (pain score 41). HA increased from 52 (18) to 89 (38). No significant change in Oxford hip score at 2 years: improved from 39 to 16 (BM) and from 35 to 19 (HA)	At 2 years, with RSA analysis, the Taperloc stem with BoneMaster® not inferior to plasma-sprayed HA, based on clinical and radiological results, bone remodelling, and micromotion
Vidalain JP, 2011 [157]	Continuous prospective study of fully HA-coated femoral component	Full HA coating applied on a straight and proximally flared stem. Cohort of 347 prostheses in 320 patients (24 bilateral THR), by single surgeon. 155 women/165 men. Mean age at surgery 63.3 (30–88)	Mean 20.9 ± 1.2 years. 36.5 % of the initial cohort (51.5 % had died at this follow-up)	Stem survival probability is 96.3 % at 23 years. Late complications (25.9 %) are dominated by revisions; 13 cases of recurrent dislocation 48/62 hips were revised due mainly to acetabular complications	83 % radiologically “silent.” 15 % have radiographic signs (calcar scalloping, osteolysis)	Fully HA-coated stem demonstrates durable survival at 201-year follow-up. Acetabular complications predominate
CampbellID et al., 2011 [158]	Prospective study (RSA) early migration pattern of HA press-fit femoral component with high reported survivorship (97 % at 15 years [16])	30 patients who underwent THA for osteoarthritis. One hydroxyapatite-coated press-fit femoral component [1, 16]	Median age 70 (55–80) years. Follow-up at 3–4 days, 6 months, 1 year, and 2 years	Mean subsidence of 0.73 mm at 6 months, 0.62 mm at 1 year, and 0.58 mm at 2 years and mean retroversion of 1.82° at 6 months, 1.90° at 1 year, and 1.59° at 2 years	Harris hip total score (35.41 ± 10.05), 1 year (87.00 ± 14.24), 2 years (88.13 ± 12.36). Improvement in mean Harris score preoperative to 1 year, but no additional improvement at second year	Subsidence occurs in first 6 months after which there was no further subsidence. Functional scores improve to 1 year

<p>Voigt J et al., 2011 [159]</p>	<p>A systematic review of prospective randomized trials to determine if they favored HA-coated tibial components</p>	<p>Data from 926 evaluable primary total knee implants in 14 studies were analyzed. Patients >65 years of age</p>	<p>2 (RSA) and 8–10 years (functional)</p>	<p>HA-coated tibial components (porous or press fit) without screw fixation were less likely to be RSA unstable at 2 years than porous and cemented metal-backed tibial components (RR = 0.58, 95 % CI: 0.34–0.98; <i>p</i> = 0.04, I(2) = 39 %)</p>	<p>No significant functional status difference at 2 and 5 years and no significant difference in adverse events</p> <p>HA-coated tibial implant may provide better durability than other forms of tibial fixation. Larger trials should be undertaken comparing the long-term durability, function, and adverse events of HA-coated implants with those of other porous-coated tibial implants in younger, more active OA patients</p>
<p>Baker PN et al., 2010 [160]</p>	<p>Case series of proximally HA-coated femoral stem</p>	<p>ABG I prosthesis (Stryker Howmedica Osteonics) HA coating proximally in 63 patients (69 hips)</p>	<p>Mean 15 (13–17) years</p>	<p>15-year survival of acetabular component was 86.9 % (95 % confidence interval, 71.7–96.0 %), and the 15-year survival of the femoral component was 98.6 % (95 % confidence interval, 88.8–100.0 %)</p>	<p>No factors associated with the presence of osteolysis (gender, age at primary surgery, Oxford hip score, cup abduction, and acetabular polyethylene wear rates)</p> <p>The ABG I femoral prosthesis shows durable results. Ongoing radiographic review is recommended to detect progressive osteolysis that otherwise remains clinically silent until failure</p>
<p>Mannan K et al., 2010 [161]</p>	<p>Longer-term follow-up of previously reported 100 Freeman hip stems, retaining neck and with proximal HA coating</p>	<p>52 men (six bilateral), 40 women (two bilateral). The mean age at THR: 58.9 years (19–84)</p>	<p>20 years (minimum 17 years). 6/92 patients lost to follow-up but were included up to last clinical review. 22/92 patients (22 hips) died, from causes unrelated to surgery</p>	<p>One (undersized) stem migrated 7.6 mm at 10 years/8.4 mm at revision at 14 years. Stem survivorship at 17 years with aseptic loosening as endpoint was 98.6 % (95 % confidence interval 95.9–100) when 62 hips were at risk</p>	<p>All remaining stems had a satisfactory clinical and radiological outcome</p> <p>The Freeman proximally hydroxyapatite-coated femoral component continued its satisfactory function with longer follow-up</p>
<p>Camazzola D et al., 2009 [162]</p>	<p>Prospective randomized trial comparing identical hydroxyapatite (HA)-coated and non-HA-coated femoral THR components</p>	<p>61 consecutive patients randomized</p>	<p>13 years and 5 months average. 48/61 hips available for follow-up</p>	<p>1 femoral stem revised secondary to femoral fracture. All femoral stems well fixed on X-ray. No statistically significant difference in revision rates</p>	<p>No statistically significant difference Harris hip score between</p> <p>This study suggests there is no clinical advantage to the use of a hydroxyapatite coating on the femoral component of this design for primary total hip arthroplasty (Incomplete follow-up of all patients)</p>

(continued)

Table 8.3 (continued)

Author, year	Type of study	Joint, patient demographics, and number	Follow-up	Revision or failure rate/subsidence	Functional measures	Author conclusions
Gandhi R et al., 2009 [163]	Meta-analysis of clinical studies of HA-coated femoral stems in hip arthroplasty	9 studies met inclusion criteria	2–13 years	The cumulative risk ratio for femoral stem survival from aseptic loosening: 1.0 (95 % CI: 0.995–1.005) $p = .98$	Pooled mean difference for the Harris Hip scores (HHS): 0.072 (95 % CI: -0.062 to 0.206), $p = .293$	The results of meta-analysis demonstrate that there are no clinical benefits in the use of HA/porous coating over porous coating alone in primary hip arthroplasty (based on risk ratio for stem survival and Harris hip score)
Emans P et al., 2009 [164]	Hydroxyapatite-coated total hip arthroplasties with polyethylene-metal articulation	Sixty-five THA in 57 patients (age <50 years)	Minimum 10 years	Around HA-coated parts of the prosthesis bone formation remained stable, regardless of the degree of polyethylene wear	The average linear polyethylene wear was 0.16 mm/year	The circumferential osseous apposition of the HA-coated implants possibly formed a protective barrier against articular wear debris.
Goosen JHM et al., 2009 [165]	Retrospective review of articles published prior to September 2007 – Eight randomized controlled studies with 857 patients	Randomized trials of porous-coated identical geometry femoral components with and without hydroxyapatite coating.	1–10.5 years	Radiologically, equal presence of endosteal bone ingrowth (RR: 1.04, $p = 0.66$) and radioactive lines (RR: 1.02, $p = 0.74$) in the surface area of the prosthesis. Subsidence data could not be pooled.	Pooled analysis for Harris hip score: no advantage for HA (WMD: 1.49, $p = 0.44$).	This meta-analysis demonstrates neither clinical (Harris hip score) nor radiologic (ingrowth but not subsidence) benefits on the application of a hydroxyapatite coating on a femoral component in uncemented primary total hip arthroplasty
Acetabular component						
Gottlieb M., 2012 [166]	Retrospective from Danish Arthroplasty Registry of HA and non-HA-coated cementless Mallory-Head acetabular cups	77 HA-coated cups and 73 non-HA-coated cups. Mean age was lower ($p = 0.001$) in the HA group (57 years) compared with the non-HA group (63 years)	Mean follow-up was 11 years	There were no cup revisions in the HA group and 7 cup revisions in the non-HA group ($p < 0.01$). Significantly more osteolysis in cups in the non-HA group	Linear PE wear rate of 0.18 mm/year was higher ($p < 0.001$) in the group with HA-coated cups compared with 0.12 mm/year in the group with non-HA-coated cups	Increased PE wear with HA-coated cups did not have a negative influence on the revision rate, but may result in a need for revision surgery over time

<p>Lazarinis S et al., 2010 [167]</p>	<p>Retrospective from Swedish Hip Arthroplasty Register (1992–2007)</p>	<p>6,646 acetabular cups of same design with or without HA coating</p>	<p>Follow-up started on the day of primary THA and ended on the day of revision, death, emigration, or December 31, 2007, whichever came first</p>	<p>HA was a risk factor for cup revision due to aseptic loosening (adjusted RR 1.7; 95 % CI: 1.3–2) as were age <50 at initial surgery, cemented stem, Romanus & Harris-Galante cups</p>	<p>“Our findings question the routine use of HA-coated cups in primary total hip arthroplasty. With some designs, this practice may even increase the risk of loosening—resulting in revision surgery.” Cup design is important</p>
<p>Stilling M et al., 2009 [168]</p>	<p>Prospective randomized, hydroxyapatite and Ti acetabular cups followed with RSA analysis</p>	<p>28 hips (Ti and HA acetabular cups); 1 lost to follow-up in each group. Total = 26 cups (13 Ti and 13 HA)</p>	<p>15 years</p>	<p>More ($p=0.045$) HA cups revised than Ti cups: eight of 14 HA cups (57 %) and two of 12 Ti cups (17 %). All cups revised had wear rates greater than 0.4 mm/year or osteolysis greater than 25,000 mm³</p>	<p>At revision surgery, aseptic loosening, massive acetabular osteolysis, and metallosis clinically evident for all revised cups</p>

Summary of clinical studies evaluating HA on primary femoral components, published 2009–2012

Table 8.4 Clinical revision implant studies on plasma-sprayed and electrochemically deposited implants

Author, year	Type of study	Joint, patient demographics, and number	Follow-up	Revision or failure rate/subsidence	Functional measures	Author conclusions
Adolphson P et al., 2009 [169]	Prospective study of proximally porous- and hydroxyapatite-coated prosthesis (Bi-Metric) in revision	22 patients with healthy contralateral hip reoperated due to aseptic loosening. Mean age at revision: 69 (55–80)	72 (30–158) months	No loosening or subsidence. Osteolysis seen at revision had diminished in 19 of the 22 hips at follow-up	The mean Harris hip score: 74 (30–100) at follow-up. Mild thigh discomfort was present in 1 patient and moderate thigh pain in 3 patients. Reduction in bone mineral density detected in Gruen regions 1, 2, 6, and 7	Revision with this stem is a reliable procedure; however, substantial proximal bone loss was detected and could lead to later mechanical complications or fractures
Philippot R et al., 2009 [170]	Continuous prospective series of patients with femoral component loosening with bone defect, revised with hydroxyapatite-coated locked modular stem	43 REEF (DePuy) femoral implants with extended trochanteric osteotomy (ETO). Age at revision 72.4 years (37–94)	58.2 (12–92) months	One failure, implant fracture secondary to nonunion of the femoral shaft. No radiographic stem migration. Mean 5-year survivorship 97.7 ± 2.3 %. Dislocation incidence: 2 %	Mean Postel and Merle d' Aubigné (PMA) score increased from six to 14.5. ETO healed around stem, (except one stem fracture). 5 proximal (stable) radiolucency; 8 with severe calcar cortical atrophy	Extended trochanteric osteotomy exposure and hydroxyapatite-coated interlocked modular stem function in revision surgery with bone loss

Summary of clinical studies evaluating HA on revision femoral components, published 2009–2012

osseointegration. Histomorphometry and SEM revealed bone in contact with the implant as woven (new) bone initially and in later specimens bridges of mature lamellar (remodelled) bone. No intervening fibrous tissue was observed and all HA coating had disappeared. Malchiodi et al. [86] saw similar osseointegration of retrieved dental implants.

The *migration* of electrochemical-deposited HA femur stems has been evaluated as a predictive factor of definitive stability and revision prognosis in studies by Boe [83, 171] and Buratti [84]. In a *clinical controlled randomized* study (Level I), Boe et al. [83, 171] found that femur stems coated with electrodeposited hydroxyapatite (EDHA) (BoneMaster[®], Biomet UK Healthcare Ltd, UK) [51, 60, 61] do not appear to be inferior to plasma-sprayed HA regarding bone remodelling and micromotion after 2-year follow-up. Fifty patients (55 hips) were included and randomized between the two different HA coatings. The stem was a tapered stem of titanium alloy (Ti-6Al-4V), porous-coated proximally and smooth distally (Taperloc, Biomet UK Healthcare Ltd, UK). On top of the porous coating was either plasma-sprayed HA or EDHA. The EDHA coating was performed in an electrolyte solution of 1.67 mM CaCl₂ and 1 mM NH₄(H₂PO₄) in equal volumes and near physiological conditions (pH 6.4, 37 °C). The implant was polarized in cathode galvanostatic mode (−75 A/m²). The coating consisted of 70–72 % crystalline HA, a thickness of 5 μm, and a Ca/P ratio of 2.0 [99, 100, 105]. At plasma-spraying, slightly molten Ca(PO₄)₂ HA granules of μm size were deposited onto the metal surface leaving a 50-μm-thick HA coating (Ca/P ratio: 1.67), a mean surface roughness of 41 μm, a maximum roughness depth of 445 μm, and 62 % crystallinity. Patients were evaluated postoperatively and after 3, 6, 12, and 24 months to measure fixation by radiostereometric analysis (RSA), bone mineral density by dual-energy X-ray absorptiometry (DXA), conventional radiography and clinically. After 2 years, the stems had subsided (CI) 0.25 (±0.32) mm (plasma-sprayed HA) and 0.28 (±0.18) mm (EDHA), and there were no statistically significant differences between the groups

in any direction, regarding both migration and rotation. The migration pattern for both stems showed that they moved during the 3 first months after surgery, and then stabilized, which is in accordance with the time period of stable uncemented femoral stems [3, 158, 172–175]. In RSA evaluation of stem migration, a subsidence of >0.33 mm 6 months after surgery is considered as increased risk of subsequent revision [176]. Reduction in bone density in the EDHA group was less than in the plasma-sprayed HA group in Gruen zone 1 during the first 2 years. No difference was seen in zones 2, 6, and 7, which also were regions with EDHA coating. It was suggested that the difference between the 2 groups in zone 1 was due to this area being dominated by trabecular bone. Higher bone density values in the EDHA group might indicate a higher degree of bone turnover in trabecular bone in this group. No radiographic osteolysis and no differences in clinical results between the two groups were seen. Burratti et al. [84] assessed the initial stability of the Symax femoral stem in a *multicenter study* of five orthopedic departments including 85 cases. Migration of the stem was measured by the radiographical migration method Einzel-Bild-Roentgen-Analysis (EBRA) [84, 177–180] on radiographs at 6, 12, 24, and 36 months postoperatively. With this method the threshold migration value as predictive factor for future revision was defined as 1.5 mm at 24 months (sensitivity rate of 69 %, a specificity rate of 80 %, accuracy rate of 79 %) [84, 177, 179, 180]. The mean migration was −0.17 mm (±0.3) at 6 months (*n*=85), −0.31 mm (±0.4) at 12 months (*n*=65), and −0.45 mm (±0.5) at 24 months (*n*=65). Two cases exceeded the threshold limit of 1.5 mm at the 2-year follow-up. In 25 cases reaching a 3-year follow-up, the mean distal migration was −0.84 (±0.7). In four of them the subsidence exceeded 1.5 mm. These data are based on the radiological initial stability during the first 2 (−3) years. Long-term follow-up may reflect the impact on clinical stability.

Periprosthetic bone remodelling and bone preservation around electrochemically deposited HA implants have been studied by ten Broeke [82] and Boe [83]. In both studies, the

electrochemical HA coatings revealed higher bone mineral density around the femoral stem compared to an HA plasma-sprayed stem in Gruen zone 7, although at different time onsets. In a randomized clinical trial, ten Broeke [82] evaluated the bone mineral density (BMD) over time around 2 uncemented femoral stems with proximal HA coatings. Forty-nine cases were included and randomized between the uncemented Symax stem and the Omnifit HA stem. The Omnifit HA stem (Stryker, Mahwah, New Jersey, USA) is forged from Ti-6Al-4V alloy with a plasma-spray HA coating on the proximal 40 % of the stem and a macrot textured surface. The primary outcome was bone mineral density from baseline to 2-year follow-up with measurements postoperatively, at 6 weeks, 3 and 6 months, and 1 and 2 years. Dual-energy X-ray absorptiometry (DEXA) has been shown to be a precise, accurate, and useful tool for assessment of periprosthetic bone remodelling following uncemented total hip arthroplasty (THA) [181–185]. Due to different stem designs, the HA coating length on comparable stem sizes is longer on the Omnifit stem than the Symax stem. Therefore, composition of cancellous and cortical bone along the implant length in the standard Gruen zones is essentially different [186]. By using modified adapted Gruen zones with an equal length and position of Gruen zones 1 and 7, comparable measurements of BMD around both stems were evaluated independent of the HA coating length. The results showed consistently higher BMD values for the Symax in Gruen zone 1 and 7. The differences in bone preservation in zone 7 between stems became statistically significant from 1 year onward. For Gruen zone 1 the difference increased from 1.3 % at 6 weeks to 2.1 % at 2 years, and for ROI-7 the difference increased from 1.5 % at 6 weeks ($p=0.38$) to 5.8 % at 2 years ($p=0.04$).

Studies on the *clinical outcome* of implants with EDHA are restricted to one with limited patients included. Bergschmidt et al. [85] evaluated the functional outcome of the Symax stem and found improved Harris hip score (HHS) and Western Ontario and McMaster Universities score 12 months postoperatively compared to preoperative evaluation.

Conclusion

From the experimental results presented, it can be concluded that HA coating has a positive effect on bone-implant fixation under stable unloaded conditions, stable loaded conditions, and unstable mechanical conditions. HA coating yielded no effect when implants were inserted in optimal press fit in normal bone. The most striking effects of HA were its enhancement of bone growth across a gap around the implant during both stable and unstable mechanical conditions and its ability to convert a motion-induced fibrous membrane to bony anchorage.

Electrodeposited HA has been shown in experimental studies to enhance mechanical and histologic fixation and clinically to result in similar or better fixation than non-HA-coated implants and than conventional HA.

Clinical studies demonstrate different findings for femoral and acetabular components. Femoral components generally show similar or better results with HA coating compared to non-HA porous coating. Results for acetabular components are more varied, with some studies demonstrating increased survival but others convincingly showing poorer results and advocating the avoidance of use of HA for primary acetabular components.

Hydroxyapatite has had the longest clinical history for a coating intended to improve implant fixation and durability. Most clinical results are promising, particularly for the femoral component, while evidence is not as strong for the acetabular component.

References

1. Soballe K. Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs. *Acta Orthop Scand.* 1993;255:S1–5.
2. Geesink RG. Osteoconductive coatings for total joint arthroplasty. *Clin Orthop.* 2002;395:53–65.
3. Karrholm J, Malchau H, Snorrason F, Herberts P. Micromotion of femoral stems in total hip arthroplasty. A randomized study of cemented, hydroxyapatite-coated, and porous-coated stems with roentgen stereophotogrammetric analysis. *J Bone Joint Surg Am.* 1994;76A:1692–705.

4. D'Antonio JA, Capello WN, Manley MT, Geesink R. Hydroxyapatite femoral stems for total hip arthroplasty: 10- to 13-year follow up. *Clin Orthop*. 2001;393:101–11.
5. Havelin LI, Engesaeter LB, Espehaug B, Furnes O, Lie SA, Vollset SE. The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties. *Acta Orthop Scand*. 2000;71(4):337–53.
6. Cook SD, Thomas KA, Dalton JE, Volkman TK, Whitecloud III TS, Kay JF. Hydroxyapatite coating of porous implants improves bone ingrowth and interface attachment strength. *J Biomed Mater Res*. 1992;26(8):989–1001.
7. Jarcho M. Calcium phosphate ceramics as hard tissue prosthetics. *Clin Orthop*. 1981;157:259–78.
8. Kobayashi T, Nakamura S, Yamashita K. Enhanced osteobonding by negative surface charges of electrically polarized hydroxyapatite. *J Biomed Mater Res*. 2001;57(4):477–84.
9. Porter AE, Taak P, Hobbs LW, Coathup MJ, Blunn GW, Spector M. Bone bonding to hydroxyapatite and titanium surfaces on femoral stems retrieved from human subjects at autopsy. *Biomaterials*. 2004;25(21):5199–208.
10. Bauer TW, Geesink RC, Zimmerman R, McMahon JT. Hydroxyapatite-coated femoral stems. Histological analysis of components retrieved at autopsy. *J Bone Joint Surg Am*. 1991;73A:1439–52.
11. Coathup MJ, Blunn GW, Flynn N, Williams C, Thomas NP. A comparison of bone remodelling around hydroxyapatite-coated, porous-coated and grit-blasted hip replacements retrieved at post-mortem. *J Bone Joint Surg Br*. 2001;83B:118–23.
12. Lacefield WR, Hench LL. The bonding of bioglass to a cobalt-chromium surgical implant alloy. *Biomaterials*. 1986;7(2):104–8.
13. Ducheyne P, Van Raemdonck W, Heughebaert JC, Heughebaert M. Structural analysis of hydroxyapatite coatings on titanium. *Biomaterials*. 1986;7(2):97–103.
14. Hero H, Wie H, Jorgensen RB, Ruyter IE. Hydroxyapatite coatings on Ti produced by hot isostatic pressing. *J Biomed Mater Res*. 1994;28(3):343–8.
15. Ishizawa H, Fujino M, Ogino M. Histomorphometric evaluation of the thin hydroxyapatite layer formed through anodization followed by hydrothermal treatment. *J Biomed Mater Res*. 1997;35(2):199–206.
16. Ban S, Maruno S, Arimoto N, Harada A, Hasegawa J. Effect of electrochemically deposited apatite coating on bonding of bone to the HA-G-Ti composite and titanium. *J Biomed Mater Res*. 1997;36(1):9–15.
17. Costa CA, Sena LA, Pinto M, Muller CA, Cavalcanti JH, Soares GA. In vivo characterization of titanium implants coated with synthetic hydroxyapatite by electrophoresis. *Braz Dent J*. 2005;6(1):75–81.
18. Schliephake H, Scharnweber D, Dard M, Robetaler S, Sewing A, Huttmann C. Biological performance of biomimetic calcium phosphate coating of titanium implants in the dog mandible. *J Biomed Mater Res*. 2003;64(2):225–34.
19. Wang H, Eliaz N, Xiang Z, Hsu HP, Spector M, Hobbs LW. Early bone apposition in vivo on plasma-sprayed and electrochemically deposited hydroxyapatite coatings on titanium alloy. *Biomaterials*. 2006;27(23):4192–203.
20. Schmidmaier G, Wildemann B, Schwabe P, Stange R, Hoffmann J, Sudkamp NP, et al. A new electrochemically graded hydroxyapatite coating for osteosynthetic implants promotes implant osseointegration in a rat model. *J Biomed Mater Res*. 2002;63(2):168–72.
21. Daugaard H, Elmengaard B, Bechtold JE, Soballe K. The effect on bone growth enhancement of implant coatings with hydroxyapatite and collagen deposited electrochemically and by plasma spray. *J Biomed Mater Res*. 2010;92A(3):913–21.
22. Schliephake H, Scharnweber D, Roesseler S, Dard M, Sewing A, Aref A. Biomimetic calcium phosphate composite coating of dental implants. *Int J Oral Maxillofac Implants*. 2006;21(5):738–46.
23. Rahbek O, Overgaard S, Lind M, Bendix K, Bunger C, Soballe K. Sealing effect of hydroxyapatite coating on peri-implant migration of particles. An experimental study in dogs. *J Bone Joint Surg Br*. 2001;83B(3):441–7.
24. Shanbhag AS, Hasselman CT, Rubash HE. The John Charnley Award. Inhibition of wear debris mediated osteolysis in a canine total hip arthroplasty model. *Clin Orthop*. 1997;344:33–43.
25. Bobyn JD, Jacobs JJ, Tanzer M, Urban RM, Aribindi R, Sumner DR, et al. The susceptibility of smooth implant surfaces to periimplant fibrosis and migration of polyethylene wear debris. *Clin Orthop*. 1995;311:21–39.
26. Huracek J, Spirig P. The effect of hydroxyapatite coating on the fixation of hip prostheses. A comparison of clinical and radiographic results of hip replacement in a matched-pair study. *Arch Orthop Trauma Surg*. 1994;113(2):72–7.
27. Rökkum M, Reigstad A, Johansson CB. HA particles can be released from well-fixed HA-coated stems: histopathology of biopsies from 20 hips 2–8 years after implantation. *Acta Orthop Scand*. 2002;73(3):298–306.
28. Rökkum M, Brandt M, Bye K, Hetland KR, Waage S, Reigstad A. Polyethylene wear, osteolysis and acetabular loosening with an HA-coated hip prosthesis. A follow-up of 94 consecutive arthroplasties. *J Bone Joint Surg Br*. 1999;81B(4):582–9.
29. Harada Y, Wang JT, Doppalapudi VA, Willis AA, Jasty M, Harris WH, et al. Differential effects of different forms of hydroxyapatite and hydroxyapatite/tricalcium phosphate particulates on human monocyte/macrophages in vitro. *J Biomed Mater Res*. 1996;31(1):19–26.
30. Bloebaum RD, Beeks D, Dorr LD, Savory CG, DuPont JA, Hofmann AA. Complications with hydroxyapatite particulate separation in total hip arthroplasty. *Clin Orthop*. 1994;298:19–26.
31. Morscher EW, Hefti A, Aebi U. Severe osteolysis after third-body wear due to hydroxyapatite particles

- from acetabular cup coating. *J Bone Joint Surg Br.* 1998;80B:267–72.
32. Luo ZS, Cui FZ, Li WZ. Low-temperature crystallization of calcium phosphate coatings synthesized by ion-beam-assisted deposition. *J Biomed Mater Res.* 1999;46(1):80–6.
 33. Wen HB, Wijn JR, Cui FZ, Groot GK. Preparation of calcium phosphate coatings on titanium implant materials by simple chemistry. *J Biomed Mater Res.* 1998;41(2):227–36.
 34. Kokubo T, Kushitani H, Sakka S, Kitsugi T, Yamamuro T. Solutions able to reproduce in vivo surface-structure changes in bioactive glass-ceramic A-W. *J Biomed Mater Res.* 1990;24(6):721–34.
 35. Barrere F, Layrolle P, Van Blitterswijk CA, De Groot K. Biomimetic coatings on titanium: a crystal growth study of octacalcium phosphate. *J Mater Sci Mater Med.* 2001;12(6):529–34.
 36. He F, Lin L, Zhao S, Chen S, Wang X. Fast formation of biomimetic apatite coatings on pure porous titanium implant's surface. *J Biomed Eng.* 2007;24(4):806–11.
 37. Filiaggi MJ, Pilliar RM, Coombs NA. Post-plasma-spraying heat treatment of the HA coating/Ti-6Al-4V implant system. *J Biomed Mater Res.* 1993;27(2):191–8.
 38. Lo WJ, Grant DM. Hydroxyapatite thin films deposited onto uncoated and (Ti, Al, V)N-coated Ti alloys. *J Biomed Mater Res.* 1999;46(3):408–17.
 39. Piveteau LD, Girona MI, Schlapbach L, Barbois P, Boilot JP, Gasser B. Thin films of calcium phosphate and titanium dioxide by a sol-gel route: a new method for coating medical implants. *J Mater Sci Mater Med.* 1999;10(3):161–7.
 40. Shirkanzadeh M. Direct formation of nanophase hydroxyapatite on cathodically polarized electrodes. *J Mater Sci Mater Med.* 1998;9(2):67–72.
 41. Zhitomirsky I, Gal-Or L. Electrophoretic deposition of hydroxyapatite. *J Mater Sci Mater Med.* 1997;4:213–9.
 42. Ong JL, Lucas LC, Lacefield WR, Rigney ED. Structure, solubility and bond strength of thin calcium phosphate coatings produced by ion beam sputter deposition. *Biomaterials.* 1992;13(4):249–54.
 43. Paldan H, Areva S, Tirri T, Peltola T, Lindholm TC, Lassila L, et al. Soft tissue attachment on sol-gel-treated titanium implants in vivo. *J Mater Sci Mater Med.* 2008;19(3):1283–90.
 44. Sharma S, Soni VP, Bellare JR. Chitosan reinforced apatite-wollastonite coating by electrophoretic deposition on titanium implants. *J Mater Sci Mater Med.* 2009;20(7):1427–36.
 45. Chai CS, Ben-Nissan B. Bioactive nanocrystalline sol-gel hydroxyapatite coatings. *J Mater Sci Mater Med.* 1999;10(8):465–9.
 46. Li P, de Groot K. Calcium phosphate formation within sol-gel prepared titania in vitro and in vivo. *J Mater Sci Mater Med.* 1993;27(12):1495–500.
 47. Yang BC, Weng J, Li XD, Zhang XD. The order of calcium and phosphate ion deposition on chemically treated titanium surfaces soaked in aqueous solution. *J Biomed Mater Res.* 1999;47(2):213–9.
 48. Yang GL, He FM, Song E, Hu JA, Wang XX, Zhao SF. In vivo comparison of bone formation on titanium implant surfaces coated with biomimetically deposited calcium phosphate or electrochemically deposited hydroxyapatite. *Int J Oral Maxillofac Implants.* 2010;25(4):669–80.
 49. Li H, Khor KA, Cheang P. Titanium dioxide reinforced hydroxyapatite coatings deposited by high velocity oxy-fuel (HVOF) spray. *Biomaterials.* 2002;23(1):85–91.
 50. Yang Y, Ong JL. Bond strength, compositional, and structural properties of hydroxyapatite coating on Ti, ZrO₂-coated Ti, and TPS-coated Ti substrate. *J Biomed Mater Res A.* 2003;64(3):509–16.
 51. Yonggang Y, Wolke JG, Yubao L, Jansen JA. In vitro evaluation of different heat-treated radio frequency magnetron sputtered calcium phosphate coatings. *Clin Oral Implants Res.* 2007;18(3):345–53.
 52. Meng X, Kwon TY, Kim KH. Hydroxyapatite coating by electrophoretic deposition at dynamic voltage. *Dent Mater J.* 2008;27(5):666–71.
 53. Zhao J, Xiao S, Lu X, Wang J, Weng J. A study on improving mechanical properties of porous HA tissue engineering scaffolds by hot isostatic pressing. *Biomed Mater.* 2006;1(4):188–92.
 54. Manders PJ, Wolke JG, Jansen JA. Bone response adjacent to calcium phosphate electrostatic spray deposition coated implants: an experimental study in goats. *Clin Oral Implants Res.* 2006;17(5):548–53.
 55. Schouten C, Meijer GJ, van den Beucken JJ, Leeuwenburgh SC, de Jonge LT, Wolke JG, et al. In vivo bone response and mechanical evaluation of electrosprayed CaP nanoparticle coatings using the iliac crest of goats as an implantation model. *Acta Biomater.* 2010;6(6):2227–36.
 56. Wie H, Hero H, Solheim T. Hot isostatic pressing-processed hydroxyapatite-coated titanium implants: light microscopic and scanning electron microscopy investigations. *Int J Oral Maxillofac Implants.* 1998;13(6):837–44.
 57. Yang GL, He FM, Hu JA, Wang XX, Zhao SF. Effects of biomimetically and electrochemically deposited nano-hydroxyapatite coatings on osseointegration of porous titanium implants. *Oral Surg Med Path Rad Endod.* 2009;107(6):782–9.
 58. Yang GL, He FM, Hu JA, Wang XX, Zhao SF. Biomechanical comparison of biomimetically and electrochemically deposited hydroxyapatite-coated porous titanium implants. *J Oral Maxillofac Surg.* 2010;68(2):420–7.
 59. Hayakawa T, Takahashi K, Yoshinari M, Okada H, Yamamoto H, Sato M, et al. Trabecular bone response to titanium implants with a thin carbonate-containing apatite coating applied using the molecular precursor method. *Int J Oral Maxillofac Implants.* 2006;21(6):851–8.
 60. Huang S, Zhou K, Huang B, Li Z, Zhu S, Wang G. Preparation of an electrodeposited hydroxyapatite coating on titanium substrate suitable for in-vivo applications. *J Mater Sci Mater Med.* 2008;19(1):437–42.

61. Dasarathy H, Riley C, Coble HD, Lacefield WR, Maybee G. HA/metal composite coatings formed by electrocodeposition. *J Mater Sci Mater Med.* 1996;31(1):81–9.
62. Lin S, LeGeros RZ, LeGeros JP. Adherent octacalciumphosphate coating on titanium alloy using modulated electrochemical deposition method. *J Biomed Mater Res A.* 2003;66(4):819–28.
63. Zeng H, Lacefield WR, Mirov S. Structural and morphological study of pulsed laser deposited calcium phosphate bioceramic coatings: influence of deposition conditions, laser parameters, and target properties. *J Biomed Mater Res.* 2000;50(2):248–58.
64. Barrere F, van der Valk CM, Dalmeijer RA, van Blitterswijk CA, de Groot K, Layrolle P. In vitro and in vivo degradation of biomimetic octacalcium phosphate and carbonate apatite coatings on titanium implants. *J Biomed Mater Res A.* 2003;64(2):378–87.
65. Hayakawa T, Yoshinari M, Nemoto K, Wolke JG, Jansen JA. Effect of surface roughness and calcium phosphate coating on the implant/bone response. *Clin Oral Implants Res.* 2000;11(4):296–304.
66. Ong JL, Bessho K, Cavin R, Carnes DL. Bone response to radio frequency sputtered calcium phosphate implants and titanium implants in vivo. *J Biomed Mater Res.* 2002;59(1):184–90.
67. Wolke JG, van Dijk K, Schaeken HG, de Groot K, Jansen JA. Study of the surface characteristics of magnetron-sputter calcium phosphate coatings. *J Biomed Mater Res.* 1994;28(12):1477–84.
68. Stigter M, de Groot K, Layrolle P. Incorporation of tobramycin into biomimetic hydroxyapatite coating on titanium. *Biomaterials.* 2002;23(20):4143–53.
69. Li P, Ducheyne P. Quasi-biological apatite film induced by titanium in a simulated body fluid. *J Biomed Mater Res.* 1998;41(3):341–8.
70. Alzubaydi TL, Alameer SS, Ismael T, Alhijazi AY, Geetha M. In vivo studies of the ceramic coated titanium alloy for enhanced osseointegration in dental applications. *J Mater Sci Mater Med.* 2009;20(S1):35–42.
71. Aniket, El-Ghannam A. Electrophoretic deposition of bioactive silica-calcium phosphate nanocomposite on Ti-6Al-4V orthopedic implant. *J Biomed Mater Res B.* 2011;99(2):369–79.
72. Yan WQ, Nakamura T, Kobayashi M, Kim HM, Miyaji F, Kokubo T. Bonding of chemically treated titanium implants to bone. *J Biomed Mater Res.* 1997;37(2):267–75.
73. Reigstad O, Franke-Stenport V, Johansson CB, Wennerberg A, Rokkum M, Reigstad A. Improved bone ingrowth and fixation with a thin calcium phosphate coating intended for complete resorption. *J Biomed Mater Res B.* 2007;83(1):9–15.
74. Reigstad O, Johansson C, Stenport V, Wennerberg A, Reigstad A, Rokkum M. Different patterns of bone fixation with hydroxyapatite and resorbable CaP coatings in the rabbit tibia at 6, 12, and 52 weeks. *J Biomed Mater Res B.* 2011;99(1):14–20.
75. Becker P, Neumann HG, Nebe B, Luthen F, Rychly J. Cellular investigations on electrochemically deposited calcium phosphate composites. *J Biomed Mater Res.* 2004;15(4):437–40.
76. Ishizawa H, Fujino M, Ogino M. Mechanical and histological investigation of hydrothermally treated and untreated anodic titanium oxide films containing Ca and P. *J Biomed Mater Res.* 1995;29(11):1459–68.
77. Schwarz ML, Kowarsch M, Rose S, Becker K, Lenz T, Jani L. Effect of surface roughness, porosity, and a resorbable calcium phosphate coating on osseointegration of titanium in a minipig model. *J Biomed Mater Res A.* 2009;89(3):667–78.
78. He F, Yang G, Wang X, Zhao S. Effect of electrochemically deposited nanohydroxyapatite on bone bonding of sandblasted/dual acid-etched titanium implant. *Int J Oral Maxillofac Implants.* 2009;24(5):790–9.
79. Lakstein D, Kopelovitch W, Barkay Z, Bahaa M, Hendel D, Eliaz N. Enhanced osseointegration of grit-blasted, NaOH-treated and electrochemically hydroxyapatite-coated Ti-6Al-4V implants in rabbits. *Acta Biomater.* 2009;5(6):2258–69.
80. Badr NA, El Hadary AA. Hydroxyapatite-electroplated cp-titanium implant and its bone integration potentiality: an in vivo study. *Implant Dent.* 2007;16(3):297–308.
81. ten Broeke RH, Alves A, Baumann A, Arts JJ, Geesink RG. Bone reaction to a biomimetic third-generation hydroxyapatite coating and new surface treatment for the Symax hip stem. *J Bone Joint Surg Br.* 2011;93B:760–8.
82. ten Broeke RH, Hendrickx RP, Leffers P, Jutten LM, Geesink RG. Randomised trial comparing bone remodelling around two uncemented stems using modified Gruen zones. *Hip Int.* 2012;22(1):41–9.
83. Boe BG, Rohrl SM, Heier T, Snorrason F, Nordsletten L. A prospective randomized study comparing electrochemically deposited hydroxyapatite and plasma-sprayed hydroxyapatite on titanium stems. *Acta Orthop Scand.* 2011;82(1):13–9.
84. Buratti CA, D'Arrigo C, Guido G, Lenzi F, Logroscino GD, Magliocchetti G, et al. Assessment of the initial stability of the Symax femoral stem with EBRA-FCA: a multicentric study of 85 cases. *Hip Int.* 2009;19(1):24–9.
85. Bergschmidt P, Bader R, Finze S, Gankovych A, Kundt G, Mittelmeier W. Cementless total hip replacement: a prospective clinical study of the early functional and radiological outcomes of three different hip stems. *Arch Orthop Trauma Surg.* 2010;130(1):125–33.
86. Malchiodi L, Ghensi P, Cucchi A, Trisi P, Szmukler-Moncler S, Corrocher G, et al. Early bone formation around immediately loaded FBR-coated implants after 8, 10 and 12 weeks: a human histologic evaluation of three retrieved implants. *Minerva Stomatol.* 2011;60(4):205–16.
87. Dhert WJ. Retrieval studies on calcium phosphate-coated implants. *Med Prog Technol.* 1994;20(3–4):143–54.
88. Porter AE, Hobbs LW, Rosen VB, Spector M. The ultrastructure of the plasma-sprayed hydroxyapatite-bone interface predisposing to bone bonding. *Biomaterials.* 2002;23(3):725–33.

89. Nakamura S, Kobayashi T, Yamashita K. Numerical osteobonding evaluation of electrically polarized hydroxyapatite ceramics. *J Biomed Mater Res A*. 2004;68(1):90–4.
90. Boskey AL. Current concepts of the physiology and biochemistry of calcification. *Clin Orthop*. 1981;157:225–57.
91. Itoh S, Nakamura S, Nakamura M, Shinomiya K, Yamashita K. Enhanced bone ingrowth into hydroxyapatite with interconnected pores by Electrical Polarization. *Biomaterials*. 2006;27(32):5572–9.
92. Teng NC, Nakamura S, Takagi Y, Yamashita Y, Ohgaki M, Yamashita K. A new approach to enhancement of bone formation by electrically polarized hydroxyapatite. *J Dent Res*. 2001;80(10):1925–9.
93. Hamamoto N, Hamamoto Y, Nakajima T, Ozawa H. Histological, histochemical and ultrastructural study on the effects of surface charge on bone formation in the rabbit mandible. *Arch Oral Biol*. 1995;40(2):97–106.
94. Wang W, Itoh S, Tanaka Y, Nagai A, Yamashita K. Comparison of enhancement of bone ingrowth into hydroxyapatite ceramics with highly and poorly interconnected pores by electrical polarization. *Acta Biomater*. 2009;5(8):3132–40.
95. LeGeros RZ. Properties of osteoconductive biomaterials: calcium phosphates. *Clin Orthop*. 2002;395:81–98.
96. Kilpadi KL, Chang PL, Bellis SL. Hydroxylapatite binds more serum proteins, purified integrins, and osteoblast precursor cells than titanium or steel. *J Biomed Mater Res*. 2001;57(2):258–67.
97. Sun L, Berndt CC, Gross KA, Kucuk A. Material fundamentals and clinical performance of plasma-sprayed hydroxyapatite coatings: a review. *J Biomed Mater Res*. 2001;58(5):570–92.
98. Overgaard S, Bromose U, Lind M, Bunger C, Soballe K. The influence of crystallinity of the hydroxyapatite coating on the fixation of implants. Mechanical and histomorphometric results. *J Bone Joint Surg Br*. 1999;81B:725–31.
99. Rossler S, Sewing A, Stolzel M, Born R, Scharnweber D, Dard M, et al. Electrochemically assisted deposition of thin calcium phosphate coatings at near-physiological pH and temperature. *J Biomed Mater Res A*. 2003;64(4):655–63.
100. Rossler S, Ogami T, Scharnweber D, Worch H. Biomimetic coating functionalized with adhesion peptides for dental implants. *J Mater Sci Mater Med*. 2001;12:871–7.
101. Barrere F, Layrolle P, van Blitterswijk CA, de Groot K. Biomimetic calcium phosphate coatings on Ti6Al4V: a crystal growth study of octacalcium phosphate and inhibition by Mg²⁺ and HCO₃⁻. *Bone*. 1999;25(S2):107–11.
102. Ban S, Maruno S. Hydrothermal-electrochemical deposition of hydroxyapatite. *J Biomed Mater Res*. 1998;42(3):387–95.
103. Ishizawa H, Ogino M. Characterization of thin hydroxyapatite layers formed on anodic titanium oxide films containing Ca and P by hydrothermal treatment. *J Biomed Mater Res*. 1995;29(9):1071–9.
104. Ishizawa H, Ogino M. Formation and characterization of anodic titanium oxide films containing Ca and P. *J Biomed Mater Res*. 1995;29(1):65–72.
105. Sewing A, Lakatos M, Scharnweber D, Roessler S, Born R, Dard M, et al. Influence of Ca/P ratio on electrochemical assisted deposition of hydroxyapatite on titanium. *Key Eng Mater*. 2004;4:419–22.
106. Kuroda K, Okido M. Hydroxyapatite coating of titanium implants using hydroprocessing and evaluation of their osteoconductivity. *Bioinorg Chem Appl*. 2012;2012:730693.
107. Cook SD, Kay JF, Thomas KA, Jarcho M. Interface mechanics and histology of titanium and hydroxyapatite-coated titanium for dental implant applications. *Int J Oral Maxillofac Impl*. 1987;2(1):15–22.
108. Hong L, Xu HC, de Groot K. Tensile strength of the interface between hydroxyapatite and bone. *J Biomed Mater Res*. 1992;26(1):7–18.
109. Gross KA, Berndt CC. Thermal processing of hydroxyapatite for coating production. *J Biomed Mater Res*. 1998;39(4):580–7.
110. Li H, Khor KA, Cheang P. Impact formation and microstructure characterization of thermal sprayed hydroxyapatite/titania composite coatings. *Biomaterials*. 2003;24(6):949–57.
111. Whitehead RY, Lacefield WR, Lucas LC. Structure and integrity of a plasma sprayed hydroxyapatite coating on titanium. *J Biomed Mater Res*. 1993;27(12):1501–17.
112. Koch B, Wolke JG, de Groot K. X-ray diffraction studies on plasma-sprayed calcium phosphate-coated implants. *J Biomed Mater Res*. 1990;24(6):655–67.
113. Ellies LG, Nelson DG, Featherstone JD. Crystallographic changes in calcium phosphates during plasma-spraying. *Biomaterials*. 1992;13(5):313–6.
114. Zyman Z, Weng J, Liu X, Zhang X, Ma Z. Amorphous phase and morphological structure of hydroxyapatite plasma coatings. *Biomaterials*. 1993;14(3):225–8.
115. Wang BC, Chang E, Lee TM, Yang CY. Changes in phases and crystallinity of plasma-sprayed hydroxyapatite coatings under heat treatment: a quantitative study. *J Biomed Mater Res*. 1995;29(12):1483–92.
116. Locardi B, Pazzaglia UE, Gabbi C, Profilo B. Thermal behaviour of hydroxyapatite intended for medical applications. *Biomaterials*. 1993;14(6):437–41.
117. Ji H, Marquis PM. Effect of heat treatment on the microstructure of plasma-sprayed hydroxyapatite coating. *Biomaterials*. 1993;14(1):64–8.
118. Ergun C, Doremus R, Lanford W. Hydroxyapatite and titanium: interfacial reactions. *J Biomed Mater Res A*. 2003;65(3):336–43.
119. Wei M, Ruys AJ, Swain MV, Milthorpe BK, Sorrell CC. Hydroxyapatite-coated metals: interfacial reactions during sintering. *J Mater Sci Mater Med*. 2005;16(2):101–6.
120. Serro AP, Fernandes AC, Saramago B, Lima J, Barbosa MA. Apatite deposition on titanium

- surfaces—the role of albumin adsorption. *Biomaterials*. 1997;18(14):963–8.
121. Ban S, Maruno S, Harada A, Hattori M, Narita K, Hasegawa J. Effect of temperature on morphology of electrochemically-deposited calcium phosphates. *Dent Mater J*. 1996;15(1):31–8.
 122. Ban S, Maruno S. Effect of temperature on electrochemical deposition of calcium phosphate coatings in a simulated body fluid. *Biomaterials*. 1995;16(13):977–81.
 123. Ban S, Maruno S. Morphology and microstructure of electrochemically deposited calcium phosphates in a modified simulated body fluid. *Biomaterials*. 1998;19(14):1245–53.
 124. Shirkhazadeh M. X-ray diffraction and fourier transform infrared analysis of nanophase apatite coatings prepared by electrocrystallization. *Nanostruct Mater*. 1994;4(6):677–84.
 125. Shirkhazadeh M, Azadegan M. Hydroxyapatite particles prepared by electrocrystallisation from aqueous electrolytes. *Mater Lett*. 1993;15(5–6):392–5.
 126. Redepenning J, McIsaac JP. Electrocrystallization of brushite coatings on prosthetic alloys. *Chem Mater*. 1990;2(6):625–7.
 127. Kumar M, Dasarathy H, Riley C. Electrodeposition of brushite coatings and their transformation to hydroxyapatite in aqueous solutions. *J Biomed Mater Res*. 1999;45(4):302–10.
 128. Kumar M, Xie J, Chittur K, Riley C. Transformation of modified brushite to hydroxyapatite in aqueous solution: effects of potassium substitution. *Biomaterials*. 1999;20(15):1389–99.
 129. Agata De Sena L, Calixto De Andrade M, Malta Rossi A, de Almeida Soares G. Hydroxyapatite deposition by electrophoresis on titanium sheets with different surface finishing. *J Biomed Mater Res*. 2002;60(1):1–7.
 130. Zhitomirsky I, Gal-Or L. Electrophoretic deposition of hydroxyapatite. *J Mater Sci Mater Med*. 1997;8(4):213–9.
 131. Ducheyne P, Radin S, Heughebaert M, Heughebaert JC. Calcium phosphate ceramic coatings on porous titanium: effect of structure and composition on electrophoretic deposition, vacuum sintering and in vitro dissolution. *Biomaterials*. 1990;11(4):244–54.
 132. Zhang B, Kwok CT, Cheng FT, Man HC. Fabrication of nano-structured HA/CNT coatings on Ti6Al4V by electrophoretic deposition for biomedical applications. *J Nanosci Nanotech*. 2011;11(12):10740–5.
 133. Redepenning J, Schlessinger T, Burnham S, Lippiello L, Miyano J. Characterization of electrolytically prepared brushite and hydroxyapatite coatings on orthopedic alloys. *J Biomed Mater Res*. 1996;30(3):287–94.
 134. Roessler S, Born R, Scharnweber D, Worch H, Sewing A, Dard M. Biomimetic coatings functionalized with adhesion peptides for dental implants. *J Mater Sci Mater Med*. 2001;12(10–12):871–7.
 135. Joschek S, Nies B, Krotz R, Goferich A. Chemical and physicochemical characterization of porous hydroxyapatite ceramics made of natural bone. *Biomaterials*. 2000;21(16):1645–58.
 136. Soballe K, Hansen ES, Brockstedt-Rasmussen H, Pedersen CM, Bunge C. Hydroxyapatite coating enhances fixation of porous coated implants. A comparison in dogs between press fit and noninterference fit. *Acta Orthop Scand*. 1990;61(4):299–306.
 137. Soballe K, Hansen ES, Brockstedt-Rasmussen H, Bunge C. Hydroxyapatite coating converts fibrous tissue to bone around loaded implants. *J Bone Joint Surg Br*. 1993;75B:270–8.
 138. Soballe K, Hansen ES, Rasmussen H, Jorgensen PH, Bunge C. Tissue ingrowth into titanium and hydroxyapatite-coated implants during stable and unstable mechanical conditions. *J Orthop Res*. 1992;10(2):285–99.
 139. Soballe K, Brockstedt-Rasmussen H, Hansen ES, Bunge C. Hydroxyapatite coating modifies implant membrane formation. Controlled micromotion studied in dogs. *Acta Orthop Scand*. 1992;63(2):128–40.
 140. Soballe K, Hansen ES, Brockstedt-Rasmussen H, Pedersen CM, Bunge C. Bone graft incorporation around titanium-alloy- and hydroxyapatite-coated implants in dogs. *Clin Orthop*. 1992;274:282–93.
 141. Soballe K, Hansen ES, Brockstedt-Rasmussen H, Hjortdal VE, Juhl GI, Pedersen CM, et al. Gap healing enhanced by hydroxyapatite coating in dogs. *Clin Orthop*. 1991;272:300–7.
 142. Schimmel JW, Huiskes R. Primary fit of the Lord cementless total hip. A geometric study in cadavers. *Acta Orthop Scand*. 1988;59(6):638–42.
 143. Burke DW, O'Connor DO, Zalenski EB, Jasty M, Harris WH. Micromotion of cemented and uncemented femoral components. *J Bone Joint Surg Br*. 1991;73B:33–7.
 144. Volz RG, Nisbet JK, Lee RW, McMurtry MG. The mechanical stability of various noncemented tibial components. *Clin Orthop*. 1988;226:38–42.
 145. Branson PJ, Steege JW, Wixson RL, Lewis J, Stulberg SD. Rigidity of initial fixation with uncemented tibial knee implants. *J Arthroplasty*. 1989;4(1):21–6.
 146. Bobyn JD, Engh CA. Human histology of the bone-porous metal implant interface. *Orthopedics*. 1984;7(9):1410–21.
 147. Bobyn JD, Engh CA, Glassman AH. Histologic analysis of a retrieved microporous-coated femoral prosthesis. A seven-year case report. *Clin Orthop*. 1987;224:303–10.
 148. Bobyn JD, Mortimer ES, Glassman AH, Engh CA, Miller JE, Brooks CE. Producing and avoiding stress shielding. Laboratory and clinical observations of noncemented total hip arthroplasty. *Clin Orthop*. 1992;274:79–96.
 149. Bobyn JD, Pilliar RM, Cameron HU, Weatherly GC. The optimum pore size for the fixation of porous-surfaced metal implants by the ingrowth of bone. *Clin Orthop*. 1980;150:263–70.
 150. Harris WH, Schiller AL, Scholler JM, Freiberg RA, Scott R. Extensive localized bone resorption in the

- femur following total hip replacement. *J Bone Joint Surg Am.* 1976;58A:612–8.
151. Harris WH, White Jr RE, McCarthy JC, Walker PS, Weinberg EH. Bony ingrowth fixation of the acetabular component in canine hip joint arthroplasty. *Clin Orthop.* 1983;176:7–11.
 152. Daugaard H, Elmengaard B, Bechtold JE, Jensen TB, Soballe K. Comparison of three different hydroxyapatite coatings in an unloaded implant model. An experimental canine study. American Society of Biomechanics, 28th annual Meeting, Portland; 2004.
 153. Kim YH, Kim JS, Joo JH, Park JW. Is hydroxyapatite coating necessary to improve survivorship of porous-coated titanium femoral stem? *J Arthroplasty.* 2012;27(4):559–63.
 154. Bercovy M, Beldame J, Lefebvre B, Duron A. A prospective clinical and radiological study comparing hydroxyapatite-coated with cemented tibial components in total knee replacement. *J Bone Joint Surg Br.* 2012;94B:497–503.
 155. Schewelov T, Ahlborg H, Sanzen L, Besjakov J, Carlsson A. Fixation of the fully hydroxyapatite-coated Corail stem implanted due to femoral neck fracture. *Acta Orthop Scand.* 2012;83(2):153–8.
 156. Pijls BG, Valstar ER, Kaptein BL, Fiocco M, Nelissen RG. The beneficial effect of hydroxyapatite lasts. *Acta Orthop Scand.* 2012;83(2):135–41.
 157. Vidalain JP. Twenty-year results of the cementless Corail stem. *Int Orthop.* 2011;35(2):189–94.
 158. Campbell D, Mercer G, Nilsson KG, Wells V, Field JR, Callary SA. Early migration characteristics of a hydroxyapatite-coated femoral stem: an RSA study. *Int Orthop.* 2011;35(4):483–8.
 159. Voigt JD, Mosier M. Hydroxyapatite (HA) coating appears to be of benefit for implant durability of tibial components in primary total knee arthroplasty. *Acta Orthop Scand.* 2011;82(4):448–59.
 160. Baker PN, McMurtry IA, Chuter G, Port A, Anderson J. THA with the ABG I prosthesis at 15 years. Excellent survival with minimal osteolysis. *Clin Orthop.* 2010;468:1855–61.
 161. Mannan K, Freeman MA, Scott G. The Freeman femoral component with hydroxyapatite coating and retention of the neck: an update with a minimum follow-up of 17 years. *J Bone Joint Surg Br.* 2010;92:480–5.
 162. Camazzola D, Hammond T, Gandhi R, Davey JR. A randomized trial of hydroxyapatite-coated femoral stems in total hip arthroplasty: a 13-year follow-up. *J Arthroplasty.* 2009;24(1):33–7.
 163. Gandhi R, Davey JR, Mahomed NN. Hydroxyapatite coated femoral stems in primary total hip arthroplasty: a meta-analysis. *J Arthroplasty.* 2009;24(1):38–42.
 164. Emans PJ, Broeke RH, Van Mulken JM, Kuijjer R, Van Rhijn LW, Geesink RG. Results of total hip arthroplasties in the young patient; further evidence for a barrier against articular wear debris by hydroxyapatite coatings. *Hip Int.* 2009;19(4):343–51.
 165. Goosen JH, Kums AJ, Kollen BJ, Verheyen CC. Porous-coated femoral components with or without hydroxyapatite in primary uncemented total hip arthroplasty: a systematic review of randomized controlled trials. *Arch Orthop Trauma Surg.* 2009;129(9):1165–9.
 166. Gottliebsen M, Rahbek O, Ottosen PF, Soballe K, Stilling M. Superior 11-year survival but higher polyethylene wear of hydroxyapatite-coated Mallory-Head cups. *Hip Int.* 2012;22(1):35–40.
 167. Lazarinis S, Karrholm J, Hailer NP. Increased risk of revision of acetabular cups coated with hydroxyapatite. *Acta Orthop Scand.* 2010;81(1):53–9.
 168. Stilling M, Rahbek O, Soballe K. Inferior survival of hydroxyapatite versus titanium-coated cups at 15 years. *Clin Orthop.* 2009;467(11):2872–9.
 169. Adolphson PY, Salemyr MO, Skoldenberg OG, Boden HS. Large femoral bone loss after hip revision using the uncemented proximally porous-coated Bi-Metric prosthesis: 22 hips followed for a mean of 6 years. *Acta Orthop Scand.* 2009;80(1):14–9.
 170. Philippot R, Delangle F, Verdout FX, Farizon F, Fessy MH. Femoral deficiency reconstruction using a hydroxyapatite-coated locked modular stem. A series of 43 total hip revisions. *Orthop Traumatol Surg Res.* 2009;95(2):119–26.
 171. Boe B, editor. Change in bone density and implantation AV taperloc cementless hip prosthetic with two different hydroxyapatite coatings. Oslo: Nordic Orthopaedic Federation 53rd Congress, 2006.
 172. Karrholm J, Borssen B, Lowenhielm G, Snorrason F. Does early micromotion of femoral stem prostheses matter? 4–7-year stereoradiographic follow-up of 84 cemented prostheses. *J Bone Joint Surg Br.* 1994;76B:912–7.
 173. Thien TM, Ahnfelt L, Eriksson M, Stromberg C, Karrholm J. Immediate weight bearing after uncemented total hip arthroplasty with an anteverted stem: a prospective randomized comparison using radiostereometry. *Acta Orthop Scand.* 2007;78(6):730–8.
 174. Malchau H, Karrholm J, Wang YX, Herberts P. Accuracy of migration analysis in hip arthroplasty. Digitized and conventional radiography, compared to radiostereometry in 51 patients. *Acta Orthop Scand.* 1995;66(5):418–24.
 175. Nistor L, Blaha JD, Kjellstrom U, Selvik G. In vivo measurements of relative motion between an uncemented femoral total hip component and the femur by roentgen stereophotogrammetric analysis. *Clin Orthop.* 1991;269:220–7.
 176. Karrholm J, Snorrason F. Subsidence, tip, and hump micromovements of noncoated ribbed femoral prostheses. *Clin Orthop.* 1993;287:50–60.
 177. Cianci R, Baruffaldi F, Fabbri F, Affatato S, Toni A, Giunti A. A computerized system for radiographical evaluation in total hip arthroplasty. *Comp Methods Programs Biomed.* 1995;46(3):233–43.
 178. Ilchmann T, Franzen H, Mjoberg B, Wingstrand H. Measurement accuracy in acetabular cup migration. A comparison of four radiologic methods versus roentgen stereophotogrammetric analysis. *J Arthroplasty.* 1992;7(2):121–7.

179. Biedermann R, Krismer M, Stockl B, Mayrhofer P, Ornstein E, Franzen H. Accuracy of EBRA-FCA in the measurement of migration of femoral components of total hip replacement. *J Bone Joint Surg Br.* 1999;81B:266–72.
180. Krismer M, Biedermann R, Stockl B, Fischer M, Bauer R, Haid C. The prediction of failure of the stem in THR by measurement of early migration using EBRA-FCA. *J Bone Joint Surg Br.* 1999;81B:273–80.
181. McCarthy CK, Steinberg GG, Agren M, Leahey D, Wyman E, Baran DT. Quantifying bone loss from the proximal femur after total hip arthroplasty. *J Bone Joint Surg Br.* 1991;73B:774–8.
182. Kilgus DJ, Shimaoka EE, Tipton JS, Eberle RW. Dual-energy x-ray absorptiometry measurement of bone-mineral density around porous-coated cementless femoral implants – methods and preliminary results. *J Bone Joint Surg Br.* 1993;75B:279–87.
183. Trevisan C, Bigoni M, Cherubini R, Steiger P, Randelli G, Ortolani S. Dual x-ray absorptiometry for the evaluation of bone density from the proximal femur after total hip arthroplasty: analysis protocols and reproducibility. *Calcif Tissue Int.* 1993;53(3):158–61.
184. Kiratli BJ, Heiner JP, McBeath AA, Wilson MA. Determination of bone mineral density by dual x-ray absorptiometry in patients with uncemented total hip arthroplasty. *J Orthop Res.* 1992;10(6):836–44.
185. Cohen B, Rushton N. Accuracy of DEXA measurement of bone mineral density after total hip arthroplasty. *J Bone Joint Surg Br.* 1995;77B:479–83.
186. Rahmy AI, Gosens T, Blake GM, Tonino A, Fogelman I. Periprosthetic bone remodelling of two types of uncemented femoral implant with proximal hydroxyapatite coating: a 3-year follow-up study addressing the influence of prosthesis design and preoperative bone density on periprosthetic bone loss. *Osteop Int.* 2004;15(4):281–9.

Trabecular Metal: Bone Interface in Total Joint Arthroplasty

9

Konstantinos A. Bargiotas

Introduction

Various types of cementless implants with rough or porous-coated surfaces for ongrowth or ingrowth have been used or are currently in use and have shown satisfactory mid- and long-term clinical results [1–4]. In no more than 60–70 % of these surfaces, direct bone apposition has been observed [5–8].

Trabecular metal (TMT), a three-dimensional structure made of tantalum with interconnecting pores throughout its volume, was developed in an effort to maximize volumetric porosity and improve the microenvironment for bone ingrowth (Fig. 9.1). Unlike most contemporary implants which are made of solid metal, trabecular metal is a space frame with a structure that closely resembles the structure and the mechanical properties of cancellous bone [9]. Tantalum is a relatively soft metal, biologically inert and highly resistant to corrosion and erosion. Medical implants used over the past seven decades like electrodes for pacemakers, femoral stems, and dental implants have proved its safety and biocompatibility. Currently no data supports any possible biological activity of tantalum microparticles and tantalum ions [10].

Structure

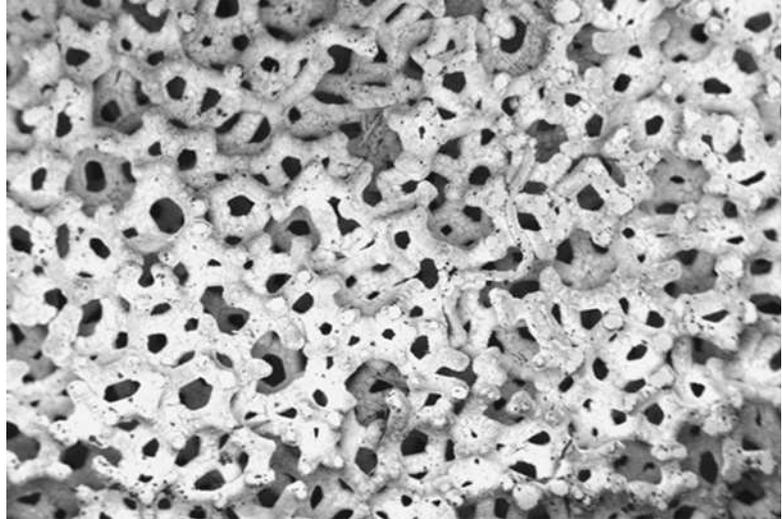
Trabecular metal is a composite porous material. Its three-dimensional frame is made of amorphous carbon, and tantalum metal covers this substrate by plasma-spray deposition techniques. Both the pore size and the amount of tantalum deposition can be regulated through the fabrication method, and thus the mechanical properties can be altered [9]. Typically, it is in use for orthopedic applications, its pore size ranging between 400 and 600 μm and with porosity of up to 75–85 % of its entire volume. Porosity, pore size, and elasticity of TMT highly resemble cancellous bone and so does its friction coefficient which is 40–75 % higher than conventional porous materials [9, 10, 11].

Experimental Data

Animal studies have shown rapid bone ingrowth in TMT implants and no implant-related adverse effects. In vitro experiments demonstrated that pretreated Ta and Ti plates are more resistant to bacteria adhesion [12]. Miyazaki T et al. [13] reported that bone creates a chemical bond with titanium and tantalum plates treated with NaOH in stimulated body fluid. They call this first layer of Ta-Bone tantalite. In an environment that resembles in vivo conditions (stimulated body fluid, SBF), alkali-treated Ti and TMT plates were found to induce apatite formation and direct bonding of the metal/apatite layer to bone. Bobynt et al. [9] have used a canine transcortical model in order to test bone ingrowth

K.A. Bargiotas, MD
Orthopaedic Department,
University General Hospital of Larissa,
Mezourlo Region, Larissa 41110, Greece
e-mail: kbargio@yahoo.gr

Fig. 9.1 Trabecular metal structure is shown



and implant stability. Rapid bone ingrowth was evident while 42 % of pores were found to be filled in the 4th week, 63 % in the 16th, and 80 % in the 52nd week. In pullout tests, resistance to shearing was significantly higher compared with porous-coated CoCr surfaces. Bobyn et al. [14] have also implanted 22 total hip arthroplasties with a cup made of TMT in dogs. The interface was examined 6 months postimplantation histologically and by electron microscopy. Bone ingrowth was evident in all specimens ranging from 0.2 to 2 mm in depth while the extent of the bone formation both as a percentage of the implant surface and in depth was found to be comparable with wire-mesh-covered Ti implants. Hacking et al. [15] and more recently Reach et al. [16] studied the ingrowth of fibrous tissue in TMT. They demonstrated that vascularized fibrous tissue rapidly filled the entire volume of the implant. The strength of the tendon-implant bone interface was found to be 99 % of the strength of the normal tendon attachment at 6 weeks and 140 % 12 weeks postimplantation. More interestingly, histology revealed the formation of Sharpey-like fibers within the TMT washers.

Retrieval Studies

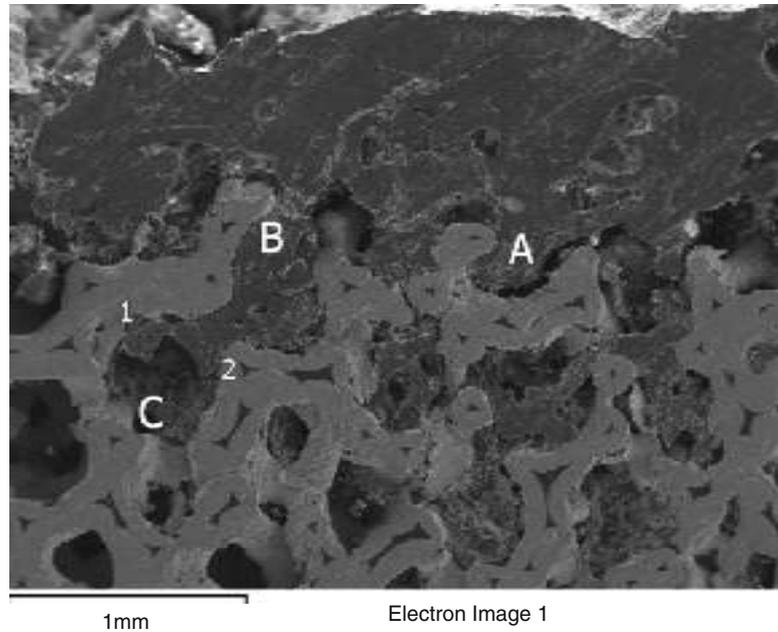
Although bone ingrowth in TMT has been experimentally tested and proved clinically by radiological and outcome studies, data from retrieval studies are rare. D'Angelo et al. [17] performed

a histological evaluation of bone-implant interface in a human specimen removed from a patient. Their study was based on polarized light microscopy, and they reported 90 % of pore filling by bone. According to our own unpublished data from a retrieved stable implant, ingrowth of bone was complete in the first two rows of cells (2–3 mm) while vascularized fibrous tissue was evident beyond the second row, and in areas of the surface that there was not bone formation. During ingrowth, bone follows the topology of the scaffold by attaching to the tantalum struts and then fills the empty space of the cells. In other words, bone attaches first to the cell boundary and then grows further to the interior of the cell. By applying EDS elemental analysis, we could compare the composition of new bone material within the cells of the trabecular metal with that of the bone attached to the surface of the cup. The bone material grown inside the first row of cells had almost identical composition with the attached bone verified by similar Ca:P ratio, indicating complete densification into hydroxyapatite. However, the composition of the bone-like material in the second row of cells had a different composition (Fig. 9.2).

Clinical Studies

TMT has been used up today in a variety of implants and clinical experience with some of them exceeds one decade. Historically the first

Fig. 9.2 Transverse metallographic section of Sp.3 showing attached bone and the region of bone ingrowth. Bone ingrowth into open cells is shown in *A* and *B* while ingrowth into cells deeper in the tantalum scaffold is shown at *C*



implant released for commercial use was an acetabular component. This cup incorporated, besides a TMT metal shell, a number of unique design characteristics. The TMT cup is elliptic in shape, designed for an interference fit at the rim of the prepared acetabular cavity and compact with the compression-molded polyethylene liner (sterilized with gamma radiation) solidly seated in the porous tantalum cell. The Monoblock TMT cup has a modulus of elasticity almost identical with subchondral bone. As the cup is elliptical, peripheral fit may prevent the complete sitting of the cup in the prepared acetabular cavity. As a consequence, gaps at the interface of the dome have been reported to be relatively frequent (13–32 %) [18–21]. Gruen et al. [21] reported that 84 % of these gaps were filled within 5 years. In our series [18], big polar gaps did not fill entirely, but they did not compromise the stability of the cup.

Several authors have reported satisfactory midterm results with this construct [18–25]. We have reported [18, 20] excellent midterm results with this particular implant demonstrating that all cups were radiographically stable with a follow-up ranging between 3 and 9 years with an overall survivorship of 98.75 %. Furthermore, in serial radiographs, thickening of the trabeculae and increased bone density at the periphery of the cup

as well as at the dome were observed. This was attributed to the load transfer pattern and the elasticity of the cup. Recent studies proved that instead of stress shielding that occurs behind Ti and CoCr cementless cups, there is increased bone density and remodelling of the subchondral bone with TMT cups [26, 27] (Fig. 9.3).

Trabecular metal implants have been used for acetabular revision surgery also. An acetabular component made of TMT with multiple screw holes is available. The cup can be fixed in a fashion that allows maximum contact of metal with viable bone, and the liner can be cemented in the desired anteversion and inclination for joint stability. Augments are available for the filling of rim and wall deficiencies. They are secured with screws and filled with bone graft, and the cup is then placed and secured. It has been proposed that a thin cement layer be placed between the two implants to prevent the production of microparticles [28, 29]. The augments support the cup in a similar fashion with structural allografts. The theoretical advantage is that augments allow bone ingrowth, and they are not subject to resorption and fatigue fractures as do the structural grafts. Few studies with optimal results have been published with revision TMT cups and the use of augments. Although bone ingrowth

Fig. 9.3 Implant removal due to infection. The surface is almost covered by bone



and healing of the pelvic discontinuity is evident in serial radiographs, the long-term behavior of this implant is as yet unknown [30–33].

A cementless tibia tray made of porous tantalum with a compression-molded polyethylene is also available. Clinical studies with relatively short follow-up time demonstrate encouraging results [34, 35]. A recent radiostereometric comparison of TMT versus a titanium tibia demonstrated a higher rate of posterior tilt and migration of the TMT tray but no loosening or revision [36]. Recent studies also suggest that stress shielding does not occur in the metaphyseal area of the tibia [37, 38].

A variety of new applications and materials are currently under development, and titanium-made porous materials resembling TMT are already being marketed. Trabecular bone-like materials represent a novel approach for cementless metallic implants (Fig. 9.4). Experimental data and retrievals support the fact that bone ingrowth is both rapid and to a better extent than traditional surfaces. Short- and midterm clinical results of tantalum trabecular metal implants support this hypothesis. Yet, the long-term clinical



Fig. 9.4 Trabecular metal cup. Strain adaptation of trabecular struts in zone 1 and 2 as early as in 3 years follow-up

performance and the significance of the unique properties of the material described above require further investigation and experience. Surgeons should use TMT and other porous materials with caution based on site and implant-specific studies, keeping in mind that TMT is still a very promising but costly alternative for hip and knee replacement surgery.

References

- Böhm P, Bösche R. Survival analysis of the Harris-Galante I acetabular cup. *J Bone Joint Surg Br.* 1998; 80B:396–403.
- Huo MH. What's new in hip arthroplasty. *J Bone Joint Surg Am.* 2002;84A:1894–905.
- Latimer HA, Lachiewicz PF. Porous-coated acetabular components with screw fixation: five to ten-year results. *J Bone Joint Surg Am.* 1996;78A:975–81.
- Udomkiat P, Dorr LD, Wan Z. Cementless hemispherical porous-coated sockets implanted with press-fit technique without screws: average ten-year follow-up. *J Bone Joint Surg Am.* 2002;84A:1195–2000.
- Engh CA, Zettl-Schaffer KF, Kukita Y, Sweet D, Jasty M, Bragdon C. Histological and radiographic assessment of well functioning porous-coated acetabular components. A human postmortem retrieval study. *J Bone Joint Surg Am.* 1993;75A:814–24.
- Bobynd JD, Tanzer M, Miller JE. Chapter 9. Fundamental principles of biologic fixation. In: Morrey BF, editor. *Reconstructive surgery of the joints.* New York: Churchill Livingstone; 1991. p. 75–94.
- Bragdon CR, Jasty M, Lowenstein JD, Burke DW. The histology of bone ingrowth at the implant/bone interface under known amount of micromotion. *Trans Orthop Res Soc.* 1993;18:468–73.
- Pidhorz LE, Urban RM, Jacobs JJ, Sumner DR, Galante JO. A quantitative study of bone and soft tissues in cementless porous-coated acetabular components retrieved at autopsy. *J Arthroplasty.* 1993;8:213–25.
- Bobynd JD, Stackpool GJ, Hacking A, Tanzer M, Krygier JJ. Characteristics of bone ingrowth and interface mechanics of a new porous tantalum biomaterial. *J Bone Joint Surg Br.* 1999;81B:907–14.
- Levine BR, Sporer S, Poggie RA, Della Valle CJ, Jacobs JJ. Experimental and clinical performance of porous tantalum in orthopedic surgery. *Biomaterials.* 2006;27:4671–81.
- Bobynd JD, Pilliar RM, Cameron HU, Weatherly GC. The optimum pore size for the fixation of porous-surfaced metal implants by the ingrowth of bone. *Clin Orthop.* 1980;150:263–70.
- Schildhauer TA, Robie B, Muhr G, Köller M. Bacterial adherence to tantalum versus commonly used orthopedic metallic implant materials. *J Orthop Trauma.* 2006;20:476–84.
- Miyazaki T, Kim HM, Kokubo T, Ohtsuki C, Kato H, Nakamura T. Mechanism of bonelike apatite formation on bioactive tantalum metal in a simulated body fluid. *Biomaterials.* 2002;23:827–32.
- Bobynd JD, Toh KK, Hacking A, Eng M, Tanzer M, Krygier JJ. Tissue response to porous tantalum acetabular cups. A canine model. *J Arthroplasty.* 1999;14: 347–53.
- Hacking SA, Bobynd JD, Toh K, Tanzer M, Krygier JJ. Fibrous tissue ingrowth and attachment to porous tantalum. *J Biomed Mater Res.* 2000;52:631–8.
- Reach Jr JS, Dickey ID, Zobitz ME, Adams JE, Scully SP, Lewallen DG. Direct tendon attachment and healing to porous tantalum: an experimental animal study. *J Bone Joint Surg Am.* 2007;89A:1000–9.
- D'Angelo F, Murena L, Campagnolo M, Zatti G, Cherubino P. Analysis of bone ingrowth on a tantalum cup. *IJO.* 2008;42:275–8.
- Malizos KN, Bargiotas K, Papatheodorou L, Hantes M, Karachalios T. Survivorship of monoblock trabecular metal cups in primary THA: midterm results. *Clin Orthop.* 2008;466:159–66.
- Macheras GA, Papagelopoulos PJ, Kateros K, Kostakos AT, Baltas D, Karachalios TS. Radiological evaluation of the metal-bone interface of a porous tantalum monoblock acetabular component. *J Bone Joint Surg Br.* 2006;88B:304–9.
- Xenakis T, Machairas G, Bargiotas K, Stafylas K, Malizos KN. A multi-center study of the use of a porous Tantalum Monoblock Acetabular component. Five years clinical and radiographic results. *Int Orthop.* 2009;33:911–6.
- Gruen TA, Poggie RA, Lewallen DG, Hanssen AD, Lewis RJ, O'Keefe TJ, et al. Radiographic evaluation of a monoblock acetabular component: a multicenter study with 2 to 5 year results. *J Arthroplasty.* 2005;20:369–78.
- Komarasamy B, Vadivelu R, Bruce A, Karshaw C, Davison J. Clinical and radiological outcome following total hip arthroplasty with an uncemented trabecular metal monoblock acetabular cup. *Acta Orthop Belg.* 2006;72:320–5.
- Mulier M, Rys B, Moke L. Hedrocel trabecular metal monoblock acetabular cups: mid-term results. *Acta Orthop Belg.* 2006;72:326–31.
- Macheras GA, Kateros K, Koutsostathis SD, Tsakotos G, Galanakis S, Papadakis SA. The Trabecular Metal Monoblock acetabular component in patients with high congenital hip dislocation: a prospective study. *J Bone Joint Surg Br.* 2010;92:624–8.
- Simon JP, Bellemans J. Clinical and radiological evaluation of modular trabecular metal acetabular cups. Short-term results in 64 hips. *Acta Orthop Belg.* 2009; 75:623–30.
- Wright JM, Pellicci PM, Salvati EA, Ghelman B, Roberts MM, Koh JL. Bone density adjacent to press-fit acetabular components: a prospective analysis with quantitative computed tomography. *J Bone Joint Surg Am.* 2001;83A:529–36.
- Meneghini RM, Ford KS, McCollough CH, Hanssen AD, Lewallen DG. Bone remodeling around

- porous metal cementless acetabular components. *J Arthroplasty*. 2010;25:741–7.
28. Paprosky W, Perona P, Lawrence J. Acetabular defect classification and surgical reconstruction in revision arthroplasty: a 6-year follow-up evaluation. *J Arthroplasty*. 1994;9:33–44.
 29. Sporer SM, Paprosky WG. Acetabular revision using a trabecular metal acetabular component for severe acetabular bone loss associated with a pelvic discontinuity. *J Arthroplasty*. 2006;21(S2):87–90.
 30. Gross AE, Goodman SB. Rebuilding the skeleton: the intraoperative use of trabecular metal in revision total hip arthroplasty. *J Arthroplasty*. 2005;20 S2:91–3.
 31. Weeden SH, Schmidt RH. The use of tantalum porous metal implants for Paprosky 3A and 3B defects. *J Arthroplasty*. 2007;22(6 S2):151–5.
 32. Malkani AL, Price MR, Crawford 3rd CH, Baker DL. Acetabular component revision using a porous tantalum biomaterial: a case series. *J Arthroplasty*. 2009;24:1068–73.
 33. Lachiewicz PF, Soileau ES. Tantalum components in difficult acetabular revisions. *Clin Orthop*. 2010;468:454–8.
 34. Lingaraj K, Teo YH, Bergman N. The management of severe acetabular bone defects in revision hip arthroplasty using modular porous metal components. *J Bone Joint Surg Br*. 2009;91B:1555–60.
 35. O’Keefe TJ, Winter S, Lewallen DG, Robertson DD, Poggie RA. Clinical and radiographic evaluation of a monoblock tibial component. *J Arthroplasty*. 2009;25:785–92.
 36. Henricson A, Linder L, Nilsson KG. A trabecular metal tibial component in total knee replacement in patients younger than 60 years: a two-year radiostereophotogrammetric analysis. *J Bone Joint Surg Br*. 2008;90:1585–93.
 37. Harrison AK, Gioe TJ, Simonelli C, Tatman PJ, Schoeller MC. Do porous tantalum implants help preserve bone?: evaluation of tibial bone density surrounding tantalum tibial implants in TKA. *Clin Orthop*. 2010;468:2739–45.
 38. Minoda Y, Kobayashi A, Iwaki H, Ikebuchi M, Inori F, Takaoka K. Comparison of bone mineral density between porous tantalum and cemented tibial total knee arthroplasty components. *J Bone Joint Surg Am*. 2010;92:700–6.

Assessment of a Failed (Painful?) Total Joint Arthroplasty

10

Theofilos Karachalios, Sotirios Michalitsis, and
Aikaterini Veloni

Introduction

Total joint arthroplasty (TJA) has provided, to patients with end stage major joint arthritis, reliable painless range of movement and functional recovery which can last for more than 15 years [1]. However, the majority of these artificial joints will eventually fail for various reasons, in a variety of failure patterns [2], and revision surgery becomes necessary. The lifetime of a TJA can be divided into three phases: the initial months during which the implant must become rigidly fixed (early stable phase) and the remainder of the implant's life, during which fixation may either be maintained (late stable phase) or lost (late unstable phase). An early unstable phase may also be seen, although infrequently these days, due mainly to errors of surgical technique. Orthopedic surgeons often face the question of how they can diagnose early loss of

interface integrity, material structural failures, and how they can diagnose and treat other painful arthroplasty conditions. It should be realized that certain patterns of TJA failures can remain silent for a long period of time (Fig. 10.1). Regular follow-up examination of even painless and well-functioning TJAs should be organized at dedicated orthopedic centers in order to diagnose problems and failures as early as possible.

In this chapter the clinical manifestations and the laboratory confirmation of major TJA (THA and TKA) failures will be analyzed and discussed.

Pain

Pain after a TJA may be localized in the groin, buttock, thigh, or knee, and the cause should be established primarily through a detailed history, careful clinical examination, and plain radiographs. The above usually provides sufficient information for a diagnosis, especially when the causative factor is not directly related to the given joint. In cases where the prosthetic components and their inadequate or impaired fixation to bone or cement is suspected to be the cause of pain, further investigation is required to enable a diagnosis to be made. Laboratory tests, fluoroscopic imaging, subtraction contrast arthrography and/or diagnostic intra-articular infiltrations, radionuclide imaging of the hip, as well as new imaging techniques and serological markers all provide valuable information about the implant-bone or implant-cement interface and, consequently,

T. Karachalios, MD, DSc (✉)
Orthopaedic Department, Faculty of Medicine,
School of Health Sciences, University of Thessalia,
CERETETH, University General Hospital
of Larissa, Mezourlo Region,
Larissa 41110, Hellenic Republic, Greece
e-mail: kar@med.uth.gr

S. Michalitsis, MD, DSc • A. Veloni, MD
Orthopaedic Department,
University General Hospital of Larissa,
Larissa, Greece



Fig. 10.1 Sixteen years follow-up radiograph of a painless THA showing proximal cup migration and femoral osteolysis in zone 7 as a reaction to wear debris

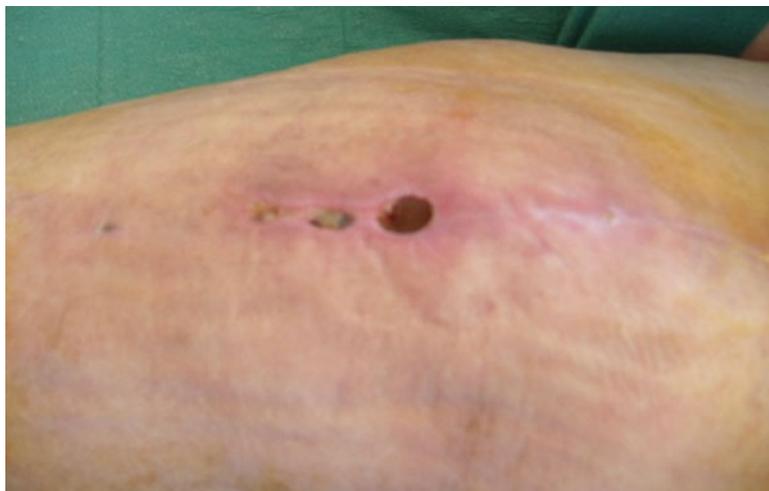
confirm or exclude the diagnosis of aseptic loosening of the hip.

History

The evaluation of a painful TJA begins with a detailed history. The information derived can significantly narrow the spectrum of differential diagnoses and thereby lead to a more targeted workup. The onset, duration, site, and character of the pain can be valuable clues towards the diagnosis of aseptic loosening of a joint component [3]. The time of pain onset is of key importance. Persistent pain since surgery with no pain-free interval is indicative of infection, failure to obtain initial implant stability, periprosthetic fracture, or misdiagnosis of the

initial joint disorder [4]. Later onset after a pain-free interval suggests aseptic loosening, periprosthetic stress fracture, osteolysis, or late infection [5]. The relation of pain to activity may be indicative of certain diagnoses. Pain on initiation of activity that resolves with continued activity should raise suspicion of a loose prosthesis. The patient typically presents with a dull aching pain in the anterolateral thigh in the case of a THA or in either side of the proximal tibia in the case of TKA. In the majority of cases, this pain is combined with limping, and the patient may have noticed that the leg becomes increasingly externally rotated (in THAs) as the component sinks into retroversion, or the knee progressively becomes varus (in most cases of TKA). Often the patient can localize the discomfort to a discrete area on the femur or on the tibia that correlates with the location of a prosthetic stem tip. This is in contradistinction to bursal pain, which tends to be more proximal at the level of the vastus tubercle and greater trochanter [6–10]. Constant pain, pain at rest, or pain at night can be indicative of sepsis or malignancy [5, 6]. Night pain may also occur with aseptic loosening [7]. Pain localized to the groin or the deep buttock often is associated with acetabular loosening, osteolysis, or iliopsoas tendinitis. Two different types of thigh pain have been described [7, 10, 11]. One is caused by a loosely fitting undersized distal stem with some relative movement; the other by a good end fill stem causing localized stresses and bone cortical hypertrophy. Pain from end fill stems is usually less than that from loosely fitting distal stems, and its onset is later. Thigh pain has been linked to femoral component loosening, whereas tip-of-stem pain may be caused by a modulus mismatch between a stiff cementless femoral or tibial stem and less stiff surrounding bone [7, 8]. In addition to the timing of the onset and the location of the pain, a careful history should be obtained to identify precipitating events, such as trauma, systemic illness, or infection. Onset of pain after a traumatic fall may be caused by fracture or traumatic loosening. Delayed and wet wound healing (Fig. 10.2), large postoperative hematoma, persistent fever, prolonged antibiotic administration, or delayed hospital discharge should be considered as potential indications of a deep infection. General factors such as immunosuppression, neoplastic

Fig. 10.2 Delayed wound healing 2 weeks following a TKA as a result of a tissue reaction to subcutaneous sutures. Early and aggressive surgery is needed in order to avoid joint infection



disease, previous hip or knee surgery or infection, diabetes mellitus, and gynecological morbidities also increase the risk of infection and should be thoroughly investigated [7].

Clinical Examination

A comprehensive musculoskeletal examination should involve the painful and contralateral hip, knee, and spine. Moreover, a thorough neurovascular assessment of the lower extremities is necessary to rule out neurogenic and vascular causes of hip and thigh pain. The patient's gait provides useful information about antalgic gait patterns, limb-length discrepancy, muscle weakness, and Trendelenburg gait [5, 6]. Progressive limb shortening documented on successive examinations after a THA suggests implant loosening [12]. Inspection of the patient's posture from all sides is useful to identify muscle atrophies and pelvic obliquity. The skin of the affected area should be inspected for scars and clinical signs of infection. Palpation may confirm other causes of hip pain such as trochanteric bursitis, lymphadenopathy, inguinal hernia, and stress fractures of the pelvic ring. The patient may have to use his hands to lift his leg onto the examination table. The inability to perform straight leg raises may be apparent. Testing the range of motion is the next step of the clinical assessment. Pain with active ROM or at extremes of motion could be indicative of

loosening, whereas pain with passive ROM may suggest occult infection. Pain or apprehension, particularly at extremes of motion, is indicative of instability or impingement [6]. A study from Switzerland has postulated that the best clinical indicators for loosening are axial compression, external rotation, and hip pain for the acetabular cup and axial compression, external rotation, thigh pain, internal rotation, and hip/knee pain for the femoral stem, with better indices values for the latter [13].

Laboratory Tests

Laboratory tests play an important role in the evaluation of the patient with a painful TJA. Blood work (WBC count with type), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and aspiration provide useful information in determining the cause of a painful TJA. As the main concern is the differentiation between septic and aseptic loosening, several studies have been organized towards this end. *WBC* count is usually not helpful and is rarely elevated, even in obviously infected TJAs [14, 15]. The value of *ESR* in the differentiation between septic and aseptic loosening after TJR is equivocal [16, 17]. A cutoff of 30 mm/h has a diagnostic sensitivity of 65–94 % and a specificity of 65–85 % for identifying infection [15–17]. *CRP* is more informative and sensitive than *ESR* in differentiating septic and mechanical loosening.

A CRP level of >20 mg/L practically excludes aseptic loosening, whereas another study suggests that an upper limit of 10 mg/L provides a sensitivity of 96 % and a specificity of 92 % for infection [14, 15, 17, 18]. Improved diagnostic accuracy can be obtained by using both ESR and CRP values. The combination of normal ESR and CRP values has a specificity of 100 % for excluding the diagnosis of infection in patients with a painful THA, leading towards the diagnosis of aseptic loosening [14]. Similarly, a CRP level <20 mg/L and an ESR <30 mm/h suggest aseptic loosening [18]. Serum *interleukin-6* levels seem to have the highest accuracy for a diagnosis of THR infection [19, 20], followed by CRP, ESR, and WBC count. In a prospective study [21], the combination of CRP and interleukin-6 identified all patients with THR infection. *Aspiration* of the hip is recommended when there is a strong clinical suspicion of infection, when ESR or CRP or both are increased, or when there is an increased uptake on gallium or indium scanning [3, 15]. Hip joint aspiration has a diagnostic accuracy of 60–70 % and knee joint aspiration of 90–95 % in diagnosing joint infection.

Plain Radiographs

True anteroposterior (AP) and lateral x-rays of the hip are the gold standard in the initial radiographic evaluation of the THA interface. These should include the entire length of the stem and cement mantle (if any) and consequently be compared with previous films (serial radiographs). Several techniques are described for a more detailed evaluation of the components; frog-leg lateral view enhances the imaging of the proximal-lateral portion of the femoral component, and a cross-table lateral view enables the assessment of bone stock in the posterior column and the neck of the ilium. The Lowenstein lateral radiograph provides a lateral view of the acetabular subchondral bone and the cup after implantation. More specific for the detection of interface loosening is the comparison between weight-bearing and non-weight-bearing views and the AP push-pull views (compression-distraction of the femur in its longitudinal axis).

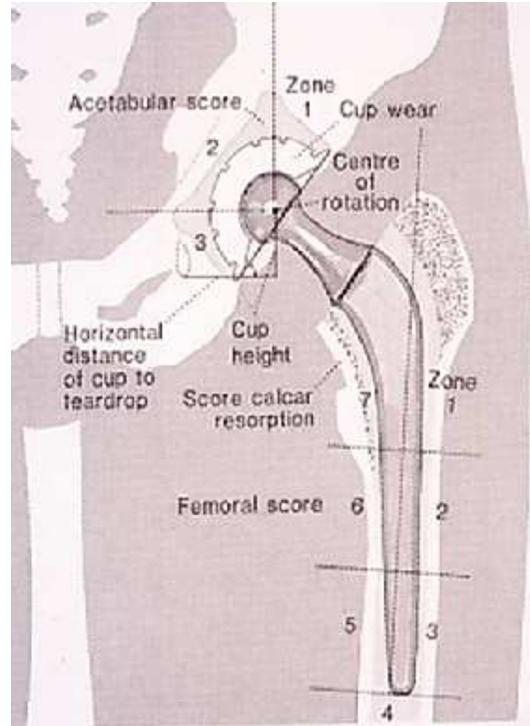


Fig. 10.3 Line drawing showing the 3 DeLee acetabular zones and the 7 Gruen femoral zones for the evaluation of aseptic loosening of cemented THAs

Cemented Components

Loosening is defined as a radiographic interpretation of change in the mechanical integrity of the load-carrying cemented femoral component, specifically, fractured acrylic cement and an interface gap such as a radiolucent zone at the stem-cement or at the cement-bone interface. Gruen et al. have suggested four modes of failure of the stem-cement or cement-bone interface, and the radiological appearance of each pattern was recorded by means of a seven-section zonal distribution (Fig. 10.3) around the femoral component in the AP radiograph [22]. (a) Pistoning behavior of the metal stem within the acrylic cement mantle (mode Ia) or of the acrylic cement-embedded stem within the bone (mode Ib). Mode Ia results in a radiolucent zone appearing in the proximal-lateral zone (zone 1), frequently with a punch-out fracture of the acrylic cement at the distal tip of the stem. On the other hand, mode Ib is characterized by a radiolucent zone around most,

if not all, of the entire cement-bone interface with a sclerotic bone “halo” reaction. (b) Medial mid-stem pivot type of failure is characterized by medial migration of the proximal stem coupled with lateral migration of the distal stem tip. The radiolucent lines, cement cracks, or interface gaps appear in the respective zones around the stem. (c) Calcar pivot mode of failure is caused due to a medial/lateral toggle of the distal tip of the embedded stem, with either an adequate proximal cement augmentation or pivoting of the medial femoral neck upon the medial cortex. The radiographic appearance is that of radiolucent zones and sclerotic bone reaction in sections 3, 4, and 5. (d) Bending cantilever fatigue is characterized by partial or total separation of the proximal stem from the cement mantle or from the cement-bone interface, while distal fixation remains intact. This can easily be recognized by the radiolucent zones in the proximal-medial (zone 7) and the proximal-lateral (zone 1) stem, while the distal stem is well cemented in the intramedullary canal. The definitions of possible, probable, and definite radiographic loosening for cemented femoral components [23–26] are the most widely accepted. Possible loosening is defined as a radiolucent line at the cement-bone interface between 50 and 100 % of the total bone-cement interface. Probable loosening is defined as a radiolucent line in the bone-cement interface that is either continuous or greater than 2 mm in width, at some point. Signs of definite loosening are migration of the component, fracture of the stem, and cement fracture. On the other hand, Dorr et al. [27] have suggested that progressive demarcation at the femoral component is diagnosed if any of the following criteria are met: (a) any increase in the radiolucent line around at least one-half of the femoral stem, (b) any subsidence or loosening of the femoral component, or (c) resorption of the calcar of more than 10 mm.

Cementless Stems

The comparison of serial x-rays may detect signs of loosening in the bone-implant interface [28]. *Migration* is a major sign of loosening and instability and is defined as a measurable change in the

implant position between two serial x-rays. *Reactive lines* parallel to the smooth implant surface suggest a fibrous rather than a bony fixation. A *pedestal formation* (hypertrophy of the distal tip) is defined as a shelf of endosteal new bone either partially or completely bridging the intramedullary canal in an apparent attempt to support the tip of the prosthesis. Although not directly indicative of a loose component, it certainly suggests an abnormal stress concentration and may represent a stress shielding of the proximal portion of the femur. *Calcar hypertrophy/atrophy* is a result of bone density changes in the medial femoral neck due to varying models of fixation and loading from the stem. The appearance of a *radiolucent interval* around the prosthesis suggests the development of a fibrous interface between implant and bone, rather than bony ingrowth, especially if this interval is noticed at the ingrowth portion of the stem. Additional appearance of reactive lines diverging from the implant in the ingrowth area indicates loosening (interface deterioration). *Particle shedding* is defined as the presence of metal particles surrounding the stem which did not appear on the immediate postoperative x-ray. An increase in the number of metal particles surrounding the stem on serial x-rays is defined as late and progressive particle shedding.

Cemented Acetabular Components

The initiation of the aseptic loosening process begins at the intra-articular margin and proceeds to the dome of the implant (Fig. 10.4). Thus, an interfacial membrane is created in the periphery of the cup and enhanced by the presence of wear debris particles; macrophage-mediated bone resorption is initiated from the periphery to the center of the cup [22, 29]. Radiolucency is produced by this dense fibrous membrane and in some areas fibrocartilage, which forms about the surface of the cement and the surrounding shell of reactive bone. DeLee and Charnley have suggested that interface loosening appears as a demarcation on the radiographs, a dark line between the radiopaque cement and the bone of the acetabulum. The dark line is rendered obvious by a condensed bright line on the surface



Fig. 10.4 Fourteen years' follow-up radiograph of an acetabular cup showing initiation of radiolucent lines from zone I, circumferential complete demarcation, and proximal migration

of cancellous bone [30]. The width of this radiolucency is measured and categorized into zones I, II, or III, according to its distribution round the circumference of the acetabular socket (Fig. 10.3). Roentgenographic appearance can be classified into 4 types, irrespective of gap width: 0 (no demarcation), 1 (demarcation in zone I), 2 (demarcation in I and II), 3 (demarcation in all zones), and 4 (socket migration) as postulated by DeLee and modified by Hodgkinson [24]. The latter study reported that with a gap width of 1 mm or more in distribution type 2 or 3, the acetabular socket is almost certainly loose. Generally, any radiolucent line that is new, progressive or not, apparent on the initial x-ray, should arouse suspicion of cement-bone interface loosening, and the extent of the radiolucency is more important than its width. According to another study, a continuous radiolucent line at least 2 mm in width along the entire circumference of the bone-cement interface is regarded as a criterion of radiological loosening [29].



Fig. 10.5 Focal osteolysis in zone I of a first-generation cementless acetabular cup

Cementless Acetabular Components

The status of osseointegration of non-cemented cups can be estimated with five radiographic signs: (1) absence of radiolucent lines, (2) presence of a superolateral buttress, (3) medial stress shielding, (4) radial trabeculae, and (5) an inferomedial buttress. The presence of three or more signs has a positive predictive value of almost 97 % for the prediction of osseointegration [31]. The appearance of continuous radiolucent lines in all three zones of the acetabulum, continuous radiolucent lines 2 mm or wider in any zone, and horizontal or vertical migration of the acetabular cup are signs of loosening. Peripheral radiolucent lines which are noncontinuous are commonly found in press fit acetabular components and are often not progressive. Focal osteolysis in the proximity of cementless acetabular cups is clinically silent for long period of time, and it is indicative of polyethylene and/or back side wear (Fig. 10.5).

Aspiration: Anesthetic Injection

The technique of preoperative aspiration of a major artificial joint is recommended when clinical suspicion for infection is high, when ESR or CRP or both are elevated, or if there is an increased uptake on gallium or indium scanning. Local anesthetic injections can be useful in localizing the origin of pain in a patient with a painful THA (intracapsular or extracapsular source). The addition of bupivacaine in the contrast material during contrast arthrography may suggest an intra-articular source of pain if the patient experiences relief of symptoms [3, 7, 15, 32].

Fluoroscopic Imaging

Arthrography

Contrast arthrography, as described by Hendrix et al. [33], is mainly used to define the accurate positioning of the needle during aspiration of the painful hip joint in order to exclude infection. It is also used to detect bursae, other than the pseudocapsule, and occult implant loosening not readily visible on plain radiographs. Sterile bursal cavities are usually large, smooth walled extensions of the pseudocapsule. In order to reduce false-negative results in tests for aseptic loosening, it is essential to inject sufficient contrast to fill the pseudocapsule and obtain post-ambulatory or post-exercise x-rays [7, 34]. Contrast leakage in any interface distal to the intertrochanteric line is considered as loosening of the acetabular component. For the acetabular component, contrast leakage is assessed according to the 3 zone distribution of DeLee and Charnley [34, 35]. Because the metal of the prostheses and the contrast medium have similar radiographic densities, conventional arthrographies may easily miss narrow gaps. Manual subtraction arthrography, although technique dependent and distorted by motion artifacts, may reveal leakages in regions hidden by conventional arthrograms. Arthrography can help rule out hidden loosening in perplexing cases, although its use is rare. It is more sensitive and more specific than plain radiographs for

excluding loosening of the acetabular component but no more accurate for excluding loosening of the femoral component [25, 26]. Generally, contrast arthrography overestimates acetabular loosening and underestimates femoral loosening [3, 25, 26], whereas the modality of subtraction arthrography proves to be equally accurate for the estimation of femoral and acetabular components.

Radionuclide Imaging

Well-established diagnostic procedures which are used to differentiate between causes of a painful TJA and lead towards the diagnosis of an interface loosening procedure are triple-phase bone scanning (TPBS) and positron emission tomography (PET) with fluorodeoxyglucose (FDG) [26, 36].

TPBS

The accumulation of bone-seeking tracers which localize on the surface of the bone mineral matrix is dependent on blood flow and especially on the rate of new bone formation. The diffuse pattern seen with infection is probably due to generalized osteolysis, which is also present in aseptic loosening secondary to inflammation. Therefore, these two entities may be indistinguishable at scintigraphy. The most frequently used radiotracers are ^{99m}Tc-labeled hydroxymethylene diphosphonate (HDP), gallium-67 citrate, and indium 111-labeled white blood cells. Blood flow, blood pool, and delayed static images are graded on a scale of 0 to III, where zero represents the uptake of normal surrounding bone. Grade I can be assessed as a mild increase, grade II a moderate increase, and grade III an intense uptake [37]. The femoral component can be considered in the seven zones pattern of plain radiography, and the acetabular changes are recorded in the three zones of DeLee and Charnley. A prosthesis can be defined as loose on the bone scans if there is a mild or moderate increase in uptake (grades I or II) in more than two zones or intense (grade III) uptake in at least one zone [38]. Wilson [39] described criteria for interpretation of bone scans;

loosening of the stem is assumed in patients with significant pathological uptake of HDP in the area of the tip in combination with at least a second substantial lesion in the region of the lesser trochanter. Loosening of the acetabular cup is diagnosed in patients with continuous pathological uptake in the cup-bone interface. Focal uptake at the distal tip of the femoral component of a cemented device more than 1 year old is often attributed to aseptic loosening. However, in the case of a porous-coated prosthesis, this pattern is often present in asymptomatic individuals for considerably longer after surgery [40, 41]. The overall accuracy of radionuclide bone imaging with $^{99m}\text{TcHDP}$ in evaluation of the prosthetic joint is about 50–70 % [26]. Nevertheless, bone imaging is useful as an initial screening test because it has a high negative predictive value [42]. Technetium scanning alone demonstrates loosening and in some cases can give a good indication of infection, but it is not as reliable in differentiating between mechanical loosening and infected loosening as is the combination of a technetium and a gallium scan [43]. Data from a meta-analysis [44] demonstrated an overall sensitivity of 85 % and specificity of 72 % for TPBS in detecting femoral interface loosening. Pooled sensitivity was 86 %, and specificity was 78 % for cemented components compared to 82 and 43 % for uncemented femoral components respectively.

Gallium-67 Citrate Imaging

In an effort to improve the specificity of bone scintigraphy, complementary gallium imaging is often performed. This is based on the different mechanism of uptake between gallium and technetium. The interpretation of sequential bone-gallium images is as follows [45]: (a) negative for infection when the gallium images are normal, regardless of the bone scan findings, or when the spatial distributions of the two tracers are congruent and the intensity of gallium uptake is less than that of the bone tracer; (b) positive for infection when the distributions of the two tracers are spatially incongruent or when their distributions are spatially congruent and the intensity of gallium uptake exceeds that of the bone agent; and (c) equivocal for infection when the distributions of

the two tracers are spatially congruent and the intensities of uptake of the tracers are similar. The uptake of gallium is related to inflammation in general and not to infection specifically. Consequently, with an overall accuracy of about 70–80 %, this technique is not well suited for distinguishing an inflamed, aseptically loosened prosthesis from an infected prosthesis [45].

Indium-111-Labeled Leukocytes Scintigraphy

The labeling of inflammatory cells that migrate to the sites of infection may represent the single most important achievement in radionuclide diagnosis of infection to date. At least in theory, labeled leukocyte imaging is thus particularly well suited for distinguishing between the inflamed aseptically loosened prosthesis, in which neutrophils are generally absent, and the infected prosthesis, in which neutrophils are present [45]. Regarding the evaluation of bone-implant and bone-cement interface, periprosthetic activity is compared with adjacent bone activity or with the activity of the contralateral joint. The increased uptake of labeled leukocytes in the hematopoietically active bone marrow may be a problem in distinguishing these normal areas from infected hip prostheses. The combination of labeled leukocytes with $^{99m}\text{TcHDP}$ is used to overcome this problem; when the distributions of the two tracers are similar or spatially congruent, the labeled leukocyte activity is due to the presence of marrow. When there is activity on the labeled leukocyte images without corresponding activity on the sulfur colloid images, the labeled leukocyte uptake is due to infection. In contrast to the results reported for labeled leukocyte imaging alone, the results of combined leukocyte-marrow imaging of prosthetic joints have been uniformly excellent, with an accuracy of 90 % or greater [45, 46].

Imaging with Investigational Agents

Labeling of monoclonal antibodies, peptides, and antibody fragments is investigated in order to overcome the laboratory demanding *in vitro*

labeling of leukocytes. A meta-analysis of diagnostic studies regarding the accuracy of antigranulocyte scintigraphy (AGS) with monoclonal antibodies in the identification of prosthesis infection demonstrated a sensitivity of 90 % for a specificity of 80 % [47]. The use of ^{99m}Tc -labeled annexin V, a marker of apoptosis and cellular stress, shows greater uptake with infection than with aseptic loosening and has a high negative predictive value for prosthetic infection [48].

PET (Positron Emission Tomography Based on 2-Fluoro-2-Deoxy-D-Glucose)

The literature is not consistent regarding the interpretation of uptake patterns; an initial opinion postulates that septic and aseptic loosening are not characterized by a topographic specific pattern, and differentiation is based on the quantity of FDG uptake, being higher in septic loosening. A second opinion affirms that radiodrug localization in the bone-prosthesis interface is a characteristic of septic loosening. Therefore, the presence of an osteolytic area visible through x-ray with PET negative or partially positive should be related to aseptic loosening. The overall sensitivity of FDG-PET in recognizing periprosthetic hip infection is higher than 92 % [36, 49–51]. PET findings and their correlation to interface clinical conditions (no loosening, loosening, or infection) can be classified according to the following patterns of uptake [36, 49–51]: pattern I, no uptake in the bone-prosthesis interface; pattern II, uptake surrounding the femoral neck; pattern III, uptake localized in the area surrounding the femoral neck and in a part of the bone acetabular cup and/or I and VII Gruen's zones; pattern IVa, uptake in the area surrounding the femoral neck and in the totality of the bone-cup interface, without compromising periprosthetic soft tissue; pattern IVb, uptake localized in the neck area and in most of the bone-stem interface, without compromising periprosthetic soft tissue; pattern IVc, IVa and IVb; and pattern V, uptake in the bone-prosthesis interface and in periprosthetic soft tissue. Patterns I, II, and III are not associated with loosening; pattern IV is probably

associated with aseptic loosening, and in pattern V there is very likely an infection.

Modern Techniques

Dynamic Computed Tomography Scanning

This CT rotational study is recommended for patients with hip pain and equivocal radiographic findings for femoral component loosening [6, 52]. Images of the extremity in external and internal rotation are obtained, with one line drawn parallel to the medial/lateral axis of the femoral component and another line parallel to the posterior femoral condyles. If the difference between the maximum external rotation femoral component version angle and maximum internal rotation femoral component version angle is two degrees or fewer, the prosthesis is considered to be rotationally stable. If this difference is greater than two degrees, the prosthesis is considered rotationally unstable [52]. The accuracy of CT measurements of the femoral component version in relation to posterior femoral condyles axis is highly dependent on interobserver error, but the method is well tolerated, noninvasive, easily applicable, and inexpensive.

In Vivo Wear Measurements of Bearing Surfaces

Currently there is no accurate in vivo method for wear recording in THA with metal-on-metal and ceramic-on-ceramic bearings. For research reasons and rarely for clinical reasons, there is a need for identification of THAs which show excessive polyethylene wear. In order to measure wear in vivo, many techniques have been developed: manual methods as Livermore has described [53, 54] and recently computer-assisted techniques that are considered to have better accuracy [55–57]. There is a variety of the latter with different levels of accuracy and precision but with various disadvantages. For example, RSA (radiostereometric analysis), which is one of the most accurate techniques today, has the disadvantage of the need for implanting metallic indicators during surgery. Another option is the

PolyWare Auto digital method (Figs. 10.6) [56, 58, 59].

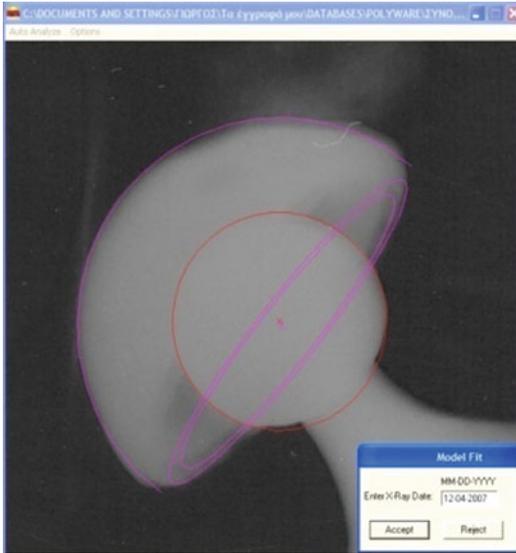


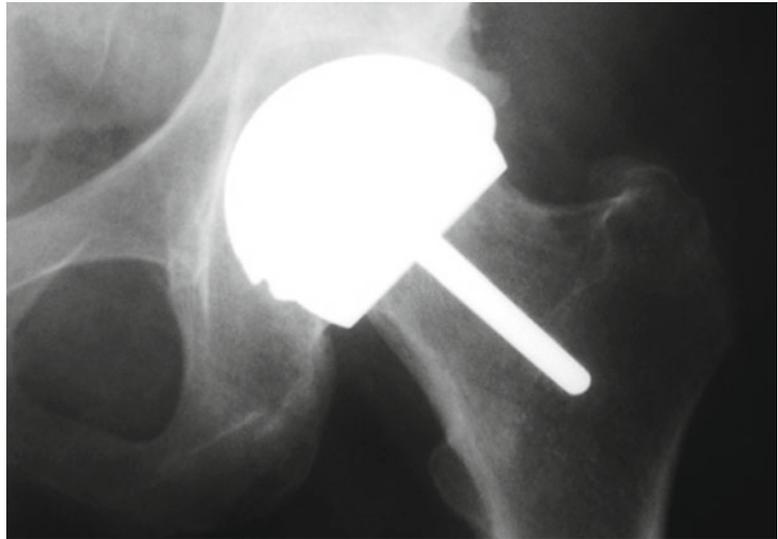
Fig. 10.6 Polyethylene wear assessed with the use of the dual cycle method “PolyWare”

Serum Metal Ion Levels

A promising diagnostic tool for the evaluation of the implant-bone or implant-cement interface is the measurement of serum and/or urine metal ion levels [3]. Higher levels of circulating metal degradation products are observed in patients who have clinical evidence of component failure caused by fretting corrosion, loosening, or other causes [60, 61]. Serum Ti, Al, Cr, or Co levels may be used in the future as a diagnostic method to evaluate the possibility of loosening or component failure in the patient with a painful TJR.

Recently, metal-on-metal articulations have been linked with excessive metallic ions production which causes serious local and systemic effects (Fig. 10.7). Establishment of normal and abnormal metallic ion serum values in symptomatic and asymptomatic THAs is still controversial and is presented in another chapter of this book.

Fig. 10.7 Satisfactory radiograph of a well-functioning resurfacing hip arthroplasty at 9 years follow-up. The question if this artificial joint is a metallic wear particle-producing machine and which is the optimal method in assessing it remains still unclear



References

- Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. *Lancet*. 2007; 370(0597):1508–19.
- Hirakawa K, Jacobs JJ, Urban R, Saito T. Mechanisms of failure of total hip replacements: lessons learned from retrieval studies. *Clin Orthop*. 2004;420:10–7.
- Bozic KJ, Rubash HE. The painful total hip replacement. *Clin Orthop*. 2004;420:18–25.
- Bohl W, Steffee A. Lumbar spinal stenosis: a cause of continued pain and disability in patients after total hip arthroplasty. *Spine*. 1979;4:168–73.
- Smith P, Rorabeck C. Clinical evaluation of the symptomatic total hip arthroplasty. In: Steinberg M, Carino J, editors. *Revision total hip arthroplasty*. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 109–20.
- White R. Evaluation of the painful total hip arthroplasty. In: Callaghan J, Rosenberg A, Rubash H, editors. *The adult hip*. Philadelphia: Lippincott-Raven Publishers; 1998. p. 1377–85.
- Robbins GM, Masri BA, Garbus DS, Duncan CP. Evaluation of pain in patients with apparently solidly fixed total hip arthroplasty components. *JAAOS*. 2002;10:86–94.
- Bourne RB, Rorabeck CH, Ghazal ME, Lee MH. Pain in the thigh following total hip replacement with a porous-coated anatomic prosthesis for osteoarthritis. *J Bone Joint Surg Am*. 1994;76A:1464–70.
- Brown TE, Larson B, Shen F, Moskal JT. Thigh pain after cementless total hip arthroplasty: evaluation and management. *JAAOS*. 2002;10(6):385–92.
- Callaghan JJ, Dysart SH, Savory CG. The uncemented porous-coated anatomic total hip prosthesis: two-year results of a prospective consecutive series. *J Bone Joint Surg Am*. 1988;70A:337–46.
- Engh CA, Massin P. Cementless total hip arthroplasty using the anatomic medullary locking stem: results using a survivorship analysis. *Clin Orthop*. 1989;247:138–47.
- Evans BG, Cuckler JM. Evaluation of the total hip arthroplasty. *Orthop Clin North Am*. 1992;23:303–11.
- Röder C, Eggli S, Aebi M, Busato A. The validity of clinical examination in the diagnosis of loosening of components in total hip arthroplasty. *J Bone Joint Surg Br*. 2003;85B:37–44.
- Spangehl MJ, Masri BA, O'Connell JX, Duncan CP. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. *J Bone Joint Surg Am*. 1999;81A:672–83.
- Barrack RL, Harris WH. The value of aspiration of the hip joint before revision total hip arthroplasty. *J Bone Joint Surg Am*. 1993;75A:66–76.
- Forster IW, Crawford C. Sedimentation rate in infected and uninfected total hip arthroplasty. *Clin Orthop*. 1982;168:48–52.
- Shih LY, Wu JJ, Yang DJ. Erythrocyte sedimentation rate and C-reactive protein values in patients with total hip arthroplasty. *Clin Orthop*. 1987;225:238–46.
- Sanzén L, Carlsson AS. The diagnostic value of C-reactive protein in infected total hip arthroplasties. *J Bone Joint Surg Br*. 1989;71B:638–41.
- Bottner F, Wegner A, Winkelmann W, Becker K, Erren M, Götz C. Interleukin-6, procalcitonin and TNF-alpha: markers of peri-prosthetic infection following total joint replacement. *J Bone Joint Surg Br*. 2007;89B:94–9.
- Barbari E, Mabry T, Tsaras G, Spangehl M, Erwin PJ, Murad MH, Steckelberg J, Osmon D. Inflammatory blood laboratory levels as markers of prosthetic joint infection: a systematic review and meta-analysis. *J Bone Joint Surg Am*. 2010;92:2102–9.
- Buttaro MA, Tanoira I, Comba F, Piccaluga F. Combining C-reactive protein and interleukin-6 may be useful to detect periprosthetic hip infection. *Clin Orthop*. 2010;468:3263–7.
- Gruen TA, McNeice GM, Amstutz HC. "Modes of failure" of cemented stem-type femoral components: a radiographic analysis of loosening. *Clin Orthop*. 1979;141:17–27.
- Mulroy WF, Estok DM, Harris WH. Total hip arthroplasty with use of so-called second-generation cementing techniques. A fifteen-year-average follow-up study. *J Bone Joint Surg Am*. 1995;77A:1845–52.
- Hodgkinson JP, Shelley P, Wroblewski BM. The correlation between the roentgenographic appearance and operative findings at the bone-cement junction of the socket in Charnley low friction arthroplasties. *Clin Orthop*. 1988;228:105–9.
- O'Neill DA, Harris WH. Failed total hip replacement: assessment by plain radiographs, arthrograms, and aspiration of the hip joint. *J Bone Joint Surg Am*. 1984;66A:540–6.
- Temmerman OP, Rajmakers PG, Deville WL, Berkhof J, Hooft L, Heyligers IC. The use of plain radiography, subtraction arthrography, nuclear arthrography, and bone scintigraphy in the diagnosis of a loose acetabular component of a total hip prosthesis: a systematic review. *J Arthroplasty*. 2007;22:818–27.
- Dorr LD, Takei GK, Conaty JP. Total hip arthroplasties in patients less than forty-five years old. *J Bone Joint Surg Am*. 1983;65A:474–9.
- Engh CA, Massin P, Suthers KE. Roentgenographic assessment of the biologic fixation of porous-surfaced femoral components. *Clin Orthop*. 1990;257:107–28.
- Schmalzried TP, Kwong LM, Jasty M, et al. The mechanism of loosening of cemented acetabular components in total hip arthroplasty: analysis of specimens retrieved in autopsy. *Clin Orthop*. 1992;274:60–78.
- DeLee JG, Charnley J. Radiological demarcation of cemented sockets in total hip replacement. *Clin Orthop*. 1976;121:20–32.
- Moore MS, McAuley JP, Young AM, Engh Sr CA. Radiographic signs of osseointegration in porous coated acetabular components. *Clin Orthop*. 2006;444:176–83.
- Crawford RW, Ellis AM, Gie GA, Ling RS. Intra-articular local anaesthesia for pain after hip arthroplasty. *J Bone Joint Surg Br*. 1997;79A:796–800.

33. Hendrix RW, Wixson RL, Rana NA, Rogers LF. Arthrography after total hip arthroplasty: a modified technique used in the diagnosis of pain. *Radiology*. 1983;148:647–52.
34. Ovesen O, Riegels-Nielsen P, Lindequist S, Jensen I, Munkner T, Torfing T, Marving J. The diagnostic value of digital subtraction arthrography and radionuclide bone scan in revision hip arthroplasty. *J Arthroplasty*. 2003;18:735–40.
35. Ginai AZ, van Biezen FC, Kint PA, Oei HY, Hop WC. Digital subtraction arthrography in preoperative evaluation of painful total hip arthroplasty. *Skeletal Radiol*. 1996;25:357–63.
36. Reinartz P, Mumme T, Hermanns B, Cremerius U, Wirtz DC, Schaefer WM, Niethard FU, Buell U. Radionuclide imaging of the painful hip arthroplasty: positron-emission tomography versus triple-phase bone scanning. *J Bone Joint Surg Br*. 2005;87B:465–70.
37. Kantor SG, Schneider R, Insall JN, Becker MW. Radionuclide imaging of asymptomatic versus symptomatic total knee arthroplasties. *Clin Orthop*. 1990;260:118–23.
38. Horoszowski H, Ganel A, Kamhin M, Zaltzman S, Farine I. Sequential use of technetium 99m MDP and gallium 67 citrate imaging in the evaluation of painful total hip replacement. *Br J Radiol*. 1980;63:1169–73.
39. Wilson MA. Musculoskeletal system. In: Wilson MA, editor. *Textbook of nuclear medicine*. Philadelphia: Lippincott-Raven Publishers; 1998. p. 3–32.
40. Spangehl MJ, Younger AS, Masri BA, Duncan CP. Diagnosis of infection following total hip arthroplasty. *Instr Course Lect*. 1998;47:285–95.
41. Ashbrooke AB, Calvert PT. Bone scan appearances after uncemented hip replacement. *J R Soc Med*. 1990;83:768–9.
42. Love C, Tomas MB, Marwin SE, Pugliese PV, Palestro CJ. Role of nuclear medicine in diagnosis of the infected joint replacement. *Radiographics*. 2001;21:1229–38.
43. Rushton N, Coakley AJ, Tudor J, Wraight EP. The value of technetium and gallium scanning in assessing pain after total hip replacement. *J Bone Joint Surg Br*. 1982;64:313–8.
44. Temmerman OP, Raijmakers PG, Berkhof J, Hoekstra OS, Teule GJ, Heyligers IC. Accuracy of diagnostic imaging techniques in the diagnosis of aseptic loosening of the femoral component of a hip prosthesis: a meta-analysis. *J Bone Joint Surg Br*. 2005;87B:781–5.
45. Seabold JE, Forstrom LA, Schauwecker DS, Brown ML, Datz FL, McAfee JG, Palestro CJ, Royal HD. Procedure guideline for gallium and indium-111-leukocyte scintigraphy for suspected infection/inflammation. *J Nucl Med*. 1997;38:994–1001.
46. Johnson JA, Christie MJ, Sandler MP, Parks Jr PF, Homra L, Kaye JJ. Detection of occult infection following joint total arthroplasty using sequential technetium-99m HDP bone scintigraphy and indium-111 WBC imaging. *J Nucl Med*. 1988;29:1347–53.
47. Pakos EE, Trikalinos TA, Fotopoulos AD, Ioannidis JP. Prosthesis infection: diagnosis after total joint arthroplasty with antigranulocyte scintigraphy with 99mTc-labeled monoclonal antibodies—a meta-analysis. *Radiology*. 2007;242:101–8.
48. Lorberboym M, Feldbrin Z, Hendl D, Blankenberg FG, Schachter P. The use of 99mTc-recombinant human annexin V imaging for differential diagnosis of aseptic loosening and low-grade infection in hip and knee prostheses. *J Nucl Med*. 2009;50:534–7.
49. Chacko TK, Zhuang H, Stevenson K, Moussavian B, Alavi A. The importance of the location of fluorodeoxyglucose uptake in periprosthetic infection in painful hip prostheses. *Nucl Med Commun*. 2002;23:851–5.
50. Mumme T, Reinartz P, Alfer J, Müller-Rath R, Buell U, Wirtz DC. Diagnostic values of positron emission tomography versus triple-phase bone scan in hip arthroplasty loosening. *Arch Orthop Trauma Surg*. 2005;125:322–9.
51. Zoccali C, Teori G, Salducca N. The role of FDG-PET in distinguishing between septic and aseptic loosening in hip prosthesis: a review of literature. *Int Orthop*. 2009;33:1–5.
52. Berger R, Fletcher F, Donaldson T, Wasielewski R, Peterson M, Rubash H. Dynamic test to diagnose loose uncemented femoral total hip components. *Clin Orthop*. 1996;330:115–23.
53. Karachalios T, Hartofilakidis G, Zacharakis N, Tsekoura M. A 12 to 18 years radiographic follow up study of Charnley low friction arthroplasty. *Clin Orthop*. 1993;296:140–7.
54. Livermore J, Ilstrup D, Morrey B. Effect of femoral head size on wear of polyethylene acetabular component. *J Bone Joint Surg Am*. 1990;72A:518–28.
55. Ebramzadeh E, Sangiorgio SN, Lattuada F, Kang JS, Chiesa R, McKellop HA, Dorr LD. Accuracy of measurement of polyethylene wear with a use of radiographs of total hip replacements. *J Bone Joint Surg Am*. 1990;85A:2378–84.
56. Martell JM, Berdia S. Determination of polyethylene wear in total hip replacements with use of digital radiographs. *J Bone Joint Surg Am*. 2003;79A:1635–41.
57. Borlin N, Thien T, Karrholm J. The precision of radiostereometric measurements. Manual vs digital measurements. *J Biomech*. 2002;35:69–79.
58. Devane PA, Horne JG. Assessment of polyethylene wear in total hip replacement. *Clin Orthop*. 1999;369:59–72.
59. Devane PA, Bourne RB, Rorabeck CH, Hardie RM, Horne JG. Measurement of polyethylene wear in metal backed acetabular cups. I. three dimensional technique. *Clin Orthop*. 1995;319:303–16.
60. Jacobs JJ, Skipor AK, Patterson LM, Hallab NJ, Paprosky WG, Black J, Galante JO. Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. *J Bone Joint Surg Am*. 1998;80A:1447–58.
61. Jacobs JJ, Skipor AK, Black J, Manion L, Urban RM, Galante JO. Metal release in patients with loose titanium alloy total hip replacements. In: *Transactions of the fourth world biomaterials congress*. Berlin: European Society for Biomaterials; 1992. p. 266.

Theofilos Karachalios and Antonios Koutalos

Introduction

Total joint replacement is an effective surgical intervention for those patients with end stage of joint diseases. The major factor limiting the survival of joint implants is wear debris which is primarily generated from the bearing articular surface of the artificial joint. Aseptic loosening is a disabling condition affecting patients 10–20 years after joint replacement surgery, leading to the failure of the artificial joint. It appears as a subtle progression of bone tissue destruction (osteolysis, periprosthetic bone loss). It is a major challenge for orthopedic surgeons due to the fact that signs and symptoms may not be clinically apparent until the late stages of destruction and failure [1].

There are several theories related to the appearance of the biological phenomenon of aseptic loosening (wear particle disease, high fluid pressure, micromotion, stress shielding, endotoxin, genetic susceptibility). Particle disease (cement, polyethylene, metal, ceramic) is currently

the dominant theory. In order to understand osteolysis and aseptic loosening, we have first to consider that following the implantation of an either cemented or cementless prosthesis, the bone-implant interface passes from an initial face of trauma and inflammation to an early (3–4 months) static stage of healing and mechanical stability (early stability). The interface remains in a biological and mechanical steady state condition for a varying period of time. Later it becomes unstable due to inadequate initial fixation (rarely seen today because of improved surgical techniques and implants), mechanical loss of fixation over time, and biological loss of fixation due to particle-induced osteolysis. This phenomenon is really a complex network of mechanical, cellular, and inflammatory responses [1]. It first appeared in the literature as “the cement disease” (Fig. 11.1), and as a result a boost in the development of cementless implants took place. Later, it became obvious that osteolysis and aseptic loosening are also seen with the use of cementless implants (Fig. 11.2), and thus the multifactorial nature of this biological process was uncovered.

T. Karachalios, MD, DSc (✉)
Orthopaedic Department, Faculty of Medicine,
School of Health Sciences, University of Thessalia,
CERETETH, University General Hospital of Larissa,
Larissa, Mezourlo Region, 41110 Larissa,
Hellenic Republic, Greece
e-mail: kar@med.uth.gr

A. Koutalos, MD
Orthopaedic Department, University General
Hospital of Larissa, Larissa, Greece

Comments on Causative Theories

Micromotion

Micromotion, as measured by radiostereometric analysis (RSA) on the clinical setting, if it exceeds a certain threshold, does not lead to



Fig. 11.1 Radiographs of a failed cemented early THA design. This radiological appearance was initially named “cement disease”

osteointegration of the implant. Just like the stabilization of a fracture which is essential for porous formation, the lack of initial stabilization of the implant inhibits bone formation and osteointegration. The threshold of micromotion that enables the formation of bone and not of weak fibrous tissue is between 20 and 40 μ strains. The clinical relevance of abnormal micromotion is the existence of weak areas in the bone-implant interface where fiber develops instead of a closed apposition of bone from where joint fluid and wear particles can reach the interface, accumulate, and initiate the biological process of osteolysis. Even in mechanically and biologically stable interfaces, cycling dynamic loading and micromotion causes a time-dependent bone



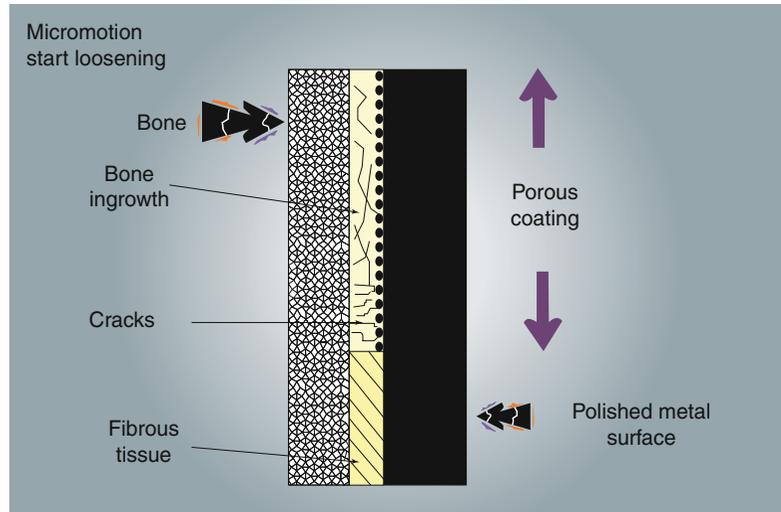
Fig. 11.2 Radiographs of a failed cementless early THA design. This kind of radiological appearance made orthopedic surgeons start thinking that osteolysis is not just a “cement disease”

structural adaptation and, eventually, fatigue bone tissue damage, microfractures, microcracks propagation, and interface separation. The latter creates weak areas through which wear particles can reach the interface (Fig. 11.3).

Stress Shielding

Stress shielding theory refers to bone loss around the implant due to bone adaptive mechanical remodeling and not due to osteolysis. The radiographic marks are quite different from osteolysis (normal architecture with trabecular bone but

Fig. 11.3 Line drawing showing the pathway with which wear particles can reach the interface



osteopenia). Stress shielding may contribute to wear debris osteolysis by opening of pathways to the bone-implant interface.

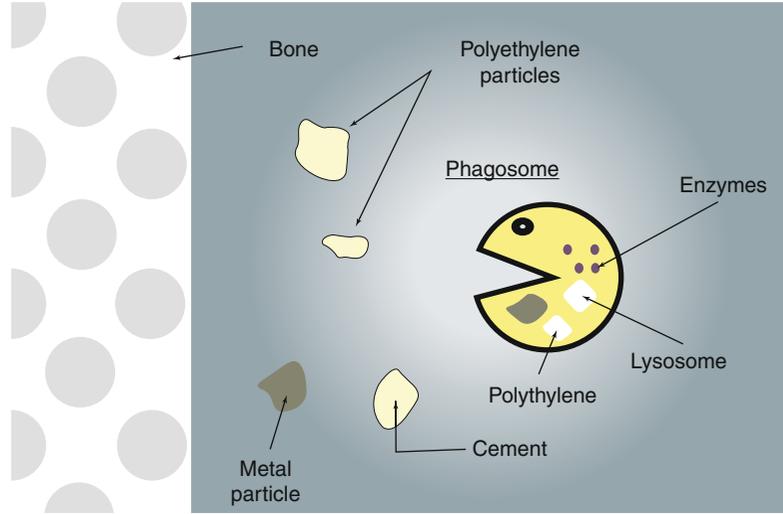
High Fluid Pressure

High fluid pressure is related to the effective joint space theory (a closed space around the artificial joint, which contains fluid loaded with wear particle debris) and to the dynamic loading of the artificial joint during walking, accelerating the transfer of wear particles through weak areas to the interface (pumping-hydraulic phenomena) [2, 3]. We now know that hydraulic phenomena facilitate and maintain the osteolytic process. This theory also highlights the fact that high pressure causes osteocyte and chondrocyte death [2], especially in the presence of a loose implant. The death of osteocytes eventually leads to osteolysis and loosening. Higher intracapsular pressure has been measured in loose implants compared with stable implants [3]. Fluid pressure can reach up to 198 mmHg and it has been shown that oscillating pressure between 70 and 150 mmHg induces osteocyte apoptosis and osteolysis [4, 5]. In addition, cyclic loading (in cases of impaired implant fixation) and polyethylene wear debris act synergistically to activate macrophages and induce osteolysis [6]. Another important issue related to aseptic loosening is the presence of endotoxins in a loose interface.

Endotoxins

Endotoxins are found in wear particles and it is assumed that they derive from the transient presence of bacteria in the joint [6, 7], from contaminated implants, or from systemic endotoxins derived from intestinal flora and dental procedures. Recent AAOS guidelines, however, point out that there is limited evidence for the utilization of antibiotics in preventing implant loosening [8]. It is accepted that even dead bacteria with parts of their cell membrane containing endotoxin (lipopolysaccharide, lipoteichoic acid) are capable of macrophage activation and osteolysis [9]. The formation of biofilms on the implants has been proposed as a source of LPS and the continuing activation of macrophages in “aseptic” loosening [10]. In the early period of osteointegration, transient bacteremia may activate macrophages to initiate bone resorption. Osteointegrated implants are more resistant to aseptic loosening [11]. It is thought that early research on wear debris was done with particles covered with endotoxin. Ti particles preparation to remove endotoxin resulted in a reduction of osteolysis by 50–70 % in experiments [12]. The addition of antibiotics to cement has been associated with 50 % reduction in revision arthroplasties [13]. However, the exact role of endotoxins in aseptic loosening has not been clarified yet. *The genetic predisposition* for aseptic loosening has also been investigated. It is believed that some patients are

Fig. 11.4 Line drawing showing phagocytosis of wear particles by macrophages



“implant looseners” [14, 15]. Variable activation of macrophages and cytokines production has been shown in different patients in the presence of the same amount of PE particles [13]. Wilkinson et al. found that the allele 238A in the promoter region of TNF is associated with increased incidence (odds ratio 1.7) of aseptic loosening [16]. Another study found an inverse relationship between single nucleotide polymorphism (SNP) rs419598 in IL-1Ra and osteolysis [17]. Conflicting evidence exists for polymorphisms in IL-6 gene and aseptic loosening [15]. Furthermore, the C allele in metalloproteinase MMP-1 is associated with aseptic failure [18]. Genetic variation of the FRZB gene (which encodes Frizzled-related protein 3, a molecule in the Wnt pathway) correlates with reduced osteolysis [17].

We now know that the biological process of osteolysis and aseptic loosening is complex, a mechanical and biological phenomenon (at least in the late stages) with particle disease being a key element. An in-depth understanding of this process is necessary in order to prevent it and to develop therapeutic strategies.

Particle Disease

The pathogenesis of implant-associated osteolysis includes wear particle generation, an inflammatory process, and an osteolytic process. Wear debris is produced mainly from the prosthetic

articulation, modular implant interfaces, nonarticulating interfaces, and impingement areas. It is estimated that during each gait cycle tens of thousands particles (<5 μm in size) are produced. Other sources of particle accumulation are implant surface wear, corrosion in response to micromotion, oxidative reactions, and pathogen contamination. The initial response is a nonspecific foreign body reaction with the characteristics of a localized pro-inflammatory reaction, increased circulation, elevated fluid levels, formation of fibrous tissue around the implant (poorly vascularized granulomatous tissue), and synovial lining membranes. Pro-inflammatory factors are secreted (gelatinases, proteases) which leads to the initiation of interface degradation. Particle phagocytosis is an important component of the local cellular response and depends mainly on the size of the particle (particles from 2 to 10 undergo phagocytosis by macrophages and removal from the interface area) (Fig. 11.4). It seems that there is a certain threshold after which an activation of a cellular and biochemical signaling mechanism starts (Fig. 11.5). A local chronic inflammatory response follows with the recruitment of a variety of cell populations which express osteoclastic and osteolytic activity (Fig. 11.6). Locally, a secretion of osteoclastogenic and inflammatory cytokines, an exacerbated osteoclastic activity and enhanced osteolysis and a vicious circle of tissue reaction leads to the formation of the aseptic loosening

Fig. 11.5 Line drawing showing that macrophages, within limits, have the ability to “digest” and remove particles

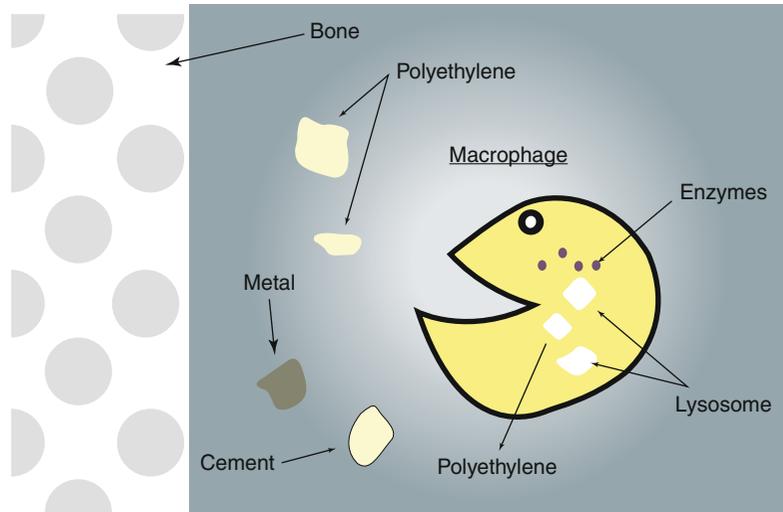
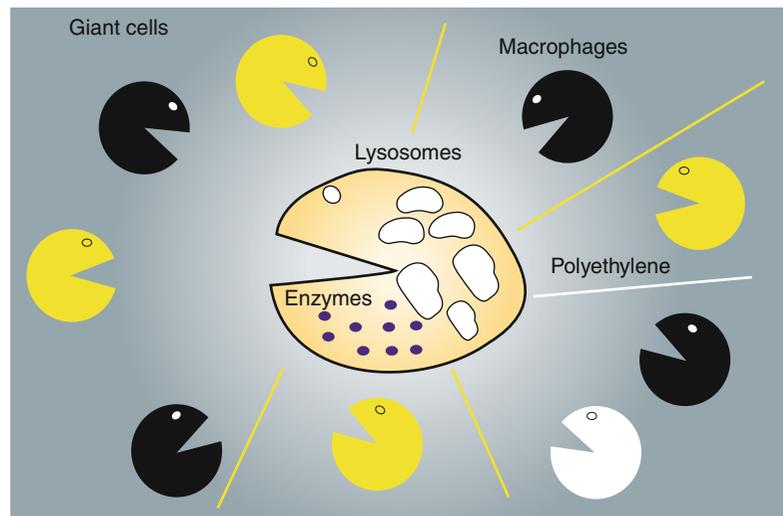


Fig. 11.6 Line drawing showing that above a threshold an activation of a cellular and biochemical signaling mechanism takes place



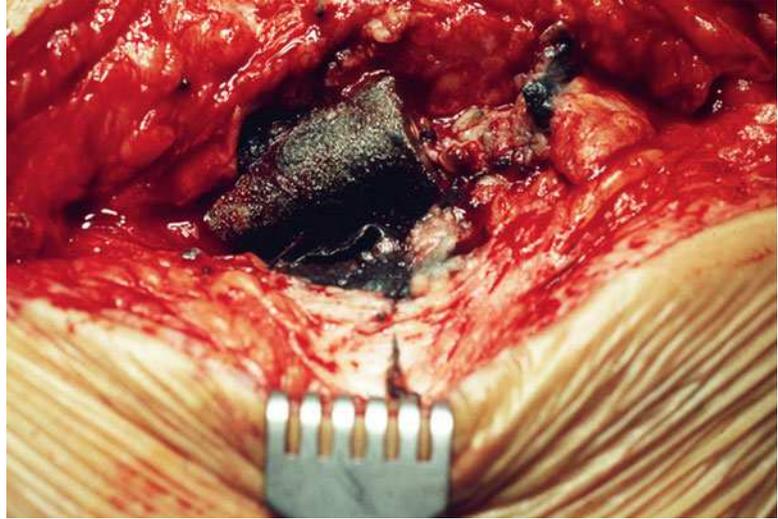
membrane. Particles which can be removed by macrophage undergo a lymphatic transport to local lymph nodes, to the spleen, to the liver, and possibly to other organs causing granulomatoid lesions. The biological response varies related to the number, charge, composition, surface, size, and surface of the particles.

Particle Production

Wear particle disease is the main biological phenomenon causing osteolysis and aseptic loosening. Bone cement (PMMA) has been initially

investigated as a source of wear particles [19]. Bone cement, which has been popularized by Charnley, is responsible for the production of particles that cause osteolysis. The rate of production is thought to be correlated to cement porosity, time (as bone cement ages, more microcracks are generated) [20, 21], the pattern of forces acting on cement (compressive forces on knees and acetabulum or shearing forces in femoral stem), and the debonding of the cement-implant interface (polished, pre-coated, or blasted) [22, 23]. Several implant modifications and techniques have been introduced in order to reduce the production of bone cement particles. Vacuum mixing of the

Fig. 11.7 “Black tissue staining” caused by metallic wear debris



cement and pressurization with a cement gun and distal plug reduce porosity, microfracture imitation, and wear production. Pre-coated or blasted stem implants were developed in order to increase the bond between cement and implant and to decrease the effective joint space where wear particles can accumulate. Investigating periprosthetic membranes from loose implants, Willert et al. found that cement particles are generated first and polyethylene particles follow as a result of third-body wear [18]. Both cement and polyethylene particles can cause osteolysis. Polyethylene particles (<5 μm average of random shape) are also capable of the activation of osteolysis. Factors affecting polyethylene wear and the production of particles are the type of resin, the manufacturing method (ram extrusion or compression molding), the sterilization method, the presence of cross-links which increase wear resistance, and the shelf life of the product (oxidative degradation occurs when storing the implants). Polyethylene wear and particles are produced mostly through abrasion in the hip joint and through abrasion and delamination in the knee joint. An important issue is the rate of wear. Studies have shown that the rate of 0.1 mm/year is not associated with aseptic loosening, while a rate 0.2 mm/year or more is [24]. Additionally, there are differences between the knee and hip artificial joints [25]. Particles from the hip joint are smaller in size. This means that high fluid pressures can be produced, and a smaller

amount of debris is required to start the phenomenon of aseptic loosening. As far as the knee is concerned, the introduction of modularity has had, as a result, the production of backside PE wear. The development of high cross-linked PE through radiation and melting or annealing increased wear resistance [26, 27]. The addition of Vit E and sequential annealing was introduced in an attempt to reduce the free radicals of radiation [28, 29]. Metal-on-metal bearing coupling is characterized by low wear particle production (2.5–5 $\mu\text{m}/\text{year}$) [30]. Biological reaction around metal particles depends on particle size (nanoparticles), corrosion products, and metal ions (Fig. 11.7). The size of the metal particles is small (average size 50 nm) [31], so they are easily phagocytosed and easily corroded and excreted from the kidneys. Round nanoparticles are more easily phagocytosed than rod-shaped ones. The mechanism of entrance into the cells includes diffusion, pinocytosis, or receptor-mediated endocytosis (clathrin). Cellular uptake is facilitated by positively charged metal nanoparticles [32]. Despite increased wear resistance, both cobalt chrome and titanium particles are capable of macrophage activation, osteolytic cytokine production, and aseptic loosening [33–35]. Concerns about metal-on-metal bearings include the possibility of renal impairment and carcinogenesis by metal ions released by bio-corrosion. Metal ions are released from the surface of the implant because of corrosion and failure of the

oxidized layer covering the implant. Metal ions (especially Co) are cytotoxic in a dose- and time-dependent manner. Ti ions, especially, bind to phosphorous-containing molecules in cells like euchromatin in the nucleus, ribosomes in the cytoplasm, and phospholipids in the membrane, interfering with cellular pathways and functions. Neither kidney failure nor carcinogenesis has been proved except for hematopoietic cancer [36, 37]. On the contrary, there is concern about the hypersensitivity reaction of type IV (ALVAL) and the creation of pseudotumors [38, 39]. These represent variations in the spectrum of metal sensitivity. Metal sensitivity is characterized by lymphocyte reaction and relative low wear, while reaction to PE particles or PMMA is characterized by high wear and predominantly macrophage activation. Metal ions (Ti) are nonantigenic but when bound with serum proteins like albumin can induce the formation of specific T lymphocytes [40]. These cells can induce hypersensitivity reactions [41]. So the type of immune reaction to metal particles is different from the immune reaction to PMMA. PMMA and metal particles induce different pro-inflammatory cytokines (TNF- α , IL-1, IL-6 for the former and IL-2, INF- γ , IL-22 for the latter) and different chemokines (increased production of IL-8 in Ti particles only), resulting in different tissue reactions independent of the number and quantity of produced wear debris [42]. Ceramic-on-ceramic prostheses have even more wear resistance (0.5–2.5 $\mu\text{m}/\text{year}$) [43]. With normal loading conditions the wear rate is 0.1 $\text{mm}^3/\text{one million cycles}$, but it can increase to 1.24–1.74 $\text{mm}^3/\text{one million cycles}$ when there is micro-separation of the prosthesis components [44]. Ceramics are also capable of activating macrophages and inducing osteolysis [45, 46]. Alumina wear debris has a bimodal distribution with larger particles (0.05–3.2 μm) coming from micro-separation and rim loading and acting like UHMWP particles. Smaller particles (5–90 nm) come from physiologic contact and act more like metal particles [45] but are less toxic than metal particles. Fewer macrophages and no giant cells have been observed around all ceramic arthroplasties [47]. This is due to the fact that all ceramic arthroplasties produce a lesser amount of particles to stimulate macrophages and

are not big enough to induce macrophage fusion as giant cells. However, the production of smaller particles when exceeding a certain threshold can be toxic to cells. Smaller ceramic particles have a reduced oxidation state and release more toxic ions. This is supported by the fact that more necrosis is identified around all ceramic arthroplasties compared with metal on PE arthroplasties. The size and the morphology of the particles have played a major role in inflammation, induced by wear debris. Most particles are smaller than 0.5 μm [48], and it has been shown that macrophage activation is greater with smaller (<20 μm) particles [49]. Polyethylene particles of 0.24 μm are most biologically reactive [49].

Aseptic Loosening Pathways

A large number of cells and molecules are implicated in the biological process of aseptic loosening. The precise mechanism is not fully understood and probably is complicated, but the initial cell that starts the reaction is the macrophage. The cell that is responsible afterwards for the osteolysis is the osteoclast through the RANKL-RANK-OPG-NF- κB axis. Other cells that contribute to loosening are the osteoblasts and the lymphocytes (Th1, Th2, Th17). The molecules that are critical in interactions between cells are the TNF- α , IL1, IL18, IL17, IL6, IL10, and INF- γ . The main cascade of reactions includes the PMMA, polyethylene, titanium, metallic, or ceramic particles being phagocytosed by macrophages. Macrophages produce TNF- α , IL1, and metalloproteinases which activate the bone-resorbing osteoclasts through the RANKL-RANK axis. Metalloproteinases, on the other hand, cause destruction of the extracellular matrix. This main interaction is enhanced by other cells (osteoblasts, lymphocytes), cytokines (IL6, IL10, IL17, IL18), and pathways (Wnt, ADP/ATP pathways, complement).

The first evidence that wear debris causes osteolysis was the correlation between the production of wear debris and the rate of aseptic loosening [50–53].

Macrophages have been shown to be activated by wear debris. The activation includes

either phagocytosis [54] of particle debris or direct interaction with the particles of critical size [55, 56] and shape [57]. Direct interaction involves the complement receptor CR3 (in case of PMMA, PE, titanium particle) [58, 59] and the scavenger receptor MARCO (in case of titanium particles) [60]. Metal particles/ions are capable of activating the inflammasome pathway in which metal ions induce inflammasome proteins activation (NADPH/ROS, nalp3) and activate caspase to produce IL-1 from inactive form [61]. In turn, IL-1 feeds back in a paracrine manner to produce TNF- α through the NF κ B pathway in macrophages. Another possible mechanism of activation and production of pro-inflammatory cytokines is through activation of protein tyrosine kinases (PTKs). Macrophage PTKs are activated by titanium particle wear and are necessary for phagocytosis and mediator release [62]. Activation of macrophages results in the production of inflammatory mediators like TNF- α , IL-1 β , IL-6, and PGE2. This activation has been shown experimentally *in vitro*, in the calvarium model and in mice [63]. Specifically, PE wear or titanium and ceramic particles are capable of inflammation induction in rat models [64]. Studies in humans are less clear [65–67] but also show the macrophage activation in the periprosthetic membrane. Joint fluid and periprosthetic membrane analyses in conjunction with *in situ* hybridization reveal increased TNF- α in patients with osteolysis [67]. Lastly, macrophages are capable of RANKL production which promotes osteoclastogenesis. The activation of macrophages to pro-inflammatory subtype requires two signal steps. Apart from phagocytosis, a second danger signal is essential for activation (either pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide or endogenous danger molecules (DAMPs)). In the case of metal particles, it was thought that endotoxin (LPS) is the second signal, but recently, it has been shown that metal ions can stimulate toll-like receptor 4 (TLR4), a receptor of PAMPs [68]. The next main step in the cascade of osteolysis is the production of pro-inflammatory cytokines (TNF- α , IL-1, IL-6). As mentioned above TNF is an osteoclastogenic cytokine found in periprosthetic membranes and

increases with the presence of particle wear. It facilitates the production of other cytokines like IL-1, IL-6, IL-8, and GM-CSF (the latter is necessary for the maturation of progenitor cells to osteoclasts) [66, 68]. It acts on stromal cells and osteoblasts to produce RANKL. Subsequently, it acts synergistically with RANKL on osteoclasts to promote maturation. The activation of the TNF receptor results in NK- κ B pathway activation [63]. TNF- α acts directly on osteoclast precursors, while IL-1 acts indirectly by increasing the production of RANKL and M-CSF from osteoblasts and stromal cells. IL-1 is a cytokine with osteoclastogenic actions. First of all it acts on stromal cells and osteoblasts to produce RANKL, induces the production of TNF- α [69], helps TNF- α -dependent RANKL production in stromal cells (through expression of IL-1RI), and finally acts as a costimulatory in osteoclast formation. Again, the activation of IL-1 results in NK- κ B pathway activation [70]. The transfer of interleukin-1 receptor antagonist (IL-1Ra) gene in a model of UHMWPE osteolysis resulted in reduction of IL-1 and TNF- α [71]. It is important to mention that different metals produce different kind of cytokines. Cobalt-chromium particles produce predominantly TNF- α , while Ti particles mediate an IL-6 response [72, 73]. This may have implications in therapy. IL-6 (as well as IL-11) has the additional property of activating osteoclasts in a RANKL-independent way which under physiologic conditions is not apparent but, in case of inflammatory conditions with cytokine production, like aseptic loosening, may play a vital role. IL-6 in the presence of M-CSF, acts through IL-6R in macrophages activating the gp130 pathway and inducing osteoclastogenesis. This is not inhibited by OPG or RANK antibodies [74]. The exact role of IL-6 is not yet clear as it has been shown that it has an anti-osteoclastogenic effect on precursor cells in a metal wear particle model through a negative feedback loop of TNF- α production [75]. Probably the indirect (through osteoblasts) pro-osteoclastogenic effect of IL-6 is more robust than the direct anti-osteoclastogenic effect on osteoclasts. TNF- α and IL-1 polymorphisms have an impact on the risk of aseptic loosening [16, 76]. PGE2, an inflammation

mediator, is produced by macrophages activated by wear particles. Cox-2, which produces PGE₂, is essential for osteoclastogenesis and the production of prostaglandins [76, 77].

Osteoblasts and stromal cells are linked with the formation of osteoclast through the RANKL axis. Activated osteoblasts produce RANKL that promotes the osteoclast formation. In addition, the wear particles have a direct influence on osteoblasts. Firstly, particle wear induces mesenchymal stem cell apoptosis [78], osteoblast apoptosis [79], and reduced differentiation of MSC to osteoblasts [80]. As a result, bone formation is impaired. On the other hand, wear debris (metal or polyethylene) halts the formation of collagen type I [81, 82] and the production of the matrix by osteoblasts [83]. Osteoblasts enter in a catabolic state. In addition, decreased IGF-I was found in periprosthetic interface tissue of loose implants. IGF-I is a growth factor acting on osteoblasts, so the reduction of this growth factor is associated with bone loss [84]. The activated cells (macrophages, lymphocytes, osteoblasts) produce RANKL as an end result. The RANKL-RANK-OPG-NK- κ B axis is the main pathway that drives the osteolysis around the implants. RANKL, a member of TNF superfamily, is produced by mature osteoblasts, stromal cells, macrophages, and lymphocytes. It can be found as membrane-anchored protein and less often as a free molecule after cleavage [85]. It acts on RANK in osteoclasts precursors and stimulates the differentiation to mature osteoclasts mediating wear debris osteolysis. Other conditions where T lymphocyte-produced RANKL causes osteolysis are asthma, autoimmune diseases, chronic viral infections, cancers, and periodontal disease [86]. RANK (receptor activator of NK- κ B) is also a member of the TNF superfamily and is found on the surface of precursors of osteoclasts, mature osteoclasts, chondrocytes, and mammary epithelial cells [87]. The absence of RANK in genetic modified mice results in the inhibition of osteoclast formation [88]. The downstream pathway includes activation of NK- κ B primarily and recruitment of protein kinase A and protein kinase C. NK- κ B exists as dimers in cytoplasm, and when the RANK

is activated NK- κ B disengages from inhibitory proteins (I κ B) and travels to the nucleus where it acts as a transcription factor, mediating the expression of genes implicated in osteoclastogenesis (rcas). PMMA wear particles induce activation of precursor osteoclasts cells through NK- κ B translocation in the nucleus and DNA binding. Inhibition of NK- κ B halts this DNA binding and osteoclastogenesis [89]. In addition NK- κ B is involved in the stress response cataract of the cell and regulates apoptosis and inflammation [90]. The other molecule that orchestrates the osteoclastogenesis together with the RANKL is osteoprotegerin (OPG). OPG is a competitive inhibitor of the RANKL, causing inhibition of the RANKL-RANK therefore inhibiting osteoclastogenesis [91]. Mice deficient of OPG are osteoporotic while transgenic mice with increased OPG have osteopetrosis [92, 93]. OPG is also increased by estrogens, explaining menopausal osteoporosis [94]. OPG blocks osteoclastogenesis of precursor cells by fluid of aseptic loosened arthroplasties and inhibits wear debris osteolysis [89, 95]. Gene transfer of the OPG gene in an osteolysis animal model caused reduction in calcium production and a decrease in RANK [96]. In general, all factors that affect osteoclastogenesis and osteolysis bottom down to the influence they have in the RANKL/OPG ratio. The osteoclast, the only bone-resorbing cell, mitigates the phenomenon of osteolysis. Osteoclast is a multinucleated cell that comes from the differentiation of precursor cells of monocyte/macrophage lineage [97]. Osteoclasts are found in abundance in the periprosthetic tissues of loose implants [98]. In addition, in these tissues there is an increased expression of chemokines like MCP-1, MIP-1-a, and IL-8. Thus, there is recruitment of precursor cells through the CCR1 receptor in the areas of osteolysis [99–101]. Differentiation of precursor cells by wear debris is done in two ways. Firstly, as described previously, through the production of RANKL by activated stromal cells by phagocytosed wear particles. Secondly by inhibition of interferon gamma and IL-6 signaling in precursor cells by wear debris. Both these molecules suppress preosteoclast differentiation [102]. Osteoclasts have also the ability to directly cor-

rode metal and release metal ions, increasing inflammation. It has been shown that osteoclasts can grow on stainless steel and produce osteolytic pits. The release of the metal ions increased the production of pro-inflammatory cytokines, which further activates osteoclasts and thus enhancing the vicious cycle [103]. Lastly metal ions (Co) have a direct influence in osteoclasts, activating them through chemical hypoxia. Co inhibits HIF prolyl hydroxylases (PHDs), activating hypoxia-inducible factor- α (HIF- α), and stimulates osteoclast formation [104]. The bone resorption by osteoclasts is mediated by the ruffled border of the osteoclast which contains H-ATPase and lowers the pH. Low pH enhances dissolution of hydroxyapatite. After demineralization, collagen is degraded by cathepsin K. Cathepsin is found in macrophages after activation with particle wear and more interestingly in periprosthetic membranes of loose implants with low pH. Maybe the low pH near loose implants together with the cathepsin which is activated by low pH may contribute to bone loss [105].

Other Cells, Molecules, and Pathways

Besides the main cataract of osteolysis, there are other cells contributing to osteolysis, molecules interacting with osteoclasts, and alternative pathways in osteolysis. Osteocytes, the end result of osteoblast differentiation, which consist up to 90 % of the cells of the bone may be involved in the initiation of osteolysis. Osteocytes are known to sense microfracture, which results in apoptosis through TNF- α , and recruit osteoclasts. This apoptotic phenomenon can also begin with metal implant debris acting on osteocytes [106]. In particular metal particles can activate calcineurin, leading to the dephosphorylation and nuclear translocation of nuclear factor of activated T-cell (NFAT) proteins in the nucleus. Subsequently NFAT activates the expression of TNF- α [107]. In addition SOST/sclerostin production of osteocytes (which reduces bone formation) has been shown to increase when osteocytes are challenged by particle wear [108]. Mesenchymal stem cells (MSC) are also affected by particle wear. Stem

cells endocytose titanium particles resulting in suppression of osteogenic differentiation and apoptosis. So there is an imbalance between osteoblasts formation from stem cells which decreases and osteoclast formation from inflammation which increases. Production of osteogenic molecules like BMP-6, IGF-1, and FGF-2 by MSC is decreased when exposed to Ti debris [109]. Mesenchymal stem cells treated with titanium particles produce IL-8, a potent chemokine, which is associated with implant loosening [110]. Fibroblasts are abundant in tissues retrieved from loose implants. Challenged with particle wear, fibroblasts increase the production of metalloproteinases like gelatinase A, collagenase, stromelysin, and tissue inhibitor of metalloproteinases [111]. All these promote the degradation of extracellular bone matrix contributing to the osteolysis phenomenon [112]. In addition synovial fibroblasts have been shown to produce RANKL in a COX-2-dependent manner when stimulated with titanium particles. PGE2 acts on EP4 receptor of fibroblasts which is coupled with G α s proteins and activates protein kinase C (PKC). This pathway leads to the production of RANKL. All these suggest the contribution of fibroblasts in aseptic loosening [113]. Lymphocytes are implicated in osteolysis caused by particle debris. They play major role in metal sensitivity. They are found in periprosthetic tissue, are capable of producing anti-osteoclastogenic (INF- γ , IL-4, IL-10), or osteoclastogenic (RANKL) cytokines [114–116]. In particular Th2 lymphocytes produce IL-4, and it has been shown that patients with erosive disease have decreased IL-4 mRNA [117]. In addition lymphocytes are involved with late-onset hypersensitivity reactions in metal-on-metal arthroplasties. The formation of pseudotumors (painful effusion or solid or cystic mass) around total hip arthroplasties is characterized histologically by diffuse and perivascular infiltration of B and T lymphocytes. The immunoreaction of lymphocytes in Ti particles can be either positive (activating the lymphocytes) or of no effect, probably, reflecting the individual predisposition for metal sensitivity. Metal ions (nickel, cobalt) linked with proteins are immunogenic and produce T lymphocytes specific for metals. Even if

failed hip arthroplasties have been reported in conjunction with hypersensitivity reactions and there is increased incident of hypersensitivity in failed implants, the causative role of hypersensitivity and osteolysis has not been robustly established [118]. In the case of metal-on-metal arthroplasties, however, excessive osteolysis has raised the possibility of metal ion-induced T-cell-mediated delayed hypersensitivity reaction. Metal ions when bound to self proteins change their structure and are presented by MHC class II on the surface. Therefore, they are recognized as non-self peptides by T-cell receptors (TCR) initiating the hypersensitivity reaction. Moreover, metal ions bound with proteins can reveal immunogenic epitopes of these proteins, can alter MHC molecules so TCRs recognize them as presented by foreign tissue, and can act as superantigens promoting polyclonal T-cell activation [119]. Activation of T-cells needs a second signal, and this comes from metal ion binding in TLR4. Another type of T lymphocyte (Th17) involved in inflammation and autoimmunity may play a role in osteolysis. The production of IL-17 by these cells can stimulate the production of RANKL by osteoblasts or directly produce RANKL [120]. Th17 cells are produced by naive T lymphocytes in the presence of TGF- β and IL-6 [121] and need IL-23 for Th17 stabilization. The source of IL-23 is the macrophage. Neurogenic inflammation also contributes to osteolysis and aseptic loosening. Substance P (SP) axons have been identified in periprosthetic membranes of loose implants. In a mouse model SP-deficient animals treated with UHMWPE particles had reduced osteolysis, smaller numbers of osteoclasts, and increased bone mass. This type of inflammation mediated by the nervous system has a role in aseptic loosening [122]. Besides, IL-18, which is a member of the IL-1 family, blocks particle-induced osteoclastogenesis. IL-18 is committed to the Th1 cells and acts synergistically with IL-12 to expand Th1 cells. Holt et al. have shown that IL-18 can inhibit wear debris-induced osteolysis in vitro [123]. IL-10, an anti-inflammatory cytokine, may also play a role in downregulation of inflammation in aseptic loosening. IL-10 is a cytokine produced by T regulatory lymphocytes. Gene transfer of

IL-10 in an animal model of wear debris osteolysis resulted in decreased production of IL-1 β and TNF- α [71]. The role of chemokines is also important to osteolysis. As previously mentioned, the CCR1 receptor in precursor osteoclast cells is important in recruitment in areas of osteolysis. Other chemokines like CCL17 and CCL22 have been found to be upregulated in osteoclast and osteoblasts by titanium particles. In addition, metal particles upregulate the CCR4 (whose ligand is CCL17 and CCL22) in precursor cells and Th17 cells, thereby enhancing their recruitment in the implant interface. The end result is the activation of precursor osteoclasts and the increased production of RANKL by Th17 cells [124]. The complement system has been also implicated in osteolysis. CR3 receptors are involved in phagocytosis of wear debris [59]. VEGF is a growth factor essential for angiogenesis. It is implicated in osteolysis in many ways and is found in tissues from failed hip arthroplasties [125]. It is produced by wear debris-activated macrophages. Increased osteoclastogenesis, acts as a chemokine for the recruitment of macrophages, increases vascular permeability in periprosthetic tissue so there is increased pressure in joints which enhance osteolysis [126, 127]. Obesity has been investigated as a factor of osteolysis. In mouse models, obese animals with implanted PE particles have lower numbers of osteoclasts and fewer osteolysis. Obesity may be protective for implant loosening as it is for osteoporosis [128].

Treatment Options

The potential therapeutic intervention relies on a combination of improvements such as improved implant integration to host bone, improved bearing surfaces, and strategies to target the cellular components [1]. The latter includes strategies to target osteoclast precursor cells which are recruited to inflammatory sites by circulating cytokines to target precursors that are stimulated by the particle-mediated cellular response to differentiate and form bone-resorbing osteoclasts and to target activation mechanisms of mature osteoclasts.

Management of osteolysis and loosening starts with prevention. Prevention has to do firstly with successful osteointegration. Modifications of implants have been introduced to increase osteointegration. These modifications include newer biomaterials with osteoinductive properties, like tantalum, plasma spraying, or grit blasting of implants (to increase the surface and become more osteoinductive), and covering with hydroxyapatite (to facilitate osteointegration). Successful osteointegration reduces the effective joint space. Newer improvements include the incorporation of growth factors like BMPs or peptides of growth factors to stimulate osteoblasts and enhance osteointegration. Lastly there is the incorporation of antibiotics in implants. Besides infections, it may reduce endotoxin osteolysis and low-grade infection which has been implicated in aseptic loosening [129]. Gene therapy has been tried to reverse the osteolysis. Therapy with anti-inflammatory genes (IL-1R and IL-10) in animal models was found to be protective of UHMWPE particle-induced bone resorption [71]. Gene transfer of TNFR (TNF receptor) had anti-resorptive results. Gene transfer of OPG had the same results [130]. Erythromycin is an antibiotic with anti-inflammatory properties. It has a tropism for macrophages/monocytes in bone marrow and inflammatory tissues. Oral erythromycin therapy has been shown to reduce osteoclasts and inflammation in tissues from revision arthroplasties when delivered preoperatively [131]. Another antibiotic with anti-resorbing capacities is doxycycline. Doxycycline inhibits metalloproteinases, inhibits osteoclastogenesis, induces apoptosis of osteoclasts, and ameliorates their bone-resorbing actions [132, 133]. In vivo and in vitro, doxycycline has shown that it halts particle-induced osteolysis [134]. Bisphosphonates have been shown to reduce particle wear-induced osteolysis [135, 136]. They induce osteoclast apoptosis. In addition they can halt the migration of the implant postoperatively [138], which has been shown to decrease the risk of osteolysis and revision rates [138]. In the Danish registry it was found that long-term use of the bisphosphonates decreases the risk of revision, but the perioperative use may increase the risk of deep infection.

Probably the osteolysis occurring in infections is essential in clearing microbes from the bone, and bisphosphonates counteract this mechanism [139]. Unfortunately, the use of bisphosphonates in loosening implants did not have the desired outcomes [140]. This may be due to the fact that bisphosphonates have to be ingested before acting and the “test bite” of continuously recruited osteoclasts results in bone loss despite treatment with bisphosphonates. Bisphosphonates may have a role in prophylaxis [141]. Indeed treatment with one dose of pamidronate postoperatively in a randomized controlled trial resulted in a reduction of bone loss around the implants as measured with bone mineral density (BMD). Again this positive result was not associated with better clinical outcomes [142]. Anti TNF- α therapy is a valuable option for treatment of implants with aseptic loosening. Because of the similarities between inflamed synovium in rheumatoid arthritis and periprosthetic pseudomembranes in aseptic loosening, etanercept was used as therapy for aseptic loosening. Etanercept is a soluble extracellular TNF- α receptor (p75 hTNF- α) fused with Fc region of immunoglobulin (IgG1) with impressive results in rheumatoid arthritis. Even if in animal models etanercept did show positive results, a randomized trial failed to show a reduction in revision arthroplasties [143]. This study, however, is criticized because it was underpowered. Targeting the RANKL-RANK-OPG axis has been associated with better results in animal models. Blocking RANKL with OPG-Fc tag, which increases the bioavailability of OPG, inhibited the osteolysis around loose implants [141]. RANK blockade with fusion protein (RANK-Fc) in a mouse model of titanium osteolysis resulted in a reduction of osteoclastogenesis and osteolysis without affecting new bone formation [144]. Treatment with COX-2 inhibitors like celecoxib may be useful in the treatment of aseptic loosening. Studies in animals demonstrated positive results (reduction in PGE2 and osteolysis). Other possible therapies regarding osteolysis include the blocking of V-ATPase in osteoclasts. Bafilomycin A₁ (a macrolide antibiotic) has the ability to block V-ATPase in osteoclasts which is located in the ruffled border and is involved in acidification of the

microenvironment and degradation of bone [145]. Purinergic signaling has been described recently in osteoclasts and can be manipulated to decrease osteolysis. The ADP receptor P2RY12 blocking by results in decreased activation of GTPase Ras-related protein (RAP1) and $\alpha 2\beta 3$ integrin. $\alpha 2\beta 3$ is essential for osteoclast formation, adhesion, and bone resorption so clopidogrel therapy can protect from pathologic osteolysis as in aseptic loosening [146]. Statins due to anabolic and anti-catabolic on bone have been shown to protect from particle-induced osteolysis in murine calvaria models [147]. Statins are HMGCoA reductase inhibitors and target the mevalonate pathway like bisphosphonates. In a population study statin users had decreased risk for revision due to aseptic loosening [148]. Lastly, the Wnt signaling on bone cells (osteoblasts) has received attention. Wnt binds to LPR5/6-stabilizing β -catenin and enables its translocation to nucleus to activate gene expression. β -catenin has a critical role in the proliferation and survival of osteoblasts. In addition it acts indirectly on osteoclasts by increasing the production of OPG. Sclerostin is an inhibitor of wints; it is produced by bone cells (especially osteocytes), and inhibition of sclerostin by antibodies results in enhanced bone formation. These pathways may have a role in osteolysis [149, 150].

References

1. Abu-Amer Y, Darwech I, Clohishy JC. Aseptic loosening of total joint replacements: mechanisms underlying osteolysis and potential therapies. *Arthritis Res Ther.* 2007;9(S1):S6.
2. Schmalzried TP, Akizuki KH, Fedenko AN, Mirra J. The role of access of joint fluid to bone in periarticular osteolysis. A report of four cases. *J Bone Joint Surg Am.* 1997;79A:447–52.
3. Robertsson O, Wingstrand H, Kesteris U, Jonsson K, Önerfält R. Intracapsular pressure and loosening of hip prostheses. Preoperative measurements in 18 hips. *Acta Orthop Scand.* 1997;68:231–4.
4. Van der Vis H, Aspenberg P, De Kleine R, Tigchelaar W, Van Noorden CJ. Short periods of oscillating fluid pressure directed at a titanium-bone interface in rabbits lead to bone lysis. *Acta Orthop Scand.* 1998;69:5–10.
5. Van der Vis HM, Aspenberg P, Marti RK, Tigchelaar W, Van Noorden CJ. Fluid pressure causes bone resorption in a rabbit model of prosthetic loosening. *Clin Orthop.* 1998;350:201–8.
6. McEvoy A, Jeyam M, Ferrier G, Evans CE, Andrew JG. Synergistic effect of particles and cyclic pressure on cytokine production in human monocyte/macrophages: proposed role in periprosthetic osteolysis. *Bone.* 2002;30:171–7.
7. Skoglund B, Larsson L, Aspenberg PA. Bone-resorptive effects of endotoxin-contaminated high-density polyethylene particles spontaneously eliminated in vivo. *J Bone Joint Surg Br.* 2002;84B:767–73.
8. Jevsevar DS, Abt E. The New AAOS-ADA clinical practice guideline on prevention of orthopaedic implant infection in patients undergoing dental procedures. *J Am Acad Orthop Surg.* 2013;21(3):195–7.
9. Akisue T, Bauer TW, Farver CF, Mochida Y. The effect of particle wear debris on NF κ B activation and pro-inflammatory cytokine release in differentiated THP-1 cells. *J Biomed Mater Res.* 2002;59(3):507–15.
10. Hoenders CS, Harmsen MC, van Luyn MJ. The local inflammatory environment and microorganisms in “aseptic” loosening of hip prostheses. *J Biomed Mater Res B.* 2008;86(1):291–301.
11. Sundfeldt M, Widmark M, Johansson CB, Campbell P, Carlsson LV. Effect of submicron polyethylene particles on an osseointegrated implant: an experimental study with a rabbit patello-femoral prosthesis. *Acta Orthop Scand.* 2002;73(4):416–24.
12. Bi Y, Seabold JM, Kaar SG, Ragab AA, Goldberg VM, Anderson JM, Greenfield EM. Adherent endotoxin on orthopedic wear particles stimulates cytokine production and osteoclast differentiation. *J Bone Miner Res.* 2001;16(11):2082–9.
13. Espehaug B, Engesaeter LB, Vollset SE, Havelin LI, Langeland N. Antibiotic prophylaxis in total hip arthroplasty. *J Bone Joint Surg Br.* 1997;79B:590–5.
14. Matthews JB, Green TR, Stone MH, Wroblewski BM, Fisher J, Ingham E. Comparison of the response of primary human peripheral blood mononuclear phagocytes from different donors to challenge with model polyethylene particles of known size and dose. *Biomaterials.* 2000;21(20):2033–44.
15. Sundfeldt M, Carlsson LV, Johansson CB, Thomsen P, Gretzer C. Aseptic loosening, not only a question of wear A review of different theories. *Acta Orthop Scand.* 2006;77(2):177–97.
16. Wilkinson JM, Wilson AG, Stockley I, Scott IR, Macdonald DA, Hamer AJ, Duff GW, Eastell R. Variation in the TNF gene promoter and risk of osteolysis after total hip arthroplasty. *J Bone Miner Res.* 2003;18(11):1995–2001.
17. Gordon A, Kiss-Toth E, Stockley I, Eastell R, Wilkinson JM. Polymorphisms in the interleukin-1 receptor antagonist and interleukin-6 genes affect risk of osteolysis in patients with total hip arthroplasty. *Arthritis Rheum.* 2008;58(10):3157–65.
18. Malik MH, Jury F, Bayat A, Ollier WE, Kay PR. Genetic susceptibility to total hip arthroplasty failure: a preliminary study on the influence of matrix metalloproteinase 1, interleukin 6 polymorphisms and vitamin D receptor. *Ann Rheum Dis.* 2007;66(8):1116–20.

19. Harris WH, Schiller AL, Scholler JM, Freiberg RA, Scott R. Extensive localized bone resorption in the femur following total hip replacement. *J Bone Joint Surg Am.* 1976;58A(5):612–8.
20. Jasty M, Maloney WJ, Bragdon CR, O'Connor DO, Haire T, Harris WH. The initiation of failure in cemented femoral components of hip arthroplasties. *J Bone Joint Surg Br.* 1991;73B(4):551–8.
21. Willert HG, Bertram H, Buchhorn GH. Osteolysis in allo arthroplasty of the hip. The role of bone cement fragmentation. *Clin Orthop.* 1990;258:108–21.
22. Lennon AB, Prendergast PJ. Evaluation of cement stresses in finite element analyses of cemented orthopaedic implants. *J Biomech Eng.* 2001;123(6):623–8.
23. Nuno N, Amabili M. Modelling debonded stem-cement interface for hip implants: effect of residual stresses. *Clin Biomech.* 2002;17(1):41–8.
24. Dumbleton JH, Manley MT, Edidin AA. A literature review of the association between wear rate and osteolysis in total hip arthroplasty. *J Arthroplasty.* 2002;17(5):649–61.
25. Landy MM, Walker PS. Wear of ultra-high-molecular-weight polyethylene components of 90 retrieved knee prostheses. *J Arthroplasty.* 1988;3:S73–85.
26. Lachiewicz PF, Geyer MR. The use of highly cross-linked polyethylene in total knee arthroplasty. *JAAOS.* 2011;19(3):143–51.
27. Kuzyk PR, Saccone M, Sprague S, Simunovic N, Bhandari M, Schemitsch EH. Cross-linked versus conventional polyethylene for total hip replacement: a meta-analysis of randomised controlled trials. *J Bone Joint Surg Br.* 2011;93B(5):593–600.
28. Bracco P, Oral E. Vitamin E-stabilized UHMWPE for total joint implants: a review. *Clin Orthop.* 2011;469(8):2286–93.
29. Sobieraj MC, Rinnac CM. Ultra high molecular weight polyethylene: mechanics, morphology, and clinical behavior. *J Mech Behav Biomed Mater.* 2009;2(5):433–43.
30. Amstutz HC, Campbell P, McKellop H, Schmalzreid TP, Gillespie WJ, Howie D, Jacobs J, Medley J, Merritt K. Metal on metal total hip replacement workshop consensus document. *Clin Orthop.* 1996;329:S297–303.
31. Doorn PF, Campbell PA, Worrall J, Benya PD, McKellop HA, Amstutz HC. Metal wear particle characterization from metal on metal total hip replacements: transmission electron microscopy study of periprosthetic tissues and isolated particles. *J Biomed Mater Res.* 1998;42(1):103–11.
32. Billi F, Campbell P. Nanotoxicology of metal wear particles in total joint arthroplasty: a review of current concepts. *J Appl Biomater Biomech.* 2010;8(1):1–6.
33. Dorr LD, Wan Z, Longjohn DB, Dubois B, Murken R. Total hip arthroplasty with use of the Metasul metal-on-metal articulation. Four to seven-year results. *J Bone Joint Surg Am.* 2000;82A(6):789–98.
34. Huo MH, Salvati EA, Lieberman JR, Betts F, Bansal M. Metallic debris in femoral endosteolysis in failed cemented total hip arthroplasties. *Clin Orthop.* 1992;276:157–68.
35. Blaine TA, Rosier RN, Puzas JE, Looney RJ, Reynolds PR, Reynolds SD, O'Keefe RJ. Increased levels of tumor necrosis factor-alpha and interleukin-6 protein and mes- senger RNA in human peripheral blood monocytes due to titanium particles. *J Bone Joint Surg Am.* 1996;78A(8):1181–92.
36. Wagner P, Olsson H, Lidgren L, Robertsson O, Ranstam J. Increased cancer risks among arthroplasty patients: 30 year follow-up of the Swedish Knee Arthroplasty Register. *Eur J Cancer.* 2011;47(7):1061–71.
37. Visuri T, Pukkala E, Pulkkinen P, Paavolainen P. Decreased cancer risk in patients who have been operated on with total hip and knee arthroplasty for primary osteoarthritis: a meta-analysis of 6 Nordic cohorts with 73,000 patients. *Acta Orthop Scand.* 2003;74(3):351–60.
38. Hart AJ, Satchithananda K, Liddle AD, Sabah SA, McRobbie D, Henckel J, Cobb JP, Skinner JA, Mitchell AW. Pseudotumors in association with well-functioning metal-on-metal hip prostheses: a case-control study using three-dimensional computed tomography and magnetic resonance imaging. *J Bone Joint Surg Am.* 2012;94(4):317–25.
39. Gonzalez MH, Carr R, Walton S, Mihalko WM. The evolution and modern use of metal-on-metal bearings in total hip arthroplasty. *Instr Course Lect.* 2011;60:247–55.
40. Chan E, Cadosch D, Gautschi OP, Sprengel K, Filgueira L. Influence of metal ions on human lymphocytes and the generation of titanium-specific T-lymphocytes. *J Appl Biomater Biomech.* 2011;9(2):37–43.
41. Martin SF. T lymphocyte-mediated immune responses to chemical haptens and metal ions: Implications for allergic and autoimmune disease. *Int Arch Allergy Immunol.* 2004;134:186–98.
42. Noordin S, Masri B. Periprosthetic osteolysis: genetics, mechanisms and potential therapeutic interventions. *Can J Surg.* 2012;55(6):408–17.
43. Yamamoto T, Saito M, Ueno M, Hananouchi T, Tokugawa Y, Yonenobu K. Wear analysis of retrieved ceramic-on-ceramic articulations in total hip arthroplasty: femoral head makes contact with the rim of the socket outside of the bearing surface. *J Biomed Mater Res B.* 2005;73(2):301–7.
44. Tipper JL, Hatton A, Nevelos JE, Ingham E, Doyle C, Streicher R, Nevelos AB, Fisher J. Alumina-alumina artificial hip joints. Part II: characterisation of the wear debris from in vitro hip joint simulations. *Biomaterials.* 2002;23(16):3441–8.
45. Hatton A, Nevelos JE, Nevelos AA, Banks RE, Fisher J, Ingham E. Alumina-alumina artificial hip joints. Part I: a histological analysis and characterisation of wear debris by laser capture microdissection of tissues retrieved at revision. *Biomaterials.* 2002;23(16):3429–40.
46. Hatton A, Nevelos JE, Matthews JB, Fisher J, Ingham E. Effects of clinically relevant alumina ceramic wear particles on TNF-alpha production by human peripheral blood mononuclear phagocytes. *Biomaterials.* 2003;24(7):1193–204.

47. Germain MA, Hatton A, Williams S, Matthews JB, Stone MH, Fisher J, Ingham E. Comparison of the cytotoxicity of clinically relevant cobalt-chromium and alumina ceramic wear particles in vitro. *Biomaterials*. 2003;24(3):469–79.
48. Gonzalez O, Smith RL, Goodman SB. Effect of size, concentration, surface area, and volume of polymethylmethacrylate particles on human macrophages in vitro. *J Biomed Mater Res*. 1996;30:463–73.
49. Sabokbar A, Pandey R, Athanasou NA. The effect of particle size and electrical charge on macrophage-osteoclast differentiation and bone resorption. *J Mater Sci Mater Med*. 2003;14:731–8.
50. Green TR, Fisher J, Matthews JB, Stone MH, Ingham E. Effect of size and dose on bone resorption activity of macrophages by in vitro clinically relevant ultra high molecular weight polyethylene particles. *J Biomed Mater Res*. 2000;53(5):490–7.
51. Maloney W, Smith R. Periprosthetic osteolysis in total hip arthroplasty: the role of particulate wear debris. *J Bone Joint Surg Am*. 1995;77A:1448–61.
52. Shanbhag AS, Jacobs JJ, Glant TT, Gilbert JL, Black J, Galante JO. Composition and morphology of wear debris in failed uncemented total hip replacement. *J Bone Joint Surg Br*. 1994;76B:60–7.
53. Shanbhag AS, Bailey HO, Hwang DS, Cha CW, Eror NG, Rubash HE. Quantitative analysis of ultrahigh molecular weight poly-ethylene (UHMWPE) wear debris associated with total knee replacements. *J Biomed Mater Res*. 2000;53:100–10.
54. Schmalzried TP, Jasty M, Harris WH. Periprosthetic bone loss in total hip arthroplasty: polyethylene wear debris and the concept of the effective joint space. *J Bone Joint Surg Am*. 1992;74A:849–63.
55. Green TR, Fisher J, Stone M, Wroblewski BM, Ingham E. Poly-ethylene particles of a ‘critical size’ are necessary for the induction of cytokines by macrophages in vitro. *Biomaterials*. 1998;19:2297–302.
56. Yagil-Kelmer E, Kazmier P, Rahaman MN, Bal BS, Tessman RK, Estes DM. Comparison of the response of primary human blood monocytes and the U937 human monocytic cell line to two different sizes of alumina ceramic particles. *J Orthop Res*. 2004;22:832–8.
57. Yang SY, Ren W, Park Y, Sieving A, Hsu S, Nasser S, Wooley PH. Diverse cellular and apoptotic responses to variant shapes of UHMWPE particles in a murine model of inflammation. *Biomaterials*. 2002;23:3535–43.
58. Nakashima Y, Sun DH, Trindade MC, Maloney WJ, Goodman SB, Schurman DJ, Smith RL. Signaling pathways for tumor necrosis factor- α and interleukin-6 expression in human macrophages exposed to titanium-alloy particulate debris in vitro. *J Bone Joint Surg Am*. 1999;81A:603–15.
59. Rakshit DS, Lim J, Ly K, Ivashkiv LB, Nestor BJ, Sculco TP, Purdue PE. Involvement of complement receptor 3 (CR3) and scavenger receptor in macrophage responses to wear debris. *J Orthop Res*. 2006;24(11):2036–44.
60. Palecanda A, Paulauskis J, Al-Mutairi E, Imrich A, Qin G, Suzuki H, Kodama T, Tryggvason K, Koziel H, Kobzik L. Role of the scavenger receptor MARCO in alveolar macrophage binding of unopsonized environmental particles. *J Exp Med*. 1999;189:1497–506.
61. Caicedo MS, Desai R, McAllister K, Reddy A, Jacobs JJ, Hallab NJ. Soluble and particulate Co-Cr-Mo alloy implant metals activate the inflammasome danger signaling pathway in human macrophages: a novel mechanism for implant debris reactivity. *J Orthop Res*. 2009;27(7):847–54.
62. Palmbo PL, Sytsma MJ, DeHeer DH, Bonnema JD. Macrophage exposure to particulate titanium induces phosphorylation of the protein tyrosine kinase lyn and the phospholipases C γ 1 and C γ 2. *J Orthop Res*. 2002;20(3):483–9.
63. Merkel KD, Erdmann JM, McHugh KP, Abu-Amer Y, Ross FP, Teitelbaum SL. Tumor necrosis factor- α mediates orthopedic implant osteolysis. *Am J Pathol*. 1999;154:203–10.
64. Wooley PH, Morren R, Andary J, Sud S, Yang SY, Mayton L, Markel D, Sieving A, Nasser S. Inflammatory responses to orthopaedic biomaterials in the murine air pouch. *Biomaterials*. 2002;23:517–26.
65. Sabokbar A, Rushton N. Role of inflammatory mediators and adhesion molecules in the pathogenesis of aseptic loosening in total hip arthroplasties. *J Arthroplasty*. 1995;10:810–6.
66. Chiba J, Rubash HE, Kim KJ, Iwaki Y. The characterization of cytokines in the interface tissue obtained from failed cementless total hip arthroplasty with and without femoral osteolysis. *Clin Orthop*. 1994;300:304–12.
67. Stea S, Visentin M, Granchi D, Ciapetti G, Donati ME, Sudanese A, Zanotti C, Toni A. Cytokines and osteolysis around total hip prostheses. *Cytokine*. 2000;12:1575–9.
68. Capper T, Lawrence AJ, Holland H, Deehan JP, Kirby JA. Metal-on-metal hips: cobalt can induce an endotoxin-like response. *Ann Rheum Dis*. 2013;72(3):460–1.
69. Wei S, Kitaura H, Zhou P, Ross FP, Teitelbaum SL. IL-1 mediates TNF-induced osteoclastogenesis. *J Clin Invest*. 2005;115:282–90.
70. Zwerina J, Hayer S, Tohidast-Akrad M, Bergmeister H, Redlich K, Feige U, Dunstan C, Kollias G, Steiner G, Smolen J, Schett G. Single and combined inhibition of tumor necrosis factor, interleukin-1, and RANKL pathways in tumor necrosis factor-induced arthritis: effects on synovial inflammation, bone erosion, and cartilage destruction. *Arthritis Rheum*. 2004;50:277–90.
71. Yang SY, Wu B, Mayton L, Mukherjee P, Robbins PD, Evans CH, Wooley PH. Protective effects of IL-1Ra or vIL-10 gene transfer on a murine model of wear debris-induced osteolysis. *Gene Ther*. 2004;11(5):483–91.
72. Horowitz SM, Luchetti WT, Gonzales JB, Ritchie CK. The effects of cobalt chromium upon macrophages. *J Biomed Mater Res*. 1998;41:468–73.

73. Wang JY, Wicklund BH, Gustilo RB, Tsukayama DT. Titanium, chromium and cobalt ions modulate the release of bone-associated cytokines by human monocytes/macrophages in vitro. *Biomaterials*. 1996; 17:2233–40.
74. Kudo O, Sabokbar A, Pocock A, Itonaga I, Fujikawa Y, Athanasou NA. Interleukin-6 and interleukin-11 support human osteoclast formation by a RANKL-independent mechanism. *Bone*. 2003;32(1):1–7.
75. Darowish M, Rahman R, Li P, Bukata SV, Gelinis J, Huang W, Flick LM, Schwarz EM, O'Keefe RJ. Reduction of particle-induced osteolysis by interleukin-6 involves anti-inflammatory effect and inhibition of early osteoclast precursor differentiation. *Bone*. 2009;45(4):661–8.
76. Gordon A, Wilkinson JM, Wilson AG, Stockley I, MacDonald D, Eastell R. Polymorphisms in the interleukin-one gene cluster and the risk of aseptic loosening after total hip arthroplasty. *J Bone Miner Res*. 2003;18:S2–326.
77. Zhang X, Morham SG, Langenbach R, Young DA, Xing L, Boyce BF, Puzas EJ, Rosier RN, O'Keefe RJ, Schwarz EM. Evidence for a direct role of cyclo-oxygenase 2 in implant wear debris-induced osteolysis. *J Bone Miner Res*. 2001;16(4):660–70.
78. Wang ML, Tuli R, Manner PA, Sharkey PF, Hall DJ, Tuan RS. Direct and indirect induction of apoptosis in human mesenchymal stem cells in response to titanium particles. *J Orthop Res*. 2003;21:697–707.
79. Pioletti DP, Leoni L, Genini D, Takei H, Du P, Corbeil J. Gene expression analysis of osteoblastic cells contacted by orthopedic implant particles. *J Biomed Mater Res*. 2002;61:408–20.
80. Wang ML, Nesti LJ, Tuli R, Lazatin J, Danielson KG, Sharkey PF, Tuan RS. Titanium particles suppress expression of osteoblastic phenotype in human mesenchymal stem cells. *J Orthop Res*. 2002;20:1175–84.
81. Vermes C, Chandrasekaran R, Jacobs JJ, Galante JO, Roebuck KA, Glant TT. The effects of particulate wear debris, cytokines, and growth factors on the functions of MG-63 osteoblasts. *J Bone Joint Surg Am*. 2001;83A:201–11.
82. Vermes C, Roebuck KA, Chandrasekaran R, Dobai JG, Jacobs JJ, Glant TT. Particulate wear debris activates protein tyrosine kinases and nuclear factor kappa B, which down-regulates type I collagen synthesis in human osteoblasts. *J Bone Miner Res*. 2000;15:1756–65.
83. Dean DD, Schwartz Z, Blanchard CR, Liu Y, Agrawal CM, Lohmann CH, Sylvia VL, Boyan BD. Ultrahigh molecular weight polyethylene particles have direct effects on proliferation, differentiation, and local factor production of MG63 osteoblast-like cells. *J Orthop Res*. 1999;17:9–17.
84. Waris V, Zhao DS, Leminen H, Santavirta S, Takagi M, Nordsletten L, Konttinen YT. Insulin-like growth factors I and II in the aseptic loosening of total hip implants. *Scand J Rheumatol*. 2004;33(6):428–31.
85. Lum L, Wong BR, Josien R, Becherer JD, Erdjument-Bromage H, Schlondorff J, Tempst P, Choi Y, Blobel CP. Evidence for a role of a tumor necrosis factor alpha (TNF-alpha)-converting enzyme like protease in shedding of TRANCE, a TNF family member involved in osteoclastogenesis and dendritic cell survival. *J Biol Chem*. 1999;274:13613–8.
86. Theill LE, Boyle WK, Penninger JM. RANKL and RANK: T cells, bone loss, and mammalian evolution. *Annu Rev Immunol*. 2002;20:795–823.
87. Hsu H, Lacey DL, Dunstan CR, Solovyev I, Colombero A, Timms E, Tan HL, Elliott G, Kelley MJ, Sarosi I, Wang L, Xia XZ, Elliott R, Chiu L, Black T, Scully S, Capparelli C, Morony S, Shimamoto G, Bass MB, Boyle WJ. Tumor necrosis factor receptor family member RANK mediates osteoclast differentiation and activation induced by osteoprotegerin ligand. *Proc Natl Acad Sci*. 1999;96:3540–5.
88. Li J, Sarosi I, Yan XQ, Morony S, Capparelli C, Tan HL, McCabe S, Elliott R, Scully S, Van G, Kaufman S, Juan SC, Sun Y, Tarpley J, Martin L, Christensen K, McCabe J, Kostenuik P, Hsu H, Fletcher F, Dunstan CR, Lacey DL, Boyle WJ. RANK is the intrinsic hematopoietic cell surface receptor that controls osteoclastogenesis and regulation of bone mass and calcium metabolism. *Proc Natl Acad Sci*. 2000;97:1566–71.
89. Clohisy JC, Frazier E, Hirayama T, Abu-Amer Y. RANKL is an essential cytokine mediator of PMMA particle induced osteoclastogenesis. *J Orthop Res*. 2003;21:202–12.
90. Kong YY, Yoshida H, Sarosi I, Tan HL, Timms E, Capparelli C, Morony S, Oliveira-dos-Santos AJ, Van G, Itie A, Khoo W, Wake-ham A, Dunstan CR, Lacey DL, Mak TW, Boyle WJ, Penninger JM. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. *Nature*. 1999;397:315–23.
91. Yasuda H, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Mochizuki SI. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis inhibitory factor and is identical to TRANCE/RANKL. *Proc Natl Acad Sci*. 1998;95:3597–602.
92. Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, Capparelli C, Scully S, Tan HL, Xu W, Lacey DL, Boyle WJ, Simonet WS. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. *Genes Dev*. 1998;12:1260–8.
93. Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS, Luthy R, Nguyen HQ, Wooden S, Bennett L, Boone T, Shimamoto G, DeRose M, Elliott R, Colombero A, Tan HL, Trail G, Sullivan J, Davy E, Bucay N, Renshaw-Gegg L, Hughes TM, Hill D, Pattison W, Campbell P, Sanders S, Van G, Tarpley J, Derby P, Lee R, Boyle WJ. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell*. 1997;89:309–19.
94. Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Spelsberg TC, Riggs BL. Estrogen stimulates gene

- expression and protein production of osteoprotegerin in human osteoblastic cells. *Endocrinology*. 1999;140:4367–70.
95. Kim KJ, Kotake S, Udagawa N, Ida H, Ishii M, Takei I, Kubo T, Takagi M. Osteoprotegerin inhibits in vitro mouse osteoclast formation induced by joint fluid from failed total hip arthroplasty. *J Biomed Mater Res*. 2001;58:393–400.
 96. Yang SY, Mayton L, Wu B, Goater JJ, Schwarz EM, Wooley PH. Adeno-associated virus-mediated osteoprotegerin gene transfer protects against particulate polyethylene-induced osteolysis in a murine model. *Arthritis Rheum*. 2002;46:2514–23.
 97. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature*. 2003;423:337–42.
 98. Sabokbar A, Fujikawa Y, Neale S, Murray DW, Athanasou NA. Human arthroplasty derived macrophages differentiate into osteoclastic bone resorbing cells. *Ann Rheum Dis*. 1997;56:414–20.
 99. Haynes DR, Crotti TN, Zreiqat H. Regulation of osteoclast activity in peri-implant tissues. *Biomaterials*. 2004;25:4877–85.
 100. Yu X, Huang Y, Collin-Osdoby P, Osdoby P. CCR1 chemokines promote the chemotactic recruitment, RANKL development, and motility of osteoclasts and are induced by inflammatory cytokines in osteoblasts. *J Bone Miner Res*. 2004;19:2065–77.
 101. Tanaka R, Yasunaga Y, Hisatome T, Yamasaki T, Iwamori H, Ochi M. Serum interleukin 8 levels correlate with synovial fluid levels in patients with aseptic loosening of hip prosthesis. *J Arthroplasty*. 2005;20:1049–54.
 102. Rakshit DS, Ly K, Sengupta TK, Nestor BJ, Sculco TP, Ivashkiv LB, Purdue PE. Wear debris inhibition of anti-osteoclastogenic signaling by interleukin-6 and interferon-gamma: mechanistic insights and implications for periprosthetic osteolysis. *J Bone Joint Surg Am*. 2006;88A:788–99.
 103. Cadosch D, Chan E, Gautschi OP, Simmen HP, Filgueira L. Bio-corrosion of stainless steel by osteoclasts in vitro evidence. *J Orthop Res*. 2009;27(7):841–6.
 104. Patntirapong S, Habibovic P, Hauschka PV. Effects of soluble cobalt and cobalt incorporated into calcium phosphate layers on osteoclast differentiation and activation. *Biomaterials*. 2009;30(4):548–55.
 105. Konttinen YT, Takagi M, Mandelin J, Lassus J, Salo J, Ainola M, Li TF, Virtanen I, Liljestrom M, Sakai H, Kobayashi Y, Sorsa T, Lappalainen R, Demulder A, Santavirta S. Acid attack and cathepsin K in bone resorption around total hip replacement prosthesis. *J Bone Miner Res*. 2001;16(10):1780–6.
 106. Kanaji A, Caicedo MS, Virdi AS, Sumner DR, Hallab NJ, Sena K. Co-Cr-Mo alloy particles induce tumor necrosis factor alpha production in MLO-Y4 osteocytes: a role for osteocytes in particle-induced inflammation. *Bone*. 2009;45(3):528–33.
 107. Orhue V, Kanaji A, Caicedo MS, Virdi AS, Sumner DR, Hallab NJ, Jahr H, Sena K. Calcineurin/nuclear factor of activated T cells (NFAT) signaling in cobalt-chromium-molybdenum (CoCrMo) particles-induced tumor necrosis factor- α (TNF α) secretion in MLO-Y4 osteocytes. *J Orthop Res*. 2011;29(12):1867–73.
 108. Atkins GJ, Welldon KJ, Holding CA, et al. The induction of a catabolic phenotype in human primary osteoblasts and osteocytes by polyethylene particles. *Biomaterials*. 2009;30:3672–81.
 109. Okafor CC, Haleem-Smith H, Laqueriere P, Manner PA, Tuan RS. Particulate endocytosis mediates biological responses of human mesenchymal stem cells to titanium wear debris. *J Orthop Res*. 2006;24(3):461–73.
 110. Haleem-Smith H, Argintar E, Bush C, Hampton D, Postma WF, Chen FH, Rimington T, Lamb J, Tuan RS. Biological responses of human mesenchymal stem cells to titanium wear debris particles. *J Orthop Res*. 2012;30(6):853–63.
 111. Nawrocki B, Polette M, Burlet H, Birembaut P, Adnet JJ. Expression of gelatinase A and its activator MT1-MMP in the inflammatory periprosthetic response to polyethylene. *J Bone Miner Res*. 1999;14(2):288–94.
 112. Yao J, Glant TT, Lark MW, Mikecz K, Jacobs JJ, Hutchinson NI, Hoerner LA, Kuettner KE, Galante JO. The potential role of fibroblasts in periprosthetic osteolysis: fibroblast response to titanium particles. *J Bone Miner Res*. 1995;10(9):1417–27.
 113. Wei X, Zhang X, Zuscik MJ, Drissi MH, Schwarz EM, O'Keefe RJ. Fibroblasts express RANKL and support osteoclastogenesis in a COX-2-dependent manner after stimulation with titanium particles. *J Bone Miner Res*. 2005;20(7):1136–48.
 114. Gravalles EM, Manning C, Tsay A, Naito A, Pan C, Amento E, Goldring SR. Synovial tissue in rheumatoid arthritis is a source of osteoclast differentiation factor. *Arthritis Rheum*. 2000;43:250–8.
 115. Kotake S, Udagawa N, Hakoda M, Mogi M, Yano K, Tsuda E, Takahashi K, Furuya T, Ishiyama S, Kim KJ, Saito S, Nishikawa T, Takahashi N, Togari A, Tomatsu T, Suda T, Kamatani N. Activated human T cells directly induce osteoclastogenesis from human monocytes: possible role of T cells in bone destruction in rheumatoid arthritis patients. *Arthritis Rheum*. 2001;44:1003–12.
 116. Cadosch D, Sutanto M, Chan E, Mhawi A, Gautschi OP, von Katterfeld B, Simmen HP, Filgueira L. Titanium uptake, induction of RANK-L expression, and enhanced proliferation of human T-lymphocytes. *J Orthop Res*. 2010;28(3):341–7.
 117. Abu-Amer Y. Mechanisms of inflammatory mediators in bone loss diseases. In: Rosier RN, Evans CH, editors. *Molecular biology in orthopedics*. Rosemont: American Academy of Orthopedic Surgeons; 2003. p. 229–39.
 118. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am*. 2001;83:428–36.

119. Gernerding K, et al. A new type of metal recognition by human T cells: contact residues for peptide-independent bridging of T cell receptor and major histocompatibility complex by nickel. *J Exp Med.* 2003;197:1345–53.
120. Sato K, Suematsu A, Okamoto K, et al. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. *J Exp Med.* 2006;203:2673–82.
121. Miossec P, Kom T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. *N Engl J Med.* 2009;361(9):888–98.
122. Wedemeyer C, Neuerburg C, Pfeiffer A, Heckelei A, von Knoch F, Hilken G, Brankamp J, Henschke F, von Knoch M, Löer F, Saxler G. Polyethylene particle-induced bone resorption in substance P-deficient mice. *Calcif Tissue Int.* 2007;80(4):268–74.
123. Holt G, Murnaghan C, Reilly J, Meek RM. The biology of aseptic osteolysis. *Clin Orthop.* 2007;460:240–52.
124. Cadosch D, Gautschi OP, Chan E, Simmen HP, Filgueira L. Titanium induced production of chemokines CCL17/TARC and CCL22/MDC in human osteoclasts and osteoblasts. *J Biomed Mater Res A.* 2010;92(2):475–83.
125. Miyanishi K, Trindade MC, Ma T, Goodman SB, Schurman DJ, Smith RL. Periprosthetic osteolysis: induction of vascular endothelial growth factor from human monocyte/macrophages by orthopaedic biomaterial particles. *J Bone Miner Res.* 2003;18(9):1573–83.
126. Roberts WG, Palade GE. Increased microvascular permeability and endothelial fenestration induced by vascular endothelial growth factor. *J Cell Sci.* 1995;108:2369–79.
127. Matsumoto Y, Tanaka K, Hirata G, Hanada M, Matsuda S, Shuto T, Iwamoto Y. Possible involvement of the vascular endothelial growth factor-Flt-1-focal adhesion kinase pathway in chemotaxis and the cell proliferation of osteoclast precursor cells in arthritic joints. *J Immunol.* 2002;168:5824–31.
128. von Knoch M, Jewison DE, Sibonga JD, Turner RT, Morrey BF, Loer F, Berry DJ, Scully SP. Decrease in particle-induced osteolysis in obese (ob/ob) mice. *Biomaterials.* 2004;25(19):4675–81.
129. Wang W, Ouyang Y, Poh CK. Orthopaedic implant technology: biomaterials from past to future. *Ann Acad Med Singapore.* 2011;40(5):237–44.
130. Wooley PH, Schwarz EM. Aseptic loosening. *Gene Ther.* 2004;11(4):402–7.
131. Ren W, Blasier R, Peng X, Shi T, Wooley PH, Markel D. Effect of oral erythromycin therapy in patients with aseptic loosening of joint prostheses. *Bone.* 2009;44(4):671–7.
132. Rawal SY, Rawal YB. Non-antimicrobial properties of tetracyclines—dental and medical implications. *West Indian Med J.* 2001;50:105–8.
133. Holmes SG, Still K, Buttle DJ, Bishop NJ, Grabowski PS. Chemically modified tetracyclines act through multiple mechanisms directly on osteoclast precursors. *Bone.* 2004;35:471–8.
134. Zhang C, Tang TT, Ren WP, Zhang XL, Dai KR. Inhibiting wear particles-induced osteolysis with doxycycline. *Acta Pharmacol Sin.* 2007;28(10):1603–10.
135. Millett PJ, Allen MJ, Bostrom MP. Effects of alendronate on particle-induced osteolysis in a rat model. *J Bone Joint Surg Am.* 2002;84A:236–49.
136. Wedemeyer C, Von KF, Pingsmann A, Hilken G, Sprecher C, Saxler G, et al. Stimulation of bone formation by zoledronic acid in particle-induced osteolysis. *Biomaterials.* 2005;26:3719–25.
137. Hilding M, Aspenberg P. Postoperative clodronate decreases prosthetic migration: 4-year follow-up of a randomized radiostereometric study of 50 total knee patients. *Acta Orthop Scand.* 2006;77:912–6.
138. Ryd L, Albrektsson BE, Carlsson L, Dansgard F, Herberts P, Lindstrand A, et al. Roentgen stereophotogrammetric analysis as a predictor of mechanical loosening of knee prostheses. *J Bone Joint Surg Br.* 1995;77B:377–83.
139. Thillemann TM, Pedersen AB, Mehnert F, Johnsen SP, Søballe K. Postoperative use of bisphosphonates and risk of revision after primary total hip arthroplasty: a nationwide population-based study. *Bone.* 2010;46(4):946–51.
140. Rubash HE, Dorr L, Jacobs J, Maloney W, Saag K, Malbecq W, et al. Does alendronate inhibit the progression of periprosthetic osteolysis? *Tran Orthop Res Soc.* 1888;2004:29.
141. Aspenberg P, Agholme F, Magnusson P, Fahlgren A. Targeting RANKL for reduction of bone loss around unstable implants: OPG-Fc compared to alendronate in a model for mechanically induced loosening. *Bone.* 2011;48(2):225–30.
142. Wilkinson JM, Stockley I, Peel NF, Hamer AJ, Elson RA, Barrington NA, Eastell R. Effect of pamidronate in preventing local bone loss after total hip arthroplasty: a randomized, double-blind, controlled trial. *J Bone Miner Res.* 2001;16(3):556–64.
143. Childs LM, Goater JJ, O’Keefe RJ, Schwarz EM. Efficacy of etanercept for wear debris-induced osteolysis. *J Bone Miner Res.* 2001;16(2):338–47.
144. Childs LM, Paschalis EP, Xing L, Dougall WC, Anderson D, Boskey AL, Puzas JE, Rosier RN, O’Keefe RJ, Boyce BF, Schwarz EM. In vivo RANK signaling blockade using the receptor activator of NF-kappaB:Fc effectively prevents and ameliorates wear debris-induced osteolysis via osteoclast depletion without inhibiting osteogenesis. *J Bone Miner Res.* 2002;17(2):192–9.
145. Xu J, Cheng T, Feng HT, Pavlos NJ, Zheng MH. Structure and function of V-ATPases in osteoclasts: potential therapeutic targets for the treatment of osteolysis. *Histol Histopathol.* 2007;22(4):443–54.
146. Su X, Floyd DH, Hughes A, Xiang J, Schneider JG, Uluckan O, Heller E, Deng H, Zou W, Craft CS, Wu K, Hirbe AC, Grabowska D, Eagleton MC, Townsley S, Collins L, Pivnicka-Worms D, Steinberg TH, Novack DV, Conley PB, Hurchla MA, Rogers M, Weilbaecher KN. The ADP receptor P2RY12 regulates osteoclast function and pathologic bone remodeling. *J Clin Invest.* 2012;122(10):3579–92.

147. Von Knoch F, Wedemeyer C, Heckeley A, Saxler G, Hilken G, Brankamp J, Sterner T, Landgraeber S, Henschke F, Loer F, von Knoch M. Promotion of bone formation by simvastatin in polyethylene particle-induced osteolysis. *Biomaterials*. 2005;26: 5783–9.
148. Thillemann TM, Pedersen AB, Mehnert F, Johnsen SP, Søballe K. The risk of revision after primary total hip arthroplasty among statin users: a nationwide population-based nested case–control study. *J Bone Joint Surg Am*. 2010;92(5):1063–72.
149. Baron R, Hesse E. Update on bone anabolics in osteoporosis treatment: rationale, current status, and perspectives. *J Clin Endocrinol Metab*. 2012;97(2): 311–25.
150. Monroe DG, McGee-Lawrence ME, Oursler MJ, Westendorf JJ. Update on Wnt signaling in bone cell biology and bone disease. *Gene*. 2012;492(1):1–18.

Theofilos Karachalios and Konstantinos G. Makridis

Revision Total Hip Arthroplasty

For primary total hip arthroplasty (THA), several fixation options are available. Cemented, cementless, or hybrid principles have been applied, and their advantages, disadvantages, and their long-term effectiveness have been well described in the literature. A recent study reported the superior survival of cemented to uncemented THA which was related to better performance of the cemented cups [1]. On the other hand, uncemented stems have proved to perform better than cemented stems; the risk of revision was found to be similar in both implants [1].

As the early THAs were performed on relatively low-demand patients with end-stage osteoarthritis, as an alternative to Girdlestone's procedure, the occurrence of clinically symptomatic mechanical failure was low during the first

10–15 years of the application of arthroplasty surgery in clinical practice. Thus, experience with revision procedures was limited, and the clinical results were not easy to evaluate. Initially, cemented fixation was considered preferable for revision surgery, but the results were not satisfactory, with a high incidence of radiographic loosening and re-revision rates of both components [2–9]. It has been shown that the problem related to cemented revision lies in the quality of the remaining bone, following the removal of the components. Bone is often sclerotic without trabecular structure for cement interdigitation (Fig. 12.1). Advances in surgical techniques and implant technology have improved the long-term survival of primary THAs. However, the number of revision procedures has also been growing, and this is probably due to the increased number of THAs performed on younger, high-demand patients and because of the variety of hip disorders. Diagnostic and treatment recommendations have evolved, and several therapeutic algorithms have been proposed by many authors [10–13]. However, there is no consensus about the optimal treatment, and there are still questions regarding the indications of different techniques.

T. Karachalios, MD, DSc (✉)
Orthopaedic Department, Faculty of Medicine,
School of Health Sciences, University of Thessalia,
CERETETH, University General
Hospital of Larissa, Larissa,
Mezourlo Region, 41110
Larissa, Hellenic Republic, Greece
e-mail: kar@med.uth.gr

K.G. Makridis, MD, MSc
Academic Unit, Leeds Teaching
Hospitals, Leeds, UK

Cemented Acetabular Revision

Bone erosion due to osteolysis and mechanical damage from the motion of a loose component often leaves cavitory, segmental, and combined defects in the acetabulum [14, 15]. These changes

Fig. 12.1 Femoral endosteal surface after the removal of a loose femoral stem. Bone is sclerotic with absence of trabecular structure



in the bone stock can make it difficult to obtain adequate fixation of a cemented component in revision operations. At present, most authors agree that cementless fixation of the acetabulum in revision operations has better results than does cemented acetabular revision. Porous-coated acetabular components have demonstrated less radiographic loosening and lower re-revision rates [16–19]. Despite these, there is still a role for cement in the revision of acetabular cups. Cement is used for the fixation of a polyethylene component with a metal acetabular reinforcement ring or cage and particulate graft material; for fixation of a polyethylene component in conjunction with a large structural allograft, such as an acetabular allograft; and, in selected cases, for use with impaction grafting [20–27]. Another modern indication for the use of cemented polyethylene cups is the revision of a failed acetabular liner within the existing, well-fixed, metal shell. The technical parameters of this technique have been studied using an ovine animal model [28].

Type I acetabular defects can be managed with conventional either cemented or cementless cups and show satisfactory, at least midterm, results [29, 30]. For more severe acetabular defects, cemented fixation in revision THA shows unfavorable results. Acetabular migration and radiological and clinical loosening vary from 15 to

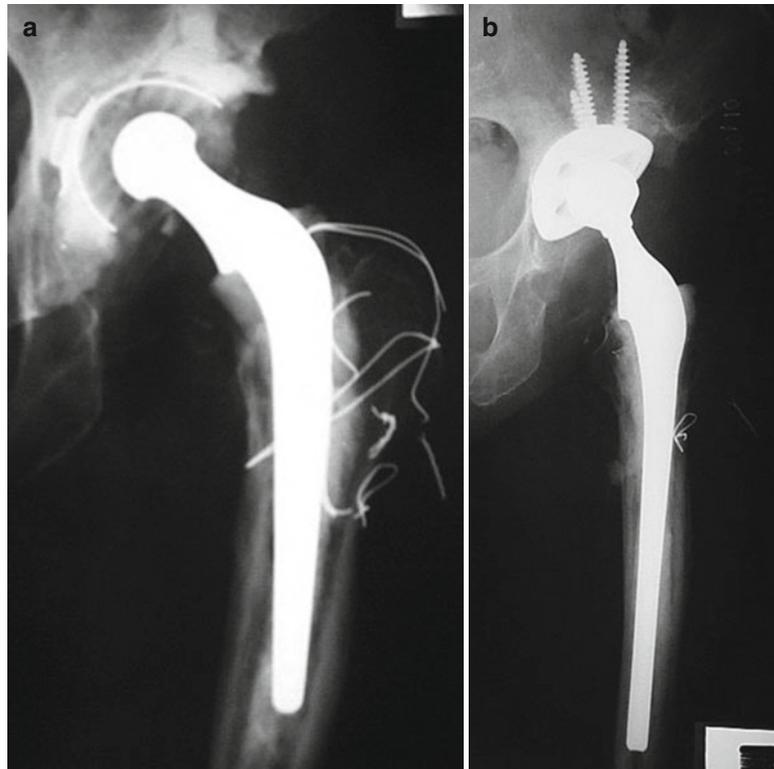
30 % in midterm [2–9, 31–33] with the best clinical outcomes reported by Marti et al. [34]. The use of reinforcement or anti-protrusion rings and cages in combination with cement fixation is a serious confounding factor in the assessment of clinical outcomes, and such an analysis is beyond the scope of this paper.

Cemented Femoral Revision

As in the acetabular side, type I femoral defects have intact cancellous and cortical bone. Any primary stem, cemented or uncemented, can be used performing third-generation cementing techniques, with a satisfactory clinical outcome [35].

Unsatisfactory clinical outcomes were also reported in early series of cemented femoral revision surgery. Fifteen to 30 % radiographic loosening and 5–9 % reoperation rate were observed in midterm at the hands of pioneers of hip reconstruction [2, 3, 5–7, 36]. The results were even worse if patients had had a previous revision, with reports of 50 % radiographic or clinical loosening at 3 years follow-up [6]. Another characteristic of this early revision surgery is the report of a high incidence of intraoperative or postoperative complications such as femoral canal perforations,

Fig. 12.2 (a) Preoperative radiograph of a THA with aseptic loosening. (b) Postoperative radiograph following a cemented femoral revision at 8-year follow-up



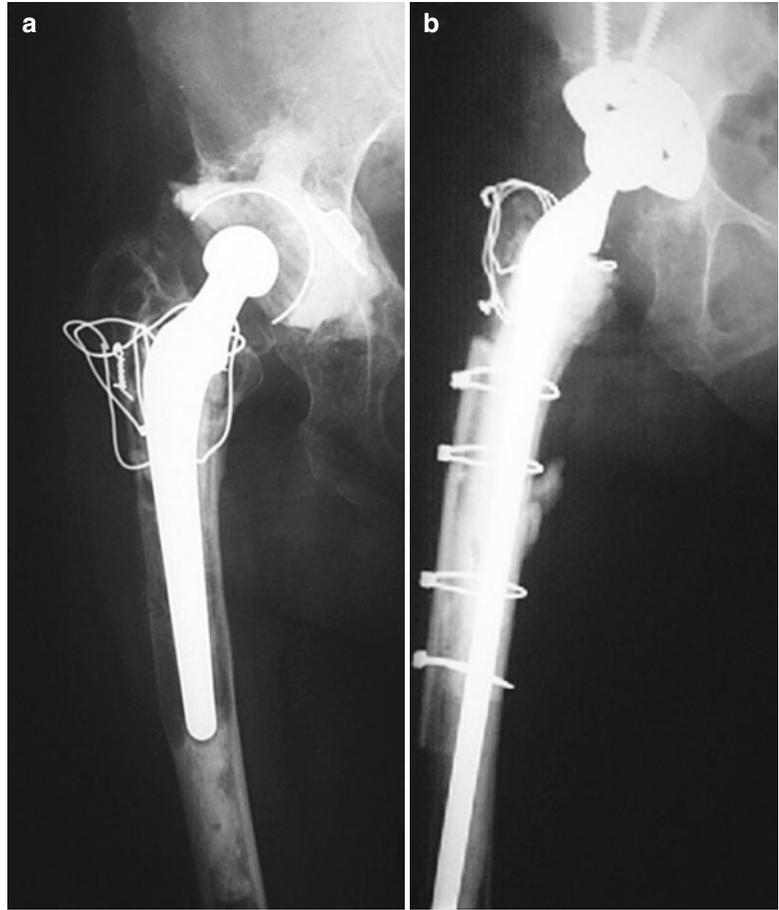
fractures, dislocations, femoral nerve palsy, and trochanteric problems. In this initial experience, the fibrous membrane between bone and loose cement and the neocortex between the fibrous membrane and any residual cancellous bone were not adequately removed. Cement delivery and pressurization systems were not available, and the distal canal was not adequately restricted (especially distal to the isthmus). Perforations of the canal were not recognized and appreciated and were bypassed. It was also not understood that perforations and canal windows can potentially act as stress risers. Modern cementing techniques, removal of the neocortex with a burr, recognition of the perforations (90 % of them to the anterolateral cortex), and bypassing the defects and windows by 1.5–3 diameters of the femoral shaft outer diameter have resulted in improved clinical outcomes. The re-revision rate of cemented revision of femoral stems dropped to 10 % at 10–15 years even in cases of extensive femoral osteolysis (Figs. 12.2 and 12.3) [32, 37–43].

Cemented Acetabular Revision with Impaction Grafting Technique

When notable bone loss and extensive bone defects exist, the impaction grafting technique with or without reconstruction rings and strut allografts should be used in cemented revision hip arthroplasty. It is important to recognize that primary implant stability in this technique depends on the adequacy of containment and impaction of the graft, together with effective cementing.

In the 1970s, clinicians began to use bone grafting to repair osseous defects in association with primary and revision hip arthroplasty. The size of the bone grafts used ranged from small morcellized to large bulk fragments [44–46]. Roffman et al. [47] have investigated the fate of autogenous chips under a layer of polymethyl methacrylate bone cement in an animal model with intrapelvic protrusion. Histologic evaluation revealed bone formation from the acetabular wall toward the graft. The graft appeared viable, and

Fig. 12.3 (a) Preoperative radiograph of a THA with aseptic loosening and severe bone loss of the proximal femur. (b) Postoperative radiograph following a cemented femoral revision and strut bone allograft at 7-year follow-up



new bone formation was induced along the surface adjoining the bone cement. Other experiments in goats were designed to histologically evaluate the processes involved in graft incorporation. Surgical technique was comparable to that used in human procedures. Rapid union of the graft with host bone was achieved, and no signs of resorption or collapse of the reconstruction were seen [48–51]. Moreover, van der Donk has reported the results of human core biopsies taken from revision operations with impacted morsellized grafts and cement [52]. It was concluded that reconstruction of bony defects with impacted graft chips results in a new bony structure which can form an ideal substrate for cemented components. Griffon et al. [53] studied the biological behavior of biomaterials being considered for impaction grafting in revision hip arthroplasty. In their opinion, the biological properties of materials

are very important and should be proved prior to evaluation under loading conditions.

On the acetabular side, the goals are to restore hip mechanics by placing the cup at the level of the anatomic acetabulum, to restore segmental defects with metal wire mesh in order to achieve containment, to restore periprosthetic bone loss by augmenting the cavitory defect with allograft bone chips, and to achieve stability by impacting the chips and using bone cement. On the femoral side, large bone chips (8–10 mm in diameter) must be used in the proximal femur to reduce subsidence of cemented stems especially when they are collarless, double tapered, and polished. Moreover, long stems are crucial in order to bypass regions of high stress concentration, while prophylactic cerclage wires and strut grafts are required when the femoral cortex is still thin and extends beyond the tip of the long-stemmed femoral component.

Recent studies have reported excellent mid-term and long-term survival of femoral component revisions with impaction bone grafting and a cemented stem [54–56]. Busch et al. have also shown satisfactory results using impacted morcellized bone grafts and a cemented cup in young patients with acetabular defects [57]. Buttaro et al. have suggested that metal mesh, impaction grafting, and a cemented cup should be considered for reconstruction of medium uncontained acetabular defects, but not for severe combined deficiencies. The reason for this is the migration of metal meshes, and the authors propose the use of acetabular reconstruction rings with impacted allografts in cases of extended segmental defects [25]. Results have been presented from the Swedish registry with its large population of patients and long-term follow-up. The survivorship of cemented stems used in combination with impaction grafting was 94 % at 15 years [58].

Cement-in-Cement Technique

If the cement is well fixed, a cement-in-cement technique appears to be a versatile and attractive alternative option (Fig. 12.4) [59]. Supporters of this technique report a low risk for bone loss, cortical perforation, and fracture as well as a lower probability of having to perform extensive osteotomies [12, 60, 61]. The concept of this technique was initially described by Greenwald et al. in 1978 [62]. The trend of removing all the old cement was questioned by their laboratory study which showed that recementing over previously hardened cement mass was feasible. They further propose rasping of the old cement surface in order to increase the area of contact and emphasize the early use of freshly polymerizing cement to allow larger amounts of monomer to interact with the old mantle. This was also supported by Weinrauch's biomechanical study in which the shear strength of 5 mm thick specimens was tested. The authors were able to analyze the possible reaction between the old and new cement mantle and attribute the quality of the chemical bond to the diffusion of new cement monomer [63]. On the other



Fig. 12.4 Postoperative radiograph of a cement-in-cement revision of a femoral stem at 5-year follow-up

hand, Li et al. [64] reported in a biomechanical study that the strength of the bond between old and new cement can be dramatically reduced in the presence of blood and marrow debris. They propose the removal of the entire cement mantle if the previous one is not able to be thoroughly cleaned. However, in a recent biomechanical study where flexural strength was tested, it was shown that the interface between old and new cement was not a point of weakness [65]. In addition, different cement combinations did not significantly affect the strength of the interface. Other factors like the elimination of pores both at the interface and within the new cement appeared to be more important for the successful application of this technique.

Surgical Technique of Cement-in-Cement Revision Surgery

The surgical approach is usually the same as in primary THA. The cement above the shoulder of the hip prosthesis must be cleared to facilitate stem removal. Thus, inspection of the cement mantle is easier, and the cement can be removed to a depth where osseointegration of the old cement bone can be confirmed. If any crack in the old cement mantle is visible beyond the lesser trochanter level, it is better to remove all of the cement and perform an alternative procedure. Pulsed lavage is meticulously applied to clear the old mantle and different rasps, and curettes and burrs are used to roughen the cement surface. The new cement is prepared and introduced using a gun device while still in a low state of viscosity. Suction and compression techniques are used to avoid leaving any blood and marrow debris and to promote pressurization [10].

Regarding the acetabular component, this can be easily removed when it is loose without using extraction devices and osteotomes. If a polyethylene liner exists and loosening is minimal, then the technique proposed by Brogan can be performed [66]. During this procedure, larger reamers are used to ream away the implant under regular lavage and suction to minimize the escape of debris. After reaming, the polyethylene can be extracted much more easily, and the cement mantle is inspected to confirm its adequate fixation. The ridges of cement corresponding to the grooves in the polyethylene are retained, and additional small pits can be made to augment the contact surface. Penetration to the underlying bone should be avoided because the presence of blood debris will interfere with the new bond. The new component is inserted as usual.

Indications for Cement-in-Cement Revision Surgery

The cement-in-cement technique can be undertaken in different situations of revision such as the replacement of a broken component, the replacement of a malpositioned implant, and the conversion

of a well-fixed hemiarthroplasty to THA [38, 67]. In addition, several authors support the use of the cement-in-cement revision in anatomically reducible periprosthetic fractures with a well-preserved preexisting cement mantle. After meticulous preoperative planning, this technique can offer decreased blood loss, decreased risk of iatrogenic fragmentation of bone during cement removal, and a safe alternative especially in elderly patients who are not fit for prolonged surgical procedures [13, 68]. Clinical studies using cement-in-cement technique in revision hip replacement have reported satisfactory outcome and long-term longevity of the implants. The majority of authors emphasize the advantages of bone stock preservation, the avoidance of extensive operating procedures, and the lesser risk of complications [12, 66, 69, 70].

Cemented Fixation of Revision Total Knee Arthroplasty

Due to the demographic development of western countries, the recent availability of technically advanced implants, and the expansion of indications for total knee arthroplasty (TKA), a further increase in primary TKA and, as a result, a corresponding rise in revision TKA are expected [71]. The most common causes of revision TKA are infection and implant loosening; the most common type of revision TKA procedure is revision of all the components [71, 72]. The literature related to clinical outcomes of revision TKA is limited, and studies are of low evidence (level III and IV), with a rather small number of patients, different implant revision systems, and short- to midterm follow-up [71]. Clinical survival rates from 71 to 94 % have been reported at the level of 10-year follow-up. Factors such as the component design, the restoration of the lower limb axis, the restoration of bone defects and knee stability, the underlying disease, and the implant bone fixation technique all influence the outcome [71, 73, 74]. Intramedullary stems improve the anchoring of implants especially in revisions with bone defects [71, 73, 75–78]; however, the fixation technique (cemented or cementless) for components and stems remains controversial [71, 77, 79, 80].

The biomechanical principles of cemented and cementless fixation in revision TKA have been studied in several experimental cadaveric studies [81–85]. It has been confirmed that tibial components with cemented stems show less micromotion than components with cementless stems of the same length. Tibial components with cementless long (150 cm) stems show similar stability as those with short (75 cm) cemented stems [81]. Tibial hybrid fixation shows less failure of fixation under cyclic loading compared to tibial cemented fixation [82]. The longer hybrid tibial stems show more equal and uniform load (shear) transfer compared to those shorter cemented tibial stems [83]. Primary stability of hybrid tibial stems is equal and even higher (depending on the tibial tray cement-bone penetration factor) compared to those of cemented tibial stems [84]. Hybrid femoral stems provide stability and minimize stress shielding of the distal femoral bone interfaces [85].

Mid- to long-term survival rates of hybrid fixation (a combination of cemented femoral and tibial components with cementless, press-fit femoral and tibial stems) vary from 71 to 96 % with an aseptic loosening rate between 0 and 29 % (Fig. 12.5) [73, 75, 77, 78, 86–90]. Mid- to long-term survival rates of cemented fixation (a combination of cemented femoral and tibial components with cemented femoral and tibial stems) vary from 89 to 97.5 % with an aseptic loosening rate between 0 and 7 % [73, 74, 79, 86, 91].

Conclusion

The revision of cemented hip arthroplasties remains a challenge even in the hands of the most experienced orthopedic surgeon. Several important factors should be considered, such as acetabular or femoral bone loss, bone deformation, compromised soft tissues, stem fracture, and osteolysis. Comprehensive and well-designed preoperative planning is of great significance in dealing with these parameters. Restoring the hip joint center, establishing bone continuity, providing an implant that is well fixed to the host bone, and using bone graft, a surgical hip reconstruction can be achieved with favorable biological and mechanical



Fig. 12.5 Postoperative radiograph of a hybrid revision TKA at 8-year follow-up

characteristics and a successful long-term outcome. Cemented revision THA is indicated in older, low-demand patients with mild bone loss or large femoral canals, when using a proximal tumor arthroplasty for proximal bone loss in elderly patients and in revisions of infected arthroplasties. Impaction bone grafting and cement-in-cement techniques offer valuable alternative options in cases with compromised bone stock.

The ideal fixation of modular revision TKA remains unclear. Cemented and hybrid fixation show equal initial stability based on cadaveric studies, as well as comparable survival rates, comparable aseptic loosening rates, and equivalent clinical outcome based on mid- to long-term low-quality clinical studies.

References

- Hailer NP, Garellick G, Kärrholm J. Uncemented and cemented primary total hip arthroplasty in the Swedish Hip Arthroplasty Register. *Acta Orthop*. 2010;81(1):34–41.
- Amstutz HC, Ma SM, Jinnah RH, et al. Revision of aseptic loose total hip arthroplasties. *Clin Orthop*. 1982;170:21–33.
- Callaghan JJ, Salvati EA, Pellici PM, et al. Results of revision for mechanical failure after cemented total hip replacement 1979 to 1982: a two to five year follow up. *J Bone Joint Surg Am*. 1985;67A:1074–85.
- Franzen H, Mjoberg B, Onnerfalt R. Early migration of acetabular components revised with cement: a roentgen stereophotogrammetric study. *Clin Orthop*. 1993;287:131–4.
- Garcia-Cimberelo E, Munuera L, Diez-Vazquez V. Long term results of aseptic cemented Charnley revisions. *J Arthroplasty*. 1995;10:121–31.
- Kavanagh BF, Fitzgerald Jr RH. Multiple revisions for failed total hip arthroplasty not associated with infection. *J Bone Joint Surg Am*. 1987;69A:1144–9.
- Kavanagh BF, Ilstrup DM, Fitzgerald Jr RH. Revision total hip arthroplasty. *J Bone Joint Surg Am*. 1985;67A:517–26.
- Raut VV, Wroblewski BM. Revision of the acetabular component of a total hip arthroplasty with cement in young patients without rheumatoid arthritis. *J Bone Joint Surg Am*. 1996;78A:1853–6.
- Snorrason F, Kärrholm J. Early loosening of revision hip arthroplasty: a roentgen stereophotogrammetric analysis. *J Arthroplasty*. 1990;5:217–29.
- Lieberman JR, Moeckel BH, Evans BG, Salvati EA, Ranawat CS. Cement-within-cement revision hip arthroplasty. *J Bone Joint Surg Br*. 1993;75B:869–71.
- Rosenstein A, MacDonald W, Iliadis A, McLardy-Smith P. Revision of cemented fixation and cement – bone interface strength. *Proc Inst Mech Eng H*. 1992;206:47–9.
- Duncan WW, Hubble MJW, Howell JR, Whitehouse SL, Timperley AJ, Gie GA. Revision of the cemented femoral stem using a cement-in-cement technique: a five- to 15-year review. *J Bone Joint Surg Br*. 2009;91B:577–82.
- Briant-Evans TW, Veeramootoo D, Tsiridis E, Hubble MJW. Cement-in-cement stem revision for Vancouver type B periprosthetic femoral fractures after total hip arthroplasty. A 3-year follow-up of 23 cases. *Acta Orthop Scand*. 2009;80(5):548–52.
- Wroblewski BM. 15-21-year results of the Charnley low-friction arthroplasty. *Clin Orthop*. 1986;211:30–5.
- Bradford MS, Paprosky WG. Acetabular defect classification: a detailed radiographic approach. *Semin Arthroplasty*. 1995;6:76–85.
- Nelson CL. Cemented cup revisions. *Am J Orthop*. 2002;31(8):479–80.
- Toossi N, Adeli B, Timperley AJ, Haddad FS, Maltenfort M, Parvizi J. Acetabular components in total hip arthroplasty: is there evidence that cementless fixation is better? *J Bone Joint Surg Am*. 2013;95A:168–74.
- Morshed S, Bozic KJ, Ries MD, Malchau H, Colford Jr JM. Comparison of cemented and uncemented fixation in total hip replacement: a meta-analysis. *Acta Orthop Scand*. 2007;78(3):315–26.
- DiFazio FA. The current status of acetabular fixation in total hip replacement. *Orthop Rev*. 1992;21(9):1067–71.
- Slooff TJ, Schimmel JW, Buma P. Cemented fixation with bone grafts. *Orthop Clin North Am*. 1993;24(4):667–77.
- Gross AE. Restoration of acetabular bone loss 2005. *J Arthroplasty*. 2006;21(S1):117–20.
- Gross AE. Revision arthroplasty of the acetabulum with restoration of bone stock. *Clin Orthop*. 1999;369:198–207.
- Haverkamp D, De Man FH, Slegt R, Besselaar PP, Marti RK. Cemented hip revision surgery in severe acetabular defects using a semirigid acetabular reinforcement ring—a 5- to 25-year follow-up study. *J Arthroplasty*. 2009;24(2):246–55.
- Oakes DA, Cabanela ME. Impaction bone grafting for revision hip arthroplasty: biology and clinical applications. *JAAOS*. 2006;14(11):620–8.
- Buttaro MA, Comba F, Pusso R, Piccaluga F. Acetabular revision with metal mesh, impaction bone grafting, and a cemented cup. *Clin Orthop*. 2008;466:2482–90.
- Schreurs BW, Bolder SB, Gardeniers JW, Verdonchot N, Slooff TJ, Veth RP. Acetabular revision with impacted morsellised cancellous bone grafting and a cemented cup. A 15- to 20-year follow-up. *J Bone Joint Surg Br*. 2004;86B:492–7.
- Schreurs BW, Luttjeboer J, Thien TM, de Waal Malefijt MC, Buma P, Veth RP, Slooff TJ. Acetabular revision with impacted morselized cancellous bone graft and a cemented cup in patients with rheumatoid arthritis. A concise follow-up, at eight to nineteen years, of a previous report. *J Bone Joint Surg Am*. 2009;91A:646–51.
- Kummer FJ, Adams MC, Dicesare PE. Revision of polyethylene acetabular liners with a cemented polyethylene cup: a laboratory study. *J Arthroplasty*. 2002;17(8):1055–7.
- Padgett DE, Kull L, Rosenberg A, Sumner DR, Galante JO. Revision of the acetabular component without cement after total hip arthroplasty. *J Bone Joint Surg Am*. 1993;75A:663–73.
- Harris WH. Reconstruction at a high hip centre in acetabular revision surgery using a cementless acetabular component. *Orthopaedics*. 1998;21:991–2.
- Pulido L, Rachala SR, Cabanela ME. Cementless acetabular revision: past, present, and future. Revision total hip arthroplasty: the acetabular side using cementless components. *Int Orthop*. 2011;35:289–98.
- Katz RP, Callaghan JJ, Sullivan PM, Johnston RC. Long-term results of revision total hip arthroplasty with improved cementing technique. *J Bone Joint Surg Br*. 1997;79B:322–6.

33. Lie SA, Havelin LI, Furnes ON, Engesaeter LB, Vollset SE. Failure rates for 4762 revision total hip arthroplasties in the Norwegian Arthroplasty Register. *J Bone Joint Surg Br.* 2004;86B:504–9.
34. Marti RK, Schuller HM, Besselaar PP, et al. Results of revision of hip arthroplasty with cement: a five to fourteen year follow up study. *J Bone Joint Surg Am.* 1990;72A:346–54.
35. Dunbar MJ, Blackley HR, Bourne RB. Osteolysis of the femur: principles of management. *Instr Course Lect.* 2001;50:197–209.
36. Pellici PM, Salvati EA, Robinson HJ. Mechanical failure in total hip replacement requiring reoperation. *J Bone Joint Surg Am.* 1979;61A:28–32.
37. Holt G, Hook S, Hubble M. Revision total hip arthroplasty: the femoral side using cemented implants. *Int Orthop.* 2011;35(2):267–73.
38. Nelson CL. Cemented femoral revision: technique and outcome. *Am J Orthop.* 2002;31(4):187–9.
39. Raut VV, Siney PD, Wroblewski BM. Revision for aseptic stem loosening using the cemented Charnley prosthesis. *J Bone Joint Surg Br.* 1995;77B:23–7.
40. Weber K, Callaghan J, Goetz D, et al. Revision of a failed cemented total hip prosthesis with insertion of an acetabular component with cement and a femoral component with cement. A five to eight year follow up study. *J Bone Joint Surg Am.* 1996;78A:982–94.
41. Mulroy WF, Harris WH. Revision total hip arthroplasty with use of so called second generation cementing techniques for aseptic loosening of the femoral component. A fifteen year average follow up study. *J Bone Joint Surg Am.* 1996;78A:325–30.
42. McLaughlin JR, Harris WH. Revision of the femoral component of a total hip arthroplasty with the calcar replacement femoral component. Results after a mean of 10.8 years postoperatively. *J Bone Joint Surg Am.* 1996;78A:331–9.
43. Hultmark PP, Karrholm J, Stromberg C, et al. Cemented first time revisions of the femoral component. *J Arthroplasty.* 2000;15:551–61.
44. Harris WH, Crothers O, Oh J. Total hip replacement and femoral head bone grafting for severe acetabular deficiency in adults. *J Bone Joint Surg Am.* 1977;59A:752–63.
45. Hirst P, Esser M, Murphy JC, et al. Bone grafting for protrusion acetabuli during total hip replacement. *J Bone Joint Surg Br.* 1987;69B:229–36.
46. Mulroy RD, Harris WH. Failure of acetabular autogenous grafts in total hip arthroplasty. *J Bone Joint Surg Am.* 1990;72A:1536–43.
47. Roffman M, Silbermann M, Mendes D. Incorporation of bone graft covered with methyl-methacrylate onto the acetabular wall. *Acta Orthop Scand.* 1983;54:580–6.
48. Schimmel JW, Buma P, Versleyen D, et al. Acetabular reconstruction with impacted morselized cancellous bone grafts in cemented revision hip arthroplasty: a histological and biomechanical study on the goat. *J Arthroplasty.* 1998;13:438–48.
49. Schreurs BW, Buma P, Huiskes R, et al. A technique for using impacted trabecular allografts in revision surgery with cemented stems. *Acta Orthop Scand.* 1994;65:267–75.
50. Schreurs BW, Huiskes R, Buma P, et al. Biomechanical and histological evaluation of a hydroxyapatite-coated titanium femoral stem fixed with an intramedullary morselized bone grafting technique: an animal experiment on goats. *Biomaterials.* 1996;17:1177–86.
51. Buma P, Schreurs BW, Verdonschot N. Skeletal tissue engineering: from in vitro studies to large animal models. *Biomaterials.* 2004;25:1487–95.
52. van der Donk S, Weernink T, Buma P, et al. Rinsing allografts improves bone and tissue ingrowth. *Clin Orthop.* 2003;408:302–10.
53. Griffon DJ, Dunlop DG, Howie CR, Pratt JN, Gilchrist TJ, Smith N. An ovine model to evaluate the biologic properties of impacted morselized bone graft substitutes. *J Biomed Mater Res.* 2001;56(3):444–51.
54. de Stroet MA, Gardeniers JW, Verdonschot N, Rijnen WH, Slooff TJ, Schreurs BW. Femoral component revision with use of impaction bone-grafting and a cemented polished stem: a concise follow-up, at fifteen to twenty years, of a previous report. *J Bone Joint Surg Am.* 2012;94A:1731–4.
55. Iwase T, Otsuka H, Katayama N, Fujita H. Impaction bone grafting for femoral revision hip arthroplasty with Exeter Universal stem in Japan. *Arch Orthop Trauma Surg.* 2012;132(10):1487–94.
56. Patil N, Hwang K, Goodman SB. Cancellous impaction bone grafting of acetabular defects in complex primary and revision total hip arthroplasty. *Orthopedics.* 2012;35(3):306–12.
57. Busch VJ, Gardeniers JW, Verdonschot N, Slooff TJ, Schreurs BW. Acetabular reconstruction with impaction bone-grafting and a cemented cup in patients younger than fifty years old: a concise follow-up, at twenty to twenty-eight years, of a previous report. *J Bone Joint Surg Am.* 2011;93A:367–71.
58. Ornstein E, Linder L, Ranstam J, Lewold S, Eisler T, Torper M. Femoral impaction bone grafting with the Exeter stem – the Swedish experience: survivorship analysis of 1305 revisions performed between 1989 and 2002. *J Bone Joint Surg Br.* 2009;91B:441–6.
59. Cross M, Bostrom M. Cement mantle retention: filling the hole. *Orthopedics.* 2009;32(9).
60. Leonidou A, Pagkalos J, Luscombe J. Cement-in-cement acetabular revision with a constrained tripolar component. *Orthopedics.* 2012;35(2):e255–8.
61. Mandziak DG, Howie DW, Neale SD, McGee MA. Cement-within-cement stem exchange using the collarless polished double-taper stem. *J Arthroplasty.* 2007;22(7):1000–6.
62. Greenwald AS, Narten NC, Wilde AH. Points in the technique of recementing in the revision of an implant arthroplasty. *J Bone Joint Surg Br.* 1978;60B:107–10.
63. Weinrauch P, Bell C, Wilson L, Goss B, Lutton C, Crawford R. Shear properties of bilaminar polymethylmethacrylate cement mantles in revision hip joint arthroplasty. *J Arthroplasty.* 2007;22:394–403.

64. Li PL, Ingle PJ, Dowell JK. Cement-within-cement revision hip arthroplasty; should it be done? A biomechanical study. *J Bone Joint Surg Br.* 1996;78B:809–11.
65. Dang K, Pelletier MH, Walsh WR. Factors affecting flexural strength in cement within cement revisions. *J Arthroplasty.* 2011;26(8):1540–8.
66. Brogan K, Charity J, Sheeraz A, Whitehouse SL, Timperley AJ, Howell JR, Hubble MJ. Revision total hip replacement using the cement-in-cement technique for the acetabular component: technique and results for 60 hips. *J Bone Joint Surg Br.* 2012;94B:1482–6.
67. Lieberman JR. Cemented femoral revision, lest we forget. *J Arthroplasty.* 2005;20:72–4.
68. Richards CJ, Duncan CP, Crawford RW. Cement-in-cement femoral revision for the treatment of highly selected vancouver B2 periprosthetic fractures. *J Arthroplasty.* 2011;26(2):335–7.
69. Keeling P, Prendergast PJ, Lennon AB, Kenny PJ. Cement-in-cement revision hip arthroplasty: an analysis of clinical and biomechanical literature. *Arch Orthop Trauma Surg.* 2008;128(10):1193–9.
70. McCallum JD, Hozack WJ. Recementing a femoral component into a stable cement mantle using ultrasonic tools. *Clin Orthop.* 1995;319:232.
71. Beckmann J, Luring C, Springorum R, Kock FX, Grifka J, Tingart M. Fixation of revision TKA: a review of the literature. *Knee Surg Sports Traumatol Arthrosc.* 2011;19:872–9.
72. Bozic KJ, Kurtz SM, Lau E, Ong K, Chiu V, Vail TP, Rubash HE, Berry DJ. The epidemiology of revision total knee arthroplasty in the United States. *Clin Orthop.* 2010;468:45–51.
73. Ferhing TK, Odum S, Olekson C, Griffin WL, Mason JB, McCoy TH. Stem fixation in revision total knee arthroplasty: a comparative analysis. *Clin Orthop.* 2003;416:217–24.
74. Al W, Trousdale RT, Rand JA, Hanssen AD. Cemented long-stem revision total knee arthroplasty. *J Arthroplasty.* 2003;18:592–9.
75. Haas SB, Insall JN, Montgomery 3rd W, Windsor RE. Revision total knee arthroplasty with the use of modular components with stems inserted without cement. *J Bone Joint Surg Am.* 1995;77A:1700–7.
76. Mabry TM, Hanssen AD. The role of stems and augments for bone loss in revision knee arthroplasty. *J Arthroplasty.* 2007;22:56–60.
77. Peters CL, Erickson JA, Gilliland JM. Clinical and radiographic results of 184 consecutive revision total knee arthroplasties placed with modular cementless stems. *J Arthroplasty.* 2009;24:48–53.
78. Wood GC, Naudie DD, MacDonald SJ, McCalden RW, Bourne RB. Results of press fit stems in revision knee arthroplasty. *Clin Orthop.* 2009;467:810–7.
79. Marby TM, Vessely MB, Schleck CD, Harmsen WS, Berry DJ. Revision total knee arthroplasty with modular cemented stems: long term follow up. *J Arthroplasty.* 2007;22:100–5.
80. Whiteside LA. Cementless fixation in revision total knee arthroplasty. *Clin Orthop.* 2006;446:140–8.
81. Jazwari LM, Bai B, Kummer FJ, Hiebert R, Stuchin SA. The effect of stem modularity and mode of fixation on tibial component stability in revision total knee arthroplasty. *J Arthroplasty.* 2009;16:759–67.
82. Skwara A, Figied J, Knott T, Paletta JR, Fuchs-Winkelmann S, Tibesku CO. Primary stability of tibial components in TKA: in vitro comparison of two cementing techniques. *Knee Surg Sports Traumatol Arthrosc.* 2009;17:1199–205.
83. Completo A, Fonseca F, Simoes JA. Strain shielding in proximal tibia of stemmed knee prosthesis: experimental study. *J Biomech.* 2008;41:560–6.
84. Peters CL, Graig MA, Mohr RA, Bachus KN. Tibial component fixation with cement: full-versus surface cementation technique. *Clin Orthop.* 2003;409:158–68.
85. Completo A, Simoes JA, Fonseca F. Revision total knee arthroplasty: the influence of femoral stems in load shearing and stability. *Knee.* 2009;16:275–9.
86. Kim YH, Kim JS. Revision total knee arthroplasty with use of a constrained condylar knee prosthesis. *J Bone Joint Surg Am.* 2009;91A:1440–7.
87. Bottner F, Laskin R, Windsor RE, Haas SB. Hybrid component fixation in revision total knee arthroplasty. *Clin Orthop.* 2006;446:127–31.
88. Peters CL, Erickson J, Kloepper RG, Mohr RA. Revision total knee arthroplasty with modular components inserted with metaphyseal cement and stems without cement. *J Arthroplasty.* 2005;20:302–8.
89. Shannon BD, Klassen JF, Rand JA, Berry DJ, Trousdale RT. Revision total knee arthroplasty with cemented components and uncemented intramedullary stems. *J Arthroplasty.* 2003;18:27–32.
90. Gofton WT, Tsigaras H, Butler RA, Patterson JJ, Barrack RL, Rorabeck CH. Revision total knee arthroplasty: fixation with modular stems. *Clin Orthop.* 2002;404:158–68.
91. Murray PB, Rand JA, Hanssen AD. Cemented long stem revision total knee arthroplasty. *Clin Orthop.* 1994;309:116–23.

Cementless Fully Porous-Coated Implant-Bone Interface in Revision Total Hip Arthroplasty

13

George A. Macheras, Stefanos D. Koutsostathis,
and Spyridon P. Galanakos

Introduction

Undoubtedly, major joint arthroplasty is one of the surgical success achievements of the twentieth century. As demand for primary total hip and knee arthroplasty (THA, TKA) is increasing, the burden of revision arthroplasties is projected to swell concomitantly. Surgeons are increasingly using cementless implants in joint revision surgery because of several reports of a high incidence of loosening in cemented fixation.

Despite the great progress that has been achieved in orthopedic biomaterials, fixation of implants to the host bone in revision surgery remains a problem. Mismatch of Young's moduli of the biomaterials and the surrounding bone has been identified as a major reason for implant loosening following stress shielding of bone [1–3]. However, the implanted material must be strong and durable enough to withstand the physiological loads placed upon it over the years. A suitable balance between strength and stiffness has to be

found to best match the behavior of bone. One consideration to achieve this has been the development of materials that exhibit substantial surface or total bulk porosity in medical applications. Porosity is defined as the percentage of void space in a solid, and it is a morphological property independent of the material. Porous metals with an interconnected pore structure are of particular interest for orthopedic implant applications due to their potential ability to facilitate tissue ingrowth. Pores are necessary for tissue formation, because they allow migration and proliferation of cells, as well as vascularization. In addition, a porous surface improves mechanical interlocking between the implant biomaterial and the surrounding natural tissue, providing greater mechanical stability at this critical interface [4–12].

Using cementless implants in revision arthroplasty requires maximized fitting, immediate press-fit stability, control of axial and rotational stability, and optimal bone remodeling for a long period of time. Many surgical options have been reported, including proximal modular and non-modular porous-coated implants, extensively porous coated with cylindrical or tapered distal geometries, impaction grafting with cemented stems, and structural proximal femoral allografts [13].

G.A. Macheras, MD, DSc (✉)
S.P. Galanakos, MD, DSc
Fourth Orthopedic Department, KAT Hospital,
2 Nikis Str, 14561 Athens, Greece
e-mail: gmacheras@gmail.com;
spyros_galanakos@yahoo.gr

S.D. Koutsostathis, MD
Second Orthopedic Department,
Mitera General Hospital, 6 Erythrou
Stavrou Str, 15123 Athens, Greece
e-mail: skoutsostathis@mitera.gr

A Historical Overview

Greenfield received the first patent for the bone ingrowth fixation concept in the late 1900s with his metallic cage-like framework for an artificial

tooth root [9]. He stated that bone would grow into the frame over time and, therefore, be held firmly in position. Investigations initiated in the late 1940s sought porous materials that might be used to fill defects in soft tissue. Design specifications included inertness, resiliency, softness, and strength for porous implants in soft tissue. In the 1950s, investigations into porous polyvinyl sponges in bone reconstruction and in autogenous grafting procedure augmentation were undertaken [14]. Polyurethane and porous polytetrafluoroethylene (Teflon) were analyzed, and the effect of pore size on bone ingrowth was studied in the late 1950s and early 1960s [15]. In 1963, Smith introduced cerosium, a porous ceramic-plastic composite. This was the first porous material that demonstrated sufficient mechanical strength to be used in load-bearing applications in orthopedics [16].

The late 1960s and early 1970s was a burgeoning era in the field of porous coatings. Hulbert appreciated the impact of pore size and material strength in promoting bone ingrowth [17]. In 1968, Hirschhorn and Reynolds were the first to report on the manufacturing of a porous metal as an implant material [18]. The fabrication of a porous cobalt–chromium alloy was performed utilizing powder metallurgy techniques. One year later, Lueck, Galante, and Rostoker described the development of a porous, commercially pure titanium fiber composite material [19]. In the 1970s, Welsh, Pilliar, and Cameron seriously investigated porous cobalt–chromium, and this effort was subsequently continued by Bobyn et al. [20, 21]. From their work, a sintering process was developed that eventually laid the groundwork for the cobalt–chromium (Co–Cr) alloy coatings used today [22]. The surface of most cementless implants during the 1970s was smooth, to which strong adherence to bone could not be expected, and a macro lock implant with a window or fin was inserted into the bone by press fitting. The outcomes of these smooth-surface-type cementless THAs (including bipolar-type femoral prosthesis) were poor, causing aseptic loosening several years after surgery, and many cases required revision surgery [23].

The first porous cobalt–chromium prostheses had sintered microspheres of cobalt–chromium alloy, approximately 100 μm in diameter. Previous

investigations had shown that porous coatings produced with these particles yielded pores approximately 50–150 μm in diameter. Porous materials with these characteristics had been found in earlier animal studies to accommodate bone ingrowth. However, investigators believed that the pore size of the coating might be too small to maintain bone as the prosthesis was being loaded. They showed that the considerable difference in the elastic modulus of bone and cobalt–chromium alloy would produce a differential strain at the interface, and they estimated that the movement of the stem relative to the bone would be approximately 25 μm . This displacement would therefore decrease the effective pore width of the prosthesis from 50 to 25 μm , and they noted that this probably would be too small to support bone ingrowth in most cases. Therefore, they said it is important that the pore size be increased [2, 22].

Properties of an Ideal Porous Coating

There are several properties that are important in creating an ideal porous coating. First, the micro-/macrostructure of the coating should resemble cancellous bone with an open-cell porous structure. Moreover, the ideal coating would possess a modulus of elasticity similar to that of cortical and/or cancellous bone, as well as a high surface coefficient of friction. The remaining properties of an ideal coating include excellent biocompatibility, a relative ease and low cost of manufacture, a reliable clinical history, a precise and reproducible insertion instrumentation, a bioactivity of the metal surface, and a high level of porosity (>60%). As a result, the ideal coating would be more biologically compatible, achieving earlier and increased levels of bone ingrowth in vivo [14].

Optimal Pore Sizes for Bone

Apart from the work investigating the minimum requirement of pore size, many researchers have explored pore sizes above 100 μm in order to define optima for bone-related outcomes. Porous

blocks of hydroxyapatite with different pore sizes (106–212, 212–300, 300–400, 400–500 and 500–600 μm) were compared when implanted subcutaneously in rats [24, 25]. Alkaline phosphatase activity, osteocalcin content, and new bone formation were higher for the 300–400 μm pore size. Onset of bone remodeling was delayed in surface laser-textured titanium alloy (Ti–6Al–4 V) with 100 μm pores versus implants with 200 and 300 μm pores that were implanted in distal femoral cortex of rabbits [24]. Although the 300 μm pore implants had the highest percentage of lamellar bone, their osseointegration was slower than the 200 μm pore size implants based on the lower percentages of total (within-pore and surface bone–implant) contact. Hydroxyapatite scaffolds with small (90–120 μm) and large tunnel (350 μm) diameters were used for BMP-2 delivery and were implanted subcutaneously in rats [26, 27]. In small diameter tunnels, chondrogenesis occurred before osteogenesis; in contrast, in tunnels with large diameter, bone was formed directly. The enhanced vascularization that was observed in tunnels with the larger diameters resulted in higher oxygen tension and supply of nutrients, conditions that favored direct osteogenesis.

Mechanical Properties of Porous Biomaterials

In spite of the great progress associated with the design of bone implants through computational bone adaptation models, the inclusion of appropriate interface bone-implant conditions is still an open problem. However, the trade-off of better biological properties due to higher porosity is diminished mechanical strength, which defines a practical upper limit for pore size and porosity. Initial stress concentrations at pores decrease flexural strength, lower resistance to fatigue, and increase wear [28, 29]. Studies have shown that both Co–Cr alloys and Ti–6Al–4 V alloys experience drastic reductions in fatigue strengths when fabricated as porous coatings on solid core structures [30, 31]. It has been shown that the high cycle fatigue strength of porous-coated Ti–6Al–4 V alloy is approximately one-third that of the solid

alloy equivalent shape, probably even less in fully porous matrices [32]. The bond sites between the coatings and implant have irregular geometries that can act as stress concentrations. This is sometimes referred to as the notch effect. This notch effect is a localized condition that affects implant strength in the region of the porous coating [33]. Cook et al. showed that an approximately 15 % improvement in fatigue properties of porous Ti–6Al–4 V could be achieved through post-sintering heat treatments that produce microstructures that are more resistant to crack initiation and propagation [34]. Ishikawa and Asaoka concluded that pressurized curing increases the mechanical strength of calcium phosphate cements by decreasing porosity [35]. Interfacial integrity between particles and matrix is the key for good mechanical properties. Sunnegardh et al. observed a similar problem for calcium aluminate cement [36]. Its heterogeneous microstructure and surface porosity limited its polishability, compared to resin composite and polyacid-modified resin composite [37]. Increasing the pore size from 45–150 to 300–600 μm increased the elastic modulus (3.1–7.8 MPa) but did not affect yield strength in scaffolds produced by photopolymerization of a multifunctional lactic-acid-based oligomer created by grafting 10 lactic acid units on each side of a di(ethylene glycol) core. The porosity of these scaffolds was 80 %, since lower porosity resulted in less interconnected pores [38] and higher porosity to scaffolds with low mechanical properties [39].

Implant stability is not only a function of strength but also depends on the fixation established with surrounding tissues. A major problem concerning metallic implants in orthopedic surgery is the mismatch of Young's modulus between bone (10–30 GPa) and bulk metallic materials (between 110 GPa for Ti and 230 GPa for Co–Cr alloys). Due to this mechanical mismatch, bone is insufficiently loaded and becomes stress shielded, which eventually leads to bone resorption [3]. Porous metals represent a promising means of reducing stiffness mismatch and avoiding stress-shielding effects. To overcome the mechanical limitations of porous materials, novel composite materials have been investigated. Chitosan sponges with 100 μm pores were formed inside hydroxyapatite/tricalcium phosphate scaffolds with macropores

(300–600 μm), and both compressive modulus and yield stress increased about four times [39]. Coating hydroxyapatite scaffolds (87 % porosity and 150–200 μm pore size) with a hydroxyapatite/poly(ϵ -caprolactone) composite improved the mechanical properties: higher amounts of the composite coating (more polymer) increased compressive strength (maximum 0.45 versus 0.16 MPa for no coating) and elastic modulus (maximum 1.43 versus 0.79 for no coating) [40]. Collagen scaffolds have been coated with hydroxyapatite (pores 30–100 μm , porosity 85 %), since osseointegration is enhanced by the surface formation of a bioactive apatite layer and this layer supported the attachment and proliferation of rabbit periosteal cells [41].

Coating porous-surfaced titanium implants (35 % porosity and 50–200 μm pore size) with calcium phosphate resulted in earlier and greater bone ingrowth and enhanced mechanical properties for implants retrieved from rabbit femorals [42]. Studies made on the correlation between the superelasticity behavior, the different pore size, and various heat treatment conditions of NiTi produced by the gas expansion method revealed that the NiTi with 16 % porosity exhibited an excellent combination of mechanical properties such as high strength (1,000 MPa), low Young's modulus (15 GPa), large compressive ductility (>7 %), large recoverable strains (>6 %), and high energy absorption (>30 MJ/m³) [43]. Most of current cementless THAs are bone ingrowth or bone ongrowth types. For surface processing of the bone-ingrowth-type implant, titanium (Ti) fiber mesh was adopted in the Harris/Galante-type THR, cobalt–chromium (Co–Cr) beads in the AML-type THR, and Ti plasma spray in the Mallory–Head-type THR [44].

Closed-Cell or Open-Cell Porosity

A major classification of porous metals, or metal foams, is between open-cell and closed-cell. In closed-cell foams each cell is completely enclosed by a thin wall or membrane of metal, while in open-cell foams the individual cells are interconnected, allowing tissue to infiltrate the foam and anchor it into position. Closed-cell porous metals

are usually the result of a random foaming process, in which the size, shape, and location of pores within the matrix vary, depending on the parameters of the fabrication process. The result is usually a porous material with limited porosity and, often significant, variations in pore size and shape, although careful selection of the foaming parameters can improve homogeneity [45].

It is recognized that there are three distinct types of porous implants [4]: (a) partly or fully porous-coated solid substrates, (b) fully porous materials, and (c) porous metal segment joined to a solid metallic part. There are several applications that can potentially use both porous-coated and fully porous implants. These include (1) spinal fixation devices, (2) fracture plates, (3) wires, pins and screws, (4) artificial ligament attachment implants, (5) craniofacial implants, (6) maxillofacial implants, and (7) bone graft material to fill tumor defects. Implants with solid cores and porous coating structures are more appropriate when the porous metal alone does not provide sufficient mechanical strength to sustain the physiological loads, such as in (1) dental implants and (2) joint arthroplasty implants. Different processes vary in complexity of preparation and also in the type of porous material that they produce. Thus, some processes such as casting or vapor deposition techniques tend to allow greater control over pore size, distribution, and interconnectivity. Other processes involving the decomposition of foaming agents in either molten or powder metal matrices give lower porosities and a less predictable pore distribution and interconnectivity. The former can produce open-cell geometries, whereas the latter usually result in closed-cell matrices [4].

Forms and Fabrication Techniques

The porous coatings can take various forms and require different technologies (Fig. 13.1).

Cobalt–chromium and titanium porous coatings can be produced from:

- Spherical metal powders made by gas atomization. The tiny spheres, or beads as they are frequently referred to in the medical field, are 175–250 μm (7–10 mils) in diameter. Porous

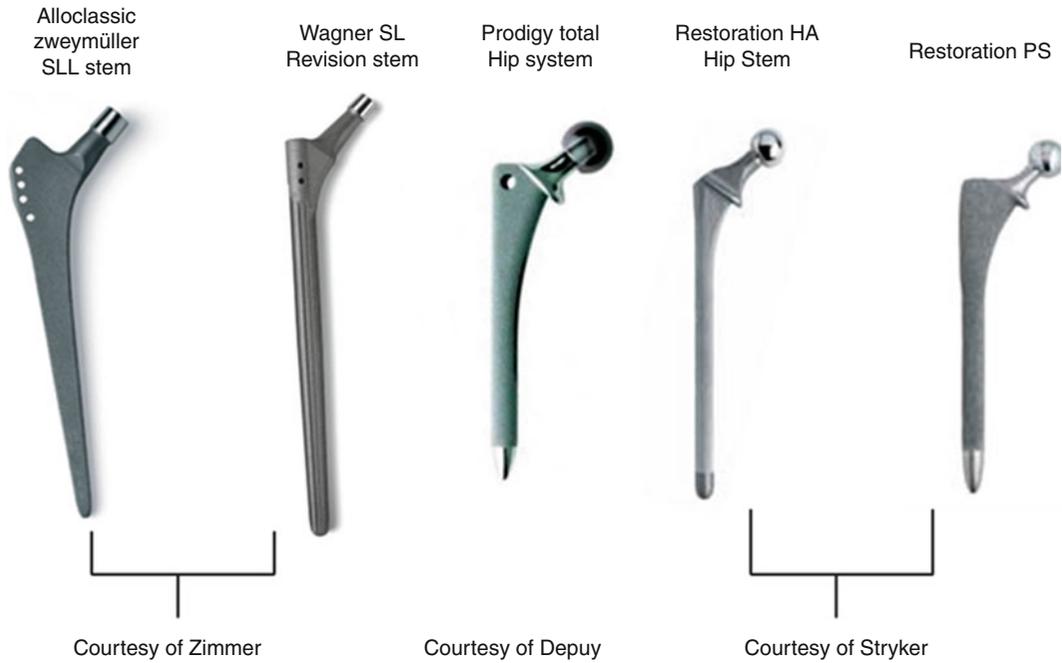


Fig. 13.1 Different examples of cementless surface implants during the decades

coatings produced from spherical powders are most frequently used on cobalt–chromium implant materials.

- Wires or fibers that are formed into porous pads. In the case of alloy beads, the manufacturer will apply the coating material using binders over specific regions of the implant surface and then attach the coating to the substrate by various high-temperature sintering stages. Generally, sintering involves heating the implant to about one-half or more of the melting temperature of the alloy to enable diffusion mechanisms to form necks that join the beads to one another and to the surface of the implant. The porous coatings so formed (35–50 vol.% porosity) are typically 500–1,000 μm (20–40 mils) thick and consist of a regular three-dimensional interconnected porous structure [46].

Traditional Metallic Coatings

The so-called classic porous metals consist of the following: cobalt–chrome-alloy sintered (Co–Cr) beads, cancellous structured titanium (CSTi),

fiber-metal mesh, and titanium plasma spray. These traditional materials generally possess low volumetric porosity in the range of 30–50 %, low frictional characteristics, and a high modulus of elasticity [47]. A plethora of implantable devices have been produced with these conventional metals and have demonstrated good to excellent long-term survival. These implants can be manufactured in a reproducible fashion and with relatively marginal cost. Their shortcomings lie in that they cannot be used for bone augmentations, bone graft substitutes, or as bulk structural materials [47]. Studies have shown that the minimum pore size for load-bearing implants, such as artificial hips and knees, should be approximately 100–150 μm (4–6 mils). The pore size of cancellous bone ranges from 400 to 500 μm (16–20 mils). Most porous coatings have pore sizes that range from 100 to 400 μm (4–16 mils) [48].

However, perceived limitations of these traditional metals include the desire for more porosity for enhanced ingrowth, low surface friction characteristics, relatively high moduli of elasticity, and availability as a coating only. This has led to the development of several highly porous, low modulus

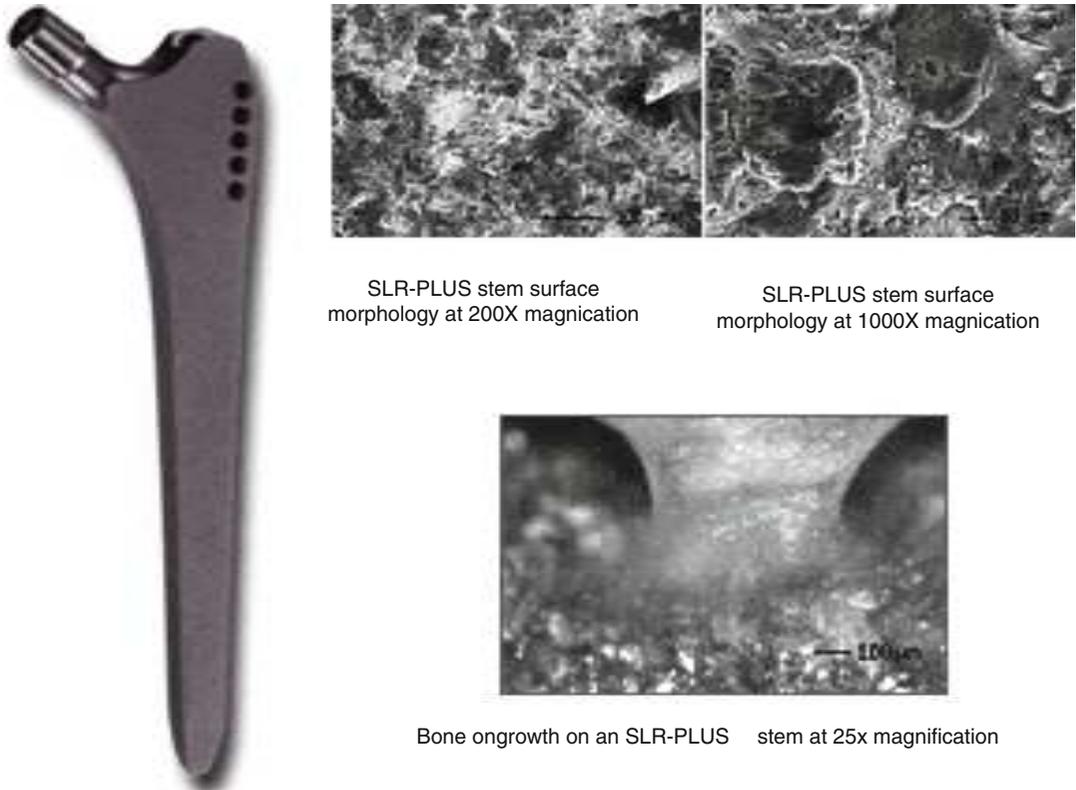


Fig. 13.2 The SLR-PLUS Zweymüller Cementless Revision Stem, showing the surface morphology and bone on growth characteristics (Courtesy of Smith & Nephew)

metals for use in orthopedic surgery, particularly in the field of total joint arthroplasty [49].

Metallic Foams

The impetus to develop open-cell, highly porous metallic foams arose from the shortcomings of the conventional porous metals. With porosities in the 30–50 % range, maximum bone ingrowth is limited and implant–bone contact must be maximized [50]. Also, these traditional materials cannot be used as bulk structural materials, for bone augmentation purposes, or as bone graft substitutes [50]. With tantalum and titanium metallic foam materials, a reticulated skeleton is created and metal is then deposited onto that surface. The characteristics of these metals are similar to those of cancellous bone, with high porosity, low modulus of elasticity, and enhanced surface coefficient of frictions, therefore providing a favorable envi-

ronment for bone ingrowth and subsequently a long-lasting bond. Polyurethane foam, reticulated vitreous carbon, and other organic substrates can be designed into various shapes and sizes for use in a wide array of orthopedic procedures [51].

Titanium-Based Coatings

Recently, encouraging long-term results have been reported for cementless tapered titanium stems and cementless cylindrical cobalt–chrome stems (Zweymüller, Fig. 13.2), CLS, Mallory–Head, Tri-Lock, anatomic medullary locking (AML) prosthesis (Fig. 13.3), Taperloc stem, anatomic hip stem, Ultralok, Spotorno stem, Omnifit, etc.) [52]. The mechanical behavior of porous titanium allows bone tissue to grow inside the structure and thus maintain a long and stable connection between replacement implant and human bone.

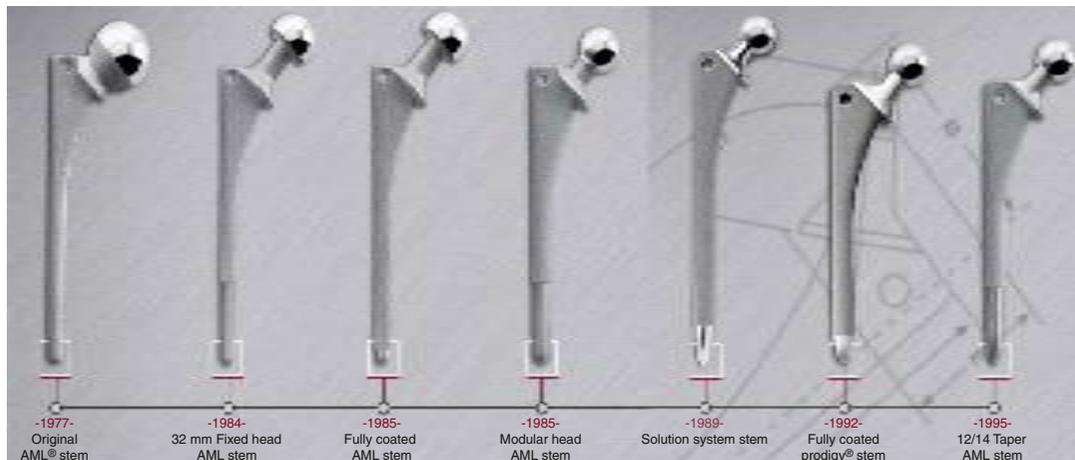


Fig. 13.3 The evolution of fully porous-coated anatomic medullary locking (AML) stem from the past to present (Courtesy of DePuy)

Characteristics of Bone Ingrowth and Interface Mechanics

By maximizing the bone-implant interface and press fitting the implant, an extensively porous-coated femoral stem can become effective in reducing femoral stem micromotion, promoting bone ingrowth and providing primary mechanical stability. Moreover, secondary stability can also be obtained through bone ingrowth in the distal portion, even when the bone quality of the proximal femur is bad and bone loss is severe [53].

Recognizing the importance of the initial mechanical stabilization of the implant, they categorized the results on the basis of initial fit. This helped to provide a quantitative substantiation of the importance of initial mechanical stabilization. In the first investigation of the 5-year performance of these porous-coated femoral stems, Engh noted prerequisites for biologic fixation [54]. He reiterated that the initial rigid fixation of the femoral stem is important and suggested that this fixation could be obtained using long prosthetic stems that could be wedged into the narrowest portion of the intramedullary cavity. He found no radiological evidence of bone resorption due to stress shielding by the relatively high-modulus implant with a fully porous-coated surface. However, initial stems, which had a diameter of approximately

10.5 mm, were relatively flexible compared with the bending stiffness of the femurs into which they were inserted. As larger-diameter stems of cobalt–chromium alloy became available to achieve canal filling of larger-diameter femoral canals, there was a higher incidence of stress shielding. These larger-diameter stems had a stiffness several times that of the femurs into which they were inserted.

As with other types of joint replacement prostheses, the clinical evaluation of porous-coated devices has been based on systems grading pain and range of motion and on radiographs. An important contribution to our understanding of the performance of porous-coated devices is the controlled and comprehensive radiographic follow-up study of porous cobalt–chromium-coated femoral stems done by Engh and Bobyn [55, 56]. The radiographs from their large numbers of patients, extending over 10 years, have yielded valuable information, in large part because of their efforts to control the orientation of the prosthesis in the radiograph and the X-ray technique. Despite the many favorable reports of the porous cobalt–chromium-coated femoral stems, problems have arisen. A report on a clinical follow-up study of ten porous cobalt–chromium-coated femoral stems implanted in 1975 revealed extensive osteolytic radiographic changes in the upper femoral shaft [57]. The authors concluded that the fixation of a fully porous-coated femoral

component by osseous ingrowth results in massive osteolytic changes in the upper femur. There is some question, however, whether these changes are due to stress-shielding effects, because similar behavior with devices of comparable design has not been observed by others. Long-term human trials with porous polymer-coated orthopedic implant have been conducted on Proplast-coated femoral stems [15, 58, 59]. Tullos et al. [59] reported 36 % failures in a series of 47 hips followed for an average of 37 months. Examination of five retrieved prostheses revealed failure through the Proplast coating, which was ingrown with fibrous tissue. They concluded that the Proplast coating had insufficient strength to withstand normal weight-bearing loads. The tensile strength of Proplast had been reported in previous studies as 1 MPa or less. The most widely reported results are those of the AML stem [60–67] with a smaller subgroup reporting on results of the solution stem [65, 66]. In a study by Paprosky et al. [65] with 170 patients at an average of 13.2 years postoperatively, the overall mechanical failure rate was 4.1 %, and failure was correlated to both canal fill and bony defects. Stable stems had a 92 % canal fill, and failure of fixation occurred more commonly with more severe defects, particularly those with less than 4 cm of diaphyseal isthmus. Paprosky and his coworkers [65] concluded that a minimum 4 cm of tight distal fit was required. Thigh pain, a frequently quoted concern in this type of prosthesis, was said to be significant in 9 % of patients. Stress shielding, another concern, was reported in association with these cases but was not considered to be a cause of subsequent problems. In addition, Glassman and Engh [67] reviewed 154 cases at an average of 9.2 years, 75 % of whom had significant metaphyseal bone loss, with a mechanical failure rate of 6.6 %.

A few years ago, porous-coated prostheses implanted in humans began to become available for postmortem histologic evaluation [56]. Investigations revealed bone ingrowth into the porous coating. In a few implants retrieved from osteoporotic patients, not only was bone ingrowth found but new bone was found within preexisting cortical porosity. This suggests that the altered strain distribution in the surrounding cortex, produced by the presence of the metallic femoral stem,

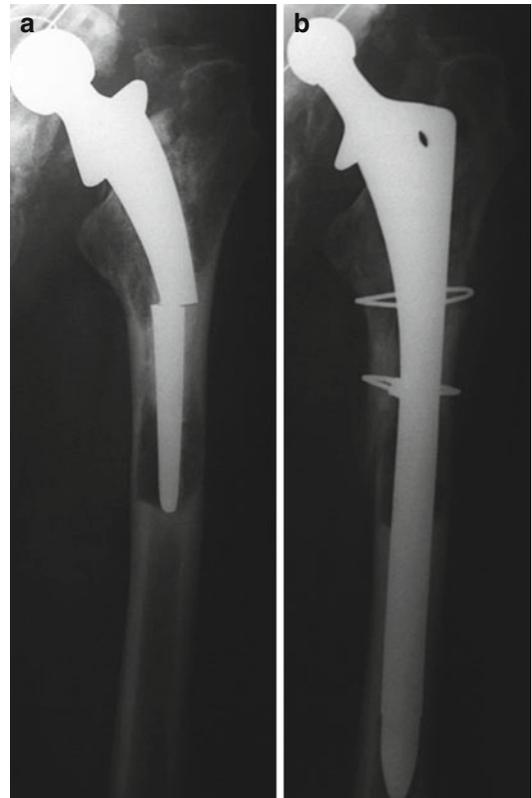


Fig. 13.4 (a) Implant structural failure in a total hip arthroplasty with extensive osteolysis and aseptic loosening, (b) 4 years following revision of the broken stem with a fully porous-coated Co–Cr femoral stem

stimulated new bone formation. The association between the measured “level with half cortical thickness” and various risk factors was investigated. Significant correlations with the age at the time of surgery, bone quality score, canal flare index, cortical ratio in the isthmus, and stem size were noted, but no apparent correlation with the time after surgery was detected [68]. Engh and Massin also reported that bone resorption progressed to the diaphysis during a period of 2–5 years after surgery in only 3 of 163 patients [69]. On the contrary, Kilgus et al. investigated cases using dual-energy X-ray absorptiometry (DEXA) and found that bone remodeling progressed for several years after surgery [70]. There is a considerable number of other recent studies which indicate satisfactory results at short-term clinical and radiographic follow-up having used extensively porous-coated femoral stems for revision of THA [65, 71–75] (Fig. 13.4).

Concerns About Porous-Coated Implants

A common assumption in the simulation of bone remodeling around cementless porous-coated prostheses is that full ingrowth applies for all the coated area. Hence, bone and stem surfaces are considered perfectly bonded during all simulation process [76, 77]. However, this assumption misrepresents both immediate and long-term postoperative realities. In the immediate postoperative situation, contact between bone and implant is scattered, and gaps up to 3 mm always exist, even after precise insertion [78]. It takes at least 1–2 weeks for bone ingrowth to occur [9]. Consequently, during this initial stage, the prosthesis behaves like a press-fitted one. On the other hand, clinical observations on retrieved femoral stem specimens showed bone ingrowth over only approximately 20 % of the available porous-coated surface which suggests that fully bonded coated interface is never achieved [79].

In the Historical Review of Porous-coated Implants by Spector M. in 1987, the author mentioned that the problems of porous-coated devices relate to the following [9]: (1) Preoperative planning and careful prosthetic selection are required to obtain sufficient canal filling and wedging to ensure initial mechanical stabilization of the device (required for bone ingrowth). (2) Surgical precision is essential for initial implant–bone contact to promote bone ingrowth. (3) Short-term results with respect to pain are less satisfactory than with cemented devices. (4) Bone ingrowth is rarely found in porous-coated tibial plateaus. (5) Stress-shielding effects resulting from biologic fixation of certain prosthetic designs lead to a greater degree of nonanatomic adaptive remodeling of bone than with cemented devices. (6) The clinical consequences of metal ion release are unknown.

To date, there are several studies in which porous-surfaced prostheses have been retrieved with minimal or no bone ingrowth present [80, 81]. Even though metals such as titanium and Co–Cr are bio-inert, they do not bond directly to bone. A fibrous layer intervenes between the implant and bone. Bioactive materials are designed to induce a specific biological activity, which can

lead to strong bonding to bone [82]. The current practice in designing porous titanium alloy implants is to avoid porous coatings on surfaces that will be subjected to significant tensile stresses in vivo [46]. Cook et al. showed that an approximately 15 % improvement in fatigue properties of porous Ti–6Al–4 V could be achieved through post-sintering heat treatments that produce microstructures that are more resistant to crack initiation and propagation [34]. Also by modeling porous-coated implants using linear elastic, plane strain finite element analysis, Wolfarth et al. predicted a doubling of fatigue strength when optimizing conventional porous geometries [32]. Mechanical properties of porous materials can be altered and optimized by controlling porosity, pore size, and shape as well as pore distribution. It is commonly accepted that, in the long term, total joint replacement is associated with adverse local and remote tissue responses that are mediated by degradation products of prosthetic materials [83]. Increased surface areas, such as in porous implants, have shown higher corrosion rates when tested in vitro compared to conventional nonporous-coated implants [84]. This has caused concerns regarding long-term safety of porous implants. Enhanced metal ion release could increase the probability of metal sensitization, and associated allergic responses in individuals could increase the susceptibility to tumor formation [85]. This matter would have to be addressed by only implanting surface-treated porous materials into the body.

The fact of failure of osseointegration with extensively porous-coated stems is not surprising. In a study by Hamilton et al. [86], the authors examined the outcome of re-revision of a failed extensively porous-coated femoral stem with yet another extensively porous-coated stem. Between 1980 and 2000, 711 femoral revisions using an extensively porous-coated device were performed. Fifteen patients (16 hips) were known to have undergone a re-revision of this femoral component using another porous-coated stem. At latest follow-up, 2 patients (3 hips) were deceased, leaving 13 patients. At a mean follow-up of 9.8 years, none of the cementless stems had required another revision (100 % survivorship), and 12 (92 %) of the 13 stems were bone ingrown based

on radiographic examination. On the contrary, a significant incidence of fracture has been reported by several authors [87–89]. Egan and DiCesare [87] reported specifically on complications associated with these stems, finding a combined incidence of complications of 44 %, with the likelihood correlated with stem length and diameter as well as with worsening bone quality. In their series of 135 cases, they reported eccentric reaming in 27 % femoral perforation in 17 % and femoral fracture in 20 %, all of which can significantly add to the morbidity of the procedure. However, the incidence of complications decreased throughout the period of the study. This finding, coupled with the lower complication rate reported by other authors with extensive experience, suggests that these complications can certainly be kept to an acceptably low level.

Newer design features such as distal slots, fluting, and bullet-shaped ends may allow a reduction in intraoperative complications such as fracture and perforation and may also decrease the incidence of thigh pain in the long term [90]. Unfortunately, the use of an extensively porous-coated femoral stem can be problematic due to stress shielding both in primary and revision surgery. The more severe the osteoporosis and the larger the diameter of a femoral stem are, the more evident the stress shielding becomes. In addition, severe stress shielding can result in poor clinical outcomes, even though mild cases can be understood as part of the bone remodeling process that does not cause clinical problems. Keaveny et al. [91] tried to identify groups of patients at risk of fatigue fracture of the prosthesis using porous coating implants and may thus jeopardize the success of the arthroplasty. The authors mentioned the following: First, to minimize the proximal loss of bone, they do not believe that porous coating of any type should be used distal to the lesser trochanter when the patient's life expectancy is longer than 20–25 years after the primary reconstruction procedure, particularly when a stem with a large diameter is to be inserted into a bone with a small diameter. Second, to prevent fatigue fracture of the prosthesis, sintered porous coating should not be used anywhere on a cobalt–chromium–alloy stem that

is less than approximately 11 mm in diameter and is to be inserted in an active or heavy patient in whom the periosteal bone is less than approximately 23 mm in diameter. While insertion of a larger stem into a larger bone may be associated with a risk of fracture of the prosthesis, depending on the level of activity and the body weight of the patient, these constraints can be relaxed if a sintered titanium alloy prosthesis is used. Taken together, these findings suggest that anatomic medullary locking prostheses with sintered porous coating are best suited for patients in whom a mid-sized stem will be implanted in a bone with a larger than average diameter [91].

Future Directions

The interest in using porous materials for orthopedic reconstructive surgery as a means of replacing autografts is of increasing interest, and the large number of scientific reports confirm this trend. For load-bearing orthopedic applications, metals have so far shown the greatest potential as the basis for such scaffolds, owing to their excellent mechanical strength and resilience when compared to alternative biomaterials, such as polymers and ceramics. The focus thereby has mainly been on applications that involve bone ingrowth into the porous scaffolds either as part of a coating or as a complete matrix. This has led to the majority of research interest to be drawn to the development of open-cell porous metals, although arguably, great potential lies within the use of closed-cell porous metals, too. In such cases, bone ingrowth would not be the major interest but rather the reduction of material stiffness that has been linked to early implant loosening following processes of bone loss due to stress shielding [92]. Closed-cell porous metals could serve as materials for the fabrication of implant stems and have either a porous-coated surface to facilitate bone ingrowth onto their surfaces for stem fixation or have polished or matt solid surfaces that could be used with regular bone cement for their fixation in the bone matrix. The successful employment of both open-cell and closed-cell porous metals relies on the same requirement that

is a suitable fabrication method that can ensure homogeneously distributed pores of similar size and shape and cell walls of consistent thickness with levels of purity and absence of cracks or crevices that can develop into potential material failure sites [4].

It is only now that researchers are starting to understand the combination of parameters that need to be addressed for the successful implementation of porous metals *in vivo*. This is a multifactorial design process that has to consider understanding of material properties, such as corrosion resistance, passivation levels, and potential for bone adherence; mechanical characteristics including stress–strain behavior of the porous metal and its match to those of bone under various loading conditions [93]; and, finally, parameters involving pore size, shape, and distribution that will optimize fatigue strength and—in case of open-cell foams—bone ingrowth.

Although great progress has been made with the various available fabrication processes in manufacturing both closed-cell and open-cell porous structures, certain limitations continue to exist. Most current techniques that use foaming agents, either in solid state sintering processes or in molten metal techniques, have limited control over pore distributions and densities and are only capable of achieving these over large areas rather than at specific desired locations in the matrix [4].

Engineering pore distributions to match the mechanical properties of bone is commonly accepted to be the next major improvement in the design of open-cell porous materials [94]. This means that a technique needs to be available that will allow the precise positioning of pores in the 3-D matrix, their interconnectivity, shape, and size. Recently, the coating of implants has engendered much interest in order to improve osseointegration and prevent adverse tissue reactions such as infection, inflammation, the foreign body response, and other events [95]. In addition, there is a great deal of interest in osteoinductive coatings to optimize the implant-tissue interface and enhance osseointegration, especially in more challenging clinical scenarios in which the host bone is not optimal (e.g., previous local infection or irradiation, extensive trauma to bone and soft tissue) [95]. Various growth

factors and other molecules, primarily proteins, are currently being examined as additives to coatings [96, 97]. This research is still in the experimental phase, as there are numerous questions concerning which molecules should be incorporated in the coating and the method, dosage, and optimal time course for delivery. Finally, coated implants must be shown to be safe, efficacious, and cost-effective prior to subsequent adoption and widespread usage.

References

1. Robertson DM, Pierre L, Chahal R. Preliminary observations of bone ingrowth into porous materials. *J Biomed Mater Res.* 1976;10:335–44.
2. Cameron HU, Macnab I, Pilliar RM. A porous metal system for joint replacement surgery. *Int J Artif Organs.* 1978;1:104–9.
3. Head WC, Bauk DJ, Emerson Jr RH. Titanium as the material of choice for cementless femoral components in total hip arthroplasty. *Clin Orthop Relat Res.* 1995;311:85–90.
4. Ryan G, Pandit A, Apatsidis DP. Fabrication methods of porous metals for use in orthopaedic applications. *Biomaterials.* 2006;27(13):2651–70.
5. Homsy CA, Cain TE, Kessler FB, Anderson MS, King JW. Porous implant systems for prosthesis stabilization. *Clin Orthop.* 1972;89:220–35.
6. Bauer TW, Schils J. The pathology of total joint arthroplasty. I. Mechanisms of implant fixation. *Skeletal Radiol.* 1999;28:423–32.
7. Galante JO, Jacobs J. Clinical performances of ingrowth surfaces. *Clin Orthop Relat Res.* 1992;276:41–9.
8. Pilliar RM. Porous surfaced endosseous dental implants: fixation by bone ingrowth. *Univ Tor Dent J.* 1988;1:10–5.
9. Spector M. Historical review of porous-coated implants. *J Arthroplasty.* 1987;2:163–77.
10. Pilliar RM. Porous-surfaced metallic implants for orthopedic applications. *J Biomed Mater Res.* 1987;21:1–33.
11. Moore AT. Metal hip joint: a new self-locking vitalium prosthesis. *South Med J.* 1952;45:1015.
12. Morscher EW. Cementless total hip arthroplasty. *Clin Orthop Relat Res.* 1985;181:76.
13. Dumbleton J, Manley MT. Hydroxyapatite-coated prostheses in total hip and knee arthroplasty. *J Bone Joint Surg Am.* 2004;86A:2526–40.
14. Levine BR, Fabi DW. Porous metals in orthopedic applications – a review [Poröse Metalle in orthopädischen Anwendungen. Eine Übersicht.]. *Mat-wiss u Werkstofftech.* 2010;41:1001–10.
15. Sadr B, Arden GP. A comparison of the stability of proplast-coated and cemented Thompson prostheses in the treatment of subcapital femoral fractures. *Injury.* 1977;8(3):234–7.

16. Smith L. Ceramic-plastic material as a bone substitute. *Arch Surg.* 1963;87:653–61.
17. Hulbert SF, Cooke FW, Klawitter JJ, Leonard RB, Sauer BW, Moyle DD, Skinner HB. Attachment of prostheses to the musculoskeletal system by tissue ingrowth and mechanical interlocking. *J Biomed Mater Res.* 1973;7(3):1–23.
18. Hirschhorn JS, Reynolds JT. Powder metallurgy fabrication of cobalt alloy surgical implant materials. In: Hirschhorn JS, Reynolds JT, Korstoff E, editors. *Research in dental and medical materials.* New York: Plenum Press; 1969. p. 137.
19. Lueck RA, Galante J, Rostoker W, Ray RD. Development of an open pore metallic implant to permit attachment to bone. *Surg Forum.* 1969;20:456–7.
20. Petersen CD, Miles JS, Solomons C, Predecki PK, Stephan JS. Union between bone and implants of open pore ceramic and stainless steel: a histologic study. In: Paper presented at The Orthopaedic Research Society, New York, 17 Jan 1969.
21. Welsh RP, Pilliar RM, Macnab I. Surgical implants. The role of surface porosity in fixation to bone and acrylic. *J Bone Joint Surg Am.* 1971;53A:963–77.
22. Bobynd JD, Pilliar RM, Cameron HU, Weatherly GC. The optimum pore size for the fixation of porous-surfaced metal implants by the ingrowth of bone. *Clin Orthop.* 1980;150:263–70.
23. Kawamoto K, Hasegawa Y, Iwase T, Iwasada S, Kanamoto T, Iwata H. Failed cementless total hip arthroplasty for osteoarthritis due to hip dysplasia: a minimum five-year follow-up study. *Bull Hosp Joint Dis.* 1998;57:130–5.
24. Kuboki Y, Jin Q, Takita H. Geometry of carriers controlling phenotypic expression in BMP-induced osteogenesis and chondrogenesis. *J Bone Joint Surg Am.* 2001;83A, S10515.
25. Tsuruga E, Takita H, Itoh H, Wakisaka Y, Kuboki Y. Pore size of porous hydroxyapatite as the cell-substratum controls BMP-induced osteogenesis. *J Biochem.* 1997; 121:317–24.
26. Jin QM, Takita H, Kohgo T, Atsumi K, Itoh H, Kuboki Y. Effects of geometry of hydroxyapatite as a cell substratum in BMP-induced ectopic bone formation. *J Biomed Mater Res.* 2000;52:491–9.
27. Kuboki Y, Jin Q, Kikuchi M, Mamood J, Takita H. Geometry of artificial ECM: sizes of pores controlling phenotype expression in BMP-induced osteogenesis and chondrogenesis. *Connect Tissue Res.* 2002;43: 529–34.
28. McCabe JF, Ogden AR. The relationship between porosity, compressive fatigue limit and wear in composite resin restorative materials. *Dent Mater.* 1987;3: 9–12.
29. Huysmans MC, Lautenschlager EP, Monaghan P. The influence of simulated clinical handling on the flexural and compressive strength of posterior composite restorative materials. *Dent Mater.* 1996;12:116–20.
30. Manley MT, Kotzar G, Stern LS, Wilde A. Effects of repetitive loading on the integrity of porous coatings. *Clin Orthop.* 1987;217:293–302.
31. David HK, Paul D. A parametric study of the factors affecting the fatigue strength of porous coated Ti-6Al-4V implant alloy. *J Biomed Mater Res.* 1990; 24:1483–501.
32. Wolfarth D, Ducheyne P. Effect of a change in interfacial geometry on the fatigue strength of porous-coated Ti-6Al-4V. *J Biomed Mater Res.* 1994;28:417–25.
33. Yue S, Pilliar RM, Weatherly GC. The fatigue strength of porous-coated Ti-6% Al-4% V implant alloy. *J Biomed Mater Res.* 1984;18:1043–58.
34. Cook SD, Thongpreda N, Anderson RC, Haddad Jr RJ. The effect of post-sintering heat treatments on the fatigue properties of porous coated Ti-6Al-4V alloy. *J Biomed Mater Res.* 1988;22:287–302.
35. Ishikawa K, Asaoka K. Estimation of ideal mechanical strength and critical porosity of calcium phosphate cement. *J Biomed Mater Res.* 1995;29:1537–43.
36. Sunnegardh-Gronberg K, Peutzfeldt A, van Dijken JW. Hardness and in vitro wear of a novel ceramic restorative cement. *Eur J Oral Sci.* 2002;110:175–8.
37. Sunnegardh-Gronberg K, van Dijken JW. Surface roughness of a novel “ceramic restorative cement” after treatment with different polishing techniques in vitro. *Clin Oral Investig.* 2003;7:27–31.
38. Burdick JA, Padera RF, Huang JV, Anseth KS. An investigation of the cytotoxicity and histocompatibility of in situ forming lactic acid based orthopedic biomaterials. *J Biomed Mater Res.* 2002;63:484–91.
39. Zhang Y, Zhang M. Three-dimensional macroporous calcium phosphate bioceramics with nested chitosan sponges for load-bearing bone implants. *J Biomed Mater Res.* 2002;61:1–8.
40. Kim HW, Knowles JC, Kim HE. Hydroxyapatite/poly(epsilon-caprolactone) composite coatings on hydroxyapatite porous bone scaffold for drug delivery. *Biomaterials.* 2004;25:1279–87.
41. Wolfe MS, Dean D, Chen JE, Fisher JP, Han S, Rinnac CM, Mikos AG. In vitro degradation and fracture toughness of multilayered porous poly(propylene fumarate)/betatricalcium phosphate scaffolds. *J Biomed Mater Res.* 2002;61:159–64.
42. Tache A, Gan L, Deporter D, Pilliar RM. Effect of surface chemistry on the rate of osseointegration of sintered porous-surfaced Ti-6Al-4V implants. *Int J Oral Maxillofac Implants.* 2004;19:19–29.
43. Ryhanen J, Niemi E, Serlo W, Niemela E, Sandvik P, Pernu H, Salo T. Biocompatibility of nickel-titanium shape memory metal and its corrosion behavior in human cell cultures. *J Biomed Mater Res.* 1997;35:451–7.
44. Pulido L, Rachala SR, Cabanela ME. Cementless acetabular revision: past, present, and future. Revision total hip arthroplasty: the acetabular side using cementless implants. *Int Orthop.* 2011;35(2):289–98.
45. Körner C, Singer RF. Foaming processes for aluminium. In: Degischer HP, Kriszt B, editors. *Handbook of cellular metals.* Weinheim: Wiley-VCH Verlag; 2002. p. 8–14.
46. Pilliar RM. Porous biomaterials. In: Williams D, editor. *Concise encyclopedia of medical & dental materials.* New York: Pergamon Press; Cambridge, MA: The MIT Press; 1990. p. 312–9.

47. Bobyn JD, Stackpool GJ, Hacking SA, Tanzer M, Krygier JJ. Characteristics of bone ingrowth and interface mechanics of a new porous tantalum biomaterial. *J Bone Joint Surg Br.* 1999;81B:907–14.
48. Levine B. A new era in porous metals: applications in orthopaedics. *Adv Eng Mater.* 2008;10:788–92.
49. Yoon TR, Rowe SM, Kim MS, Cho SG, Seon JK. Fifteen- to 20-year results of uncemented tapered fully porous-coated cobalt-chrome stems. *Int Orthop.* 2008;32(3):317–23.
50. Landon GC, Galante JO, Maley MM. Noncemented total knee arthroplasty. *Clin Orthop.* 1986;205:49–57.
51. Lachiewicz PF, Soileau ES, Bryant P. Second-generation proximally coated titanium femoral component: minimum 7-year results. *Clin Orthop.* 2007;465:117–21.
52. Della Valle CJ, Berger RA, Rosenberg AG, Galante JO. Cementless acetabular revision. *Clin Orthop.* 2004;420:96–100.
53. Nourbash PS, Paprosky WG. Cementless femoral design concerns: rationale for extensive porous coating. *Clin Orthop.* 1998;355:189–99.
54. Engh CA. Hip arthroplasty with a Moore prosthesis with porous coating. A five-year study. *Clin Orthop.* 1983;176:52–66.
55. Engh CA, Bobyn JD, Matthews JG 2nd. Biologic fixation of a modified Moore prosthesis. Part I. Evaluation of early clinical results. *Hip.* 1984;95–110.
56. Engh CA, Bobyn JD. Biologic fixation of a modified Moore prosthesis. Part II. Evaluation of adaptive femoral bone modeling. *Hip.* 1984;110–32.
57. Brown IW, Ring PA. Osteolytic changes in the upper femoral shaft following porous-coated hip replacement. *J Bone Joint Surg Br.* 1985;67B:218–21.
58. Wapner KL, Morris DM, Black J. Release of corrosion products by F-75 cobalt base alloy in the rat. II: morbidity apparently associated with chromium release in vivo: a 120-day rat study. *J Biomed Mater Res.* 1986;20(2):219–33.
59. Tullos HS, McCaskill BL, Dickey R, Davidson J. Total hip arthroplasty with a low-modulus porous-coated femoral component. *J Bone Joint Surg Am.* 1984;66A:888–98.
60. Krishnamurthy AB, MacDonald SJ, Paprosky WG. 5- to 13-year follow-up study on cementless femoral components in revision surgery. *J Arthroplasty.* 1997;12(8):839–47.
61. Lawrence JM, Engh CA, Macalino GE, Lauro GR. Outcome of revision hip arthroplasty done without cement. *J Bone Joint Surg Am.* 1994;76A:965–73.
62. Lawrence JM, Engh CA, Macalino GE. Revision total hip arthroplasty. Long-term results without cement. *Orthop Clin North Am.* 1993;24(4):635–44.
63. Moreland JR, Bernstein ML. Femoral revision hip arthroplasty with uncemented, porous-coated stems. *Clin Orthop Relat Res.* 1995;319:141–50.
64. Engh CA, Culpepper 2nd WJ, Kassapidis E. Revision of loose cementless femoral prostheses to larger porous coated components. *Clin Orthop.* 1998;347:168–78.
65. Paprosky WG, Greidanus NV, Antoniou J. Minimum 10-year-results of extensively porous-coated stems in revision hip arthroplasty. *Clin Orthop Relat Res.* 1999;369:230–42.
66. Greidanus N, Antoniou J, Paprosky W. Extensively coated cementless femoral components in revision hip arthroplasty. *Surg Technol Int.* 2000;9:267–72.
67. Glassman AH, Engh CA. Cementless revision for femoral failure. *Orthopedics.* 1995;18(9):851–3.
68. Yamada H, Yoshihara Y, Henmi O, Morita M, Shiromoto Y, Kawano T, Kanaji A, Ando K, Nakagawa M, Kosaki N, Fukaya E. Cementless total hip replacement: past, present, and future. *J Orthop Sci.* 2009;14(2):228–41.
69. Engh CA, Massin P. Cementless total hip arthroplasty using the anatomic medullary locking stem. Results using a survivorship analysis. *Clin Orthop.* 1989;249:141–58.
70. Kilgus DJ, Shimaoka EE, Tipton JS, Eberle RW. Dual-energy X-ray absorptiometry measurement of bone mineral density around porous-coated cementless femoral implants: methods and preliminary results. *J Bone Joint Surg Br.* 1993;75B:279–87.
71. Walter WL, Walter WK, Zicat B. Clinical and radiographic assessment of a modular cementless ingrowth femoral stem system for revision hip arthroplasty. *J Arthroplasty.* 2006;21(2):172–8.
72. Hamilton WG, Cashen DV, Ho H, Hopper Jr RH, Engh CA. Extensively porous-coated stems for femoral revision: a choice for all seasons. *J Arthroplasty.* 2007;22(4S1):106–10.
73. Moon KH, Kang JS, Lee SH, Jung SR. Revision total hip arthroplasty using an extensively porous coated femoral stem. *Clin Orthop Surg.* 2009;1(2):105–9.
74. Mahoney OM, Kinsey TL, Asayama I. Durable fixation with a modern fully hydroxylapatite-coated long stem in complex revision total hip arthroplasty. *J Arthroplasty.* 2010;25(3):355–62.
75. Jayakumar P, Malik AK, Islam SU, Haddad FS. Revision hip arthroplasty using an extensively porous coated stem: medium term results. *Hip Int.* 2011;21(2):129–35.
76. Kerner J, Huiskes R, van Lenthe GH, Weinans H, van Rietbergen B, Engh CA, Amis AA. Correlation between pre-operative periprosthetic bone density and post-operative bone loss in THA can be explained by strain-adaptive remodelling. *J Biomech.* 1999;32(7):695–703.
77. Weinans H, Huiskes R, Grootenboer HJ. Effects of fit and bonding characteristics of femoral stems on adaptive bone remodeling. *J Biomech Eng.* 1994;116(4):393–400.
78. Schimmel JW, Huiskes R. Primary fit of the Lord cementless total hip. A geometric study in cadavers. *Acta Orthop Scand.* 1988;59(6):638–42.
79. Fernandes PR, Folgado J, Jacobs C, Pellegrini V. A contact model with ingrowth control for bone remodeling around cementless stems. *J Biomech.* 2002;35(2):167–76.
80. Collier JP, Mayor MB, Chae JC, Surprenant VA, Surprenant HP, Dauphinais LA. Macroscopic and microscopic evidence of prosthetic fixation with porous-coated materials. *Clin Orthop.* 1988;235:173–80.
81. Cook SD, Barrack RL, Thomas KA, Haddad Jr RJ. Quantitative histologic analysis of tissue growth into

- porous total knee components. *J Arthroplasty*. 1989;4S: S33–43.
82. Rawlings RD. Bioactive glasses and glass-ceramics. *Clin Mater*. 1993;14:155–79.
 83. Jacobs JJ, Skipor AK, Patterson LM, Hallab NJ, Paprosky WG, Black J, Galante JO. Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. *J Bone Joint Surg Am*. 1998;80A:1447–58.
 84. Reclaru L, Eschler PY, Lerf R, Blatter A. Electrochemical corrosion and metal ion release from Co–Cr–Mo prosthesis with titanium plasma spray coating. *Biomaterials*. 2005;26:4747–56.
 85. Black J. Systemic effects of biomaterials. *Biomaterials*. 1984;5:11–8.
 86. Hamilton WG, McAuley JP, Tabarae E, Engh Sr CA. The outcome of rerevision of an extensively porous-coated stem with another extensively porous-coated stem. *J Arthroplasty*. 2008;23(2):170–4.
 87. Egan EJ, DiCesare PE. Intraoperative complications of revision hip arthroplasty using a fully porous-coated straight cobalt-chrome femoral stem. *J Arthroplasty*. 1995;10S:S45–51.
 88. Chappell JD, Lachiewicz PF. Fracture of the femur in revision hip arthroplasty with a fully porous-coated component. *J Arthroplasty*. 2005;20(2):234–8.
 89. Sangüesa-Nebot MJ, Soriano FC, Gabarda RF, Mordt CV. Revision hip arthroplasty with a short femoral component in fractured hydroxyapatite fully coated femoral stem. *J Arthroplasty*. 2010;25(7):1168.e13–6.
 90. Taylor JW, Rorabeck CH. Hip revision arthroplasty. Approach to the femoral side. *Clin Orthop*. 1999; 369:208–22.
 91. Keaveny TM, Bartel DL. Mechanical consequences of bone ingrowth in a hip prosthesis inserted without cement. *J Bone Joint Surg Am*. 1995;77A:911–23.
 92. Kroger H, Venesmaa P, Jurvelin J, Miettinen H, Suomalainen O, Alhava E. Bone density at the proximal femur after total hip arthroplasty. *Clin Orthop*. 1998;352:66–74.
 93. Nazarian A, Stauber M, Müller R. Design and implementation of a novel mechanical testing system for cellular solids. *J Biomed Mater Res B*. 2005;73(2): 400–11.
 94. Karageorgiou V, Kaplan D. Porosity of 3D biomaterial scaffolds and osteogenesis. *Biomaterials*. 2005;26:5474–91.
 95. Goodman SB, Yao Z, Keeney M, Yang F. The future of biologic coatings for orthopaedic implants. *Biomaterials*. 2013;34(13):3174–83.
 96. Muszanska AK, Busscher HJ, Herrmann A, van der Mei HC, Norde W. Pluronic-lysozyme conjugates as anti-adhesive and antibacterial bifunctional polymers for surface coating. *Biomaterials*. 2011;32(26): 6333–41.
 97. Brohede U, Forsgren J, Roos S, Mhryanyan A, Engqvist H, Strømme M. Multifunctional implant coatings providing possibilities for fast antibiotics loading with subsequent slow release. *J Mater Sci Mater Med*. 2009;20(9):1859–67.

Cementless Tapered Fluted Implant-Bone Interface in Revision Total Joint Arthroplasty

14

Panagiotis Megas and Christos S. Georgiou

Introduction

Surgical revision of the failed total hip arthroplasty (THA) due to implant failure and osteolysis is becoming an increasingly more common surgical procedure. Even with the improvement of prosthetic designs, the number of necessary revisions will increase due to increased life expectancy as well as younger average age of initial implantation [1]. In general, revision arthroplasty has a higher complication rate than primary surgery in all types of complications [2, 3]. After loosening of a femoral component in THA, a proximal femoral defect is usually left in the proximal femur. In this poor bone environment, it is difficult to fixate a cemented or a cementless prosthesis. The proximal femoral bone loss thus continues to challenge adequate fixation and osseointegration with proximally fixed components. Cemented stems [4, 5] and proximally porous-coated ones [6, 7] have been used, but the results were unsatisfactory.

A solution seems to be fixing the stem in the femoral diaphysis, distal to the deficient bone. Long-term uncemented fixation in the diaphysis can be achieved by different methods, including extensively porous-coated stems and fluted, tapered

grit-blasted stems [6]. Uncemented extensively porous-coated stems have long-term published fixation rates and have been popular because they provide a highly effective method of femoral revision [6, 8, 9]. These stems gain rotational stability in the diaphysis from a scratch fit and axial stability from the diaphyseal scratch fit and engagement of the metaphyseal triangle and a collar [6]. An alternative strategy of uncemented diaphyseal stem fixation in revision, one that has been popularized in Europe, is the use of cementless, long, distally tapered, fluted, grit-blasted stems. Wagner [10, 11] first described the use of such a femoral component in 1987. The Wagner self-locking (SL) prosthesis (Sulzer Orthopedics, Baar, Switzerland) is made of a high-strength titanium-aluminum-niobium alloy (Protasul 100) with excellent biocompatibility (Fig. 14.1). The shaft of the prosthesis is straight with a stem-neck angle of 145° and has a conus angle of 2° and eight longitudinal ridges arranged in a circle around the stem [12]. These flutes provide rotational stability and the tapered geometry axial stability of the implant (Fig. 14.2). A grit-blasted rough titanium surface promotes bone ongrowth for long-term fixation. The stem is available in lengths of 190–385 mm. For implantation, the femur is reamed to a tapered cone. Then the fluted, tapered implant is impacted into the tapered cone of the milled diaphysis [12]. The conical design further allows an even transmission of load between the bone and the prosthesis so that the stress distribution to bone is uniform [13]. Since tapered stems are prepared by so-called line-to-line reaming and the fixation flutes cut into the bone,

P. Megas, MD, PhD, DSc (✉) • C.S. Georgiou, MD
Department of Orthopaedics
and Traumatology, University Hospital
of Patras, Rion GR-26504, Greece
e-mail: panmegas@gmail.com



Fig. 14.1 An old (*left*) and new (*right*) version of a Wagner fluted stem



Fig. 14.2 The fluted cross section of a Wagner stem

the tapered stem design allows for safer insertion with a potentially lower risk of intraoperative fracture. With cylindrical stems, the stems are oversized relative to reaming, engaged early, and require a minimum of 5 cm of adequate press fit. The last few centimeters of stem insertion therefore require a fair bit of force, which increases the potential risk of fracture [13]. The ridges are less likely to burst the femoral shaft than designs with a square or rectangular cross section. However, to create a cone for the tapered implant, straight reamers are necessary. When a long stem is needed, there is a risk of anterior femoral perforation because of the anterior femoral bow. The solution to this problem, popularized by Wagner [10], is to use an anterior extended femoral osteotomy or transfemoral osteotomy. This approach allows the surgeon to gain a straight trajectory down a bowed femur with a much lower risk of anterior perforation. The Wagner anterior extended femoral osteotomy involves lifting up a vascular osteotomy fragment consisting of the anterior third of the circumference of the upper femur in continuity with the anterior half of the abductors and the anterior half of the vastus lateralis [10]. This approach is beneficial in gaining access to the prosthetic bed for removal of the old prosthesis and cement without risking the distal femur and is associated with florid bone remodeling [14]. Another similar femoral osteotomy approach used with fluted tapered stems is the extended trochanteric osteotomy, popularized by Younger et al. [15]. Although the shorter prosthetic lengths may be implanted by the posterior approach, lengths over 265 mm are usually required when the transfemoral approach is used [14]. This monoblock fluted, tapered titanium stem is the implant to which most newer fluted, tapered stems owe their heritage.

Clinical Results

There is a discrete difference in the short- and long-term results of femoral reconstruction with fluted, distally tapered, cementless stems [16]. Several early studies reported unacceptable subsidence rates [17–19], with values up to 55 % [20]. Significant subsidence (i.e., greater than 10 mm)

has been reported to vary between 15 % [21] and 19 % [19, 22, 23]. Concern has been raised regarding the subsidence which occurs with the SL prosthesis with its potential for decreased tissue tension and increased risk of dislocation, sometimes requiring re-revision [24]. Isaacson et al. reported 9 of 27 hips that dislocated subsequent to revision [18]. However, increased incidence of subsidence and dislocation does not necessarily mean an increased revision rate. Boisgard et al. found a high rate of dislocation (8 %), leg-length discrepancy (15 %), stem subsidence (7.7 %), and limp in their series of 52 Wagner prostheses [25]. However, only 2 out of the 52 hips (3.8 %) were eventually revised at a mean follow-up of 44 months [25]. Gutiérrez Del Alamo et al. have recently reported 79 revision of Wagner femoral components followed up for a minimum of 5 years [22]. Eleven dislocations (13.9 %) required five re-revisions in the early postoperative period, but the cumulative probability of not having a stem re-revision for any reason remained high (92.32 %) [22]. As the surgeons became more familiar with the use of the fixation method, results gradually improved [16]. Grünig et al. reported 4 revisions in 40 hips, 3 of them due to undersized stems and continuous subsidence [21]. Bohm and Bischel reported on 129 revisions with the stem, at a mean of 4.8 years [26]. Only 6 stems had required another revision operation, with a cumulative survival of 95.2 % at 14.1 years. Only one of these stems was revised for subsidence. Bircher et al. reported a 92 % 10-year stem survivorship in 99 revisions with the same stem [27].

In response to the successes and problems of the Wagner stem, fluted, tapered titanium stems with a proximal modular body and/or curved distal shape have been developed. The modularity allows the surgeon to engage the fluted, tapered distal stem in the diaphysis for optimal stem axial and rotational stability and then to choose a proximal stem body that optimizes leg length, femoral offset, and stability. The practical advantages of this approach from the surgeon's point of view are obvious. There are engineering challenges, however, because these stems have a modular junction at a high-stress location of the femoral component [16, 28, 29]. Schuh et al. reported satisfactory results in 77 of 79 revision arthroplasties with the

modular MRP-Titan revision stem (Peter Brehm GmbH, Weisendorf, Germany) at 4-year follow-up [30]. Wirtz et al. documented results using the MRP-Titan modular stem in 142 revisions [31]. The implant survival rate was 95.8 % at an average of 2.3 years. Dislocation occurred in 11 patients treated by closed reduction. Five of the patients had recurrent dislocation successfully treated by surgical alteration of the anteversion of the proximal body [31]. Mumme et al. reported a 97 % survival rate with the MRP-Titan modular stem [32]. Tamvakopoulos et al. had an overall survival rate of 92.5 % in their series of 40 cases with this stem [33]; 5 dislocations occurred with 1 revision of the proximal modular segment for impingement. They advocated the use of proximal modular segments with CCD angle of 126 to avoid dislocation [33]. Kwong et al. reported on the Link MP stem (Exactech Inc., Gainesville, Fla.) [34]. Implant survival rate was 97.2 % at 2–6 years follow-up. Average subsidence was only 2.1 mm. There was one mechanical failure in the 143 stems implanted. Murphy and Rodriguez reported also minimal subsidence in 34 of 35 revision arthroplasties with the same stem followed for a minimum of 2 years, although six reoperations were necessary for recurrent dislocations [35]. Rodriguez et al. reviewed a series of 102 patients revised with the Link MP stem in 3 centers [28]. At an average of 39 months, two stems were revised due to gross migration in the first months and one because of a stem fracture. Dislocation occurred in 10 cases and six of them were recurrent and were revised by altering the proximal segment [28]. Sporer and Paprosky also reported satisfactory results in 15 of 16 patients revised with the Link or ZMR (Zimmer, Warsaw, Ind.), however, at only 2 years of follow-up [36]. For the ZMR prosthesis, Ovesen et al. reported a large series of 125 arthroplasties, with a survival rate of 94 % after an average follow-up of 50 months [29]. The rate of dislocation was 6 % and of stem fracture 1 % [29]. Recently, Restrepo et al. reported a prospective study of 118 revision arthroplasties with the Restoration Modular Stem (Stryker Orthopaedics, Mahwah, NJ) [37]. After an average 4 years of follow-up, distal bone ingrowth fixation was obtained in 100 % of the patients, offset was corrected in 66 %, leg-length

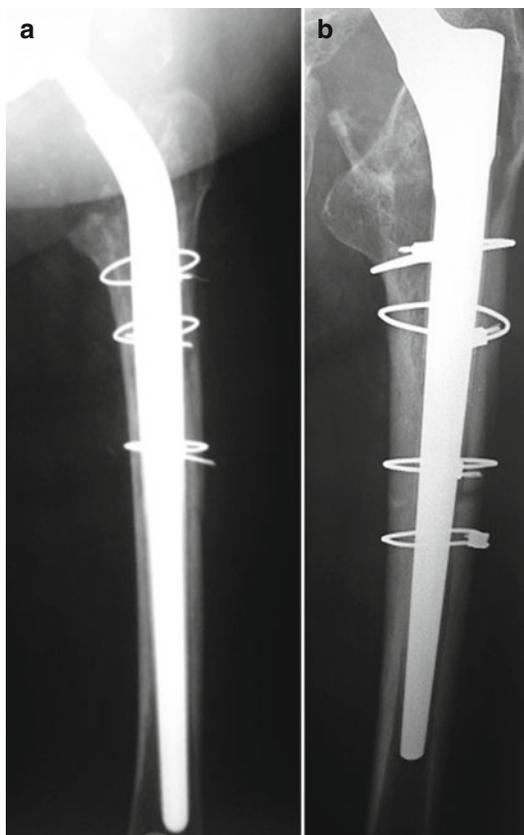


Fig. 14.3 Satisfactory clinical and radiological outcome: (a) an old Wagner stem at 12-year follow-up and (b) modern non-modular Wagner-type stem at 8-year follow-up

discrepancy was corrected in 78 %, and stability was achieved in 97 %. No failures or fractures at the body to stem junction were seen. Survival rate for revision for any reason was 92 %. Subsidence of the femoral component was more than 5 mm only in two patients (1.6 %), while dislocation occurred in four (3 %) hips at a mean of 11 weeks [37]. However, some modular, distally tapered revision stems have not fared as well. McInnis et al. reviewed 70 PFM stems (Zimmer, Warsaw, Ind.) followed for a mean of 47 months. Eighty-four percent of the stems subsided a mean 9.9 mm with one stem subsiding 52 mm [38]. In addition, 10 % of the hips dislocated, with a mean subsidence of 23 mm. Revision rate was 8.6 %.

Given the above, the results of the cementless, tapered, fluted implant-bone interface in revision THA generally have been favorable (Fig. 14.3).

The reason behind this seems to be the adequate primary stability that this interface provides. The rigid fixation, in turn, allows the development of an intimate contact of the bone tissue with the surface of the implant and, thus, facilitates secondary stability. Due to different parameters of this interface, proximal femoral bone remodeling and reconstitution take place, even without grafting.

Primary Stability

The term primary stability usually indicates the amount of relative micromovement at the bone-implant interface, induced by the physiological joint loading early after the operation and before any biological process takes place [39]. Rigid initial implant stability is essential for ingrowth of bone into porous surfaces and eventual secondary stability. It depends on the geometric and mechanical properties of the prosthesis, the accuracy of the preparation of the bone bed, and the quality of the patient's bone [40, 41]. Despite increasing numbers of implantations of cementless revision prostheses, little attention has been paid objectively to the importance of the stem cross-sectional shape for the rotational stability. Conical-shaped revision stems seem to achieve their primary rotational stability by a continuous cortical press-fit within the diaphyseal part of the femur, whereas cylindrical stems need a metaphyseal cancellous support, which is rarely available [24, 42, 43]. By maximizing the bone-implant interface, press-fitting and resisting to torsional forces, a femoral stem can become effective in reducing micromotion and providing primary mechanical stability. Fluted, tapered stem design provides these; the stems are tapered to gain axial stability and fluted to gain rotational stability in the femoral diaphysis.

The key to successful fixation is reaming a taper into the diaphysis such that the stem taper wedges snugly into the femur canal. Good preoperative planning is essential. If the taper is too far proximal or distal, axial stability of the stem in the canal cannot be achieved. If the diaphysis cannot be milled to a supportive tapered cone, axial stability of the implants cannot be achieved on a reliable basis. The surgeon may need to

ream an additional 2–3 cm of the canal diameter to create a firm cortical contact, sufficient enough to provide good axial support for the tapered stem. The magnitude of the distal taper angle affects the resistance to subsidence and the amount of taper in contact with bone [16]. With a 3° taper angle, each millimeter of increased diameter reamed increases the longitudinal contact area by 19 mm. For a 2° taper, each millimeter of reaming provides 29 mm additional longitudinal contact. However, the smaller the taper angle, the closer to parallel the surfaces of the stem and bone become. The geometry eventually approaches a cylinder in a tube, which can resist subsidence only by friction and not by the geometric attributes of the taper [16]. Of note, according to the manual of the prosthesis, when bypassing a cortical defect, the implant should extend past the defect by a minimum of two and one-half times the measured canal diameter to provide adequate support. In addition it is described as important for the tip of the stem to extend into the intact medullary canal at least 7 cm distal to the end of the previous prosthetic bed [44]. However, some authors recommend fixation of the implant into the femoral isthmus for a minimum of 40 mm as solid [8, 16, 45, 46]. In a study by Weiss et al., the femoral stem-bone anchorage had been defined as being adequate in a CT slice if 50 % or more of the stem flutes had cortical bone contact [47]. The median anchorage length derived was 33 mm, and only in 3 out of the 14 patients was this length greater than 7 cm. Only a moderate degree of correlation between the Harris Hip Score and anchorage length was found [47]. On the other hand the longitudinal ridges make a large amount of rotational stability possible. Kendrick et al. investigated the cross-sectional design of the femoral stem at the level of the femoral isthmus with respect to its effect on the rotational stability [48]. Four designs, a fluted stem, a finned stem, a porous-coated stem, and a slotted fluted stem, were implanted in cadaveric femurs and loaded in torsion, whereas a knurled cemented stem acted as a control stem. The solid, fluted stem was the only design to show sufficient resistance to torsional forces to stabilize a femoral prosthesis solely through

distal fixation. The porous-coated cylindrical design, on the other hand, has the advantage of a larger area of contact between the surface of the stem and the endosteal surface. In practice, however, the first few rows of beads entering the bone during implantation tend to erode the reamed surface, thus reducing the effective interference between the canal and the coating. Furthermore, an area of coating is actually sheared off the surface of the prosthesis, further deteriorating the bone-implant interface [48].

Jacobowitz et al. have investigated the effect of multifilaments (Dall-Miles cables) and monofilaments cerclage wiring of the extended proximal femoral osteotomy on primary stability of metaphyseal and diaphyseal fixated revision stems [14]. Both effected a major reduction of relative micromovements, which were more than halved, for both fixation principles. There were no differences in relative movements between the multifilament and monofilament treatments for the diaphyseal fixating stem. Yet for the metaphyseal fixating stem, a significantly better restabilization was observed with multifilaments. It should be noticed that both wire types had no effect on the primary stability of the diaphyseal stem. However, wiring in the area between the proximal isthmus and the metaphysis seems to function more to attach the bony structures and the bony lid to the stem and augment bony apposition at this area and thus secondary stability [14]. Warren et al. have found indeed that closure of the proximal osteotomy with wires conferred a more reliable rate of union in comparison with those closed with heavy sutures [24]. They have also found that those patients prophylactically wired with Dall-Miles cables demonstrated no subsidence in comparison with those in whom heavy wire cerclage had been utilized.

The initial stability of femoral stems with respect to the surrounding bone is reflected by the stem's motion. Two types of motion may be characterized: (a) a dynamic movement of the stem in response to one loading cycle of the prosthesis, termed "instability," "toggle," or "micromotion" and (b) the stem's irreversible displacement within the femoral canal overtime, called "migration" or "subsidence" [49]. Excessive dynamic

micromovement at the implant-bone interface may encourage the formation of a fibrous tissue layer which may have some stabilizing effect, but the lasting stability of the implant is thought to be provided by the strong osseointegration of the prosthesis [49]. The amount of motion at the metal-bone interface which can be tolerated without endangering the biological osseointegration process has been discussed by several authors. Pilliar et al. found in their animal study that a movement of 150 μm or more could result in connective-tissue ingrowth, whereas movements of up to 28 μm did not interfere with bony ingrowth of porous-coated implants (Co-Cr-Mo alloy) [50]. Jasty et al. reported a similar value being compatible with osseous apposition (34 μm) [51]. Engle et al. reported a maximum relative motion between the cortex and the implant in the areas of bone ingrowth of 40 μm [52]. McKellop et al. described motions up to 100 μm as tolerable [53]. Today micromovement values of 100–150 μm are accepted to still ensure bony ingrowth by most authors [42, 54]. On the other hand, early subsidence of a stem in the first 2 years after implantation may predict late aseptic loosening [55].

The fluted, tapered stem design was tested in composite femur revision arthroplasty model with simulation of proximal bone loss and compared with cylindrical stem design [42]. In cases with extensive defects, the conical implants showed lesser relative movements, while cylindrical stems were advantageous for minor defects because they provide a proximal fixation. Notably, the Wagner SL stem showed, except from a firm diaphyseal fixation with micromovement values well below the threshold for bony apposition, a relative slipping at metaphyseal areas within the critical range of 100–150 μm in cases of minor or no proximal bone loss. Thus, it shows also a metaphyseal fixation component that reduces with decreasing defect position. However, with the use of conical implants in minor proximal defects, these areas, still capable of load bearing, would be partly unnecessarily bridged. In a similar cadaveric revision total hip arthroplasty model with simulation of extended proximal bone loss, the fluted, tapered stem design demonstrated superior initial biomechanical stability in terms of

axial and rotational displacement, compared with that of the cylindrical design tested. However, both stems demonstrated motion below the threshold necessary for bony ingrowth [40]. On the other hand, the newer curved designs seem to perform even better with regard to interface motion, perhaps due to the anatomic shape that better engages the diaphysis, thus providing enhanced rotational stability [42, 54].

Secondary Stability

The term secondary stability indicates the amount of micromotion between bone and implant induced under load secondarily, once the biological adaptation process is completed [39]. The physiologic response to an inserted implant resembles the healing cascade of cancellous defects, with the newly formed tissues occupying the void spaces of the material [56]. With the prerequisite of a stable implant-bone interface, woven bone formation occurs, with no intermediate fibrocartilaginous tissue. Osteogenesis is thought to be intramembranous and not endochondral unless there is excessive motion at the interface [57]. For the porous materials, bone ingrowth refers in the literature mainly to bone formation within the porous surface structure of the implant. For the rest rough or textured implants, the term bone ongrowth is used to describe the development of bone onto their surface [58]. When an intimate contact of the bone tissue with the surface of an implant has been developed, osseointegration has been achieved [56]. Similarly, for the fluted, tapered stems, rigid initial stability allows for bone ongrowth at the grit-blasted surface, especially at the distal anchorage region. Secondary stability can be obtained even when the bone quality of the proximal femur is bad and bone loss is severe. Its strength is determined by the extent of bone formation on the grit-blasted surface and its shear properties [59].

Among others, three methods of applying a porous coating to a solid substrate are prominent within the orthopedic industry, namely, sintering, diffusion bonding, and plasma spray processing [60]. The sintering technique offers a porous coating composed of layers of spherical beads

(cobalt-chrome or titanium), differing only in bead size, bonded to the substrate. In diffusion bonding, titanium fiber metal pads may be attached to a titanium alloy substrate using heat and pressure (less heat than sintering). The plasma spray process is a refined version of the gas tungsten-arc welding process. To apply a plasma spray coating, only the coating material is heated within the spray nozzle. Coating powder (titanium) and a pressurized gas mixture then are injected into a high-energy arc created within the nozzle and then the molten powder is propelled against the implant surface. The substrate does not undergo intensive direct heating, and thus the material retains 90 % or more of the fatigue strength characteristics [60]. Almost all porous-coated prostheses produced with these methods have pore sizes in the range from 100 to 400 μm . Most studies [56, 61, 62] analyzing pores in this range have shown no relationship between pore size and strength of fixation except from one for fiber metal [59], which has demonstrated a decrease of bone ingrowth and strength of fixation when the pore size was increased. In studies examining pore sizes less than 100 μm , the increasing pore size was associated with increasing strength of fixation [56].

Although these coatings can present satisfactory clinical results, some problems have been recognized: decreased fatigue strength of porous-coated substrates due to intensive heating during manufacturing; increased release of harmful metal ions from the large surface of the porous coatings, separation, dissolution, and resorption of the coatings; and finally migration of wear and separated coating particles into the joint space, causing third-body wear [63]. On the other hand, another common way of creating a rough surface is grit blasting resulting in roughness (Ra) of 4–6 μm . Surface roughening is accomplished by bombardment of the implant with a pressurized spray of high-purified corundum (Al_2O_3) particles using a sand blaster. While coating methods are “addition” techniques for surface roughening, grit blasting is a “subtraction” technique. It is simpler than an addition technique, can create a more uniform and controlled surface roughness, and may not have the complications that the coating methods do [63, 64]. However, the

effectiveness of surface blasting is still controversial. In a rabbit model, surface blasting by Al_2O_3 or stainless-steel particles enhanced direct bone ongrowth and interfacial shear strength of solid titanium alloy implants [65]. In a similar model, the interfacial shear strength of surface-blasted implants was comparable to that of Ti fiber metal implants with and without hydroxyapatite/tricalcium phosphate coating [63, 66]. Better quality at the bone-implant interface, without unmineralized tissue (cartilage or osteoid), is found on blasted surfaces of titanium than on similar surfaces made of cobalt-chromium [63]. In vitro studies have also found enhanced extracellular matrix production and mineralization by osteoblasts when they are cultured on the blasted surface. Furthermore, in several culture models on blasted titanium surfaces, an enhanced upregulation of differentiation markers in osteoblast-like cells was found [67–69]. An osteoconductive effect of the blasted implant surface can be concluded [63, 70]. On the other hand, in a press-fit rabbit model, the plasma-sprayed cobalt-chromium and the grit-blasted titanium surfaces demonstrated the lowest shear strength and bone apposition among various porous surfaces [71]. Another, histomorphometric study in miniature pigs has shown that the sandblasted implant surfaces had the lowest percentage of bone contact with mean values ranging between 20 and 25 % [72]. Remarkably, increasing the surface roughness of a grit-blasted titanium implant led to less bone-to-metal contact in an animal in vivo study [73]. Similarly, in another in vitro study, analyzing the effects of surface finish on osteoblast cell adhesion to polished or grit-blasted cobalt-chromium-molybdenum alloys, cell binding was 48 % reduced with the grit-blasted cobalt alloy [74].

In contrast to these studies, clinical reports of grit-blasted hip implants have repeatedly shown excellent long-term survival [75–78]. Furthermore, histological and morphometric retrieval studies demonstrated excellent osseointegration in vivo [79–81]. Direct new bone formation was evident as early as 3 weeks postoperatively [79] and obtained a maximum at 5 years postoperatively [80]. In the only, to our knowledge, histological study of bony incorporation of a Wagner stem, primary bone formation was demonstrated between the endosteal surface and the eight wings of the stem at the distal

Fig. 14.4 Proximal femoral remodeling: (a) post-revision radiograph, (b) radiograph at 6-year follow-up



diaphysis. However, direct bone apposition and good bony anchorage, as well as signs of revascularization and revitalization, were also found further proximally, especially on the medial aspect of the stem [82]. These findings are in line with the aforementioned micromotion studies and the reports on proximal femoral bone reconstitution after revision arthroplasty with the Wagner stem. Furthermore, at terms of radiographic osseointegration, a study by Rodriguez et al. confirmed distal fixation, directly from the presence of endosteal spot welds and indirectly from the absent radiolucent lines along the porous distal surface and also from the absence of progressive subsidence [83]. The development of a complete pedestal at this area is associated with a stable distal stem. Proximal segment radiolucent lines were common and were thought to present micromotion between the proximal stem and deficient bone. The exclusion of radiolucency at this part of the implant from the criteria of stem stability is justified. Therefore, the well-established criteria by Engh et al. of

osseointegration for cylindrical cobalt-chrome stems may have to be altered slightly for application to this implant, as its mechanical behavior is much different [83].

Proximal Femoral Bone Restoration

Favorable proximal femoral bone remodeling and reconstitution after revision with the Wagner stem have been reported by several authors [6, 18, 19, 22, 84, 85] (Fig. 14.4). Kolstad et al. have classified subjectively femoral restoration into three categories: no bone regeneration, possible regeneration, and definite new bone formation [19]. Definite radiographic bone regeneration in the bone defects and the osteotomies was recognized within a few months in 30 out of 31 cases [19]. McInnis et al. have also subjectively classified the restoration of the proximal femur as A (increasing defects), B (stable defects), or C (osseous restoration) [38]. Fifty-six percent of their patients had incontrovertible

evidence of proximal bone restoration, whereas in another 33 % the bone stock appeared static [38]. Similarly, Isaacson et al. have graded arbitrarily the new bone formation as 0=no new bone, 1=some indication of new formation, 2=cancellous bone surrounding the stem, and 3=large areas of cortical bone adjacent to the stem surface [18]. The overwhelming majority of the patients showed a strong tendency to form new bone around the prosthetic stem. Only one patient out of 43 had a small degree of new bone (score 1) and another one no new bone formation (score 0) [18]. Gutiérrez Del Alamo et al. found proximal new bone regeneration in 50 of 79 hips revised with the Wagner stem and an increase in the thickness of the femoral cortex and outer femoral diameter compared with immediate postoperative radiographs [22]. Restoration of bone and density of the proximal femur is quantitatively estimated using the cortical index, as reported by Bohm and Bischel [26], and first described by Callaghan et al. [4]. The cortical index is calculated at a point 1 cm distal to the inferior margin of the lesser trochanter by dividing the width of the cortical and cancellous bone to the outside diameter of the femoral shaft. In order to classify the restoration of the proximal bone stock, the radiographs made immediately after the index operation are compared with those made at the latest follow-up examination [26]. In their series, the mean relative bone mass of the proximal part of the femur increased from 24.9 % preoperatively to 46.6 % at the latest follow-up examination [26].

Femoral bone restoration associated with the Wagner SL revision stem may be due to the higher elasticity of the titanium alloy and the good histocompatibility of the grit-blasted surface [2, 26]. Titanium has a lower modulus of elasticity than cobalt-chromium, resulting in reduced femoral component stiffness for an equivalent diameter stem. By reducing the modulus mismatch between the femoral component and the host bone, titanium stems may result in less thigh pain and less proximal femoral stress shielding, particularly for smaller stem diameters [6]. Because stiffness is a function of the radius raised to the power of 4, this effect is much less with larger diameter stems [13]. It is worth noticing that the longitudinal ridges contribute to the reduction of the core cross section, which makes the prosthetic stem somewhat

more elastic [86]. Proximal transmission of force because of the conical shape of the prosthesis may also contribute to the proximal bone restoration [26, 86]. With the tapered design, the conical stem is driven into the tapered medullary cavity. This produces continuous contact between the implant and the bone, despite the distal anchorage, so that the size of the load transmitted depends on the extent of the contact surface. Strength is therefore conducted proximally because, with a taper, the surface per unit of length increases with the diameter, i.e., the supporting surface is greater per unit of length in the proximal section of the stem with a larger diameter than in the distal section [86]. Alternative explanations for the proximal bone restoration with these stems include (1) a fracture healing response related to the extended femoral osteotomy and (2) bone reconstitution related to the gradual resumption of normal activities after the revision operation [6, 38]. Furthermore, the space between the ridges, where the implant does not come into direct contact with the bone cortex, may facilitate revascularization of the medullary cavity, because blood vessels can grow here prior to bone resorption [86].

Stem Subsidence

If there is such firm initial and secondary fixation, why does the stem subside? The most obvious reason for subsidence could be stem undersizing, as there is certainly a learning curve to its use. The learning curve in implanting this stem is multifactorial. Firstly, meticulous preoperative planning is needed to identify points of contact distally with the reamer and the proper angle of insertion of the reamer. The second factor relates to achieving a tactile understanding of how much resistance to hand reaming with a given bone type is associated with adequate endosteal contact rather than a 3-point fixation. With both these factors, understanding is achieved using a mini C-arm to correlate the reamer placement within the canal with preoperative measurements along with the observed reamer depth and orientation. In this way, perforation is prevented, and optimal endosteal contact of the reamer and thus of the final implant is confirmed [6, 16]. On the other hand, the monoblock stem

sometimes leads the surgeon to seat the implant at a level in the femur based on leg length, not axial stem stability [6]. From the practical viewpoint, uncertainty about where the implant should seat in the femur made the combination of ideal leg length, hip stability, and implant axial stability difficult to achieve [18, 25, 26].

Initial limited subsidence does not equate to failed osseointegration, at least with this stem design. The axial stability of this implant is maintained by hoop stresses within the diaphysis. As such, a discontinuity in the diaphyseal ring will compromise that axial stability and predispose to subsidence [83]. Park et al. reported indeed greater predilection for subsidence in hips with more advanced bone loss (Paprosky type 3B or more), although no statistical relation could be established [87]. Subsidence may also be considered to be a function of axial loading and post-operation regime of weight bearing. Rinaldi et al., who maintained bed rest for 20 days followed by partial weight bearing for up to 2 months, report the lowest subsidence rate of 5 % [85]. On the other hand, in early series, significant (i.e., greater than 10 mm) subsidence was associated with the development of spiral fractures in osteoporotic femora [88]. In contrast, although three propagatory cracks were seen in their patients, either intraoperatively or on immediate postoperative radiographs, Warren et al. could not identify any trend for these fractures to be associated with subsequent subsidence [24]. They have found, instead, that those patients prophylactically wired with Dall-Miles cables presented no subsidence in comparison with those in whom heavy wire cerclage had been utilized [24]. This is probably because it is difficult to attain adequate tension in wire without specialized tightening instruments [89], while the Dall-Miles system allows maintenance of cable tension as the cable is clamped after tightening [90].

References

- Mäkelä KT, Eskelinen A, Pulkkinen P, et al. Results of 3,668 primary total hip replacements for primary osteoarthritis in patients under the age of 55 years. *Acta Orthop Scan.* 2011;82:521–9.
- Estok 2nd DM, Harris WH. Long-term results of cemented femoral revision surgery using second-generation techniques. An average 11.7-year follow-up evaluation. *Clin Orthop.* 1994;299:190–202.
- Head WC, Wagner RA, Emerson Jr RH, Malinin TI. Revision total hip arthroplasty in the deficient femur with a proximal load-bearing prosthesis. *Clin Orthop.* 1994;298:119–26.
- Callaghan JJ, Salvati EA, Pellicci PM, et al. Results of revision for mechanical failure after cemented total hip replacement, 1979 to 1982. A two to five-year follow-up. *J Bone Joint Surg Am.* 1982;1979(67A):1074–85.
- Kavanagh BF, Ilstrup DM, Fitzgerald Jr RH. Revision total hip arthroplasty. *J Bone Joint Surg Am.* 1985;67A:517–26.
- Berry DJ. Femoral revision: distal fixation with fluted, tapered grit-blasted stems. *J Arthroplasty.* 2002;17(4 Suppl 1):142–6.
- Chandler HP, Ayres DK, Tan RC, et al. Revision total hip replacement using the S-ROM femoral component. *Clin Orthop.* 1995;319:130–40.
- Paprosky WG, Greidanus NV, Antoniou J. Minimum 10-year-results of extensively porous-coated stems in revision hip arthroplasty. *Clin Orthop.* 1999;369:230–42.
- Engh Jr CA, Ellis TJ, Koralewicz LM, et al. Extensively porous-coated femoral revision for severe femoral bone loss: minimum 10-year follow-up. *J Arthroplasty.* 2002;17(8):955–60.
- Wagner H. Revision prosthesis for the hip joint in severe bone loss. *Orthopade.* 1987;16(4):295–300.
- Wagner H. Revisionsprothese für das Hüftgelenk. *Orthopade.* 1989;18:438–53.
- Ko PS, Lam JJ, Tio MK, et al. Distal fixation with Wagner revision stem in treating Vancouver type B2 periprosthetic femur fractures in geriatric patients. *J Arthroplasty.* 2003;18(4):446–52.
- Richards CJ, Duncan CP, Masri BA, Garbuz DS. Femoral revision hip arthroplasty: a comparison of two stem designs. *Clin Orthop.* 2010;468:491–6.
- Jakubowitz E, Kinkel S, Nadorf J, et al. The effect of multifilaments and monofilaments on cementless femoral revision hip components: an experimental study. *Clin Biomech.* 2011;26(3):257–61.
- Younger TI, Bradford MS, Magnus RE, Paprosky WG. Extended proximal femoral osteotomy. A new technique for femoral revision arthroplasty. *J Arthroplasty.* 1995;10(3):329–38.
- Swanson T. Chapter 36: Tapered, fluted femoral fixation. Part VII: Revision THA: the femur. In: Brown T, Cui Q, Mihalko W, Saleh K, editors. *Arthritis and arthroplasty: the hip.* Amsterdam: Elsevier Inc.; 2009. p. 354–62.
- Ponziani L, Rollo G, Bungaro P, et al. Revision of the femoral prosthetic component according to the Wagner technique. *Chir Organi Mov.* 1995;80(4):385–9.
- Isaacson J, Stark A, Wallensten R. The Wagner revision prosthesis consistently restores femoral bone structure. *Int Orthop.* 2000;24(3):139–42.

19. Kolstad K, Adalberth G, Mallmin H, et al. The Wagner revision stem for severe osteolysis: 31 hips followed for 1.5-5 years. *Acta Orthop Scand*. 1996; 67:541.
20. Suominen S, Santavirta S. Revision total hip arthroplasty in deficient proximal femur using a distal load-bearing prosthesis. *Ann Chir Gynaecol*. 1996;85(3):253-62.
21. Grünig R, Morscher E, Ochsner PE. Three-to 7-year results with the uncemented SL femoral revision prosthesis. *Arch Orthop Trauma Surg*. 1997;116(4):187-97.
22. Gutiérrez Del Alamo J, Garcia-Cimbreló E, et al. Radiographic bone regeneration and clinical outcome with the Wagner SL revision stem: a 5-year to 12-year follow-up study. *J Arthroplasty*. 2007;22(4):515-24.
23. Hartwig CH, Böhm P, Czech U, et al. The Wagner revision stem in allarthroplasty of the hip. *Arch Orthop Trauma Surg*. 1996;115(1):5-9.
24. Warren PJ, Thompson P, Fletcher MD. Transfemoral implantation of the Wagner SL stem. The abolition of subsidence and enhancement of osteotomy union rate using Dall-Miles cables. *Arch Orthop Trauma Surg*. 2002;122(9-10):557-60.
25. Boisgard S, Moreau PE, Tixier H, Levai JP. Bone reconstruction, leg length discrepancy, and dislocation rate in 52 Wagner revision total hip arthroplasties at 44-month follow-up. *Rev Chir Orthop Reparat Mot*. 2001;87(2):147-54.
26. Böhm P, Bischel O. Femoral revision with the Wagner SL revision stem : evaluation of one hundred and twenty-nine revisions followed for a mean of 4.8 years. *J Bone Joint Surg Am*. 2001;83A:1023-31.
27. Bircher HP, Riede U, Lüem M, Ochsner PE. The value of the Wagner SL revision prosthesis for bridging large femoral defects. *Orthopade*. 2001;30(5): 294-303.
28. Rodriguez JA, Fada R, Murphy SB, et al. Two-year to five-year follow-up of femoral defects in femoral revision treated with the link MP modular stem. *J Arthroplasty*. 2009;24(5):751-8.
29. Ovesen O, Emmeluth C, Hofbauer C, Overgaard S. Revision total hip arthroplasty using a modular tapered stem with distal fixation: good short-term results in 125 revisions. *J Arthroplasty*. 2010;25(3):348-54.
30. Schuh A, Werber S, Holzwarth U, Zeiler G. Cementless modular hip revision arthroplasty using the MRP Titan Revision Stem: outcome of 79 hips after an average of 4 years' follow-up. *Arch Orthop Trauma Surg*. 2004;124(5):306-9.
31. Wirtz DC, Heller KD, Holzwarth U, et al. A modular femoral implant for uncemented stem revision in THR. *Int Orthop*. 2002;24(3):134-8.
32. Mumme T, Müller-Rath R, Andereya S, Wirtz DC. Uncemented femoral revision arthroplasty using the modular revision prosthesis MRP-TITAN revision stem. *Oper Orthop Traumatol*. 2007;19(1):56-77.
33. Tamvakopoulos GS, Servant CT, Clark G, Ivory JP. Medium-term follow-up series using a modular distal fixation prosthesis to address proximal femoral bone deficiency in revision total hip arthroplasty. A 5- to 9-year follow-up study. *Hip Int*. 2007;17(3):143-9.
34. Kwong LM, Miller AJ, Lubinus P. A modular distal fixation option for proximal bone loss in revision total hip arthroplasty: a 2- to 6-year follow-up study. *J Arthroplasty*. 2003;18(3 Suppl 1):94-7.
35. Murphy SB, Rodriguez J. Revision total hip arthroplasty with proximal bone loss. *J Arthroplasty*. 2004; 19(4 Suppl 1):115-9.
36. Sporer SM, Paprosky WG. Revision total hip arthroplasty: the limits of fully coated stems. *Clin Orthop*. 2003;417:203-9.
37. Restrepo C, Mashadi M, Parvizi J, et al. Modular femoral stems for revision total hip arthroplasty. *Clin Orthop*. 2011;469:476-82.
38. McInnis DP, Horne G, Devane PA. Femoral revision with a fluted, tapered, modular stem seventy patients followed for a mean of 3.9 years. *J Arthroplasty*. 2006; 21(3):372-80.
39. Viceconti M, Brusi G, Pancanti A, Cristofolini L. Primary stability of an anatomical cementless hip stem: a statistical analysis. *J Biomech*. 2006;39(7):1169-79.
40. Kirk KL, Potter BK, Lehman Jr RA, Xenos JS. Effect of distal stem geometry on interface motion in uncemented revision total hip prostheses. *Am J Orthop*. 2007;36(10):545-9.
41. Schneider E, Kinast C, Eulenberger J, et al. A comparative study of the initial stability of cementless hip prostheses. *Clin Orthop*. 1989;248:200-9.
42. Jakobowitz E, Bitsch RG, Heisel C, et al. Primary rotational stability of cylindrical and conical revision hip stems as a function of femoral bone defects: an in vitro comparison. *J Biomech*. 2008;41(14):3078-84.
43. Wagner H, Wagner M. Konische Schaftverankerung zementfreier Hüftprothesen-Primärimplantation und Prothesenwechsel. In: Morscher EW, editor. *Endoprothetik*. Berlin: Springer; 1996. p. 278-88.
44. Wagner SL Revision® Hip Stem Surgical Technique. Available at: <http://www.zimmer.com/en-US/hcp/hip/product/wagner-sl-revision-hip.jsp>. Accessed on 27 Aug 2013
45. Krishnamurthy AB, MacDonald SJ, Paprosky WG. 5- to 13-year follow-up study on cementless femoral components in revision surgery. *J Arthroplasty*. 1997; 12(8):839-47.
46. Jones RE. Modular revision stems in total hip arthroplasty. *Clin Orthop*. 2004;420:142-7.
47. Weiss RJ, Strömwall F, Beckman MO, et al. Distal femoral stem-bone anchorage of a cementless revision total hip arthroplasty: evaluation of 14 patients by CT. *Acta Orthop Scand*. 2009;80(3):298-302.
48. Kendrick 2nd JB, Noble PC, Tullos HS. Distal stem design and the torsional stability of cementless femoral stems. *J Arthroplasty*. 1995;10(4):463-9.
49. Bühler DW, Berlemann U, Lippuner K, et al. Three-dimensional primary stability of cementless femoral stems. *Clin Biomech*. 1997;12(2):75-86.
50. Pilliar RM, Lee JM, Maniopoulos C. Observations on the effect of movement on bone ingrowth into porous-surfaced implants. *Clin Orthop*. 1986;208:108-13.
51. Jasty M, Krushell R, Zalenski E, et al. The contribution of the nonporous distal stem to the stability of

- proximally porous-coated canine femoral components. *J Arthroplasty*. 1993;8(1):33–41.
52. Engh CA, O'Connor D, Jasty M, et al. Quantification of implant micromotion, strain shielding, and bone resorption with porous-coated anatomic medullary locking femoral prostheses. *Clin Orthop*. 1992;285:13–29.
 53. McKellop H, Ebramzadeh E, Niederer PG, Sarmiento A. Comparison of the stability of press-fit hip prosthesis femoral stems using a synthetic model femur. *J Orthop Res*. 1991;9(2):297–305.
 54. Callaghan JJ, Fulghum CS, Glisson RR, Stranne SK. The effect of femoral stem geometry on interface motion in uncemented porous-coated total hip prostheses. Comparison of straight-stem and curved-stem designs. *J Bone Joint Surg Am*. 1992;74A:839–48.
 55. Freeman MA, Plante-Bordeneuve P. Early migration and late aseptic failure of proximal femoral prostheses. *J Bone Joint Surg Br*. 1994;76B:432–8.
 56. Kienapfel H, Sprey C, Wilke A, Griss P. Implant fixation by bone ingrowth. *J Arthroplasty*. 1999;14(3):355–68.
 57. Callaghan JJ. The clinical results and basic science of total hip arthroplasty with porous-coated prostheses. *J Bone Joint Surg Am*. 1993;75A:299–310.
 58. Branemark PI. Introduction to osseointegration. In: Branemark PI, Zarb GA, Albrektsson T, editors. *Tissue-integrated prosthesis. Osseointegration in clinical dentistry*. Chicago: Quintessence Publishing Co, Inc; 1985. p. 11–76.
 59. Clemow AJ, Weinstein AM, Klawitter JJ, et al. Interface mechanics of porous titanium implants. *J Biomed Mater Res*. 1981;15(1):73–82.
 60. Bourne RB, Rorabeck CH, Burkart BC, Kirk PG. Ingrowth surfaces. Plasma spray coating to titanium alloy hip replacements. *Clin Orthop*. 1994;298:37–46.
 61. Cook SD, Walsh KA, Haddad Jr RJ. Interface mechanics and bone growth into porous Co-Cr-Mo alloy implants. *Clin Orthop*. 1985;193:271–80.
 62. Boby JD, Pilliar RM, Cameron HU, Weatherly GC. The optimum pore size for the fixation of porous-surfaced metal implants by the ingrowth of bone. *Clin Orthop*. 1980;150:263–70.
 63. Jinno T, Goldberg VM, Davy D, Stevenson S. Osseointegration of surface-blasted implants made of titanium alloy and cobalt-chromium alloy in a rabbit intramedullary model. *J Biomed Mater Res*. 1998;42(1):20–9.
 64. Gotfredsen K, Wennerberg A, Johansson C, et al. Anchorage of TiO₂-blasted, HA-coated, and machined implants: an experimental study with rabbits. *J Biomed Mater Res*. 1995;29(10):1223–31.
 65. Feighan JE, Goldberg VM, Davy D, et al. The influence of surface-blasting on the incorporation of titanium-alloy implants in a rabbit intramedullary model. *J Bone Joint Surg Am*. 1995;77A(9):1380–95.
 66. Tisdell CL, Goldberg VM, Parr JA, et al. The influence of a hydroxyapatite and tricalcium-phosphate coating on bone growth into titanium fiber-metal implants. *J Bone Joint Surg Am*. 1994;76A:159–71.
 67. Klinger A, Tadir A, Halabi A, Shapira L. The effect of surface processing of titanium implants on the behavior of human osteoblast-like Saos-2 cells. *Clin Implant Dent Relat Res*. 2011;13(1):64–70.
 68. Bächle M, Kohal RJ. A systematic review of the influence of different titanium surfaces on proliferation, differentiation and protein synthesis of osteoblast-like MG63 cells. *Clin Oral Implants Res*. 2004;15(6):683–92.
 69. Kieswetter K, Schwartz Z, Hummert TW, et al. Surface roughness modulates the local production of growth factors and cytokines by osteoblast-like MG-63 cells. *J Biomed Mater Res*. 1996;32(1):55–63.
 70. Groessner-Schreiber B, Tuan RS. Enhanced extracellular matrix production and mineralization by osteoblasts cultured on titanium surfaces in vitro. *J Cell Sci*. 1992;101:209–17.
 71. Friedman RJ, An YH, Ming J, et al. Influence of bio-material surface texture on bone ingrowth in the rabbit femur. *J Orthop Res*. 1996;14(3):455–64.
 72. Buser D, Schenk RK, Steinemann S, et al. Influence of surface characteristics on bone integration of titanium implants. A histomorphometric study in miniature pigs. *J Biomed Mater Res*. 1991;25(7):889–902.
 73. Wennerberg A, Albrektsson T, Andersson B. Bone tissue response to commercially pure titanium implants blasted with fine and coarse particles of aluminum oxide. *Int J Oral Maxillofac Implants*. 1996;11(1):38–45.
 74. Kornu R, Maloney WJ, Kelly MA, Smith RL. Osteoblast adhesion to orthopaedic implant alloys: effects of cell adhesion molecules and diamond-like carbon coating. *J Orthop Res*. 1996;14(6):871–7.
 75. Delaunay C, Bonnomet F, North J, et al. Grit-blasted titanium femoral stem in cementless primary total hip arthroplasty: a 5- to 10-year multicenter study. *J Arthroplasty*. 2001;16(1):47–54.
 76. Paleochoridis IS, Badras LS, Skretas EF, et al. Clinical outcome study and radiological findings of Zweymüller metal on metal total hip arthroplasty. a follow-up of 6 to 15 years. *Hip Int*. 2009;19(4):301–8.
 77. Suckel A, Geiger F, Kinzl L, et al. Long-term results for the uncemented Zweymüller/Alloclassic hip endoprosthesis. A 15-year minimum follow-up of 320 hip operations. *J Arthroplasty*. 2009;24(6):846–53.
 78. Grübl A, Chiari C, Giurea A, et al. Cementless total hip arthroplasty with the rectangular titanium Zweymüller stem. A concise follow-up, at a minimum of fifteen years, of a previous report. *J Bone Joint Surg Am*. 2006;88A:2210–5.
 79. Zweymüller KA, Lintner FK, Semlitsch MF. Biologic fixation of a press-fit titanium hip joint endoprosthesis. *Clin Orthop*. 1998;235:195–206.
 80. Böhm G, Lintner F, Auerth A, et al. Morphometric examination of straight, tapered titanium stems: a retrieval study. *Clin Orthop*. 2001;393:13–24.
 81. Lintner F, Zweymüller K, Böhm G, Brand G. Reactions of surrounding tissue to the cementless hip implant Ti-6Al-4V after an implantation period of several years. Autopsy studies in three cases. *Arch Orthop Trauma Surg*. 1988;107(6):357–63.
 82. Schenk RK, Wehrli U. Reaction of the bone to a cement-free SL femur revision prosthesis. Histologic

- findings in an autopsy specimen 5 1/2 months after surgery. *Orthopade*. 1989;18(5):454–62.
83. Rodriguez JA, Deshmukh AJ, Klauser WU, et al. Patterns of osseointegration and remodeling in femoral revision with bone loss using modular, tapered, fluted, titanium stems. *J Arthroplasty*. 2011;26(8):1409–17.
84. Michelinakis E, Papapolychronlou T, Vafiadis J. The use of a cementless femoral component for the management of bone loss in revision hip arthroplasty. *Bull Hosp Jt Dis*. 1996;55(1):28–32.
85. Rinaldi E, Marengi P, Vaienti E. The Wagner prosthesis for femoral reconstruction by transfemoral approach. *Chir Organi Mov*. 1994;79(4):353–6.
86. Wagner H, Wagner M. Cone prosthesis for the hip joint. *Arch Orthop Trauma Surg*. 2000;120(1–2):88–95.
87. Park MS, Lee JH, Park JH, et al. A distal fluted, proximal modular femoral prosthesis in revision hip arthroplasty. *J Arthroplasty*. 2010;25(6):932–8.
88. Wilkes RA, Birch J, Pearse MF, et al. The Wagner technique for revision arthroplasty of the hip: a review of 24 cases. *J Orthop Rheumatol*. 1994;7:196–8.
89. Wagner M, Knorr-Held F, Hohmann D. Measuring stability of wire cerclage in femoral fractures when performing total hip replacement. In vitro study on a standardized bone model. *Arch Orthop Trauma Surg*. 1996;115(1):33–7.
90. Haddad FS, Marston RA, Muirhead-Allwood SK. The Dall-Miles cable and plate system for periprosthetic femoral fractures. *Injury*. 1997;28(7):445–7.

Nikolaos Roidis and Athanasios Pollalis

Introduction

Bone grafting is a surgical procedure that places new bone or a replacement material into spaces between or around fractured bone or in bone defects to aid in healing. Bone grafting is used to repair bone fractures that are extremely complex, pose a significant risk to the patient, or fail to heal properly. It is also used to help fusion between vertebrae, correct deformities, or provide structural support for fractures of the spine. In addition to fracture repair, bone grafting is used to repair defects in bone caused by congenital disorders, traumatic injury, or complex reconstructive surgery [1, 2].

Tissues transplantation into humans has been attempted since the time of Hippocrates, while Egyptians and ancient Hindus have also been involved in transplantation procedures. However, it was the Dutch surgeon Job van Meekren in 1600s who has used part of a dog's skull to fill a defect in a soldier's cranium and therefore has been documented as the first person to perform a xenograft procedure. Later in 1821, the first autogenous bone-grafting procedure has been performed in Germany in an attempt to fill experimental animal skull defects. In 1879, Sir William Macewen has successfully used bone graft from other patients to reconstruct a 4-year-old boy's

proximal humerus, which is considered to be the first documented allograft procedure [2, 3]. The science of bone grafting has evolved significantly, particularly in the past two decades, with the fundamental understanding of osseous healing now incorporating principles of cellular and molecular biology. Bone grafts are used in virtually every aspect of reconstructive orthopedics, from the simple treatment of fractures to extensive limb salvage procedures and complex spinal reconstructions. Bone graft is the second most common transplantation tissue, with blood being by far the commonest [4–6].

Biology of Bone Grafting

Bone possesses the intrinsic capacity for regeneration as part of the repair process in response to injury, as well as during skeletal development or continuous remodeling throughout adult life. Bone regeneration is comprised of a well-orchestrated series of biological events of bone induction and conduction, involving a number of cell types and intracellular and extracellular molecular signaling pathways, with a definable temporal and spatial sequence, in an effort to optimize skeletal repair and restore skeletal function. Unlike in other tissues, the majority of bony injuries (fractures) heal without the formation of scar tissue, and bone is regenerated with its pre-existing properties largely restored, and with the newly formed bone being eventually indistinguishable from the adjacent uninjured bone.

N. Roidis, MD, DSc (✉) • A. Pollalis, MD
Third Orthopaedic Department, KAT Hospital,
Nikis 2, Kifisia, 14561 Athens, Greece
e-mail: roidisnt@hotmail.com

Bone grafting is possible because of this unique ability of bone tissue to regenerate completely if provided the space into which to grow. The biologic mechanisms that provide a rationale for bone grafting are osteoconduction, osteoinduction, and osteogenesis [7–9].

Osteoconduction

Osteoconduction occurs when the bone graft material serves as a scaffold for new bone growth that is perpetuated by the native bone. An ingrowth of capillaries, perivascular tissue, and mesenchymal stem cells (MSCs) takes place from the host site along the implanted graft. Osteoblasts from the margin of the defect that is being grafted, utilize the bone graft material as a framework upon which to spread and generate new bone. In the very least, a bone graft material should be osteoconductive. New bone must be distributed evenly in the grafted volume and must unite with the local host bone. Failure results in discontinuous bone formation without adequate mechanical strength to support function.

Osteoinduction

Osteoinduction involves the stimulation of mesenchymal stem cells (MSCs) at and around the host site to differentiate into chondroblasts and osteoblasts that then begin new bone formation. The most widely studied type of osteoinductive cell mediators is bone morphogenetic proteins (BMPs). Other growth factors involved with bone formation include mitogens, such as platelet-derived growth factors, interleukins, fibroblast growth factors, insulin-like growth factors, granulocyte colony-stimulating factors, and granulocyte-macrophage colony-stimulating factors. Angiogenic factors, such as vascular endothelial-derived growth factor, are also released. A bone graft material that is osteoconductive and osteoinductive will not only serve as a scaffold for currently existing osteoblasts but will also trigger the formation of new osteoblasts, theoretically promoting faster integration of the graft.

Osteogenesis

Osteogenesis is the synthesis of new bone by cells derived from either the graft or the host. When correctly handled, cells from cortical and cancellous grafts can survive the transfer to the host site and form new bone that is critical in the initial phase of bone repair. The properties of cancellous grafts, which consist of an intimate trabecular structure lined with osteoblasts and a large surface area, make them very attractive at sites where new bone formation is desired. Indeed, this concept of osteogenesis forms the biologic justification of decortication for spinal fusion. Exposing the intramedullary space of the transverse processes, lamina, and pedicles with a burr opens local bone marrow to the fusion site. Marrow elements then provide the fusion bed with osteoinductive proteins, potential osteogenic cells, and a local blood supply. Several factors dictate the successful incorporation of grafted bone, including the type of bone graft used, the site of implantation, the vascularity of the graft and the host-graft interface, the immunogenetics between the donor and the host, preservation techniques, local and systemic factors, and the mechanical properties that depend on the size, shape, and type of graft used. Graft site preparation is of particular importance, as adequate surface area contact between graft and recipient site is required, without interposition of soft tissue. Excessive heat generation by use of power tools that may lead to necrosis should also be avoided. Decreased harvest-to-implant time, storage of grafts in covered containers, attention to hydration, and meticulous adherence to surgical principles are essential to the success of the grafting procedure [10].

Bone Graft Options [11–17]

Bone grafts serve a combined mechanical and biologic function; depending on the desired clinical outcome, one function may be more important than the other. Therefore, an understanding of various bone graft options along with their unique characteristics is essential (Table 15.1).

Table 15.1 Characteristics of various bone graft options

Graft	Osteoconduction	Osteoinduction	Osteogenesis	Mechanical properties
<i>Autograft</i>				
Bone marrow	≈	✓	✓	✗
Cancellous	✓	✓	✓	✓
Cortical	✓	≈	✓	✓
Vascularized	✓	✓	✓	✓
<i>Allograft</i>				
Cancellous	✓	✓	✗	✓
Cortical	≈	≈	✗	✓
Demineralized	✓	✓	✗	✗

Modified from Khan et al. [8]

Autograft

Autologous (or autogenous) bone grafting involves utilizing bone obtained from the same individual receiving the graft. Autologous bone is typically harvested from nonessential bone sources, such as the iliac crest, the fibula, the ribs, the mandible, and even parts of the skull. As indicated in Table 15.1, such a graft would contain osteogenic properties (marrow-derived osteoblastic cells as well as preosteoblastic precursor cells), osteoinductive properties (noncollagenous bone matrix proteins, including growth factors), and osteoconductive properties (bone mineral and collagen). Autologous bone graft is completely histocompatible, and there is no associated risk for disease transmission. Therefore, autologous bone grafting is still considered to be the gold standard for restoring bone defects in musculoskeletal reconstruction. However, there are drawbacks to the use of autologous bone grafts. An additional surgical site is required, in effect adding another potential location for postoperative pain and complications, such as infection, hemorrhage, muscle weakness, and nerve damage. Limited graft availability is another drawback, particularly in children and in revision reconstructive surgery. Several types of autografts are available and each one presents with different features.

Autologous Bone Marrow

Autologous bone marrow, usually aspirated from the iliac crest, is often used to stimulate skeletal repair. Mesenchymal stem cells in bone marrow are able to differentiate into various tissue types,

such as bone, cartilage, ligament, and tendons under the influence of tissue-specific growth factors. A frequent clinical application of this concept is the treatment of tibia nonunions with the injection of autogenous bone marrow at the fracture site. Drawbacks include diffuse of the injected material away from the graft site, as well as limited numbers of stem cells in the bone marrow.

Autologous Cancellous Bone

Cancellous autografts are incorporated by the formation of new bone on a necrotic bed. Autologous cancellous bone presents with increased osteoconductive and osteogenic activity as a result of its large surface area and its ease in revascularization. However, mechanical strength is limited in early stages following implantation. Cancellous bone incorporation is divided in two phases. During the primary phase, a sequence of hemorrhage, inflammation, revascularization, and osteoinduction takes place for a period of 4 weeks following implantation. During the secondary phase, osteoblasts line the scaffold presented by the trabeculae of the graft and deposit a seam of osteoid that surrounds and entraps the original dead bone, thus increasing mechanical strength of the construct. This entrapped dead bone is eventually resorbed by osteoclasts as part of a remodeling process, which may take several months to complete.

Autologous Cortical Bone

Although cancellous and nonvascularized cortical bone grafts incorporate in a similar manner during the early stages, cortical grafts present with impeded

revascularization ability and reduced osteoinductive activity. Unlike cancellous autografts, cortical grafts remain a combination of necrotic and new bone for a prolonged period. Remodeling of nonvascularized cortical grafts initiated by osteoclastic activity may lead to bone loss, resulting in up to 75 % reduction in mechanical strength. This weakness persists for months to years after surgery depending on the size of the bone graft used. The end result is complete resorption of the graft with concomitant replacement with viable new bone, known as creeping substitution. Cortical autografts demonstrate creeping substitution most prominently at the graft-recipient site. The substitution progresses transversely and parallel to the long axis of the graft. As a result, initial repair is greater at the graft-host junction; repair then proceeds to the mid-regions between the graft-host interfaces.

Vascularized Autologous Bone Graft

All bone requires a blood supply in the transplanted site. Depending on where the transplant site is and the size of the graft, an additional blood supply may be required. For these types of grafts, extraction of the part of the periosteum and accompanying blood vessels along with donor bone is required. This kind of graft is known as a vascularized bone graft. Common sites for vascularized graft harvesting include the fibula and the distal radius. Vascularized cortical autografts heal quickly at the graft-recipient junction, because the resorption and remodeling process closely resembles that of normal bone. Residual weakness of the construct is minimal [11–17].

Allograft [11–15, 18]

Allograft bone, like autogenous bone, is derived from humans; the difference is that allograft is harvested from an individual other than the one receiving the graft. Main reasons for choosing allograft instead of autograft include insufficient autograft quantities, donor site morbidity, and occasionally unsatisfactory biologic activity. The primary goal of allograft use is increased structural support. Allograft bone is taken from cadavers that have donated their bone so that it can be used for

living people who are in need of it; it may also be taken from removed bone tissue during an operation, such as a femoral head during hip replacement surgery. It is typically sourced from a bone bank. The greatest concern with using allograft materials is the possibility of viral disease transmission, including hepatitis C, hepatitis B, and human immunodeficiency virus (HIV). However, strict measures have been applied to ensure safety of the transplanted tissue. At the same time, processing technology has incorporated methods, such as low-dose (<20 kGy) irradiation, physical debridement, ultrasonic or pulsative water washes, ethanol treatment, and antibiotic soaking (4 °C for at least 1 h), to remove antigenic components of the graft to avoid induction of a host immune response, to ensure sterility, and to retain certain biologic and biomechanical functions. There are several types of allografts available, and each one presents with different features.

Allograft Cancellous Bone

As with autologous cancellous bone, cancellous allografts act as a scaffold onto which the host lays down new bone. However, results with cancellous allograft are significantly poorer, especially due to an aggressive immune response of the host following implantation. This aggressive immune response leads to the destruction and eventual inhibition of the essential osteoinductive growth factor-mediated response requisite for bone graft incorporation. Revascularization is also delayed. The most common type of cancellous allograft is cancellous chips. Allograft cancellous chips are incorporated more completely and significantly faster than the allogenic cortical bone grafts because they are revascularized more easily. However, the allografts are never completely resorbed by the host osteoclasts and remain entrapped within the host bone many years after transplantation. Cancellous chips have been used in numerous clinical scenarios, such as spinal fusion augmentation and filling of bone defects, particularly in revision joint reconstruction.

Allograft Cortical Bone

Cortical allograft incorporation occurs by sporadic formation of new appositional bone. The lack of vascularization leads to significant weakness of the

graft (compared with cortical autografts) for up to 1 year after surgery. Poor vascularization of large cortical allografts has been attributed to the density of cortical bone, lack of stability (in larger allograft constructs), and immunologic reaction to the grafts. However, smaller segments of allogenic cortical grafts, such as fibular strut grafts used in cervical spine surgery, are more rapidly incorporated because of potentially easier revascularization. Fresh allografts incorporate unsatisfactorily; therefore, processed and preserved allografts (deep-frozen) are favored in clinical practice.

Massive Osteochondral Allografts

Massive osteochondral allografts, comprising diaphyseal cortical bone, metaphyseal cancellous bone, and articular cartilage, are used primarily in joint reconstruction after limb salvage procedures for tumor resection. Osteochondral grafts are deep-frozen to ensure reduction in graft antigenicity. Radiographs are taken as part of preoperative planning to allow the graft to be matched anatomically with the needs of the recipient. During the procedure, the allografts are washed in an antibiotic-free tissue culture medium and cleaned of excessive soft-tissue attachment and bone marrow prior to implantation. The host tissue allows creeping substitution, leading to slow incorporation of these grafts. Most common complication with the use of such massive allografts is nonunion at the site of the host-graft interface. Other complications include allograft fracture, articular surface degeneration that could lead to the need of a subsequent arthroplasty, joint instability, and infection. Clinical and radiographic results of massive osteochondral allografts reproduce variable success rates, ranging from 60 to 90 % in several series.

Allogenic Demineralized Bone Matrix

Mild acid extraction of bone leaves behind growth factors, noncollagenous proteins, and collagen while removing the mineral phase of bone. This demineralized, partially defatted homologous bone matrix provides a suitable framework for cells to populate and produce new bone and also may stimulate the healing response by encouraging MSCs to differentiate into bone-forming osteoblasts. Demineralized

bone matrix (DBM) acts as an osteoconductive, and possibly as an osteoinductive, material. It is widely used in orthopedic, neurosurgical, plastic, and dental areas. More than 500,000 bone-grafting procedures with DBM are performed annually in the USA. It does not offer structural support, but it is well suited for filling bone defects and cavities. The osteoinductive nature of DBM is presumably attributed to the presence of matrix-associated bone morphogenetic proteins (BMPs) and growth factors, which are made available to the host environment by the demineralization process. The osteoinductive properties of DBM are influenced by several factors related to processing methods, such as choosing the appropriate demineralizing agent, applying sonication during processing, demineralizing time, and reducing mineral content in the implant, and size of the DBM particle. Clinical results have not been uniformly favorable; however, a variable clinical response is attributed partly to nonuniform processing methods found among numerous bone banks and commercial suppliers. DBMs remain reasonably safe and effective products [4, 18, 21–23].

Synthetic Bone Substitutes

Bone-graft substitutes have also been developed as alternatives to autologous or allogenic bone grafts. They consist of scaffolds made of synthetic or natural biomaterials that promote the migration, proliferation, and differentiation of bone cells for bone regeneration. Although they lack osteoinductive or osteogenic properties, synthetic bone substitutes and biomaterials are already widely used in clinical practice for osteoconduction. DBM and collagen are biomaterials, used mainly as bone-graft extenders, as they provide minimal structural support. A large number of synthetic bone substitutes are currently available, such as HA, β -TCP and calcium phosphate cements, and glass ceramics. These are being used as adjuncts or alternatives to autologous bone grafts, as they promote the migration, proliferation, and differentiation of bone cells for bone regeneration. Especially for regeneration of large bone defects, where the requirements for grafting material are substantial, these synthetics can be used in combination with autologous

Table 15.2 Bone graft incorporation

Factor	Positive	Negative
Local	Vascular supply	Vascular impairment
	Large surface area	Local bone disease
	Mechanical stability	Mechanical instability
	Mechanical loading	Mechanical unloading
	Growth factors	Infection
Systemic	Growth hormone	Corticosteroids
	Thyroid hormone	NSAIDs
	Vitamins A and D	Smoking
	Insulin	Sepsis
	Parathyroid hormone	Diabetes
		Metabolic bone disease

Modified from Khan et al. [8]

bone graft, growth factors, or cells. Furthermore, there are also nonbiological osteoconductive substrates, such as fabricated biocompatible metals (e.g., porous tantalum) that offer the potential for absolute control of the final structure without any immunogenicity. Research is ongoing to improve the mechanical properties and biocompatibility of scaffolds; to promote osteoblast adhesion, growth, and differentiation; and to allow vascular ingrowth and bone-tissue formation. Improved biodegradable and bioactive three-dimensional porous scaffolds are being investigated, as well as novel approaches using nanotechnology, such as magnetic bio-hybrid porous scaffolds acting as a cross-linking agent for collagen for bone regeneration guided by an external magnetic field or injectable scaffolds for easier application [4, 19–22].

Impairment of Bone Graft Healing

A variety of factors have been associated with impairment of bone graft incorporation (Table 15.2). Smoking inhibits cellular proliferation and causes vasoconstriction. Systemic steroid use leads to inhibition of the differentiation of progenitor cells down the osteoblastic pathway. The effects of nonsteroidal anti-inflammatory drugs are well known; they inhibit prostaglandin formation, leading to diminished local blood flow,

thereby delaying graft resorption. Malnutrition, especially calcium and phosphorus deficiencies, has been associated with delayed mineralization of new bone [10].

Bone Grafting in Hip Surgery

Total hip replacement (THR) is a common procedure that is performed increasingly often. Approximately 285,000 THR procedures are performed in the USA each year. Although most patients have satisfactory long-term stability, approximately 17 % of prosthetic hips fail, thus requiring revision surgery. This failure is attributed to patients being more active and having hip replacements earlier and more frequently than in the past. Frequently, when hip prosthesis revision is undertaken, there is significant bone deficiency present; this clinical setting presents one of the most challenging circumstances in hip surgery. There is a variety of surgical technique and hardware strategies available to address this problem [4, 22, 23].

Acetabular Bone Grafting [4, 9, 22, 23, 25–36]

In revision hip arthroplasty, bone stock deficiency is the major challenge in reconstructing the acetabulum. The most common causes of bone deficiency include debris-induced periprosthetic osteolysis (with or without loosening), stress shielding, implant migration, infection, and iatrogenic bone loss during implant extraction. Wear debris-generated osteolysis and loosening of the acetabular cup usually cause proximal and posterior migration of the cup with bone resorption in the posterosuperior wall, giving the acetabular cavity an oblong shape. With advancing bone loss, reconstructive techniques became more complex. As primary hip arthroplasty is used to treat younger and more active patients, the incidence of revision surgery is likely to further increase, although this factor may be affected by modern wear-resistant bearing surfaces and vigilant follow-up analysis. In patients treated with revision acetabular surgery, the best

chance of long-term stable fixation can be achieved with initial stable socket fixation, restoring the center of rotation, and maximizing contact between the host bone and the implant. Limiting the loss of acetabular bone stock is a major factor in achieving these goals.

Diagnosing and Assessing Acetabular Bone Loss

Plain Radiographs and Special Views

Preoperative assessment of acetabular bone loss before revision surgery is critical because the amount and location of pelvic osteolysis can determine the type and success of revision surgery. Plain AP and cross-table lateral radiographs provide important initial information about the size and location of osteolytic lesions involving the acetabulum and the status of cup fixation. Judet oblique views add valuable information, especially about the integrity of the acetabular columns. Changes in the location or orientation of the cup on serial radiographs, along with the width and extent of bone-implant radiolucent lines, indicate whether socket fixation is stable or loose. The amount and location of bone stock loss are assessed with the Paprosky classification system [23, 24].

CT Scans

CT with metal artifact minimization has been shown to be more sensitive than plain radiographs for identifying and quantifying osteolysis around cemented and cementless cups. Because CT scans show the actual extent and location of the osteolysis, they are useful adjuncts in planning cup revision in selected patients. CT scans can also be used to more accurately evaluate the quality of graft incorporation.

Magnetic Resonance Imaging

Recent advances in imaging techniques make visualization and quantification of osteolysis feasible with MRI, particularly if titanium alloy prostheses are used. The metal artifact from a prosthesis can make it challenging to assess periacetabular osteolysis, and images are prone to motion artifact, particularly if the patient is uncomfortable lying in a

fixed position for a prolonged period. MRI is most effective in showing small areas of osteolysis, whereas CT is the most accurate modality for calculating lesion volume. Other advantages of MRI include superior soft-tissue contrast, which allows assessment of the surrounding soft-tissue envelope including regional neurovascular structures relative to the pseudo-capsule and implant-bone interface, as well as particle-induced synovitis.

Acetabular Defect Classification

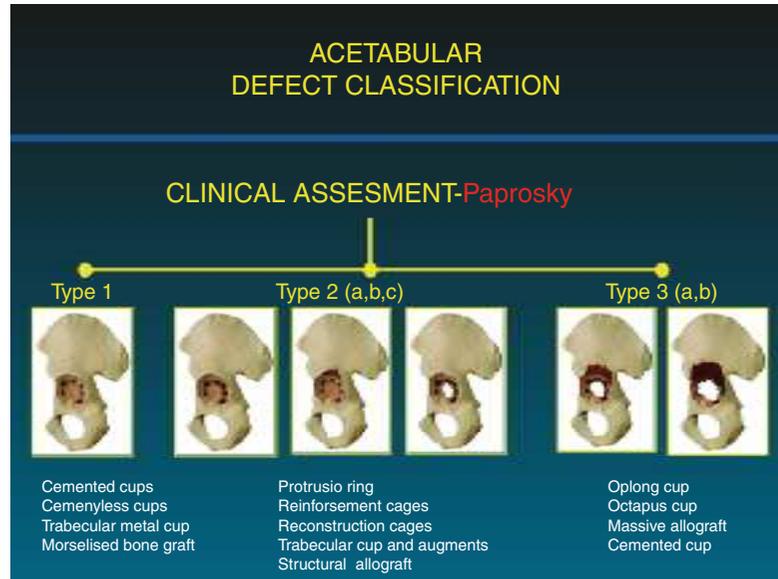
[27, 33, 36]

There are two major classifications of bone stock loss associated with a previously placed acetabular cup. The American Academy of Orthopaedic Surgeons (AAOS) developed its acetabular defect classification system to improve uniformity in how acetabular revisions are reported. Type 1 describes peripheral segmental (superior, anterior, posterior) or central segmental defects, type 2 cavitary peripheral (superior, anterior, posterior) or central defects, type 3 combined deficiency, type 4 pelvic discontinuity, and type 5 arthrodesis. Although the appropriate classification category may be suggested by findings seen at radiography or advanced imaging, the final determination of the defect type is made at surgery. The Paprosky acetabular defect classification system was subsequently proposed and includes assessments made both by using radiologic findings and at surgery. In addition, this classification system includes treatment recommendations (Fig. 15.1).

Surgical Management Options for Massive Acetabular Bone Loss

The reconstruction of massive acetabular bone defects remains a challenging issue in hip arthroplasty, especially in revision surgery. The method of acetabular revision must be individualized to meet the mechanical and biologic challenges specific to each reconstruction. A variety of surgical options are available for treating Paprosky 3 defects. Jumbo cups, the high hip center technique, bilobed

Fig. 15.1 Paprosky acetabular defect classification system and treatment options



implants, anti-protrusio cages, and nonmodular, high porous metal components (Trabecular Metal System) are part of the armamentarium available for revision hip arthroplasty. However, the use of bone graft is often essential for addressing bone defects in addition to the techniques mentioned before. Bone graft alternatives include the impaction grafting technique, the use of a structural allograft, and the use of a total acetabular segmental allograft with a cage. Defects, other than Paprosky type 3 defects, can usually be managed with hemispherical shells with or without bone graft or particulate allograft. If massive bone loss is anticipated, extensile approach is required. This can be achieved with a posterior approach, trochanteric slide, or in some instances, with a direct lateral approach [36].

Acetabular Impaction Grafting [9, 23, 25, 27, 32–36]

When the surgeon is faced with large cavitory acetabular defects or a large ectatic femoral metaphysis or diaphysis, impaction bone-grafting techniques are useful (Fig. 15.2). Impaction bone grafting of the acetabulum involves packing the cavitory defects with compressed particulate graft followed by insertion of either a cemented



Fig. 15.2 Cotyloplasty: an old satisfactory impaction autografting technique (cemented cup) for the reconstruction of a deficient acetabulum. Sound consolidation of the graft at 25-year follow-up

or cementless component. When applied properly, impaction grafting can provide sufficient support for an implant that otherwise would be inadequately supported by native bone. Impaction grafting can fill bone deficiencies to provide

better bone stock for future reconstructions, should they be required. As more recent long-term data become available on the results of impaction grafting, ongoing evaluation will provide perspective on the value of the techniques and their place in the revision hip armamentarium.

Biology of Impaction Bone Grafting [11, 14]

Preparation of Particulate Graft for Impaction Bone Grafting

Allogenic particulate graft is the most common source of graft material used in impaction bone grafting. Although autogenic bone graft can be used, its source of supply is limited, and it carries the risk of donor site morbidity. For most revision hip reconstruction applications, the size and shape of the bone defects encountered favor the use of allograft rather than autograft bone. Particulate grafts typically are easier to use than bulk grafts because they do not require contouring to fit a defect. The use of particulate bone graft for impaction grafting requires uncontained bone defect or conversion of an uncontained defect into a contained one with the use of allograft struts, bulk structural allografts, or metal mesh. Particulate grafts are thought to have a better chance of being incorporated into host bone than structural grafts. The mechanical properties of particulate grafts vary according to the size of the particles of the graft and how densely the particles are packed into the bone. Although traditionally only bulk grafts have been used when structural prosthetic support is needed, densely packed particulate grafts also have been used recently to provide structural support of implants.

Incorporation of Particulate Graft

Little is known about the biologic fate of particulate bone grafts in joint arthroplasty. This deficiency in knowledge is related in large part to the difficulty of interpreting what has happened to the bone graft on radiographs and to the paucity of long-term autopsy retrievals that provide histological data on the fate of bone grafts. Cancellous autograft bone is the benchmark for osseous integration against which impaction allografting is measured. Autograft has

all of the characteristics required to stimulate new bone formation: osteoconductivity, osteogenicity, and osteoinductivity. Autograft provides the biologic stimulus via local growth factors to induce the mesenchymal cells to differentiate into mature osteoblasts. In contrast, allograft bone is primarily osteoconductive, acting as a scaffold to enhance bone formation on its surface. When densely packed, particulate bone graft can provide mechanical support for a construct. In a recent biomechanical study, Dunlop et al. suggested that mechanical properties of particulate cancellous allograft can be improved by prewashing the graft to remove fat and marrow fluid, thus yielding a compacted graft that is more resistant to shear. Some investigators feel that the optimal size for graft particles should be 7–10 mm; this is certainly notable because most standard bone mills yield graft particles that are 2–5 mm in size. Little information is available on the influence of cancellous graft thickness, cancellous graft particle size, cancellous graft preparation, and packing density on speed and completeness of graft incorporation. The biology of bone graft incorporation in total joint arthroplasty is characterized by an early phase of inflammation followed by revascularization. The graft matrix is invaded by host granulation tissue as early as 2 days after implantation. Osteoclastic bone resorption and new bone formation are observed by 4 weeks. This phase is gradually followed by the resorption and replacement of the graft, which is completely replaced by viable new bone between 6 months and 1 year after surgery. Compared with autograft, the process of incorporation of allograft occurs at a slower rate, in part because of an inflammatory and immunologic host response to the grafted bone. Sorensen et al. used positron emission tomography scans to assess angiogenesis after impaction femoral grafting. They noted increased blood flow and bone formation adjacent to the allograft as early as 8 days after surgery.

Histology of Retrieved Particulate Allograft for Treatment of Acetabular Defects

In revision hip arthroplasty, particulate allograft has been used to treat cavitary acetabular defects, some segmental acetabular defects, and contained

or containable cavitory femoral defects. In a post-mortem analysis of three specimens, Heekin et al. [11–14] found a time-dependent incorporation process with progressive envelopment of the allograft trabeculae by host bone, rimmed by normal osteoblasts. The morcellized allograft bone had been in situ in three patients for 18, 53, and 83 months. Distinction between the allograft and host bone was difficult by 83 months. Van der Donk et al. [11–14] reported on 24 biopsies of acetabular impaction bone grafts in 21 hips (20 patients). Sixteen of the patients had been treated originally with impaction grafting for defects encountered at revision surgery. The biopsies were obtained during surgical procedures for revision surgery at 3 months to 15 years after the initial impaction grafting. The histology findings were similar to those described above, with a few exceptions. Three stages of incorporation were described: stage 1 consisted of nonvascularized graft remnants; stage 2 showed revascularized incorporating bone graft, dynamic bone resorption, and new bone apposition; and stage 3 resulted in graft incorporation with newly formed trabecular bone structures. The investigators also noted areas of loose fibrous stroma on which new bone had formed. In addition, variable amounts of unincorporated graft also were noted: 30 % of the graft incorporated by 6 months and 90 % by 10 years [11–14].

Acetabular Impaction Grafting Surgical Technique [27]

Acetabular impaction grafting has been popularized by Schreurs et al. [27]. The technique was initially described with a cemented acetabular component but has since become commonly applied with cementless designs. After exposure of the acetabulum, the failed component is removed and the bony defect is assessed. All existing cement and fibrous tissue must be removed. A contained defect must be present. When the defect is uncontained, it can be converted to a contained defect with the use of mesh. When a cementless component is to be used, the acetabulum is reamed to allow press-fit fixation of the cup between the

anterior and posterior wall or posterior column. Morcellized bone graft is impacted into the defect with tamps or reverse reaming. The cementless cup is impacted into place and fixation is supplemented by screws. When a cemented component is to be used, the contained defect is filled with particulate graft that is aggressively impacted to allow for seating of the cemented component. Cement is placed into the grafted defect and pressurized. The acetabular polyethylene component is cemented into place.

Clinical Applications and Results of Impaction of Particulate Grafts for Acetabular Reconstruction [23, 27, 32–38]

Since its initial description as a treatment of acetabular protrusion, impaction bone grafting in combination with a cemented socket has been used in revision total hip arthroplasty when there is a loss of bone stock. The initial proponents of this procedure impacted the graft using the trial components and stressed that this is a key technical step. When segmental defects are present, they can be converted to cavitory defects by closure with a metal wire mesh that provides containment for the particulate graft. Results with up to a 15-year follow-up have been reported with this technique in 60 revision procedures using allograft bone in 35 hips, autograft bone from the iliac crest in 9 hips, and a combination of both in the remaining 16 hips. The implant survival rate at 12 years was 85 %, with revision of the acetabular component for loosening as the end point. These encouraging clinical results were supported by histological examination of biopsy specimens showing remodeling into a new trabecular bone structure [23]. More recently, Schreurs et al. [27] reported on a series of 62 consecutive acetabular revisions in 58 patients (mean follow-up, 16.5 years). The Kaplan-Meier survivorship for the cup with end-point revisions for any reason was 79 % at 15 years. Schreurs et al. [37] also reported on the use of this technique in 42 hips (37 patients) younger than 50 years of age (average age, 37.2 years). The technique was

used to increase bone stock in 23 primary and 19 acetabular revisions. The Kaplan-Meier survivorship with acetabular revision for any reason as the end point was 80 % at 20 years. The quality of the impaction grafting, which is a demanding and time-consuming procedure and the use of fresh-frozen allograft bone were important factors in their success. The ability to restore bone in this subset of patients undergoing arthroplasty is encouraging. Other reports of similar procedures with a shorter follow-up, however, have not been as satisfactory; failure rates were as high as 31 %. Risk factors associated with failures include combined segmental and cavitary defects, malpositioned components, and use of allograft rather than autograft [27, 37]. The same group updated their results [38] up to 20–28 years follow-up. Eight additional cups had to be revised, four because of aseptic loosening, three because of wear, and one during a revision of the stem. Three additional cups were considered loose on radiographs. Survivorship of the acetabular reconstructions, with an end point of revision for any reason, was 73 % after 20 years and 52 % after 25 years. With revision for aseptic loosening as the end point, survival was 85 % after 20 years and 77 % after 25 years; for signs of loosening on radiographs, survival was 71 % at 20 years and 62 % at 25 years. In conclusion, their previous results have declined, but the technique of using impacted morcellized bone graft and a cemented cup is useful for the purpose of restoring bone stock in young patients whose acetabular defects require primary or revision total hip arthroplasty. In North America, cementless implants have become the most common method of reconstruction in acetabular revision surgery because of their technical simplicity, good clinical results, and potential for long-term biologic implant fixation. For cementless sockets, the more host bone contact that can be achieved, the better the likelihood of long-term success. Implant surface contact with <40 to 50 % of native bone has been associated with a higher rate of failure. Most cavitary and medial segmental acetabular defects can be filled with morcellized bone graft, followed by implantation of a cementless hemispherical acetabular component

[35]. Non-cemented reconstruction is the preferred method of acetabular reconstruction in revision THA, specifically for Paprosky types I and II defects [39]. Several studies have demonstrated favorable midterm (minimum, 5- to 10-year) results using non-cemented acetabular sockets with a rate of aseptic loosening ranging from zero to 11 % and >90 % survivorship with aseptic loosening as the end point [40–43]. Della Valle et al. [44] reported the longest clinical follow-up (mean, 15 years; maximum, 19 years) of non-cemented acetabular cup use in revision THA. In a cohort of 138 hips (131 patients), only 1 cup (0.7 %) was revised for aseptic loosening. Cup survivorship was 96 % using revision for aseptic loosening as an end point. A total of 19 cups were revised for recurrent instability, infection, or femoral component complications. These results are consistent with other revision series, which demonstrate worse clinical outcomes following revision THA than following primary THA because of soft-tissue compromise, bone deficit, and an inability to perfectly restore hip biomechanics. Non-cemented acetabular reconstruction requires column and partial rim support as well as the use of supplemental fixation. Many manufacturers now market porous metal options to enhance initial stability and promote biologic fixation in deficient bone beds. Structural allografts also can be used in these cases. Early results have demonstrated enhanced biologic fixation and decreased stress shielding surrounding porous metal surfaces [45].

Structural Allograft

Bulk structural allograft is an excellent option in cases of inadequate host acetabular bone to address the issues of component fixation and stability. The allograft can provide initial structural stability of the cementless component until host bone ingrowth into the acetabular component occurs. The need for increased bone stock, especially in young patients for any future reconstructions, makes allografts the preferred choice of treatment in this group of patients. However, concerns exist regarding the potential for allograft

resorption, infection, and potential loosening of the construct. Several studies have evaluated the midterm results of structural allograft in revision THA. Graft type (femoral head, distal femur, total acetabulum) and surgical technique are the most important factors in determining clinical success. Recently, Lee et al. [46] retrospectively reviewed 74 patients treated with minor column shelf structural allograft for uncontained host acetabular bone deficits measuring 30–50 %. Minimum clinical follow-up was 5 years (mean, 16 years). With re-revision for aseptic loosening as an end point, cup survivorship at 15 and 20 years was 67 and 61 %, respectively, and graft survivorship was 81 %. Satisfactory mid- and long-term results have been achieved with the use of structural allograft in revision THA; however, the availability of porous metal augments has led to a reduction in the use of allograft [36].

Modular Porous Metal Augments in Cementless Reconstructions

Recently, severe acetabular bone loss may be treated with the use of non-cemented hemispheric or elliptical components in combination with modular augments [47]. As it is obvious, the use of a metal shell and one or more modular augments optimizes bone contact and positioning of the used components. Most surgeons utilize cement to stabilize these implants to host pelvic bone, although independent fixation is another option. The augment offers structural support for the acetabular component until bone ingrowth occurs (Fig. 15.3). All augments are secured first to the host bone with screws, then to the non-cemented acetabular shell with cement. Morcellized bone graft is placed into any remaining cavities before the shell is impacted into position. Additional screws are placed through the cup into the ilium. Non-cemented porous sockets used in conjunction with modular porous metal augments have demonstrated acceptable clinical results in the setting of Paprosky type IIIA defects. Van Kleunen et al. [48] evaluated 97 hips (90 patients) with Paprosky types II, IIIA, and IIIB defects that were managed with non-cemented acetabular shells with porous metal augments.

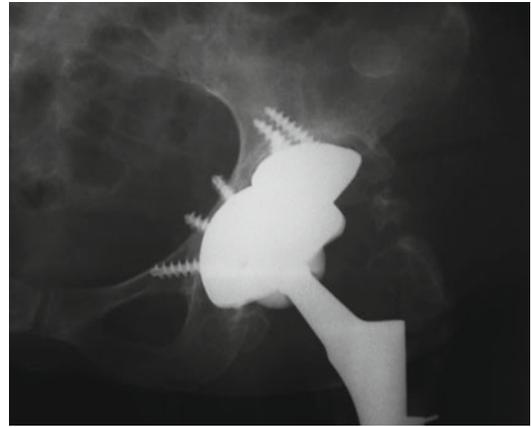


Fig. 15.3 Trabecular metal acetabular cup and augments. Satisfactory clinical and radiological result at 6-year follow-up

There were no cases of aseptic loosening at a mean follow-up of 45 months. For patients with pelvic discontinuity and severe bone loss, treatment options include custom triflange cups with plate fixation, cup-cage constructs, a hemispheric shell, or acetabular impaction grafting. Recently, a distraction technique that combines a hemispheric shell and porous metal augments has been used to manage pelvic discontinuity. Regardless of the reconstruction option selected, healing of pelvic discontinuity is difficult. In the setting of pelvic discontinuity, the distraction technique involves the use of non-cemented, hemispheric components and augments. A reamer is used until two points of contact are made, typically posteroinferior to anterosuperior. Once contact is made, the size of the non-cemented acetabular shell is estimated. A series of augments is used to decrease the volume of the acetabulum. The augments may provide primary stability or primary fixation. The use of augment distraction for the management of pelvic discontinuity is technically difficult, and only short-term follow-up data are currently available. The use of modular porous metal augments with a non-cemented socket using distraction has been shown to be effective in managing Paprosky type IIIB defects with pelvic discontinuity. In one study, 13 patients were retrospectively reviewed at a mean follow-up of 2.6 years [49]. At final follow-up, only 1 hip had possible radiographic loosening



Fig. 15.4 Reconstruction acetabular cage with allograft. Satisfactory clinical and radiological outcome at 7 years

secondary to screw breakage, and the other 12 were radiographically stable. No patient required repeat surgical intervention. The early results with porous metal augments appear to be promising. However, long-term follow-up data are necessary because of concerns regarding the management of these augments should infection develop after ingrowth has occurred [36].

Ring and Cage Reconstruction

In a revision THA, setting rings and cages are used when deficient bone stock is present (Fig. 15.4). These devices can act as a scaffold while protecting morcellized or structural allograft during the bone remodeling phase. The two types of ring used are the roof reinforcement ring and the anti-protrusion cage. The major advantages of rings and cages are the ability to cement a liner in any position independent of the ring position and the elution of local antibiotics from the cement. The major disadvantage is the risk of cage fracture or loosening resulting from lack of biologic fixation. The use of cages has decreased because of cage breakage over time and because of increased enthusiasm for the use of porous metal components and augments. Midterm results with the use of a ring or cage have been satisfactory [36, 50–52].

Cup-Cage Reconstruction

The cup-cage construct can be used. Recent studies reveal that cup-cage constructs may be a reliable option for the management of pelvic discontinuity [53, 54]. In this technique, a non-cemented acetabular shell with or without a porous metal augment is fixed to host bone. An anti-protrusion cage is then placed in the non-cemented shell to stabilize the discontinuity. Proponents of this technique believe that the cage provides initial stabilization of the discontinuity, thereby allowing time for biologic fixation of the porous non-cemented shell and augment to host bone. Although early results following reconstruction with a porous metal shell in conjunction with modular porous augments and an anti-protrusion cage seem promising, long-term follow-up studies are needed [36].

Triflange Reconstruction

In some cases, defect bridging techniques are required instead of defect matching techniques. Paprosky type IIIA and IIIB defects typically require management with a defect bridging technique; major structural allografts or anti-protrusion cages may be considered as salvage options for these defects. To generate a custom triflange construct, a plastic hemi-pelvic model is developed based on a three-dimensional CT scan of the patient's pelvis [55, 56]. This model is used to create a custom porous or hydroxylapatite-coated flanged titanium device. Model generation preoperatively can be very helpful for understanding bone defects and for teaching purposes before surgery [36].

Femoral Bone Grafting in Hip Surgery [57–78]

Most failed arthroplasties manifest some degree of bone loss, which can range in severity from negligible to unsalvageable. The causes of bone loss include (1) osteolysis secondary to particulate debris, (2) stress shielding secondary to

adaptive remodeling, (3) fretting of the bone from repetitive micromovement of a loose prosthesis, (4) fracture, and (5) damage to residual bone stock during failed implant removal. Proximal femoral bone stock deficiency provides a major challenge for revision hip arthroplasty and is likely to account for a significant future caseload. Various surgical techniques have been advocated including impaction allografting, distal press-fit fixation, and massive endoprosthetic reconstruction.

Diagnosing and Assessing Femoral Bone Loss

Accurate assessment of the condition of the host bone is imperative during preoperative planning to ensure a successful revision outcome. The most comprehensive and widely accepted classification system for proximal femoral bone loss is the American Academy of Orthopaedic Surgeons (AAOS) system, which was designed to aid in the preoperative planning and treatment of femoral deficiency in primary and revision arthroplasty. Bone loss is classified as segmental, cavitary, or combined, and each type is subclassified according to severity. A segmental defect is defined as loss of any portion of the supporting cortical shell of the femur. Cavitary defects are characterized by erosion of the cancellous bone with an intact cortex. Other abnormalities include femoral ectasia (femoral expansion with severe cortical thinning and complete loss of cancellous bone, which is found in long-standing implant failure), malalignment (either angular or rotational), femoral stenosis (narrowing or obliteration of the canal), and femoral discontinuity (resulting from femoral fracture, with or without the presence of an implant). The type and severity of the bone loss generally dictate the available treatment options [61–65]. The Paprosky femoral defect classification system has also been proposed and includes assessments made both by using radiologic findings and at surgery [23, 24]. In addition, this classification system includes treatment recommendations (Fig. 15.5).

Surgical Management Options for Massive Femoral Bone Loss

Mild deficiency can generally be treated by using standard primary reconstructive techniques, using either cemented or non-cemented prostheses. With considerable bone loss, however, the femur does not have the structural integrity to support an implant, and other options must be explored. The surgeon must decide between reconstruction of bone loss with either an implant (e.g., calcar-replacement design) or an allograft. Calcar-replacement and proximal femoral replacement prostheses were initially developed for reconstruction of the femur after tumor resection, but the indications were later broadened to include failed hip arthroplasty and significant proximal femoral bone loss. However, these types of implants are associated with a high incidence of complications, including dislocations, abductor problems, limb length discrepancy, fractures, heterotopic ossification, and sciatic nerve palsy. On the basis of available reports, the use of a proximal femoral replacement prosthesis should generally be limited to elderly and inactive patients with massive bone loss for whom the only other option is resection arthroplasty [65–71].

Structural and Cancellous Allograft

An alternative for management of proximal femoral bone loss is the use of allograft bone, which is available in either bulk form (i.e., structural grafts) or cancellous grafts. Cancellous grafts differ from cortical grafts in the rate and completeness of incorporation into the host. The increased porosity of cancellous grafts allows more rapid vascularization and the recruitment of osteogenic cells. New bone forms on the preexisting cancellous trabeculae, which are eventually completely replaced. Vascular ingrowth into cortical grafts is slower, and the incorporation process is never as complete as it is for cancellous grafts. Even after several years, a mixture of viable new bone and a cellular allograft bone remains. The theoretical advantages of reconstruction with structural or bulk allograft bone instead of metal include biologic reattachment of host bone and muscle, more



Fig. 15.5 Paprosky femoral defect classification system and treatment options. (a) Type I, (b) type 2, (c) type IIIA, (d) type IIIB, and (e) type IV

normal gradation of forces from the prosthesis to the host bone, use of a more conventional design and a less expensive implant, and restoration of bone stock. Restoration of bone stock with either

bulk or structural graft offers the potential advantage of facilitating future revision surgery. The disadvantages associated with the use of allograft bone include the risk of disease transmission. The

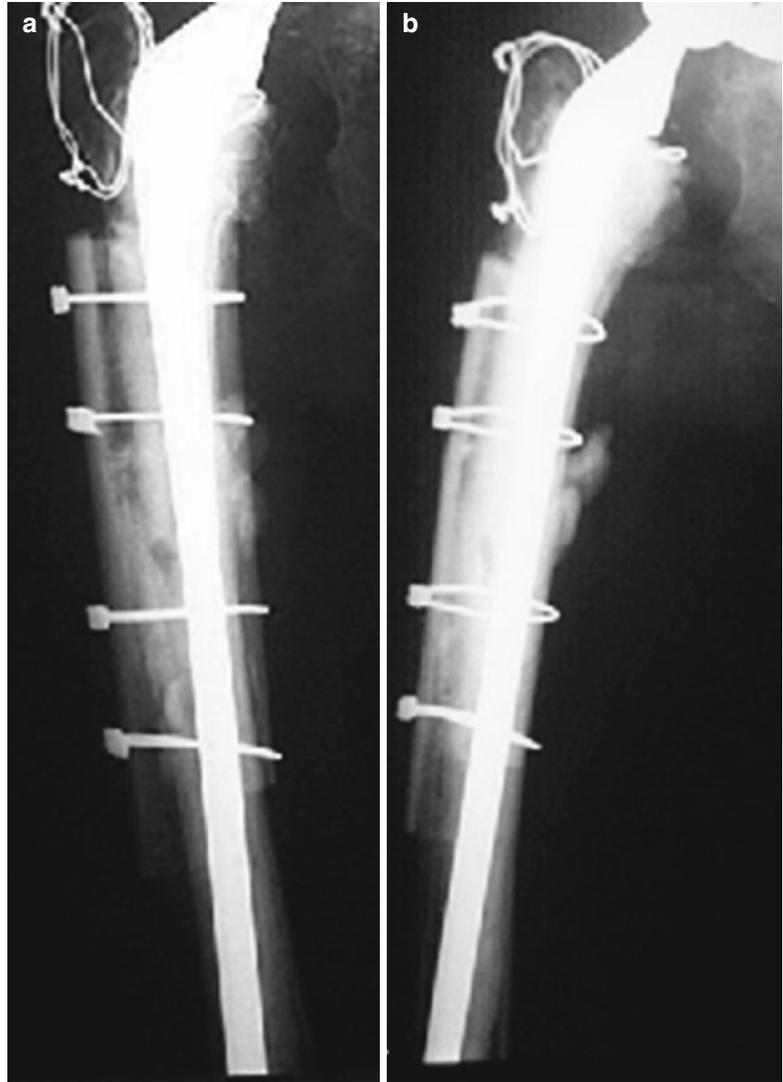
risk of viral transmission from processed, freeze-dried cancellous chips is extremely low (less than 1 in 3,000,000). The risk of transmission through fresh-frozen, unprocessed bone is similar, although not identical, to the risk of disease transmission through blood transfusion (1 in 440,000 to 600,000). Even with the use of post-processing techniques such as radiation and chemosterilization, the risk of viral disease transmission cannot be totally eliminated. The risk of pyogenic infection is also increased with the use of bulk allograft. Infection is usually caused by Gram-positive organisms, with a reported incidence of 11.7 %, although most infections are not directly transmitted by the graft. Nonunion or graft resorption may occur; autografting host-allograft junctions and rigid fixation will decrease the risk of nonunion [62, 65].

Clinical Applications and Results of Use of Structural and Cancellous Grafts for Femoral Reconstruction

Cortical strut allografts are often used to reconstruct non-circumferential segmental defects (Fig. 15.6). Emerson [57] reviewed the data on 58 patients who underwent revision total hip arthroplasty with cortical onlay strut grafts (proximal medial strut placement was most commonly used) for reconstruction of femoral bone deficiencies. At an average of 34 months of follow-up, the rate of graft union was 96.6 %, the average time to union was 8.4 months, and only 22 % of the grafts showed any evidence of resorption. The radiographic sequence of strut graft incorporation to the host includes edge roundoff, scalloping, incomplete and complete bridging to the host cortex, formation of cancellous bone, incorporation, and resorption. Pak et al. [58] studied 95 cases in which cortical strut allografts had been used. At a mean follow-up of 4.75 years, bone union had occurred in 87 cases (92 %); in those cases in which the bone did not unite, it resorbed, resulting in a mechanical failure rate of 7 %. Head et al. [59] examined 265 revisions in which onlay cortical grafting had been used. At follow-up, an average of 8.5 years after surgery, the graft union rate was 99 %, with a mean time to union

of 8.6 months. All of these authors concluded that cortical struts could reliably be used to reconstitute the deficient proximal femur and that they function best with a proximal load-bearing prosthesis that allows the graft to survive and remodel. Circumferential segmental defects extending less than 3 cm distally have been reconstructed with calcar grafts (napkin ring allografts). Allan et al. [60] followed 30 calcar grafts for an average of 36 months. The nonunion rate was 17 %. Resorption of more than half of the graft occurred in 40 % of cases, and subsidence occurred in 43 % of the grafts. Polymethyl methacrylate within the calcar allograft reduced the risk of resorption. Pak et al. [58] followed in which calcar allografts had been in place for a mean of 4.75 years and found that 61 % of the grafts resorbed. On the basis of the results from these studies, the usefulness of these types of grafts appears questionable. Alternatives, such as leaving the components proud, increasing the neck length of the prosthesis, and using cemented calcar-replacement prostheses or extensively coated non-cemented implants with diaphyseal fitting, should be sought. More extensive circumferential defects require large-segment proximal femoral allografts for reconstruction. Reported success rates range from 80 to 85 %. Most series, however, have reported a high rate of complications associated with the use of the grafts, such as nonunion of the graft to the host, dislocation, infection, and allograft fracture. The most commonly used technique involves long-stem components that are cemented to the graft, press-fitted into the host femur, and stabilized at the graft-host junction with a step cut and cerclage wires along with placement of autograft to facilitate union. Allan et al. [60] reported on 40 hips reconstructed with large-fragment allografts followed for an average of 36 months. Union of the allograft bone occurred in 81 % of hips, and graft resorption was not a problem. The success rate was 80 % by these authors. The high rates of dislocation in these series were attributed to decreased postoperative gluteus medius function. The authors stressed the importance of meticulous attachment of the abductors to the allograft, as well as postoperative abduction protection to

Fig. 15.6 Femoral onlay strut allograft. **(a)** 2-year follow-up. **(b)** 7-year follow-up (complete incorporation of the graft)



permit soft-tissue healing. Despite the relatively high rate of complications, reconstruction with large proximal femoral allografts appears to provide potentially better results than use of proximal femoral replacement prostheses. However, long-term follow-up will be necessary to confirm these initial results.

Femoral Impaction Grafting

Femoral impaction grafting has been popularized by Gie et al. and Slooff et al. [9, 14]. Impaction allografting technique, based on the same princi-

ples developed for acetabular reconstruction with the use of morcellized bone graft for the treatment of protrusio acetabuli, has been utilized for femoral reconstruction. Impaction grafting of the femur makes use of special instruments that allow dense packing of the particulate bone graft to create a neo-medullary canal, after which a stem is cemented into the graft. When full-thickness cortical defects are present, they must first be reconstituted with wire mesh or cortical bone grafts. The method relies on the densely packed cancellous graft and cement composite for early support of the femoral implant (Fig. 15.7). Theoretically, with time, the graft gradually is vascularized and

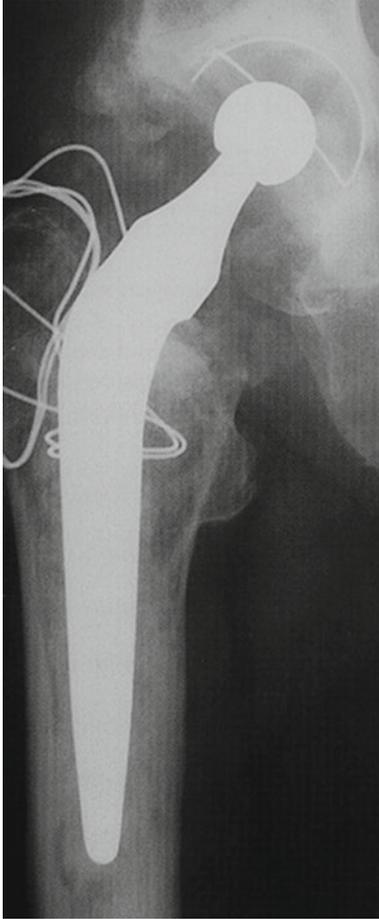


Fig. 15.7 Revision total hip arthroplasty using Charnley Elite femoral stem and impaction grafting technique. Satisfactory clinical and radiological outcome at 9 years

incorporated. Midterm tissue retrievals subjected to histological analysis support this hypothesis, as does radiographic evidence of graft remodeling (visualized as conversion of the graft from an amorphous appearance to a more trabecular appearance).

Histology of Retrieved Particulate Allograft for Treatment of Femoral Defects

The histology of graft incorporation on the femoral side comes from a few postmortem retrievals after impaction grafting for revision of failed femoral components. In these cases, particulate cancellous

allograft (usually fresh-frozen allograft) was packed very densely into the femur; a cemented femoral component was then inserted. At retrieval, three zones of the graft were identified histologically: the “deep” layer closest to the implant, which contained necrotic bone embedded in cement; the “regenerated cortical bone” or outer layer, which was composed of normal cortex and fatty bone marrow with few islands of dead bone; and the “interface zone,” which showed direct contact between methyl methacrylate and osteoid with scattered giant cells [9, 14]. Ullmark and Obrant [72] reported on a prospective series of 19 patients treated with impaction femoral grafting during revision surgery. Biopsy specimens were obtained percutaneously from Gruen zones 1 and 2 at 1–48 months postoperatively. The authors described a healing process that mimics fracture healing as endochondral bone formation occurs in a graft bed of morcellized and impacted allograft containing a fibrin clot. Within the first month, mesenchymal stroma forms within the graft. Over the next few months, new appositional bone formation occurs on dead allograft trabeculae. Fibrous tissue invasion of the graft and new bone formation occurred from the periphery of the graft and was complete by 11 months. As noted above, the innermost layer of the graft bed consisted of dead trabecular graft with fibrous invasion but without evidence of graft resorption. By 48 months, the healing was more nearly complete, but areas of necrotic graft persisted.

Femoral Impaction Grafting Surgical Technique

The femur can be accessed through an anterior, posterior, or transtrochanteric approach. After the femoral component is removed, any remaining cement, fibrous tissue, or debris is removed. When a distal, well-fixed cement mantle is present, it may be left in place as the distal plug for the column of bone graft. Every effort should be made to ensure that the endosteal surface of the femur is clean to facilitate future graft incorporation. Before beginning the insertion of bone graft, the presence of a femoral tube must be confirmed. When segmental defects exist, they must be con-

tained with some type of mesh material, such as Vicryl (Ethicon, Piscataway, NJ) or cobalt-chromium mesh, or allograft struts, to create a continuous femoral tube. The canal is occluded 3 cm below the most distal cavitory deficiency or below the tip of the implant to be used. Cancellous bone graft is prepared in fragments 4–6 mm in size. Using a centering guide to ensure a uniform bone mantle, progressively sized cylindrical packers are used, starting at the bottom of the canal, to compress the morcellized bone; the diameter of the packers is increased until the canal is two-thirds full [9]. At this point, tamps of the same shape but larger than the real prosthesis are used to shape the proximal femoral endosteal cavity. This will create a neo-medullary canal. Impaction of the tamp must be vigorous enough to achieve rotational stability but not so vigorous as to fracture the femur. Once the appropriately sized tamp is in place, a trial reduction may be performed to assess leg length and soft-tissue tension. When the tamp is removed, vacuum-mixed cement is injected into the canal in a retrograde fashion and pressurized before inserting the femoral component.

Clinical Applications and Results of Impaction of Particulate Grafts for Femoral Reconstruction

Short-term clinical results of impaction grafting as originally reported by Gie et al. were encouraging in 56 hips followed for a period of 1.5–4 years [9, 14, 73]. Both radiologic results and histological data demonstrated bone graft incorporation and partial reconstitution of the bone stock. Halliday et al. [74] have reported on longer-term follow-up from the same center. In their study, 226 hips were treated with femoral impaction allografting. Stem survivorship at 10 years was 90.5 %. Fourteen stems required revision: 2 for infection, 10 for femoral fractures, and 2 for loosening. The results have led the authors to recommend the use of long stems when performing this technique. Cabanela et al. have reported on 53 hips at 6.3-year follow-up. Subsidence >3 mm was seen in only two hips [9]. Cancellous remodeling

was observed in 42 hips. Six fractures distal to the tip of the stem were noted. Other short-term studies of the method have reported similar good results, but recently several teams of investigators also have reported early implant failures caused by marked loosening and subsidence and late femoral fractures near the stem tip. The quality of the results may well be correlated with the technical quality of the procedure. This technique was not designed to be executed with expediency; the cancellous bone impaction must be done meticulously to ensure implant rotational and axial stability, and this takes a considerable amount of time. This time factor, along with the risk of disease transmission by the graft and the surging popularity of the titanium, tapered, modular prostheses that can be inserted rather quickly and successfully, has caused the use of impaction grafting to diminish considerably in the last few years. When done well in the proper situation, the results of impaction grafting are excellent. Furthermore, it appears to be the only technique capable of restoring bone stock. The use of impaction bone grafting has not been limited to revisions for aseptic loosening. Tsiridis et al. [75] retrospectively reviewed 89 patients with Vancouver type B2 and B3 periprosthetic fractures treated with impaction allografting and long femoral stems. At 4-year follow-up, 84.3 % of the fractures had achieved union. English et al. [76] reported on the use of femoral impaction allografting during two-stage revisions for infection. In a series of 44 hips followed for a mean of 4.5 years, they noted an infection-free rate of 92.5 % and a revision rate of 2 %. The optimal stem design for use in impaction grafting of the femur is a subject of ongoing debate. The original proponents of the technique have advocated the use of a highly polished, collarless, double-tapered cemented stem to allow for controlled subsidence. However, Leopold et al. [77] demonstrated 92 % survivorship at 6 years in 29 hips treated with a pre-coated, collared, cemented stem. Using a collared stem with impaction grafting, Fetzner et al. [78] found no radiographic loosening in 26 stems at an average follow-up of 6 years. More recently Garvin et al. [69] asked what the survivorship of impaction bone grafting

was at longer follow-up, if the severity of bone loss was associated with failure, and, finally, if longer length stems had improved survival compared with shorter stems. Between 1993 and 2002, 78 femoral revisions were performed in 71 patients using impaction grafting. The average age of the patients was 67 years (range, 33–84 years). Sixty-nine of the 71 patients were available for follow-up evaluation. Harris hip scores were obtained preoperatively and postoperatively. Radiographs were measured for radiolucent lines. Patients were followed a minimum of 2 years (average, 10.6 years; range, 2–19 years). Survival of the femoral component without revision for any cause was 93 % (confidence interval [CI], 83–97 %) and for aseptic loosening was 98 % (CI, 87–100 %) at 19 years. Neither severity of bone loss nor the length of the stem predicted failure. Impaction bone grafting has a high survival of 93 % at the 19-year follow-up for patients with severe bone loss of their femur.

Complications of Femoral Impaction Grafting

Although intraoperative fractures were a frequent complication during the early experience with impaction allografting, it is now apparent that intraoperative fractures are usually technique related and should be avoidable. In contrast, postoperative femoral fractures are less likely to be related to the technique and more so to the poor quality of bone that this procedure attempts to address and perhaps to the bone remodeling process. Two strategies have been adopted to reduce the incidence of femoral fractures: the use of cortical struts and the use of longer stem lengths. These strategies appear to have minimized complications. Although the use of cortical onlay struts may reduce the risk of fracture, placement of these struts requires extensive stripping of the femur, may adversely affect the blood supply to bone, and thus may affect revascularization of the graft. Massive femoral subsidence also has been cited as a complication of this procedure; however, this may be technique related because most larger series show a low incidence

of massive stem subsidence, suggesting that surgical technique (density of impacted bone, restoration of a cortical tube, and a longer stem) is a key factor in the success of the approach.

Induced Membrane Technique for Reconstruction of Bone Loss

Masquelet and colleagues [63, 64] developed the use of induced membrane-assisted massive autograft for segmental bony defects and successfully managed defects ≤ 25 cm with associated severe soft-tissue injury by use of this technique. Reported advantages of this technique include protection against autograft resorption, relative maintenance of graft position, and prevention of soft-tissue interposition. This technique was discovered largely by accident; the induction of this membrane was an unanticipated finding. Masquelet and Begue used cement spacers to manage infected nonunions with bone loss, and the resultant membrane was initially maintained at the time of final grafting only to limit surgical devitalization and subsequent blood loss. In this two-stage technique, induced biologic membranes are used with delayed placement of bone graft to manage this clinical challenge. In the first stage, a polymethyl methacrylate spacer is placed in the defect to produce a bioactive membrane, which appears to mature biochemically and physically 4–8 weeks after spacer placement. In the second, cancellous autograft is placed within this membrane, and, via elution of several growth factors, the membrane appears to prevent graft resorption and promote revascularization and consolidation of new bone. The induced membrane technique for reconstruction of bone loss exhibits promisingly clinical and radiographic outcomes; however, consensus and/or evidence regarding many aspects of the procedure is lacking. In studies to date, the membrane appears to eliminate local soft-tissue ingrowth into the bone defect, prevent graft resorption, and promote neovascularization and corticalization of the graft. In addition, the membrane may have osteoinductive and weak osteogenic capabilities. Early results with this technique are encouraging. This

treatment method should be considered for patients with significant lower and/or upper extremity bone loss.

Future Developments

Theoretical improvements in achieving bone ingrowth may be seen with agents such as recombinant bone morphogenetic proteins BMP-7 (osteogenic protein (OP)-1) and BMP-2 used to enhance osteoinduction or osteogenesis. However, other animal studies have not shown benefits with the use of BMP-7 (OP-1) when the animal was allowed to load the graft, and there are no clinical data to recommend their use in revision knee surgery. In animal studies, alterations in the graft mix have been used to improve the mechanical stability of a graft/stem construct, although the effect of this in vivo is not known. Biomechanical and animal studies have suggested that improved stability can be achieved with cancellous bone particles of more than 2 mm with the further addition of stiffer particles such as ceramics, cortical bone, bovine bone, and hydroxylapatite [79, 80].

References

- Cameron HU, editor. Bone implant interface. St. Louis: Mosby-Year Book; 1994.
- Older J, editor. Bone implant grafting. London/New York: Springer; 1992.
- De Boer HH. The history of bone grafts. *Clin Orthop*. 1988;226:293–8.
- Buttaro MA. Bone grafting and two-stage revision total hip arthroplasty. *Hip Int*. 2012;22(S8):S69–74.
- McNamara IR. Impaction bone grafting in revision hip surgery: past, present and future. *Cell Tissue Bank*. 2010;11(1):57–73.
- Beswick A, Blom AW. Bone graft substitutes in hip revision surgery: a comprehensive overview. *Injury*. 2011;42(S2):S40–6.
- Pape HC, Evans A, Kobbe P. Autologous bone graft: properties and techniques. *J Orthop Trauma*. 2010;24(S1):S36–40.
- Khan SN, Cammisa Jr FP, Sandhu HS, Diwan AD, Girardi FP, Lane JM. The biology of bone grafting. *J Am Acad Orthop Surg*. 2005;13(1):77–86.
- Oakes DA, Cabanela ME. Impaction bone grafting for revision hip arthroplasty: biology and clinical applications. *J Am Acad Orthop Surg*. 2006;14(11):620–8.
- Stevenson S, Emery SE, Goldberg VM. Factors affecting bone graft incorporation. *Clin Orthop*. 1996;324:66–74.
- Callaghan JJ, Heiner AD, Brown TD. The basic science of impaction allografting in revision hip surgery. *Instr Course Lect*. 2000;49:103–10.
- Bauer TW, Muschler GF. Bone graft materials. An overview of the basic science. *Clin Orthop*. 2000;371:10–27.
- Emerson Jr RH. Basic science of onlay allografts: a review. *Instr Course Lect*. 2000;49:97–102.
- Schreurs BW, Slooff TJ, Buma P, Verdonshot N. Basic science of bone impaction grafting. *Instr Course Lect*. 2001;50:211–20.
- Theler JM. Bone tissue substitutes and replacements. *Curr Opin Otolaryngol Head Neck Surg*. 2011;19(4):317–22.
- Dinopoulos HT, Giannoudis PV. Safety and efficacy of use of demineralised bone matrix in orthopaedic and trauma surgery. *Expert Opin Drug Saf*. 2006;5(6):847–66.
- Giannoudis PV, Dinopoulos HT. Autologous bone graft: when shall we add growth factors? *Orthop Clin North Am*. 2010;41(1):85–94.
- Lavernia CJ, Malinin TI, Temple HT, Moreyra CE. Bone and tissue allograft use by orthopaedic surgeons. *J Arthroplasty*. 2004;19(4):430–5.
- Bhatt RA, Rozental TD. Bone graft substitutes. *Hand Clin*. 2012;28(4):457–68.
- Grabowski G, Cornett CA. Bone graft and bone graft substitutes in spine surgery: current concepts and controversies. *J Am Acad Orthop Surg*. 2013;21(1):51–60.
- Zwingenberger S, Nich C, Valladares RD, Yao Z, Stiehler M, Goodman SB. Recommendations and considerations for the use of biologics in orthopedic surgery. *BioDrugs*. 2012;26(4):245–56.
- Blumenfeld TJ. Implant choices, technique, and results in revision acetabular surgery: a review. *Hip Int*. 2012;22(3):235–47.
- Toms AD, Barker RL, Jones RS, Kuiper JH. Impaction bone-grafting in revision joint replacement surgery. *J Bone Joint Surg Am*. 2004;86A:2050–60.
- Saleh KJ, Holtzman J, Gafni A, Saleh L, Davis A, Resig S, Gross AE. Reliability and intraoperative validity of preoperative assessment of standardized plain radiographs in predicting bone loss at revision hip surgery. *J Bone Joint Surg Am*. 2001;83A:1040–6.
- Markovich GD. Acetabular reconstruction in revision total hip arthroplasty: a review of options. *Am J Orthop*. 1998;27(10):662–70.
- Stamos KG, Karachalios T, Papagelopoulos PJ, Xenakis T, Korres DS, Koroneos E, Hartofilakidis G. Long-term mechanical stability of the impacted morselized graft-cement interface in total joint replacement: an experimental study in dogs. *Orthopedics*. 2000;23(8):809–14.
- Schreurs BW, Gardeniers JW, Slooff TJ. Acetabular reconstruction with bone impaction grafting: 20 years of experience. *Instr Course Lect*. 2001;50:221–8.

28. Roidis N, Karachalios T, Khaldi L, Stamos K, Lyritis GP. The role of stainless steel wire mesh and cement in bone allograft incorporation in impaction grafting technique: an experimental study in rabbits. *J Arthroplasty*. 2003;18(4):484–93.
29. Choplin RH, Henley CN, Edds EM, Capello W, Rankin JL, Buckwalter KA. Total hip arthroplasty in patients with bone deficiency of the acetabulum. *Radiographics*. 2008;28(3):771–86.
30. Issack PS, Nousiainen M, Beksac B, Helfet DL, Sculco TP, Buly RL. Acetabular component revision in total hip arthroplasty. Part II: management of major bone loss and pelvic discontinuity. *Am J Orthop*. 2009;38(11):550–6.
31. Richards CJ, Garbuz DS, Masri BA, Duncan CP. Vancouver type B3 periprosthetic fractures: evaluation and treatment. *Instr Course Lect*. 2009;58:177–81.
32. Haddad FS, Rayan F. The role of impaction grafting: the when and how. *Orthopedics*. 2009;32(9). pii: orthosupersite.com/view.asp?rID=42842. doi:10.3928/01477447-20090728-19
33. Noordin S, Masri BA, Duncan CP, Garbuz DS. Acetabular bone loss in revision total hip arthroplasty: principles and techniques. *Instr Course Lect*. 2010; 59:27–36.
34. Rigby M, Kenny PJ, Sharp R, Whitehouse SL, Gie GA, Timperley JA. Acetabular impaction grafting in total hip replacement. *Hip Int*. 2011;21(4):399–408.
35. Van Egmond N, De Kam DC, Gardeniers JW, Schreurs BW. Revisions of extensive acetabular defects with impaction grafting and a cement cup. *Clin Orthop*. 2011;469:562–73.
36. Sheth NP, Nelson CL, Springer BD, Fehring TK, Paprosky WG. Acetabular bone loss in revision total hip arthroplasty: evaluation and management. *J Am Acad Orthop Surg*. 2013;21(3):128–39.
37. Schreurs BW, Busch VJ, Welten ML, Verdonshot N, Slooff TJ, Gardeniers JW. Acetabular reconstruction with impaction bone-grafting and a cemented cup in patients younger than fifty years old. *J Bone Joint Surg Am*. 2004;86A:2385–92.
38. Busch VJ, Gardeniers JW, Verdonshot N, Slooff TJ, Schreurs BW. Acetabular reconstruction with impaction bone-grafting and a cemented cup in patients younger than fifty years old: a concise follow-up, at twenty to twenty-eight years, of a previous report. *J Bone Joint Surg Am*. 2011;93A:367–71.
39. Sporer SM, Paprosky WG, O'Rourke MR. Managing bone loss in acetabular revision. *Instr Course Lect*. 2006;55:287–97.
40. Templeton JE, Callaghan JJ, Goetz DD, Sullivan PM, Johnston RC. Revision of a cemented acetabular component to a cementless acetabular component: a ten to fourteen-year follow-up study. *J Bone Joint Surg Am*. 2001;83A:1706–71.
41. Jamali AA, Dungey DS, Mark A, Schule S, Harris WH. Isolated acetabular revision with use of the Harris-Galante Cementless Component: Study with intermediate-term follow-up. *J Bone Joint Surg Am*. 2004;86A:1690–7.
42. Hallstrom BR, Golladay GJ, Vittetoe DA, Harris WH. Cementless acetabular revision with the Harris-Galante porous prosthesis: results after a minimum of ten years of follow-up. *J Bone Joint Surg Am*. 2004; 86A:1007–11.
43. Jones CP, Lachiewicz PF. Factors influencing the longer-term survival of uncemented acetabular components used in total hip revisions. *J Bone Joint Surg Am*. 2004;86A:342–7.
44. Della Valle CJ, Berger RA, Rosenberg AG, Galante JO. Cementless acetabular reconstruction in revision total hip arthroplasty. *Clin Orthop*. 2004;420:96–100.
45. Meneghini RM, Ford KS, McCollough CH, Hanssen AD, Lewallen DG. Bone remodeling around porous metal cementless acetabular components. *J Arthroplasty*. 2010;25(5):741–7.
46. Lee PT, Raz G, Safir OA, Backstein DJ, Gross AE. Long-term results for minor column allografts in revision hip arthroplasty. *Clin Orthop*. 2010;468:3295–303.
47. Sporer SM. How to do a revision total hip arthroplasty. Revision of the acetabulum. *J Bone Joint Surg Am*. 2011;93A:1359–66.
48. Van Kleunen JP, Lee GC, Lementowski PW, Nelson CL, Garino JP. Acetabular revisions using trabecular metal cups and augments. *J Arthroplasty*. 2009;24(S6):64–8.
49. Sporer SM, Paprosky WG. Acetabular revision using a trabecular metal acetabular component for severe acetabular bone loss associated with a pelvic discontinuity. *J Arthroplasty*. 2006;21(S2):87–90.
50. Zehntner MK, Ganz R. Midterm results (5.5–10 years) of acetabular allograft reconstruction with the acetabular reinforcement ring during total hip revision. *J Arthroplasty*. 1994;9(5):469–79.
51. Goodman S, Saastamoinen H, Shasha N, Gross A. Complications of ilioischial reconstruction rings in revision total hip arthroplasty. *J Arthroplasty*. 2004; 19(4):436–46.
52. Gaiani L, Bertelli R, Palmonari M, Vicenzi G. Total hip arthroplasty revision in elderly people with cement and Burch-Schneider anti-protrusion cage. *Chir Organi Mov*. 2009;93(1):15–9.
53. Ballester Alfaro JJ, SueiroFernández J. Trabecular Metal buttress augment and the Trabecular Metal cup-cage construct in revision hip arthroplasty for severe acetabular bone loss and pelvic discontinuity. *Hip Int*. 2010;20(S7):119–27.
54. Kosashvili Y, Backstein D, Safir O, Lakstein D, Gross AE. Acetabular revision using an anti-protrusion (ilioischial) cage and trabecular metal acetabular component for severe acetabular bone loss associated with pelvic discontinuity. *J Bone Joint Surg Br*. 2009;91B:870–6.
55. Dennis DA. Management of massive acetabular defects in revision total hip arthroplasty. *J Arthroplasty*. 2003;18(S1):121–5.
56. DeBoer DK, Christie MJ, Brinson MF, Morrison JC. Revision total hip arthroplasty for pelvic discontinuity. *J Bone Joint Surg Am*. 2007;89A:835–40.
57. Emerson Jr RH, Malinin TI, Cuellar AD, Head WC, Peters PC. Cortical strut allografts in the reconstruction of the femur in revision total hip arthroplasty.

- A basic science and clinical study. *Clin Orthop*. 1992; 285:35–44.
58. Pak JH, Paprosky WG, Jablonsky WS, Lawrence JM. Femoral strut allografts in cementless revision total hip arthroplasty. *Clin Orthop*. 1993;295:172–8.
 59. Head WC, Malinin TI. Results of onlay allografts. *Clin Orthop*. 2000;371:108–12.
 60. Allan DG, Lavoie GJ, McDonald S, Oakeshott R, Gross AE. Proximal femoral allografts in revision hip arthroplasty. *J Bone Joint Surg Br*. 1991;73B:235–40.
 61. Leone Jr WA, Naughton M, Gratto-Cox G, Luland CM, Kilgore JE, Hill GE. The effect of preoperative planning and impaction grafting surgical technique on intraoperative and postoperative complication rate for femoral revision patients with moderate to severe bone loss mean 4.7-year results. *J Arthroplasty*. 2008; 23(3):383–94.
 62. Dattani R, Blunn G. Revision of the femoral prosthesis with impaction allografting. *Acta Orthop Belg*. 2007;73(5):558–65.
 63. Masquelet AC, Begue T. The concept of induced membrane for reconstruction of long bone defects. *Orthop Clin North Am*. 2010;41(1):27–37.
 64. Taylor BC, French BG, Fowler TT, Russell J, Poka A. Induced membrane technique for reconstruction to manage bone loss. *J Am Acad Orthop Surg*. 2012;20(3): 142–50.
 65. Maurer SG, Baitner AC, Di Cesare PE. Reconstruction of the failed femoral component and proximal femoral bone loss in revision hip surgery. *J Am Acad Orthop Surg*. 2000;8(6):354–63.
 66. Holt G, Hook S, Hubble M. Revision total hip arthroplasty: the femoral side using cemented implants. *Int Orthop*. 2011;35(2):267–73.
 67. Board TN, Rooney P, Kearney JN, Kay PR. Impaction allografting in revision total hip replacement. *J Bone Joint Surg Br*. 2006;88B:852–7.
 68. Morgan HD, McCallister W, Cho MS, Casnellie MT, Leopold SS. Impaction allografting for femoral component revision: clinical update. *Clin Orthop*. 2004;420:160–8.
 69. Garvin KL, Konigsberg BS, Ommen ND, Lyden ER. What is the long-term survival of impaction allografting of the femur? *Clin Orthop Relat Res*. 2013;471(7):2411.
 70. Ten Have BL, Brouwer RW, van Biezen FC, Verhaar JA. Femoral revision surgery with impaction bone grafting: 31 hips followed prospectively for ten to 15 years. *J Bone Joint Surg Br*. 2012;94B:615–8. Erratum in: *J Bone Joint Surg Br* 2013; 95B(2):286. Brouwer Md, R W [corrected to Brouwer, R W].
 71. Masterson S, Lidder S, Scott G. Impaction femoral allografting at revision hip arthroplasty: uncemented versus cemented technique using a Freeman femoral component. *J Bone Joint Surg Br*. 2012;94B:51–5.
 72. Ullmark G, Obrant KJ. Histology of impacted bone-graft incorporation. *J Arthroplasty*. 2002;17(2): 150–7.
 73. Padgett DE, Kinkel S. Cancellous impaction grafting in femoral revision THA. *Orthopedics*. 2011;34(9): e482–4.
 74. Halliday BR, English HW, Timperley AJ, Gie GA, Ling RS. Femoral impaction grafting with cement in revision total hip replacement. Evolution of the technique and results. *J Bone Joint Surg Br*. 2003;85B: 809–17.
 75. Tsiridis E, Narvani AA, Haddad FS, Timperley JA, Gie GA. Impaction femoral allografting and cemented revision for periprosthetic femoral fractures. *J Bone Joint Surg Br*. 2004;86B:1124–32.
 76. English H, Timperley AJ, Dunlop D, Gie G. Impaction grafting of the femur in two-stage revision for infected total hip replacement. *J Bone Joint Surg Br*. 2002;84B: 700–5.
 77. Leopold SS, Rosenberg AG. Current status of impaction allografting for revision of a femoral component. *Instr Course Lect*. 2000;49:111–8.
 78. Fetzer GB, Callaghan JJ, Templeton JE, Goetz DD, Sullivan PM, Johnston RC. Impaction allografting with cement for extensive femoral bone loss in revision hip surgery: a 4- to 8-year follow-up study. *J Arthroplasty*. 2001;16(S1):195–202.
 79. Alsousou J, Thompson M, Hulley P, Noble A, Willett K. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: a review of the literature. *J Bone Joint Surg Br*. 2009;91B:987–96.
 80. Dimitriou R, Jones E, McGonagle D, Giannoudis PV. Bone regeneration: current concepts and future directions. *BMC Med*. 2011;9:66.

The Effect of Pharmacological Agents on the Bone-Implant Interface

16

Ioannis K. Triantafillopoulos
and Nikolaos A. Papaioannou

Introduction

Terminology

In joint replacement surgery, the prerequisite for clinical success is the achievement of good and fast bone-implant osseointegration. *Osseointegration* can be defined as the contact which intervenes, without interposition of non-bone tissue, between normal remodeled bone and an implant which can bear the distribution of load from the implant to and inside the bone tissue [1]. The contact area between the implant surface and the bone is called *bone-implant interface*. This is the area where the biology of bone ingrowth takes place.

Bone ingrowth can be defined as the formation of bone tissue inside the porous surface of an implant [1]. The ideal bone ingrowth should lead to osseointegration that provides early implant fixation with long-term stability of the prosthesis. The process of osseointegration reflects an anchorage mechanism whereby non-vital components can be reliably incorporated into living bone and which persist under

all normal conditions of loading [2]. Thus, an implant is considered as osseointegrated when there is no progressive relative movement between the implant and the bone with which it has direct contact [3, 4]. The long-term durability of joint prostheses is critically dependent on adequate peri-implant bone stock which can be compromised by wear debris-mediated osteolysis.

Osteolysis is a chronic inflammatory response initiated by particulate debris at the bone-implant interface and manifested by recruitment of a wide array of cell types, neutrophils, lymphocytes, and most importantly osteoclasts, which are the principal resorbing cells [5]. The cellular response entails secretion of osteoclastogenic and inflammatory cytokines that favor exacerbated osteoclast activity, leading to the *aseptic loosening* of the implanted prostheses (Table 16.1) [6].

The Role of Pharmacological Agents at the Bone-Implant Interface

The increasing knowledge of bone metabolism mechanisms and the clarification of the biological pathways that lead to either osseointegration or osteolysis and aseptic loosening of an implant is a prerequisite in understanding the role of pharmacological agents applied at an experimental or clinical level and how these agents could

I.K. Triantafillopoulos, MD, MSc, DSc, FEBOT (✉)
N.A. Papaioannou, MD, DSc
Laboratory for the Research of Musculoskeletal System,
Medical School, University of Athens, 6, Dimitras Street,
Maroussi, 15124 Athens, Greece
e-mail: sportdoc@otenet.gr

Table 16.1 Potential reasons for implant osseointegration failure and treatment strategies

Reason of failure	Treatment targets
Wear debris	Improvement of tribology and biomechanical properties in order to decrease the production of bone debris
Transfer of wear debris into the effective joint space	1. Use of bone cement 2. Implant surfaces coatings with materials (hydroxyapatite, trabecular metal) and rough surfaces manufactured with nanotechnology in order to stop the transfer of wear particles into the interface
Inflammatory (cellular and molecular) response to wear debris (particle-induced osteolysis)	1. Pharmacological agents that induce bone formation or stop osteolysis 2. Molecular approaches to arrest osteoclast activity 3. Anti-inflammatory strategies
Poor peri-implant bone quality	Pharmacological agents that increase bone density and quality

Table 16.2 The biology of osteolytic response

Cell types recruited into the bone-implant interface	Phagocytes, macrophages, osteoclasts, fibroblasts, osteoblasts/stromal cells
Mechanisms of particle-induced cellular activation	1. Particle recognition by phagocytosis of small-sized particles 2. Cell surface interactions with the particles including: (a) Nonspecific physical induction of transmembrane proteins (b) Recognition of cell surface molecules by particles or proteins/factors that are adherent to the surface
Mechanisms of cellular reaction	Release large quantities of proinflammatory cytokines, growth factors, metalloproteinases, prostanoids, lysosomal enzymes, including the very critical TNF, IL-1 α , IL-1 β , IL-6, RANKL, and PGE2

enhance osseointegration or prevent osteolysis (Table 16.2). In this chapter we will discuss current research exploring the systemic or local administration of many pharmacological agents and how these factors could effectively prevent or treat osteolysis. In vitro and in vivo studies, experimental models, and clinical trials will be considered, and evidence-based medicine will also be provided.

The agents presented in this chapter are practically selected according to two criteria: (a) they are commonly taken by the group of (older) patients that commonly undergo total joint arthroplasty, or (b) they are routinely prescribed after such an orthopedic operation. These agents include antibiotics, anti-inflammatory agents, statins, antiosteoporotic agents, and bone anabolic factors as well as newly discovered biological agents administered

Table 16.3 Investigated pharmacological agents that affect osseointegration

Positive effect	Negative effect
Antibiotics	Cyclosporine A
Anti-inflammatory	Methotrexate
RANK/RANKL/OPG system	Cisplatin
Statins	Warfarins
Calcitonin	Indomethacin ^a
Bisphosphonates	
Strontium ranelate	
Parathyroid hormone	
Teriparatide	
Biocoating agents	

^aThere is controversy on the role of indomethacin (see chapter)

systemically (orally, intravenous, or intramuscular) or locally (on the implant's surface) (Table 16.3).

Pharmacological Agents Positively Affecting Osseointegration

Antibiotics

There are very few studies testing the role of antibiotics on the bone-implant interface after total arthroplasty implantation. However, such studies would be very useful, because all patients take antibiotic chemoprophylaxis for a few days post-operatively after a joint arthroplasty and the knowledge of how antibiotics could affect implant osseointegration would be very useful. There is one *in vitro* and *in vivo* study [7] that explored the effect of doxycycline (DOX) on osteoclastogenesis, mature osteoclast fate and function, and wear particle-induced osteolysis and provided some foundation for treating aseptic loosening and osteolysis after joint arthroplasty. Doxycycline is a semisynthetic antibiotic, member of the tetracycline group, and is commonly used to treat a variety of infections. In this study, osteoclasts were generated from mouse bone marrow monocytes with the receptor activator of NF- κ B ligand and a macrophage colony-stimulating factor. DOX at a concentration of 5, 10, 15, and 20 μ g/mL was respectively added to the medium. Seven days later, the osteoclasts were determined through tartrate-resistant acid phosphatase (TRAP) staining. Mature osteoclasts were isolated from newborn rabbits and cultured for 3 days in 24-well plates or on bone slices. DOX at a concentration of 5, 10, 15, and 20 μ g/mL was respectively added to the medium. After TRAP staining, the osteoclasts were counted, resorption on bone slices was quantified, and the area was calculated after toluidine blue and Mayer's hematoxylin staining. Polymethyl methacrylate (PMMA) or ultra-high molecular weight polyethylene (UHMWPE) particles were implanted on the calvariae of C57BL/J6 mice. DOX, at a dose of 2 and 10 mg \times kg⁽⁻¹⁾ \times d⁽⁻¹⁾, was respectively given intraperitoneally for 7 days. Seven days later, the calvariae were removed and processed for pathological analysis.

The results of the study showed that DOX treatment effectively inhibited *in vitro* osteoclastogenesis, affected the fate of mature osteoclasts, and inhibited mature osteoclasts, causing bone resorption. *In vivo* data indicated that DOX strongly inhibited PMMA- or UHMWPE-induced osteolysis and osteoclastogenesis. In conclusion, DOX can be useful in the treatment or prevention of wear particle-induced osteolysis and aseptic loosening because of its effect on osteoclast generation and mature osteoclast fate and function. In another *in vitro* study [8], erythromycin, a macrolide antibiotic, suppressed wear debris-induced osteoclastic bone resorption. Erythromycin significantly inhibited mRNA expression of NF- κ B, cathepsin K (CPK), IL-1 β , and TNF- α , but not RANK in mice cells stimulated with wear debris. Furthermore, electrophoretic mobility-shift assay showed that erythromycin could reduce the DNA-binding activity of NF- κ B in the same cells. The inhibition of inflammatory osteoclastogenesis by erythromycin treatment was further confirmed by an osteoclast formation assay using primary cultures of mouse bone marrow progenitor cells stimulated with macrophage colony-stimulating factor and RANKL. Erythromycin treatment resulted in more than 70 % reduction in multinucleated osteoclast formation and 50 % reduction of TRAP+ cells by bone marrow progenitor cells. It appears that antibiotics represent a potential therapeutic candidate for the treatment and prevention of aseptic loosening, but clinical studies are needed to produce data that would confirm the *in vitro* and *in vivo* results.

Anti-inflammatory Agents

Anti-inflammatory agents have proved effective when used in the treatment of osteolysis in animal models. Gene therapy with the anti-inflammatory cytokines IL-1Ra or viral IL-10 protects mice from the polyethylene debris-induced osteolysis [9]. Inhibition of TNF- α

action by deletion of genes encoding TNF receptors reduced PMMA- and titanium debris-induced inflammation [10, 11]. In animal models, the administration of TNF antagonists, such as etanercept (a decoy receptor) and pentoxifylline (an inhibitor of secretion), diminished the particle-induced osteolysis [12, 13]. However, despite the encouraging animal studies, it is not well understood how anti-TNF factors would prevent human osteolysis. There are studies reporting elevated levels of TNF- α in the peri-prosthetic tissues and the joint synovial fluid of patients with osteolysis [14–16], while other studies found these as lower than in control groups or as undetectable [17, 18]. This confusion is (a) partially related to the measurement methods used, which are nonquantitative (mRNA detection) or semiquantitative (e.g., immunohistochemistry or in situ hybridization approaches) and cannot be reliably translated into quantitative measurements [19–23], and (b) partially because human TNF is involved only in the early stages of pathogenesis, but not in the end stages of osteolytic progression. According to the current data, it is uncertain whether TNF- α and other proinflammatory cytokines are elevated in the end-stage osteolysis interface area, and they may not be useful pharmacological targets for treating patients with established disease. IL-4 is also secreted by T lymphocytes, as the abovementioned IL-10, and is effective in antagonizing proinflammatory cytokine actions. Recently, IL-4 messenger RNA was found more frequently in patients with non-erosive than erosive disease (38 % vs. 15 %) [24]. These findings provide indirect evidence that IL-4 has bone-sparing effects in vivo. After this finding, a study with a mouse model of adjuvant-induced arthritis confirmed that IL-4 adenoviral gene therapy reduced inflammation, inhibited proinflammatory cytokine secretion, and spared bone destruction [24]. Although a direct role of interferons in particle-induced osteolysis has not yet been established, it seems that INF- γ (gamma) blocks peri-implant bone loss. IFN- γ interferes with the RANK/RANKL signal transduction in osteoclasts and their precursors. It reduces degradation of tumor necrosis factor receptor-associated

factor 6 (TRAF6), a RANK adaptor protein. This action results in failure to activate RANK downstream signals such as NF- κ B and cJun/JNK pathways [24].

The RANK/RANKL/OPG System

The critical role of RANKL in inhibiting osteoclastogenesis makes this cytokine a very interesting pharmacological agent for the therapy of osteolysis. In animal models, RANK:Fc and osteoprotegerin have been utilized to prevent osteolysis [25–27]. Based on the experimentally established knowledge of osteoclast involvement in the process of peri-implant osteolysis and the requirements of receptor activator of NF- κ B (RANK) signaling in osteoclastogenesis and bone resorption, the efficacy of RANK blockade in preventing and ameliorating particle-induced osteolysis has already been investigated. In a titanium (Ti)-induced osteolysis in a mouse calvaria model [27], all doses of RANK:Fc above 1 mg/kg intraperitoneally (ip) per 48 h significantly inhibited osteoclastogenesis and bone resorption in response to Ti implanted locally. Complete inhibition occurred at 10 mg/kg ip per 48 h, yielding results that were statistically equivalent to data obtained with Ti-treated RANK knockout mice. In the same study, after a single injection of RANK:Fc on day 5 of established osteolysis, it was found that Ti-treated mice were still depleted of multinucleated tartrate-resistant acid phosphatase-positive (TRAP+) cells 16 days later. More importantly, this osteoclast depletion did not affect bone formation because the bone lost from the osteolysis on day 5 was restored by day 21. An assessment of the quantity and quality of the newly formed bone in these calvariae by calcein labeling and infrared (IR) microscopy, respectively, showed no significant negative effect of RANK:Fc treatment. These findings show that osteoclast depletion via RANK blockade is an effective method of preventing and reversing wear debris-induced osteolysis without jeopardizing osteogenesis. An important factor known to counteract the process of RANKL-induced osteoclastogenesis and osteoclastic bone

resorption is the natural RANKL receptor antagonist protein osteoprotegerin (OPG). In a mouse calvaria model [25], the potential of ex vivo OPG gene therapy for aseptic loosening was explored by evaluating the efficacy of stably transfected fibroblast-like synoviocytes (FLS) expressing OPG in preventing wear debris-induced osteoclastogenesis. Although the stably transfected fibroblasts produced small amounts of OPG, this protein was very effective in preventing osteoclastic resorption as determined in a bone wafer assay. More importantly, implantation of FLS expressing OPG, together with Ti wear debris, onto the calvaria of mice, completely inhibited osteoclastogenesis 3 days after surgery. Animals given FLS control cells, which persisted for 3 days as determined by X-gal staining, together with the Ti particles, had a 6-fold increase in osteoclastogenesis compared to controls without Ti. This increased osteoclastogenesis was completely inhibited by the FLS-OPG, as osteoclast numbers in the calvaria of these animals were similar to those seen in the sham controls. In accordance with these findings, there is another experimental study [26] investigating whether a gene therapy using a recombinant adeno-associated viral vector that expresses OPG (rAAV-OPG) can inhibit wear debris-induced osteolysis. Treatment with rAAV-OPG reduced resorption sevenfold compared with parathyroid hormone-stimulated controls and 11-fold compared with rAAV-non-OPG controls. Furthermore, a 17-fold decrease in RANKL and macrophage colony-stimulating factor-induced splenocyte osteoclastogenesis was observed in cocultures containing rAAV-OPG-infected fibroblasts. In vivo administration of rAAV-OPG resulted in detectable transduction of myocytes at the injection site and a significant increase in expression of serum OPG levels by the second day ($p < 0.05$). Maximal concentrations were obtained on day 6 and then leveled off throughout the observation period. In contrast, serum OPG could not be detected in the sham-treated, uninfected titanium-stimulated, or rAAV-non-OPG-infected mice. In the control mice, titanium implantation resulted in a threefold increase in the mean number of osteoclasts as well as a twofold increase in the

mean area of soft tissue compared with the sham-treated mice. In contrast, osteoclast numbers remained at basal levels, and the area of soft tissue was markedly reduced in titanium-implanted animals that had received rAAV-OPG treatment, demonstrating a complete inhibition of osteolysis in response to titanium particles. In conclusion, OPG effectively inhibits wear debris-induced osteoclastogenesis and osteolysis. The clinical relevance of the above findings is the first evidence that in vivo OPG gene therapy can be used to prevent wear debris-induced osteolysis. Recently, data from cell-based OPG therapy for debris-induced prosthetic loosening on murine models [28, 29] suggested that cell-based ex vivo OPG gene therapy was comparable in efficacy with in vivo local gene transfer technique to deliver functional therapeutic OPG activities. Furthermore, these studies show that OPG gene therapy effectively halted the debris-induced osteolysis, reduced local bone collagen loss, and restored the implant stability in these murine models. At a clinical level, the development of denosumab [30], a fully human monoclonal antibody that acts by binding to and inhibiting RANKL, could be a potential pharmacological agent that could lead to loss of osteoclasts at the bone-implant interface area and thus positively affect osseointegration. However, there are still no clinical studies proving this hypothesis.

Statins

Statins have been also considered as possible pharmacological agents for osteolysis due to their role in blocking the mevalonate pathway. The recent discovery that statins act as bone anabolic factors suggests that these pharmacological agents can have a potential effect not only on the treatment of osteoporosis but also on implant osseointegration. Simvastatin is a hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor and a potent lipid-lowering drug [30]. In addition to a lipid-lowering effect, it stimulates bone growth, mostly by increasing the expression of BMP-2 and BMP-4, but it also has osteogenic effects independent of these factors [30, 31]. Although

the detailed mechanism of this osteogenic action of simvastatin is still unclear, rho-kinase inhibition, differentiation of endothelial progenitor cells with Akt protein kinase, and osteoblastic differentiation and its effect on vitamin K metabolism are possible explanations for the mode of action [31–33]. Clinically, simvastatin has also been shown to increase bone mineral density and reduce the incidence of osteoporotic fractures in several retrospective series [30–32]. Preliminary studies in murine calvarial models [33, 34] show that simvastatin treatment markedly promoted bone formation and net bone growth and decreased osteolysis in UHMWPE particle-induced osteolysis. These early findings suggest that simvastatin may have favorable osteoanabolic effects on wear debris-mediated osteolysis after total joint arthroplasty and thus may have a role in noninvasive prevention and treatment of wear debris-mediated periprosthetic osteolysis. More recently, in an in vitro study [35], simvastatin-loaded titanium porous surfaces were used to investigate the effect of simvastatin on the promotion of osteogenesis in preosteoblasts. The control group consisted of cells cultured on titanium disks without any intervention for different time intervals (4, 7, and 14 days), and the experimental groups (simvastatin-loaded groups) consisted of cells cultured on titanium disks that were preincubated in varying concentrations (10(–7) mol/L, 10(–6) mol/L, 10(–5) mol/L, and 10(–4) mol/L) of simvastatin for the same time intervals of the control group. Alkaline phosphatase (ALP) activity, type I collagen synthesis, and osteocalcin release were used to measure the cellular osteoblastic activities. The simvastatin-loaded groups showed increased alkaline phosphatase (ALP) activity compared with the control group at every time point, especially the 10(–7) mol/L group, in which activity significantly increased almost fourfold at 4 days ($p < .05$). In the type I collagen synthesis assay, all simvastatin-loaded groups showed an increase, and the effect was inverse dose dependent (maximal at 10(–7) mol/L). This stimulatory effect of simvastatin was also observed in the osteocalcin release assay ($p < .05$; at 10(–7) mol/L, 10(–6) mol/L, maximal at 10(–7) mol/L). The results indicate

that simvastatin-loaded porous implant surfaces promote accelerated osteogenic differentiation of preosteoblasts, which have the potential to improve the nature of osseointegration.

Realizing this potential for improving osseointegration, research has been already performed on how simvastatin can affect osseous response in animal arthroplasty models by its stimulatory effect on bone growth. In these in vivo animal studies with canine total hip arthroplasty models [36], rabbit titanium femoral implantation models [37], and osteoporotic or non-osteoporotic rat titanium tibial implantation models [38, 39], simvastatin was examined mechanically and histologically in bone growth. The findings show that simvastatin, administered either orally or by injection, enhanced peri-implant bone ingrowth and contributed significantly to implant osseointegration. However, controlled clinical trials are needed to determine the role of simvastatin in the enhancement of bone ingrowth and osseointegration in cementless fixation in total and revision joint replacement and in the prevention of early migration of cementless prostheses especially in severely osteoporotic patients.

Calcitonin

Calcitonin is a commonly used antiosteoporosis drug in current clinical practice; it has also been confirmed experimentally that it produces the effect of promoting osseointegration at the interface between prosthesis and host bone and enhances the long-term stability of the prosthesis. Early animal studies have evaluated the effects of calcitonin administration on bone healing following titanium implant insertion. In a rabbit study [40], the influence of salmon calcitonin administration on the initial period of bone healing was first evaluated after the insertion of titanium implants in the femur of healthy animals. Animals were randomized to provide test (calcitonin) and control (saline solution) groups and sacrificed 7, 14, 21, 28, and 42 days after the surgical procedure. The analyzed parameters were new endosteal/periosteal bone length (EB/PB), new endosteal/periosteal bone area (EBA/PBA), and

total cortical length (TCL). The histometric measurements performed showed significant differences ($p < 0.05$) favoring the control group regarding periosteal bone length and periosteal bone area. The other parameters were statistically similar between control and test groups. The results did not show any significant benefits of calcitonin. However, the data observed for the 6-week (42 days) group indicated that calcitonin administration could promote some improvement after the initial phase of bone healing. Therefore, another experimental rabbit study was carried out to investigate the effects of calcitonin administration on the later period of bone healing following titanium implant insertion [41]. The animals were sacrificed at later stages: 6, 8, 12, and 18 weeks after surgery. Endosteal/periosteal bone length (EB/PB), endosteal/periosteal bone area (EBA/PBA), and total cortical length (TCL) around the implants were analyzed. After 6, 8, 12, and 18 weeks, a positive time effect was strongly observed ($p < 0.05$). There was a positive effect of calcitonin on EBA and EB variables at 12 weeks and TCL at 18 weeks. It seems that salmon calcitonin administration has a positive effect on peri-implant bone mass at the later stages of bone healing. However, further investigations should be carried out to determine if the greater extension observed histologically in these studies represents mechanical benefits to the implants. Another question is if calcitonin administration could prevent or reduce wear debris osteolysis around the implants. A very recent experimental animal study has investigated the impact of calcitonin deficiency and calcitonin substitution on particle-induced osteolysis [42]. The murine calvarial osteolysis model based on ultra-high molecular weight polyethylene (UHMWPE) particles in wild-type (WT) mice and Calca knockout mice was used. Calca gene codes for calcitonin. The mice were divided into six groups: WT without UHMWPE particles (Group 1), WT with UHMWPE particles (Group 2), Calca $-/-$ mice without UHMWPE particles (Group 3), Calca $-/-$ mice with UHMWPE particles (Group 4), Calca $-/-$ mice without UHMWPE particles and calcitonin substitution (Group 5), and Calca $-/-$ mice with UHMWPE

particle implantation and calcitonin substitution (Group 6). Analytes were extracted from serum and urine. Bone resorption was measured by bone histomorphometry. The number of osteoclasts was determined by counting the tartrate-resistant acid phosphatase positive (TRACP+) cells. Bone resorption was significantly increased in Calca $-/-$ mice compared with their corresponding WT. The eroded surface in Calca $-/-$ mice with particle implantation was reduced by 20.6 % after CT substitution. Osteoclast numbers were significantly increased in Calca $-/-$ mice after particle implantation. Serum OPG (osteoprotegerin) increased significantly after CT substitution. In this very interesting study, Calca $-/-$ mice showed extensive osteolysis compared with wild-type mice, and CT substitution reduced particle-induced osteolysis.

The reason why calcitonin has not been clinically tested as monotherapy for the prevention or reduction of the osteolysis phenomenon or the enhancement of implant osseointegration is that bisphosphonates produce more pronounced effectiveness when compared to calcitonin. A recent experimental rat study compared the effects of the two commonly used antiosteoporosis drugs, alendronate (ALO) and calcitonin (CT), on the bone-prosthesis osseointegration to provide a valuable reference for current clinical choices of medication [43]. Animals were randomly set into A, B, C, and D groups. Except for Group A, the others were ovariectomized to establish osteoporosis models (lumbar bone mineral density (BMD) decreased by 20 % 4 weeks after ovariectomy). All the rats received prosthesis implantation at their tibial plateau. Then, the rats in Groups C and D were given ALO (7 mg/kg/week) orally and CT (5 IU/kg/day) subcutaneously for 12 weeks, respectively. Prior to the execution, application of tetracycline hydrochloride for staining in vivo was done. After harvesting and embedding, the tibia with implants were cut into thin slides, then the bone histomorphometry was measured to observe the new bone around the prosthesis and to calculate the osseointegration rate of the implants. According to the findings of this study, both ALO and CT can effectively enhance the volume of bone mass

surrounding the hydroxyapatite (HA) prosthesis and also significantly lever up the osseointegration rate to 63.7 and 45.7 %, respectively ($p < 0.05$). However, ALO produced a greater periprostheses osseointegration rate than CT, with a difference of 18 % ($p < 0.05$). The rats' lumbar BMD increased in both ALO and CT groups, from 0.081 ± 0.009 and 0.078 ± 0.009 to 0.116 ± 0.008 and 0.109 ± 0.010 g/cm, respectively, but the effect of ALO was more pronounced than that of CT. The research proved that in osteoporotic conditions, both administration of ALO orally and CT subcutaneously can enhance periprostheses bone mass and the effects on osseointegration between host bone and prosthesis. However, bisphosphonates seem to produce a more pronounced effect than calcitonin.

Bisphosphonates

Bisphosphonates have been considered as therapeutic pharmacological agents for osteolysis. This is based on their role in the osteoclastic apoptosis by blocking the mevalonate pathway of isoprenoid biosynthesis [44]. In animal studies, alendronate administration inhibited particle debris-induced peri-implant osteolysis [45–47]. Zoledronic acid single-dose administration suppressed particle-induced osteolysis in mouse calvaria [48]. In a rabbit femoral model, alendronate and zoledronate treatment increased periprosthetic bone stock particularly in the presence of UHMWPE wear debris [49]. In a rat model, animals were fitted with femoral external fixators, and alendronate was administered once a week during a 5-week postoperative period. Alendronate reduced the width of the fibrous loosening membrane and the number of osteoclasts at the bone-screw interface. These findings indicate that systemic treatment with alendronate exerts an inhibitory effect on local bone resorption at the bone-screw interface [50]. The effect of zoledronic acid on bone ingrowth was examined in a dog model in which porous tantalum implants were placed bilaterally within the ulnae of even dogs [51]. Zoledronic acid was administered via a single postoperative intravenous injection at

a dose of 0.1 mg/kg. The mean extent of bone ingrowth was 6.6 % for the control implants and 12.2 % for the zoledronic acid-treated implants, a difference which was statistically significant. Individual islands of new bone formation within the implant pores were similar in number in both groups but were 69 % larger in the zoledronic acid-treated group. According to these findings, zoledronic acid causes enhancement of bone ingrowth into porous implants.

Avoiding the side effects of systematic administration (oral or intravenous) of bisphosphonates, local delivery and elution of these pharmacological agents is a new field of research. In animal studies, orthopedic implants are tested as drug delivery systems in experimentally induced osteoporosis. The aim of such studies is to show that local elution of a bisphosphonate can cause substantial bone augmentation around and within porous orthopedic implants. In a dog study [52], pure porous implants (*control group*) or zoledronic acid-dosed (0.05 mg) porous implants (*study group*) were implanted intramedullary into the ulnae of the animals. The peri-implant bone occupied a mean of 13.8 % of the canal space in controls and 32.2 % of the canal space in zoledronic acid-dosed dogs, a relative difference of 134 % (2.34-fold) that was significant. The mean extent of bone ingrowth was 12.5 % for the control implants and 19.8 % for the zoledronic acid-dosed dogs, a relative difference of 58 % that was also statistically significant. Individual islands of new bone formation within the implant pores were similar in number in both implant groups but were 71 % larger on average in the ZA-dosed group. In an osteoporotic rat model [53], implants were used with different zoledronate concentrations in HA coating: 0, 0.2, 2.1, 8.5, and 16 $\mu\text{g}/\text{implant}$. A remarkable result showed the existence of a window of zoledronate content (0.2–8.5 $\mu\text{g}/\text{implant}$) in which the mechanical fixation of the implant increased. More recent experimental animal studies have used soaked morselized allografts in different concentrations of bisphosphonates for impaction grafting techniques. It is known that impaction grafting enhances early implant fixation but very often is subject to resorption. The purpose of

such studies was to show that the local use of bisphosphonates could inhibit allograft resorption or even better enhance fixation. In a pilot dose–response study [54], unloaded titanium implants surrounded by a 2.5 mm gap into the proximal humerus of dogs were filled with impacted morselized allograft soaked in saline (control group) or a low-, middle-, or high-dose bisphosphonate solution (0.005, 0.05, or 0.5 mg zoledronate/mL). At 4 weeks, the implants were evaluated by histomorphometric analysis and mechanical pushout test. The low dose of zoledronate increased new bone formation in the allograft, but the high dose decreased new bone formation. The high dose of zoledronate resulted in the greatest inhibition of allograft resorption, whereas the low dose of zoledronate resulted in the lowest inhibition of allograft resorption. Implant surrounded by allograft soaked in the low dose of zoledronate or saline had better fixation for all three mechanical parameters compared with implants surrounded by allograft soaked in the middle or high dose of zoledronate. These data suggest bisphosphonate may enhance osseointegration of allografted implants. In conclusion, the concept of the above animal studies represents a potential tool for restoration of bone stock and enhancement of implant fixation in primary and revision cementless joint arthroplasty surgeries in the face of compromised or deficient bone. An issue that needs to be clarified is whether locally eluted bisphosphonate remains localized around the peri-implant area and the interface or becomes systemically distributed. In a dog study [55], hydroxyapatite-coated porous tantalum implant dosed with 100 μg (^{14}C -labeled zoledronic acid) was implanted into the femoral intramedullary canal. Bone samples near to and distant from the implant were harvested from three dogs at 6 weeks and three dogs at 52 weeks. The concentration of radiolabeled bisphosphonate in each sample was quantified using liquid scintillation spectrophotometry, and its distribution in peri-implant bone was revealed by exposing histologic sections to autoradiography film. In all dogs, the concentration of zoledronic acid in immediate peri-implant bone was two orders of magnitude higher than in any other

sampled tissue. Minute amounts of zoledronic acid were detected throughout the skeleton, indicating some escape into the circulation after local elution. Autoradiographs revealed the greatest concentration of zoledronic acid on and within the implant, with a rapid decrease short distances away and no uptake within the femoral cortex. The findings of this study prove that zoledronic acid eluted from the implant remains mainly localized with minimal systemic distribution. The clinical relevance of these findings is that local bisphosphonate elution reduces the risk of systemic side effects and skeletal bisphosphonate exposure. This becomes very important in non-osteoporotic patients in that whom there is no indication for systemic exposure to bisphosphonates.

On a clinical basis, the effectiveness of bisphosphonates in treating patients with osteolysis was initially unclear. Pamidronate treatment shortly after total hip arthroplasty transiently decreased postoperative bone loss and contributed to the prevention or delay of osteolysis [56]. However, this effect was lost by 2 years postoperatively, and it is not known whether additional regimens would have maintained the positive effect of pamidronate. It has been suggested that the high local levels of TNF at the initial phase of the osteolytic progress could protect the osteoclasts from bisphosphonate-induced apoptosis [57]. This theory renders the early administration of bisphosphonates after a total hip arthroplasty useless. However, this theory has not been proved on a clinical basis since more recent clinical studies have revealed a positive effect of bisphosphonates on osseointegration. Alendronate was tested in osteoporotic human patients who had sustained pertrochanteric fractures [58]. Fractures were fixed with the use of a trochanteric fixator and hydroxyapatite-coated pins. In the patients who received an oral dose of 70 mg of alendronate per week, the extraction torque increased twofold with the pins implanted in cancellous bone when compared with a control group. In the last decade, many clinical studies have shown the positive role of systemic administration of bisphosphonates on the peri-implant bone mineral density (BMD) after total hip and knee

arthroplasty [59, 60] as well as the therapeutic effect against local osteoporosis after cementless total hip arthroplasty [61]. Recently, a population-based retrospective cohort study [62] has revealed that in patients undergoing lower limb arthroplasty, bisphosphonate use was associated with an almost twofold increase in implant survival time. All patients underwent primary total arthroplasty of the knee ($n = 18,726$) or hip ($n = 23,269$) during 1986–2006 within the UK's General Practice Research Database. Patients with a history of hip fracture before surgery or rheumatoid arthritis and individuals younger than 40 years at surgery were excluded. Bisphosphonate users were classified as patients with at least six prescriptions of bisphosphonates or at least 6 months of prescribed bisphosphonate treatment with more than 80 % adherence before revision surgery. Of 41,995 patients who underwent primary hip or knee arthroplasty, 1,912 bisphosphonate users were identified, who had a lower rate of revision at 5 years than nonusers (0.93 % (95 % confidence interval 0.52–1.68 %) vs. 1.96 % (1.80–2.14 %)). Implant survival was significantly longer in bisphosphonate users than in nonusers in propensity-adjusted models (hazard ratio 0.54 (0.29–0.99), $p = 0.047$) and had an almost twofold increase in time to revision after hip or knee arthroplasty (time ratio, 1.96 (1.01–3.82)). Assuming 2 % failure over 5 years, the estimated number to treat to avoid one revision was 107 for oral bisphosphonates. However, these impressive findings require replication and testing in experimental studies for confirmation.

To determine the short- and long-term effect of bisphosphonates on periprosthetic bone mineral density after THA, computerized searches for randomized, controlled trials evaluating the use of alendronate in patients treated with cementless primary THA were conducted [63]. A review of PubMed, the Cochrane Central Register of Controlled Trials, Web of Science, and Embase from their inception to May 2010 was completed, and the methodological quality and abstracted relevant data were assessed. Of 310 citations that were initially identified, 5 studies assessing 146 patients were reviewed. These studies showed that significantly less periprosthetic bone loss

had occurred in the alendronate-treated group than in the placebo-treated group during the short-term period after THA. For long-term investigation, the studies reported that the periprosthetic bone density was slightly higher in the alendronate-treated group compared to the placebo-treated group, but the differences did not reach statistical significance. This systematic review suggests that alendronate has a beneficial effect with regard to preservation of periprosthetic bone short term after cementless THA. However, the study could not provide enough evidence that the positive effect noted in the early postoperative period is maintained long term. A longer follow-up with a larger number of participants is needed to confirm the outcome of cementless THA patients treated with alendronate or other bisphosphonates. In conclusion, several bisphosphonates are intensively tested, especially alendronate, pamidronate, and zoledronate, with either systemic (oral, iv) or local (localized drug delivery from implant coatings) administration in animal and clinical studies. Most of these studies show that bisphosphonates (a) increase peri-implant BMD in cementless prostheses, (b) increase peri-implant BMD even in cemented prostheses when administered systemically, (c) reduce or prevent particle-induced osteolysis, (d) reduce or prevent peri-implant osteopenia induced by the stress-shielding phenomenon, (e) enhance osseointegration of cementless prostheses at the level of bone-implant interface, (f) increase implant mechanical stability, and (g) eventually positively effect the long-standing durability of the prostheses. However, there are still many questions to be answered: (a) there are still no studies comparing treatment with different bisphosphonates in order to investigate which bisphosphonate is the most effective, (b) there are no studies providing enough evidence that the positive effect of bisphosphonates treatment – noted in the early postoperative period – is maintained long term, and (c) there are no studies comparing systemic with the local administration of bisphosphonates in terms of osseointegration enhancement, peri-implant BMD increase, osteolysis prevention, as well as implant survival time.

Strontium Ranelate

Strontium ranelate is well known as an effective antiosteoporotic agent because of its dual effect of anti-resorbing and bone-forming activity. There are several recent studies testing this pharmacological agent, hypothesizing that if strontium ranelate has a peri-implant bone anabolic effect, then it would eventually improve biomaterial properties and implant osseointegration. In a rabbit hip replacement model, strontium-containing hydroxyapatite (Sr-HA) cement, in which 10 % calcium ions were substituted by strontium, was implanted [64]. Six months later, the morphology and chemical composition of interfaces between Sr-HA cement with cancellous bone and cortical bone were evaluated by field emission scanning electron microscopy (FESEM) and time-of-flight secondary ion mass spectrometry (ToF-SIMS). Remarkable differences between these two interfaces were suggested in both morphology and chemical compositions. Regarding morphology, an apatite layer was found between Sr-HA cement and cancellous bone with a thickness of about 70 μm , but only a very thin interface (about 1 μm) was formed with cortical bone. Regarding chemical compositions, at the cancellous bone-cement interface, high ion intensities of Ca, P, Sr, Na, and O were confirmed by FESEM-EDX and ToF-SIMS. These differences in morphology and chemical component between the two interfaces provide convincing evidence for the proposed dissolution-precipitation coupling mechanism in the formation of biological apatite. Furthermore, local administration of strontium ranelate by elution from the prosthesis surface shows the anabolic effect of this pharmacological agent of increasing periprosthetic bone formation. In a rat study, titanium implants were inserted into the proximal tibiae of Sprague-Dawley female rats [65]. During the 8 weeks following implantation, the animals received oral strontium ranelate 5 days a week (625 mg/kg/day) or a saline vehicle. Pullout strength, micro-CT, and nano-indentation were assessed on the implanted tibiae. Strontium ranelate significantly increased pullout strength compared to controls (+34 %). This

was associated with a significant improvement of bone microarchitecture around the implant with a more plate-shaped structure and an increase in bone-to-implant contact (+19 %). Furthermore, strontium ranelate had a significant beneficial effect on parameters of bone biomaterial properties at both cortical (modulus +11.6 %, hardness +13 %) and trabecular areas (modulus +7 %, hardness +16.5 %). The improvement of biomechanical properties was associated with an improvement of implant osseointegration, leading to the conclusion that strontium ranelate has a positive effect both on bone microarchitecture and on bone biomaterial properties in the bone-implant interface and peri-implant bone area. In another rat study, systemic administration of strontium ranelate was tested for dose-dependent results [66]. Twelve weeks after being ovariectomized (OVX group, $n=30$) or sham operated (control group, $n=10$), 40 female Sprague-Dawley rats received unilateral hydroxyapatite (HA)-coated titanium screws in the proximal tibiae. The OVX rats were randomly divided into the following groups: OVX, OVX+SR (“L” refers to low SR dose of 500 mg/kg/day), and OVX+SRH (“H” refers to high SR dose of 1,000 mg/kg/day). Twelve weeks after treatment, bone blocks with implants were evaluated with micro-CT and biomechanical pushout tests. Compared to OVX animals, SR treatment increased the bone volume ratio by 51.5 % and 1.1-fold, the percentage osseointegration by 1.0-fold and 1.9-fold in micro-CT evaluation, and the maximal force by 1.9-fold and 3.3-fold in biomechanical pushout test, for the low and high dose of SR, respectively. A significant correlation between micro-CT and biomechanical properties demonstrated that trabecular parameters play an important role in predicting the biomechanical properties of implant fixation. According to this study, systemic strontium ranelate treatment can dose dependently improve HA-coated screw fixation in OVX rats and facilitate the stability of the implant in the osteoporotic bone. To conclude, strontium ranelate is not only an antiosteoporotic agent with anabolic bone effect used in osteoporosis but can also be used systemically or locally as a pharmacological agent that would have a

positive effect at the bone-implant interface by increasing the mechanical fixation of the implant and improving implant osseointegration. However, all the abovementioned studies are *in vivo* animal experiments, and further investigation with clinical studies by oral or local administration of strontium ranelate is needed.

Parathyroid Hormone (PTH) and Teriparatide

Endogenous parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. PTH increases serum calcium, partially accomplishing this by increasing bone resorption. Thus, chronically elevated PTH will deplete bone stores. However, intermittent exposure to PTH will activate osteoblasts more than osteoclasts. Thus, once-daily injections of teriparatide have a net effect of stimulating new bone formation, leading to increased bone mineral density [67]. Teriparatide is a portion of the human parathyroid hormone (PTH), amino acid sequence 1 through 34, of the complete molecule (containing 84 amino acids). Teriparatide is the first, and to date only, FDA-approved agent for the treatment of osteoporosis that stimulates new bone formation. It has an anabolic effect on bone tissue, leading to an increase in bone strength with a reduction in the risk of fragility fractures in osteoporotic women. This anabolic effect of teriparatide benefits fracture healing by reducing the time of callus formation and remodeling. Recently, it has been shown that teriparatide also seems to have an effect in the early postoperative period after osteosynthesis or joint replacement, by stimulating new bone formation, increasing bone-implant contact as early as after 1 week, and enhancing the tensile strength of the bone-cement interface, thereby decreasing the risk of late aseptic loosening [68, 69]. In rat animal models, systemic administration of teriparatide has enhanced implant osseointegration, increasing screw fixation by 2.5-fold after 2 weeks and screw torsional strength by 3.5-fold after 4 weeks [70]. In a canine implant model [71], the hypothesis that administration of

parathyroid hormone may improve osseointegration of implants surrounded by bone graft was tested. In 20 dogs a cylindrical porous-coated titanium alloy implant was inserted into normal cancellous bone in the proximal humerus and surrounded by a circumferential gap of 2.5 mm. Morselized allograft was impacted around the implant. Half of the animals were given daily injections of human parathyroid hormone (1–34) 5 µg/kg for 4 weeks and half received control injections. The two groups were compared by mechanical testing and histomorphometry. A significant increase in new bone formation within the bone graft in the parathyroid hormone group was noticed. There were no significant differences in the volume of allograft, in the bone-implant contact, or in the mechanical parameters. These findings suggest that parathyroid hormone improves new bone formation in impacted morselized allograft around an implant and retains the graft volume without significant resorption. Fixation of the implant was neither improved nor compromised at the final follow-up of 4 weeks. In another canine implant model [72], the effect of human PTH (1–34) on implant fixation in an experimental gap was examined. Cylindrical (10×6 mm) porous-coated titanium alloy implants were inserted in a concentric 1 mm gap in normal cancellous bone of proximal tibia in 20 canines. Animals were randomized to treatment with PTH (1–34) 5 µg/kg daily. After 4 weeks, fixation was evaluated by histomorphometry and pushout test. Bone volume was found to have increased significantly in the gap. In the outer gap (500 µm), the bone volume fraction median (interquartile range) was 27 % (20–37 %) for PTH and 10 % (6–14 %) for control. In the inner gap, the bone volume fraction was 33 % (26–36 %) for PTH and 13 % (11–18 %) for control. At the implant interface, the bone fraction improved with 16 % (11–20 %) for PTH and 10 % (7–12 %) ($p=0.07$) for control. Mechanical implant fixation was improved for implants exposed to PTH. For PTH, median (interquartile range) shear stiffness was significantly higher (PTH 17.4 [12.7–39.7] MPa/mm and control 8.8 [3.3–12.4] MPa/mm) ($p<0.05$). Energy absorption was significantly enhanced

for PTH (PTH 781 [595–1198.5] J/m(2) and control 470 [189–596] J/m(2)). Increased shear strength was observed but was not significant (PTH 3.0 [2.6–4.9] and control 2.0 [0.9–3.0] MPa) ($p=0.08$). The results from the abovementioned animal studies show that PTH or teriparatide has a positive effect on implant fixation in regions where gaps exist in the surrounding bone. In joint replacement surgery, implants are unavoidably surrounded by gaps despite meticulous surgical technique and osseointegration is challenging. Furthermore, in revision arthroplasty surgery, where larger bone gaps exist, impaction allograft is an established method of securing initial stability of the arthroplasty implant. In such cases, subsequent bone integration can be prolonged, and the volume of allograft may not be maintained. The clinical application of the findings of the above animal studies PTH could be that PTH may potentially be used clinically to enhance tissue integration in challenging environments such as primary and revision arthroplasty surgery.

There are no clinical studies investigating the effects of PTH/teriparatide on the osseointegration of implants in orthopedic surgery. Recently, in dental surgery [73], an open-label randomized controlled feasibility study was performed including 24 individuals with edentulous lower jaws. The participants received two study implants in the mandible during interforaminal dental implant surgery. They were randomly assigned to receive either 20 μ g of teriparatide once daily for 28 days or no treatment. Study implants were retrieved from 23 participants after 9 weeks and were subjected to histomorphometric analyses. Endpoints were new bone volume per tissue volume (NBV/TV) and new bone-to-implant contact (NBIC). The median values of NBV/TV in the control and the teriparatide groups were 15.4 % vs. 17.6 % in the periosteal compartment, 11.3 % vs. 16.5 % in the cortical compartment, and 7.3 % vs. 12.0 % in the medullary compartment, respectively. NBIC median values in the control and the teriparatide groups were 3.3 % vs. 4.1 % in the periosteal compartment, 5.0 % vs. 4.4 % in the cortical compartment, and 0.3 % vs. 1.4 % in the medullary compartment, respectively. The results provide the first histologic data on the

osseointegration of titanium study implants in individuals treated with teriparatide. Orthopedic surgery clinical studies are needed to prove that teriparatide as an anabolic osteoporosis therapeutic agent can also positively affect the osseointegration of arthroplasty implants.

Biocoatings

Many differentiation and growth factors have been used either alone or combined as biological coatings of implant surfaces to enhance or accelerate osseointegration directly at the bone-implant microenvironment [74–77]. Studies on BMP-2, BMP-7, and osteogenic protein (OP-1) have shown that these factors applied as biocoatings augment bone formation and osseointegration of implants [78–83]. Platelet-derived growth factors (PDGF), insulin growth factor (IGF), and transforming growth factor-beta 1 (TGFb-1), alone or in combination with IGF-1 and TGFb-2, have been also used to improve implant osseointegration [74, 75, 84, 85]. However, there are studies with osteoinductive factors with contradictory results [86], and there are many issues that need to be solved, including dose–response, degradation or elution rhythm, half-life time, and clinical safety.

Pharmacological Agents Negatively Affecting Osseointegration

Various pharmacological agents have been found to impair implant osseointegration, including cyclosporine A, methotrexate, and cis-platinum [87–89]. The administration of warfarin was found to significantly impair both the attachment strength and the ingrowth of bone-uncoated porous implants made of cobalt–chromium–molybdenum alloy; however, no such inhibitory effect was observed in hydroxyapatite-coated implants [90]. It has also been suggested that perioperative administration of the NSAID indomethacin causes an early and transient decrease in attachment strength, but this finding does not seem to significantly affect the long-term osseointegration of porous-coated implants [91].

Conclusions

Contemporary research on joint arthroplasty is aimed at the bone-implant interface; the clarification of the post-implantation biological responses that are activated and how these mechanisms lead to osseointegration or minimize the risk of aseptic loosening remain hot topics. Despite current knowledge, there are still many unknown fields and many questions that need to be answered in order to avoid the phenomenon of aseptic loosening which is a serious complication in reconstructive surgery and joint replacement, in order to reduce patient morbidity and health-care costs. Modern research is focused on the role of pharmacological agents on the cellular and molecular mechanisms that rule the processes of osseointegration and aseptic loosening. Pharmacological agents, including a wide spectrum from clinically established drugs to new biological factors, have been tested. In vitro experiments, in vivo animal studies, as well as clinical tests show the positive or negative effect of such agents on bone-implant osseointegration when administered either locally or systemically. However, there are still many questions that need to be answered in terms of administration route, dose-response balance, rhythm of local drug elution, side effects, and long-term endurance of the promising results. Another issue is that due to interspecies differences, the results of animal studies may not always be reliable when applied as clinical tests. In this case, clinical trials are needed to elucidate in vivo contradictory results and to solve problems regarding optimal dose and safety for clinical use.

References

1. Kienapfel H, Sprey C, Wilke A, Griss P. Implant fixation by bone ingrowth. *J Arthroplasty*. 1999;14(3):355–68.
2. Branemark PI. Vital microscopy of bone marrow in rabbit. *Scand J Clin Lab Invest*. 1959;11(S38):1–82.
3. Branemark PI. Osseointegration and its experimental studies. *J Prosthet Dent*. 1983;50:399–410.
4. Rigo ECS, Boschi AO, Yoshimoto M, Allegrini Jr S, Konig Jr B, Carbonari MJ. Evaluation in vitro and in vivo of biomimetic hydroxyapatite coated on titanium dental implants. *Mater Sci Eng*. 2004;24:647–51.
5. Abu-Amer Y, Darwech I, Clohishy JC. Aseptic loosening of total joint replacements: mechanisms underlying osteolysis and potential therapies. *Arthritis Res Ther*. 2007;9(S1):S6.
6. Kim YH, Kim VE. Uncemented porous-coated anatomic total hip replacement. Results at six years in a consecutive series. *J Bone Joint Surg Br*. 1993;75B:6–13.
7. Zhang C, Tang TT, Ren WP, Zhang XL, Dai KR. Inhibiting wear particles-induced osteolysis with doxycycline. *Acta Pharmacol Sin*. 2007;28:1603–10.
8. Ren W, Li XH, Chen BD, Wooley PH. Erythromycin inhibits wear debris-induced osteoclastogenesis by modulation of murine macrophage NF-kappaB activity. *J Orthop Res*. 2004;22:21–9.
9. Yang SY, Wu B, Mayton L, Mukherjee P, Robbins PD, Evans CH, Wooley PH. Protective effects of IL-1Ra or vIL-10 gene transfer on a murine model of wear debris-induced osteolysis. *Gene Ther*. 2004;11:483–91.
10. Merkel KD, Erdmann JM, McHugh KM, Abu-Amer Y, Ross FP, Teitelbaum SL. Tumor necrosis factor-alpha mediates orthopaedic implant osteolysis. *Am J Pathol*. 1999;154:203–10.
11. Schwarz EM, Lu AP, Goater JJ, Benz EB, Kollias G, Rosier RN, Puzas JE, O'Keefe RJ. Tumor necrosis factor-alpha/nuclear transcription factor-kappaB signaling in periprosthetic osteolysis. *J Orthop Res*. 2000;18:472–80.
12. Childs LM, Goater JJ, O'Keefe RJ, Schwartz EM. Efficacy of etanercept for wear debris-induced osteolysis. *J Bone Miner Res*. 2001;16:338–47.
13. Rakshit DS, Lim J, Ly K, Ivashkiv LB, Nestor BJ, Sculco TP, Purdue PE. Involvement of complement receptor 3 (CR3) and scavenger receptor in macrophage responses to wear debris. *J Orthop Res*. 2006;24:2036–44.
14. Chiba J, Rubash HE, Kim KJ, Iawaki Y. The characterization of cytokines in the interface tissue obtained from failed cementless total hip arthroplasty with and without femoral osteolysis. *Clin Orthop*. 1994;300:304–12.
15. Nivbrant B, Karlsson K, Karrhorn J. Cytokine levels in synovial fluid from hips with well-functioning or loose prostheses. *J Bone Joint Surg Br*. 1999;81B:163–6.
16. Stea S, Visantin M, Granchi D, Ciapetti G, Donati ME, Sudanese A, Zanotti C, Toni A. Cytokines and osteolysis around total hip prostheses. *Cytokine*. 2000;12:1575–9.
17. Shanbhag AS, Jacobs JJ, Black J, Galante JO, Glant TT. Cellular mediators secreted by interfacial membranes obtained at revision total hip arthroplasty. *J Arthroplasty*. 1995;10:498–506.
18. Sabokbar A, Rushton N. Role of inflammatory mediators and adhesion in the pathogenesis of aseptic loosening in total hip arthroplasties. *J Arthroplasty*. 1995;10:810–6.

19. Ishiguro N, Kojima T, Ito T, Saga S, Anma H, Kurokouchi K, Iwahori Y, Iwase T, Iwata H. Macrophage activation and migration in interface tissue around loosening total hip arthroplasty components. *J Biomed Mater Res.* 1997;35:399–406.
20. Haynes DR, Crotti TN, Potter AE, Loric M, Atkins GJ, Howie DW, Findlay TM. The osteoclastogenic molecules RANKL and RANK are associated with periprosthetic osteolysis. *J Bone Joint Surg Br.* 2001;83B:902–11.
21. Suh KT, Chang JW, Jung JS. The role of inducible nitric oxide synthase in aseptic loosening after total hip arthroplasty. *J Bone Joint Surg Br.* 2002;84B:753–7.
22. Goodman SB, Huie P, Song Y, Schurman D, Maloney W, Woolson S, Sibley R. Cellular profile and cytokine production at prosthetic interfaces: study of tissues retrieved from revised hip and knee replacements. *J Bone Joint Surg Br.* 1998;80B:531–9.
23. Xu JW, Kontinen YT, Lassus J, Natas H, Ceponis A, Solovieva S, Aspenberg P, Santavirta S. Tumor necrosis factor- α (TNF- α) in loosening of total hip replacement (THR). *Clin Exp Rheumatol.* 1996;14:643–8.
24. Abu-Amer Y, Clohisy JC. Chapter 20: The biologic response to orthopaedic implants. In: Einhorn TA, O'Keefe RJ, Buckwalter JA, editors. *Orthopaedic basic science. Foundations of clinical practice.* 3rd ed. Rosemont: American Academy of Orthopaedic Surgeons; 2007. p. 365–77.
25. Goater JJ, O'Keefe RJ, Rosier RN, Puzas JE, Schwarz EM. Efficacy of ex vivo OPG gene therapy in preventing wear debris induced osteolysis. *J Orthop Res.* 2002;20:169–73.
26. Ulrich-Vinther M, Carmody EE, Goater JJ, Sb K, O'Keefe RJ, Schwarz EM. Recombinant adeno-associated virus-mediated osteoprotegerin gene therapy inhibits wear debris-induced osteolysis. *J Bone Joint Surg Am.* 2002;84A:1405–12.
27. Childs LM, Paschalis EP, Xing L, Dougall WC, Anderson D, Boskey AL, Puzas JE, Rosier RN, O'Keefe RJ, Boyce BF, Schwarz EM. In vivo RANK signaling blockade using the receptor activator of NF- κ B:Fc effectively prevents and ameliorates wear debris-induced osteolysis via osteoclast depletion without inhibiting osteogenesis. *J Bone Miner Res.* 2002;17:192–9.
28. Zhang T, Yu H, Gong W, Zhang L, Jia T, Wooley PH, Yang SY. The effect of osteoprotegerin gene modification on wear debris-induced osteolysis in a murine model of knee prosthesis failure. *Biomaterials.* 2009;30:6102–8.
29. Zhang L, Jia TH, Chong AC, Bai L, Yu H, Gong W, Wooley PH, Yang SY. Cell-based osteoprotegerin therapy for debris-induced aseptic prosthetic loosening on a murine model. *Gene Ther.* 2010;17:1262–9.
30. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. *Bone.* 2011;48:677–92.
31. Maeda T, Matsunuma A, Kawane T, Horiuchi N. Simvastatin promotes osteoblast differentiation and mineralization in MC3T3-E1 cells. *Biochem Biophys Res Commun.* 2001;280:874–7.
32. Montagnani A, Gonnelli S, Cepollaro C, Pacini S, Campagna MS, Franci MB, Lucani B, Gennari C. Effect of simvastatin treatment on bone mineral density and bone turnover in hypercholesterolemic postmenopausal women; a 1-year longitudinal study. *Bone.* 2003;32:427–33.
33. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H. HMG-CoA reductase inhibitors and the risk of fractures. *JAMA.* 2000;283:3205–10.
34. Von Knoch F, Wedemeyer C, Heckelei A, Saxler G, Hilken G, Brankamp J, Sterner T, Landgraeber S, Henschke F, Loer F, von Knoch M. Promotion of bone formation by simvastatin in polyethylene particle-induced osteolysis. *Biomaterials.* 2005;26:5783–9.
35. Yang F, Zhao SF, Zhang F, He FM, Yang GL. Simvastatin-loaded porous implant surfaces stimulate preosteoblasts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2011;111:551–6.
36. Yin H, Li J, Yu X, Fu Z. Effects of simvastatin on osseointegration in canine total hip arthroplasty model: an experimental study. *J Arthroplasty.* 2011;26:1534–9.
37. Basarir K, Erdemli B, Can A, Erdemli E, Zeyrek T. Osseointegration in arthroplasty: can simvastatin promote bone response to implants? *Int Orthop.* 2009;33:855–9.
38. Ayukawa Y, Ogino Y, Moriyama Y, Atsuta I, Jinno Y, Kihara M, Tsukiyama Y, Koyano K. Simvastatin enhances bone formation around titanium implants in rat tibiae. *J Oral Rehabil.* 2010;37:123–30.
39. Du Z, Chen J, Yan F, Xiao Y. Effects of simvastatin on bone healing around titanium implants in osteoporotic rats. *Clin Oral Implants Res.* 2009;20:145–50.
40. Nociti Jr FH, Sallum EA, Toledo S, Newman HN, Sallum AW. Effect of calcitonin on bone healing following titanium implant insertion. *J Oral Sci.* 1999;41:77–80.
41. Januário AL, Sallum EA, de Toledo S, Sallum AW, Nociti Jr JF. Effect of calcitonin on bone formation around titanium implant. A histometric study in rabbits. *Braz Dent J.* 2001;12:158–62.
42. Kauter MD, Hagen S, Bachmann HS, Neuerburg L, Broecker-Preuss M, Hilken G, Grabellus F, Koehler G, von Knoch M, Wedemeyer C. Calcitonin substitution in calcitonin deficiency reduces particle-induced osteolysis. *BMC Musculoskelet Disord.* 2011;12:186.
43. Chen BL, Xie DH, Zheng ZM, Lu W, Ning CY, Li YQ, Li FB, Liao WM. Comparison of the effects of alendronate sodium and calcitonin on bone-prosthesis osseointegration in osteoporotic rats. *J Bone Joint Surg Am.* 2008;90:824–32.
44. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA. Ten year's experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med.* 2004;350:1189–99.
45. Millet PJ, Allen MJ, Bostrom MP. Effects of alendronate on particle-induced osteolysis in a rat model. *J Bone Joint Surg Am.* 2002;84A:236–49.

46. Sabokbar A, Fujikawa Y, Neale S, Murray DW, Athanasou NA. Human arthroplasty derived macrophages differentiate into osteoclastic bone resorbing cells. *Ann Rheum Dis*. 1997;56:414–20.
47. Shanbhag AS, Hasselman CT, Rubash HE. The John Charnley Award: inhibition of wear debris mediated osteolysis in a canine total hip arthroplasty model. *Clin Orthop*. 1997;344:33–43.
48. Von Knoch M, Wedemeyer C, Pingsmann A, von Knoch F, Hilken G, Sprecher C, Henschke F, Barden B, Loer F. The decrease of particle-induced osteolysis after a single dose of bisphosphonate. *Biomaterials*. 2005;26:1803–8.
49. Von Knoch F, Eckhardt C, Alabre CI. Anabolic effects of bisphosphonates on peri-implant bone stock. *Biomaterials*. 2007;28:3549–59.
50. Miyaji T, Nakase T, Azuma Y, Shimizu N, Uchiyama Y, Yoshikawa H. Alendronate inhibits bone resorption at the bone-screw interface. *Clin Orthop*. 2005;430:195–201.
51. Bobynd JD, McKenzie K, Karabasz D, Krygier JJ, Tanzer M. Locally delivered bisphosphonate for enhancement of bone formation and implant fixation. *J Bone Joint Surg Am*. 2009;91A(S6):23–31.
52. Tanzer M, Karabasz D, Krygier JJ, Cohen R, Bobynd JD. The Otto Aufranc Award: bone augmentation around and within porous implants by local bisphosphonate elution. *Clin Orthop*. 2005;441:30–9.
53. Peter B, Gauthier O, Laïb S, Bujoli B, Guicheux J, Janvier P, van Lenthe GH, Müller R, Zambelli PY, Bouler JM, Pioletti DP. Local delivery of bisphosphonate from coated orthopedic implants increases implants mechanical stability in osteoporotic rats. *J Biomed Mater Res A*. 2006;76(1):133–43.
54. Jakobsen T, Baas J, Bechtold JE, Elmengaard B, Søballe K. The effect of soaking allograft in bisphosphonate: a pilot dose–response study. *Clin Orthop*. 2010;468:867–74.
55. McKenzie K, Dennis Bobynd J, Roberts J, Karabasz D, Tanzer M. Bisphosphonate remains highly localized after elution from porous implants. *Clin Orthop*. 2011;469:514–22.
56. Wilkinson JM, Eagleton AC, Stockley I, Peel NF, Hamer AJ, Eastell R. Effect of pamidronate on bone turnover and implant migration after total hip arthroplasty; a randomized trial. *J Orthop Res*. 2005;23:1–8.
57. Zhang Q, Badell IR, Schwarz EM, Boulukos KE, Yao Z, Boyce BF, Xing L. Tumor necrosis factor prevents alendronate-induced osteoclast apoptosis in vivo by stimulating Bcl-xL expression through Ets-2. *Arthritis Rheum*. 2005;52:2708–18.
58. Moroni A, Faldini C, Hoang-Kim A, Pegreff F, Giannini S. Alendronate improves screw fixation in osteoporotic bone. *J Bone Joint Surg Am*. 2007;89A:96–101.
59. Wang CJ, Wang JW, Weng LH, Hsu CC, Huang CC, Chen HS. The effect of alendronate on bone mineral density in the distal part of the femur and proximal part of the tibia after total knee arthroplasty. *J Bone Joint Surg Am*. 2003;85:2121–6.
60. Peter B, Ramaniraka N, Rakotomanana LR, Zambelli PY, Pioletti DP. Peri-implant bone remodeling after total hip replacement combined with systemic alendronate treatment: a finite element analysis. *Comput Methods Biomech Biomed Engin*. 2004;7:73–8.
61. Yamaguchi K, Masuhara K, Yamasaki S, Nakai T, Fuji T. Cyclic therapy with etidronate has a therapeutic effect against local osteoporosis after cementless total hip arthroplasty. *Bone*. 2003;33:144–9.
62. Prieto-Alhambra D, Javaid MK, Judge A, Murray D, Carr A, Cooper C, Arden NK. Association between bisphosphonate use and implant survival after primary total arthroplasty of the knee or hip: population based retrospective cohort study. *BMJ*. 2011;343:d7222.
63. Zeng Y, Lai O, Shen B, Yang J, Zhou Z, Kang P, Pei F. A systematic review assessing the effectiveness of alendronate in reducing periprosthetic bone loss after cementless primary THA. *Orthopedics*. 2011;34(4). doi:10.3928/01477447-20110228-09.
64. Ni GX, Lu WW, Xu B, Chiu KY, Yang C, Li ZY, Lam WM, Luk KD. Interfacial behaviour of strontium-containing hydroxyapatite cement with cancellous and cortical bone. *Biomaterials*. 2006;27:5127–33.
65. Maïmoun L, Brennan TC, Badoud I, Dubois-Ferriere V, Rizzoli R, Ammann P. Strontium ranelate improves implant osseointegration. *Bone*. 2010;46:1436–41.
66. Li Y, Feng G, Gao Y, Luo E, Liu X, Hu J. Strontium ranelate treatment enhances hydroxyapatite-coated titanium screws fixation in osteoporotic rats. *J Orthop Res*. 2010;28:578–82.
67. Bauer DC. Review: human parathyroid hormone reduces fractures and increases bone mineral density in severe osteoporosis. *ACP J Club*. 2006;145:71.
68. Iolascon G, Gimigliano F, Resmini G. Teriparatide and orthopedic surgery. *Aging Clin Exp Res*. 2007;19(S4):22–5.
69. Knecht TP. Teriparatide and fracture healing in cortical bone. *Endocr Pract*. 2004;10:293.
70. Skripitz R, Aspenberg P. Implant fixation enhanced by intermittent treatment with parathyroid hormone. *J Bone Joint Surg Br*. 2001;83B:437–40.
71. Daugaard H, Elmengaard B, Andreassen TT, Baas J, Bechtold JE, Søballe K. The combined effect of parathyroid hormone and bone graft on implant fixation. *J Bone Joint Surg Br*. 2011;93B:131–9.
72. Daugaard H, Elmengaard B, Andreassen T, Bechtold J, Lamberg A, Søballe K. Parathyroid hormone treatment increases fixation of orthopedic implants with gap healing: a biomechanical and histomorphometric canine study of porous coated titanium alloy implants in cancellous bone. *Calcif Tissue Int*. 2011;88:294–303.
73. Kuchler U, Luvizuto ER, Tangl S, Watzek G, Gruber R. Short-term teriparatide delivery and osseointegration: a clinical feasibility study. *J Dent Res*. 2011;90:1001–6.

74. Lynch SE, Buser D, Hernandez RA, Weber HP, Stich H, Fox CH, Williams RC. Effects of the platelet-derived growth factor/insulin-like growth factor-I combination on bone regeneration around titanium dental implants. Results of a pilot study in beagle dogs. *J Periodontol.* 1991;62:710–6.
75. Lamberg A, Schmidmaier G, Soballe K, Elmengaard B. Locally delivered TGF-beta1 and IGF-1 enhance the fixation of titanium implants; a study in dogs. *Acta Orthop Scand.* 2006;77:799–805.
76. Mannai C. Early implant loading in severely resorbed maxilla using xenograft, autograft, and platelet-rich plasma in 97 patients. *J Oral Maxillofac Surg.* 2006;64:1420–6.
77. Sumner DR, Turner TM, Urban RM, Virdi AS, Inoue N. Additive enhancement of implant fixation following combined treatment with rhTGF-beta2 and rhBMP-2 in a canine model. *J Bone Joint Surg Am.* 2006;88A:806–17.
78. Cole BJ, Bostrom MP, Pritchard TL, Sumner DR, Tomin E, Lane JM, Weiland AJ. Use of bone morphogenetic protein 2 on ectopic porous coated implants in the rat. *Clin Orthop.* 1997;345:219–28.
79. Koempel JA, Patt BS, O'Grady K, Wozney J, Toriumi DM. The effect of recombinant human bone morphogenetic protein-2 on the integration of porous hydroxyapatite implants with bone. *J Biomed Mater Res.* 1998;41:359–63.
80. Jennissen HP. Accelerated and improved osteointegration of implants biocoated with bone morphogenetic protein 2 (BMP2). *Ann N Y Acad Sci.* 2002;961:139–42.
81. Becker J, Kirsch A, Schwarz F, Chatzinikolaidou M, Rothamel D, Lekovic V, Laub M, Jennissen HP. Bone apposition to titanium implants biocoated with recombinant human bone morphogenetic protein-2 (rhBMP-2). A pilot study in dogs. *Clin Oral Investig.* 2006;10:217–24.
82. Lind M, Overgaard S, Song Y, Goodman SB, Bunger C, Soballe K. osteogenic protein 1 device stimulates bone healing to hydroxyapatite-coated and titanium implants. *J Arthroplasty.* 2000;15:339–46.
83. Zhang R, An Y, Toth CA, Draugh RA, Dimaano NM, Hawikns MV. Osteogenic protein-1 enhances osseointegration of titanium implants coated with periapatite in rabbit femoral defect. *J Biomed Mater Res B Appl Biomater.* 2004;71:408–13.
84. Sumner DR, Turner TM, Purchio AF, Gombotz WR, Urban RM, Galante JO. Enhancement of bone ingrowth by transforming growth factor-beta. *J Bone Joint Surg Am.* 1995;77A:1135–47.
85. De Ranieri A, Virdi AS, Kuroda S, Shott S, Leven RM, Hallab NJ, Sumner DR. Local application of rhTGF-beta2 enhances peri-implant bone volume and bone-implant contact in a rat model. *Bone.* 2005;37:55–62.
86. Salata LA, Burgos PM, Rasmusson L, Novaes AB, Papalexiou V, Dahlin C, Sennerby L. Osseointegration of oxidized and turned implants in circumferential bone defects with and without adjunctive therapies: an experimental study on BMP-2 and autogenous bone graft in the dog mandible. *Int J Oral Maxillofac Surg.* 2007;36:62–71.
87. Sakakura CE, Marcantonio Jr E, Wenzel A, Scaf G. Influence of cyclosporine A on quality of bone around integrated dental implants: a radiographic study in rabbits. *Clin Oral Implants Res.* 2007;8:34–9.
88. Eder A, Watzek G. Treatment of a patient with severe osteoporosis and chronic polyarthritis with fixed implant-supported prosthesis: a case report. *Int J Oral Maxillofac Implants.* 1999;15:587–90.
89. McDonald AR, Pogrel MA, Sharma A. effects of chemotherapy on osseointegration of implants: a case report. *J Oral Implantol.* 1998;24:11–3.
90. Callahan BC, Lisecki EJ, Banks RE, Dalton JE, Cook SD, Wolff JD. The effect of warfarin on the attachment of bone to hydroxyapatite-coated and uncoated porous implants. *J Bone Joint Surg Am.* 1995;77A:225–30.
91. Cook SD, Barrack RL, Dalton JE, Thomas KA, Brown TD. Effects of indomethacin on biologic fixation of porous-coated titanium implants. *J Arthroplasty.* 1995;10:351–3.

Bone-Implant Interface in Biofilm-Associated Bone and Joint Infections

17

Konstantinos N. Malizos and Maria Ioannou

Introduction

Total hip and knee arthroplasties are considered the procedures of the twentieth century, with dramatic improvement to the overall quality of life for millions of patients around the globe. The application of fracture fixation implants and the replacement of the arthritic joints became a common practice in modern orthopedics, relieving hundreds of thousands of patients of pain and functional disability. With a share of 38 %, orthopedics and traumatology are the worldwide leading markets of implanted biomaterials, involving millions of new patients each year as an increasing trend [1]. Commonly used implants in orthopedics are mainly employed for the fixation or reconstruction of bones and joints or their parts and adjacent soft tissues (ligaments, tendons, menisci, etc.) and are made of biocompatible metals, polymers, ceramics, hydroxyapatite, and their combinations. The first requirement of a material's biocompatibility is that, whatever the desired function, the material should not induce

any adverse effects in the patient, "just as the first principle of Hippocrates was that the doctor should do no harm" [2].

Although the clinical results are excellent, a number of complications, most of which present with signs and symptoms related to implant loosening, are associated with these procedures. The pathological processes that occur in bone-implant interface reflect pathogenetic mechanisms such as nonspecific macrophage response to wear particles (aseptic loosening), a specific hypersensitivity immune reaction to wear particles from the bearing surfaces, infection (septic loosening), primary joint-related pathology in revision arthroplasty tissues, and tumor formation in peri-implant tissues [3, 4].

Bacterial infections around implants of bones and joints represent the most devastating complication involving millions of citizens. The frequency of these infections varies with regard to the location. In the upper extremities, the rate of infection is reported to be higher for the elbow joint (7.7 %) than that for the wrist (2.39 %) or the shoulder (1.06 %) endoprotheses [5]. The overall rate of infection in primary major joint arthroplasty or fracture fixation implants ranges between 1 and 2 % and becomes much higher in patients with compromised immune response. The incidence increases with revision operations (e.g., 3.2 % in total hip replacement and 5.6 % in total knee replacement) [6–10]. Considering the hundreds of thousands of bone and joint implants applied every year around the world, the absolute number of patients needing costly reconstructive

K.N. Malizos, MD, PhD, DSc (✉)
Department of Orthopaedic Surgery and
Musculoskeletal Trauma, Faculty of Medicine,
School of Health Sciences, University of Thessalia,
41110 Biopolis, Larissa, Greece
e-mail: malizos@med.uth.gr,
<http://www.ortho-uth.org>

M. Ioannou, MD, DSc
Pathology Department, Faculty of Medicine,
School of Health Sciences, University of Thessalia,
41110 Biopolis, Larissa, Greece
e-mail: mioan@med.uth.gr



Fig. 17.1 Intraoperative picture showing the development of biofilm on the surface and around the femoral component of a total knee arthroplasty

surgery at multiple stages, as the only option, is rapidly increasing. In patients with osteosynthesis and particularly, after severe open fractures and open joint trauma with extensive soft tissue injury, infection rate is even higher [6–10]. In situations where an inert foreign material is implanted into the human body, a competition develops for the colonization of the implant surfaces between bacteria and the hosts' cells. Bacteria have some advantages over the immune system cells: they are of faster reproductive processes and are extremely flexible in adapting to the environment. Studies indicate that the procedures of implantation and the compromised local tissue environment from the presence of the prosthesis itself into a joint or at the site of a fracture may reduce the number of bacteria required to cause an infection by a factor of even 10,000 [11]. Infection into implanted bone and joint is directly related to the capability of the bacteria of establishing multilayered, highly structured biofilms on the artificial surfaces and the bare bone surfaces (Fig. 17.1). Indeed, implanted biomaterials are still known to be particularly susceptible to microbial colonization and able to favor the onset of infections [12]. Once biofilm is established, the infection becomes chronic and does not respond any longer to conventional systemic antibiotic therapy [13].

The high prevalence and the increasing social and financial burden of implant-related infections is mainly due to the (1) large number of surgical procedures (more than one million new total joint prosthesis performed annually in Europe), (2) expanding indications in the elderly and in patients with compromised immune defense, (3) frequent chronic and long-lasting behavior of bone and joint infections, (4) difficulty of eradicating the septic process and frequent relapses, (5) frequent occurrence (20–60 %) of multiresistant bacterial strains and mixed florae, and (6) variable incidence, from approximately 1 % after prosthetic surgery, in a normal host, to more than 25 % after osteosynthesis in contaminated fractures with local and/or systemic comorbidities or up to 40 % in bone tumor surgery, in spite of the best available surgical practice and antibiotic prophylaxis. Given the severe socioeconomic burden for the patient, his/her family, the treating physicians, as well as for the budget of the health-care system, it is imperative to devise efficient preventive and more effective treatment strategies. To improve the outcome in the management of biofilm infections around implants, it is necessary to combine the efforts of biologists, biochemists, engineers, microbiologists, and pathologists with those of the treating physicians for a better understanding of the interactions between the implant, the bacteria, and the host.

Herein, we present the current knowledge regarding the pathogenesis of implant-related biofilm infections, the histopathology of the bone-implant interface, and the mechanisms of tissue destruction resulting in osteolysis, which destroys the fixation of the fractures or the stability and function of the joint implants. We also discuss the current concepts in biofilm infection prevention and management.

Pathogenesis of Implant-Related Infections

The time span between trauma or surgery and the clinically apparent infection varies among patients. In some patients, the infection occurs either in the immediate postoperative period or within weeks after surgery, while in others,

Fig. 17.2 Intraoperative picture showing pus evacuation during the initial stages of wound debridement in acute infection after a total hip arthroplasty



the infection becomes clinically apparent after years. An early acute infection may be attributed to direct intraoperative contamination by either exogenous or by endogenous bacteria (e.g., the skin-colonizing bacteria) (Fig. 17.2). In contrast, the late-onset infection usually results from bacteria contracted by the host at a later stage either through a hematogenous spreading or from a contiguous infected site. It is not uncommon, however, for “harmless” bacteria colonizing the skin or the epithelium (e.g., in the nose) to become invasive for reasons still remaining unknown [14–16].

The pathogenesis of infection has been extensively investigated in experimental studies. The microorganisms infecting the implants are either introduced during implantation of the prosthesis or derived from a temporary bacteremia. Then, they adhere to biomaterials establishing a bacterial colony and grow to form a biofilm. The trigger effect for the inflammatory response against infection is induced by the local release of chemokines (e.g., platelet-activating factor (PAF) or complement C5a) subsequently diffused into the adjacent intercellular space. At the nearby endothelial cells, upregulation of the specialized adhesion proteins make them “sticky,” capturing thus the circulating leukocytes, predominantly the polymorphonuclear leukocytes (PMNs), from the peripheral blood, then becoming further activated and firmly attaching to the endothelial cells; they then actively migrate towards the source of infection. They start with phagocytosis of the individual floating bacteria, known as “planktonic” bacteria, followed by intracellular killing and apoptosis of PMNs. Triggering the Fc γ and the

complement receptors provides the optimal signal for the phagocytosis and the killing by the PMNs [17]. In addition, Stroh et al. showed phagocytosis in *S. aureus* biofilms using human serum as a source of antibodies and as a complement for the “opsonization” [18]. The apoptotic PMNs in turn are phagocytosed by the macrophages [19–22]. This is a self-limiting process protecting from further spilling of the cytotoxic enzymes [23–25], and it results in the cleaning of the infected site, as prerequisite for healing and regeneration [22, 25, 26]. The study of natural ecosystems has demonstrated that “planktonic” bacteria are rare; instead, bacteria grow predominantly in biofilm formations. Biofilm formation is the result of a genetically driven process triggered by specific biochemical signals and resulting from the activation and expression of defined sets of genes, e.g., of those coding for adhesion proteins [27–30]. A structural examination of biofilm shows that about 15 % in volume is constituted by microbial cells, embedded in a matrix material in which channels carry bulk fluid into the bacterial community by convective flow. The physiological differentiation of sessile versus individual floating “planktonic” cells, as well as the complexity of the biofilm structure elaborated, suggests that bacterial communities forming biofilms are finely organized and necessarily regulated by signals analogous to the hormones and pheromones typical of multicellular communities of eukaryotic cells [31]. The formation of this community undergoes various stages, starting with an initial attachment of bacteria to an inert or a living surface. As they are multiplied they form microcolonies attached to the surface

and gradually differentiate into biofilm structure. Despite the many possible definitions, bacterial biofilms can simply be described as a structured consortium of bacteria encased in a self-produced matrix which are able to communicate by cell-to-cell signals. Depending on the bacterial species, strain type, and environmental conditions, the biofilm matrix consists of exo-polysaccharides, proteins, teichoic acids, and extracellular DNA (eDNA). The extracellular polysaccharide substance (EPS) produced in abundance by the overgrown number of bacteria is clinically visible even to the naked eye as “slime” or as a jelly film gluing together buds of bacteria on to the implant and tissue surface. eDNA has been up to now described in a variety of bacterial species, and its importance is recognized as a component which may contribute to structural solidity of biofilms and to their recalcitrance to antibiotics by inducing expression of antibiotic resistance genes [32]. Facilitated by the mobility within the liquid environment as in tissue or synovial fluid or blood, buds of bacteria in abundance may be released or tear off from the biofilm and subsequently form additional new colonies at adjacent or remote locations. Bacterial detachment and dispersion therefore characterize this final step of the bacterial life cycle, with many bacteria returning into a planktonic state.

In contrast to the single-living “planktonic” bacterial cells, the biofilms constitute a protected form of bacterial growth, allowing bacterial survival in a hostile environment, as they are resistant to antibiotics, disinfectants, and phagocytic components of the innate and adaptive immune system defense of the host [33–36]. Protective mechanisms include altered chemical microenvironment, slow-growing or non-multiplied biofilm cells, gradually developing resistant phenotypes as an adaptive response to stress, and incomplete biofilm penetration by antibiotics and antibodies [33, 37, 38]. Therefore, in a manner reminiscent of a vicious cycle, the protected bacteria within the biofilm could enhance host defense mechanisms and inflammation, and the sustained inflammation could further stimulate the development of resistant bacterial phenotypes. These properties

could explain the persistent nature of chronic bacterial infections.

Bacterial Biofilms as the Cause of Tissue Destruction

The majority of biofilm infections presents with an insidious onset imposing diagnostic difficulties within the traditional microbiological methods [39]. Over the last decades, management with the administration of antibiotics has not provided any effective treatment against infections associated with implants [40–43] since the bacteria are growing, not as isolated microorganisms (“planktonic” phenotype) but as a distinct phenotype comprised of sessile microorganisms enclosed within a glycocalyx known as biofilm. The biofilms act as an impenetrable mechanical barrier against soluble agents, and multiresistant bacteria are often involved [44] and they persist, giving rise to a progressively destructive inflammatory process, with surrounding tissue damage and osteolysis, leading to septic loosening of the bone and joint implants [6, 7, 37, 45, 46]. Using scanning and transmission electron microscopy, Gristina and Costerton demonstrated the association of persistent bone and joint infections with biofilm formation on their surface [47]. More recent studies employing modern technologies such as confocal laser microscopy have demonstrated stable biofilm structures not only on biomaterials retrieved from patients with chronic bone or joint infections but also on the adjacent viable soft tissues [48, 49]. *Staphylococcus aureus* is the most common bacterium identified in periprosthetic infections. It binds to bone matrix with adhesion molecules and secretes toxins able to attract PMNs and macrophages in the very first hours after its formation, as the first line of cellular defense around the fresh biofilm. The examination of tissue samples from the infected site, during implant revision surgery, reveals pus composed of dead leukocytes, cellular debris, and serum. Using flow cytometry Wagner et al. have identified the infiltrated cells as polymorphonuclear neutrophils (PMNs comprising the 65–85 %), T-lymphocytes (5–15 %), natural

killer (NK) cells (5–15 %), B cells (<1 %), and monocytes (<1 %) [50, 51]. The cellular protagonists of the inflammatory response to biofilm infection and the specific role of PMNs and macrophages in the consequent tissue destruction are presented in the following paragraphs.

The Innate Immune Response

The innate immune system, also known as non-specific immune system and the first line of defense, comprises the cells and mechanisms that provide the immediate defense of the host against infection in a generic, nonspecific manner [52, 53]. The cells of the innate system recognize and respond to pathogens by recruiting immune cells to site of infections, through the production of chemical factors, including specialized chemical mediators called cytokines. Other major functions of the vertebrate innate immune system include activation of the complement cascade to identify bacteria, activation of cells, and promotion of clearance of dead cells or antibody complexes, as well as the identification and removal of foreign substances present in organs, tissues, blood, and lymph by specialized white blood cells. In addition, the innate immune system contributes to the activation of an adaptive immune system through a process known as antigen presentation which acts as a physical and chemical barrier to infectious agents. The cellular component of the innate immune system include leukocytes (polymorphonuclear, B-, T-, and NK lymphocytes, basophils, eosinophils), monocytes/macrophages, mast cells, dendritic cells, and natural killer cells. The parts of the innate immune system have different specificity for different pathogens. In the case of extracellular bacteria such as staphylococcus, the certain strategy of defense is phagocytosis [54]. Although the host defense mechanisms against bacteria organized in biofilms are not completely understood and are still under investigation, previous studies have shown the essential role of innate immunity cells against staphylococcal biofilms, giving evidence that tissue degradation and (in bone) osteolysis are not direct effects caused by the infection per se [50, 51, 55].

The Role of Neutrophils Against Staphylococcus Biofilms

The PMNs are the first cells to arrive at the site of infection through chemical mediators, which are emitted at the infected site and act on the close-by endothelium. The endothelial cells upregulate adhesion proteins that capture the PMNs, which then bind to the endothelial cells and transmigrate between the endothelial cells towards the site of infection. Having reached the site, the PMNs exhibit upregulation of the surface receptors required for bacteria recognition and killing, such as high-affinity Fc-gamma receptor 1 (FcγR1, CD64), “lipopolysaccharide” receptor CD14, interleukin-8 (IL-8) which attracts more PMNs, the monocyte inflammatory proteins MIP-1a and MIP-1b, and the monocyte attractant MCP-1 [46, 50, 51]. Simultaneously in these PMNs the production of reactive oxygen species (ROS) is enhanced while they exhibit down-modulation of L-selectin (CD62L), which is required for the PMN emigration. Then, the PMNs take up and phagocytose the bacteria. The phagocytosis results in killing the bacteria and also induces the programmed cell death (“apoptosis”) of the PMN. In addition to phagocytosis, other investigators have demonstrated that PMNs release lactoferrin and elastase upon contact with biofilm, and after prolonged contact, they also discharge DNA, which is involved in the formation of the so-called neutrophil extracellular traps (NETs), a further mechanism of bacterial killing [56]. It is of interest to note the differential behavior of PMNs towards the biofilm of *S. aureus* and of *S. epidermidis*, which has been documented in a previous study by employing time-lapse video microscopy [57]. In the case of *S. aureus* formed biofilm, the PMNs moving across were observed to scavenge bacteria along their path. Conversely, PMNs in contact with *S. epidermidis* biofilm were nearly immobile and only phagocytosed bacteria in close proximity [57]. Why biofilms of *S. aureus* appear more sensitive to a PMN attack compared to those produced by *S. epidermidis* is still not understood. Since killing of bacteria in biofilms is possible, the question remains, *why biofilms persist in patients and why biofilm-related*

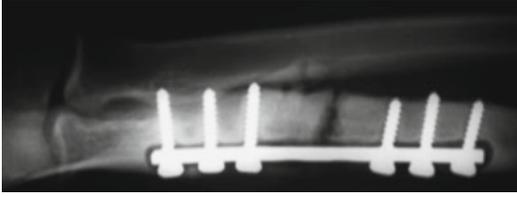


Fig. 17.3 Radiograph showing osteolysis and loosening of a plate fixation due to infection

implant infections become chronic? In cases with impaired local blood circulation, tissue scarring, and compromised immune response, infiltration of the infected site with PMNs is initially rather slow. Clinical studies suggest that lower local levels of PMN in the early surgical wound are directly related to the subsequent occurrence of septic complications, whereas higher early local leukocyte concentrations at the end of the surgical procedure do play a significant protective role against postoperative infection [58, 59]. However, since PMNs arrive at the infected site, they lose their migratory capacity, and thus, they cannot infiltrate the biofilm. Thus, PMNs surround the biofilm and become activated while they do not migrate into the biofilm, probably because of a lack of a chemotactic signal, as well as by the hindrance of migration into the “slimy” material. Although highly activated, the PMNs are not able to engulf the bacteria within the biofilm and to control the infection. Since living bacteria could still be isolated from the infected site inside the biofilm, an evasion of the local host immune defenses has been postulated [50]. Therefore, the rapidly established bacterial adhesions and biofilm formation on the implant surface is initially unchallenged. Consequently, phagocytosis and killing of the bacteria occur only on the surface, leaving the bulk of the biofilm unaffected.

What then is the fate of biofilm? The infection persists and progresses and the PMNs, in their attempt to kill bacteria, express their powerful cytotoxic (e.g., superoxides, ROS) and proteolytic armory to the point of damaging and even destroying the surrounding tissue. Further dire effects are osteolysis and resorption of bone, which usually result in implant loosening (Figs. 17.3 and 17.4). As a consequence, the



Fig. 17.4 Intraoperative picture showing osteolytic areas of the femoral condyles following the removal of the femoral component of an infected total knee arthroplasty

implant has to be removed, and in the most severe cases, also extensive reconstruction of the bone has to be performed.

The Role of Macrophages Against Staphylococcus Biofilms

Macrophages are the most efficient phagocytes and can phagocytose substantial numbers of bacteria or other cells, foreign substances, and cellular debris. In tissues, organ-specific macrophages are differentiated from phagocytic cells present in the blood called monocytes. At the site of infection, the bacterial biofilm attracts monocytes from the peripheral blood [46, 50, 51] through the production of cytokines (e.g., IL-8, monocyte attractant MCP-1). The monocytes in tissues are differentiated to macrophages and to osteoclasts with bone-resorbing activity [60–63]. The macrophages clear the infected tissues from apoptotic PMNs, resulting in limiting of the biofilm-induced inflammatory process in a time and spatial manner; however, they exhibit down-regulation of IL-1b, tumor necrosis factor (TNF) alpha, CXCL2, and CCL2 expression. They also exhibit reduced bacterial uptake, minimal iNOS expression, and consequent low efficiency in killing phagocytosed bacteria and a reduced induction of lymphocyte production of interferon-gamma. Thus, these scavenging cells appear able to migrate into the biofilm but cannot clear the site

from the pathogen causing the infection, as their bactericidal activity appears compromised [64]. On the other hand, the generation and activation of osteoclasts initiate a bone-resorbing activity, further enhancing tissue destruction and osteolysis. Osteoclasts originate from the differentiation of monocytes either following their interaction with T-lymphocytes or through a T-cell independent differentiation action of pro-inflammatory cytokines, such as TNF alpha, IL-1, IL-6, or IL-8, on the monocytes [65–68]. Since these cytokines are generated at the site of infection, the osteolysis is more pronounced adjacent to the implants, from osteoclasts with bone-resorbing activity [46]. Osteolysis is the hallmark of osteomyelitis. Although the link between bacterial infection and osteolysis has not been established yet and direct effects of bacteria cannot be ruled out, bone loss as a consequence of persistent inflammation is presumed [69–72], and the most likely mechanism is enhanced synthesis and/or activation of the bone-resorbing osteoclasts [46].

In conclusion, the “attempt without success” of the first line of defense causes the release of pro-inflammatory mediators from PMNs and of tissue-destroying substances. Moreover, additional bone resorption is further enhanced by osteoclastogenesis. All the above evidence indicates that staphylococcal biofilms evoke the persistent attack of activated leukocytes and so indirectly trigger tissue damage. At the same time sessile biofilm-encased bacteria escape the leukocyte-mediated bactericidal response through biofilm-mediated immune evasion mechanisms.

Septic Interface Pathology

The histological changes at the bone-implant interface reflect pathogenetic mechanisms that lead to complications of implant loosening and provide diagnostic information about the causes of failure [3]. Insertion of a joint implant component into the bone results in necrosis of the bone and bone marrow elements surrounding the implant [73]. Following necrosis, there is formation of granulation and cellular reparative fibrous tissue around the implant. The membrane itself

is subsequently surrounded by reparative woven and lamellar bone that is remodeled along the lines of stress to which the bone is subjected. In a well-fixed stable implant, there is usually little intervening fibrous tissue between the implant and the surrounding cortical or cancellous bone; few or no macrophages are found in the pseudomembrane of a stable prosthesis since there is little generation of implant-derived wear particles [74]. In contrast, loose implants have a thick fibrous tissue membrane that often contains numerous implant-derived wear particles and a heavy foreign-body macrophage response. Active bone remodeling is also seen on the surface of the thickened bone at the bone-implant interface of a loose prosthesis.

The pathological changes in bone-implant interface membranes from cases of aseptic loosening represent reparative changes. There is granulation tissue with areas of hemorrhage and scattered lymphocytes and macrophages. It is of note that a few PMNs may be seen, but they are not as numerous as in cases of septic loosening, unless an inflammatory arthropathy such as rheumatoid arthritis is superimposed. Inside the pseudomembranes, there is deposition of numerous biomaterial wear particles which induce a heavy foreign-body macrophage reaction [75]. The cytokines produced by these foreign-body macrophages (e.g., IL-1, TNF alpha, IL-6) promote osteoclastogenesis and bone resorption. The fibroblasts within the pseudomembrane produce a macrophage colony-stimulating factor (M-CSF) and a receptor activator for the nuclear factor kappaB-ligand (RANKL), which are required for the differentiation of macrophages into bone-resorbing osteoclasts [62]. Interestingly, Krohmer et al. showed a similar immunohistochemical expression level of inflammatory factors in septic and aseptic interface membranes, suggesting that the pathological mechanisms of the progression of inflammation seem to be similar in both septic and aseptic interface membranes of wear particle type [76]. Histopathological examination of biopsy aspirates and specimens of periprosthetic tissues is commonly used to distinguish between septic and aseptic loosening [77]. Histological findings can be reported intraoperatively, to

give a guide as to whether a one- or a two-stage procedure needs to be carried out, or they may be used postoperatively to confirm the preoperative diagnosis of septic or aseptic loosening. Usually more than 5 PMNs per high-power ($\times 400$) field on average, after examination of at least 10 high-power fields, are found in cases of septic loosening. Only PMNs within peri-implant tissues and not on the surface of these tissues or in areas of hemorrhage should be counted. It is important that adequate sampling is undertaken because the focal PMN infiltrate may be present in only one of the sampled areas. According to Bori et al., the most accurate sample for histological diagnosis of prosthetic joint infections is the interface membrane [78]. In addition to a heavy infiltrate of PMNs, plasma cells and lymphocytes may also be seen in the samples.

It of crucial importance to provide the pathologist with information about the history as well as the clinical and operative findings of each case under investigation, since a heavy PMN infiltrate can be noted in the peri-implant tissues of patients with an inflammatory arthropathy such as rheumatoid arthritis. The histological and microbiological findings, as well as the clinical features, need to be carefully considered by the clinician and pathologist in making the diagnosis of septic loosening.

In conclusion, histological examination of bone-implant interface provides clues regarding the nature of the pathological processes that lead to the complications of implant-related joint disease and is required for diagnosis of infection-associated implant failure. Moreover, histological assessment is required for evaluation of the biological tissue response to biomaterials and other agents used in clinical trials, in order to evaluate the efficacy of these new therapeutic strategies.

Prevention of Biofilm Infections

The prevention of biofilm infections in bone and joint implants is an exciting new concept that can be pursued via elimination of organic debris from bone and joint implants, killing of planktonic bacteria prior to biofilm development, modulation

and enhancement of local immune defense, and inhibition of bacterial cell communication that precedes biofilm formation.

Surface Cleaning of Orthopedic Implants

The presence of any residual matrices on the surface of an implant or even on a suture favors bacterial colonization and infection; therefore, polymeric or metal biomaterials must be perfectly clean and/or minimally exposed to air or to surgeons' gloves or "aseptic skin surface" prior to implantation. Data from the water industry have demonstrated that contamination of surfaces by organic materials (especially residual biofilm matrices) accelerates the process of planktonic cell adhesion and biofilm formation by at least tenfold [79]. Simple sterilization (e.g., ethylene oxide) of bone and joint implants kills the bacteria but fails to remove the residues, and thus, removal of these deposits is currently a standard preventive procedure for all implantable devices. Combination of enzymes and chemical agents (alkaline detergent and sodium hypochlorite solution) has been proven effective in eradicating biofilm both *in vitro* and in a clinically used dialysis machine [80].

Quorum Sensing Inhibition

Bacterial cell-to-cell signaling (quorum sensing) is a key feature inside biofilms. The discovery that the development of microbial biofilms is controlled by the quorum sensing process offers a new approach to the prevention of chronic biofilm infections. Bacteria produce and release chemical signaling molecules, the concentration of which increases as a function of cell density [31]. The signals that exercise this control are simple acyl-homoserine lactones (AHLs), in the case of gram-negative bacteria [81] and simple cyclic octapeptides in gram-positive bacteria [82]. When the concentration of these signaling molecules – and therefore the bacterial population – exceeds a threshold, distinct patterns of

gene expression are promoted and biofilm formation is initiated. It has been shown that natural and synthetic molecules that mimic these signals react with the cognitive signal receptor proteins and attenuate biofilm formation [83–86]. Biofilm formation by *Staphylococcus aureus* and virulence factor synthesis are controlled by a regulatory RNA molecule III [RNA-III], which is inhibited by the naturally occurring and synthetically available RNA-III-inhibiting peptide (RIP) [82]. Balaban et al. demonstrated that the RIP prevents biofilm formation by *Staphylococcus aureus* and *Staphylococcus epidermidis* [85, 87]. This inhibition of biofilm formation was shown in animal models of device-related infection, and the inhibitor was shown to be especially effective in infection control if it was combined with an antibiotic such as mupirocin [85]. The recently reported synergistic action of RIP with antibiotics may improve not only prevention but also treatment of staphylococcal infections [88].

Future Perspectives and Innovative Strategies to Combat Implant Infections: The Role of Biomaterial Science

The knowledge of the constituents and of the architecture of staphylococcal biofilms has allowed the development of strategies to disrupt biofilm, on which bacterial resistance to host defenses and therapeutic antibacterial measures mainly resides. While bacteria are hidden deep inside the biofilm and are thus protected against antibacterial agents, the biofilm matrix is instead accessible to the outside environment. In addition, the matrix is a porous network in which fluids run along channels. These features make the biofilm matrix a good target for antibiofilm therapies.

In order to achieve the development of an infection-resistant material, different strategies have been employed: (1) through modification of the biomaterial surface to give anti-adhesive properties, with adsorption of molecules conferring hydrophilic properties to the material surface and competing with the interaction

between bacteria and host matrix proteins that film the implant. Heparin, with its strong hydrophilic properties, ascribed to the inhibition of the bacterium-fibronectin interaction, prevents adhesion of bacterial cells and is an excellent tool for an anti-adhesive coating [89–91]. A recent study showed how local activation of human leukocytes on a prosthetic surface, due to the use of tantalum metal, significantly increased local host defense [92], while others provide evidence that either coating an implant with granulocyte-stimulating factor [93, 94] or applying locally leukocytes or their stimulating factors to a wound [95–97] may significantly reduce the proliferation of bacteria and prevent or probably treat infections. (2) The second strategy is through doping the material with antimicrobial substances, such as the local delivery of antibiotics through carrier biomaterials. The use of coated materials that release conventional antimicrobial agents in order to kill planktonic bacteria before biofilm formation on the implant surface is an alternative concept. Elution of antibiotics from currently available local antibiotic delivery systems (e.g., PMMA cement) follows a biphasic pattern with an initial rapid phase in very high concentrations and a secondary slow phase with decreasing concentrations [98]. This may prevent colonization of implants during the early postoperative period; however, the subinhibitory antibiotic concentrations after the initial phase may favor the development of resistant strains of bacteria.

Newer technologies are tested for drug delivery through a ciprofloxacin-retaining polymer matrix coated with ordered methylene chains that form an ultrasound-responsive coating [99]. This system showed significant drug release when low-intensity ultrasound was applied and demonstrated significantly reduced accumulation of *Pseudomonas aeruginosa* biofilms, compared to biofilms grown in control experiments [99]. The future development of medical devices sensitive to external ultrasonic impulses and capable of preventing biofilm growth via “on-demand” release of antibiotics may be a useful addition to the orthopedic surgeon’s armament. Besides antibiotics, chitosan, a natural cationic polysaccharide and weak polyelec-

trolyte, has proved effective as antimicrobial coating, and various sophisticated technologies have been studied for its grafting onto material surfaces [100]. It is also one of the most promising biopolymers for tissue engineering and has possible orthopedic applications since it enhances osteoblast functions. Quaternized chitosan-loaded PMMA has been shown to inhibit surface biofilm formation by antibiotic-resistant staphylococci, more strongly than PMMA alone, gentamicin-loaded PMMA, and chitosan-loaded PMMA [101]. *N*-acetylcysteine (NAC) is able to inhibit the production of biofilm polysaccharide and to promote the disruption of mature biofilms [102]. NAC could potentially be used, either alone or in combination with other antimicrobials, for prevention or treatment of biofilm-related implant infections [103]. (3) The 3rd strategy combining anti-adhesive and antimicrobial effects in the same coating is the most innovative. An example of an anti-adhesive and antibacterial biomaterial is the multilayer film constructed by assembling heparin and chitosan layer by layer which reduced bacterial adhesion and also killed the bacteria adhering to the surface [104]. Since the raising of antibiotic resistance is the major limit in the use of antibiotic-loaded biomaterials [105], recent interest has turned to cationic antimicrobial peptides against periprostheses infections; perhaps they could be employed as such or could be immobilized on a biomaterial surface [106]. Some bacterial resistance to natural antimicrobial peptides has recently been reported [107]. Bagheri has reported examples of different biomaterials employed as surface supports for immobilizing cationic antimicrobial/peptides, such as resin beads, gold surfaces, polymer brushes, cellulose membranes, and block copolymers and iodine composites [108]. (4) With regard to the fourth strategy, in orthopedics, new biomaterials are being sought to resist the biofilm formation and, at the same time, to support bone repair. Hydroxyapatite coatings, besides their properties as infection-resistant material [109], have been proposed as a coating surface undergoing slow *in vivo* degradation and as a stable interface for osseointegration and bone fixation

[110]. Hydrophobic polycationic coatings on stainless steel or titanium implants have proved to be effective in completely preventing biofilm formation and in supporting bone healing even in the presence of significant bacterial contamination [111]. Recently, bioglasses doped with gold nanoparticles, characterized by a very large surface area to volume ratio, were shown to integrate with living bone and to exert an antibacterial and antibiofilm activity [112]. Copper, zinc, and magnesium but especially silver and gold nanoparticles also display antibacterial activity [113]. The antimicrobial activity of titanium oxide (TiO₂) as a photocatalyst and of silver oxide (Ag₂O) nanoparticles can be enhanced by irradiation with visible light [114, 115].

Conclusion

The pathogenesis of biofilm-associated osteolysis includes a local inflammatory response, characterized by the infiltration of leukocytes, predominantly PMNs and T cells. The PMNs cannot phagocytose the biofilm efficiently, as they cannot migrate into the film under *in vivo* conditions. When the PMNs become activated, they will undergo cell death, resulting in release of their cytotoxic and proteolytic entities into the surrounding tissue, which will cause tissue damage. The escape from apoptosis is also associated with a synthesis of cytokines, e.g., IL-8, which, in turn, may attract more leukocytes but can also cause differentiation of monocytes to osteoclasts. Thus, the microenvironment created by the infiltrating leukocytes would, on one hand, perpetuate the inflammatory process and, on the other hand, promote osteolysis and tissue destruction. Immunological approaches blocking early bacterial adhesion and colonization, applications of enzymes able to interfere with biofilm synthesis or able to disrupt formed biofilms, and exploitation of quorum sensing inhibitors may have a role in preventing or treating these infections. The use of materials coated with immobilized antibacterial substances, particularly cationic antimicrobial peptides, appears very innovative and promising. Nanotechnologies and nanomaterials in

medical research have created new therapeutic horizons and are rapidly growing.

The substantial progress made over the last few years in understanding the functional and structural factors involved in biofilm formation and in the regulatory mechanisms controlling their expression, the advancements in molecular epidemiology [116], as well as improvements in the experimental models [117–119] and in diagnostic methods [120–124] are undoubtedly opening the way to new strategies to combat implant infections [120, 125]. Close collaboration between microbiologists, pathologists, and surgeons is essential to optimize management and maximize benefit to patients with chronic orthopedic infections.

References

1. <http://marketsandmarkets.wordpress.com/2009/08/29/biomaterials-find-wide-usage-in-the-medical-devices-industry/>
2. Williams DF. On the mechanisms of biocompatibility. *Biomaterials*. 2008;29:2941–53.
3. Athanasou NA. Peri-implant pathology-relation to implant failure and tumor formation. *J Long Term Eff Med Implants*. 2007;17(3):193–206.
4. Morawietz L, Classen RA, Schroeder JH, Dynybil C, Perka C, Skwara A, Neidel J, Gehrke T, Frommelt L, Hansen T, Otto M, Barden B, Aigner T, Stiehl P, Schubert T, Meyer-Scholten C, König A, Strobel P, Rader CP, Kirschner S, Lintner F, Ruther W, Bos I, Hendrich C, Kriegsmann J, Krenn V. Proposal for a histopathological consensus classification of the periprosthetic interface membrane. *J Clin Pathol*. 2006;59:591–7.
5. Rand JA, Morrey BF, Bryan RS. Management of the infected total joint arthroplasty. *J Bone Joint Surg Am*. 1983;64A:491–504.
6. Lew DP, Waldvogel FA. Osteomyelitis. *N Engl J Med*. 1997;363:999–1007.
7. Tsukayama DT. Pathophysiology of posttraumatic osteomyelitis. *Clin Orthop*. 1999;360:22–9.
8. Ehrlich GD, Hu FZ, Lin Q, Costerton JW, Post JC. Intelligent implants to battle biofilms. *ASM News*. 2004;70:127–33.
9. Gustillo RB, Anderson JT. Prevention of infection in the treatment of 1025 open fractures of long bones: retrospective and prospective analysis. *J Bone Joint Surg Am*. 1976;58A:453–8.
10. Schmidt AH, Swiontkowski MF. Pathophysiology of infections after internal fixations of fractures. *J Am Acad Orthop Surg*. 2000;8:285–91.
11. Fluckiger U, Zimmerli W. Factors influencing antimicrobial therapy of surface adhering microorganisms. *Recent Res Devel Antimicrob Agents Chemother*. 2000;4:165–75.
12. Gristina AG. Biomaterial-centered infection: microbial adhesion versus tissue integration. *Science*. 1987;237(4822):1588–95.
13. Campoccia D, Montanaro L, Arciola CR. The significance of infection related to orthopedic devices and issues of antibiotic resistance. *Biomaterials*. 2006;27(11):2331–9.
14. Creech 2nd CB, Kernodle DS, Alsentzer A, Wilson C, Edwards KM. Increasing rates of nasal carriage of methicillin-resistant *Staphylococcus aureus* in healthy children. *Pediatr Infect Dis J*. 2005;24:617–21.
15. Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, Nouwen JL. The role of nasal carriage in *Staphylococcus aureus* infections. *Lancet Infect Dis*. 2005;5:751–62.
16. Frebourg NB, Cauliez B, Lemeland JF. Evidence for nasal carriage of methicillin-resistant staphylococci colonizing intravascular devices. *J Clin Microbiol*. 1999;37:1182–5.
17. Nimmerjahn F, Ravetch JV. Fcγ receptors: old friends and new family members. *Immunity*. 2006;24:19–28.
18. Stroh P, Günther F, Meyle E, Prior B, Wagner C, Hänsch GM. Host defence against *Staphylococcus aureus* biofilms by polymorphonuclear neutrophils: oxygen radical production but not phagocytosis depends on opsonisation with immunoglobulin G. *Immunobiology*. 2011;216(3):351–7.
19. Kubes P, Ward PA. The leukocyte recruitment and the acute inflammatory response. *Brain Pathol*. 2000;10:127–35.
20. Rubin RH, Ferraro MJ. Understanding and diagnosing infectious complications in the immunocompromised host. *Current issues and trends. Hematol Oncol Clin North Am*. 1993;7:795–812.
21. Takagi J, Springer TA. Integrin activation and structural rearrangement. *Immunol Rev*. 2000;186:141–63.
22. Kaplanski G, Marin V, Montero-Julian F, Mantovani A, Farnarier C. IL-6: a regulator of the transition from neutrophil to monocyte recruitment during inflammation. *Trends Immunol*. 2003;24:47–52.
23. Savill J. Apoptosis in resolution of inflammation. *J Leukoc Biol*. 1997;61:375–80.
24. Sendo F, Tsuchida H, Takeda Y. Regulation of neutrophil apoptosis – its biological significance in inflammation and the immune response. *Hum Cell*. 1999;9:215–22.
25. Kobayashi SD, Voyich JM, Buhl CL, Stahl RM, DeLeo FR. Global changes in gene expression by human polymorphonuclear leukocytes during receptor-mediated phagocytosis: cell fate is regulated at the level of gene expression. *Proc Natl Acad Sci U S A*. 2002;99:6901–6.
26. Savill J, Wyllie AH, Henson JE, Walport MJ, Henson PM, Haslett C. Macrophage phagocytosis of aging neutrophils in inflammation. Programmed cell death in the neutrophil leads to its recognition by macrophages. *J Clin Invest*. 1989;83:865–75.

27. Watnik P, Kolter R. Biofilm, City of microbes. *J Bacteriol.* 2000;182:2675–9.
28. Davey ME, O'Toole GA. Microbial biofilms: from ecology to molecular genetics. *Microbiol Mol Biol Rev.* 2000;64:847–67.
29. Dunne WM. Bacterial adhesion: seen any good biofilms lately? *Clin Microbiol Rev.* 2002;15:155–66.
30. Arciola CR, Campoccia D, Gamberini S, Donati ME, Baldassarri L, Montanaro L. Occurrence of ica genes for slime synthesis in a collection of *Staphylococcus epidermidis* strains from orthopedic prosthesis infections. *Acta Orthop Scand.* 2003;74:617–21.
31. Davies DG, Parsek MR, Pearson JP, Iglewski BH, Costerton JW, Greenberg EP. The involvement of cell-to-cell signals in the development of a bacterial biofilm. *Science.* 1998;280:295–8.
32. Rice KC, Firek BA, Nelson JB, Yang SJ, Patton TG, Bayles KW. The *Staphylococcus aureus* cidAB operon: evaluation of its role in regulation of murein hydrolase activity and penicillin tolerance. *J Bacteriol.* 2003;185:2635–43.
33. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. *Lancet.* 2001;358(9276):135–8.
34. Costerton JW, Montanaro L, Arciola CR. Biofilm in implant infections: its production and regulation. *Int J Artif Organs.* 2005;28(11):1062–8.
35. Højby N, Ciofu O, Johansen HK, Song ZJ, Moser C, Jensen PØ, Molin S, Givskov M, Tolker-Nielsen T, Bjarnsholt T. The clinical impact of bacterial biofilms. *Int J Oral Sci.* 2011;3(2):55–65.
36. Arciola CR, Campoccia D, Gamberini S, Donati ME, Pirini V, Visai L, Speziale P, Montanaro L. Antibiotic resistance in exopolysaccharide-forming *Staphylococcus epidermidis* clinical isolates from orthopaedic implant infections. *Biomaterials.* 2005;26(33):6530–5.
37. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science.* 1999;284(5418):1318–22.
38. Fux CA, Costerton JW, Stewart PS, Stoodley P. Survival strategies of infectious biofilms. *Trends Microbiol.* 2005;13(1):34–40.
39. Montanaro L, Testoni F, Poggi A, Visai L, Speziale P, Arciola CR. Emerging pathogenetic mechanisms of the implant-related osteomyelitis by *Staphylococcus aureus*. *Int J Artif Organs.* 2011;34(9):781–8.
40. Petty W, Spanier S, Shuster JJ, Silverthorne C. The influence of skeletal implants on incidence of infection. Experiments in a canine model. *J Bone Joint Surg Am.* 1985;67:1236–44.
41. Barth E, Myrvik QM, Wagner W, Gristina AG. In vitro and in vivo comparative colonization of *Staphylococcus aureus* and *Staphylococcus epidermidis* on orthopaedic implant materials. *Biomaterials.* 1989;10(5):325–8.
42. Wassall MA, Santin M, Isalberti C, Cannas M, Denyer SP. Adhesion of bacteria to stainless steel and silver-coated orthopedic external fixation pins. *J Biomed Mater Res.* 1997;36(3):325–30.
43. Lowy FD. *Staphylococcus aureus* infections. *N Engl J Med.* 1998;339(8):520–32.
44. http://www.eurekalert.org/pub_releases/2011-01/hu-apb010711.php
45. Donlan RM. Biofilms and device-associated infections. *Emerg Infect Dis.* 2001;7:277–81.
46. Wagner C, Obst U, Hänsch GM. The implant-associated posttraumatic osteomyelitis: collateral damage by the local host defence? *Int J Artif Organs.* 2005;28(11):1172–80.
47. Gristina AG, Costerton JW. Bacterial adherence and the glycocalyx and their role in musculoskeletal infection. *Orthop Clin North Am.* 1984;15(3):517–35.
48. Marrie TJ, Costerton JW. Mode of growth of bacterial pathogens in chronic polymicrobial human osteomyelitis. *J Clin Microbiol.* 1985;22(6):924–33.
49. Gristina AG, Costerton JW. Bacterial adherence to biomaterials and tissue. The significance of its role in clinical sepsis. *J Bone Joint Surg Am.* 1985;67A:264–73.
50. Wagner C, Kondella K, Bernschneider T, Heppert V, Wentzensen A, Hänsch GM. Post traumatic osteitis: analysis of inflammatory cells recruited into the site of infection. *Shock.* 2003;20(6):503–10.
51. Wagner C, Kaksa A, Müller W, Deneffle B, Heppert V, Wentzensen A, Hänsch GM. Polymorphonuclear neutrophils in posttraumatic osteomyelitis: cells recovered from the inflamed site lack chemotactic activity but generate superoxides. *Shock.* 2004;22:108–15.
52. Medzhitov R. Recognition of microorganisms and activation of the immune response. *Nature.* 2007;449(7164):819–26.
53. Janeway Jr CA, Medzhitov R. Innate immune recognition. *Annu Rev Immunol.* 2002;20:197–216.
54. Verbrugh HA. Phagocytosis and destruction of *Staphylococcus aureus*. *Vet Q.* 1981;3(2):91–7.
55. Arciola CR. Host defense against implant infection: the ambivalent role of phagocytosis. *Int J Artif Organs.* 2010;33(9):565–77.
56. Meyle E, Stroh P, Günther F, Hoppy-Tichy T, Wagner C, Hänsch GM. Destruction of bacterial biofilms by polymorphonuclear neutrophils: relative contribution of phagocytosis, DNA release, and degranulation. *Int J Artif Organs.* 2010;33(9):608–20.
57. Guenther F, Stroh P, Wagner C, Obst U, Hänsch GM. Phagocytosis of staphylococci biofilms by polymorphonuclear neutrophils: *S. aureus* and *S. epidermidis* differ with regard to their susceptibility towards the host defense. *Int J Artif Organs.* 2009;32(9):565–73.
58. Bettin D, Härle A. Die diagnostische Wertigkeit der Labor- und Wundsekretanalyse zur Erkennung einer latenten Frühinfektion in der Endoprothetik. Das infizierte Implantat Kongressband 7. Berlin: Steglitzer Unfalltagung; 1988, p. 50–6.
59. Bettin D, Härle A. The diagnostic value of wound secretion analysis. *Z Orthop Ihre Grenzgeb.* 1989;127(4):518–21.
60. Verschoor CP, Puchta A, Bowdish DM. The macrophage. *Methods Mol Biol.* 2012;844:139–56.
61. Gordon S. The macrophage: past, present and future. *Eur J Immunol.* 2007;37(S1):9–17.

62. Haynes DR, Crotti TN, Potter AE, Loric M, Atkins GJ, Howie DW, Findlay DM. The osteoclastogenic molecules RANKL and RANK are associated with periprosthetic osteolysis. *J Bone Joint Surg Br*. 2001;38B:902–11.
63. Del Fattore A, Teti A. The tight relationship between osteoclasts and the immune system. *Inflamm Allergy Drug Targets*. 2012;11(3):181–7.
64. Otto M. Molecular basis of *Staphylococcus epidermidis* infections. *Semin Immunopathol*. 2012;34(2):201–14.
65. Horowitz MC, Lorenzo JA. The origins of osteoclasts. *Curr Opin Rheumatol*. 2004;16:456–64.
66. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature*. 2003;423:337–42.
67. Kudo O, Fujikawa Y, Itonaga I, Sabokbar A, Torisu T, Athanasou NA. Proinflammatory cytokine (TNF α /IL-1 α) induction of human osteoclast formation. *J Pathol*. 2002;198:220–7.
68. Theill LE, Boyle WJ, Penninger JM. RANK-L and RANK: T cells, bone loss, and mammalian evolution. *Annu Rev Immunol*. 2002;20:795–823.
69. Nair SP, Meghji S, Wilson M, Krisanavane R, White P, Henderson B. Bacterially induced bone destruction: mechanisms and misconceptions. *Infect Immun*. 1996;64:2371–80.
70. Hendersen B, Nair SP. Hard labour: bacterial infection of the skeleton. *Trends Microbiol*. 2003;11:570–7.
71. Goldring SR. Inflammatory mediators as essential elements in bone remodeling. *Calcif Tissue Int*. 2003;73:97–100.
72. Walsh NC, Gravellese EM. Bone loss in inflammatory arthritis: mechanisms and treatment strategies. *Curr Opin Rheumatol*. 2004;16:419–27.
73. McCarthy EF, Frassica FJ. The pathology of failed total joint arthroplasty. In: *Pathology of bone and joint disorders with clinical and radiographic correlation*. Philadelphia: WB Saunders; 1998. p. 353–63.
74. Colliers JP, Bauer TW, Bloebaum RD, Bobynd JD, Cook SD, Galante JO, Harris WH, Head WC, Jasty MJ, Mayer MB, Sumner DR, Whiteside LA. Results of implant retrieval from postmortem specimens in patients with well-functioning, long-term total hip replacement. *Clin Orthop*. 1992;274:97–112.
75. Wright TM, Goodman SB, editors. *Implant wear in total joint replacement*. Rosemont: AAOS; 2001.
76. Krohmer G, Koleganova N, Hadjicostas PT, Fink B, Berger I. Degenerative changes in the interface membrane as a possible reason for prosthesis loosening. *Histol Histopathol*. 2008;23:925–33.
77. Müller M, Morawietz L, Hasart O, Strube P, Perka C, Tohtz S. Diagnosis of periprosthetic infection following total hip arthroplasty – evaluation of the diagnostic values of pre- and intraoperative parameters and the associated strategy to preoperatively select patients with a high probability of joint infection. *J Orthop Surg Res*. 2008;3:31–8.
78. Bori G, Munoz-Mahamad E, Garcia S, Mallofre C, Gallart X, Bosch J, Garcia E, Riba J, Mensa J, Soriano A. Interface membrane is the best sample for histological study to diagnose prosthetic joint infection. *Mod Pathol*. 2011;24:579–894.
79. Costerton JW, Lewandowski Z, Caldwell DE, Korber DR, Lappin-Scott HM. Microbial biofilms. *Annu Rev Microbiol*. 1995;49:711–45.
80. Marion K, Pasmore M, Frenay J, Delawari E, Renaud F, Costerton JW, Traeger J. A new procedure allowing the complete removal and prevention of hemodialysis biofilms. *Blood Purif*. 2005;23(5):339–48.
81. Fuqua WC, Winans SC, Greenberg EP. Quorum sensing in bacteria: the LuxR-LuxI family of cell density-responsive transcriptional regulators. *J Bacteriol*. 1994;76(2):269–75.
82. Balaban N, Goldkorn T, Nhan RT, Dang LB, Scott S, Ridgley RM, Rasooly A, Wright SC, Larrick JW, Rasooly R, Carlsson JR. Autoinducer of virulence as a target for vaccine and therapy against *Staphylococcus aureus*. *Science*. 1998;280(5362):438–40.
83. Hentzer M, Wu H, Andersen JB, Riedel K, Rasmussen TB, Bagge N, Kumar N, Schembri MA, Song Z, Kristoffersen P, Manefield M, Costerton JW, Molin S, Eber L, Steinberg P, Kjelleberg S, Høiby N, Givskov M. Attenuation of *Pseudomonas aeruginosa* virulence by quorum sensing inhibitors. *EMBO J*. 2003;22(15):3803–15.
84. De Nys R, Givskov M, Kumar N, Kjelleberg S, Steinberg PD. Furanones. *Prog Mol Subcell Biol*. 2006;42:55–86.
85. Balaban N, Giacometti A, Cirioni O, Gov Y, Ghiselli R, Mocchegiani F, Viticchi C, Del Prete MS, Saba V, Scalise G, Dell'Acqua G. Use of the quorum-sensing inhibitor RNAIII inhibiting peptide to prevent biofilm formation in vivo by drug-resistant *Staphylococcus epidermidis*. *J Infect Dis*. 2003;187(4):625–30.
86. Balaban N, Stoodley P, Fux CA, Wilson S, Costerton JW, Dell'Acqua G. Prevention of staphylococcal biofilm-associated infections by the quorum sensing inhibitor RIP. *Clin Orthop*. 2005;437:48–54.
87. Balaban N, Gov Y, Bitler A, Boelaert JR. Prevention of *Staphylococcus aureus* biofilm on dialysis catheters and adherence to human cells. *Kidney Int*. 2003;63(1):340–5.
88. Giacometti A, Cirioni O, Ghiselli R, Dell'Acqua G, Orlando F, D'Amato G, Mocchegiani F, Silvestri C, Del Prete MS, Rocchi M, Balaban N, Saba V, Scalise G. RNAIII-inhibiting peptide improves efficacy of clinically used antibiotics in a murine model of staphylococcal sepsis. *Peptides*. 2005;26(2):169–75.
89. Arciola CR, Radin L, Alvergnà P, Cenni E, Pizzoferrato A. Heparin surface treatment of poly(methylmethacrylate) alters adhesion of a *Staphylococcus aureus* strain: utility of bacterial fatty acid analysis. *Biomaterials*. 1993;14(15):1161–4.
90. Arciola CR, Caramazza R, Pizzoferrato A. In vitro adhesion of *Staphylococcus epidermidis* on heparin-surface-modified intraocular lenses. *J Cataract Refract Surg*. 1994;20(2):58–61.

91. Arciola CR, Bustanji Y, Conti M, Campoccia D, Baldassarri L, Samorì B, Montanaro L. Staphylococcus epidermidis-fibronectin binding and its inhibition by heparin. *Biomaterials*. 2003;24(18):3013–9.
92. Schildhauer TA, Peter E, Muhr G, Köller M. Activation of human leukocytes on tantalum trabecular metal in comparison to commonly used orthopedic metal implant materials. *J Biomed Mater Res A*. 1999;88(2):332–41.
93. Rozalska B, Sadowska B, Ljungh A, Rudnicka W. Granulocyte-macrophage colony-stimulating factor (GM-CSF)-coated implants and their potential for reducing biomaterial-associated infection in neutropenic hosts. *Zentralbl Bakteriol*. 1998;288(2):237–51.
94. Bai X, Zhang C, Ruan D, He Q, Hou L, Li H. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) could be an effective adjuvant therapy for orthopedic implant-related infections (OIRI). *Med Hypotheses*. 2011;76(5):703–5.
95. Simbirtsev A, Variouchina E, Konusova V, Kotov A, Ketlinsky S, Salamатов A, Bisenkov L. Local administration of interleukin-1beta for the treatment of lung abscesses induces neutrophil activation and changes in proinflammation cytokine production. *Eur Cytokine Netw*. 2001;12(3):420–9.
96. Kaplan SS, Simmons RL. Effect of plasma and matrix proteins on defensin-induced impairment of phagocytic killing by adherent neutrophils. *J Biomed Mater Res*. 2001;57(1):1–7.
97. Kreyden OP, Hafner J, Burg G, Nestle FO. Case report on therapy with granulocyte stimulating factor in diabetic foot. *Hautarzt*. 2001;52(4):327–30.
98. Zalavras CG, Patzakis MJ, Holtom P. Local antibiotic therapy in the treatment of open fractures and osteomyelitis. *Clin Orthop*. 2004;427:86–93.
99. Norris P, Noble M, Francolini I, Vinogradov AM, Stewart PS, Ratner BD, Costerton JW, Stoodley P. Ultrasonically controlled release of ciprofloxacin from self-assembled coatings on poly(2-hydroxyethyl methacrylate) hydrogels for *Pseudomonas aeruginosa* biofilm prevention. *Antimicrob Agents Chemother*. 2005;49(10):4272–9.
100. Neoh KG, Kang ET. Combating bacterial colonization on metals via polymer coatings: relevance to marine and medical applications. *ACS Appl Mater Interfaces*. 2011;3(8):2808–19.
101. Tan H, Peng Z, Li Q, Xu X, Guo S, Tang T. The use of quaternised chitosan-loaded PMMA to inhibit biofilm formation and downregulate the virulence-associated gene expression of antibiotic-resistant *Staphylococcus*. *Biomaterials*. 2012;33:365–77.
102. Schwandt LQ, van Weissenbruch R, Stokroos I, Van der Mei HC, Busscher HJ, Albers FW. Prevention of biofilm formation by dairy products and N-acetylcysteine on voice prostheses in an artificial throat. *Acta Otolaryngol*. 2004;124:726–31.
103. Aslam S, Darouiche RO. Role of antibiofilm-antimicrobial agents in controlling device-related infections. *Int J Artif Organs*. 2011;34(9):752–8.
104. Fu J, Ji J, Yuan W, Shen J. Construction of anti-adhesive and antibacterial multilayer films via layer-by-layer assembly of heparin and chitosan. *Biomaterials*. 2005;26(33):6684–92.
105. Campoccia D, Montanaro L, Speziale P, Arciola CR. Antibiotic-loaded biomaterials and the risks for the spread of antibiotic resistance following their prophylactic and therapeutic clinical use. *Biomaterials*. 2010;31:6363–77.
106. Kang SJ, Kim DH, Mishig-Ochir T, Lee BJ. Antimicrobial peptides: their physicochemical properties and therapeutic application. *Arch Pharm Res*. 2012;35(3):409–13.
107. Gruenheid S, Le Moual H. Resistance to antimicrobial peptides in Gram negative bacteria. *FEMS Microbiol Lett*. 2012;330:81–9.
108. Bagheri M, Beyermann M, Dathé M. Immobilization reduces the activity of surface-bound cationic antimicrobial peptides with no influence upon the activity spectrum. *Antimicrob Agents Chemother*. 2009;53(3):1132–41.
109. Arciola CR, Montanaro L, Moroni A, Giordano M, Pizzoferrato A, Donati ME. Hydroxyapatite-coated orthopaedic screws as infection resistant materials: in vitro study. *Biomaterials*. 1999;20(4):323–7.
110. Campoccia D, Arciola CR, Cervellati M, Maltarello MC, Montanaro L. In vitro behaviour of bone marrow-derived mesenchymal cells cultured on fluorohydroxyapatite-coated substrata with different roughness. *Biomaterials*. 2003;24:587–96.
111. Schaer TP, Stewart S, Hsu BB, Klibanov AM. Hydrophobic polycationic coatings that inhibit biofilms and support bone healing during infection. *Biomaterials*. 2012;33:1245–54.
112. Grandi S, Cassinelli V, Bini M, Saino E, Mustarelli P, Arciola CR, Imbriani M, Visai L. Bone reconstruction: Au nanocomposite bioglasses with antibacterial properties. *Int J Artif Organs*. 2011;34(9):920–8.
113. Kurek A, Grudniak AM, Kraczkiewicz-Dowjat A, Wolska KI. New antibacterial therapeutics and strategies. *Pol J Microbiol*. 2011;60:3–12.
114. Wu P, Xie R, Imlay K, Shang JK. Visible-light-induced bactericidal activity of titanium dioxide codoped with nitrogen and silver. *Environ Sci Technol*. 2010;44:6992–7.
115. Visai L, De Nardo L, Punta C, Melone L, Cigada A, Imbriani M, Arciola CR. Titanium oxide antibacterial surfaces in biomedical devices. *Int J Artif Organs*. 2011;34(9):929–46.
116. Montanaro L, Campoccia D, Arciola CR. Advancements in molecular epidemiology of implant infections and future perspectives. *Biomaterials*. 2007;28(34):5155–68.
117. Rupp ME, Ulphani JS, Fey PD, Mack D. Characterization of *Staphylococcus epidermidis* polysaccharide intercellular adhesin/hemagglutinin in the pathogenesis of intravascular catheter-associated infection in a rat model. *Infect Immun*. 1999;67(5):2656–9.

118. Rupp ME, Fey PD, Heilmann C, Götz F. Characterization of the importance of *Staphylococcus epidermidis* autolysin and polysaccharide intercellular adhesin in the pathogenesis of intravascular catheter-associated infection in a rat model. *J Infect Dis.* 2001;183(7):1038–42.
119. An YH, Kang QK, Arciola CR. Animal models of osteomyelitis. *Int J Artif Organs.* 2006;29(4):407–20.
120. Costerton JW. Biofilm theory can guide the treatment of device-related orthopaedic infections. *Clin Orthop.* 2005;437:7–11.
121. Costerton JW, Post JC, Ehrlich GD, Hu FZ, Kreft R, Nistico L, Kathju S, Stoodley P, Hall-Stoodley L, Maale G, James G, Sotereanos N, DeMeo P. New methods for the detection of orthopedic and other biofilm infections. *FEMS Immunol Med Microbiol.* 2011;61(2):133–40.
122. Mack D, Becker P, Chatterjee I, Dobinsky S, Knobloch JK, Peters G, Rohde H, Herrmann M. Mechanisms of biofilm formation in *Staphylococcus epidermidis* and *Staphylococcus aureus*: functional molecules, regulatory circuits, and adaptive responses. *Int J Med Microbiol.* 2004;294(2–3):203–12.
123. Campoccia D, Baldassarri L, Pirini V, Ravaioli S, Montanaro L, Arciola CR. Molecular epidemiology of *Staphylococcus aureus* from implant orthopaedic infections: ribotypes, agr polymorphism, leukocidal toxins and antibiotic resistance. *Biomaterials.* 2008;29:4108–16.
124. Arciola CR, Montanaro L, Costerton JW. New trends in diagnosis and control strategies for implant infections. *Int J Artif Organs.* 2011;34(9):727–36.
125. Brady RA, O'May GA, Leid JG, Prior ML, Costerton JW, Shirtliff ME. Resolution of *Staphylococcus aureus* biofilm infection using vaccination and antibiotic treatment. *Infect Immun.* 2011;79:1797–803.

George C. Babis and Vasileios I. Sakellariou

Introduction

Modularity is defined as the ability to combine variable components of an implant in order to accommodate clinical hip, knee, or shoulder cases where standard monoblock designs may not offer optimum outcomes [1]. Modular designs have been used for decades in adult reconstruction surgery [1]. However, recent innovations, such as a second neck-stem taper junction in hip implants (Fig. 18.1) or multi-modular revision implants for hip (Fig. 18.2), knees, and shoulder cases, have been presented and favored in clinical use for their advantages in facilitating the anatomic restoration of the defective joints [2]. Intraoperative adjustment of limb length, head-neck angle, neck-shaft version in hip and shoulder cases, and accurate reestablishment of joint line in knee arthroplasties, all provide flexibility and a variety of available options [2–6].

However, new problems have also arisen from the presence of additional metal interfaces. Catastrophic fractures at the junction sites, cold welding, corrosion and fretting as well as the



Fig. 18.1 Neck-stem modularity. A variety of necks facilitates leg length and joint stability

G.C. Babis, MD, DSc (✉)
 First Department of Orthopaedic Surgery,
 University of Athens, Attikon University
 General Hospital, Chaidari, Attica, Greece

First Department of Orthopaedics, Attikon University
 Hospital, University of Athens Medical School,
 1 Rimini Street, 12462 Chaidari, Attica, Greece
 e-mail: george.babis@gmail.com

V.I. Sakellariou, MD, DSc
 First Department of Orthopaedic Surgery,
 University of Athens, Attikon University General
 Hospital, Chaidari, Attica, Greece



Fig. 18.2 A modern modular revision femoral stem is shown

clinical implications of early implant loosening, and systemic immune reactions have been noted [2, 7–10].

With regard to the above statements and concerns, we present in this chapter up-to-date experimental and clinical data about the use of modular implants in hip, knee, and shoulder arthroplasties. We show the advantages and disadvantages associated with their use and known future directions.

Total Hip Replacement

Acetabular Components

Modular acetabular components have a history of almost 30 years [1]. Although clinical reports did not show a clear advantage of the primary cemented modular over monoblock implants in terms of longevity and loosening, their ability to replace the liner without disrupting the prosthesis-bone interface in future procedures has been a significant evolution in implant design [1]. New cementless metal-backed implant designs with different surface porous coatings have been used, showing at least an outcome equal to that of cemented cups, while in revision cases modular implants have outperformed monoblock-cemented components [11–13]. The major advantage of modular metal-backed acetabular components lies in the option of screw placement through holes in the metal shell [11–13]. These screws, especially in the setting of revision surgery, provide adjunctive fixation when primary scratch fit is not considered adequate. Moreover, multi-hole implants increase screw placement options, when bone loss and poor bone quality limit the available sites of screw insertion [11–13]. Another potential advantage of modular acetabular components is the interchangeability of liners, according to clinical demands [1, 14]. Standard, high-lip, high-offset, or constraint liners can be selected on the basis of trial reduction and tests of the stability and range of motion. Moreover, the ability to exchange a liner years after insertion because of excessive wear is an occasional advantage [1, 2]. A number of potential complications associated with the use of modular acetabular components have also been reported. Simple liner exchange is not always feasible. Concomitant acetabular shell loosening and damage, and insufficiency of locking mechanism are often a problem [13, 15]. Of greater concern is the possibility of increased polyethylene wear at the interface of the acetabular shell and rear of the liner, the so-called backside wear [16, 17]. Production of particulate debris due to micromotion and wear may occur, and subsequent bone lysis may be observed [16, 17]. The magnitudes of micromotion vary among different implant designs, ranging from 5 to 311 μm . The linear

wear rate is estimated to range between 0.03 and 0.42 mm/year [18–21]. Other concerns are the abrasion of polyethylene from protruding screw heads, the cold flow of polyethylene into screw holes, and the perforation of a congruent liner by sharp metal components of the locking mechanism [16–20]. Several predisposing factors related to increased wear have been identified [22]. Inadequate thickness of the polyethylene, ineffective metal backing, and liner-metal surfaces incongruities are the most commonly reported [19, 20, 23, 24]. Kurtz et al., using a finite analysis model, showed that backside nonconformity and locking restraints substantially influence relative motion as well as load transfers at the liner-shell modular interface [25]. With regard to the liner thickness, it is generally recommended that current implant designs should include a minimum thickness for conventional polyethylene liners of 6–8 mm, with adequate congruency, and ability to bottom out at physiologic loads [22]. However, new ultra-high molecular weight polyethylene and ceramic liners show better wear resistance and conformity, allowing for thinner liners to be used, and greater sizes of ball heads to be accommodated from smaller-diameter acetabular shells [26, 27]. Examination of retrieved specimens and laboratory testing suggest that improving implant design could eliminate most of these potential problems [16, 17, 28]. Since the shell is now appreciated to represent a wear interface with the backside of the liner, it should be highly conforming as well as smooth and the surface treated, like any other weight-bearing surface [19, 29, 30]. Hemispheric cups have been shown to have the best conformity between the shell and the liner [31, 32]. The locking mechanism should be strong enough to resist levering out. The force necessary for dissociation of the modular liner from acetabular shell has been reported to be extremely variable ranging from 14.9 to 1,380 lb [19, 24, 30]. However, novel liner locking mechanisms have shown efficient pullout and lever-out strength (399 ± 53 N) (28.03 ± 2.8 Nm) for up to ten million cycles of loading of 5 Nm, without significant reduction in strength, no detectable fretting wear and substantial sealing [15, 19, 24, 29, 30]. Liners may also rotate within the shell cavity without dissociation, causing impingement on the femoral neck,

especially when high-lip liners are used [33, 34]. When the relative lack of conformity is combined with the empty space for screw holes, the actual surface area supported by metal varies from 25 to 75 % [35–37]. Therefore, screw holes should be as few as possible to minimize the risk of debris generation and to give effective joint space; non-used screw holes should be tapped before the fixation of the liner to eliminate this problem. In revision components, making provision for adjunctive screw fixation is still advisable in most cases [35–37]. Several finite element models support the improved stress distribution in the subchondral bone through the metal-backed implants [22, 25, 38]. This is also confirmed by histologic analyses of early retrieved porous-coated acetabular components indicating that adequate bone ingrowth is present when adjunctive fixation is utilized [22, 25, 38].

Modular Stems

Clinical Advantages and Disadvantages

Modular implants have a number of advantages comparing to monoblock implants. Variability in femoral head length allows for better restoration of limb length inequalities and femoral offset, resulting in improvement of hip stability and hip biomechanics (Fig. 18.3) [2]. Blaha in 2006 presented his theory of a “sweet spot” on the femur and the need to duplicate it during reconstruction as accurately as possible [39]. Optimum neck height and anteversion can be achieved independently of the femoral neck position using modular neck and head implants [39]. Moreover, different implant materials can now be combined, giving several options in bearing surface selection, according to the patient’s specific needs and/or surgeon’s preferences [1, 2]. In revision cases, in which only an acetabular component is being replaced, modular heads can be removed facilitating hip exposure. Intraoperative variability and flexibility provided by choices of different diameter stem lengths, fixation types, proximal metaphyseal sizes, and orientation enable the establishment of a stable hip joint [1, 22].



Fig. 18.3 Cementless femoral stem with a modular neck. Satisfactory clinical and radiological outcome at 5 years follow-up



Fig. 18.4 Cementless modular S-ROM stem for primary hip arthroplasty. Satisfactory clinical and radiological outcome at 9 years follow-up

Additionally, stem modularity enhances fit and fill, provides greater initial fixation, and more uniform stress distribution while minimizing stress shielding, bone loss, and incidence of thigh pain (Fig. 18.4) [1, 22]. Proponents of stem modularity believe that the modular components offer optimal proximal metaphyseal fill and proximal stress transfer with distal fit for initial torsional stability [1, 22, 40–42]. Modularity potentially provides an adequate number of proximal and distal geometry combinations to facilitate the achievement of maximal direct bone contact with porous coating proximally and stem contact with endosteal cortex distally [40–42].

However, problems with femoral stem-head modularity had been recognized early. Dissociation of the head, corrosion at the modular head-neck

interface, and fractures at the base of the modular trunnion have been extensively reported [43–48]. Negative effects on range of motion have also been recognized especially whenever skirted femoral heads are used. This is owing to the reduction of head-neck ratio, which induces earlier impingement of the neck onto the acetabular rim, excessive polyethylene wear, and liner dissociation [49, 50]. Head-liner mismatch is another effect of head-stem modularity. The large available number of component combinations increases the potential risk of mismatch. Head-taper mismatch has also been reported and is shown to be related to increased micromotion and development of corrosion [51, 52]. Awareness is therefore needed when combining components from different manufacturers, which is not unusual especially in revision cases.

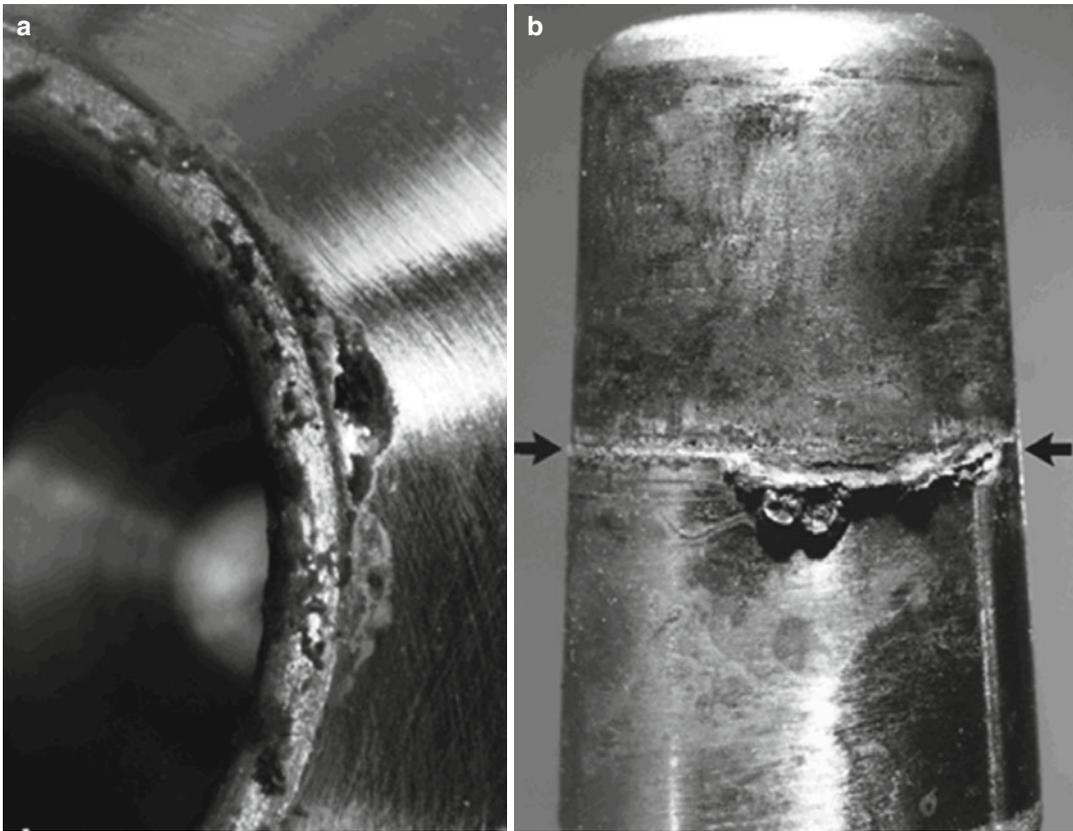


Fig. 18.5 Damaged head-neck junction. (a) Head, (b) neck

Mechanisms of Corrosion, Fretting, Cracking, and Failure of Modular Interface

Corrosion products and wear debris generated at the head-neck (Fig. 18.5) and neck-stem interfaces are well documented in the current literature [53–56]. It is generally agreed that the surface damage seen at the head-neck taper is initiated by fretting. Fretting has been demonstrated in 100 % of test specimens *in vitro* and in over 50 % of retrieved implants [46, 55, 56]. Fretting increases the development of crevice and galvanic corrosion by disrupting the passive oxide layer of the taper interface. Gilbert et al. tried to document the taper corrosion processes better using metallographic sectioning techniques and scanning electron microscopy [54]. They showed that a pitting attack on both sides of the taper interface evolves into plunging pits. The latter ultimately develop into cracks where the crack propagation process

is one of corrosion resulting in oxide formation and subsequent reorganization. The oxide that forms has a complex evolving structure including a network of transport channels that provide access of fluid to the crack tip. This emergent behavior does not appear to require continued fretting corrosion to propagate the pitting and cracking. This mechanism is similar to stress corrosion cracking where the crack tip stresses arise from the oxide formation in the crack and not externally applied tensile stresses. Rodriguez et al. investigated the surface of hip implants with Ti-6Al-4V/Ti-6Al-4V modular taper interfaces and showed that an *in vivo* hydrogen embrittlement is the mechanism of degradation in modular connections, which results from electrochemical reactions induced in the crevice environment of the tapers during fretting-crevice corrosion [57]. Hardening by nitriding or nitrogen implantation also can improve the strength and wear resistance of the Morse taper [57].

Several parameters are associated with corrosion and fretting of modular taper surfaces. The impact of different material combinations, flexural rigidity, head and neck moment arm, neck length, and implantation time has been evaluated [46, 56, 58]. Material combination, head offset, and assembling conditions are reported by different authors as independent causative factors in fretting [59]. In single modular implants (modularity at the head-neck junction), stainless steel/cobalt-chromium and titanium/cobalt alloy couplings have shown increased corrosion compared to cobalt alloy/cobalt alloy ones. Moreover, metal/metal junctions induce significantly higher cobalt and chromium metal releases and fretting compared to ceramic/metal junctions [46, 56, 58, 60]. Double modular implants (modularity at both head-neck and neck-stem junctions) fretting and crevice corrosion are expected to be increased due to increased modular interfaces. Fretting and corrosion have been shown to be common at both head-neck junction (54 % showing corrosion; 88 % showing fretting) and stem-sleeve junction (88 % corrosion ; 65 % fretting) in a series of 78 retrieved hip implants [53]. Metal ion and particulate debris generation is increased [53]. Titanium releases measured from titanium (Ti6Al4V) modular interfaces are extremely low. However, titanium neck adapters show larger micromotions than cobalt-chrome neck adapters [61]. Neck adapters made of cobalt-chrome alloy show significantly reduced micromotions especially in the case of contaminated cone connection. Grupp et al. demonstrated that with cobalt-chromium neck, the micromotions can be reduced by a factor of 3 compared to the titanium neck [46]. The incidence of fretting corrosion was also lessened with cobalt-chrome necks. Modular titanium alloy neck adapters may fail due to decreased stiffness and increased surface micromotion and should be used with great caution on patients with an average weight over 100 kg [46].

In revision implants, distal modularity has been associated with erosion of the shaft and migration of the distally modular component in some cases. This raises the concern of wear debris and lysis originating at this interface [1].

Implant geometry and neck-shaft angle also play a significant role in fretting and corrosion at the junction of head and neck. Higher offset is associated with increased fretting damage. Corrosion and fretting is higher for heads than necks. Larger-diameter necks increase neck stiffness and therefore could possibly reduce fretting and corrosion of the taper interface regardless of the alloy used. Carlson et al. showed that small-diameter femoral stems with large offsets have an increased risk of stem fracture [53].

Debris and Wear

Every combination of materials may generate the production of millions of particles in the 1- to 2- μ m range. The most important factor in increasing the particle count is dimensional mismatch. Roughened and nitrogen-implanted surfaces produce fewer particles, while heads larger than 10 mm produce more particles [62, 63]. It is now agreed that metal particles may act as a third body to accelerate polyethylene wear and subsequently cause bone lysis and implant loosening [62, 63]. Corrosion products from modular head and neck tapers increase the particulate debris in the joint and migrate along membranes at the bone-implant interface to sites remote from their origin. Urban et al. showed that these particles could also migrate to the prosthetic bearing surface inducing third-body wear [64, 65]. The increased production of polyethylene debris from third-body wear could contribute to periprosthetic bone loss and aseptic loosening, with implications for possible systemic toxicity [64, 65].

Stress Distribution and Micromotion

Stress distribution within components and the micromotion of the interface significantly influence the function of the taper lock in the long term [51, 61, 63]. Bending-induced gap opening between the cone and the sleeve in double modular implants (head and neck modularity) can lead to an inflow of biological fluids and thus acceler-

ate implant corrosion [51, 61, 63]. Local areas of high stress can accelerate the corrosive process and initiate local yielding. This may lead to fracture in one of the modular components, especially when high-offset necks are selected for heavy-weighting individuals [46]. However, Chu et al. observed that for titanium (Ti6Al4V) components, cortical bone bridging and ingrowth occurs across the taper lock gap, which induces a reduction in the peak stress by 45 % and in the contact interface separation by 55 % [44]. Such tissue formation around the taper lock joint could also form a closed capsule to restrict the migration of wear particles and prevent bone resorption and implant loosening.

Assembling Process

Special attention should be paid during the assembling process. If the prosthesis is cemented, the head should be impacted with several firm blows on the back table prior to implantation. Forceful blows shortly after cement polymerization can damage the implant-cement interface. Assembly prior to insertion is therefore advisable [66, 67]. When implanting an uncemented stem, the head should be impacted onto the trunnion after implantation of the stem, because the vibration of striking the implant can disrupt the lock of the Morse taper. In either case, extreme care should be taken to keep the interface clean, dry, and free of any debris [67, 68]. Contaminated surfaces exhibit significantly larger micromotion comparing to meticulously cleaned ones. Even a fraction of a millimeter of blood can substantially adversely affect the taper lock and accelerate corrosion and wear [61]. There are several studies reporting on optimizing the assembling technique of modular components. Rehmer et al. tried to assess the influence of assembly force, assembly tool, and number of hammer strokes on the taper junction strength of various metal combinations [66]. The authors showed that taper strength linearly increased with assembly forces. Multiple impactions did not increase taper strength. A single impact is sufficient to achieve fixation. Ceramic and cobalt-chromium heads

showed similar fixation patterns on titanium tapers. It was also suggested that impaction forces of at least 4kN achieve sufficient head-taper junction strength in all bearing conditions. Pallini et al., on the other hand, tried to determine the disassembly force and showed that blows to the proximal end of the neck-stem coupling should be avoided as this could compromise the cleanliness of the head-neck modularity and damage the bearing surfaces [68]. They also reported that disassembly force after manual insertion followed by the first small postoperative loads imposed by the patient during walking was as high as that obtained with hammer blows, and therefore application of hammer blows to fix neck-stem coupling is unnecessary. Nganbe et al. assessed the distraction forces after in vitro cycling in bovine serum and showed that the neck-stem pull-off force initially increases during cycling and reaches a maximum value of 5.704 kN at 100,000 cycles [67].

Total Knee Replacement

Tibial Inserts

The benefit of modularity in total knee arthroplasty implants is widely recognized and includes the ability to fine-tune soft tissue balance and reestablish more accurately the height of the joint line. Modular tibial components offer a variety of options especially for the difficult revision cases with significant bone loss. Modular inserts provide a number of choices of thickness as well as the degree of constraint of the articular surface. This increases intraoperative variability, mainly by providing the option of switching from a posterior cruciate ligament – retaining (CR) to a posterior stabilized (PS) insert utilizing the same tibial baseplate. The use of modular inserts is also useful for these cases of excessive polyethylene wear, without implant loosening, that a simple polyethylene insert exchange with a thicker and/or more constrained liner could be sufficient [1]. However, modularity of tibial components has not shown any superiority in terms of implant survivorship comparing to non-modular implants.

Several disadvantages of modularity have been reported. The unintended bearing surface between the back surface of the tibial implant and the metallic tray results in micromotion that increases polyethylene wear [69, 70]. The main contributing factors include the following: insufficiency of locking mechanism, failure of thin polyethylene modular inserts, abrasion of the tibial spine with secondary wear, impingement of the locking pin against the femoral component, and corrosion between screws and the baseplate [71]. A membrane invariably forms at this interface, and concern has been expressed about the possibility that this increases the potential for late infection [1]. To date, there is no evidence to support this concern.

The clinical relevance of micromotion and backside wear is now well understood. Parks et al. investigated the anteroposterior and mediolateral motion between the tibial inserts and baseplate that were measured with an extensometer placed across the modular interface [72]. The authors observed hundreds of microns of motion even under a 100 N load and variability between implants of the same design, showing that more efforts should be made in the improvement of locking mechanisms in modular knee implants. Engh et al. highlighted the insufficiency of the capture mechanisms of some modular fixed-bearing tibial components [73]. In this study, a uniaxial mechanical testing machine was used to evaluate a variety of total knee components applying loads along the anteroposterior and mediolateral axes of the tibial component. It is significant that motion between the polyethylene insert and the metal baseplate increases after a period of *in vivo* loading. The same study group tried to quantify the relative motion of the modular interface, which was measured in the transverse plane, and correlate it to the backside wear that was observed. For this purpose they used these measurements to compute the insert motion index, which served to quantify unrestricted motion of the insert with respect to the baseplate. It was shown that the mean insert motion index for the tibial components was 416 μm , ranging from 104 to 760 μm . This insert

motion was positively correlated with backside polyethylene wear ($p=0.003$) and baseplate wear ($p<0.001$). Moreover, baseplate wear was found to be strongly correlated with backside polyethylene wear ($p<0.001$). Wasielewski also observed a micromotion between 2 and 25 μm in the shear plane relative to metal backing, suggesting that undersurface motion may be inevitable [74]. The author demonstrated that forces at the modular interface, created during physiologic loading, are influenced by the insert type, the articular design, and the surgical technique. Increasing articular insert constraint can increase the forces at the main articulation to be resisted and transferred to this and the other interfaces. Designs with a cam-post mechanism that force rollback at a certain flexion angle create a significant force in this shear plane. Inserts with highly conforming articular geometries can have a similar effect. Component alignment and position, and ligament balance also may influence backside wear as suggested by the great variability of wear patterns seen on similar insert retrievals and by kinematic differences observed in fluoroscopic studies of the same implant design [69, 71, 75].

Several studies have found that micromotion at the tibial tray-polyethylene interface is associated with increased risk for increased particulate debris generation. Conditt et al. found that pitting, burnishing, and measurable polyethylene protrusions may occur on the backside of polyethylene inserts [71]. Li et al. showed that the amount of polyethylene wear found after examining 55 retrieved tibial inserts with four different locking mechanisms was as high as 591 mg from the inferior surface [76]. This corresponded to a polyethylene wear rate from the backside of the tibial insert of greater than 100 mg, which is two to four times higher than wear rates associated with total hip replacements. Debris from backside wear combined with wear from the articular side might account for the increasing prevalence of osteolysis since modular components have become widely used [70]. Peters et al. reported that the incidence of osteolysis in an uncemented modular tibial component is 16 % [77]. Surace

et al. found that in the anteroposterior profile of the polyethylene insert, a concave deformation of the back surface is developed in 96 % of the retrieved implants they examined, using a stereomicroscope with a digital optical system [78]. Akisue et al. reported that the backside deformation is associated with polyethylene thickness and the type of locking mechanism [79]. This concave deformation may facilitate accumulation and transportation of wear debris to the tibial bone-implant interface.

Augmentation Devices

The use of metal augmentation devices to reconstruct femoral or tibial bone deficiencies during a revision knee arthroplasty has been another impetus to increase the modularity of total knee replacement components [80–82]. Utilization of these devices is generally faster and technically easier when compared with the reconstructive techniques that use autograft or allograft bone segments [80, 83]. Metal augments are better indicated for small- and medium-sized structural bone defects. Metal blocks and wedges have both been utilized. However, there is some evidence that the block configuration is biomechanically superior, as it distributes the load more evenly than does wedge augmentation [5, 80, 84]. Trabecular metal augmentation has added new treatment options for severe proximal tibial bone defects in revision knee arthroplasty [5, 80]. Porous tantalum tibial cones provide mechanical support for the tibial component and have the potential for long-term biologic fixation [80, 85, 86]. The major disadvantage of adding modular components is the potential for fretting or failure of the interface, although these events have not yet been reported. In order to prevent this type of complication, most modular revision implant designs have tried to reduce the number of modular parts to a minimum by using components that require assembly and providing a large inventory of one-piece integral components with wedge or block augments incorporated into the tibial baseplate [80].

Stems

Modular stems add additional fixation, which is often necessary because of bone loss in revision knee replacement [80]. A press fit can be obtained in the femoral and tibial canals by utilizing a wide range of lengths, diameters, and offsets [5, 80, 87]. Options of both straight and curved stems are also available. Hybrid type of fixation with cementing of the articular surfaces and press fitting of the stems in the medullary canals is usually applied. Improved results with press fitting of stems and cementing of only the surface of the tibia and femur have been reported [88, 89]. One major advantage is that press-fit stems are easier to revise when necessary, since cement does not have to be inserted into the medullary canal of the tibia or femur [88, 89]. Disadvantages include increased potential for fracture of the tibial or femoral shaft in an attempt to achieve a press fit with large stems. Stress shielding due to the stiffness of the stems may cause bone resorption of the distal femur and proximal tibia [90, 91]. In addition, there is an increased concern regarding fretting corrosion and the generation of particulate debris from the modular connection or failure of the connection [1].

Shoulder Arthroplasty

In recent years there has been an increasing interest in humeral component modularity. Modular shoulder implants offer a wide variety of diameters and sizes in both humeral and glenoid components [92, 93]. The modularity of total shoulder arthroplasty implants has demonstrated several advantages compared to monoblock implants [92, 93]. Humeral stem insertion is much easier without the attached humeral head component. Diameter and offset may be varied according to the desired soft tissue tension, thus maximizing stability and range of motion. Moreover, the glenoid component and the humeral head may be revised without removal of the humeral stem, and conversion to inverse type prosthesis can now be done [92–94]. At the glenoid side, modularity of

polyethylene and metal backing can also facilitate simple exchange of the insert without the need to remove the metal-back component [95]. Potential disadvantages of modular shoulder implants include instability or stiffness when the selected humeral head is too small or too large, respectively, corrosion and fretting at the head-stem interface, component dissociation (head-stem and polyethylene-metal back), and stress shielding at the glenoid side [92, 96].

Humeral Head-Stem

Dissociation of the humeral component has been of great concern [97, 98]. Improper taper fit caused by contamination of the head-stem interface with blood is reported as the most likely factor responsible for in vivo dissociations in types of commercially available implants. Blevins et al. conducted a biomechanical and implant retrieval study investigating the effect of loading rate, load amplitude, and the number of impactions on fixation of the humeral head component [98]. These authors demonstrated that the dissociation force is linearly proportional to the impaction force. However, repetitive loading beyond two impactions does not significantly increase taper strength. Chao and Kasman noted only a 6 % increase in dissociation force after 1,000 loading cycles with a maximum sliding distance for the shank inside the socket of 0.1 mm [99]. The mean dissociation force after two impactions with a mallet was $2,926 \pm 955$ N [98]. Cooper and Brems measured a mean force of 2,996 N to dissociate a retrieved Biomet humeral component [100]. Asgfan et al. reported dissociation forces in excess of 4,000 N after the loading of an 8° included angle titanium taper [101]. Chao and Kasman reported dissociation forces of approximately 1,300 N after an impaction force of 2,225 N (4° included cone angle titanium taper) [99]. It is shown that contamination of the taper with as little as 0.4 ml of fluid could lessen the fixation strength of the taper. Contamination with liquid (water, oil, and blood) and solid debris (polymerized, morselized polymethyl methacrylate cement) may affect the fixation of the taper [98]. With regard to the effect of the

taper material, Blevins et al. showed that the coefficient of friction for the cobalt-chrome-titanium taper (0.7 ± 2.5) is not statistically different from that of the titanium tapers but does show considerable variation (range from -8.60 to 8.06) [98]. Regression analysis between the impaction force and coefficient of friction for titanium-titanium and cobalt-chrome-titanium tapers shows no significant effect. However, Chao and Kasman found that titanium tapers had a higher dissociation force than those of stainless steel [99]. This difference between studies may be due to the wide variation in the measured coefficients of friction for cobalt-chrome-titanium tapers.

Metal-Backed Glenoid Components

At the glenoid side, when compared with the cemented all-polyethylene components, the uncemented modular metal-backed components display lower subchondral stresses. This effect is more pronounced during eccentric loading. However, high polyethylene stress regions are present at the polyethylene-metal interface in relation to the all-polyethylene components. This result suggests that this interface will be the site of initial polyethylene yielding and ultimately, component failure, at loads that are lower than those necessary to cause failure in the all-polyethylene component. In a 3D finite element analysis model, Gupta et al. showed that, although the indications of stress shielding and separation of modular parts of the prosthesis are apparent, the implant-bone interface seems less likely to fail as compared to cemented designs [102]. Once initial fixation of the implant is achieved, the uncemented modular design appears to have better prospects than cemented non-modular ones. The use of highly stiff (5 mm) metal backing offers rigidity to the implant and therefore causes reduction of stresses in the polyethylene cup and the underlying bone. On the one hand, stresses in the polyethylene cup are reduced by 20 % as compared to the cemented total polyethylene design, thereby decreasing the risk of polyethylene wear [102]. On the other hand, the use of thicker metal-backing results in higher metal-bone and polyethylene-metal interface

stresses. These high stresses indicate potential interface disruption, separation of the prosthesis from bone, or separation of polyethylene cup from the metal backing. A thicker polyethylene cup (7 mm) with a thinner circular metal backing (3 mm) might result in lower stresses in the polyethylene cup as well as reduction in the weight of the glenoid component. Stresses in polyethylene cups of thinner metal-backed designs are also reduced when cement is used (8 %), but these reductions are less compared to the thicker metal-backed non-cemented cup (20 %) [102, 103]. As with modular hip and knee components, the potential for generation of wear debris is a concern [1]. Lysis has not been reported to date; however, experience with these modular components is of relatively short duration. Long-term implications are yet to be determined.

Conclusions

The introduction of modular implants has been revolutionary in reconstructive surgery of the hip, knee, and shoulder. Implant modularity allows for more anatomical restoration of limb length inequalities, better implant fit and fill, improved soft tissue tensioning, increased stability, and better overall restoration of joint biomechanics. It facilitates surgical exposure in revision cases and permits the exchange of only the parts that need to be revised, thus preserving a patient from any additional bone loss which may be created during well-fixed implant removal. However, new problems have been recognized in the presence of additional metal interfaces. Dissociation of modular parts, corrosion, fretting, cracking, and failure of the modular interfaces have been presented, and the mechanisms thereof have been extensively studied. Improvements in stress distribution and micromotion between surfaces have been achieved through better manufacturing and machining processes aiming at a reduction of the wear products. Technical features regarding the combination of different materials and the assembling process have also been well studied, and useful recommendations for the everyday clinical practice have been presented.

In conclusion, modularity is a significant renovation in the field of adult reconstruction surgery. Surgical options have been increased, and the variety of random unexpected intraoperative events and problems may now be addressed easily. Acknowledgment of the particular technical specifications and problems related to the presence of additional modular interfaces is of paramount importance, and therefore, it is recommended limiting their use where appropriate.

References

1. Barrack RL. Modularity of prosthetic implants. *JAAOS*. 1994;2(1):16–25.
2. Srinivasan A, Jung E, Levine BR. Modularity of the femoral component in total hip arthroplasty. *JAAOS*. 2012;20(4):214–22.
3. Benazzo F, Rossi SM. Modular tibial plate for minimally invasive total knee arthroplasty. *Knee Surgery Sports Traumatol Arthrosc*. 2012;20(9):1796–802.
4. Archibeck MJ, et al. A comparison of two implant systems in restoration of hip geometry in arthroplasty. *Clin Orthop*. 2011;469:443–6.
5. Lombardi AV, Berend KR, Adams JB. Management of bone loss in revision TKA: it's a changing world. *Orthopedics*. 2010;33(9):662.
6. Cuff D, et al. Torsional stability of modular and non-modular reverse shoulder humeral components in a proximal humeral bone loss model. *J Shoulder Elbow Surg*. 2011;20(4):646–51.
7. Lakstein D, et al. Fracture of cementless femoral stems at the mid-stem junction in modular revision hip arthroplasty systems. *J Bone Joint Surg Am*. 2011;93A:57–65.
8. Fraitzl CR, et al. Corrosion at the stem-sleeve interface of a modular titanium alloy femoral component as a reason for impaired disengagement. *J Arthroplasty*. 2011;26(1):113–9.
9. Kretzer JP, et al. Metal release and corrosion effects of modular neck total hip arthroplasty. *Int Orthop*. 2009;33(6):1531–6.
10. Engh GA, et al. Analysis of wear in retrieved mobile and fixed bearing knee inserts. *J Arthroplasty*. 2009;24(6):S28–32.
11. Markel D, et al. Deformation of metal-backed acetabular components and the impact of liner thickness in a cadaveric model. *Int Orthop*. 2011;35(8):1131–7.
12. Hallan G, et al. Metal-backed acetabular components with conventional polyethylene: a review of 9113 primary components with a follow-up of 20 years. *J Bone Joint Surg Br*. 2010;92B:196–201.
13. Werle J, et al. Polyethylene liner dissociation in Harris-Galante acetabular components: a report of 7 cases. *J Arthroplasty*. 2002;17(1):78–81.

14. Callaghan JJ, et al. Concerns and improvements with cementless metal-backed acetabular components. *Clin Orthop*. 1995;311:76–84.
15. Poole CE, et al. Early follow-up for a hybrid total hip arthroplasty using a metal-backed acetabular component designed to reduce “backside” polyethylene wear. *HSS J*. 2005;1(1):31–4.
16. Bradford L, et al. Wear and surface cracking in early retrieved highly cross-linked polyethylene acetabular liners. *J Bone Joint Surg Am*. 2004;86A:1271–82.
17. Chen PC, et al. Polyethylene wear debris in modular acetabular prostheses. *Clin Orthop*. 1995;317:44–56.
18. Amirouche F, et al. Study of micromotion in modular acetabular components during gait and subluxation: a finite element investigation. *J Biomech Eng*. 2008;130(2):021002.
19. Wasielewski RC, et al. The acetabular insert-metal backing interface: an additional source of polyethylene wear debris. *J Arthroplasty*. 2005;20(7):914–22.
20. von Schewelov T, et al. Catastrophic failure of an uncemented acetabular component due to high wear and osteolysis: an analysis of 154 omnifit prostheses with mean 6-year follow-up. *Acta Orthop Scand*. 2004;75(3):283–94.
21. Fehring TK, et al. Motion at the modular acetabular shell and liner interface. A comparative study. *Clin Orthop*. 1999;367:306–14.
22. Kurtz SM, Edidin AA, Bartel DL. The role of backside polishing, cup angle, and polyethylene thickness on the contact stresses in metal-backed acetabular components. *J Biomech*. 1997;30(6):639–42.
23. Young AM, et al. Effect of acetabular modularity on polyethylene wear and osteolysis in total hip arthroplasty. *J Bone Joint Surg Am*. 2002;84A:58–63.
24. Gonzalez della Valle A, et al. Dislodgment of polyethylene liners in first and second-generation Harris-Galante acetabular components. A report of eighteen cases. *J Bone Joint Surg Am*. 2001;83A:553–9.
25. Kurtz SM, et al. Backside nonconformity and locking restraints affect liner/shell load transfer mechanisms and relative motion in modular acetabular components for total hip replacement. *J Biomech*. 1998;31(5):431–7.
26. Orradre Burusco I, et al. Cross-linked ultra-high-molecular weight polyethylene liner and ceramic femoral head in total hip arthroplasty: a prospective study at 5 years follow-up. *Arch Orthop Trauma Surg*. 2011;131(12):1711–6.
27. Kim YH, Kim JS. Tribological and material analyses of retrieved alumina and zirconia ceramic heads correlated with polyethylene wear after total hip replacement. *J Bone Joint Surg Br*. 2008;90B:731–7.
28. Teeter MG, et al. Technique to quantify subsurface cracks in retrieved polyethylene components using micro-CT. *J Long Term Eff Med Implants*. 2010;20(1):27–34.
29. Akbari A, et al. Minimal backside surface changes observed in retrieved acetabular liners. *J Arthroplasty*. 2011;26(5):686–92.
30. Kyle RF, et al. Factors influencing the initial micromotion between polyethylene acetabular cups and titanium alloy shells. *J Arthroplasty*. 2006;21(3):443–8.
31. D’Angelo F, et al. Failure of dual radius hydroxyapatite-coated acetabular cups. *J Orthop Surg Res*. 2008;3:35.
32. Weber D, et al. Cementless hemispheric acetabular component in total hip replacement. *Int Orthop*. 2000;24(3):130–3.
33. Min BW, et al. Polyethylene liner failure in second-generation Harris-Galante acetabular components. *J Arthroplasty*. 2005;20(6):717–22.
34. Shon WY, et al. Impingement in total hip arthroplasty a study of retrieved acetabular components. *J Arthroplasty*. 2005;20(4):427–35.
35. Kurtz SM, et al. Simulation of initial frontside and backside wear rates in a modular acetabular component with multiple screw holes. *J Biomech*. 1999;32(9):967–76.
36. Mantell SC, et al. A parametric study of acetabular cup design variables using finite element analysis and statistical design of experiments. *J Biomech Eng*. 1998;120(5):667–75.
37. Bartel DL, Bicknell VL, Wright TM. The effect of conformity, thickness, and material on stresses in ultra-high molecular weight components for total joint replacement. *J Bone Joint Surg Am*. 1986;68A:1041–51.
38. Kummer FJ, et al. Loading of the acetabulum by polyethylene and all-ceramic inserts in metal-backed acetabular cups. *Bull Hosp Jt Dis*. 2003;61(3–4):132–4.
39. Blaha JD. The modular neck: keystone to functional restoration. *Orthopedics*. 2006;29(9):804–5.
40. De la Torre BJ, et al. 10 years results of an uncemented metaphyseal fit modular stem in elderly patients. *Indian J Orthop*. 2011;45(4):351–8.
41. Goyal N, Hozack WJ. Neck-modular femoral stems for total hip arthroplasty. *Surg Technol Int*. 2010;20:309–13.
42. Khmel'nitskaya E, et al. Optimizing for head height, head offset, and canal fit in a set of uncemented stemmed femoral components. *Hip Int*. 2008;18(4):286–93.
43. Buttaro M, Comba F, Piccaluga F. Modular femoral head dissociation after dislocation and entrapment in reconstruction ring: a case report. *Hip Int*. 2007;17(1):49–51.
44. Chu CM, Wang SJ, Lin LC. Dissociation of modular total hip arthroplasty at the femoral head-neck interface after loosening of the acetabular shell following hip dislocation. *J Arthroplasty*. 2001;16(6):806–9.
45. Skendzel JG, Blaha JD, Urquhart AG. Total hip arthroplasty modular neck failure. *J Arthroplasty*. 2011;26(2):338.e1–4.
46. Grupp TM, et al. Modular titanium alloy neck adapter failures in hip replacement – failure mode analysis and influence of implant material. *BMC Musculoskelet Disord*. 2010;11:3.

47. Dangles CJ, Altstetter CJ. Failure of the modular neck in a total hip arthroplasty. *J Arthroplasty*. 2010;25(7):1169.e5-7.
48. Shiga T, et al. Disassembly of a modular femoral component after femoral head prosthetic replacement. *J Arthroplasty*. 2010;25(4):659.e17-19.
49. Malik A, Maheshwari A, Dorr LD. Impingement with total hip replacement. *J Bone Joint Surg Am*. 2007;89A:1832-42.
50. Chandler DR, et al. Prosthetic hip range of motion and impingement. The effects of head and neck geometry. *Clin Orthop*. 1982;166:284-91.
51. Shareef N, Levine D. Effect of manufacturing tolerances on the micromotion at the Morse taper interface in modular hip implants using the finite element technique. *Biomaterials*. 1996;17(6):623-30.
52. Lieberman JR, et al. An analysis of the head-neck taper interface in retrieved hip prostheses. *Clin Orthop Relat Res*. 1994;(300):162-7.
53. Huot Carlson JC, et al. Femoral stem fracture and in vivo corrosion of retrieved modular femoral hips. *J Arthroplasty*. 2012;27(7):1389-96.e1.
54. Gilbert JL, et al. In vivo oxide-induced stress corrosion cracking of Ti-6Al-4V in a neck-stem modular taper: emergent behavior in a new mechanism of in vivo corrosion. *J Biomed Mater Res B Appl Biomater*. 2011 Nov 24. doi:10.1002/jbm.b.31943. [Epub ahead of print].
55. Kop AM, Keogh C, Swarts E. Proximal component modularity in THA-At what cost? An implant retrieval study. *Clin Orthop Relat Res*. 2012;470(7):1885-94.
56. Kop AM, Swarts E. Corrosion of a hip stem with a modular neck taper junction: a retrieval study of 16 cases. *J Arthroplasty*. 2009;24(7):1019-23.
57. Rodriguez D, et al. Low cycle fatigue behavior of Ti6Al4V thermochemically nitrided for its use in hip prostheses. *J Mater Sci*. 2001;12(10-12):935-7.
58. Gilbert JL, Mehta M, Pinder B. Fretting crevice corrosion of stainless steel stem-CoCr femoral head connections: comparisons of materials, initial moisture, and offset length. *J Biomed Mater Res B*. 2009;88(1):162-73.
59. Chandra A, et al. Life expectancy of modular Ti6Al4V hip implants: influence of stress and environment. *J Mech Behav Biomed Mater*. 2011;4(8):1990-2001.
60. Dalmigli M, et al. The effect of surface treatments on the fretting behavior of Ti-6Al-4V alloy. *J Biomed Mater Res B*. 2008;86(2):407-16.
61. Jauch SY, et al. Influence of material coupling and assembly condition on the magnitude of micromotion at the stem-neck interface of a modular hip endoprosthesis. *J Biomech*. 2011;44(9):1747-51.
62. MacQuarrie RA, et al. Wear-particle-induced osteoclast osteolysis: the role of particulates and mechanical strain. *J Biomed Mater Res B*. 2004;69(1):104-12.
63. Chu Y, et al. Stress and micromotion in the taper lock joint of a modular segmental bone replacement prosthesis. *J Biomech*. 2000;33(9):1175-9.
64. Urban RM, et al. Accumulation in liver and spleen of metal particles generated at nonbearing surfaces in hip arthroplasty. *J Arthroplasty*. 2004;19(8 Suppl 3):94-101.
65. Urban RM, et al. Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. *J Bone Joint Surg Am*. 2000;82A:457-76.
66. Rehmer A, Bishop NE, Morlock MM. Influence of assembly procedure and material combination on the strength of the taper connection at the head-neck junction of modular hip endoprotheses. *Clin Biomech*. 2012;27(1):77-83.
67. Nganbe M, et al. Retrieval analysis and in vitro assessment of strength, durability, and distraction of a modular total hip replacement. *J Biomed Mater Res A*. 2010;95(3):819-27.
68. Pallini F, et al. Modular hip stems: determination of disassembly force of a neck-stem coupling. *Artif Organs*. 2007;31(2):166-70.
69. Conditt MA, et al. Backside wear of polyethylene tibial inserts: mechanism and magnitude of material loss. *J Bone Joint Surg Am*. 2005;87(2):326-31.
70. Engh GA, Ammeen DJ. Epidemiology of osteolysis: backside implant wear. *Instr Course Lect*. 2004;53:243-9.
71. Conditt MA, Stein JA, Noble PC. Factors affecting the severity of backside wear of modular tibial inserts. *J Bone Joint Surg Am*. 2004;86A:305-11.
72. Parks NL, et al. The Coventry Award. Modular tibial insert micromotion. A concern with contemporary knee implants. *Clin Orthop*. 1998;356:10-5.
73. Engh GA, et al. In vivo deterioration of tibial base-plate locking mechanisms in contemporary modular total knee components. *J Bone Joint Surg Am*. 2001;83A:1660-5.
74. Wasielewski RC, et al. Tibial insert undersurface as a contributing source of polyethylene wear debris. *Clin Orthop*. 1997;345:53-9.
75. Conditt MA, et al. Backside wear of modular ultra-high molecular weight polyethylene tibial inserts. *J Bone Joint Surg Am*. 2004;86A:1031-7.
76. Li S, et al. Assessment of backside wear from the analysis of 55 retrieved tibial inserts. *Clin Orthop*. 2002;404:75-82.
77. Peters Jr PC, et al. Osteolysis after total knee arthroplasty without cement. *J Bone Joint Surg Am*. 1992;74A:864-76.
78. Surace MF, et al. Coventry Award paper. Backsurface wear and deformation in polyethylene tibial inserts retrieved postmortem. *Clin Orthop*. 2002;404:14-23.
79. Akisue T, et al. "Backside" polyethylene deformation in total knee arthroplasty. *J Arthroplasty*. 2003;18(6):784-91.
80. Qiu YY, et al. Review article: treatments for bone loss in revision total knee arthroplasty. *J Orthop Surg*. 2012;20(1):78-86.

81. Engh GA, Ammeen DJ. Bone loss with revision total knee arthroplasty: defect classification and alternatives for reconstruction. *Instr Course Lectures*. 1999;48:167–75.
82. Haas SB, et al. Revision total knee arthroplasty with use of modular components with stems inserted without cement. *J Bone Joint Surg Am*. 1995;77A:1700–7.
83. Kuchinad RA, et al. The use of structural allograft in primary and revision knee arthroplasty with bone loss. *Adv Orthop*. 2011;2011:578952.
84. Frehill B, et al. Initial stability of type-2 tibial defect treatments. *Proc Inst Mech Eng H*. 2010;224(1):77–85.
85. Haidukewych GJ, Hanssen A, Jones RD. Metaphyseal fixation in revision total knee arthroplasty: indications and techniques. *JAAOS*. 2011;19(6):311–8.
86. Wilson DA, et al. Continued stabilization of trabecular metal tibial monoblock total knee arthroplasty components at 5 years-measured with radiostereometric analysis. *Acta Orthop Scand*. 2012;83(1):36–40.
87. Pandit H, et al. Total knee arthroplasty: the future. *J Surg Orthop Adv*. 2006;15(2):79–85.
88. Marx R, et al. Surface pretreatment for prolonged survival of cemented tibial prosthesis components: full- vs. surface-cementation technique. *Biom Eng Online*. 2005;4:61.
89. Peters CL, et al. Tibial component fixation with cement: full- versus surface-cementation techniques. *Clin Orthop*. 2003;409:158–68.
90. Completo A, Fonseca F, Simoes JA. Strain shielding in proximal tibia of stemmed knee prosthesis: experimental study. *J Biomech*. 2008;41(3):560–6.
91. Lonner JH, et al. Changes in bone density after cemented total knee arthroplasty: influence of stem design. *J Arthroplasty*. 2001;16(1):107–11.
92. Mileti J, et al. Monoblock and modular total shoulder arthroplasty for osteoarthritis. *J Bone Joint Surg Br*. 2005;87(4):496–500.
93. van de Sande MA, Rozing PM. Modular total shoulder system with short stem. A prospective clinical and radiological analysis. *Int Orthop*. 2004;28(2):115–8.
94. Groh GI, Wirth MA. Results of revision from hemiarthroplasty to total shoulder arthroplasty utilizing modular component systems. *J Shoulder Elbow Surg*. 2011;20(5):778–82.
95. Cheung EV, Sperling JW, Cofield RH. Polyethylene insert exchange for wear after total shoulder arthroplasty. *J Shoulder Elbow Surg*. 2007;16(5):574–8.
96. Churchill RS, et al. Humeral component modularity may not be an important factor in the outcome of shoulder arthroplasty for glenohumeral osteoarthritis. *Am J Orthop*. 2005;34(4):173–6.
97. Skirving AP. Total shoulder arthroplasty – current problems and possible solutions. *J Orthop Sci*. 1999;4(1):42–53.
98. Blevins FT, et al. Dissociation of modular humeral head components: a biomechanical and implant retrieval study. *J Shoulder Elbow Surg*. 1997;6(2):113–24.
99. Chao EY, Kasman R. Conical press-fit in tumor prosthesis design. *Trans Orthop Res Soc*. 1983;8:107.
100. Cooper RA, Brems JJ. Recurrent disassembly of a modular humeral prosthesis. A case report. *J Arthroplasty*. 1991;6(4):375–7.
101. Asgfan CGI, Hori R. Fatigue of tapered joints. In: *Transactions of the second world congress on biomaterials tenth annual meeting of the society of biomaterials*, Washington, DC, 1984.
102. Gupta S, van der Helm FC, van Keulen F. Stress analysis of cemented glenoid prostheses in total shoulder arthroplasty. *J Biomech*. 2004;37(11):1777–86.
103. Gupta S, van der Helm FC, van Keulen F. The possibilities of uncemented glenoid component – a finite element study. *Clin Biomech*. 2004;19(3):292–302.

Panagiotis Megas and Christos S. Georgiou

Introduction

Total hip arthroplasty (THA) and hip resurfacing arthroplasty (HRA) have become some of the most successful elective surgical procedures in modern medicine that it has been described as “the operation of the twentieth century” [1]. Worldwide, it is estimated that approximately one million are implanted every year. About 270,000 hip arthroplasties are done in the United States, and this is projected to increase by 174 % between 2005 and 2030 [2, 3]. The National Joint Registry of England and Wales reported 68,907 primary operations in 2010 [4]. The number of younger patients receiving a THA is continuously increasing. In England and Wales, 12 % of patients are younger than 55 years [4]. In Canada, the number of patients aged less than 45 years having hip replacements during 2002 rose by 11.0 % compared with 1994 [5].

The long-term problem with THA is failure, resulting in revision surgery. The leading cause of failure is aseptic loosening. Loosening of the implants occurs mainly due to the particulate wear debris particles that the different materials of prostheses generate [6]. Activity level seems to be important. The Finnish Arthroplasty Registry reports only 60 % of 15-year survival

in patients younger than 55 years [7]. In an attempt to reduce wear and osteolysis following THA, especially in high-demand young patient populations, alternative bearing surfaces, such as ultrahigh-molecular-weight (UHMW) polyethylene, ceramic-on-ceramic (CoC), and metal-on-metal (MoM) articular surfaces, have been introduced [8]. Highly cross-linked offers lower wear than conventional polyethylene, but the bioactivity of the particles remains [7]. Ceramic bearing surfaces have the lower wear from all the alternative bearings but are expensive, and there have been reports of ceramic fracture [9] and audible squeaking [10]. MoM bearings offer also limited wear. They have a long history of use that dates back to the introduction of the McKee–Farrar prosthesis in the 1960s. MoM bearings fell out of favor because of high failure rates, primarily because of early cup loosening [11], impingement [12], and metal sensitivity [13], and because of the excellent clinical results of the Charnley low-friction arthroplasty concept. However, their use was revisited in the 1990s as polyethylene-associated osteolysis emerged as a major clinical problem [14]. MoM THA, thereafter, has become popular, especially over the past decade and now accounts for 35 % of hip replacements in the United States [15] and 14 % of hip replacements recorded on the National Joint Registry of England and Wales [4]. One additional reason for their extensive use is the improved joint stability (e.g., lower risk of dislocation), due to the ability to use larger-diameter femoral heads [15].

P. Megas, MD, PhD, DSc (✉) • C.S. Georgiou
Department of Orthopaedics and Traumatology,
University Hospital of Patras, Rion GR-26504, Greece
e-mail: panmegas@gmail.com

MoM bearings, however, generate metallic wear particles. These particles have a size in the nanometer scale and are soluble. The soft tissue reactions to these nanoparticles have introduced new reasons for revision, while systemic distribution through the body fluids has an unpredictable long-term effect. In this chapter, we will examine the biological activity of the metallic wear particles released from MoM bearings and review the local and distant reactions to them. We will, also, review the exposure, uptake, and dissemination processes of these particles.

Wear Particle Origin and Composition

Transmission electron microscopic analysis of metal particulate debris has shown that MoM articulations generate approximately 6.7×10^{12} to 2.5×10^{14} particles every year, which is 13–500 times the number of polyethylene particles produced from a typical metal-on-polyethylene (MoP) bearing. Despite this, the actual volumetric wear of a MoM articulation is lower because of the nanoscale size of the particles (generally <50 nm) when compared with polyethylene particles, which are rarely less than $0.1 \mu\text{m}$ [5, 16]. Of note, the distribution of particle size and shape changes with the severity of wear. Difficulties associated in isolating particles smaller than 10 nm suggest that the actual number of particles may well have been underestimated [6, 17]. Implant-derived debris is generated by mechanical wear and tear, as well as surface corrosion [18]. These degradation products may be present as (1) particulate wear debris, (2) free metallic ions, (3) metal–protein complexes, (4) sequestered in an organic storage form such as hemosiderin, and/or (5) inorganic metal salts or oxides [18, 19]. Corrosion can occur at all metal surfaces, resulting in either the formation of a protective passive layer or dissolution of the bulk metal alloy. Cobalt (Co(II)), titanium (Ti(V)), aluminum (Al(III)), iron (Fe(III)), nickel (Ni(II)), and chromium (Cr(III)) have all been detected in solution during the corrosion of metal alloys. Despite evidence supporting the release of Cr(VI) from the Co–Cr–Mo (molybdenum) alloy,

this remains controversial. Even if corrosion leads to the release of Cr(VI), this chromium is rapidly reduced to trivalent chromium intracellularly [5, 20]. Corrosion products predominantly consist of metal oxides (Cr_2O_3 , CoO , TiO_2 , Al_2O_3 , etc.) and hydroxides ($\text{Cr}(\text{OH})_3$, $\text{Co}(\text{OH})_2$, etc.) within the synovial environment. Synovial fluid has properties, or compounds, that prevent the deposition of calcium phosphate and results in a thin oxide passive layer on the implant [5, 21]. The deposition of calcium phosphate and the subsequent formation of metal phosphates (CrPO_4 , $\text{Co}_3(\text{PO}_4)_2$, etc.) occur in non-synovial environments [21]. Therefore, it is expected that corroded particles found in the human body are predominantly orthophosphate, hydroxides, and oxides rather than base metal. Metal immersed in synovial fluid will lack the thick calcium phosphate deposit, unlike the parts of the implant that are exposed to blood serum [21]. For those particles that are exposed to serum, metal corrosion products are trapped in the surface deposit, and these may then be released during further wear [21]. Metallic particles are ingested by macrophages (>150 nm) or may be disseminated via lymphatics to the reticuloendothelial system [22]. The small size of some of these particles or their existence in ionic forms also allows dissemination through the vascular system [23], which has not been extensively investigated yet [6, 24]. They continue to corrode, and thereafter, metal ions are present in the circulation and concentrated in erythrocytes. Excretion of metal ions via the kidneys seems to balance their generation [25]. The uptake of metal nanoparticles (<150 nm) by cells occurs by endocytotic processes, particularly non-specific receptor-mediated endocytosis and pinocytosis [26]. The uptake of Cr(VI) occurs readily through anionic channels because of the structure of the chromate anion [27]. Divalent metal transporter ((DMT)-1), expressed in a range of tissues, and natural resistance-associated macrophage protein (NRAMP)1, located on the phagosomal membrane, may facilitate the uptake of Co(II) and Ni(II) [5, 28, 29]. Larger particles (>150 nm) can directly stimulate phagocytosis [30]. Transferrin-bound Fe(III), Al(III), Cr(III), or vanadium(V) can be internalized by cell-surface transferrin receptors [31–33].

Biological Responses to Metal Wear Debris

Cytotoxicity

Once internalized, metal particles can induce cytotoxicity and oxidative stress [5, 34]. Biological responses of human cells to metal wear particles *in vitro* depend on the particle size [35]. Papageorgiou et al. [36] compared the cytotoxicity of nanoparticles and micron-sized particles of Co–Cr alloy using human fibroblasts in tissue culture. Nanoparticles appeared to disintegrate within the cells faster and cause more cellular damage than microparticles [36]. Kwon et al. [35] have found that only Co nanoparticles and ions have dose-dependent cytotoxic effects on macrophages *in vitro*. Similar cytotoxicity was not observed with Cr nanoparticles. A greater release of metal ions in solution from Co nanoparticles in comparison to Cr nanoparticles may, in part, explain why Co is more cytotoxic [35]. Although synergistic effects of nanoparticles together with ions cannot be excluded, cytotoxicity of Co nanoparticles *in vitro* may be a result of nanoparticles, rather than diffusion of metal ions, produced extracellularly [35]. Inside the cells, Co ions are released during corrosion and participate in Fenton-like reactions, leading to the generation of free radicals which further lead to cellular damage [37]. Furthermore, the mitochondria appear to be the target of cobalt toxicity in cultures of mouse astrocytes, creating conditions similar to hypoxia. It seems that, in excess, Co blocks cellular metabolism and can damage multiple organs [38]. However, the high concentrations of nanoparticles required for cytotoxic effects *in vitro* (greater than 10^{12} particles ml⁻¹) are likely to occur *in vivo* only when there is excessive wear. However, different toxic-effect threshold among patients may exist, as the individual biologic response to the metallic wear debris differ [35]. The Co–Cr nanoparticles were found to be more toxic not only than the ions but also than the alumina ceramic particles [39]. The *in vitro* cytotoxicity of metal nanoparticles would be consistent with the observed areas of necrosis, separated from viable tissue by macrophages

containing large numbers of metal particles, in pseudotumor *in vivo*. A vicious circle of necrosis, recruitment of macrophages to areas of dead macrophages and rephagocytosis leading to an expanding necrotic zone, may exist [35]. Pseudotumor-like histological appearance has been observed in a postmortem study in subjects with Co–Cr prostheses [22]. Necrosis was observed only in organs with high metal concentrations, whereas it was not observed in others with low concentration of metallic debris, like the liver and kidney [22].

Except from Co, other metals and corrosion products are also cytotoxic. Hallab et al. [40] treated *in vitro* representatives of human perimplant cell types with Al(III), Co(II), Cr(III), Fe(III), Mo(V), Ni(II), V(III), and Na(II) (control) chloride solutions, at concentrations that have been observed *in vivo*. Metals that were toxic include Co (0.6 mM), Ni (0.8 mM), and V (0.5 mM) for lymphocytes; Co (0.8 mM), V (0.3 mM), Al (1–5 mM), and Fe (1–5 mM) for fibroblasts; and Co (0.8 mM), Ni (0.7 mM), and V (0.1 mM) for osteoblasts. Only Co and V were toxic *in vitro* at concentrations below those detected *in vivo* in synovial fluid [40]. Some corrosion products, like oxides and/or phosphates of Cr, Co, and Ni, also show moderate cytotoxicity, while others including oxides and phosphates of Ti and Al do not [41]. Only one oxide each of Ni and Co was noncytotoxic, while the others were cytotoxic. Specifically cytotoxicity was detected for CoO, Co₃O₄, and Co₃(PO₄)₂ but not for Co₂O₃. Ni₂O₃ was also cytotoxic, while NiO was not. In addition, the cytotoxicity of the phosphate of a metallic element was considerably smaller than that of the oxide of the element when the valencies of the elements were the same [41].

Immunologic Response

As compared with MoP THA, the extent of the granulomatous inflammatory reaction is much less intense in MoM articulation, perhaps because of the overall smaller size of the metal wear debris particles [42]. The histologic pattern in the tissues around, both first [43] and second [44]

generation, loose MoM articulations is significantly different from that of MoP articulations and is characterized by perivascular infiltration of lymphocytes and the accumulation of plasma cells. The lymphocytic infiltration is more pronounced in samples obtained at the time of revision because of aseptic failure than in samples retrieved for other reasons [44]. On the other hand, the inflammation in tissue samples obtained from hips with MoP implants is predominantly histiocytic [45]. Infiltrates of lymphocytes or plasma cells have not been reported around CoC prostheses [46]. These findings suggest a potential hypersensitivity response to metallic debris. The mechanisms and causes of this hypersensitivity remain largely unknown. They may be due to metal degradation products that can combine with serum proteins [47, 48] to form haptens [49], to which individuals may have a different response threshold [50]. It is also possible that proteins combined with the particles detaching from the tribolayers form haptens [50], especially considering that these proteins are likely to be denatured from exposure to high shear rates and elevated temperatures. Implant-related hypersensitivity response has been thought to be a delayed type-IV reaction [49]. Perivascular accumulation of CD3+/CD4+, CD20+ T cells, and CD68+ macrophages in periprosthetic tissues collected during revision of THAs with MOM bearings has indeed been described [51–53]. However, Willert et al. [43] reported the presence of plasma cells, B lymphocytes, and massive fibrin exudation that is not characteristic of a delayed type-IV hypersensitivity reaction. The authors described this reaction histologically as an aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) or as a lymphocyte-dominated immunological answer (LYDIA) [43]. These histologic findings are the same for both low-carbide [52] and high-carbide [43] bearings, although they are not limited only to MoM bearings [54]. The associated soft tissue adverse reactions will be presented in the chapter concerning the local sequelae to metallic wear debris.

Some cohort studies have suggested that patients with MoM devices are at a higher risk of

developing lymphopenia [55, 56]. Patients with MoM hips, compared with control subjects, had reduced peripheral blood absolute counts of CD8+ [55] and CD4 helper/inducer [56] T lymphocytes in particular and B lymphocytes [55], although this did not form a linear correlation with serum metal concentrations [5]. These findings raise the possibility that metallic debris may have a toxic effect on myelopoiesis and the immune system [57, 58]. It is possible that a reduction in certain T-cell subsets may relatively increase overall mortality in the elderly [59, 60]. No obvious clinical evidence that the reduction in the T-lymphocyte count found in MoM patients is detrimental, although this has yet to be investigated [55].

Mutagenesis

Ionic Cr, Co, Ni, V, Al, and Ti have mutagenic actions on cells in tissue culture. In metal genotoxicity, there appears to be two predominant modes of action; either direct action, causing DNA breaks through attacks on free radicals, or an indirect effect by inhibiting the repair of DNA [61–64]. Cr, Ni, Co, and Ti are redox metals and can generate reactive oxygen species (ROS), such as the superoxide radical (O_2^-) and the hydroxyl radical ($\cdot OH$) via a Fenton-driven reaction with hydrogen peroxide (H_2O_2) [64]. ROS can induce oxidative damage to DNA [61]. In an analysis of DNA damage caused by Fenton-type oxygen radical-generating systems, based on Cu(II), Cr(VI), Co(II), iron(II), Ni(II), or V(III), the highest total yield of DNA lesions was generated by the Cu system, followed by Co, Ni, Cr, Fe, and V [61]. Cr(VI) primarily enters the cells and undergoes metabolic reduction; reduction by cysteine can cause mutagenesis, in the absence of oxidative damage, by the extensive formation of Cr–DNA adducts and Cys–Cr–DNA and interstrand DNA–DNA cross-links [65]. Studies have shown that Cr(VI) reduction induce guanine–guanine DNA interstrand cross-links in living cells, thus blocking the DNA replication process [66, 67]. Cr(III) is reported to be 1,000-fold less

toxic than Cr(VI), partly because of difficulties in entering the cell [68]. However, this consideration may not apply to the release of Cr(III) within the cell from reduction of Cr(VI) or from particles after phagocytosis. Cr(III) has been shown to cause DNA strand breakage [69] and so decrease the fidelity of human DNA polymerase beta, thus affecting DNA synthesis [70]. Furthermore, studies in cell cultures have shown that Ni(II) and Co(II) damage or distort zinc finger domains, thus inhibiting DNA repair [62, 71, 72]. Zinc finger motifs participate in protein–nucleic acid and protein–protein interactions in many groups of proteins, including those involved in DNA repair [62]. Co(II), on the other hand, causes DNA strand breaks [73], but, in addition, it inhibits the incision and polymerization step of excision DNA repair [74]. Moreover, some metals are known to have interactive effects which may be synergistic or antagonistic. Cobalt in particular has been shown to increase the mutagenicity of other metals in particulate form [73]. Altered signal transduction and gene expression have all been documented in response to a range of orthopedic metal ions, notably Ni(II), Cr(VI), and Co(II) [75, 76]. On a macroscopic scale, both Cr(VI) and Cr(III) lead to chromosome breakage [69]. Likewise V(V), Cr(VI), and Cr(III) have been reported to cause aneuploidy [69, 77].

In patients at revision of MoP prostheses, there is evidence of mutagenic damage in bone marrow and peripheral blood lymphocytes. The mean incidence of aneuploidy in peripheral blood lymphocytes was increased approximately threefold, whereas the mean incidence of chromosomal aberrations was approximately doubled in all patients at revision arthroplasty compared with the primary operation [78]. The type of damage observed depends on the composition of the prosthesis. In patients with Ti–V–Al prostheses, there is a fivefold increase in aneuploidy with no increase in chromosomal translocations. In those with Co–Cr prostheses, there is a 3.5-fold increase in chromosomal translocations and a smaller 2.5-fold increase in aneuploidy [78]. This differential response was confirmed also *in vitro*,

when human cells in tissue culture were exposed to Ti-alloy- or Co–Cr-alloy-based wear debris which had been extracted from the periprosthetic tissues of patients at revision arthroplasty [79]. A similar twofold increase in chromosomal aberrations is present in femoral bone marrow adjacent to worn MoP prostheses [80].

For MoM articulation, specifically, a prospective study has shown statistically significant increase of both chromosome translocations and aneuploidy in peripheral blood lymphocytes [81]. These types of aberrations can be theoretically explained by the abovementioned actions of metals. However, only the molybdenum level could be correlated with chromosome translocations [81]. Similarly, a prospective multicentric study of patients having Metasul MoM components did not show any correlation of chromosomal damage at any of the ion levels [82]. On the contrary, Daley et al. [63] tested mutagenic effects of wear debris from 21 worn hip and knee replacements, on human cells in tissue culture. They found that the concentration of Ti or the combination of Ti, V, and Al within the wear debris was linearly related both to the level of aneuploidy *in vitro* and *in vivo*. The concentration of Co or Cr or the combination of Co, Cr, Ni, and Mb in the wear debris correlated with both chromosomal breakage and aneuploidy events [63]. Similarly, Davies et al. [83] stated that synovial fluid from failed Co–Cr-alloy prostheses, either MoM or MoP, causes DNA damage to human fibroblasts in tissue cultures *in vitro*. In contrast, synovial fluid from failed stainless-steel MoP prostheses did not cause any damage, implying that the key factor must be the composition differences between the two alloys [83]. The clinical consequences, of the increase in chromosome aberrations, if any, are unknown [81]. Detectable genetic damage was reduced, however, following revision to a MoP device [84]. As far as comparison with CoC articulation is concerned, ceramic particles are weakly genotoxic on human fibroblasts. The *in vitro* genotoxicity of aluminum particles does not depend on size, while Co–Cr particle size correlates inversely with the genotoxicity [85].

Local Sequelae

Soft Tissue Reactions

The localized effect of metal debris on the soft tissues in the vicinity of a Co–Cr–Mo MoM implant can manifest as groin pain, which may be indicative of an adverse reaction to metallic debris (ARMED) [86, 87]. ARMED is a general term that includes a spectrum of reactivity and soft tissue changes, from joint effusions to cystic lesions and solid pseudotumors. These reactions can result in implant loosening and may ultimately cause devastating necrosis of surrounding muscle and bone [87, 88]. Extensive collection of metal-stained macrophages in periprosthetic tissues, a phenomenon known as metallosis, may be associated with prosthetic failure and has been documented in both conventional and MoM systems [89, 90]. Metallosis is common, particularly in patients with a predominantly necrotic component that lack an inflammatory component on subsequent histological analysis [91]. Histological examination of periarticular tissue in established ARMED reveals an immunological response that includes a diffuse and perivascularly oriented infiltration of lymphocytes, plasma cells, sometimes eosinophilic granulocytes, high endothelial venules, localized bleeding, fibrin exudation, necrosis, and macrophages with drop-like periodic acid-Schiff (PAS)-positive inclusions. Histology may reveal varying amounts of metal particulate debris. This set of histologic features, consistent with a chronic inflammatory response, is, as already mentioned, termed ALVAL [92]. With the exception of the perivascular lymphocytic infiltrate, all other features can be also seen to some degree in other types of prosthetic failure [93]. Nevertheless, the arrangement (perivascular) and extent of chronic inflammation are “specific” of ALVAL [44, 92, 94]. A delayed-type hypersensitivity reaction has been advocated as the proximate cause of ALVAL, although it is not a universally accepted conclusion [95]. Apart from hypersensitivity, cytotoxicity and subsequent necrosis seem to have a role in the pathogenesis of ARMED [91].

Although there is considerable variability in the presenting symptoms, as well as in intraoperative findings of patients exhibiting ARMED, a pattern has emerged that is considered characteristic of an ARMED [43, 86, 90]. Persistent pain or the new onset of pain, particularly in the groin, may manifest early, perhaps within the first 1–3 years post surgery. Radiographs may be normal or reveal developing radiolucency. Aspiration of the joint frequently reveals joint effusion with a turbid fluid that does not show evidence of infection. Variable amounts of metallic particulate debris may be present. Indices of infection may be normal or slightly elevated. Blood metal ion levels can indicate whether excessive wear is occurring, which might enhance the possibility of an ARMED [86, 96]. Computed tomographic scans, ultrasound, and magnetic resonance imaging with metal artifact reduction sequences (MARS MRI) may be used to identify fluid collections and synovial abnormalities [86]. At surgery, there frequently are a creamy fluid, sometimes under pressure, and a thickened joint capsule. In advanced cases, a pseudotumor may be found that may involve extensive necrosis of the surrounding muscle and bone [86].

Although the soft tissue reactions may be rare, the precise prevalence remains unknown, although it seems to be on the rise. Without exception, the literature reports an increased incidence of these problems in women [97, 98]. Studies of different MoM systems report ARMED-related revision rates between 0.53 % [99] and 3.3 % [100], while for large-diameter MoM configuration around 1 % [86, 87, 101]. Care should be taken in estimating the occurrence of revisions for ARMED, however, as published reports of revisions for persistent pain or for aseptic loosening, without further investigation, may in fact be ARMED related [86]. While the incidence of symptomatic ARMED seems to be around 1 %, there may be an appreciable number of unrecognized conditions, especially of asymptomatic pseudotumors [102], and it is of concern that these may become symptomatic [97].

Efforts to define risk factors for development of ARMED have not produced definitive conclusions. Findings in HRA studies and THA studies

suggest that female gender and diagnosed metal allergies may predispose patients to ARMED [86, 97]. Evidence is accumulating that high cup abduction angle and excessive anteversion may be a significant factor in predisposing patients to ARMED [86, 103]. However, ARMED can occur in cases with abduction angles within the Lewinnek safe zone and with no obvious excess anteversion [86, 88, 102]. It seems that hemispheric components are somewhat less sensitive to the functional arc of coverage [86]. A recent study links ARMED with the higher corrosion of the head taper junction seen in large-diameter MoM articulation. The corrosion situation is assumed to get worse by increasing the stresses and head/neck moment arms around the taper by placing a larger, stiffer femoral head on a relatively flexible neck [104]. Given the potentially severe debilitating results of ARMED, it is critical to recognize early symptoms, differentiate from infection, and revise the patient before the progress of the syndrome results in serious tissue damage [96, 97]. The outcome of revision surgery for these cases has been reported to be inferior to the outcome of other revisions [88]. Symptoms are relieved only by following revision without an all-metal articulation [43, 88]. Although it would be useful to predict which patients may be predisposed to the ARMED immune response, to date, there is no reliable method for doing so. Patch testing and lymphocyte assays may lack the sensitivity necessary to indicate a likely immunological reaction to implant metals [86, 95].

A considerable amount of literature focuses on pseudotumors. The term pseudotumor was originally used to describe solid granulomatous masses related to wear debris in MoP implants and leading to pressure effects or extensive tissue necrosis [105]. Currently the term is used for a spectrum of lesions, neither infective nor neoplastic, surrounding MoM hip prostheses and ranging from small, fluid-filled cysts to large, complex, and destructive lesions with solid components [102, 106]. They can communicate or not to the joint, and the exact location may be related to pathways of low resistance created by the capsulotomy [102]. Risk factors for pseudotumor

include female gender, hip dysplasia, age < 40 years, and use of small components [107]. Once this reaction has developed, it is believed to worsen progressively, resulting in pain, pressure effects, and bone and soft tissue destruction requiring revision arthroplasty to halt the process [97]. Some of these lesions were thought to be highly destructive [96, 97], and the presenting symptoms included pain, rash, pathological fractures, spontaneous dislocations, femoral nerve palsy, and the presence of a lump [97]. Even "asymptomatic" patients with pseudotumors were found to have inferior functional outcome scores. These patients were, also, reported to have elevated metal ion rates and wear rates compared to controls [108]. In contrast, other, recent studies, question the effect of pseudotumors in prosthesis function. The prevalence of pseudotumors was found to be similar in patients with a well-functioning hip prosthesis and patients with a painful hip [102]. Periprosthetic pseudotumors may be diagnosed around asymptomatic, symptomatic [102], and well-positioned [109, 110] total hip prostheses with MoM bearing surfaces. Furthermore, patients revised with pseudotumors had similar whole-blood metal ion levels and component wear rates to those who were not revised [109]. Concern, however, for the solid pseudotumors and for the fluid collections, with high signal on both T1- and T2-weighted images, remains [102]. Although MARS MRI is useful for surgical planning of the necessary debridement, the presence of a pseudotumor may not necessarily indicate the need for revision arthroplasty [102].

Lymphocyte infiltrations seen in the patients with pseudotumors were similar to ALVAL, suggesting metal hypersensitivity to be an important factor [43]. However, a recent study demonstrated systemic hypersensitivity type-IV reactions, as measured by lymphocyte proliferation response to Co and Cr, and did not significantly differ in MoM HRA patients with pseudotumors compared to those patients without pseudotumors [111]. The prevalence of pseudotumor (1.8 [107]–61 % [102]) far exceeds the metal hypersensitivity reactions, which are currently estimated to affect less than 1 % of the patients [95].

Moreover, ALVAL-type response was not seen histologically in all pseudotumors [102], whereas necrosis and a macrophage infiltrate were consistently seen, indicating that other mechanisms are likely to be involved [108]. A dose-dependent cytotoxicity of clinically relevant Co nanoparticles on macrophages *in vitro* has been recently reported [35]. Although the toxic dose of Co ions *in vitro* is 2 orders of magnitude higher than the concentration found in hip aspirates [35], study findings suggest that intracellular corrosion of Co nanoparticles and resultant Co ion release lead to tissue necrosis and pseudotumors formation [112]. This would further lead to the vicious cycle previously described [108, 112].

Aseptic Loosening and Osteolysis

Over the last several years, it has become evident that contemporary MoM bearings, as it was originally intended, are not immune to some of the problems, including periprosthetic osteolysis, that have plagued other bearing surface combinations. In fact, the present survival data of aseptic loosening of the second-generation MoM THAs appear to be inferior compared to those from previous reports on other bearing surfaces. Neuerburg et al. [113] in a study of 1,270 second-generation 28 mm Metasul-based MoM primary THA found a 0.94 (95 % CI 0.92–0.96) probability of survival at 10 years for revision due to aseptic loosening. Eswaramoorthy et al. [114] reported a 10-year survival of 94 % with revision for any reason as the end point in 85 Metasul-based THA. Analyzing 640 Sikomet-based MoM THA, Milosev et al. [94] reported a 10-year survivorship of 93 % with revision for aseptic loosening as the alternative end point. Similarly, two clinical studies on Sikomet THAs reported an apparently increased (3.75–5.1 %) aseptic loss of biologic fixation associated with focal and expansile osteolysis [94, 115]. On the contrary, Dorr et al. [116] investigating Metasul MoM articulation couples reported no focal or linear osteolysis but only calcar resorption in 6.25 % of the hips. Low carbon alloys such as Sikomet are suspected to be less wear resistant than those with

higher carbon content (Metasul) and therefore evoke more extensive tissue reaction [117]. On the other hand, the 10-year survival rate for MoP bearing couples in either cemented or cementless primary THA as previously reported ranged from 94 to 96.4 % [118, 119]. In third-generation alumina-on-alumina ceramic bearings, the cumulative survival of both components with revision due to aseptic loosening as the end point was 99 % at 7 years follow-up [120]. MoM was associated with higher occurrence of revision compared with MoP in the adjusted analyses of three national registries: Australian, New Zealand, and England and Wales National Registries (including over 720,000 patients) [4, 121, 122]. However, only in the Australian Registry differences in the incidence of aseptic loosening were clearly identified. Specifically, the 2011 annual report of the Australian National Joint Replacement Registry based on 196,582 primary THR with various bearing surfaces revealed a cumulative incidence of 3.9 % of revision for loosening/lysis for MoM THR at 10 years of follow-up, which was inferior and almost double compared to 2 % for the MoP [122]. The overall 10-year cumulative percent revision incidence was 4.7 (4.3, 5.1), 5.4 (4.8, 6.1), and 8.8 (7.7, 10.1) for MoP, CoC, and MoM THA, respectively [122]. Remarkably, the percentage of Sikomet and Metasul bearing couples was not recorded in any of these registries.

Why is the prevalence of osteolysis associated with MoM bearings reported seemingly greater, or at best similar, to that associated with conventional bearing couples despite the dramatically lower volumetric wear rate [123]? The very small size of metallic debris released by MoM bearings [16], which makes them partially soluble, combined with the fact that the bioavailability is thought to be a function of the total surface area of the released debris rather than on its volume [124], casts doubt on the supposition that the net adverse biologic response will be reduced by modern MoM designs [18]. Other characteristics of the degradation products (such as size, shape, and chemical form) are important in the determination of bio-reactivity [124]. In the case of MoM THAs, it is likely that metal-stimulated lymphocytes, and not macrophages as in MoP

articulation, participate in the pathogenesis of aseptic osteolysis given that activated lymphocytes release powerful cytokines such as IL-2 (interleukin-2), IFN- γ (interferon-gamma), and RANKL (receptor activator of NF- κ B ligand) [123]. Increased recruitment of osteoclast precursors, their subsequent differentiation into mature osteoclasts, and the increased osteoclast survival in response to the released cytokines may be involved in the patho-mechanisms of aseptic implant loosening [125]. Furthermore, investigations have demonstrated that Ti wear particles inhibit the expression of the osteoblastic genes that code for collagen type I and type III [126]. Other studies have revealed that nontoxic concentrations of metal ions affect the differentiation and function of osteoblastic cells in vitro [127, 128]. Cobalt and chromium ions reduce human osteoblast activity, reduce OPG/RANKL ratio, and lead to oxidative stress [129]. Queally et al. [130] have shown in vitro that Co ions, apart from suppressing osteoblast function, stimulate the secretion of chemokines that attract inflammatory and osteoclastic cells to the periprosthetic area. Andrews et al. [131] examined the effects of exposure to Co and Cr on human osteoblast and osteoclast formation and function over clinically relevant concentrations. They found that Cr(VI) reduced osteoblast survival and function, while Co(II) and Cr(III) did not affect them [131]. In contrast, osteoclasts were more sensitive to metal ion exposure. At normal serum levels, a mild stimulatory effect on developing osteoclasts was found for Co(II) and Cr(III), while at higher serum and synovial equivalent concentrations, and with Cr(VI), a reduction in cell number and bone resorption was observed [131]. In conclusion, wear debris from MoM bearings may well have a negative effect on osteoblastic functions, resulting eventually in increasing implant loosening [125]. Alternatively, there may be specific design, geometric, and/or manufacturing parameters that contribute to the failures, independent of the composition of the bearing couple [123]. It should be clearly understood that, at present, the evidence linking osteolysis and aseptic loosening with metal hypersensitivity is circumstantial: cause and effect have not been established [123].

Infection

Recently there have been increasing reports suggesting that the combination of metal debris, ALVAL, and tissue necrosis provides a unique environment for periprosthetic bacterial growth and rapid spread of infection [132, 133]. Lymphopenia, as already mentioned, can contribute to that. Arguments for both promoting and inhibiting effect of wear particles on the development of infection have been expressed. In vitro research on influences of Co and Cr ions on bacteria has provided evidence of bacteriostatic effects [134]. Wear products of MoM prostheses may be toxic not only to human cells but also to bacteria through generation of ROS [135]. On the other hand, metal nanoparticles show in vitro toxicity for macrophages [35], while alterations in spleen architecture have been reported [136]. Furthermore, both reduced [137] and increased [134] biofilm growth in the presence of Co–Cr particles have been described, while there is growing concern that metal contamination may function as a selective agent in the proliferation of antibiotic resistance [138]. Long-term clinical data on infection rates for MoM bearings are not yet available, and, therefore, actual clinical influences on infection cannot be evaluated [135].

Systemic Sequelae

Hematopoietic Tissues

Altered cellular iron utilization resulting in anemia is seen with Al and Cr (VI) [139, 140]. In particular, as shown in in vivo studies on rats, the erythropoiesis impairment induced by Al may be a combined effect of direct action on circulating erythrocytes and interference with the cellular iron metabolism in erythroid progenitors [139, 141]. Almost all the investigated Ni compounds decrease water permeability across erythrocyte membranes, erythrocyte thermostability, deformability, and the rate of O₂ release by erythrocytes [142]. A recent in vitro study considered the effect of seven nanoparticles, including Co and TiO₂ nanoparticles, on growth and differentiation

of bone marrow-derived CD34+ human hematopoietic progenitor cells, with colony-forming unit (CFU) assay. Only Co nanoparticles showed a dose-dependent toxicity on both types of colonies [143]. The *in vitro* exposure of both Co and Ni nanoparticles in human endothelial cell cultures induced a concentration-dependent reduction of cell numbers within 24 h. Again, the exposure to the respective ions (Co²⁺, Ni²⁺) induced smaller effects [144, 145].

Hepatobiliary System

Hepatotoxicity is often observed in response to high levels of circulating metal within the body. Chromate compounds in very high levels cause toxicity directly resulting in hepatic malfunction, potentially severe hepatic lesions, hepatocellular necrosis, and possibly disseminated intravascular coagulation [146]. Similarly, during short-term excessive Al administration, it was shown that Al concentrations in both hepatocytes and macrophages increased and that the hepatocyte–lysosome ratio and macrophage count increased in liver tissues of treated mice [147]. Recently, Wang et al. [148] investigated the potential toxicological effect of intra-articular injected TiO₂ nanoparticles on major organs, such as the liver, lungs, and heart, in rats. Fatty degeneration of hepatocytes and inflammatory responses were demonstrated [148]. Similarly, Urban et al. [149] in postmortem specimens with THA discovered metal particles (cobalt–chromium–nickel–tungsten alloy) within macrophages in the liver and/or the spleen mainly in patients with a revised arthroplasty, but no toxic effects were apparent [149].

Renal System

The renal excretion in patients with MoM prostheses is much less for Cr than Co, suggesting Cr is more protein bound or Co is actively secreted by the kidney. The elevated urinary Co concentrations may not be physiologically inert; similar amounts in experimental models stimulate

production of hypoxia-inducible factor (HIF) which controls mechanisms to protect against hypoxia [150]. Similar models demonstrate that HIF activation with Co chloride may protect against renal damage [151]. While Co may be protective, evidence exists that Cr can impair renal function and induce tubular necrosis and interstitial cell damage in experimental animals and humans [152, 153]. Indicators of tubular dysfunction have been identified in human subjects exposed to Cr(VI) through occupation [154]. Finally, Al and Ni are excreted by the kidney in a rapid fashion and therefore only cause renal toxicity at significantly high concentrations [155].

Nervous System

Cobalt poisoning (cobaltism) from beer additives, industrial exposure, or medicinal use (treatment of refractory anemia with cobalt chloride) is well known [156]. Cobaltism can result in hand tremor, incoordination, cognitive decline, depression, vertigo, tinnitus, deafness, blindness, optic nerve atrophy, convulsions, headaches, polyneuropathy [157–159], cardiomyopathy [157], and endocrine (hypothyroidism) symptoms [156]. The term “arthroprosthetic cobaltism” has been coined to describe these manifestations in patients with joint replacements [160]. It is a rare condition with 10 cases reported so far [157–163]. Half of them refer to revised fractured ceramic components with a MoP articulation [157–159, 163]. Only four refer to MoM components; the withdrawn articular surface replacement implants (ASR; DePuy, Warsaw, Indiana) have been used in all of them [160, 162]. Clinical manifestations may occur immediately after operation [162] or many years after [160] and appear to stay elevated over extended periods of time [162]. The patients with hip implants who are at the highest risk for cobaltism are those with renal dysfunction and those with excessive wear such as those with the ASR MoM components [160, 162], those with mismatch of implants (metal-on-ceramic THA instead of ceramic-on-metal THA) [161], and those with potential third-body wear

[157–159, 163]. There is no documented threshold of the cobalt levels for the onset of the symptoms. All of the reported patients, except one, had a serum cobalt level of >60 $\mu\text{g/L}$ [162]. Cerebrospinal fluid levels were also found to be elevated, showing that ions cross the blood–brain barrier. However, in case series, higher values of serum Co concentration have been reported, without the occurrence of cobaltism [164]. Recovery after revision was recorded for all symptoms except for vision, which was limited to partial improvement [159, 161, 162].

Neurological manifestations have been described in relation to Al intoxication and include memory loss, gait disturbance, and involuntary movements. The development of some neuropathological conditions, including amyotrophic lateral sclerosis, Parkinsonian dementia, dialysis encephalopathy, and senile plaques of Alzheimer's disease, may be related to the accumulation of Al in the brain [165]. The pathogenic and etiologic role of Al specifically on Alzheimer's disease has been the source of debate for 40 years [166]. Furthermore, Co may, also, contribute to development and/or progression of neurodegenerative disorders by increasing the secretion of certain types of β -amyloid [167]. Travacio et al. [168] found in mice that Cr (VI) produced an expected increased formation of ROS and brain lipid peroxidation. Other animal experimental studies focused on vanadium (V)-induced neurotoxicity. Garcia et al. [169] recorded that the main areas affected by vanadium-mediated free-radical generation were the hippocampus and the cerebellum. Vanadium exposure through lactation produces behavioral alterations and myelin deficit in neonatal rats [170]. It was further found that vanadium induces dopaminergic neurotoxicity via protein kinase C delta-dependent oxidative signalling mechanisms in nigral culture cells, a possible link to the pathogenesis of Parkinson's disease [171]. Finally, it is important to mention that in male workers with a mean vanadium concentration of 14.4 $\mu\text{g/L}$ in urine and 7.5 $\mu\text{g/L}$ in serum, significant alterations in visuospatial ability and attention span were observed [172].

Respiratory System

The effects of exposure to Co, Ni, and Cr through inhalation on the respiratory system are well documented because of the frequency of occupational exposure [173]. An extensive literature search identified a single article that referred to exposure via the vascular route. TiO_2 nanoparticles, which possess a small aggregated size, were taken up and disseminated in lung tissues via the circulation in TiO_2 -exposed rats. Numerous brown particulates were deposited in the pulmonary microvasculature and were associated with passive lung congestion. Particles phagocytosed by macrophages were discovered in the pulmonary alveoli. Thickened alveolar walls and follicular lymphoid hyperplasia with inflammatory cell aggregates around bronchia were also discovered in the lungs of these rats [148].

Cardiovascular System

Cardiotoxic effects have been described (“beer drinker's cardiomyopathy”) [156] in relation to Co and are usually in the form of cardiomyopathy and impairment of the left ventricular function. Interstitial fibrosis has been identified after myocardial fibrosis in cases of arthroprosthetic cobaltism [157]. As far as occupational inhalation exposure in Co plants is concerned, the results of an echocardiography study indicated left ventricular relaxation and early filling, but without significant clinical consequences [174]. Pathological evaluation showed that high-dose cobalt chloride had toxic effects on the heart and liver of mice, but not on the kidneys [175]. Frustaci et al. [176] observed a large increase in the levels of different trace elements in the myocardium of 13 patients with idiopathic dilated cardiomyopathy, with a 13-fold increase in the concentration of Co and a fourfold increase in the concentration of Cr compared to controls. The relationship of the elevated Co and Cr concentrations in the serum of THA patients and cardiomyopathy requires further studies [177].

As far as other trace metals are concerned, after intra-articular injections of TiO₂ nanoparticles for 7 days in rats at different concentrations, the heart and lungs were seriously affected [148]. In a fairly recent combined experimental animal and human epidemiologic study, the authors found significant associations between Ni and acute cardiac function changes in mice and increased cardiovascular mortality in people at low ambient air concentrations [178]. A more recent epidemiologic study of the New York City population found that among the components of the particulate matter, only Ni concentrations showed consistent associations and only with heart rate in the COPD patients [179]. Further research is warranted to elucidate the possible effects of exposure via the vascular route.

The Visual and Auditory Systems

Al may cause severe retinal degeneration and the destruction of the photoreceptors cells at high concentrations in experimental animal studies [180]. Due to neurological toxicity, as mentioned above, excess blood cobalt can cause nerve deafness, optic nerve atrophy, and eventually blindness. This is a rare adverse effect and has been reported only three times [159, 161, 162]. Partial recovery was observed with time after revision. Similarly, with regard to “non-endoprosthetic” exposure, only three case reports of optic atrophy caused by chronic cobalt poisoning have been published, one concerning a 48-year-old man 20 months after occupational, working 50 h a week, who was subjected to cobalt powder inhalation and another concerning a 32-year-old man treated for 15 weeks with cobalt chloride [181, 182]. Another case developed (with the same treatment for 6 months) limb paresthesia, unsteady gait, impaired hearing, and dizzy spells [183]. Bilateral nerve deafness has been described following chronic occupational exposure to cobalt powder or during long-term treatment of anemia with cobalt chloride. Deafness typically resolves completely after discontinuation of exposure [182].

Endocrine and Reproductive Effects

Effects of metals on thyroid and parathyroid hormone pathways have also been described. Co(II) prevents the uptake of iodine into the hormone thyroxine by its inhibition of the enzyme tyrosine iodinase. The latter may cause hypothyroidism [184]. Hypothyroidism has been observed as an undesirable side effect of Co therapy used for the treatment of anemia [185]. Swennen et al. [186] reported a slight and subclinical elevation of TSH and decreased T3 and T4 levels in workers exposed to Co. On the contrary, exposure in a small series of pottery painters showed no effect [187]. Similarly, a recent cross-sectional survey of 249 male workers from a cobalt production department detected no effects on the thyroid [185]. Furthermore, Al is known to disrupt parathyroid hormone levels in human and animals, which may account for Al-induced bone disorders in dialysis patients [188]. Recent studies have highlighted the potential ability of certain metal ions to bind to estrogen receptors and give rise to estrogen agonist responses *in vitro* and *in vivo* [189]. Such xenoestrogens have been termed metalloestrogens [190] and include Al, Cr (II), Co, Ni, and V. These metal ions, particularly Al, may add to the burden of aberrant estrogen signalling within the human breast [190]. Chronic exposure to Cr has detrimental effects on male and female fertility as a result of decreased sperm production and impaired sperm and ova quality. It seems that Cr(VI) disrupts spermatogenesis, leading to accumulation of prematurely released spermatocytes, spermatids, and uni- and multinucleated giant cells in the lumen of seminiferous tubules, by inducing free-radical toxicity [191]. In a survey of welders exposed to fumes having Ni and Cr, Danadevi et al. [192] found that the sperm concentration showed a negative correlation with Cr blood levels. In another study on workers exposed to high concentration of Cr(VI), damage to convoluted seminiferous tubules epithelium, a reduction of spermatozoa formation, and an increase in the prevalence of teratospermia were found [193]. As far as female fertility is concerned, in a study of orally administered Cr(VI) in female mice,

ovarian physiology and rate of ovulation were altered [194]. Exposure to Ni(II), V, Al, and Co(II) has been shown to induce some limited reproductive toxic effects in male experimental animals, such as abnormal histopathology and spermatogenesis [195, 196]. Taken together, the studies suggest that exposure to heavy metals leads to negative impact on fertility and the reproductive outcome, probably by affecting male reproductive system at multiple levels.

Skin

Metallic orthopedic devices are composed of elements that are known to be skin sensitizers in the general population. Metals known as sensitizers (haptenic moieties in antigens) are beryllium, Ni, Co, and Cr; in addition, occasional responses to tantalum, Ti, and V have been reported [95]. Contact dermatitis, urticaria, and vasculitis have been described in relation to Co, Ni, and Cr. The combined results of approximately 50 studies show that the prevalence of metal sensitivity among the general population is approximately 10–15 % [197] with Ni sensitivity being the highest (approximately 14 % up to 17 % of women and 3 % of men), followed by Co and Cr (1–3 %) [198]. Cross-reactivity between Ni and Co is the most common [95, 197, 199].

There is concern about the possibility of sensitivity reactions in patients bearing THA implants. Accumulated reports of metal allergy in THA patients showed that the incidence of dermal reactions and positive skin-patch testing to Co, Ni, and Cr in patients with THA with stable and loose prostheses increases by 15 and 50 %, respectively, above those of the general population [95]. However, in a more recent large case-control study, the prevalence of metal allergy was not increased in patch-tested dermatitis patients who underwent THA in comparison with patch-tested dermatitis patients who were not operated on [200]. Another question is whether patients with a preexisting sensitivity had a greater risk of having an unsatisfactory performance of the device than did those with no sensitivity. In early MoM THA patients, an elevated rate of metal

allergy has been reported [201]. Despite the lack of prospective longitudinal studies, the incidence of reactions necessitating implant removal was thought to be low, probably less than 0.1 % [202]. A recent case-control study comparing the prevalence of complications following THA in patients with and without a previous metal allergy found no overall difference. Specifically, despite limitations of statistical analysis, there was no evidence of elevated risk of allergy-induced failure for second-generation MoM prostheses [200]. The overall allergy-induced failure rate of new MoM arthroplasty is indeed considered to be low [203]. Thomas et al. [204], however, studied a cohort of 16 patients with failed MoM arthroplastic implants; 81 % of the patients were found to have metal sensitivity. Reed et al. [205], on the other hand, studied 44 patients, 22 of them had a history of metal reactions evaluated prior to metal implantation and 22 had symptoms following implantation, either cutaneous or chronic joint pain and loosening. None of the symptomatic patients had had positive patch-test reactions to a component of the implanted device [205].

The conclusion from these studies is that there is no reason to deviate from normal surgical decisions because a patient is known to be allergic to metal [202]. It is uncertain whether metal allergy causes device failure or vice versa [206]. At this time, there is no evidence that there is an increased risk of a reaction to an implanted device in patients who have skin-patch sensitivity but no history of reaction to metallic materials. A perfectly functioning THA prosthesis, causing no pain and without evidence of loosening, should not be removed in most cases, despite a positive patch-test result [206]. However, patients who have reacted to a previous implant are more likely to have problems with another implant than are nonallergic patients [202]. Patients who develop a cutaneous eruption months to years after receiving a metal implant should be patch-tested with an appropriate series of metals. If relevant allergens are identified and corticosteroid therapy proves insufficient, removal of the implant may be considered [206]. There is no general support for preimplantation patch-test evaluation, but it may be considered

for individuals who are suspected of having a strong metal allergy [206]. It is obvious that prospective longitudinal studies are strongly needed to shed further light on this subject. Such intensive studies have not been performed to date, in large part because standardized, effective testing methodologies have not been established [95].

Musculoskeletal System

Chronic Al exposure has been linked to osteomalacia, pathological fractures, impaired bone remodeling, impaired response to vitamin D, and proximal myopathy [188]. As mentioned before, soluble orthopedic metal particles may adversely affect osteoblastic function, influencing bone remodeling as well [207], with unclear clinical consequences.

Developmental Toxicology

Exposure of the unborn fetus to metals has been the subject of a number of studies as translocation of metal particles can occur through the maternofetal circulation and through lactation. As is known already from experimental animal studies, metals such as Cr, Ni, Co, V, and Al have potential effects on conception, fetal implantation, and later teratogenicity [208]. For Cr specifically, the number of implantation sites and the number of viable fetuses were found to be significantly reduced when either the female or the male mice were exposed to chromium compounds [209]. In rats, skeletal abnormality in the form of reduced ossification in parietal, interparietal, and caudal bones was found in the fetuses of Cr(VI)-treated mothers. Gross structural abnormalities in the form of subdermal hemorrhagic patches were, also, observed on the thoracic and abdominal regions [210]. The same effect of V on fertility and offspring abnormalities was revealed in another study on rats [211].

Nevertheless, there has never been a report of fetal malformations associated with THA and especially MoM implants in humans [8]. In addition, both Co (5–45 mg/day) and Cr (recommended

200 mg/day) are often included in large quantities in dietary supplements. Barcelouc [212] found no evidence of teratogenicity associated with high doses of cobalt (100,000 mg/day) used to treat anemia in pregnancy. In a large survey regarding pregnancy and childbirth after THA, 343 young women with 420 THAs were involved. Of these, 47 (13.7 %) had a successful pregnancy. The results showed that childbirth is not affected by the presence of a THA and also that pregnancy after THA is not associated with decreased survival of the prosthesis [213]. Other studies with limited number of patients (13–14) with THA having given birth confirmed these findings [214, 215]. In none of these studies was the type of bearings specified.

Concerning MoM bearings in particular, we were able to identify a limited number of surveys [216–218], with the largest counting ten patients having had pregnancy [217]. Brodner et al. [216] reported that in three cases in which women with MoM implants and serum levels of ions within the normal range of concentrations gave birth, no metal ions levels were measured in fetal cord blood. In these three women, any transfer of metal ions across the placenta was undetectable and the risk to the fetus would have been negligible. Contrary to Brodner's findings, Ziaee et al. [217] in a study using high-resolution inductively coupled plasma mass spectrometry demonstrated that Co and Cr are able to cross the placenta in ten patients with MoM hip resurfacings, as well as in control subjects without any metal implants. Again the maternal serum concentrations of Co and Cr measured in this study were within the normal range of concentrations. The transplacental transfer rate was in excess of 95 % in the controls for both metals but only 29 % for Cr and 60 % for Co in study patients, suggesting that the placenta exerts a modulatory effect on the rate of metal ion transfer. At low maternal metal ion levels, there is a higher transfer rate than at higher maternal levels [217]. The more recent report of Desouza et al. [218] on three patients with MoM HRA who had the prosthesis in situ during pregnancy agreed with these results. Umbilical cord blood chromium and cobalt levels were under a quarter and approximately half of the maternal

serum levels, respectively. All three children were healthy [218]. In addition to the transplacental route, the passage of metals from the mother to the developing offspring may occur during lactation. However, only one study on rats treated with V focused on this period [211]. During lactation, the pups behavioral responses (such as learning and memory responses) and viability indices were decreased [211].

Carcinogenesis

The carcinogenic potential of the metallic orthopedic implants has historically been of interest. A hip prosthesis differs from a static implant because it continuously liberates metal and plastic particles, which especially burden the pseudocapsule and bone in the whole effective joint space. Oncogenesis, thereafter, around the prosthesis could be in solid or particulate state. Both aspects have been studied in animal experiments. Since the 1960s, solid nondegradable implants, not only metals, have been shown to induce sarcomas in high percentages in rodents after subcutaneous and intraperitoneal applications (the so-called Oppenheimer phenomena) [219]. Smooth surface, mature fibrosis, dormancy of macrophage activity, and inflammatory reaction are preconditions for foreign body (FB) tumorigenesis. On the other hand, macrophage response and the porosity of the FB surface have an inhibitory effect on sarcomagenesis [219]. In a rat model, small increases in sarcomas were observed to correlate with metal implants that had high Co, Cr, or Ni content. Furthermore, lymphomas with bone involvement were more common in rats with metallic implants [220]. Kirkpatrick et al. [221] implanted discs of 15 mm of size subcutaneously in 490 Fischer rats, made of commonly used prosthetic materials: UHMW polyethylene, polymethylmethacrylate, 99 % purity Ti, Ni–Cr and Co–Cr alloys, and Al₂O₃. Within 2 years, local sarcomas developed from the frequency of 12 % at Ti implant to 35 % at polyethylene implant. There was no correlation between the different prosthetic materials and histology of the tumor. Malignant fibrous

histiocytoma was the most common tumor (65 %), followed by pleomorphic sarcoma (34 %). The authors also reported proliferative or preneoplastic lesions in the capsules adjacent to implant. Ti group revealed the highest incidence of such premalignant changes, but the lowest incidence of sarcoma development [221]. Contradictory to that, Brand and Brand [222] could not show any premalignant changes in specimens obtained from 27 human FB-reactive tissues. Particulate forms of prosthetic metals, on the other hand, did not cause neoplastic transformation in the mouse fibroblast cell line *in vitro*. Soluble salts of Co, Cr, Ni, and Mo significantly increased these transformations [223]. Meachim et al. [224] were unable to induce sarcoma in rats or guinea pigs with intramuscular implantation of particulate debris of Co–Cr–Mo. Furthermore, Lewis et al. [225] could not introduce local tumors in rats with intra-articular administration of Co–Cr–Mo or Ti–Al–V wear debris powder, which contrasted with tumor induction after nickel subsulfide administration.

It may be speculated that the chemical component of FB- tumorigenesis might be minimal, as the biomaterials span a vast spectrum of chemical structure (polymers, metals, ceramic) [221]. Chronic, particle-induced inflammation around the prosthesis, on the other hand, characterized by free-radical stress and release of cytokines, can be a significant contributor to sarcomagenesis. One could easily imagine that this microenvironment around the implants might interfere with the replication repair enzymes. Such a defect is expected to be reflected by microsatellite instability. However, no evidence of such instability was identified [226]. Alternatively, sarcomagenesis is probably associated with genetic instability on the chromosomal level. It appears that oxidative and nitrate stress of chronic inflammation results in loss of the remaining wild-type p53 allele and loss of p53 function in Trp53+/- mice, which in turn induce the development of sarcomas at the implantation site [227]. On the other hand, cytokines have both stimulating and inhibitory effects on cancerogenesis. It seems that this cytokine-related immune system could eliminate developing tumor cells around the

prosthesis in their early phases [228]. Conclusively, pathogenesis of FB tumorigenesis, as of sarcomagenesis in general, still remains obscure. Recorded incidence, though, in humans is low.

Indeed, in a review of the literature that included publications until 2006, 46 cases of malignancies, including 41 sarcomas, 4 non-Hodgkin lymphomas, and 1 epidermoid carcinoma, adjacent to a THA device were cited. Twenty of these (43 %) were malignant fibrous histiocytomas [228]. Since that report, six more cases were added in the relevant literature, four of malignant fibrous histiocytomas and two of angiosarcomas [229–233]. More than 70 % of the sarcomas occurred in MoP bearing systems, five sarcomas have been reported in MoM prostheses, and two in CoC arthroplasties [229]. Twenty-two patients were exposed to Co–Cr alloy (42 %), 13 to stainless-steel alloy, 9 to titanium alloy, 2 to ceramic prosthesis, and in the rest the composition was not reported [228–230]. Thus, the patients were exposed to all common metal alloys used for THA. Half of the tumors occurred during the first 5 years after surgery [228]. The mean latent period of the sarcomas in MoM prostheses was 2.9 years and 6.7 years MoP prostheses, with the difference found not significant [228]. Because of the large number of joint replacement devices inserted until now, this would seem to be a relatively small number of cases. Thus, the occurrence of peri-implant malignancies may be coincidental. However, because many such cases may go unreported and because these tumors may have relatively long latency periods, additional surveillance and broad-based epidemiologic studies are warranted. In a study of the data of the Scandinavian Sarcoma Group Registry [234], the expected incidence of local sarcomas – with and without prostheses and excluding acetabular tumors – was estimated at 1.43/100,000 person-years. Reported incidence of tumors in joint replacement series, though, is far less, maybe due to the abovementioned reasons [228].

From the prosthetic metals, Cr and Ni are established carcinogens for respiratory cancers to humans. Noteworthy, a series of meta-analyses concluded that Cr(VI) is a weak cause of lung

cancer and is not a cause of any of the other forms of cancer evaluated, namely prostate, kidney, central nervous system malignancy, leukemia, Hodgkin's disease, and other lymphohematopoietic malignancies [235]. Nevertheless, biological and atmospheric guidance values have been assigned for Cr and Co by health and safety organizations such as the Health and Safety Executive and the Deutsche Forschungsgemeinschaft [5]. Specifically, exposure equivalents of carcinogenic substances (EKA values) corresponding to the workplace exposure limits, in the United Kingdom for Co are 5.0 and 60 μgL^{-1} in whole blood and urine, and for Cr are 17 and 20 μgL^{-1} in erythrocytes and urine, respectively [5]. Several studies have observed THA/HRA patients with metal levels greater than one or more of these values [5]. However, currently, the association of metal release from orthopedic implants with carcinogenesis remains conjectural because causality has not been definitely established in human subjects.

There have been several human epidemiologic studies of remote cancer incidence in the first and second decades after THR. In two early studies, slight increases in the risk of lymphoma and leukemia were observed in patients who had a Co-alloy THR, particularly in those patients who had a MoM device [236, 237]. Specifically for McKee–Farrar patients, Visuri et al. [238] report a standardized incidence ratio (SIR) of all site cancer of 1.29 (0.92–1.78). Larger, more recent studies, however, have showed no significant increase in leukemia or lymphoma, but these studies did not include as large a proportion of subjects with MoM prostheses [239, 240]. A later meta-analysis of Nordic cohorts, with special emphasis on MoM bearings and 116,727 patients, found no significant excess of cancer in target organs, i.e., liver, kidney, or haematopoietic cancers and a cancer incidence in line with the general population. However, attention was drawn to prostate cancer and skin melanoma which had an elevated incidence [241]. This was also confirmed in a similar cohort study from Sweden [242]. In contrast, Goldachre et al. [243] have found no elevated risk for any type of cancer among 25,047 THA patients from the United

Kingdom, with a mean follow-up, however, of only 7.7 years. In the larger and most recent meta-analysis of patients, with 1.1 million person-years operated on for all indications, the SIR was close to unity, 0.98, (95 % confidence interval (CI) 0.98–0.99) [244]. Increased risk with MoM bearings was seen for cancer of the prostate (SIR, 1.12; 95 % CI 1.08–1.16) and for melanoma, for which relative risks increased with follow-up to a SIR of 1.43 (95 % CI 1.13–1.79) for 10 or more years after arthroplasty. Risks of kidney/bladder/ureter cancer also tended to increase over time to a SIR ~ 1.2 at 10 or more years of follow-up. However, there is no obvious mechanism for these associations, possibly except from urinary excretion of metals [244]. Furthermore, in a retrospective comparative study of mortality, patients with MoM THA had a higher cancer mortality (SIR 1.01) than those with MoP THA (SIR 0.66) during the first 20 years postoperatively, but not thereafter [177]. However, the study included only 579 McKee–Farrar prostheses, which is an insufficient number for reliable conclusions. In contrast, a recent linkage study between the National Joint Registry of England and Wales and hospital episode statistics, including 40,576 patients with MoM and 248,995 with alternative bearings, found no increased cancer risk after MoM hip replacement. There was no increase in the risk of malignant melanoma or hematological, prostate, and renal tract cancers. However, follow-up was only 7 years [245].

Interestingly, studies have shown a decreased incidence of certain tumors, including breast carcinoma, sarcoma, and gastrointestinal carcinomas in recipients of THA. The effect of including healthy patients has been used to explain this reduction. This clearly confounds the interpretation of these epidemiologic investigations [18]. Although the excesses of melanoma, multiple myeloma, and urinary cancers may be due to increased physician surveillance, chance, confounding, or detection bias, they warrant further investigation because of the ever-increasing use of hip implants at younger ages [242]. The International Agency for Research on Cancer, which publishes information on the

risks posed by chemicals on the development of human cancers, has classified Cr(VI) and Ni(II) as carcinogenic, metallic Ni and soluble Co as possibly carcinogenic, and metallic Cr, Cr(III) compounds, and implanted orthopedic alloys as unclassifiable [246].

References

1. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. *Lancet*. 2007;370:1508–19.
2. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. 2007;89A(4):780–5.
3. Smith AJ, Dieppe P, Vernon K, Porter M, Blom AW. Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. *Lancet*. 2012;379(9822):1199–204.
4. National Joint Registry for England and Wales. 8th annual report 2011. <http://www.njrcentre.org.uk/NjrCentre/Portals/0/Documents/NJR%208th%20Annual%20Report%202011.pdf>. Last accessed 5 May 2012.
5. Keegan GM, Learmonth ID, Case CP. Orthopaedic metals and their potential toxicity in the arthroplasty patient: a review of current knowledge and future strategies. *J Bone Joint Surg Br*. 2007;89B:567–73.
6. Polyzois I, Nikolopoulos D, Michos I, Patsouris E, Theocharis S. Local and systemic toxicity of nanoscale debris particles in total hip arthroplasty. *J Appl Toxicol*. 2012;32(4):255–69.
7. Mäkelä KT, Eskelinen A, Pulkinen P, Paavolainen P, Remes V. Results of 3,668 primary total hip replacements for primary osteoarthritis in patients under the age of 55 years. *Acta Orthop Scand*. 2011;82:521–9.
8. Cobb AG, Schmalzreid TP. The clinical significance of metal ion release from cobalt-chromium metal-on-metal hip joint arthroplasty. *Proc Inst Mech Eng H*. 2006;220(2):385–98.
9. Aldrian S, Nau T, Gillesberger F, Petras N, Ehall R. Medium-term analysis of modern ceramic-on-ceramic bearing in THA. *Hip Int*. 2009;19(1):36–40.
10. Choi IY, Kim YS, Hwang KT, Kim YH. Incidence and factors associated with squeaking in alumina-on-alumina THA. *Clin Orthop*. 2010;468(12):234–9.
11. Dorr LD, Wan Z, Longjohn DB, Dubois B, Murken R. Total hip arthroplasty with use of the Metasul metal-on-metal articulation. Four to seven-year results. *J Bone Joint Surg Am*. 2000;82A(6):789–98.
12. Long WT, Dorr LD, Gendelman V. An American experience with metal-on-metal total hip arthroplasties: a 7-year follow-up study. *J Arthroplasty*. 2004;19(8 Suppl 3):29–34.

13. Evans EM, Freeman MA, Miller AJ, Vernon-Roberts B. Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement. *J Bone Joint Surg Br.* 1974;56B:626–42.
14. Jacobs JJ. The utility of MARS MRI in patients with metal-on-metal bearings: commentary. *J Bone Joint Surg Am.* 2012;94(4):e26.
15. Bozic KJ, Ong K, Lau E, Kurtz SM, Vail TP, Rubash HE, Berry DJ. Risk of complication and revision total hip arthroplasty among Medicare patients with different bearing surfaces. *Clin Orthop.* 2010;468:357–62.
16. Doorn PF, Campbell PA, Worrall J, Benya PD, McKellop HA, Amstutz HC. Metal wear particle characterization from metal on metal total hip replacements: transmission electron microscopy study of periprosthetic tissues and isolated particles. *J Biomed Mater Res.* 1998;42(1):103–11.
17. Billi F, Campbell P. Nanotoxicology of metal wear particles in total joint arthroplasty: a review of current concepts. *J Appl Biomater Biomech.* 2010;8(1):1–6.
18. Jacobs JJ, Hallab NJ, Skipor AK, Urban RM. Metal degradation products: a cause for concern in metal-metal bearings? *Clin Orthop.* 2003;417:139–47.
19. Hallab NJ, Jacobs JJ, Skipor A, Black J, Mikecz K, Galante JO. Systemic metal-protein binding associated with total joint replacement arthroplasty. *J Biomed Mater Res.* 2000;49(3):353–61.
20. Merritt K, Brown SA. Release of hexavalent chromium from corrosion of stainless steel and cobalt-chromium alloys. *J Biomed Mater Res.* 1995;29(5):627–33.
21. Lewis AC, Heard PJ. The effects of calcium phosphate deposition upon corrosion of CoCr alloys and the potential for implant failure. *J Biomed Mater Res A.* 2005;75(2):365–73.
22. Case CP, Langkamer VG, James C, Palmer MR, Kemp AJ, Heap PF, Solomon L. Widespread dissemination of metal debris from implants. *J Bone Joint Surg Br.* 1994;76B:701–12.
23. Olmedo DG, Tasat D, Guglielmotti MB, Cabrini RL. Titanium transport through the blood stream. An experimental study on rats. *J Mater Sci Mater Med.* 2003;14(12):1099–103.
24. Urban RM, Jacobs JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoc'h M. Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. *J Bone Joint Surg Am.* 2000;82A:457–76.
25. Caicedo MS, Desai R, McAllister K, Reddy A, Jacobs JJ, Hallab NJ. Soluble and particulate Co-Cr-Mo alloy implant metals activate the inflammasome danger signaling pathway in human macrophages: a novel mechanism for implant debris reactivity. *J Orthop Res.* 2009;27(7):847–54.
26. Shukla R, Bansal V, Chaudhary M, Basu A, Bhonde RR, Sastry M. Biocompatibility of gold nanoparticles and their endocytotic fate inside the cellular compartment: a microscopic overview. *Langmuir.* 2005;21(23):10644–54.
27. Messer RL, Lucas LC. Localization of metallic ions with gingival fibroblast subcellular fractions. *J Biomed Mater Res.* 2002;59(3):466–72.
28. Chen H, Davidson T, Singleton S, Garrick MD, Costa M. Nickel decreases cellular iron level and converts cytosolic aconitase to iron-regulatory protein 1 in A549 cells. *Toxicol Appl Pharmacol.* 2005;206(3):275–87.
29. Forbes JR, Gros P. Iron, manganese, and cobalt transport by Nramp1 (Slc11a1) and Nramp2 (Slc11a2) expressed at the plasma membrane. *Blood.* 2003;102(5):1884–92.
30. Trindade MC, Lind M, Sun D, Schurman DJ, Goodman SB, Smith RL. In vitro reaction to orthopaedic biomaterials by macrophages and lymphocytes isolated from patients undergoing revision surgery. *Biomaterials.* 2001;22(3):253–9.
31. Clodfelder BJ, Vincent JB. The time-dependent transport of chromium in adult rats from the bloodstream to the urine. *J Biol Inorg Chem.* 2005;10(4):383–93.
32. Pérez G, Garbossa G, Di Risio C, Vittori D, Nesse A. Disturbance of cellular iron uptake and utilisation by aluminium. *J Inorg Biochem.* 2001;87(1–2):21–7.
33. De Cremer K, Van Hulle M, Chéry C, Cornelis R, Strijckmans K, Dams R, Lameire N, Vanholder R. Fractionation of vanadium complexes in serum, packed cells and tissues of Wistar rats by means of gel filtration and anion-exchange chromatography. *J Biol Inorg Chem.* 2002;7(7–8):884–90.
34. Soloviev A, Schwarz EM, Darowish M, O'Keefe RJ. Sphingomyelinase mediates macrophage activation by titanium particles independent of phagocytosis: a role for free radicals, NFκB, and TNFα. *J Orthop Res.* 2005;23(6):1258–65.
35. Kwon YM, Xia Z, Glyn-Jones S, Beard D, Gill HS, Murray DW. Dose-dependent cytotoxicity of clinically relevant cobalt nanoparticles and ions on macrophages in vitro. *Biomed Mater.* 2009;4(2):025018.
36. Papageorgiou I, Brown C, Schins R, Singh S, Newson R, Davis S, Fisher J, Ingham E, Case CP. The effect of nano- and micron-sized particles of cobalt-chromium alloy on human fibroblasts in vitro. *Biomaterials.* 2007;28(19):2946–58.
37. Dizdaroglu M, Jaruga P, Birincioglu M, Rodriguez H. Free radical-induced damage to DNA: mechanisms and measurement. *Free Radic Biol Med.* 2002;32(11):1102–15.
38. Karovic O, Tonazzini I, Rebola N, Edström E, Lövdahl C, Fredholm BB, Daré E. Toxic effects of cobalt in primary cultures of mouse astrocytes. Similarities with hypoxia and role of HIF-1α. *Biochem Pharmacol.* 2007;73(5):694–708.
39. Germain MA, Hatton A, Williams S, Matthews JB, Stone MH, Fisher J, Ingham E. Comparison of the cytotoxicity of clinically relevant cobalt-chromium and alumina ceramic wear particles in vitro. *Biomaterials.* 2003;24(3):469–79.
40. Hallab NJ, Anderson S, Caicedo M, Brasher A, Mikecz K, Jacobs JJ. Effects of soluble metals on

- human peri-implant cells. *J Biomed Mater Res A*. 2005;74(1):124–40.
41. Hanawa T, Kaga M, Itoh Y, Echizenya T, Oguchi H, Ota M. Cytotoxicities of oxides, phosphates and sulphides of metals. *Biomaterials*. 1992;13(1):20–4.
 42. Doorn PF, Mirra JM, Campbell PA, Amstutz HC. Tissue reaction to metal on metal total hip prostheses. *Clin Orthop*. 1996;329:S187–205.
 43. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Köster G, Lohmann CH. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am*. 2005;87A:28–36.
 44. Davies AP, Willert HG, Campbell PA, Learmonth ID, Case CP. An unusual lymphocytic perivascular infiltration in tissues around contemporary metal-on-metal joint replacements. *J Bone Joint Surg Am*. 2005;87A:18–27.
 45. Boss JH, Misselevich I, Behar J, Mendes DG. Histologic analysis of the periprosthetic tissues of long-term surviving cemented total hip arthroplasties. *J Long Term Eff Med Implants*. 1996;6(2):73–90.
 46. Willert H, Buchhorn G, Fayyazi A, Lohmann C. Histopathological changes around metal/metal joints indicate delayed type hypersensitivity. Primary results of 14 cases. *Osteologie*. 2000;9:2–16.
 47. Hallab NJ, Mikecz K, Vermes C, Skipor A, Jacobs JJ. Orthopaedic implant related metal toxicity in terms of human lymphocyte reactivity to metal-protein complexes produced from cobalt-base and titanium-base implant alloy degradation. *Mol Cell Biochem*. 2001;222(1–2):127–36.
 48. Tkaczyk C, Huk OL, Mwale F, Antoniou J, Zukor DJ, Petit A, Tabrizian M. Investigation of the binding of Cr(III) complexes to bovine and human serum proteins: a proteomic approach. *J Biomed Mater Res A*. 2010;94(1):214–22.
 49. Goodman SB. Wear particles, periprosthetic osteolysis and the immune system. *Biomaterials*. 2007;28(34):5044–8.
 50. Catelas I, Wimmer MA. New insights into wear and biological effects of metal-on-metal bearings. *J Bone Joint Surg Am*. 2011;93 Suppl 2:76–83.
 51. Pandit H, Vlychou M, Whitwell D, Crook D, Luqmani R, Ostlere S, Murray DW, Athanasou NA. Necrotic granulomatous pseudotumours in bilateral resurfacing hip arthroplasties: evidence for a type IV immune response. *Virchows Arch*. 2008;453(5):529–34.
 52. Aroukatos P, Repanti M, Repantis T, Bravou V, Korovessis P. Immunologic adverse reaction associated with low-carbide metal-on-metal bearings in total hip arthroplasty. *Clin Orthop*. 2010;468(8):135–42.
 53. Kalish RS, Askenase PW. Molecular mechanisms of CD8+ T cell-mediated delayed hypersensitivity: implications for allergies, asthma, and autoimmunity. *J Allergy Clin Immunol*. 1999;103:192–9.
 54. Ng VY, Lombardi Jr AV, Berend KR, Skeels MD, Adams JB. Perivascular lymphocytic infiltration is not limited to metal-on-metal bearings. *Clin Orthop*. 2011;469(2):523–9.
 55. Hart AJ, Skinner JA, Winship P, Faria N, Kulinskaya E, Webster D, Muirhead-Allwood S, Aldam CH, Anwar H, Powell JJ. Circulating levels of cobalt and chromium from metal-on-metal hip replacement are associated with CD8+ T-cell lymphopenia. *J Bone Joint Surg Br*. 2009;91B:835–42.
 56. Granchi D, Savarino L, Ciapetti G, Cenni E, Rotini R, Mieti M, Baldini N, Giunti A. Immunological changes in patients with primary osteoarthritis of the hip after total joint replacement. *J Bone Joint Surg Br*. 2003;85B:758–64.
 57. LaFuppa JA, McAdams TA, Papoutsakis ET, Miller WM. Culture materials affect ex vivo expansion of hematopoietic progenitor cells. *J Biomed Mater Res*. 1997;36(3):347–59.
 58. Savarino L, Granchi D, Ciapetti G, Stea S, Donati ME, Zinghi G, Fontanesi G, Rotini R, Montanaro L. Effects of metal ions on white blood cells of patients with failed total joint arthroplasties. *J Biomed Mater Res*. 1999;47(4):543–50.
 59. Pawelec G, Gouttefangeas C. T-cell dysregulation caused by chronic antigenic stress: the role of CMV in immunosenescence? *Aging Clin Exp Res*. 2006;18(2):171–3.
 60. Vasto S, Colonna-Romano G, Larbi A, Wikby A, Caruso C, Pawelec G. Role of persistent CMV infection in configuring T cell immunity in the elderly. *Immun Ageing*. 2007;4:2.
 61. Lloyd DR, Phillips DH, Carmichael PL. Generation of putative intrastrand cross-links and strand breaks in DNA by transition metal ion-mediated oxygen radical attack. *Chem Res Toxicol*. 1997;10(4):393–400.
 62. Witkiewicz-Kucharczyk A, Bal W. Damage of zinc fingers in DNA repair proteins, a novel molecular mechanism in carcinogenesis. *Toxicol Lett*. 2006;162(1):29–42.
 63. Daley B, Doherty AT, Fairman B, Case CP. Wear debris from hip or knee replacements causes chromosomal damage in human cells in tissue culture. *J Bone Joint Surg Br*. 2004;86B:598–606.
 64. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact*. 2006;160(1):1–40.
 65. Zhitkovich A, Shrager S, Messer J. Reductive metabolism of Cr(VI) by cysteine leads to the formation of binary and ternary Cr–DNA adducts in the absence of oxidative DNA damage. *Chem Res Toxicol*. 2000;13(11):1114–24.
 66. Xu J, Bublely GJ, Detrick B, Blankenship LJ, Patierno SR. Chromium (VI) treatment of normal human lung cells results in guanine-specific DNA polymerase arrest, DNA–DNA cross-links and S-phase blockade of cell cycle. *Carcinogenesis*. 1996;17(7):1511–7.
 67. Bridgewater LC, Manning FC, Patierno SR. Base-specific arrest of in vitro DNA replication by carcinogenic chromium: relationship to DNA interstrand crosslinking. *Carcinogenesis*. 1994;15(11):2421–7.

68. Bagchi D, Stohs SJ, Downs BW, Bagchi M, Preuss HG. Cytotoxicity and oxidative mechanisms of different forms of chromium. *Toxicology*. 2002;180(1):5–22.
69. Seoane AI, Dulout FN. Genotoxic ability of cadmium, chromium and nickel salts studied by kinetochore staining in the cytokinesis-blocked micronucleus assay. *Mutat Res*. 2001;490(2):99–106.
70. Singh J, Snow ET. Chromium(III) decreases the fidelity of human DNA polymerase beta. *Biochemistry*. 1998;37(26):9371–8.
71. Bal W, Schwerdtle T, Hartwig A. Mechanism of nickel assault on the zinc finger of DNA repair protein XPA. *Chem Res Toxicol*. 2003;16(2):242–8.
72. Kopera E, Schwerdtle T, Hartwig A, Bal W. Co(II) and Cd(II) substitute for Zn(II) in the zinc finger derived from the DNA repair protein XPA, demonstrating a variety of potential mechanisms of toxicity. *Chem Res Toxicol*. 2004;17(11):1452–8.
73. De Boeck M, Lombaert N, De Backer S, Finsy R, Lison D, Kirsch-Volders M. In vitro genotoxic effects of different combinations of cobalt and metallic carbide particles. *Mutagenesis*. 2003;18(2):177–86.
74. Hartwig A. Carcinogenicity of metal compounds: possible role of DNA repair inhibition. *Toxicol Lett*. 1998;102–103:235–9.
75. Chen F, Shi X. Intracellular signal transduction of cells in response to carcinogenic metals. *Crit Rev Oncol Hematol*. 2002;42(1):105–21.
76. Harris GK, Shi X. Signaling by carcinogenic metals and metal-induced reactive oxygen species. *Mutat Res*. 2003;533(1–2):183–200.
77. Ramírez P, Eastmond DA, Laclette JP, Ostrosky-Wegman P. Disruption of microtubule assembly and spindle formation as a mechanism for the induction of aneuploid cells by sodium arsenite and vanadium pentoxide. *Mutat Res*. 1997;386(3):291–8.
78. Doherty AT, Howell RT, Ellis LA, Bisbinas I, Learmonth ID, Newson R, Case CP. Increased chromosome translocations and aneuploidy in peripheral blood lymphocytes of patients having revision arthroplasty of the hip. *J Bone Joint Surg Br*. 2001;83B:1075–81.
79. Case CP. Chromosomal changes after surgery for joint replacement. *J Bone Joint Surg Br*. 2001;83:1093–5.
80. Case CP, Langkamer VG, Howell RT, Webb J, Standen G, Palmer M, Kemp A, Learmonth ID. Preliminary observations on possible premalignant changes in bone marrow adjacent to worn total hip arthroplasty implants. *Clin Orthop*. 1996;329:S269–79.
81. Ladon D, Doherty A, Newson R, Turner J, Bhamra M, Case CP. Changes in metal levels and chromosome aberrations in the peripheral blood of patients after metal-on-metal hip arthroplasty. *J Arthroplasty*. 2004;19(8 Suppl 3):78–83.
82. Massè A, Bosetti M, Buratti C, Visentin O, Bergadano D, Cannas M. Ion release and chromosomal damage from total hip prostheses with metal-on-metal articulation. *J Biomed Mater Res B*. 2003;67(2):750–7.
83. Davies AP, Sood A, Lewis AC, Newson R, Learmonth ID, Case CP. Metal-specific differences in levels of DNA damage caused by synovial fluid recovered at revision arthroplasty. *J Bone Joint Surg Br*. 2005;87B:1439–44.
84. Dunstan E, Ladon D, Whittingham-Jones P, Carrington R, Briggs TW. Chromosomal aberrations in the peripheral blood of patients with metal-on-metal hip bearings. *J Bone Joint Surg Am*. 2008;90A:517–22.
85. Tsaousi A, Jones E, Case CP. The in vitro genotoxicity of orthopaedic ceramic (Al₂O₃) and metal (CoCr alloy) particles. *Mutat Res*. 2010;697(1–2):1–9.
86. Barrett WP, Kindsfater KA, Lesko JP. Large-diameter modular metal-on-metal total hip arthroplasty: incidence of revision for adverse reaction to metallic debris. *J Arthroplasty*. 2012;27A(6):976–83.e1.
87. Engh Jr CA, Ho H, Engh CA. Metal-on-metal hip arthroplasty: does early clinical outcome justify the chance of an adverse local tissue reaction? *Clin Orthop*. 2010;468:406–12.
88. Grammatopolous G, Pandit H, Kwon YM, Gundler R, McLardy-Smith P, Beard DJ, Murray DW, Gill HS. Hip resurfacings revised for inflammatory pseudotumour have a poor outcome. *J Bone Joint Surg Br*. 2009;91B:1019–24.
89. Cipriano CA, Issack PS, Beksac B, Della Valle AG, Sculco TP, Salvati EA. Metallosis after metal-on-polyethylene total hip arthroplasty. *Am J Orthop*. 2008;37(2):E18–25.
90. Campbell P, Shimmin A, Walter L, Solomon M. Metal sensitivity as a cause of groin pain in metal-on-metal hip resurfacing. *J Arthroplasty*. 2008;23(7):1080–5.
91. Browne JA, Bechtold CD, Berry DJ, Hanssen AD, Lewallen DG. Failed metal-on-metal hip arthroplasties: a spectrum of clinical presentations and operative findings. *Clin Orthop*. 2010;468:2313–20.
92. Watters TS, Cardona DM, Menon KS, Vinson EN, Bolognesi MP, Dodd LG. Aseptic lymphocyte-dominated vasculitis-associated lesion: a clinicopathologic review of an underrecognized cause of prosthetic failure. *Am J Clin Pathol*. 2010;134(6):886–93.
93. Carli A, Reuven A, Zukor DJ, Antoniou J. Adverse soft-tissue reactions around non-metal-on-metal total hip arthroplasty – a systematic review of the literature. *Bull NYU Hosp Jt Dis*. 2011;69:S47–51.
94. Milosev I, Trebse R, Kovac S, Cör A, Pisot V. Survivorship and retrieval analysis of Sikomet metal-on-metal total hip replacements at a mean of seven years. *J Bone Joint Surg Am*. 2006;88A:1173–82.
95. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am*. 2001;83A:428–36.
96. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natsu S, Nargol AV. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: a consequence of excess wear. *J Bone Joint Surg Br*. 2010;92B:38–46.

97. Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, Ostlere S, Athanasou N, Gill HS, Murray DW. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br.* 2008;90B:847–51.
98. Ollivere B, Darrah C, Barker T, Nolan J, Porteous MJ. Early clinical failure of the Birmingham metal-on-metal hip resurfacing is associated with metallosis and soft-tissue necrosis. *J Bone Joint Surg Br.* 2009;91B:1025–30.
99. Fricka KB, Engh Jr CA, Hamilton WG, et al. Metal on metal bearing surfaces. Pathologically confirmed metal-on-metal THA adverse local tissue reactions from one center. Podium Presentation 066, AAOS, San Diego, 2011
100. Park YS, Moon YW, Lim SJ, et al. Metal on metal bearing surfaces. Osteolysis following cementless total hip arthroplasty with a contemporary metal-on-metal bearing. Podium Presentation 063, AAOS, San Diego, 2011
101. Barnett CD, Peters CL, Erickson J, et al. Metal on metal bearing surfaces. Short-term results of large diameter metal on metal total hip arthroplasty. Podium Presentation 061, AAOS, San Diego, 2011
102. Hart AJ, Satchithananda K, Liddle AD, Sabah SA, McRobbie D, Henckel J, Cobb JP, Skinner JA, Mitchell AW. Pseudotumors in association with well-functioning metal-on-metal hip prostheses: a case-control study using three-dimensional computed tomography and magnetic resonance imaging. *J Bone Joint Surg Am.* 2012;94A:317–25.
103. Jeffers JR, Roques A, Taylor A, Tuke MA. The problem with large diameter metal-on-metal acetabular cup inclination. *Bull NYU Hosp Jt Dis.* 2009;67(2):189–92.
104. Fricka KB, Ho H, Peace WJ, Engh Jr CA. Metal-on-metal local tissue reaction is associated with corrosion of the head taper junction. *J Arthroplasty.* 2012;27(8 Suppl):26–31.e1.
105. Griffiths HJ, Burke J, Bonfiglio TA. Granulomatous pseudotumors in total joint replacement. *Skeletal Radiol.* 1987;16(2):146–52.
106. Daniel J, Holland J, Quigley L, Sprague S, Bhandari M. Pseudotumors associated with total hip arthroplasty. *J Bone Joint Surg Am.* 2012;94A:86–93.
107. Glyn-Jones S, Pandit H, Kwon YM, Doll H, Gill HS, Murray DW. Risk factors for inflammatory pseudotumour formation following hip resurfacing. *J Bone Joint Surg Br.* 2009;91B:1566–74.
108. Kwon YM, Ostlere SJ, McLardy-Smith P, Athanasou NA, Gill HS, Murray DW. “Asymptomatic” pseudotumors after metal-on-metal hip resurfacing arthroplasty: prevalence and metal ion study. *J Arthroplasty.* 2011;26(4):511–8.
109. Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ. Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. *Clin Orthop.* 2012;470(7):1895–906.
110. Donell ST, Darrah C, Nolan JF, Wimhurst J, Toms A, Barker TH, Case CP, Tucker JK. Norwich Metal-on-Metal Study Group. Early failure of the Ultima metal-on-metal total hip replacement in the presence of normal plain radiographs. *J Bone Joint Surg Br.* 2010;92B:1501–8.
111. Kwon YM, Thomas P, Summer B, Pandit H, Taylor A, Beard D, Murray DW, Gill HS. Lymphocyte proliferation responses in patients with pseudotumors following metal-on-metal hip resurfacing arthroplasty. *J Orthop Res.* 2010;28(4):444–50.
112. Xia Z, Kwon YM, Mehmood S, Downing C, Jurkschat K, Murray DW. Characterization of metal-wear nanoparticles in pseudotumor following metal-on-metal hip resurfacing. *Nanomedicine.* 2011;7(6):674–81.
113. Neuerburg C, Impellizzeri F, Goldhahn J, Frey P, Naal FD, von Knoch M, Leunig M, von Knoch F. Survivorship of second-generation metal-on-metal primary total hip replacement. *Arch Orthop Trauma Surg.* 2012;132(4):527–33.
114. Eswaramoorthy V, Moonot P, Kalairajah Y, Biant LC, Field RE. The Metasul metal-on-metal articulation in primary total hip replacement: clinical and radiological results at ten years. *J Bone Joint Surg Br.* 2008;90B:1278–83.
115. Korovessis P, Petsinis G, Repanti M, Repantis T. Metallosis after contemporary metal-on-metal total hip arthroplasty. Five to nine-year follow-up. *J Bone Joint Surg Am.* 2006;88A:1183–91.
116. Dorr LD, Wan Z, Sirianni LE, Boutary M, Chandran S. Fixation and osteolysis with Metasul metal-on-metal articulation. *J Arthroplasty.* 2004;19(8):951–5.
117. St John KR, Zardiackas LD, Poggie RA. Wear evaluation of cobalt-chromium alloy for use in a metal-on-metal hip prosthesis. *J Biomed Mater Res B.* 2004;68(1):1–14.
118. Berry DJ, Harmsen WS, Cabanela ME, Morrey BF. Twenty-five-year survivorship of two thousand consecutive primary Charnley total hip replacements: factors affecting survivorship of acetabular and femoral components. *J Bone Joint Surg Am.* 2002;84A:171–7.
119. Archibeck MJ, Berger RA, Jacobs JJ, Quigley LR, Gitelis S, Rosenberg AG, Galante JO. Second-generation cementless total hip arthroplasty. Eight to eleven-year results. *J Bone Joint Surg Am.* 2001;83A:1666–73.
120. Lusty PJ, Tai CC, Sew-Hoy RP, Walter WL, Walter WK, Zicat BA. Third-generation alumina-on-alumina ceramic bearings in cementless total hip arthroplasty. *J Bone Joint Surg Am.* 2007;89A:2676–83.
121. New Zealand National Registry. 2012. <http://www.cdhb.govt.nz/njr/reports/A2D65CA3.pdf>
122. Australian Orthopaedic Association. National joint replacement. Annual report 2011. Adelaide: Australian Orthopaedic Association. <http://www.dmac.adelaide.edu.au/aoanjirr/publications.jsp?sectionreports>
123. Jacobs JJ, Hallab NJ. Loosening and osteolysis associated with metal-on-metal bearings: a local effect of metal hypersensitivity? *J Bone Joint Surg Am.* 2006;88A:1171–2.
124. Shanbhag AS, Jacobs JJ, Black J, Galante JO, Glant TT. Macrophage/particle interactions: effect of size,

- composition and surface area. *J Biomed Mater Res.* 1994;28(1):81–90.
125. Cadosch D, Chan E, Gautschi OP, Filgueira L. Metal is not inert: role of metal ions released by biocorrosion in aseptic loosening—current concepts. *J Biomed Mater Res A.* 2009;91(4):1252–62.
 126. Fanti P, Kindy MS, Mohapatra S, Klein J, Colombo G, Malluche HH. Dose-dependent effects of aluminum on osteocalcin synthesis in osteoblast-like ROS 17/2 cells in culture. *Am J Physiol.* 1992;263(6 Pt 1):E1113–8.
 127. Thompson GJ, Puleo DA. Effects of sublethal metal ion concentrations on osteogenic cells derived from bone marrow stromal cells. *J Appl Biomater.* 1995;6(4):249–58.
 128. Yao J, Cs-Szabó G, Jacobs JJ, Kuettner KE, Glant TT. Suppression of osteoblast function by titanium particles. *J Bone Joint Surg Am.* 1997;79A:107–12.
 129. Zijlstra WP, Bulstra SK, van Raay JJ, van Leeuwen BM, Kuijjer RJ. Cobalt and chromium ions reduce human osteoblast-like cell activity in vitro, reduce the OPG to RANKL ratio, and induce oxidative stress. *J Orthop Res.* 2012;30(5):740–7.
 130. Queally JM, Devitt BM, Butler JS, Malizia AP, Murray D, Doran PP, O’Byrne JM. Cobalt ions induce chemokine secretion in primary human osteoblasts. *J Orthop Res.* 2009;27(7):855–64.
 131. Andrews RE, Shah KM, Wilkinson JM, Gartland A. Effects of cobalt and chromium ions at clinically equivalent concentrations after metal-on-metal hip replacement on human osteoblasts and osteoclasts: implications for skeletal health. *Bone.* 2011;49(4):717–23.
 132. Donaldson JR, Miles J, Sri-Ram K, Poullis C, Muirhead-Allwood S, Skinner J. The relationship between the presence of metallosis and massive infection in metal-on-metal hip replacements. *Hip Int.* 2010;20(2):242–7.
 133. Judd KT, Noiseux N. Concomitant infection and local metal reaction in patients undergoing revision of metal on metal total hip arthroplasty. *Iowa Orthop J.* 2011;31:59–63.
 134. Anwar HA, Aldam CH, Visuvanathan S, Hart AJ. The effect of metal ions in solution on bacterial growth compared with wear particles from hip replacements. *J Bone Joint Surg Br.* 2007;89B:1655–9.
 135. Hosman AH, van der Mei HC, Bulstra SK, Busscher HJ, Neut D. Effects of metal-on-metal wear on the host immune system and infection in hip arthroplasty. *Acta Orthop Scand.* 2010;81(5):526–34.
 136. Ferreira ME, de Lourdes Pereira M, Garcia e Costa F, Sousa JP, de Carvalho GS. Comparative study of metallic biomaterials toxicity: a histochemical and immunohistochemical demonstration in mouse spleen. *J Trace Elem Med Biol.* 2003;17(1):45–9.
 137. Hosman AH, van der Mei HC, Bulstra SK, Kuijjer R, Busscher HJ, Neut D. Influence of Co-Cr particles and Co-Cr ions on the growth of staphylococcal biofilms. *Int J Artif Organs.* 2011;34(9):759–65.
 138. Baker-Austin C, Wright MS, Stepanauskas R, McArthur JV. Co-selection of antibiotic and metal resistance. *Trends Microbiol.* 2006;14(4):176–82.
 139. Vittori D, Nesse A, Pérez G, Garbossa G. Morphologic and functional alterations of erythroid cells induced by long-term ingestion of aluminium. *J Inorg Biochem.* 1999;76(2):113–20.
 140. Ani M, Moshtaghi AA. The effect of chromium on parameters related to iron metabolism. *Biol Trace Elem Res.* 1992;32:57–64.
 141. Bazzoni GB, Bollini AN, Hernández GN, Contini Mdel C, Chiarotto MM, Rasia ML. In vivo effect of aluminium upon the physical properties of the erythrocyte membrane. *J Inorg Biochem.* 2005;99(3):822–7.
 142. Tkeshelashvili LK, Tsakadze KJ, Khulusauri OV. Effect of some nickel compounds on red blood cell characteristics. *Biol Trace Elem Res.* 1989;21:337–42.
 143. Bregoli L, Chiarini F, Gambarelli A, Sighinolfi G, Gatti AM, Santi P, Martelli AM, Cocco L. Toxicity of antimony trioxide nanoparticles on human hematopoietic progenitor cells and comparison to cell lines. *Toxicology.* 2009;262(2):121–9.
 144. Peters K, Unger RE, Gatti AM, Sabbioni E, Tsaryk R, Kirkpatrick CJ. Metallic nanoparticles exhibit paradoxical effects on oxidative stress and pro-inflammatory response in endothelial cells in vitro. *Int J Immunopathol Pharmacol.* 2007;20(4):685–95.
 145. Wilson MR, Lightbody JH, Donaldson K, Sales J, Stone V. Interactions between ultrafine particles and transition metals in vivo and in vitro. *Toxicol Appl Pharmacol.* 2002;184(3):172–9.
 146. Kurosaki K, Nakamura T, Mukai T, Endo T. Unusual findings in a fatal case of poisoning with chromate compounds. *Forensic Sci Int.* 1985;75(1):57–65.
 147. Kametani K, Nagata T. Quantitative elemental analysis on aluminum accumulation by HVTEM-EDX in liver tissues of mice orally administered with aluminum chloride. *Med Mol Morphol.* 2006;39(2):97–105.
 148. Wang JX, Fan YB, Gao Y, Hu QH, Wang TC. TiO₂ nanoparticles translocation and potential toxicological effect in rats after intraarticular injection. *Biomaterials.* 2009;30(27):4590–600.
 149. Urban RM, Tomlinson MJ, Hall DJ, Jacobs JJ. Accumulation in liver and spleen of metal particles generated at nonbearing surfaces in hip arthroplasty. *J Arthroplasty.* 2004;19(8 Suppl 3):94–101.
 150. Shrivastava K, Ram MS, Bansal A, Singh SS, Ilavazhagan G. Cobalt supplementation promotes hypoxic tolerance and facilitates acclimatization to hypobaric hypoxia in rat brain. *High Alt Med Biol.* 2008;9(1):63–75.
 151. Ohtomo S, Nangaku M, Izuhara Y, Takizawa S, Strihou CY, Miyata T. Cobalt ameliorates renal injury in an obese, hypertensive type 2 diabetes rat model. *Nephrol Dial Transplant.* 2008;23(4):1166–72.
 152. Oliveira H, Santos TM, Ramalho-Santos J, de Lourdes Pereira M. Histopathological effects of

- hexavalent chromium in mouse kidney. *Bull Environ Contam Toxicol.* 2006;76(6):977–83.
153. Barceloux DG. Chromium. *J Toxicol Clin Toxicol.* 1999;37(2):173–94.
154. Bonde JP, Vittinghus E. Urinary excretion of proteins among metal welders. *Hum Exp Toxicol.* 1999;15(1):1–4.
155. Newton AW, Ranganath L, Armstrong C, Peter V, Roberts NB. Differential distribution of cobalt, chromium, and nickel between whole blood, plasma and urine in patients after metal-on-metal (mom) hip arthroplasty. *J Orthop Res.* 2012;30(10):1640–6.
156. Goyer RA. Toxic effects of metal. In: Klaassen CD, Amdur MO, Doull J, editors. *Toxicology: the basic science of poisons.* New York: McGraw-Hill; 1996. p. 691–736.
157. Oldenburg M, Wegner R, Baur X. Severe cobalt intoxication due to prosthesis wear in repeated total hip arthroplasty. *J Arthroplasty.* 2009;24(5):825.e15–20.
158. Ikeda T, Takahashi K, Kabata T, Sakagoshi D, Tomita K, Yamada M. Polyneuropathy caused by cobalt-chromium metallosis after total hip replacement. *Muscle Nerve.* 2010;42(1):140–3.
159. Rizzetti MC, Liberini P, Zarattini G, Catalani S, Pazzaglia U, Apostoli P, Padovani A. Loss of sight and sound. Could it be the hip? *Lancet.* 2009;373(9668):1052.
160. Mao X, Wong AA, Crawford RW. Cobalt toxicity – an emerging clinical problem in patients with metal-on-metal hip prostheses? *Med J Aust.* 2011;194(12):649–51.
161. Steens W, von Foerster G, Katzer A. Severe cobalt poisoning with loss of sight after ceramic-metal pairing in a hip – a case report. *Acta Orthop Scand.* 2006;77(5):830–2.
162. Tower SS. Arthroprosthetic cobaltism: neurological and cardiac manifestations in two patients with metal-on-metal arthroplasty: a case report. *J Bone Joint Surg Am.* 2010;92A:2847–51.
163. Pazzaglia UE, Apostoli P, Congiu T, Catalani S, Marchese M, Zarattini G. Cobalt, chromium and molybdenum ions kinetics in the human body: data gained from a total hip replacement with massive third body wear of the head and neuropathy by cobalt intoxication. *Arch Orthop Trauma Surg.* 2011;131(9):1299–308.
164. De Haan R, Pattyn C, Gill HS, Murray DW, Campbell PA, De Smet K. Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. *J Bone Joint Surg Br.* 2008;90B:1291–7.
165. Yokel RA. The toxicology of aluminum in the brain: a review. *Neurotoxicology.* 2000;21(5):813–28.
166. Savory J, Ghribi O. Can studies of aluminum toxicity in vivo and in vitro provide relevant information on the pathogenesis and etiology of Alzheimer's disease? *J Alzheimers Dis.* 2007;11(4):429–30; discussion 431–2.
167. Olivieri G, Novakovic M, Savaskan E, Meier F, Baysang G, Brockhaus M, Müller-Spahn F. The effects of beta-estradiol on SHSY5Y neuroblastoma cells during heavy metal induced oxidative stress, neurotoxicity and beta-amyloid secretion. *Neuroscience.* 2002;113(4):849–55.
168. Travacio M, Polo JM, Llesuy S. Chromium (VI) induces oxidative stress in the mouse brain. *Toxicology.* 2001;162(2):139–48.
169. Garcia GB, Biancardi ME, Quiroga AD. Vanadium (V)-induced neurotoxicity in the rat central nervous system: a histo-immunohistochemical study. *Drug Chem Toxicol.* 2005;28(3):329–44.
170. Soazo M, Garcia GB. Vanadium exposure through lactation produces behavioral alterations and CNS myelin deficit in neonatal rats. *Neurotoxicol Teratol.* 2007;29(4):503–10.
171. Afeseh Ngwa H, Kanthasamy A, Anantharam V, Song C, Witte T, Houk R, Kanthasamy AG. Vanadium induces dopaminergic neurotoxicity via protein kinase Cdelta dependent oxidative signaling mechanisms: relevance to etiopathogenesis of Parkinson's disease. *Toxicol Appl Pharmacol.* 2009;240(2):273–85.
172. Barth A, Schaffer AW, Konnaris C, Blauensteiner R, Winker R, Osterode W, Rüdiger HW. Neurobehavioral effects of vanadium. *J Toxicol Environ Health A.* 2002;65(9):677–83.
173. Nemery B. Metal toxicity and the respiratory tract. *Eur Respir J.* 1990;3(2):202–19.
174. Linna A, Oksa P, Groundstroem K, Halkosaari M, Palmroos P, Huikko S, Uitti J. Exposure to cobalt in the production of cobalt and cobalt compounds and its effect on the heart. *Occup Environ Med.* 2004;61(11):877–85.
175. Liu YK, Xu H, Liu F, Tao R, Yin J. Effects of serum cobalt ion concentration on the liver, kidney and heart in mice. *Orthop Surg.* 2010;2(2):134–40.
176. Frustaci A, Magnavita N, Chimenti C, Caldarulo M, Sabbioni E, Pietra R, Cellini C, Possati GF, Maseri A. Marked elevation of myocardial trace elements in idiopathic dilated cardiomyopathy compared with secondary cardiac dysfunction. *J Am Coll Cardiol.* 1999;33(6):1578–83.
177. Visuri T, Borg H, Pulkkinen P, Paavolainen P, Pukkala E. A retrospective comparative study of mortality and causes of death among patients with metal-on-metal and metal-on-polyethylene total hip prostheses in primary osteoarthritis after a long-term follow-up. *BMC Musculoskelet Disord.* 2010;11:78.
178. Lippmann M, Ito K, Hwang JS, Maciejczyk P, Chen LC. Cardiovascular effects of nickel in ambient air. *Environ Health Perspect.* 2006;114(11):1662–9.
179. Hsu SO, Ito K, Lippmann M. Effects of thoracic and fine PM and their components on heart rate and pulmonary function in COPD patients. *J Expo Sci Environ Epidemiol.* 2011;21(5):464–72.
180. Lu ZY, Gong H, Amemiya T. Aluminum chloride induces retinal changes in the rat. *Toxicol Sci.* 2002;66(2):253–60.

181. Licht A, Oliver M, Rachmilewitz EA. Optic atrophy following treatment with cobalt chloride in a patient with pancytopenia and hypercellular marrow. *Isr J Med Sci.* 1972;8(1):61–6.
182. Meecham HM, Humphrey P. Industrial exposure to cobalt causing optic atrophy and nerve deafness: a case report. *J Neurol Neurosurg Psychiatry.* 1991;54(4):374–5.
183. Schirrmacher UO. Case of cobalt poisoning. *Br Med J.* 1967;1(5539):544–5.
184. Brock T, Stopford W. Bioaccessibility of metals in human health risk assessment: evaluating risk from exposure to cobalt compounds. *J Environ Monit.* 2003;5(4):71N–6.
185. Lantin AC, Mallants A, Vermeulen J, Speybroeck N, Hoet P, Lison D. Absence of adverse effect on thyroid function and red blood cells in a population of workers exposed to cobalt compounds. *Toxicol Lett.* 2011;201(1):42–6.
186. Swennen B, Buchet JP, Stănescu D, Lison D, Lauwerys R. Epidemiological survey of workers exposed to cobalt oxides, cobalt salts, and cobalt metal. *Br J Ind Med.* 1993;50(9):835–42.
187. Prescott E, Netterstrøm B, Faber J, Hegedüs L, Suadicaní P, Christensen JM. Effect of occupational exposure to cobalt blue dyes on the thyroid volume and function of female plate painters. *Scand J Work Environ Health.* 1992;18(2):101–4.
188. Jeffery EH, Abreo K, Burgess E, Cannata J, Greger JL. Systemic aluminum toxicity: effects on bone, hematopoietic tissue, and kidney. *J Toxicol Environ Health.* 1996;48(6):649–5.
189. Watson CS, Jeng YJ, Kochukov MY. Nongenomic signaling pathways of estrogen toxicity. *Toxicol Sci.* 2010;115(1):1–11.
190. Darbre PD. Metalloestrogens: an emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. *J Appl Toxicol.* 2006;26(3):191–7.
191. Aruldas MM, Subramanian S, Sekar P, Vengatesh G, Chandrahasan G, Govindarajulu P, Akbarsha MA. Chronic chromium exposure-induced changes in testicular histoarchitecture are associated with oxidative stress: study in a non-human primate (*Macaca radiata Geoffroy*). *Hum Reprod.* 2005;20(10):2801–13.
192. Danadevi K, Rozati R, Reddy PP, Grover P. Semen quality of Indian welders occupationally exposed to nickel and chromium. *Reprod Toxicol.* 2003;17(4):451–6.
193. Li H, Chen Q, Li S, Xu Y, Yao W, Chen C. Studies on male reproductive toxicity caused by hexavalent chromium. *Zhonghua Yu Fang Yi Xue Za Zhi.* 1999;33(6):351–3 (Chinese).
194. Murthy RC, Junaid M, Saxena DK. Ovarian dysfunction in mice following chromium (VI) exposure. *Toxicol Lett.* 1996;89(2):147–54.
195. Anderson MB, Pedigo NG, Katz RP, George WJ. Histopathology of testes from mice chronically treated with cobalt. *Reprod Toxicol.* 1992;6(1):41–50.
196. Domingo JL. Vanadium: a review of the reproductive and developmental toxicity. *Reprod Toxicol.* 1996;10(3):175–82.
197. Jacobs JJ, Goodman SB, Sumner DR, Hallab NJ. Biologic response to orthopaedic implants. In: Buckwalter JA, Einhorn TA, Simon SR, editors. *Orthopaedic basic science: biology and biomechanics of the musculoskeletal system.* 2nd ed. Rosemont: American Academy of Orthopaedic Surgeons; 2000. p. 401–26.
198. Thyssen JP, Menné T. Metal allergy – a review on exposures, penetration, genetics, prevalence, and clinical implications. *Chem Res Toxicol.* 2010;23(2):309–18.
199. Merritt K, Brown SA. Distribution of cobalt chromium wear and corrosion products and biologic reactions. *Clin Orthop.* 1996;329:S233–43.
200. Thyssen JP, Jakobsen SS, Engkilde K, Johansen JD, Søballe K, Menné T. The association between metal allergy, total hip arthroplasty, and revision. *Acta Orthop Scand.* 2009;80(6):646–52.
201. Elves MW, Wilson JN, Scales JT, Kemp HB. Incidence of metal sensitivity in patients with total joint replacements. *Br Med J.* 1975;4(5993):376–8.
202. Merritt K, Rodrigo JJ. Immune response to synthetic materials. Sensitization of patients receiving orthopaedic implants. *Clin Orthop.* 1996;326:71–9.
203. Gawkrödger DJ. Metal sensitivities and orthopaedic implants revisited: the potential for metal allergy with the new metal-on-metal joint prostheses. *Br J Dermatol.* 2003;148(6):1089–93.
204. Thomas P, Braathen LR, Dörig M, Auböck J, Nestle F, Werfel T, Willert HG. Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. *Allergy.* 2009;64(8):1157–65.
205. Reed KB, Davis MD, Nakamura K, Hanson L, Richardson DM. Retrospective evaluation of patch testing before or after metal device implantation. *Arch Dermatol.* 2008;144(8):999–1007.
206. Basko-Plluska JL, Thyssen JP, Schalock PC. Cutaneous and systemic hypersensitivity reactions to metallic implants. *Dermatitis.* 2011;22(2):65–79.
207. Vermes C, Glant TT, Hallab NJ, Fritz EA, Roebuck KA, Jacobs JJ. The potential role of the osteoblast in the development of periprosthetic osteolysis: review of in vitro osteoblast responses to wear debris, corrosion products, and cytokines and growth factors. *J Arthroplasty.* 2001;16(8 Suppl 1):95–100.
208. Domingo JL. Metal-induced developmental toxicity in mammals: a review. *J Toxicol Environ Health.* 1994;42(2):123–41.
209. Elbetieha A, Al-Hamood MH. Long-term exposure of male and female mice to trivalent and hexavalent

- chromium compounds: effect on fertility. *Toxicology*. 1997;116(1-3):39-47.
210. Kanojia RK, Junaid M, Murthy RC. Embryo and fetotoxicity of hexavalent chromium: a long-term study. *Toxicol Lett*. 1998;95(3):165-72.
 211. Morgan AM, El-Tawil OS. Effects of ammonium metavanadate on fertility and reproductive performance of adult male and female rats. *Pharmacol Res*. 2003;47(1):75-85.
 212. Barceloux D. Cobalt. *J Toxicol Clin Toxicol*. 1999;37:201-16.
 213. Sierra RJ, Trousdale RT, Cabanela ME. Pregnancy and childbirth after total hip arthroplasty. *J Bone Joint Surg Br*. 2005;87(1):21-4.
 214. Stea S, Bordini B, De Clerico M, Traina F, Toni A. Safety of pregnancy and delivery after total hip arthroplasty. *J Womens Health*. 2007;16(9):1300-4.
 215. Meldrum R, Feinberg JR, Capello WN, Detterline AJ. Clinical outcome and incidence of pregnancy after bipolar and total hip arthroplasty in young women. *J Arthroplasty*. 2003;18(7):879-85.
 216. Brodner W, Grohs JG, Bancher-Todesca D, Dorotka R, Meisinger V, Gottsauner-Wolf F, Kotz R. Does the placenta inhibit the passage of chromium and cobalt after metal-on-metal total hip arthroplasty? *J Arthroplasty*. 2004;19(8 Suppl 3):102-6.
 217. Ziaee H, Daniel J, Datta AK, Blunt S, McMinn DJ. Transplacental transfer of cobalt and chromium in patients with metal-on-metal hip arthroplasty: a controlled study. *J Bone Joint Surg Br*. 2007;89B:301-5.
 218. de Souza RM, Wallace D, Costa ML, Krikler SJ. Transplacental passage of metal ions in women with hip resurfacing: no teratogenic effects observed. *Hip Int*. 2012;22(1):96-9.
 219. Brand KG. Do implanted medical devices cause cancer? *J Biomater Appl*. 1994;8:325.
 220. Memoli VA, Urban RM, Alroy J, Galante JO. Malignant neoplasms associated with orthopedic implant materials in rats. *J Orthop Res*. 1986;4(3):346-55.
 221. Kirkpatrick CJ, Alves A, Köhler H, Kriegsmann J, Bittinger F, Otto M, Williams DF, Eloy R. Biomaterial-induced sarcoma: a novel model to study preneoplastic change. *Am J Pathol*. 2000;156(4):1455-67.
 222. Brand KG, Brand I. Risk assessment of carcinogenesis at implantation sites. *Plast Reconstr Surg*. 1980;66(4):591-5.
 223. Doran A, Law FC, Allen MJ, Rushton N. Neoplastic transformation of cells by soluble but not particulate forms of metals used in orthopaedic implants. *Biomaterials*. 1998;19(7-9):751-9.
 224. Meachim G, Pedley RB, Williams DF. A study of sarcogenicity associated with Co-Cr-Mo particles implanted in animal muscle. *J Biomed Mater Res*. 1982;16(4):407-16.
 225. Lewis CG, Belniak RM, Plowman MC, Hopfer SM, Knight JA, Sunderman Jr FW. Intraarticular carcinogenesis bioassays of CoCrMo and TiAlV alloys in rats. *J Arthroplasty*. 1995;10(1):75-82.
 226. Weber A, Strehl A, Springer E, Hansen T, Schad A, Kirkpatrick CJ. Biomaterial-induced sarcomagenesis is not associated with microsatellite instability. *Virchows Arch*. 2009;454(2):195-201.
 227. French JE, Lacks GD, Trempus C, Dunnick JK, Foley J, Mahler J, Tice RR, Tennant RW. Loss of heterozygosity frequency at the Trp53 locus in p53-deficient (+/-) mouse tumors is carcinogen- and tissue-dependent. *Carcinogenesis*. 2001;22(1):99-106.
 228. Visuri T, Pulkkinen P, Paavolainen P. Malignant tumors at the site of total hip prosthesis. Analytic review of 46 cases. *J Arthroplasty*. 2006;21(3):311-23.
 229. Yoon PW, Jang WY, Yoo JJ, Yoon KS, Kim HJ. Malignant fibrous histiocytoma at the site of an alumina-on-alumina-bearing total hip arthroplasty mimicking infected trochanteric bursitis. *J Arthroplasty*. 2012;27(2):324.e9-12.
 230. Mallick A, Jain S, Proctor A, Pandey R. Angiosarcoma around a revision total hip arthroplasty and review of literature. *J Arthroplasty*. 2009;24(2):323.e17-20.
 231. Fabbri N, Rustemi E, Masetti C, Kreshak J, Gambarotti M, Vanel D, Toni A, Mercuri M. Severe osteolysis and soft tissue mass around total hip arthroplasty: description of four cases and review of the literature with respect to clinico-radiographic and pathologic differential diagnosis. *Eur J Radiol*. 2011;77(1):43-50.
 232. Lucas DR, Miller PR, Mott MP, Kronick JL, Unni KK. Arthroplasty-associated malignant fibrous histiocytoma: two case reports. *Histopathology*. 2001;39(6):620-8.
 233. Schuh A, Zeiler G, Holzwarth U, Aigner T. Malignant fibrous histiocytoma at the site of a total hip arthroplasty. *Clin Orthop*. 2004;425:218-22.
 234. Bauer HC, Alvegård TA, Berlin O, Erlanson M, Gustafson P, Kivioja A, Klepp R, Lehtinen T, Lindholm P, Möller TR, Rydholm A, Saeter G, Trovik CS, Wahlström O, Wiklund T. The Scandinavian Sarcoma Group Register. *Acta Orthop Scand*. 1999;285:S41-4.
 235. Cole P, Rodu B. Epidemiologic studies of chrome and cancer mortality: a series of meta-analyses. *Regul Toxicol Pharmacol*. 2005;43(3):225-31.
 236. Gillespie WJ, Frampton CMA, Henderson RJ, Ryan PM. The incidence of cancer following total hip replacement. *J Bone Joint Surg Br*. 1988;70B:539-42.
 237. Visuri T, Pukkala F, Paavolainen P, Pulkkinen P, Riska EB. Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. *Clin Orthop*. 1996;329:S280-9.

238. Visuri T, Koskenvuo M. Cancer risk after Mckee-Farrar total hip replacement. *Orthopaedics*. 1991;14(2):137–42.
239. Mathiesen EB, Ahlbom A, Bermann G, Lindgren JU. Total hip replacement and cancer. A cohort study. *J Bone Joint Surg Br*. 1995;77B:345–50.
240. Nyrén O, McLaughlin JK, Gridley G, Ekblom A, Johnell O, Fraumeni Jr JF, Adami HO. Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. *J Natl Cancer Inst*. 1995;87(1):28–33.
241. Visuri TI, Pukkala E, Pulkkinen P, Paavolainen P. Cancer incidence and causes of death among total hip replacement patients: a review based on Nordic cohorts with a special emphasis on metal-on-metal bearings. *Proc Inst Mech Eng H*. 2006;220(2):399–407.
242. Signorello LB, Ye W, Fryzek JP, Lipworth L, Fraumeni Jr JF, Blot WJ, McLaughlin JK, Nyrén O. Nationwide study of cancer risk among hip replacement patients in Sweden. *J Natl Cancer Inst*. 2001;93(18):1405–10.
243. Goldacre MJ, Wotton CJ, Seagroatt V, Yeates D. Cancer following hip and knee arthroplasty: record linkage study. *Br J Cancer*. 2005;92(7):1298–301.
244. Onega T, Baron J, MacKenzie T. Cancer after total joint arthroplasty: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006;15(8):1532–7.
245. Smith AJ, Dieppe P, Porter M, Blom AW. On behalf of the National Joint Registry of England and Wales. Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: linkage study between the National Joint Registry of England and Wales and hospital episode statistics. *Br Med J*. 2012;344:e2383.
246. IARC. Monographs on the evaluation of carcinogenic risk to humans. 2012. Available from: <http://monographs.iarc.fr/>.

Pavlos G. Katonis and Kalliopi I. Alpentaki

Biomechanics of Bone-Implant Interface

Biomechanics is the science that uses the principles of engineering and physics in order to solve various biologic problems. Regarding the spine, biomechanics aims at understanding the normal and pathological function of the spine as well as the way that various mechanisms and interpositions affect it. Spinal surgery affects the normal function of the spine; thus, a knowledge of biomechanics can help contribute to its recovery, mobility, and stability [1].

Basic Principles

The spine moves and acts in three axes (x -axis, y -axis, z -axis) enabling translational and rotational forces to be applied on them [2]. Moreover, the spine is subjected to various loads during spinal surgery, and force couples are created (Newton's third law of motion) resulting in the spinal segments being at risk of damage or failure [3]. More specifically, according to Newton's third law of motion, for every action, there is an equal (in magnitude) though opposite (in direction) reaction that affects the placement of an

implant [4, 5]. Since there is no movement in the spine during the placement of an implant, the forces applied to the spine are always in pairs so that the net result is zero. In fact, no spinal implant is placed in a neutral position because once upright posture is assumed, the implant is under some degree of stress and it must resist [3]. This factor should be taken into serious consideration during surgery and especially during the use or placement of materials, as there must be knowledge of the elastic properties of each material [4]. According to Hooke's law, when force is applied to a solid body, this body tends to be deformed [4, 5]. Based on this, the size of deformation or ectopia is proportional to the applied force [5].

Another important concept is section modulus, which is a figure that is calculated and used to define the resistance of an object [3]. Regarding the use of materials, section modulus can be used as an indicator to describe the overall resistance and possible failure of an implant. Section modulus is defined by the equation $Z=D^3$ (Z =section modulus and D =diameter). For example, section modulus or screw endurance is exponentially related to screw diameter [5]. Another important factor which is related to potential implant failure is the force applied to it (load, moment arm, bending moment): this is defined as $\Theta=M/Z$ (Θ =stress, M =bending moment, Z =section modulus) [5–7]. Finally, the stiffness of an implant is defined as its ability to resist deformation. In this case, stiffness is more affected by diameter than strength, and it increases when

P.G. Katonis, MD, DSc (✉) • K.I. Alpentaki, MD, DSc
Faculty of Medicine, University of Crete,
Iraklion, Crete 71003, 2208, Greece
e-mail: katonis@med.uoc.gr; katonis@hol.gr

diameter increases [2, 3]. It is defined by the equation $I = \pi \times D^4 / 16$ (I =inertia moment, D =diameter) [5].

Types of Bone-Implant Interface

Surgical implants should be designed based on biomechanical principles such as those mentioned above. At the same time, there must be knowledge of the forces applied during surgery. The new condition that arises and alters the mechanical structures must also be taken into account. This new condition is the interface between the implant and the bone, known as bone-implant interface [3, 5]. Implants can be made of various materials including metal, non-metal, and bone. Each material has certain properties that make it the most suitable for a particular surgery. The interface between the implant and the bone is very important to ensure stability [3]. In spinal surgery, there are five basic types of bone-implant interface: (1) abutting (e.g., interbody bone, interbody acrylic), (2) penetrating (e.g., nail, spike, screw), (3) gripping (e.g., hook, wire), (4) conforming (e.g., acrylic), and (5) osseointegration (e.g., titanium, ceramic) [5].

Abutting Bone-Implant Interface

The role of the interbody implant is to resist axial loads. The most frequent position where an abutting implant is applied is the interbody region. The main reason for this is that an abutting construction must bear a load in order to be effective [5]. The interbody region is the most appropriate since it is an approximate position of neutral axes where most of the axial load is applied [2].

Numerous experimental studies using calf or human cadaver spines have found that various types and designs of interbody fusion devices (IFD) have static and fatigue endurance much greater than the expected normal loads [8, 9]. Moreover, they exhibit good kinematic stability on segment movement under various loading forces [10–12]. Generally, abutting implants

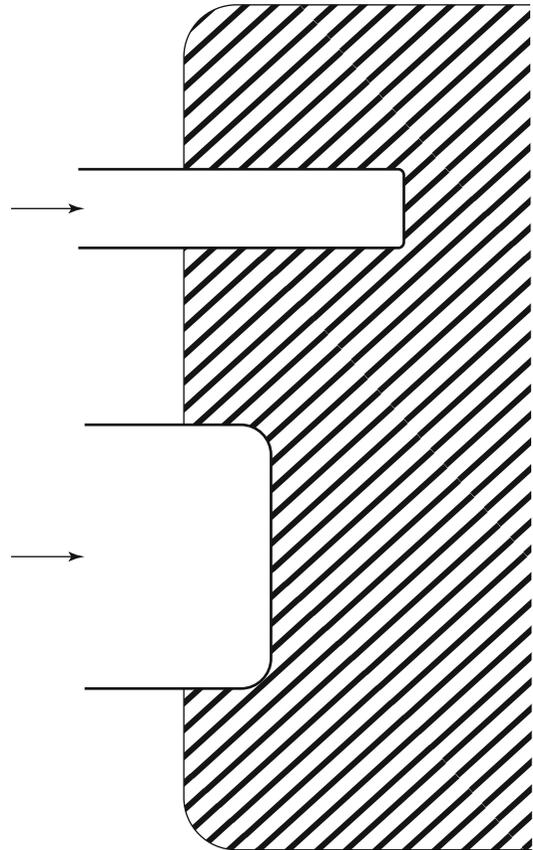


Fig. 20.1 An implant with small diameter penetrates farther, while an implant with larger diameter resists axial loading more effectively

distribute loading forces uniformly over a relatively large surface area due to their construction. Therefore, the larger the contact surface between the implant and the bone, the more effective is the resistance of the implant to axial forces. More specifically, the larger the circumference of the interbody abutting implant (bone, acrylic, etc.), the more effective is the implant regarding resistance to the applied axial loads [2] (Fig. 20.1). However, there are studies where, when both monotonic and dynamic compression forces were applied to the IFD-motion segment constructions, there was failure since the device subsided onto the adjacent vertebrae when the forces were greater than those applied during daily living [13, 14]. However, the presence and causes of such failure have not been adequately

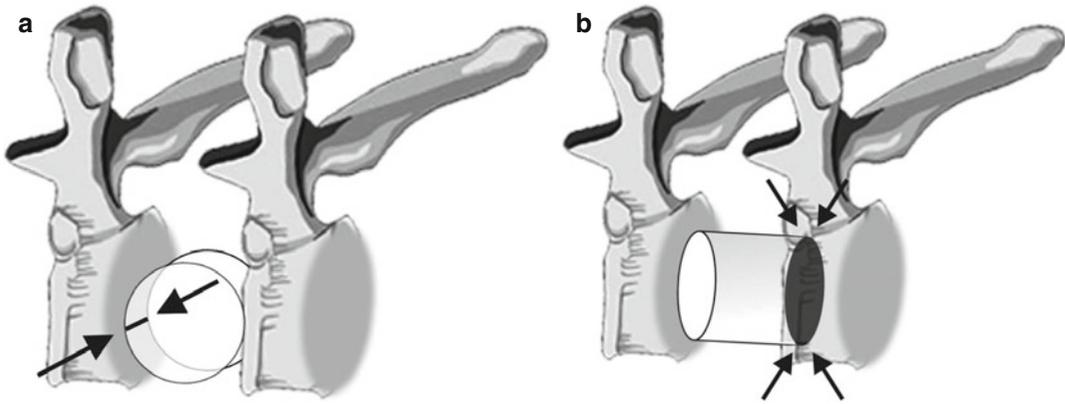


Fig. 20.2 (a) A round-faced interbody cage has a small area of contact. (b) A flat-faced cage has a large surface area of contact

clarified. Therefore, information on the biomechanics of this particular implant is limited. Subsidence and failure are the main concerns regarding these devices. Keeping interbody abutting implants in the desired interbody position is the main aim [15]. This is the reason why the use of an additional graft, such as an interbody acrylic implant, is required. This implant penetrates the end plates of the adjacent vertebrae with a rigid wire stabilizer reducing the possibility of implant displacement. The Rezaian spinal fixator and bone graft struts can be used for the same reason [3].

Finally, this category includes cage implants which can contact the vertebral body end plate in two ways, with either its flat surface or its convex surface. A flat-faced interbody cage has a large surface area of contact with the end plate, while a round-faced cage has a very small area of contact with the end plate. Generally, the use of interbody fusion cages has increased dramatically over the last few years [10, 16] (Fig. 20.2). Usually, they are combined with allograft bone, autograft bone, or bone substitutes to facilitate fusion and to provide a stable biomechanical construction. It has also been shown that interbody fusion using a PT-ring cage packed with autologous bone achieves higher interface healing and more reliable fusion when it is fixated with supplementary pedicle screws than when it is fixated anteriorly with two staples [17].

There are several types of cage including threaded titanium cylinders, vertical titanium mesh cages, and impacted box or wedge-shaped cages. Despite the continuously increasing use of cages, there is very little implant retrieval data to determine the number of biologic reactions and the effects of the cage on human patients [11, 18]. However, the biomechanical and clinical success of interbody fusion cages has been proven, and they are usually used to facilitate fusion after discectomy or corpectomy on the thoracolumbar spine. They include autograft or allograft bone, and they are placed between vertebral bodies to provide fixation, immediate compression strength, anterior column support, and containment of the graft material [10, 16, 19, 20].

Penetrating Bone-Implant Interface

In spinal surgery, three types of screws are mainly used:

1. Machine screws (cortical screws): These are mostly used in hard, incompressible bones.
2. Self-tapping machine screws: These obviate the need for multistep processing.
3. Wood screws (cancellous screws): These are used on softer materials, such as cancellous bones.

Compression during the entrance of the screw may cause minor fractures that reduce the integrity

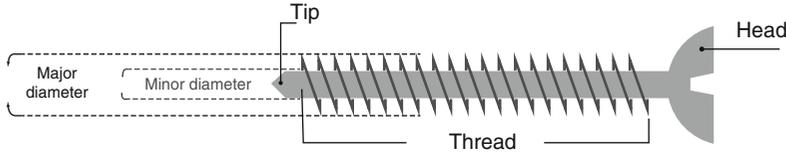


Fig. 20.3 The depth of the screw, outer diameter, and thread depth are important to pullout resistance

of the bone [5, 21] when cortical screws are used. On the other hand, although pre-tapping screws are more effective on the cortex, they are less effective on cancellous bone because tapping weakens the bone-implant interface [22]. Based on this, the tapping of the pedicle holes where the screws will be placed remains of questionable value. Regarding the cortex, the screws used for the pedicle of the vertebrae rarely succeed in shoring on the cortex within the pedicles. However, cortex microracking around screw threads is greater with untapped screws than tapped ones. Therefore, regarding the cortex, untapped screws loosen more frequently than tapped ones [21].

Another very important factor in penetrating implants is the pullout resistance of the screw, which correlates with insertional torque [21, 23]. The screw's insertional torque is defined by the equation $y = (x/1,142) + 0.02$ (y =insertional torque (Nm), x =pullout resistance (N)). It is also known that the diameter of the body of a screw is proportional to the force that can be exerted on it [6]. Based on this, the most important factors in pullout resistance are maximum screw diameter and thread depth [2] (Fig. 20.3). A typical example is the report of Liljenqvist et al. [24] which mentions that the pullout resistance of screws is greater at the lower part of the thoracic spine compared to the top and that this can be explained by the larger pedicle widths at the lower part of the thoracic spine and therefore the larger diameter of the screws placed in this area. Other important factors are the depth of screw penetration, thread design, screw shape and length, etc. However, the quantification of these parameters and their objective correlation with pullout resistance are extremely difficult. Chapman et al. [22] have attempted to quantify these factors, but their equation did not include factors such as the

connection between the screw and the bone and screw geometry.

What we definitely know is that the bicortical purchase of screws and expandable tip screws increase pullout resistance. Furthermore, the pullout resistance of screws increases with participation of the cortical bone which resists output stress in a remarkable way [22, 25]. On the other hand, ensuring good bone-implant interface is not easy in cases of osteoporosis [23].

Gripping Bone-Implant Interface

Hooks and wires are types of implants that are based on grip, and they are mostly used in osteoporotic bones [26]. Their pullout resistance is very important. They are preferred for osteoporotic bones mostly because of their greater contact surface since almost the entire implant surface has contact with cortical bone [24, 26]. The relaxation process of the implant begins with the local failure of bone structure around the point of maximum stress during load application on the structure bone implant. If trabecular bone is significantly reduced in quantity and thickness, as in osteoporosis, then the interface that accepts the entire load between bone and implant is reduced and therefore subjected to higher levels of stress, even under a specific load. Thus, the risk of failure in osteoporotic bone increases [26].

It has been found that laminar hooks have greater axial pullout strength compared to pedicle screws [24, 26] in osteoporotic bones. Also, it has been noted that laminar hooks that are placed in the lower thoracic spine have a higher resistance compared to pedicle hooks that are placed in the upper thoracic spine [24]. Another study suggests that the final resistance of two triangulated

pedicle screws in osteoporotic vertebrae is better than both laminar hooks and single pedicle screws [27]. Hooks obviously provide a larger contact surface compared to wires. Hooks effectively resist dorsally directed forces, while double wires double the contact surface by increasing the pullout resistance. Specifically, regarding osteoporotic bones, the wire can be looped around the laminae and spinous processes of adjacent vertebrae and can be secured via twisting the loops together. The hooks may be placed at the laminae, pedicles, or transverse processes to increase dorsal instrumentation [4, 28]. In conclusion, regarding osteoporotic bones, greater endurance is exhibited by double triangulated pedicle screws, followed by hooks and finally wires and single pedicle screws.

Finally, we should refer to the depth of graft entry. A pedicle hook that is inserted too deeply may cut into the pedicle, diminishing its torsional stability. Also, a hook that is inserted insufficiently reduces the ability of the interface to increase torsional stability. Moreover, the addition of a transverse process hook applies a torque on the pedicle, leading to failure of the pedicle, the facets, or the transverse processes [5]. Pullout resistance of the screw may be increased by screw-hook claw application at the thoracic and lumbar regions. Additionally, a caudal sublaminar hook, placed at the same spinal level as the pedicle screw, significantly increases pullout resistance of the screw. Generally, deformation and the ability to resist fatigue are two of the most important characteristics of spinal implants because the materials do not fail due to excessive static loads applied to them but due to rotative loading and fatigue (continuous application of loads for long periods of time) [2].

Conforming Bone-Implant Interface

It has been shown that acrylic does not usually conform adequately to the bone because of the effect blood has on the acrylic, the bone, and the gravity which causes acrylic to flow away from important interface points [5]. Moreover, there is no osseointegration between the bone and the

acrylic, and therefore, loosening of acrylic-bone interfaces is common. Generally, while some researchers claim that acrylic is a very useful spinal implant, others mention that its use is limited [29]. On the other hand, it is suggested that polymethylmethacrylate (PMMA) can be used with very good results but only in special situations because it has a high resistance to elasticity and it is very sensitive. However, it has been shown that wire reinforcement, especially with Vitallium, yields a stronger construction [28, 30].

Osseointegration

The most common materials used for osseointegration are titanium or stainless steel. Stainless steel is mainly used because of its mechanical properties (fatigue endurance and higher modulus of elasticity). However, stainless steel is more susceptible to corrosion than titanium, and that makes it possibly more harmful for a patient's body [31]. On the other hand, titanium is known for its significant biocompatibility [32, 33]. Pure titanium is classified based on its purity and degree of contamination. The more the oxygen content of the titanium increases, the more its endurance increases. Although endurance to the elasticity of titanium remains the same, its basic and elastic power increases [30]. The corrosion of the materials appears because of the unintended micromotion between the two surfaces, a process that removes the passive oxide layer. The removal of this layer, which acts as both a kinetic and thermodynamic barrier to corrosion, leaves the material exposed to electrochemical reaction [34]. Basically, the corrosion appears when a small gap between the plate and the screw allows for an environment depleted in oxygen and highly concentrated in chloride ions. These chemical reactions cause a crevice result in metal ions [35].

Concerning stainless steel, it has been shown that panned or matted stainless steel outweighs smooth or non-matted stainless steel materials in terms of osseointegration [30]. At the same time, 316 stainless steel and 22-13-5 stainless steel are more resistant than titanium, resulting in less

transfer of compression forces from the implant to the bone. Although controversy on this issue remains, other studies report that titanium Ti-13Nb-13Z exhibits greater endurance [32].

However, it has been clarified that titanium presents a better application than steel in low charging frequencies. There was a study with osteoporotic sheep where an anti-rotation screw was placed in continuation of the bridging elements to prevent rotation around the longitudinal axis of the cylinder. The cylinders were coated with Bonit® (hydroxyapatite/brushite 1.67/1.1) in order to enhance osseointegration. The histological examination of the trabeculae bridging between adjacent end plates and tricortical iliac struts in all vertebrae shows that bridging was adequate to promote fusion [33].

Generally, the process of osseointegration is very important for the success of the unification of the materials and therefore for surgery. The total contact surface between an implant and bone is involved in the transfer of the load from the implant to the bone. When osseointegration occurs, the load is distributed over a much larger surface area [5]. Based on all this, it is understandable that when planning surgery and choosing a graft, a surgeon should take into consideration the area of the spine where he or she is going to intervene, the position of fusion (ventral or dorsal), and the forces that will be applied later to the graft when load is exerted on the spine. Selection of the right material and a knowledge of the mechanical structures of the area where the graft will be placed significantly contribute to achieving a good surgical result and a correct bone-implant interface.

Toe-In and Toe-Out Screws (Triangulation)

Screw-bone interface failure may be minimized by paying attention to the screw trajectory and its final position. A steady divergence or convergence of the screws (triangulation) or their placement at a 90° angle with respect to each other can increase pullout resistance [36]. The use of toe-in and toe-out placement of the screws produces the so-called triangulation effect at any level it is applied to (transverse or axial) [5]. Toe-in placement is defined as the use of paired converging and cross-fixed moment arm screws, whereas toe-out placement is defined as the use of paired diverging and cross-fixed moment arm screws (Fig. 20.4). The triangulation effect is basically the lateral position of each screw which increases pullout resistance due to its position [27]. The triangulation effect is proportional to the area defined by the triangle that is created by each screw inside the bone [36] (Fig. 20.5a). Triangle surface inside the bone can be increased by lengthening the screws (Fig. 20.5b) or altering screw trajectory (Fig. 20.5c). Also, the pullout resistance of the screw may be enhanced by using the injection of pressurized polymethylmethacrylate (PMMA) into the screw hole before placing the screw. Nonpressurized injection is less effective because it does not cause penetration of the PMMA into the bone interstices [2]. Bone slivers or cement can be used to increase pullout resistance [28, 37].

Finally, it is worth mentioning that triangulation is affected by:

1. Orientation of the loads resisted. More specifically, toe-in and toe-out placements differ regarding their ability to resist axial forces

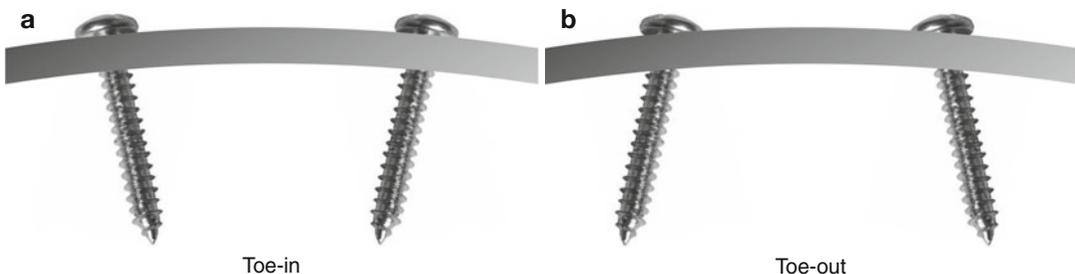


Fig. 20.4 Toe-in (a) and toe-out (b) placement

[27]. For example, sagittally toed-in screws are much more prone to back out after the application of axial loads. This is due to the sub-optimal orientation of the component vectors that resist axial deformation [25]. Therefore,

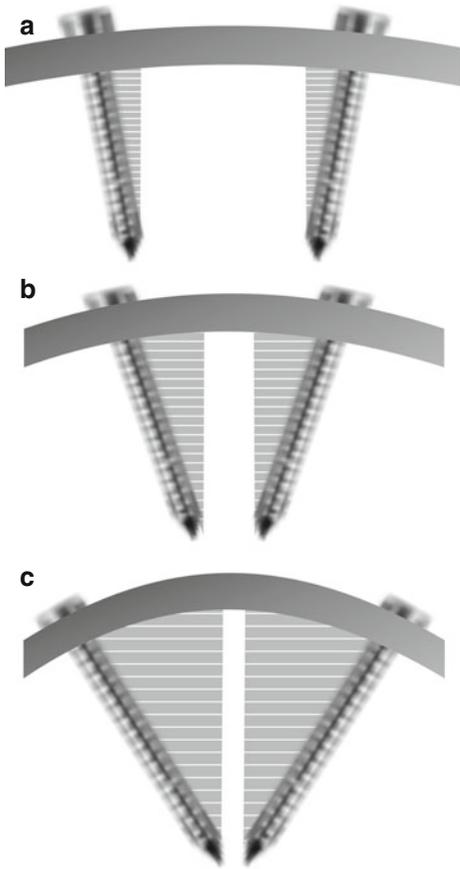


Fig. 20.5 The triangulation effect is proportional to the area that is created by each screw (a), the length of the screw (b) and the screw trajectory (c)

toed-out screws are more effective against axial loads at the vertical plane. Moreover, the simultaneous placement of toed-in or toed-out screws can increase the triangulation effect even more [36] (Fig. 20.6).

2. Consistency of the bone into which the screws will be placed [26, 28].
3. The limitations that derive from the structure and geometry of the bone where the implant will be placed [22].

Size of the Implant: Disc Replacement

The use of correct implant size is of great importance for achieving maximum positive effect. Several researchers have investigated this area [38–40]. Knowledge of the anatomy of the area and biomechanical variations is very important for the understanding of the graft end-plate interface and the risk of failure or subsidence [39]. There is general agreement that proper implantation technique and sizing play a defining role in the optimization of implantation device performance and clinical outcome [38–44].

More specifically, regarding the effect of cage implant size as a mechanical factor at the implant end plate, it was found in a cadaveric model that there was significantly greater endurance (regarding the implant failure) in loads and applied force when larger cage indenters were used [45, 46]. Lowe et al. [47] reached the same conclusion highlighting that cages of larger



Fig. 20.6 Toed-in or toed-out screws in different planes (sagittal or coronal) simultaneously provide further advantages

diameter facilitated a more effective transfer of force toward the stronger posterolateral area of the end plate and, therefore, they provided greater resistance during subsidence. On the other hand, smaller arthroplasty implants can subject the central part of the vertebral body to higher stress and increase the risk of implant subsidence. Several studies mention smaller size of the implant as a reason for subsidence or migration [47–50].

Moreover, it has been found that total disc replacement (TDR) produces a statistically significant reduction in end-plate stiffness. Specifically, regarding small-sized keel-type implants, end-plate stiffness was not significantly altered. However, when medium- or large-sized implants were used, end-plate stiffness was significantly reduced at a rate of 19 and 26 %, respectively. Therefore, based on these results, the use of the largest footplate possible helps to avoid large end-plate displacements and greatly reduces the chances of device subsidence and end-plate failure [51]. Moreover, Lin et al. [52] have observed that, although the rigid core of Prestige LP and ProDisc-C increases contact stress at the interface between the metallic end plates and the vertebral bodies, this is in fact very beneficial, when placement and alignment are correct in order to secure partial integrity during motion and maintain sufficient disc height. As indicated in their experiments, although Prestige LP and the ProDisc-C underwent little displacement in the cervical spine vertebral units, the corresponding displacement was five to ten times greater with the Bryan disc under the same pressure.

Generally, it is very important for fusion or disc replacement to secure sufficient contact surface area and strong initial fixation in order to avoid mechanical failure due to subsidence, expulsion, or component failure [52]. Most of the time, the implant that is preferred is smaller than the vertebra for safety reasons during surgery, despite the fact that the largest graft possible should be used. However, there are no clear guidelines regarding the size of the implant that should be chosen in each case [53].

Graft End-Plate Interface

As well as implant size, end-plate interface is also important. For example, regarding disc replacement, variation in vertebral end-plate curvature makes it difficult to obtain accordance of the surfaces between the flat and stiff implant end plate and the vertebral end plate even with vertebral end-plate preparation. Voids at the interface between disc and bone, which reduce the total available area for load transfer, are inevitable [54]. Regarding cervical end plates, it is known that their posterior and lateral fold is thicker and stronger than their anterior and middle end plate. Also, the quality of each patient's bones is a very important factor that correlates with the strength of vertebral end plates [15, 55–58]. In general, an implant interface is an important component of a construction's overall endurance. However, while some cervical prostheses require partial or aggressive burning, others do not. This is the reason why it is necessary to fully understand how burning can affect end-plate endurance before any evaluation of failure characteristics [59].

Often, partial or aggressive removal of the end plate is the factor that affects the subsidence of an interbody device. It has been shown with indentation techniques that the removal of the end plates affects cervical end-plate endurance [47, 60, 61]. Regarding the cervical spine, it has been shown that end-plate removal significantly reduced the spine's endurance [62]. Similar results were noted for the thoracic spine [61] and the lumbar spine [47]. However, the preparation of the end plate did not significantly reduce the endurance of the area in studies where actual implants were used.

The depth of burning is another important factor. The study of Cheng et al. [63] noted that there were statistically significant differences regarding end-plate endurance between intact end plates and burned end plates (1 mm depth, 2 mm depth), while the posterior end plate had significantly greater endurance than the anterior one at burning depths of both 1 and 2 mm. Also, there was a greater loss of stiffness at a burning depth of 2 mm rather than 1 mm, and this is why it must

be mentioned that during end-plate preparation, the smallest contact surface possible should be burned to maintain overall endurance of the end plate. Researchers stress that although the implant surface plays an important role in the degree of subsidence of the device, the end plate increases endurance of the entire construction.

Conclusion

From a mechanical point of view, the spine is considered to be a complex structure. Spinal interventions alter normal mechanical properties due to an interplay between the spine and implants. Abutting implants (e.g., cages, artificial discs) distribute loads over large surface areas; therefore, efficiency depends on the circumference of the implant and the graft end-plate interface. Penetrating implants are mostly represented by screws, and their pull-out resistance relies on their outer diameter and thread depth. Moreover, screw trajectory and configuration can also affect the screw-bone interface. Hooks and wires are described as gripping bone implants. Their ability to resist loads is quite efficient, especially in osteoporotic bone. Conforming bone-implant interfaces are mainly represented by PMMA. In this case, osseointegration does not exist. On the contrary, titanium and stainless steel can both be used for this purpose.

References

1. Hafer TR, Valdevit A, Caruso S. Spinal biomechanics. In: Bono CM, Garfin SR, editors. *Spine*. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 278–84.
2. Butler J, Ferrara LA, Benzel EC. Chapter 105: Basic biomechanically relevant anatomy. In: Benzel EC, editor. *Spine surgery: techniques, complication avoidance and management*. Philadelphia: Elsevier; 2003. p. 1397–417.
3. Zindrick MR, Wiltse LL, Widell EH, Thomas JC, Holland WR, Field BT, Spencer CW. A biomechanical study of intrapeduncular screw fixation in the lumbosacral spine. *Clin Orthop*. 1986;203:99–112.
4. Benzel EC. Chapter 1: Biomechanically relevant anatomy and material properties of the spine and associated elements. Chapter 13: Implant-bone interface. Chapter 30: Construct failure and failure prevention. In: Benzel EC, editor. *Biomechanics of spine stabilization*. New York: Thieme Medical Publishers; 2001. p. 155–70, 455–68.
5. Benzel EC. Chapter 2: Physical principles and kinematics. In: Benzel EC, editor. *Biomechanics of spine stabilization*. New York: Thieme Medical Publishers; 2001. p. 19–28.
6. Schlenk RP, Stewart T, Benzel EC. The biomechanics of iatrogenic spinal destabilization and implant failure. *Neurosurg Focus*. 2003;15(3):1–11.
7. Kanayama M, Cunningham BW, Weis JC, Parker LM, Kaneda K, McAfee PC. The effects of rigid spinal instrumentation and solid bony fusion on spinal kinematics. A posterolateral spinal arthrodesis model. *Spine*. 1998;23(7):767–73.
8. DePuy-AcroMed. Lumbar IF Cage® with VSP® spine system, summary of safety and effectiveness. Rockville: FDA, CDRH; 1999.
9. Medtronic Sofamor-Danek. InFUSE™ Bone Graft/LT-CAGE™ lumbar tapered fusion device, summary of safety and effectiveness data. Rockville: FDA, CDRH; 2002.
10. Lund T, Oxland TR, Jost B, et al. Interbody cage stabilization in the lumbar spine: biomechanical evaluation of cage design, posterior instrumentation and bone density. *J Bone Joint Surg Br*. 1998;80B:351–9.
11. Brantigan JW, Steffee AD, Geiger JM. A carbon fiber implant to aid interbody lumbar fusion. Mechanical testing. *Spine*. 1991;16:S277–82.
12. Tencer AF, Hampton D, Eddy S. Biomechanical properties of threaded inserts for lumbar interbody spinal fusion. *Spine*. 1995;20:2408–14.
13. Jost B, Crompton PA, Lund T, et al. Compressive strength of interbody cages in the lumbar spine: the effect of cage shape, posterior instrumentation and bone density. *Eur Spine J*. 1998;7:132–41.
14. Kettler A, Wilke HJ, Dietl R, et al. Stabilizing effect of posterior lumbar interbody fusion cages before and after cyclic loading. *J Neurosurg*. 2002;92:87–92.
15. Grant JP, Oxland TR, Dvorak MF, et al. The effects of bone density and disc degeneration on the structural property distributions in the lower lumbar vertebral end-plates. *J Orthop Res*. 2002;20(5):1115–20.
16. McAfee PC. Interbody fusion cages in reconstructive operations on the spine. Current concepts review. *J Bone Joint Surg Am*. 1999;81A:859–80.
17. Zou X, Li H, Teng X, Xue Q, Egund N, Lind M, Bünger C. Pedicle screw fixation enhances anterior lumbar interbody fusion with porous tantalum cages: an experimental study in pigs. *Spine*. 2005;30(4):392–9.
18. Brodke DS, Dick JC, Kunz DN, et al. Posterior lumbar interbody fusion. A biomechanical comparison, including a new threaded cage. *Spine*. 1997;22:26–31.
19. Kuslich SD, Ulstrom CL, Griffith SL, et al. The Bagby and Kuslich method of lumbar interbody fusion. History, techniques, and 2-year follow-up results of a United States prospective, multicenter trial. *Spine*. 1998;23:1267–79.

20. Ray CD. Threaded titanium cages for lumbar interbody fusions. *Spine*. 1997;22:667–80.
21. Vangsness Jr CT, Carter DR, Frankel VH. In vitro evaluation of the loosening characteristics of self-tapped and non-self-tapped cortical bone screws. *Clin Orthop*. 1981;157:279–86.
22. Chapman JR, Harrington RM, Lee KM, Anderson PA, Tencer AF, Kowalski D. Factors affecting the pullout strength of cancellous bone screws. *J Biomech Eng*. 1996;118(3):391–8.
23. Lieberman IH, Khazim R, Woodside T. Anterior vertebral body screw pullout testing. A comparison of Zeilke, Kaneda, Universal Spine System, and Universal Spine System with pullout-resistant nut. *Spine*. 1998;23(8):908–10.
24. Liljenqvist U, Hackenberg L, Link T, Halm H. Pullout strength of pedicle screws versus pedicle and laminar hooks in the thoracic spine. *Acta Orthop Belg*. 2001;67(2):157–63.
25. Sell P, Collins M, Dove J. Pedicle screws: axial pullout strength in the lumbar spine. *Spine*. 1988;13(9):1075–6.
26. Coe JD, Warden KE, Herzig MA, McAfee PC. Influence of bone mineral density on the fixation of thoracolumbar implants. *Spine*. 1990;15:903–7.
27. Ruland CM, McAfee PC, Warden KE, Cunningham BW. Triangulation of pedicular instrumentation. A biomechanical analysis. *Spine*. 1991;16(6):S270–6.
28. Taitsman JP, Saha S. Tensile strength of wire-reinforced bone cement and twisted stainless-steel wire. *J Bone Joint Surg Am*. 1997;59A:419–25.
29. Duff TA. Surgical stabilization of traumatic cervical spine dislocation using methyl methacrylate. Long-term results in 26 patients. *J Neurosurg*. 1986;64(1):39–44.
30. Knott PT, Mardjetko SM, Kim RH, Cotter TM, Dunn MM, Patel ST, Spencer MJ, Wilson AS, Tager DS. A comparison of magnetic and radiographic imaging artifact after using three types of metal rods: stainless steel, titanium, and vitallium. *Spine*. 2010;10(9):789–94.
31. Villarraga ML, Cripton PA, Teti SD, et al. Wear and corrosion in retrieved thoracolumbar posterior internal fixation. *Spine*. 2006;31:2454–62.
32. Seligson D, Mehta S, Mishra AK, et al. In vivo study of stainless steel and Ti-13Nb-13Zr bone plates in a sheep model. *Clin Orthop*. 1997;343:213–22.
33. Stambough JL, Genaidy AM, Huston RL, Serhan H, El-khatib F, Sabri EH. Biomechanical assessment of titanium and stainless steel posterior spinal constructs: effects of absolute/relative loading and frequency on fatigue life and determination of failure modes. *J Spinal Disord*. 1997;10(6):473–81.
34. Goldhahn J, Neuhoff D, Schaeren S, Steiner B, Linke B, Aebi M, Schneider E. Osseointegration of hollow cylinder based spinal implants in normal and osteoporotic vertebrae: a sheep study. *Arch Orthop Trauma Surg*. 2006;126(8):554–61.
35. Kocijan A, Milosev I, Pihlar B. The influence of complexing agent and proteins on the corrosion of stainless steels and their metal components. *J Mater Sci Mater Med*. 2003;14:69–77.
36. Jacobs JJ, Gilbert JL, Urban RM. Corrosion of metal orthopaedic implants. *J Bone Joint Surg Am*. 1998;80A:268–82.
37. Benzel EC, Baldwin NG. Crossed-screw fixation of the unstable thoracic and lumbar spine. *J Neurosurg*. 1995;82(1):11–6.
38. Awasthi D, Voorhies RM. Posterior cervical fusion with methylmethacrylate, wire and bone: technical note. *Surg Neurol*. 1994;42(3):259–64.
39. McAfee PC, Cunningham B, Holsapple G, et al. A prospective, randomized, multicenter food and drug administration investigational device exemption study of lumbar total disc replacement with the CHARITE Artificial Disc versus Lumbar Fusion: part II: evaluation of radiographic outcomes and correlation of surgical technique accuracy with clinical outcomes. *Spine*. 2005;30(5):1576–83.
40. Leary SP, Regan JJ, Lanman TH, Wayner WH. Revision and explantation strategies involving the CHARITE lumbar artificial disc replacement. *Spine*. 2007;32(9):1001–11.
41. Shim CS, Lee S, Maeng DH, Lee SH. Vertical split fracture of the vertebral body following total disc replacement using ProDisc: report of two cases. *J Spinal Disord Tech*. 2005;18(5):465–9.
42. Van OA, Oner FC, Verbout AJ. Complications of artificial disc replacement: a report of 27 patients with the SB Charite disc. *J Spinal Disord Tech*. 2003;16(4):369–83.
43. Wagner WH, Regan JJ, Leary SP, et al. Access strategies for revision or explantation of the Charite lumbar artificial disc replacement. *J Vasc Surg*. 2006;44(6):1266–72.
44. Stieber JR, Donald III GD. Early failure of lumbar disc replacement: case report and review of the literature. *J Spinal Disord Tech*. 2006;19(1):55–60.
45. David T. Long-term results of one-level lumbar arthroplasty: minimum 10-year follow-up of the CHARITE artificial disc in 106 patients. *Spine*. 2007;32(6):661–6.
46. Tan JS, Bailey CS, Dvorak MF, Fisher CG, Oxland TR. Intervertebral device shape and size are important to strengthen the vertebra-implant interface. *Spine*. 2005;30:638–44.
47. Lowe TG, Hashim S, Wilson LA, et al. A biomechanical study of regional end-plate strength and cage morphology as it relates to structural interbody support. *Spine*. 2004;29(21):2389–94.
48. van Ooij A, Schurink GW, Oner FC, Verboot AJ. Findings in 67 patients with recurrent or persistent symptoms after implantation of a disc prosthesis for low back pain. *Ned Tijdschr Geneesk*. 2007;151(28):1577–84.

49. Cinotti G, David T, Postacchini F. Results of disc prosthesis after a minimum follow-up period of 2 years. *Spine*. 1996;21(8):995–1000.
50. Zeegers WS, Bohnen LM, Laaper M, Verhaegen MJ. Artificial disc replacement with the modular type SB Charite III: 2-year results in 50 prospectively studied patients. *Eur Spine J*. 1999;8(3):210–7.
51. Auerbach JD, Ballester CM, Hammond F, Carine ET, Balderston RA, Elliott DM. The effect of implant size and device keel on vertebral compression properties in lumbar total disc replacement. *Spine J*. 2010;10(4):333–40.
52. Lin CY, Kang H, Rouleau JP, Hollister SJ, Marca FL. Stress analysis of the interface between cervical vertebrae end-plates and the Bryan, Prestige LP, and ProDisc-C cervical disc prostheses: an in vivo image-based finite element study. *Spine*. 2009;34(15):1554–60.
53. Bono CM, Garfin SR. History and evolution of disc replacement. *Spine J*. 2004;4:S145–50.
54. Grant JP, Oxland TR, Dvorak MF. Mapping the structural properties of the lumbosacral vertebral end-plates. *Spine*. 2001;26(8):889–96.
55. Kumar N, Judith MR, Kumar A, Mishra V, Robert MC. Analysis of stress distribution in lumbar interbody fusion. *Spine*. 2005;30(15):1731–5.
56. Lim TH, Kwon H, Jeon CH, et al. Effect of end-plate conditions and bone mineral density on the compressive strength of the graft-end-plate interface in anterior cervical spine fusion. *Spine*. 2001;26(8):951–6.
57. Hasegawa K, Abe M, Washio T, Hara T. An experimental study on the interface strength between titanium mesh cage and vertebra in reference to vertebral bone mineral density. *Spine*. 2001;26(8):957–63.
58. Steffen T, Tsantrizos A, Aebi M. Effect of implant design and end-plate preparation on the compressive strength of interbody fusion constructs. *Spine*. 2000;25(9):1077–84.
59. Truumees E, Demetropoulos CK, Yang KH, Herkowitz HN. Failure of human cervical end-plates: a cadaveric experimental model. *Spine*. 2003;28(19):2204–8.
60. Hollowell JP, Vollmer DG, Wilson CR, Pintar FA, Yoganandan N. Biomechanical analysis of thoracolumbar interbody constructs: how important is the end-plate? *Spine*. 1996;21(9):1032–6.
61. Li JY, Zhu QA, Yuan L, et al. Role of the biomechanical property of the end-plate in anterior cervical fusion. *Di Yi Jun Yi Da Xue Xue Bao*. 2003;23(5):402–8.
62. Oxland TR, Grant JP, Dvorak MF, Fisher CG. Effects of end-plate removal on the structural properties of the lower lumbar vertebral bodies. *Spine*. 2003;28(8):771–7.
63. Cheng CC, Ordway NR, Zhang X, Lu YM, Fang H, Fayyazi AH. Loss of cervical end-plate integrity following minimal surface preparation. *Spine*. 2007;32(17):1852–5.

Alexander Tsarouhas and Michael E. Hantes

Introduction

Reconstruction or repair of ligaments and tendons to bone, following injury, to improve joint function is a very common surgical procedure in orthopedics. The most common surgical ligament reconstruction in humans is anterior cruciate ligament (ACL) reconstruction. Because ACL is not amenable to repair after tear, replacement of the ligament using autograft or allograft tissue is currently the treatment of choice for young and active patients. On the other hand, surgical reattachment to bone is the most reliable treatment in case of rotator cuff tendon tears. Tendon grafting or repair to bone is performed during hand, foot, and ankle surgery. Nowadays, ACL reconstruction and repair of rotator cuff tendon tears are the most commonly performed surgical procedures for soft tissue injuries in orthopedics.

Historically, the bone–patellar tendon–bone (BPTB) autograft was the commonest graft used for the procedure. Direct bone-to-bone healing in

this case leads to fast and solid incorporation of the graft by the fourth to sixth week. However, soft tissue auto- and allografts have recently become increasingly popular given the morbidity induced by BPTB autograft harvest. For a successful reconstruction, healing of the soft tissue graft to the bone tunnel is required. With the increasing popularity of soft tissue grafts in ACL reconstruction, healing within a bone tunnel has been brought to the center of current research in the biology and mechanics of tendon-to-bone healing.

Healing of tendon or ligament to a bone tunnel after surgical ligament reconstruction or reattachment of tendon to a bone surface remains a poorly understood, complex process. Multiple surgical, postoperative, and patient-related variables can influence its outcome. However, a growing body of recent experimental and clinical data has added significantly to our understanding of the biological mechanisms that regulate this process and of interventions to potentially enhance its progress.

A. Tsarouhas, MD, DSc
Department of Orthopaedic Surgery,
University Hospital of Larissa, Mezzourlo,
Larissa 41110, Greece

M.E. Hantes, MD, DSc (✉)
Department of Orthopaedic Surgery,
School of Health Sciences, University Hospital
of Larissa, Mezzourlo, Larissa 41110, Greece

Faculty of Medicine, School of Health Sciences,
University of Thessaly,
Larissa, Hellenic Republic, Greece
e-mail: hantesmi@otenet.gr

Morphology of the Native Bone–Tendon Insertion Site

The structure of the native tendon attachment to bone is highly differentiated in order to achieve the optimum distribution of loading at the interface between a soft compliant (tendon) and a stiffer (bone) material. Two types of attachments have been identified based on the direction in which the

collagen fibers attach to the bone surface: indirect and direct. Indirect insertions (also called periosteal insertions or fibrous entheses) can be found at the tibial insertion of the MCL and at the insertion of the deltoid tendon into the humerus. In general, indirect insertions are mainly present with short ligaments or tendons, which have a relatively large and broad insertion area to bone. The typical characteristic of an indirect insertion type is the continuity of the periosteum distal and proximal to the insertion site. The tendon or ligament passes obliquely along the bone surface and inserts at an acute angle into the periosteum. A high number of collagen fibers continue from the tendon into the underlying periosteum and then into bone and serve to reinforce the tendon's attachment. They are called Sharpey's fibers in recognition of their first description by William Sharpey in 1856. Direct insertions (also called fibrocartilaginous entheses) are found at the insertion sites of the ACL, Achilles, patellar, and rotator cuff tendons. They are primarily differentiated from indirect insertions by the fact that the periosteum is non-contiguous and tendon or ligament tissue directly attaches to the underlying bone. They are composed of four gradual transitional zones: tendon, uncalcified fibrocartilage, calcified fibrocartilage, and bone. No sharp boundaries between these zones exist, and their proportions vary between entheses. The presence of a mineralized cartilage tidemark or cement line between the fibrocartilage and the bone has also been described. The mineralized cartilage tidemark forms deep interdigitations, thus increasing the contact area and reducing the stiffness gradient between mechanically different tissues [1]. Consequently, the ability of this unit to resist shear and tensile forces is improved. There is a strong correlation between the distribution of fibrocartilage within an entheses and the levels of compressive stress to which it is subjected [1, 2]. This fibrocartilage zone is also thought to act as a barrier to endosteal-derived vascular ingrowth [3].

Tendon Healing in a Bone Tunnel

Reconstructive ligament surgery aims to establish a new ligament with similar morphology and mechanical properties to the native one and to

recreate the normal insertion to bone, which is necessary for normal ligament function. Soft tissue ACL reconstruction, in particular, produces a unique configuration because nowhere else in the human body is a ligament found within a cancellous bone tunnel. To obtain a better understanding of the biology of tendon-to-bone tunnel healing and develop strategies to improve outcome, animal models are essential. Rabbit, rat, canine, and sheep models have been developed and used for the study of natural tendon graft-to-bone tunnel healing and treatment outcomes. Compared with other animal models, rabbit and sheep models are more commonly used because of their low cost and large size, respectively. Intra- and extra-articular animal models have been developed. Extra-articular models present the advantage that they can easily be performed on smaller animals. In addition, their mechanical properties can be more precisely studied, as they do not undergo such an extensive remodeling as intra-articular models. However, the latter are more clinically relevant, when focusing on ACL reconstructive surgery, because the implanted graft is subjected to local boundary conditions that more realistically resemble the human joint.

Physiology of Tendon Healing in a Bone Tunnel

Tendon graft-to-bone tunnel healing can be divided into four stages: inflammatory phase, proliferative phase, matrix synthesis, and matrix remodeling. During the inflammatory phase (first week after implantation), the space between the tendon graft and bone is filled with fibrovascular tissue. Neutrophils and recruited macrophages present in the tendon-bone tunnel interface as early as the 4th postoperative day, whereas resident macrophages are identified after 10 days [4]. Inflammatory mediators, such as cytokines, and growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), transforming growth factor-beta (TGF- β), and platelet-derived growth factor (PDGF), are released by inflammatory and marrow-derived stem cells that infiltrate the interface. Interactions between these molecules contribute to the

enhancement of the inflammatory cascade. During the proliferative phase, beginning 1–2 weeks post-implantation, osteoblasts, chondrocytes, and fibroblasts appear around the bone tunnel wall and, consequently, the cellularity and vascularity of the interface tissue increases. Cell ingrowth progresses from the interface towards the inner tendon [4]. Blood vessels and nerves increase in density, presumably as a result of hypoxia or growth factor stimulation [5]. The matrix synthesis phase (around 4 weeks) is characterized by the degradation of provisional tissue by matrix metalloproteinases (MMPs) and serine proteases. In turn, new extracellular matrix with immature collagen type II is deposited. However, the orientation of collagen fibers is still poor. New denser lamellar bone is also formed, and early fibrocartilage progressively grows into the interface tissue. At the matrix-remodeling phase, the continuity and orientation of collagen fiber between tendon graft and newly formed bone is established. Perpendicularly oriented fibers, composed of type III collagen and resembling Sharpey's fibers, can be seen along the interface at around 8 weeks after implantation and are considered the earliest sign of graft osteointegration. In their experimental study on dogs, Rodeo et al. correlated the progressive increase in pullout strength with the degree of bone ingrowth, mineralization, and maturation of the healing tissue noted histologically [6]. The time interval that the most obvious improvement in graft strength occurs varies between studies, ranging between 2–4 and 12–24 weeks post-implantation [6, 7]. The density of Sharpey's fibers that can be considered as a sign for a solid-graft incorporation is still unclear. Several authors have described only a sparse occurrence of such fibers in animal models as well as in human graft tissue harvested during second-look arthroscopies [8]. Progressive osteointegration of the graft has been shown to alter its mode of failure. Rodeo et al. found that between 2 and 8 weeks, the graft tissue failed by pullout, whereas at 12 and 26 weeks, the tissue failed in its mid-substance or at the clamp, suggesting a change in failure mode between 8 and 12 weeks [6]. Weiler et al. described a so-called degloving mechanism, which signified that the central part of the graft was pulled out of the

tunnel, whereas the peripheral part was still attached to the bone tunnel wall even at 24 weeks after implantation [9]. In cases of degloving mechanism failure, it is considered that failure occurs at the interface between the fibrocartilaginous interzone and the tendon instead of the bone. Local mechanical and biological factors in this setting can either favorably or adversely affect the healing process. Bone necrosis due to trauma or drilling, graft necrosis due to avascularity (particularly in allograft tissue), and increased pressure of the graft against the bone tunnel can lead to the prolongation of the inflammatory phase against tissue regeneration. Influx of synovial fluid into the interface in the presence of a small gap or due to micromotion can adversely affect graft healing by activating various MMPs. Increased levels of collagenases and stromelysins have been found in the synovial fluid after ACL rupture or reconstruction [10]. Most importantly, the micromotion of the tendon within the tunnel may induce chronic inflammation, by activating osteoclasts for bone resorption and stimulating MMP secretion for matrix degradation. Inhibiting osteoclastic activity with osteoprotegerin in an animal model of tendon-to-bone tunnel healing has been shown to improve bone formation around the grafted tendon, whereas increased osteoclastic activity induced by applying receptor activator of nuclear factor-kappa- β ligand (RANKL) impaired bone ingrowth [11]. There is currently no consensus on the type of osteointegration achieved with tendon-to-bone tunnel healing. Most studies agree that the graft-bone tunnel interface evolves to an indirect type of insertion, in which Sharpey's fibers develop during the remodeling phase and primarily account for the early biomechanical properties of the complex [6, 12, 13]. Others, however, have implied that a direct-like type of insertion may be formed [14, 15]. These studies were based on histological findings of chondrocytes in the interface tissue, which demonstrated the formation of a fibrocartilaginous zone resembling the native ACL insertion. Chondrocytes have been identified at the juxta-articular tunnel apertures probably due to greater contact stress at the joint level, which favors chondrogenesis. Therefore, it is probable that controversies regarding the type of

ligament insertion that develops during tendon-to-bone tunnel healing have resulted from methodological inconsistencies regarding the site of the healing tissue being studied. Although an indirect type of ligament insertion is mechanically inferior compared to a direct one, current evidence suggests that it is mainly found within the bone tunnel, whereas the latter might develop at the articular aperture site of the tunnel with certain mechanical boundary conditions.

Factors Affecting Tendon-to-Bone Tunnel Healing (Table 21.1)

Type of Graft Used

BPTB vs. Soft Tissue Autografts

The healing characteristics of BPTB and soft tissue autografts have been compared in various studies. Tomita et al. compared a BPTB graft and flexor tendon graft for ACL reconstruction in an intra-articular model in rabbits. They found a significantly lower maximum load to failure for the flexor tendon graft group after 3 weeks, but no difference after 6 and 9 weeks [16]. Similarly, Park et al. studied the osseous integration of a patellar bone-tendon and bone-tendon-bone graft in rabbits. They also found a significantly lower failure load in the bone-tendon group at 4 and 6 weeks. In contrast, no difference was noted 12 weeks post-implantation [17]. Yamazaki et al. found only a notable difference already by 3 weeks after ACL reconstruction in dogs between flexor tendon and BPTB grafts [18]. Findings of these studies strongly suggest that despite the slower incorporation rate of soft tissue autografts

into a bone tunnel compared with bone plug grafts, no variation in strength and failure load exists between graft types by the time substantial joint loading is assumed. In addition to direct bone-to-bone healing of the bone plugs within the tunnel, some authors consider the preservation of the native direct-type junction between the harvested ligament and bone plugs is an advantage of BPTB grafts. Panni et al. suggested that when this junction is placed inside the bone tunnel, it undergoes a remodeling process, being absorbed originally and then reappearing at 6 months. In contrast, when placed at the intra-articular exit of the tunnel, it is preserved throughout the healing process [19]. Yoshiya et al. found, in a dog model, the morphologic characteristics and location of the reestablished attachment of the BPTB graft were similar to those of the native ACL [20], thus theoretically offering the advantage of improved stress distribution.

Allografts vs. Autografts

The use of allograft tissue in ACL reconstruction was introduced in an attempt to eliminate donor site morbidity and reduce surgical time. The major factors that contribute to a successful allograft implantation are sterility, reduction of antigenicity, and preservation of the biomechanical and biological properties of the graft [21]. Allografts, in general, heal in the same manner as autografts: donor cell death is followed by inflammation, revascularization-repopulation, and remodeling of the graft. In the case of deep-frozen or freeze-dried allografts, donor cell death has already occurred before implantation. Tendon allografts heal through the formation of fibrovascular scar tissue at the graft-tunnel interface followed by the formation of Sharpey's fibers and new bone production. Bone blocks contained in allografts first undergo osteonecrosis, followed by incorporation of the graft by the surrounding host cancellous bone. The intra-articular part of the graft acts as a collagen scaffold for host cells to repopulate. Collagen remodeling involves the replacement of the original large-diameter fibrils with smaller-diameter ones. Compared with autografts, allografts have

Table 21.1 Factors affecting tendon-to-bone tunnel healing

1. Type of graft used
2. Graft placement
3. Graft fixation
4. Graft length and diameter within the bone tunnel
5. Graft tensioning
6. Rehabilitation
7. Variations within and between tunnels

demonstrated a prolonged inflammatory response, a greater decrease in structural and mechanical properties, and a reduced rate of biological incorporation after implantation [22]. Allogeneic tendons also demonstrated a slower onset and rate of revascularization [23]. Greater bone tunnel enlargement observed after allograft ACL reconstruction may also suggest suboptimal healing of allograft tissue [24]. A recent sheep model study demonstrated inferior mechanical properties at 52 weeks in fresh-frozen allograft when compared with autograft [25]. Such findings have raised concerns about the long-term implications of allograft use [26]. However, although allografts seem to lose more of their time-zero strength during remodeling, this has not been associated with a poorer prognosis. Several clinical studies have conversely reported similar clinical outcomes when comparing autografts vs. allografts [27–29]. It is possible that inconsistencies in both laboratory and clinical studies, regarding allograft processing, sterilization, graft tissue, surgical technique, and endpoint evaluations, account for the diversity seen in their results. Sterilization of allograft tissue from bacterial and viral agents is considered imperative to prevent disease transmission. Gamma irradiation has been proven effective for sterilization through the generation of free radicals and direct destruction of the organism's genome. Doses of 40 kGy are required to neutralize HIV from BPTB allografts [30]. Bacteria can be eliminated at lower doses. Studies, however, have indicated that there is a dose-dependent effect of irradiation on the biomechanical properties of the graft [31]. Doses as low as 25 and 40 kGy have been shown to significantly alter the tensile strength of ACL reconstruction allografts [32], possibly through the disorganization of the collagen structure by free-radical production. Other studies have suggested that doses less than 25 kGy have no effect on ACL reconstruction outcomes [28]. To prevent such adverse effects, radiation doses between 1.5 and 2.5 Mrad are currently used in most tissue banks [33]. Most recently, Bhatia et al. compared bony incorporation after ACL reconstruction in rabbits between autografts and low-dose (1.2 Mrad) irradiated

and non-irradiated allografts. They found that the maximum load and stiffness of a healing tendon allograft appeared to be unaltered by low-dose irradiation and that, despite a faster remodeling response seen in autograft specimens, low-dose gamma irradiation did not compromise graft properties at early time points [34]. However, the effectiveness of low-dose gamma irradiation against viral agents remains debatable.

Graft Placement

Although optimal tunnel placement in ACL reconstruction is still a matter of debate, most authors agree that misplacement of the graft is a major cause of failure in ACL surgery [35, 36]. Anatomic tunnel placement is essential to restore knee stability, reduce residual laxity, and consequently achieve physiological loading of the graft. Biomechanical laxity of the graft has been correlated with reduced stress shielding and smaller cross-sectional area of the graft over time [37]. Mechanical stress applied on the graft has been shown, in an experimental model, to affect the type and quality of tendon-to-bone tunnel healing [15]. The findings of these studies have indirectly supported the association between tunnel placement and the biological incorporation of the graft. However, a direct association between graft placement and healing has not yet been established. Most recently, though, Ekdahl et al. compared in a goat model of ACL reconstruction the effect of anatomic and non-anatomic tunnel placement on the biological healing and biomechanical properties of the graft. They found less tunnel enlargement on the tibial side, fewer osteoclasts on both tibial and femoral sides, and more vascularity in the femoral side of the anatomic group, in addition to reduced anterior tibial translation and greater in situ forces [38]. Further research is warranted, however, to validate these findings, as well as to examine the effect of more recent trends, such as more horizontal graft placement (10 o'clock femoral tunnel drilling) or double-bundle reconstructions, on the biology of graft incorporation.

Graft Fixation

Graft fixation devices aim to provide strong and secure fixation during the early postoperative period when the original biomechanical properties of the graft are diminished, due to early necrosis and revascularization. Although several studies have examined the biomechanical properties of different fixation methods, little is known about their effect on bone–tendon healing. In their studies on sheep ACL reconstruction models, Weiler et al. compared two different techniques of ACL soft tissue graft fixation: one with biodegradable interference screw fixation and the other with extra-cortical Endobutton and tibial postfixation [39, 40]. They found that with the Endobutton fixation, a direct type of ligament insertion was partially present in the tibial specimens after 24 weeks, whereas on the femur, none of the specimens developed this type of ligament insertion. In contrast, in the interference screw group, all specimens developed a direct type of ligament insertion in both tibia and femur at 24 weeks. Interestingly, at 2 years post-implantation, the graft inside the tunnel was completely resorbed and replaced by bone in some specimens [41]. However, other studies have shown a deterioration of the healing process in the early postoperative period when using bio-absorbable interference screws compared with extra-articularly fixed grafts. Singhatat et al. and Zantop et al. showed that the strength and stiffness of soft tissue grafts fixed with bio-absorbable interference screws deteriorated by up to 81 and 67 %, respectively, at 4 weeks compared with time-point zero [42, 43]. The findings of these studies indicate that although a direct chondral insertion can be obtained with interference screw fixation, it might make the graft more vulnerable to failure during the early postoperative period, necessitating specific adaptations in the postoperative rehabilitation protocol. The optimum interference screw–bone tunnel diameter disparity has also been tested. Micucci et al. evaluated the effect of interference screw diameter on the fixation strength of a soft tissue ACL graft in fresh-frozen bone tibial specimens. Although no statistical significance was found

using 8, 9, 10, and 11 mm screws for a 9 mm tunnel, a trend was observed towards less graft-site motion when a screw diameter equal to tunnel size was used [44].

Graft Length and Diameter Within the Bone Tunnel

The current evidence on what should be considered the optimum length and diameter of a soft tissue graft within a bone tunnel is contradictory. Yamazaki et al. examined the effect of graft–tunnel diameter disparity on intraosseous healing of a flexor tendon graft during ACL reconstruction in dogs. They found no significant difference in the ultimate failure load between groups of 0 and 2 mm disparities at 3 and 6 weeks postoperatively. Interestingly, a higher number of perpendicular fibers connecting the graft to the bone were evident in the 2 mm group [18]. In contrast, using an extra-articular model, Greis et al. found a significantly higher load to failure 6 weeks after implantation when a more intimate bone-to-tendon contact was achieved [45]. At the same time interval, they found increased tendon length inside the tunnel to be advantageous in terms of load to failure. Although these findings were not directly confirmed by other studies, it seems rational to consider that because a more firmly inserted implant potentially minimizes graft micromotion, synovial fluid influx, and consequent tunnel widening, such an option might be preferable.

Graft Tensioning

There is no consensus nowadays on the clinical, biomechanical, and biological features of different graft tensioning alternatives during time-zero fixation. Current evidence, however, suggests that both excessively high and low tensioning can adversely affect graft incorporation within the bone tunnel. In a rabbit model, Labs et al. found, at 32 weeks postoperatively, improved pullout force and stiffness with higher (17.5 vs. 1N) initial graft tension [46]. Yoshiya et al., on the other hand, found no differences in graft

laxity and strength after 3 months when comparing one vs. 39N of graft pretensioning in a dog model. However, evidence of poor vascularity and focal myxoid degeneration were evident in the 39N group [47]. In a goat model study, Abramowitch et al. found, at time-point zero, biomechanical properties closer to the native ACL in a 35N compared with a 5N tension group but similar anterior tibial translation, in situ forces, stiffness, and ultimate failure load after 6 weeks [48].

Rehabilitation

Postoperative rehabilitation regimens after soft tissue ACL reconstruction have nowadays progressed to include less immobilization and increased joint range of motion and loading exercises. There is a general consensus that early aggressive rehabilitation before definite biological incorporation of the graft may aggravate the healing process by increasing early graft-tunnel motion and consequently contributing to bone tunnel enlargement [49]. Sakai et al. found improved healing and graft attachment strength with postoperative immobilization of the limb compared with the amount of healing and strength seen in animals that were allowed normal cage activity postoperatively [50]. However, later studies have supported the notion that some degree of joint movement and loading may be acceptable or even beneficial to the healing process. Recently, Brophy et al. examined the effect of short-duration low-magnitude cyclic loading on tendon-to-bone healing after ACL reconstruction in a rat model. Load-to-failure testing at 2 and 4 weeks showed that it was not detrimental to the strength of the healing tendon-bone interface. However, their micro-CT evaluation demonstrated that loading was associated with greater inflammation and less bone formation in the tunnel compared with immobilization [51]. Thomopoulos et al. examined in a canine flexor tendon-to-bone injury and repair model the effect of muscle loading on the healing process. They found that repaired tendons with the proximal end of the tendon intact (resulting in loading of

the tendon) healed with greater stiffness than did repaired tendons with the proximal end of the tendon cut [52]. In that canine study, paws in both groups were cast and subjected to daily passive motion. These studies were limited by the fact that the mechanical stimulation of the healing tendon-bone interface was neither quantified nor controlled.

Variations Within and Between Tunnels

Recent research has suggested that the healing response is not uniform either between different or within the same tunnel. Healing in the tibial tunnel has been found to be inferior compared with the femoral tunnel. Wen et al. found significantly lower cell density at weeks 2 and 6 and poorer collagen fiber organization at week 12 postoperatively in the tibial compared with the femoral tunnel, after ACL reconstruction in rabbits [53]. Similarly, using micro-CT evaluation, Lui et al. found inferior bone mass and mineral density in the tibial compared with the femoral tunnel of ACL-reconstructed rabbits, thus confirming histological findings of reduced graft remodeling and integration at the tibial side [54]. Although available data cannot adequately support a solid theory, it is considered that the individual structure of the tunnel walls may account for this finding. The femoral tunnel walls comprise mainly of cancellous bone, whereas only the juxta-articular part of the tibial tunnel wall is cancellous. Incorporation and remodeling of the graft in the chondral callus is believed to be more extensive at the cancellous-filled femoral insertion than within the marrow-dominated tibial insertion [55]. Variations in healing capacity and outcomes have also been documented across the length or circumference of the same tunnel. Perpendicular Sharpey-like fibers have been reported to develop close to the articular tunnel outlet rather than at its distal aperture [16, 56]. Sequential differentiations along the first postoperative weeks have also been found around the circumference of the bone tunnel in experimental models [15]. Stress distribution in the bone

tunnel and resultant mechanical forces applied to the graft, structural characteristics of the tunnel wall, and influx of synovial fluid due to graft micromotion or graft–tunnel incongruity have been correlated with spatial variations within bone tunnels [15, 57, 58].

Tunnel Widening After ACL Reconstruction

Placing a soft tissue graft inside an artificially created bone tunnel, while providing a large bone surface for tendon graft-to-bone tunnel healing, also disrupts the physiological mechanical loading, resulting in regional-dependent stress shielding and subsequent bone loss. Wen et al. found a regional-dependent loss of surrounding trabeculae in the tibia and femur after ACL reconstruction [59]. Zerahn et al. also demonstrated a decline in BMD of the proximal tibia after arthroscopic ACL reconstruction, which was only partially reversible, and correlated the improvement in knee performance with an increase in BMD of the injured leg [60]. Local bone loss may delay healing by prolonging the inflammatory reaction induced by degradative enzymes produced during bone resorption. Bone tunnel resorption can also destabilize the tendon–bone tunnel construct and result in graft failure, whereas poor bone quality at the tunnel walls may endanger the success of revision surgery.

Interventions to Enhance Tendon-to-Bone Tunnel Healing

Recent research has focused on achieving controlled modulation of the early graft–host interaction in ACL reconstruction. Theoretically, such a possibility offers the exciting possibility of a reproducible, accelerated clinical response to surgical intervention and a reduced incidence of clinical failures.

Biomaterials

The idea of applying biological materials to substitute bone was based on their availability in the

clinical market and ease of use. Injectable tricalcium phosphate (TCP), hydroxyapatite (HA) and brushite calcium phosphate cement (CPC), HA powder in collagen gel, magnesium-based bone adhesive, and hybridization of CP onto the tendon graft have all been reported to augment grafted tendon-to-bone tunnel healing. To date, encouraging results have been reported on CPC, whose chemical composition is close to bone and is available in injectable and solid forms. Because of its osteoconductive properties, CPC may suppress fibrous tissue formation and promote bone ingrowth into the interface gap as evidenced by animal model studies [61, 62]. Recently, the augmentation of screw fixation with injectable HA in the weight-bearing area of osteopenic goats has been reported. This material was highly osteoconductive and increased screw pullout force and energy required to failure when used in screw augmentation [63]. Mutsuzaki et al. introduced a novel technique to improve tendon-to-bone attachment by hybridizing CP with a tendon graft using an alternate soaking process. They found this method enhanced bone–tendon healing and reduced bone tunnel enlargement 2 years after ACL reconstruction in goats and, therefore, concluded that it can promote knee stability [64, 65]. The use of a magnesium-based bone adhesive has been reported recently. It is believed to possess better biomechanical properties compared with calcium-based cement and to increase new bone formation in bone defects. Using this material, Gulotta et al. found more fibrocartilage, less fibrous tissue, and increased osteointegration compared with controls, in the bone tunnel around the semitendinosus ACL graft of a rabbit model [66].

Chemical and Biological Agents

Improved understanding of the biology of tendon–bone interface healing has led to interventions purposed to modulate (induce or inhibit) the activity of molecules that participate in the healing process and may facilitate osteointegration, such as the MMPs, macrophages, and osteoclasts. Blockage of synovial MMPs with alpha2-macroglobulin, a plasma glycoprotein and

endogenous MMP inhibitor, has been reported to improve healing of tendon graft in a bone tunnel in rabbits resulting in a denser and more mature interface tissue. The ultimate load to failure was also significantly higher in the treatment group [12]. In another study, Hays et al. targeted macrophages that accumulate at the tendon-to-bone tunnel interface and may contribute to the formation of a scar tissue interface rather than a normal insertion site [67]. They found that rats injected with liposomal clodronate, a bisphosphonate that selectively induces macrophage apoptosis, showed decreased macrophage and TGF- β (beta) accumulation at the tendon-bone interface and a significantly narrower fibrous tissue interface between tendon and bone at all time points compared with control specimens. In addition, they found an accelerated healing rate, significantly increased osteoid formation and mineral apposition rates, as well as higher load-to-failure values in the clodronate-treated specimens. Osteoclasts acting at the tendon-bone tunnel interface have also been targets of intervention. Rodeo et al. demonstrated that the inhibition of osteoclastic activity by OPG could increase bone formation around a tendon graft and improve stiffness in a rabbit ACL reconstruction model [11]. They concurrently confirmed the role of osteoclasts in this setting when they inversely induced increased osteoclastic activity by the application of RANKL and demonstrated impaired bone ingrowth [11].

Biophysical Modalities

Shock wave, low-intensity pulsed ultrasound (LiPUS), and hyperbaric oxygen therapy have been reported to augment bone-tendon interface healing. Shock-wave treatment has shown to exert a time-dependent effect on the healing rate of the tendon-to-bone tunnel interface in rabbits [68]. The exact mechanism of its action has not been clarified. Low-intensity pulsed ultrasound has also been shown in animal models to augment bone and ligament healing, by inducing angiogenic, chondrogenic, and osteogenic activities. Walsh et al. found increased cellular activity at the tendon-bone interface in an ovine ACL reconstruction model and general improvement

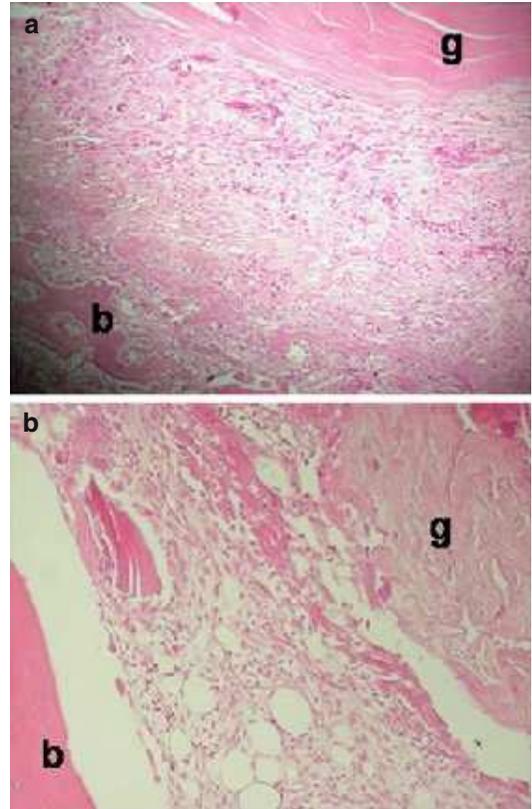


Fig. 21.1 (a) LiPUS treatment at first week showed an active interface with plump cells and blood vessels between graft and bone (hematoxylin and eosin stain original magnification $\times 20$). (b) Control at first week. Interface showed more loose connective tissue with few blood vessels (hematoxylin and eosin stain original magnification $\times 40$). *b* bone, *g* graft

in tendon-bone integration and vascularity after LiPUS treatment. Stiffness and peak load were also greater compared with controls at 26 weeks after surgery [69]. Papatheodorou et al. later evidenced by histology and rt-PCR findings a faster healing rate and more efficient ligamentization process at the tibial tunnel after ultrasound treatment [70] (Figs. 21.1, 21.2, and 21.3). Hyperbaric oxygen (HBO) treatment is considered to modulate the original ischemic necrosis and subsequent revascularization process that tendon grafts undergo after implantation. Yeh et al. reported this intervention to increase neovascularization at the tendon-bone tunnel interface, collagen organization, tendon osteointegration, and maximal pullout strength in a rabbit ACL model [71].

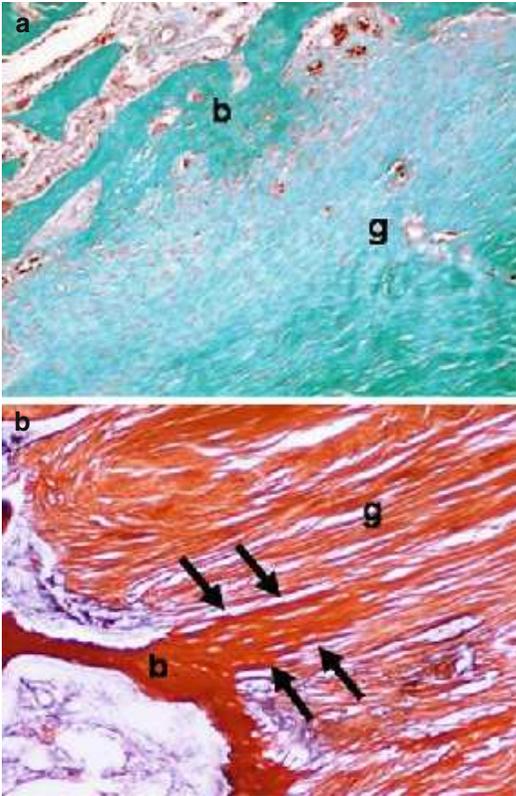


Fig. 21.2 (a) Tendon graft-bone interface, at the end of the third week (LiPUS-treated animal). Note that in the interposed connective tissue, there were collagen fibers connecting the bone with the graft. See also insert where the fibers are more distinct in higher magnification (Original magnification 100 \times , insert 400 \times , Masson trichrome stain). (b) Tendon graft-bone interface, at the end of the third week (LiPUS-treated animal). Note that in the intervening connective tissue, there are collagen fibers that clearly connect the graft and the surrounding bone (arrows) (Original magnification \times 100, Gordon–Sweet stain). *b* bone, *g* graft

Growth Factors and Gene Therapy

Exogenous bone growth factors that are known to have osteoinductive activity, which may modulate bone formation, were thought to result in a more favorable course of tendon-to-bone tunnel healing. Factors investigated in experimental models include bone morphogenetic protein (BMP)-2 and BMP-7, transforming growth factor-beta1 (TGF- β 1), TGF- β combined with epithelial growth factor (EGF), and granulocyte colony-stimulating factor. The most studied factors are the BMPs.

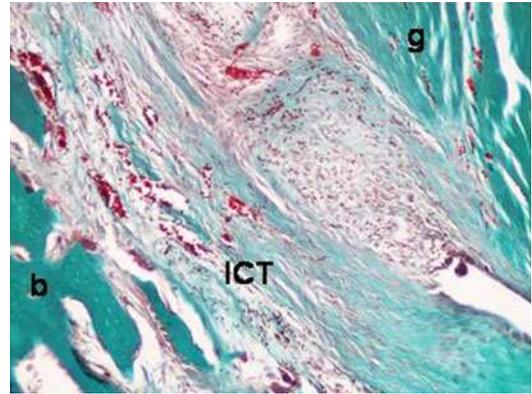


Fig. 21.3 Tendon graft-bone interface, at the end of the third week (control animal). In the intervening connective tissue (ICT), there are blood vessels and few random thin collagen fibers (Original magnification 100 \times , Masson trichrome stain). *b* bone, *g* graft

Early studies by Rodeo et al. demonstrated extensive new bone formation and greater adherence to bone with recombinant human BMP-2 [72]. However, minor bone resorption was evident at lower doses. Ma et al. suggested a dose-dependent effect of BMP-2 on new bone formation and integration to the tendon graft and noted that a slow delivering BMP carrier may reduce the bone resorption effect seen in previous studies [73]. Similarly, favorable results in new bone formation and pullout strength were reported when applying BMP-7 in a sheep model [74]. Other growth factors have also been tested. Yamazaki et al. in a dog ACL reconstruction model found that local administration of TGF- β 1 augmented both perpendicular collagen fiber and new bone formation in the tunnel wall [75]. Anderson et al. reported a study on the effects of applying in a rabbit ACL reconstruction model a product that combined various bone growth factors [76]. In a dog model, Sasaki et al. examined the effect of granulocyte colony-stimulating factor, incorporated in gelatin that surrounded the graft, on the maturation of bone-tendon interface in ACL reconstruction. Histological, biomechanical, CT, and rt-PCR findings demonstrated significantly accelerated bone-tendon interface strength via enhanced angiogenesis and osteogenesis [77].

In contrast to the single-time application of protein derivatives, delivery of genes to the target

tissue has the advantage of sustained and prolonged release of growth factors. The feasibility of gene delivery to the tendon-bone interface has been established in the experimental setting [78, 79]. Martinek et al. reported that tendon graft infected with adenovirus-BMP-2 gene improved the integration of tendon graft to bone tunnel in a rabbit ACL model [79]. Similarly, Wang et al. found a significant increase in molecular markers of angiogenesis and osteogenesis at the tendon-bone interface compared with controls when examining the effect of plasmid cytomegalovirus (pCMV)-BMP-2 gene therapy on the healing of the tendon-bone interface [80].

Cell Therapy

The use of periosteal autograft or progenitor cells, autologous bone and synovial mesenchymal stem cells (MSC), bone marrow aspirate, and platelet concentrate has been reported to augment early tendon graft–bone tunnel healing. Bone MSCs have been shown to enhance the formation of various structural and connective tissues. In a rabbit model study, grafts were coated with fibrin glue containing MSCs [14]. By 8 weeks, a mature and distinct fibrocartilage transitional zone from bone into the tendon grafts was seen in the MSC-treated tendon, whereas control knees healed by the presence of Sharpey's fibers. Biomechanically, the MSC-treated knees had significantly higher failure loads and stiffness when compared to contralateral controls at 8 weeks. Similar results were obtained using allograft coated with MSCs in a rabbit model [81]. A limitation of these studies was that the MSCs were not labeled and therefore a direct evaluation of their contribution to healing could not be made. Recently, Ju et al. examined the effect of synovial MSCs on bone–tendon healing. Labeled MSCs were used, and histological findings showed that implantation of synovial MSCs into the bone tunnel accelerated early remodeling of tendon-to-bone healing [82]. In an experimental study in rats, Li et al. examined the effect of double-labeled bone marrow MSCs on tendon-to-bone tunnel healing and found significantly higher pullout strength at 4

and 8 weeks after implantation compared with controls [83]. The findings of these experimental studies indicated a promising role for this approach to reconstructive ligament surgery. The application of autogenous fresh periosteum to promote tendon-to-bone tunnel healing has been extensively examined mainly because it is readily available and therefore appears to be more applicable than other biological interventions. Experimental studies have shown that enveloping a soft tissue graft with a periosteal layer resulted in accelerated and improved quality interface healing. In particular, Youn et al. also showed that when the inner layer of periosteum was facing towards the bone tunnel, the new bone formed around the bone tunnel was highly organized. Better mechanical strength was achieved in pullout testing at 6 weeks [84]. Recently, Karaoglu et al. also reported favorable effects of either bone marrow or periosteum use on tendon-to-bone tunnel healing in a rabbit model [85]. In one of the few prospective randomized clinical studies currently available, Robert et al. found significantly reduced tunnel enlargement at the outlet to the articular side when using a periosteal flap compared with controls [86]. Another prospective randomized clinical study examined the effectiveness of using platelet concentrate (PC) and bone plug (BP) to accelerate the healing process in ACL reconstruction. Orrego et al. found that PC had an enhancing effect on the graft maturation process seen by MRI signal intensity, without showing any significant effect in the osteoligamentous interface or tunnel widening evolution. The use of a BP effectively prevented tunnel widening, whereas no synergistic effect was established when the two interventions were combined [87].

Artificial Tissue Engineering

Using artificially engineered tissue to augment the healing process in the bone-tendon interface is a relatively novel approach. Chen et al. examined the feasibility of a photopolymerizable hydrogel based on poly (ethylene glycol) diacrylate with hyaluronic acid-tethered BMP-2, which

was injected and photogelated in a bone tunnel [88]. Interface fibrocartilage and new bone formed by photoencapsulation of BMP-2 and periosteal progenitor cells at 6 weeks. In addition, significantly higher maximum pullout strength and stiffness were found at 3 and 6 weeks after tendon transplantation compared with controls. Lu et al. examined in a sheep model whether the use of a bioresorbable interference screw coated with a hydroxyapatite-based mineral layer designed to release an engineered peptide growth factor (linkBMP-2) could improve tendon-bone healing compared with screws without coating. They found similar peak load at failure and stiffness but significantly improved histologic scores in the linkBMP-2 group and concluded that linkBMP-2 coating may improve early tendon or ligament fixation [89]. In an *in vivo* evaluation of two types of bioactive scaffold used in ACL reconstruction, Pan et al. compared fibrin glue combined with bone morphogenetic protein (BMP) with recombined bone xenograft (RBX). They found histological and biomechanical proof that RBX was advantageous on accelerating tendon-bone interface healing [90]. Spalazzi et al. reported a study on a novel triphased scaffold seeded with fibroblasts, chondrocytes, and osteoblasts in the first, middle, and last phases, respectively. In an athymic rat model of ACL reconstruction, they found that these three types of cells reacted well in the scaffold, with distinct mineral and fibrocartilage-like tissue formed. The host tissue infiltrated successfully into the engineered tissue [91].

Tendon Healing to a Bone Surface

Tendon healing to a bone surface can be observed in numerous structures, including the rotator cuff tendons in the shoulder, flexor tendons in the hand, tibial insertion of the knee's medial collateral ligament, and Achilles tendon. The supraspinatus tendon presents the most commonly studied model, possibly because of the frequency of its rupture. Its insertion to the superior aspect of the humeral head greater tuberosity is considered to be a direct insertion comprised by four zones

with a successive transition from tendon to non-mineralized cartilage, mineralized cartilage, and bone [92].

Factors Affecting Tendon-to-Bone Surface Healing

Surgical treatment of rotator cuff tears, open or arthroscopic, involves re-approximating the tendon edge to the bony surface of the humeral head. A firm reattachment of the torn tendon to the bony surface is considered essential for accelerated healing. An early animal model study examined differences between reattaching the tendon directly to cancellous bone surface or to a bony trough. Both techniques resulted to a similar tendon-to-bone healing process, and biomechanical parameters were approximately equal [93]. With the advent of novel suture-anchor devices [94], various configurations of either suture stitches and/or anchor positioning have been demonstrated to produce a stronger initial repair construct and overall improved results. Recently, the double-row technique, which incorporates a medial and lateral row of suture anchors in the repair configuration, has been suggested to present biomechanical advantages compared with single-row repairs, such as increased load to failure, improved contact areas and pressures, and decreased gap formation at the healing entheses [95, 96]. However, comparative clinical studies have not yet demonstrated a substantial improvement over single-row repair in either the degree of structural healing or functional outcomes, which would justify the increased implant cost and surgical time required [97].

The role of rehabilitation has been thoroughly examined. The response of healing tendons to mechanical load varies upon anatomic location [98]. Controlled loading can enhance healing in most settings. However, a fine balance must be reached between loads that are too low (leading to a catabolic state) or too high (leading to micro-damage). Thomopoulos et al. found that early exercise impaired rotator cuff tendon healing in a rat model [99]. Gimbel et al. also showed that long durations of immobilization in the rat

resulted in enhanced mechanical properties of the healing supraspinatus tendon insertion site [100]. Rehabilitation regimens should be appropriately initiated during early stages of the healing process, when the tendon-bone interface is still weak and complete functional recovery has yet to take place, to provide moderate mechanical stimulation of the tendon and prevent bone loss at the humeral head.

Interventions to Enhance Tendon-to-Bone Surface Healing

Currently, several biologic strategies have been employed to augment tendon-to-bone healing after rotator cuff repair in both the clinical and experimental setting. They can be divided into strategies that are clinically available now in humans (e.g., allograft, xenografts, scaffolds (ECMs), and platelet-rich plasma (PRP)) and strategies that have mainly been tested in animal models (e.g., growth factors, mesenchymal stem cells (MSCs), and gene therapy). Recent research has focused on applying growth factors in rotator cuff repair models in an attempt to augment tendon-to-bone healing by modulating the sequence of inflammation, repair, and remodeling. BMP-13, TGF- β (beta), PDGF- α (alpha), FGF-2, scleraxis (Scx), and membrane type 1-MMP have been studied in rotator cuff repair animal models and produced encouraging results in terms of histological maturation of the repair tissue and biomechanical properties of the tendon-to-bone complex [101–105]. MSCs have been used in rotator cuff research both as carriers for gene therapy strategies and as a primary means to augment tendon-to-bone healing. However, although their effectiveness has been shown in animal model studies of tendon-to-bone tunnel healing, Gulotta et al. failed to show any histological or biomechanical evidence of improvement in rat rotator cuff repair when MSCs were applied [106]. It is possible that the smaller repair site, in case of rotator cuff repairs, limits the amount of MSCs that can actively adhere to it. Recently, Mazzocca et al. demonstrated that connective tissue progenitor cells

(CTPs) with osteogenic potential can be harvested from the proximal humerus during arthroscopic rotator cuff repair and confirmed by rt-PCR their osteogenic potential [107]. However, experimental and clinical data on the effectiveness of applying CTPs are lacking. Using a periosteal flap to augment rotator cuff repair has also been studied. Chang et al. found evidence of improved healing with greater attachment strength by suturing a periosteal flap between the end of supraspinatus tendon and the bone trough in rats [108]. Several recent studies have focused on the use of synthetic scaffolds to augment rotator cuff repair. Scaffolds are known to affect cell recruitment and adherence, nutrient diffusion, growth factor delivery, and cell behavior. Advantages of their use in tendon-to-bone healing include providing initial mechanical integrity at the tendon-bone repair site and providing a conductive scaffold for tendon ingrowth after rotator cuff repair [109]. Their use has been advocated either as an interposition device for irreparable tears or to reinforce the suture repair line. Recently, nanofiber technology has been introduced in the design of synthetic biological scaffolds and proved to significantly improve scaffold properties *in vitro* [110]. Xenografts, mainly composed of porcine small intestine mucosa, have also been used as biological scaffolds to enhance rotator cuff tendon healing. However, in a prospective randomized clinical trial, Iannotti et al. demonstrated no improvement in healing or clinical outcomes compared with controls when using this type of repair augmentation [111]. Acellular dermal matrix grafts were introduced in an attempt to minimize problems associated with graft rejection. Experimental studies have confirmed the efficacy of this method compared with control rotator cuff repairs and other biological modalities [112, 113]. In a large clinical study, Wong et al. found improved clinical scores when employing a Graft Jacket allograft acellular human dermal matrix (Wright MT Inc, Arlington, TN) to augment the arthroscopic repair of massive rotator cuff tears [114]. PRP is a rich source of several growth factors deriving from platelets and plasma. It has been used for numerous orthopedic applications

to augment healing. However, the results of three prospective randomized clinical trials have failed to demonstrate a significant effect of PRP on the healing rates of rotator cuff repairs [115–117]. To date, available data do not support routine use of PRP in rotator cuff repair. Biophysical modalities, such as shock-wave therapy and LiPUS, have been suggested in an attempt to benefit from mechanical stimulation of the healing tendon without the risk of early range of motion activity. Qin et al. investigated the role of extracorporeal shock-wave therapy in a rabbit model of delayed osteotendinous junction healing and found that it induces osteogenesis by enhancing endochondral ossification and regeneration of the fibrocartilage zone [118]. Lu et al. provided biomechanical and histological evidence as well as microarray analysis data to support the value of LiPUS in accelerating osteotendinous junction healing [119, 120].

Challenges and Controversies

A good combination of surgical, biological, and biophysical enhancement may improve surgical prognosis and enhance postoperative repair. However, despite recent advances, failure rates of reconstructive ligament surgery and tendon repair procedures remain high. Regarding ACL reconstruction in particular, the mechanical properties of the femur–tendon graft–tibia complex are still inferior to that of the normal ACL. Strength and ultimate failure loads of the graft have been reported to reach at best 37 and 57 % of control values, respectively [121]. Although this is also determined by graft mid-substance remodeling besides tendon-to-bone tunnel healing, current studies evidence that the graft never returns to its original strength at the time of implantation. Biological interventions also present considerable limitations. The application of growth factors is a single-time method, and the appropriate dosage has not been definitively determined. The biological half-lives of these factors typically range from minutes to hours. Although gene therapy techniques seem to address this issue, the duration of growth factor availability in the local tendon-bone interface is

still unknown. Moreover, recombinant viruses used to transfer genes to target tissues are of unknown tolerance. Safety and regulatory issues concerning the use of gene transfer techniques are still pending. In addition, biological interventions, such as scaffolds and gene therapy, are costly and may increase the cost of the procedure significantly. Cost-effectiveness issues, even for interventions that have been clinically applied, have not been clarified. Some surgeons still debate the value of applying such modalities to tears that already have a poor potential to heal. Most importantly, although many of the biological and biophysical interventions described have produced promising results in animal models, most of them have not been tested in the clinical setting and their effectiveness remains unknown. The ability of animal models to reproduce the exact local conditions that tendon healing occurs within the human body remains limited. Even when studies in humans are performed, obtaining direct histological proof of healing can be extremely difficult. Such limitations have undermined the clinical relevance of current findings and pose significant challenges to future research.

Conclusions

The native tendon or ligament insertion to bone is a highly specialized and organized tissue that functions to transmit complex mechanical loads from soft tissue to bone. Local boundary conditions may modulate the sequence of inflammation, repair, and remodeling either in favor or against a mature tendon-to-bone osteointegration. Current research on bone–tendon and ligament healing has significantly improved our understanding of the healing of soft tissue graft to the host bone tunnel in ACL reconstruction models or to a bony surface. However, extrapolating the results of basic science studies to clinical practice and postoperative rehabilitation regimens remains a challenge. Biological interventions to enhance healing cannot at the present time be applied to clinical practice without prospective, randomized clinical trials confirming their findings.

References

- Benjamin M, Ralphs JR. Fibrocartilage in tendons and ligaments—an adaptation to compressive load. *J Anat.* 1998;193:481–94.
- Gao J, Messner K. Quantitative comparison of soft tissue-bone interface at chondral ligament insertions in the rabbit knee joint. *J Anat.* 1996;188:367–73.
- Arnoczky SP. Anatomy of the anterior cruciate ligament. *Clin Orthop.* 1983;172:19–25.
- Kawamura S, Ying L, Kim HJ, Dynybil C, Rodeo SA. Macrophages accumulate in the early phase of tendon-bone healing. *J Orthop Res.* 2005;23(6):1425–32.
- Aune AK, Hukkanen M, Madsen JE, Polak JM, Nordsletten L. Nerve regeneration during patellar tendon autograft remodelling after anterior cruciate ligament reconstruction: an experimental and clinical study. *J Orthop Res.* 1996;14(2):193–9.
- Rodeo SA, Arnoczky SP, Torzilli PA, Hidaka C, Warren RF. Tendon-healing in a bone tunnel. A biomechanical and histological study in the dog. *J Bone Joint Surg Am.* 1993;75A(12):1795–803.
- Goradia VK, Rochat MC, Grana WA, Rohrer MD, Prasad HS. Tendon-to-bone healing of a semitendinosus tendon autograft used for ACL reconstruction in a sheep model. *Am J Knee Surg.* 2000;13(3):143–51.
- Pinczewski LA, Clingeleffer AJ, Otto DD, Bonar SF, Corry IS. Integration of hamstring tendon graft with bone in reconstruction of the anterior cruciate ligament. *Arthroscopy.* 1997;3(5):641–3.
- Weiler A, Scheffler SU, Sudkamp NP. Current aspects of anchoring hamstring tendon transplants in cruciate ligament surgery. *Chirurg.* 2000;71(9):1034–44.
- Dahlberg L, Friden T, Roos H, Lark MW, Lohmander LS. A longitudinal study of cartilage matrix metabolism in patients with cruciate ligament rupture – synovial fluid concentrations of aggrecan fragments, stromelysin-1 and tissue inhibitor of metalloproteinase-1. *Br J Rheumatol.* 1994;33(12):1107–11.
- Rodeo SA, Kawamura S, Ma CB, Deng XH, Sussman PS, Hays P, et al. The effect of osteoclastic activity on tendon-to-bone healing: an experimental study in rabbits. *J Bone Joint Surg Am.* 2007;89A:2250–9.
- Demirag B, Sarisozen B, Ozer O, Kaplan T, Ozturk C. Enhancement of tendon-bone healing of anterior cruciate ligament grafts by blockade of matrix metalloproteinases. *J Bone Joint Surg Am.* 2005;87A:2401–10.
- Grana WA, Egle DM, Mahnken R, Goodhart CW. An analysis of autograft fixation after anterior cruciate ligament reconstruction in a rabbit model. *Am J Sports Med.* 1994;22(3):344–51.
- Lim JK, Hui J, Li L, Thambyah A, Goh J, Lee EH. Enhancement of tendon graft osteointegration using mesenchymal stem cells in a rabbit model of anterior cruciate ligament reconstruction. *Arthroscopy.* 2004;20(9):899–910.
- Yamakado K, Kitaoka K, Yamada H, Hashiba K, Nakamura R, Tomita K. The influence of mechanical stress on graft healing in a bone tunnel. *Arthroscopy.* 2002;18(1):82–90.
- Tomita F, Yasuda K, Mikami S, Sakai T, Yamazaki S, Tohyama H. Comparisons of intraosseous graft healing between the doubled flexor tendon graft and the bone-patellar tendon-bone graft in anterior cruciate ligament reconstruction. *Arthroscopy.* 2001;17(5):461–76.
- Park MJ, Lee MC, Seong SC. A comparative study of the healing of tendon autograft and tendon-bone autograft using patellar tendon in rabbits. *Int Orthop.* 2001;25(1):35–9.
- Yamazaki S, Yasuda K, Tomita F, Minami A, Tohyama H. The effect of graft-tunnel diameter disparity on intraosseous healing of the flexor tendon graft in anterior cruciate ligament reconstruction. *Am J Sports Med.* 2002;30(4):498–505.
- Panni AS, Milano G, Lucania L, Fabbriani C. Graft healing after anterior cruciate ligament reconstruction in rabbits. *Clin Orthop.* 1997;343:203–12.
- Yoshiya S, Nagano M, Kurosaka M, Muratsu H, Mizuno K. Graft healing in the bone tunnel in anterior cruciate ligament reconstruction. *Clin Orthop.* 2000;376:278–86.
- Suarez LS, Richmond JC. Overview of procurement, processing, and sterilization of soft tissue allografts for sports medicine. *Sports Med Arthrosc Rev.* 2007;15(3):106–13.
- Jackson DW, Grood ES, Goldstein JD, Rosen MA, Kurzweil PR, Cummings JF, et al. A comparison of patellar tendon autograft and allograft used for anterior cruciate ligament reconstruction in the goat model. *Am J Sports Med.* 1993;21(2):176–85.
- Muramatsu K, Hachiya Y, Izawa H. Serial evaluation of human anterior cruciate ligament grafts by contrast-enhanced magnetic resonance imaging: comparison of allografts and autografts. *Arthroscopy.* 2008;24(9):1038–44.
- Fahey M, Indelicato PA. Bone tunnel enlargement after anterior cruciate ligament replacement. *Am J Sports Med.* 1994;22(3):410–4.
- Dustmann M, Schmidt T, Gangey I, Unterhauser FN, Weiler A, Scheffler SU. The extracellular remodeling of free-soft-tissue autografts and allografts for reconstruction of the anterior cruciate ligament: a comparison study in a sheep model. *Knee Surg Sports Traumatol Arthrosc.* 2008;16(4):360–9.
- Jackson DW, Corsetti J, Simon TM. Biologic incorporation of allograft anterior cruciate ligament replacements. *Clin Orthop.* 1996;324:126–33.
- Poehling GG, Curl WW, Lee CA, Ginn TA, Rushing JT, Naughton MJ, et al. Analysis of outcomes of anterior cruciate ligament repair with 5-year follow-up: allograft versus autograft. *Arthroscopy.* 2005;21(7):774–85.
- Rihn JA, Irrgang JJ, Chhabra A, Fu FH, Harner CD. Does irradiation affect the clinical outcome of patellar tendon allograft ACL reconstruction? *Knee Surg Sports Traumatol Arthrosc.* 2006;14(9):885–96.
- Ozenci AM, Inanmaz E, Ozcanli H, Soyuncu Y, Samanci N, Dageven T, et al. Proprioceptive comparison of allograft and autograft anterior cruciate

- ligament reconstructions. *Knee Surg Sports Traumatol Arthrosc.* 2007;15(12):1432–7.
30. Fideler BM, Vangness Jr CT, Lu B, Orlando C, Moore T. Gamma irradiation: effects on biomechanical properties of human bone-patellar tendon-bone allografts. *Am J Sports Med.* 1995;23(5):643–6.
 31. Salehpour A, Butler DL, Proch FS, Schwartz HE, Feder SM, Doxey CM, et al. Dose-dependent response of gamma irradiation on mechanical properties and related biochemical composition of goat bone-patellar tendon-bone allografts. *J Orthop Res.* 1995;13(6):898–906.
 32. Mae T, Shino K, Maeda A, Toritsuka Y, Horibe S, Ochi T. Effect of gamma irradiation on remodeling process of tendon allograft. *Clin Orthop.* 2003;414:305–14.
 33. Miller SL, Gladstone JN. Graft selection in anterior cruciate ligament reconstruction. *Orthop Clin North Am.* 2002;33(4):675–83.
 34. Bhatia S, Bell R, Frank RM, Rodeo SA, Bach Jr BR, Cole BJ, et al. Bony incorporation of soft tissue anterior cruciate ligament grafts in an animal model: autograft versus allograft with low-dose gamma irradiation. *Am J Sports Med.* 2012;40:1789–98.
 35. Denti M, Lo Vetere D, Bait C, Schonhuber H, Melegati G, Volpi P. Revision anterior cruciate ligament reconstruction: causes of failure, surgical technique, and clinical results. *Am J Sports Med.* 2008;36(10):1896–902.
 36. Getelman MH, Friedman MJ. Revision anterior cruciate ligament reconstruction surgery. *J Am Acad Orthop Surg.* 1999;7(3):189–98.
 37. Grood ES, Walz-Hasselfeld KA, Holden JP, Noyes FR, Levy MS, Butler DL, et al. The correlation between anterior-posterior translation and cross-sectional area of anterior cruciate ligament reconstructions. *J Orthop Res.* 1992;10(6):878–85.
 38. Ekdahl M, Nozaki M, Ferretti M, Tsai A, Smolinski P, Fu FH. The effect of tunnel placement on bone-tendon healing in anterior cruciate ligament reconstruction in a goat model. *Am J Sports Med.* 2009;37(8):1522–30.
 39. Weiler A, Peine R, Pashmineh-Azar A, Abel C, Sudkamp NP, Hoffmann RF. Tendon healing in a bone tunnel. Part I: biomechanical results after biodegradable interference fit fixation in a model of anterior cruciate ligament reconstruction in sheep. *Arthroscopy.* 2002;18(2):113–23.
 40. Weiler A, Hoffmann RF, Bail HJ, Rehm O, Sudkamp NP. Tendon healing in a bone tunnel. Part II: histologic analysis after biodegradable interference fit fixation in a model of anterior cruciate ligament reconstruction in sheep. *Arthroscopy.* 2002;18(2):124–35.
 41. Hunt P, Rehm O, Weiler A. Soft tissue graft interference fit fixation: observations on graft insertion site healing and tunnel remodeling 2 years after ACL reconstruction in sheep. *Knee Surg Sports Traumatol Arthrosc.* 2006;14(12):1245–51.
 42. Singhatat W, Lawhorn KW, Howell SM, Hull ML. How four weeks of implantation affect the strength and stiffness of a tendon graft in a bone tunnel: a study of two fixation devices in an extraarticular model in ovine. *Am J Sports Med.* 2002;30(4):506–13.
 43. Zantop T, Weimann A, Wolle K, Musahl V, Langer M, Petersen W. Initial and 6 weeks postoperative structural properties of soft tissue anterior cruciate ligament reconstructions with cross-pin or interference screw fixation: an in vivo study in sheep. *Arthroscopy.* 2007;23(1):14–20.
 44. Micucci CJ, Frank DA, Kompel J, Muffly M, Demeo PJ, Altman GT. The effect of interference screw diameter on fixation of soft-tissue grafts in anterior cruciate ligament reconstruction. *Arthroscopy.* 2010;26(8):1105–10.
 45. Greis PE, Burks RT, Bachus K, Luker MG. The influence of tendon length and fit on the strength of a tendon-bone tunnel complex. A biomechanical and histologic study in the dog. *Am J Sports Med.* 2001;29(4):493–7.
 46. Labs K, Perka C, Schneider F. The biological and biomechanical effect of different graft tensioning in anterior cruciate ligament reconstruction: an experimental study. *Arch Orthop Trauma Surg.* 2002;122(4):193–9.
 47. Yoshiya S, Andrish JT, Manley MT, Bauer TW. Graft tension in anterior cruciate ligament reconstruction. An in vivo study in dogs. *Am J Sports Med.* 1987;15(5):464–70.
 48. Abramowitch SD, Papageorgiou CD, Withrow JD, Gilbert TW, Woo SL. The effect of initial graft tension on the biomechanical properties of a healing ACL replacement graft: a study in goats. *J Orthop Res.* 2003;21(4):708–15.
 49. Hantes ME, Mastrokalos DS, Yu J, Paessler HH. The effect of early motion on tibial tunnel widening after anterior cruciate ligament replacement using hamstring tendon grafts. *Arthroscopy.* 2004;20(6):572–80.
 50. Sakai H, Fukui N, Kawakami A, Kurosawa H. Biological fixation of the graft within bone after anterior cruciate ligament reconstruction in rabbits: effects of the duration of postoperative immobilization. *J Orthop Sci.* 2000;5(1):43–51.
 51. Brophy RH, Kovacevic D, Imhauser CW, Stasiak M, Bedi A, Fox AJ, et al. Effect of short-duration low-magnitude cyclic loading versus immobilization on tendon-bone healing after ACL reconstruction in a rat model. *J Bone Joint Surg Am.* 2011;93A:381–93.
 52. Thomopoulos S, Zampiakos E, Das R, Silva MJ, Gelberman RH. The effect of muscle loading on flexor tendon-to-bone healing in a canine model. *J Orthop Res.* 2008;26(12):1611–7.
 53. Wen CY, Qin L, Lee KM, Wong MW, Chan KM. Grafted tendon healing in tibial tunnel is inferior to healing in femoral tunnel after anterior cruciate ligament reconstruction: a histomorphometric study in rabbits. *Arthroscopy.* 2010;26(1):58–66.

54. Lui PP, Ho G, Shum WT, Lee YW, Ho PY, Lo WN, et al. Inferior tendon graft to bone tunnel healing at the tibia compared to that at the femur after anterior cruciate ligament reconstruction. *J Orthop Sci*. 2010;15(3):389–401.
55. Grassman SR, McDonald DB, Thornton GM, Shrive NG, Frank CB. Early healing processes of free tendon grafts within bone tunnels is bone-specific: a morphological study in a rabbit model. *Knee*. 2002; 9(1):21–6.
56. Yamazaki S, Yasuda K, Tomita F, Minami A, Tohyama H. The effect of intraosseous graft length on tendon-bone healing in anterior cruciate ligament reconstruction using flexor tendon. *Knee Surg Sports Traumatol Arthrosc*. 2006;14(11):1086–93.
57. Lui P, Zhang P, Chan K, Qin L. Biology and augmentation of tendon-bone insertion repair. *J Orthop Surg Res*. 2010;5:59.
58. Deehan DJ, Cawston TE. The biology of integration of the anterior cruciate ligament. *J Bone Joint Surg Br*. 2005;87B:889–95.
59. Wen CY, Qin L, Lee KM, Wong MW, Chan KM. Influence of bone adaptation on tendon-to-bone healing in bone tunnel after anterior cruciate ligament reconstruction in a rabbit model. *J Orthop Res*. 2009;27(11):1447–56.
60. Zerahn B, Munk AO, Helweg J, Hovgaard C. Bone mineral density in the proximal tibia and calcaneus before and after arthroscopic reconstruction of the anterior cruciate ligament. *Arthroscopy*. 2006;22(3): 265–9.
61. Tien YC, Chih TT, Lin JH, Ju CP, Lin SD. Augmentation of tendon-bone healing by the use of calcium-phosphate cement. *J Bone Joint Surg Br*. 2004;86B:1072–6.
62. Huangfu X, Zhao J. Tendon-bone healing enhancement using injectable tricalcium phosphate in a dog anterior cruciate ligament reconstruction model. *Arthroscopy*. 2007;23(5):455–62.
63. Leung KS, Siu WS, Li SF, Qin L, Cheung WH, Tam KF, et al. An in vitro optimized injectable calcium phosphate cement for augmenting screw fixation in osteopenic goats. *J Biomed Mater Res B*. 2006; 78(1):153–60.
64. Mutsuzaki H, Sakane M. Calcium phosphate-hybridized tendon graft to enhance tendon-bone healing two years after ACL reconstruction in goats. *Sports Med Arthrosc Rehabil Ther Technol*. 2011;3(1):31.
65. Mutsuzaki H, Sakane M, Fujie H, Hattori S, Kobayashi H, Ochiai N. Effect of calcium phosphate-hybridized tendon graft on biomechanical behavior in anterior cruciate ligament reconstruction in a goat model: novel technique for improving tendon-bone healing. *Am J Sports Med*. 2011;39(5):1059–66.
66. Gulotta LV, Kovacevic D, Ying L, Ehteshami JR, Montgomery S, Rodeo SA. Augmentation of tendon-to-bone healing with a magnesium-based bone adhesive. *Am J Sports Med*. 2008;36(7):1290–7.
67. Hays PL, Kawamura S, Deng XH, Dagher E, Mithoefer K, Ying L, et al. The role of macrophages in early healing of a tendon graft in a bone tunnel. *J Bone Joint Surg Am*. 2008;90A:565–79.
68. Wang CJ, Wang FS, Yang KD, Weng LH, Sun YC, Yang YJ. The effect of shock wave treatment at the tendon-bone interface—an histomorphological and biomechanical study in rabbits. *J Orthop Res*. 2005;23(2):274–80.
69. Walsh WR, Stephens P, Vizesi F, Bruce W, Huckle J, Yu Y. Effects of low-intensity pulsed ultrasound on tendon-bone healing in an intra-articular sheep knee model. *Arthroscopy*. 2007;23(2):197–204.
70. Papatheodorou LK, Malizos KN, Poultsides LA, Hantes ME, Grafanaki K, Giannouli S, et al. Effect of transosseous application of low-intensity ultrasound at the tendon graft-bone interface healing: gene expression and histological analysis in rabbits. *Ultrasound Med Biol*. 2009;35(4):576–84.
71. Yeh WL, Lin SS, Yuan LJ, Lee KF, Lee MY, Ueng SW. Effects of hyperbaric oxygen treatment on tendon graft and tendon-bone integration in bone tunnel: biochemical and histological analysis in rabbits. *J Orthop Res*. 2007;25(5):636–45.
72. Rodeo SA, Suzuki K, Deng XH, Wozney J, Warren RF. Use of recombinant human bone morphogenetic protein-2 to enhance tendon healing in a bone tunnel. *Am J Sports Med*. 1999;27(4):476–88.
73. Ma CB, Kawamura S, Deng XH, Ying L, Schneidkraut J, Hays P, et al. Bone morphogenetic proteins-signaling plays a role in tendon-to-bone healing: a study of rhBMP-2 and noggin. *Am J Sports Med*. 2007; 35(4):597–604.
74. Mihelic R, Pecina M, Jelic M, Zoricic S, Kusec V, Simic P, et al. Bone morphogenetic protein-7 (osteogenic protein-1) promotes tendon graft integration in anterior cruciate ligament reconstruction in sheep. *Am J Sports Med*. 2004;32(7):1619–25.
75. Yamazaki S, Yasuda K, Tomita F, Tohyama H, Minami A. The effect of transforming growth factor-beta1 on intraosseous healing of flexor tendon autograft replacement of anterior cruciate ligament in dogs. *Arthroscopy*. 2005;21(9):1034–41.
76. Anderson K, Seneviratne AM, Izawa K, Atkinson BL, Potter HG, Rodeo SA. Augmentation of tendon healing in an intraarticular bone tunnel with use of a bone growth factor. *Am J Sports Med*. 2001;29(6):689–98.
77. Sasaki K, Kuroda R, Ishida K, Kubo S, Matsumoto T, Mifune Y, et al. Enhancement of tendon-bone osteointegration of anterior cruciate ligament graft using granulocyte colony-stimulating factor. *Am J Sports Med*. 2008;36(8):1519–27.
78. Lattermann C, Zelle BA, Whalen JD, Baltzer AW, Robbins PD, Niyibizi C, et al. Gene transfer to the tendon-bone insertion site. *Knee Surg Sports Traumatol Arthrosc*. 2004;12(5):510–5.
79. Martinek V, Latterman C, Usas A, Abramowitch S, Woo SL, Fu FH, et al. Enhancement of tendon-bone integration of anterior cruciate ligament grafts with bone morphogenetic protein-2 gene transfer: a histological and biomechanical study. *J Bone Joint Surg Am*. 2002;84A:1123–31.

80. Wang CJ, Weng LH, Hsu SL, Sun YC, Yang YJ, Chan YS, et al. PCMV-BMP-2-transfected cell-mediated gene therapy in anterior cruciate ligament reconstruction in rabbits. *Arthroscopy*. 2010;26(7):968–76.
81. Soon MY, Hassan A, Hui JH, Goh JC, Lee EH. An analysis of soft tissue allograft anterior cruciate ligament reconstruction in a rabbit model: a short-term study of the use of mesenchymal stem cells to enhance tendon osteointegration. *Am J Sports Med*. 2007;35(6):962–71.
82. Ju YJ, Muneta T, Yoshimura H, Koga H, Sekiya I. Synovial mesenchymal stem cells accelerate early remodeling of tendon-bone healing. *Cell Tissue Res*. 2008;332(3):469–78.
83. Li YG, Wei JN, Lu J, Wu XT, Teng GJ. Labeling and tracing of bone marrow mesenchymal stem cells for tendon-to-bone tunnel healing. *Knee Surg Sports Traumatol Arthrosc*. 2011;19(12):2153–8.
84. Youn I, Jones DG, Andrews PJ, Cook MP, Suh JK. Periosteal augmentation of a tendon graft improves tendon healing in the bone tunnel. *Clin Orthop*. 2004;419:223–31.
85. Karoglu S, Celik C, Korkusuz P. The effects of bone marrow or periosteum on tendon-to-bone tunnel healing in a rabbit model. *Knee Surg Sports Traumatol Arthrosc*. 2009;17(2):170–8.
86. Robert H, Es-Sayeh J. The role of periosteal flap in the prevention of femoral widening in anterior cruciate ligament reconstruction using hamstring tendons. *Knee Surg Sports Traumatol Arthrosc*. 2004;12(1):30–5.
87. Orrego M, Larrain C, Rosales J, Valenzuela L, Matas J, Durruty J, et al. Effects of platelet concentrate and a bone plug on the healing of hamstring tendons in a bone tunnel. *Arthroscopy*. 2008;24(12):1373–80.
88. Chen CH, Liu HW, Tsai CL, Yu CM, Lin IH, Hsiue GH. Photoencapsulation of bone morphogenetic protein-2 and periosteal progenitor cells improve tendon graft healing in a bone tunnel. *Am J Sports Med*. 2008;36(3):461–73.
89. Lu Y, Markel MD, Nemke B, Lee JS, Graf BK, Murphy WL. Influence of hydroxyapatite-coated and growth factor-releasing interference screws on tendon-bone healing in an ovine model. *Arthroscopy*. 2009;25(12):1427–34.e1.
90. Zhang W, Pan W, Zhang M, Wei Y. In vivo evaluation of two types of bioactive scaffold used for tendon-bone interface healing in the reconstruction of anterior cruciate ligament. *Biotechnol Lett*. 2011;33(4):837–44.
91. Spalazzi JP, Dagher E, Doty SB, Guo XE, Rodeo SA, Lu HH. In vivo evaluation of a multiphased scaffold designed for orthopaedic interface tissue engineering and soft tissue-to-bone integration. *J Biomed Mater Res A*. 2008;86(1):1–12.
92. Woo S-Y, Akeson W. Ligament, tendon, and joint capsule insertion to bone. In: Woo S-Y, Buckwalter JA, editors. *Injury and repair of the musculoskeletal soft-tissues*. Park Ridge: AAOS; 1988. p. 133–66.
93. St Pierre P, Olson EJ, Elliott JJ, O'Hair KC, McKinney LA, Ryan J. Tendon-healing to cortical bone compared with healing to a cancellous trough. A biomechanical and histological evaluation in goats. *J Bone Joint Surg Am*. 1995;77A:1858–66.
94. Barber FA, Herbert MA. Suture anchors—update 1999. *Arthroscopy*. 1999;15(7):719–25.
95. Nelson CO, Sileo MJ, Grossman MG, Serra-Hsu F. Single-row modified Mason-Allen versus double-row arthroscopic rotator cuff repair: a biomechanical and surface area comparison. *Arthroscopy*. 2008;24(8):941–8.
96. Meier SW, Meier JD. The effect of double-row fixation on initial repair strength in rotator cuff repair: a biomechanical study. *Arthroscopy*. 2006;22(11):1168–73.
97. Dines JS, Bedi A, El Attrache NS, Dines DM. Single-row versus double-row rotator cuff repair: techniques and outcomes. *J Am Acad Orthop Surg*. 2010;18(2):83–93.
98. Killian ML, Cavinatto L, Galatz LM, Thomopoulos S. The role of mechanobiology in tendon healing. *J Shoulder Elbow Surg*. 2012;21(2):228–37.
99. Thomopoulos S, Williams GR, Soslowky LJ. Tendon to bone healing: differences in biomechanical, structural, and compositional properties due to a range of activity levels. *J Biomech Eng*. 2003;125(1):106–13.
100. Gimbel JA, Van Kleunen JP, Williams GR, Thomopoulos S, Soslowky LJ. Long durations of immobilization in the rat result in enhanced mechanical properties of the healing supraspinatus tendon insertion site. *J Biomech Eng*. 2007;129(3):400–4.
101. Kovacevic D, Rodeo SA. Biological augmentation of rotator cuff tendon repair. *Clin Orthop*. 2008;466:622–33.
102. Manning CN, Kim HM, Sakiyama-Elbert S, Galatz LM, Havlioglu N, Thomopoulos S. Sustained delivery of transforming growth factor beta three enhances tendon-to-bone healing in a rat model. *J Orthop Res*. 2011;29(7):1099–105.
103. Uggen C, Dines J, McGarry M, Grande D, Lee T, Limpisvasti O. The effect of recombinant human platelet-derived growth factor BB-coated sutures on rotator cuff healing in a sheep model. *Arthroscopy*. 2010;26(11):1456–62.
104. Gulotta LV, Kovacevic D, Montgomery S, Ehteshami JR, Packer JD, Rodeo SA. Stem cells genetically modified with the developmental gene MT1-MMP improve regeneration of the supraspinatus tendon-to-bone insertion site. *Am J Sports Med*. 2010;38(7):1429–37.
105. Gulotta LV, Kovacevic D, Packer JD, Deng XH, Rodeo SA. Bone marrow-derived mesenchymal stem cells transduced with scleraxis improve rotator cuff healing in a rat model. *Am J Sports Med*. 2011;39(6):1282–9.
106. Gulotta LV, Kovacevic D, Ehteshami JR, Dagher E, Packer JD, Rodeo SA. Application of bone marrow-derived mesenchymal stem cells in a rotator cuff

- repair model. *Am J Sports Med.* 2009;37(11):2126–33.
107. Mazzocca AD, McCarthy MB, Chowanec DM, Cote MP, Arciero RA, Drissi H. Rapid isolation of human stem cells (connective tissue progenitor cells) from the proximal humerus during arthroscopic rotator cuff surgery. *Am J Sports Med.* 2010;38(7):1438–47.
108. Chang CH, Chen CH, Su CY, Liu HT, Yu CM. Rotator cuff repair with periosteum for enhancing tendon-bone healing: a biomechanical and histological study in rabbits. *Knee Surg Sports Traumatol Arthrosc.* 2009;17(12):1447–53.
109. Edwards SL, Lynch TS, Saltzman MD, Terry MA, Nuber GW. Biologic and pharmacologic augmentation of rotator cuff repairs. *J Am Acad Orthop Surg.* 2011;19(10):583–9.
110. Moffat KL, Kwei AS, Spalazzi JP, Doty SB, Levine WN, Lu HH. Novel nanofiber-based scaffold for rotator cuff repair and augmentation. *Tissue Eng Part A.* 2009;15(1):115–26.
111. Iannotti JP, Codsi MJ, Kwon YW, Derwin K, Ciccone J, Brems JJ. Porcine small intestine submucosa augmentation of surgical repair of chronic two-tendon rotator cuff tears. A randomized, controlled trial. *J Bone Joint Surg Am.* 2006;88A:1238–44.
112. Fini M, Torricelli P, Giavaresi G, Rotini R, Castagna A, Giardino R. In vitro study comparing two collagenous membranes in view of their clinical application for rotator cuff tendon regeneration. *J Orthop Res.* 2007;25(1):98–107.
113. Ide J, Kikukawa K, Hirose J, Iyama K, Sakamoto H, Mizuta H. The effects of fibroblast growth factor-2 on rotator cuff reconstruction with acellular dermal matrix grafts. *Arthroscopy.* 2009;25(6):608–16.
114. Wong I, Burns J, Snyder S. Arthroscopic Graft Jacket repair of rotator cuff tears. *J Shoulder Elbow Surg.* 2010;19(2 Suppl):104–9.
115. Castricini R, Longo UG, De Benedetto M, Panfoli N, Pirani P, Zini R, et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. *Am J Sports Med.* 2011;39(2):258–65.
116. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. *J Shoulder Elbow Surg.* 2011;20(4):518–28.
117. Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: a prospective, randomized clinical study. *Am J Sports Med.* 2012;40:1234–41.
118. Qin L, Wang L, Wong MW, Wen C, Wang G, Zhang G, et al. Osteogenesis induced by extracorporeal shockwave in treatment of delayed osteotendinous junction healing. *J Orthop Res.* 2010;28(1):70–6.
119. Lu H, Qin L, Lee K, Cheung W, Chan K, Leung K. Identification of genes responsive to low-intensity pulsed ultrasound stimulations. *Biochem Biophys Res Commun.* 2009;378(3):569–73.
120. Lu H, Qin L, Fok P, Cheung W, Lee K, Guo X, et al. Low-intensity pulsed ultrasound accelerates bone-tendon junction healing: a partial patellectomy model in rabbits. *Am J Sports Med.* 2006;34(8):1287–96.
121. Butler DL, Grood ES, Noyes FR, Olmstead ML, Hohn RB, Arnoczky SP, et al. Mechanical properties of primate vascularized vs. nonvascularized patellar tendon grafts; changes over time. *J Orthop Res.* 1989;7(1):68–79.

Vasileios Kontogeorgakos

Introduction

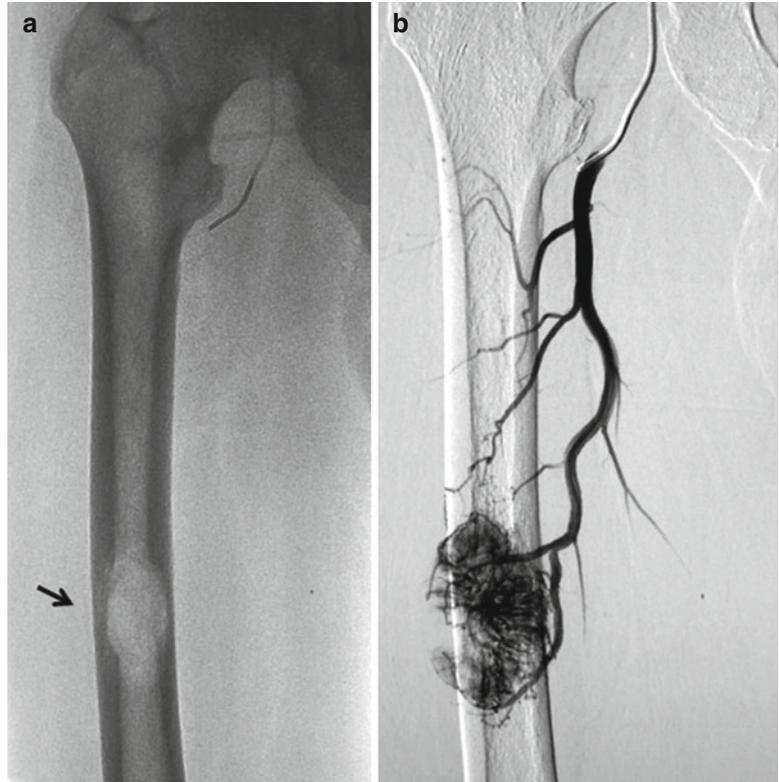
The term osseointegration refers to a direct bone-to-metal interface without interposition of non-bone tissue [1]. Essentially, the process of osseointegration reflects an anchorage mechanism whereby non-vital components can be reliably incorporated into living bone and which persist under all normal conditions of loading [1, 2]. Although for most clinicians an implant is considered as osseointegrated when there is no progressive relative movement between the implant and the bone interface [3], the concept of osseointegration has been studied and defined at multiple levels – clinically [4], anatomically [1], histologically, and ultrastructurally [5]. These biological events include the activation of osteo-productive processes similar to those of the bone healing process, at least in terms of initial host response [4, 6, 7]. This cascade of biological events is regulated by growth and differentiation factors released by activated blood cells at the bone-implant interface [8]. Several *in vivo* and *in vitro* studies have been performed in order to delineate the optimum characteristics of the material of an implant for successful osseointegration.

Osseointegration, however, is not a biological property of any implant system or metal; thus, it is not considered as the result of an advantageous biological tissue response but rather as the lack of a negative tissue response [5, 9]. Factors inhibiting osseointegration include excessive implant mobility and micromotion [10, 11], inappropriate porosity of the porous coating of the implant [12], radiation therapy [13, 14], and pharmacological agents such as cyclosporin A, methotrexate, cis-platinum [15–17], warfarin and low-molecular-weight heparins [18], and nonsteroid anti-inflammatory drugs especially selective COX-2 inhibitors [19]. There are also patient-related factors such as osteoporosis, rheumatoid arthritis, advanced age, nutritional deficiency, smoking, and renal insufficiency [20–23].

In patients with neoplastic disease, the process of osseointegration can be compromised either by the local biology of the disease itself or by the adjuvant therapeutic applications that intervene in the healing process. Bone lesions can be primary or metastatic, malignant or benign. These lesions can be osteoblastic, lytic, or more commonly mixed. In lytic lesions, it is the osteoclastic activity that predominates, while in bone-forming lesions, it is the osteoblastic activity. However, due to the coupling phenomenon, both osteoclastic and osteoblastic activity are present [24]. The discovery of the RANK (receptor activator of nuclear factor kappa B) and its ligand RANKL system has rapidly advanced our understanding of the mechanisms that regulate osteoclast–osteoblast interactions

V. Kontogeorgakos, MD, DSc
Department of Orthopaedic Surgery,
University General Hospital of Larissa,
Larissa, Greece
e-mail: vaskonto@gmail.com, <http://www.ortho-uth.org/>

Fig. 22.1 (a) A 72-year-old man with metastatic renal cell carcinoma to the diaphysis of the right femur. (b) The lesion is lytic (arrow) and hypervascular with arterial feeding branches from the deep femoral artery



and osteoclast formation and activation [25–27]. Osteoprotegerin (OPG) is a soluble member of the tumor necrosis factor (TNF) receptor superfamily that functions as a decoy receptor for RANKL and is a very effective inhibitor of osteoclast differentiation and maturation [28–30]. Tumor cells produce different factors that manipulate the RANK/RANKL/OPG pathway in order to stimulate bone destruction. Furthermore, pending on the tumor type, RANKL plays a role in the migration, invasion, and proliferation of malignant cells within the bone, while OPG increases survival of tumor cells [31].

A typical example of metastatic aggressive bone lytic lesion is that of renal cell carcinoma (Fig. 22.1). Implantation of a prosthesis in the area of an active lytic lesion is probably doomed to failure as the osteoclastic activity will preclude osseointegration and bone healing. This is the reason why cement is frequently used when a prosthesis is needed for reconstruction of a lytic lesion, enhanced by delivery of local radiation therapy (Fig. 22.2).

Chemotherapy can potentially have an adverse effect on bone turnover, formation, and healing [32–35]. In evaluating the effects of chemotherapeutic agents at a cellular level, two distinct types of biochemical injury must be considered. Firstly, protein synthesis is important for normal cellular function and homeostasis. Secondly, cells must have the ability to reproduce themselves, and this requires the replication of DNA [36]. Friedlaender et al. studied the effect of chemotherapy on trabeculae bone at the proximal tail vertebrae in rats [36]. They used doxorubicin and methotrexate. Both drugs significantly and profoundly diminished bone-formation rates by nearly 60%. The toxic effect of chemotherapy on osteoblasts was reflected in reduced volume and thickness of the osteoid, but the total numbers of osteoblasts and the percentage of trabecular surface covered by bone-forming cells were not affected. The numbers of osteoclasts and the extent of their activity were not clearly different from those in untreated rats. Chemotherapeutic agents have an adverse

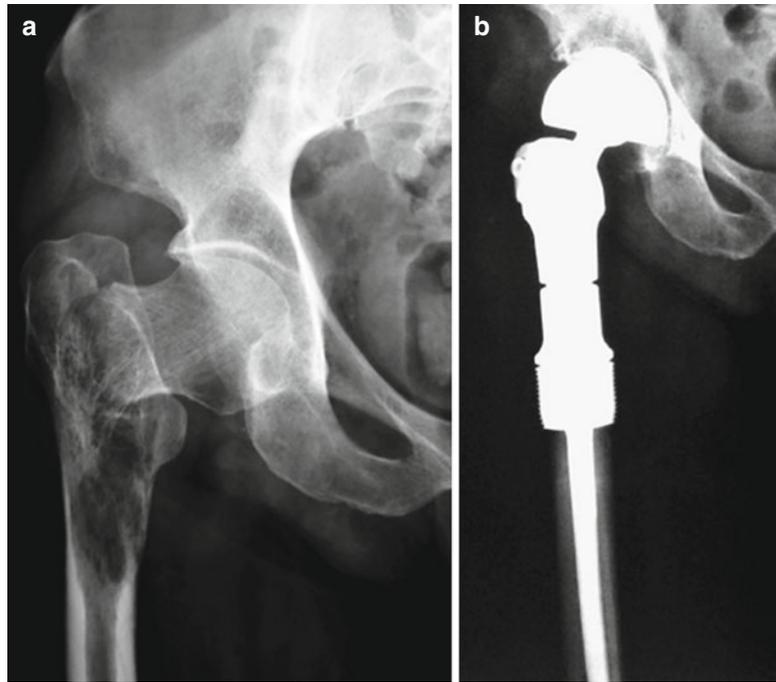


Fig. 22.2 A 65-year-old woman with breast cancer sustained a pathologic subcapital fracture through a metastatic lytic lesion of the left femoral neck. She was treated with cemented bipolar hemiarthroplasty. No postoperative radiation was offered. Three years later experienced vague pain at the femur. X-rays revealed a new lytic lesion at the tip of the stem. Biopsy reported metastatic tumor recurrence

effect on normal physiological bone turnover, especially osteoblastic activity, and would also be expected to alter fracture healing and bone-allograft incorporation by these same mechanisms [36]. Fourteen dogs were used to study the effect of a doxorubicin, cisplatin, and ifosfamide combination in normal bone turnover [37]. The results showed no differences in mechanical properties after 22 weeks of chemotherapy. The porosity, osteonal activity, and mineral apposition rate of the cortical bone were unaffected. The results also showed no difference in porosity of perimeter in cancellous bone, but the mineral

apposition rate was significantly reduced. The authors concluded that although the effect of temporary chemotherapy on bone may have minor effects on normal turnover and that the effect may be reversible, it causes disturbance in bone mass accumulation. This may later raise the risk of fragility fractures and osteoporosis. Gravel et al. studied the effect of neoadjuvant chemotherapy on distraction osteogenesis in the goat model [38]. In a multifactorial analysis of the lengthened bones, there was no statistically significant difference between the control goats versus goats that received chemotherapy; indicating that there was no sustained inhibitory effect on bone formation by the chemotherapy. Cañadell et al. studied the effect of chemotherapy on bone transport after resection of a tumor [34]. In their clinical study, chemotherapy had an adverse effect on bone consolidation, and thus, it is recommended that this method of reconstruction is used only in very young patients. However, Kapukaya et al. studied nine patients who underwent distraction osteogenesis after bone tumor resection [39]. Three patients received pre- and postoperative chemotherapy. In this small clinical study, they found no significant adverse effects of chemotherapy on callus distraction. Tsuchiya et al. studied 17 patients who underwent distraction osteogenesis and 11 patients with vascularized fibular graft for reconstruction after tumor resection and postoperative chemotherapy [40]. They concluded that postoperative chemotherapy for malignant bone tumors did not adversely affect the ability to achieve union or cause hypertrophy of the vascularized fibular graft and had a minimal effect on distraction osteogenesis. Campanna et al. identified chemotherapy as a factor that significantly influences the host-allograft junction healing rate [41]. Another large clinical study of 200 osteoarticular allografts revealed that the use of chemotherapy materially affects the outcome of an osteoarticular allograft implanted for tumor management, particularly in the distal femur [35]. Because the infection and fracture rates did not differ appreciably for the control and the chemotherapy groups, this can be taken as clear evidence that the administration of

Fig. 22.3 (a) A 68-year-old man sustained a pathologic subcapital fracture of the right ischium. Severe osteolysis is noted extending to the subtrochanteric area. (b) The patient was treated with resection of the proximal femur and reconstruction with hemiarthroplasty proximal femur cemented mega-prosthesis



chemotherapy has a significant and independent effect on allograft outcome. More specifically, regarding bone healing, union was achieved in 32 % of the non-chemotherapy group vs 12 % of the chemotherapy group ($p < 0.002$) [35]. Virolainen et al. studied the effect of chemotherapy on bone-graft incorporation and fixation of porous-coated prostheses [42]. On eight mixed-breed dogs, under perioperative chemotherapy with doxorubicin, cisplatin, and ifosfamide, they performed unilateral resection of a 6-cm segment of the femoral diaphysis and reconstruction with a porous-coated segmental prosthesis. Chemotherapy showed a significant effect on new bone formation as seen in reduced callus size and lower ultimate strength of extracortical fixation.

In clinical practice, tumor prosthesis is usually cemented for two reasons (Fig. 22.3). First, cement fixation does not need osseointegration, thus allowing for early weight bearing. The second reason is the fear of early loosening due to the negative effect of chemotherapy on osseointegration and the increased stress applied to the intramedullary stems. In addition, chemotherapy adversely affects nutritional status [43]. There is evidence that malnutrition can impair osseointegration with decreased strength needed to completely loosen

the implant and that it can alter bone microarchitecture in the vicinity of the implant in the proximal tibia of rats [44]. Eckardt et al. in 2010 reported on cemented endoprosthetic reconstructions of the proximal tibia after tumor resection, and the 15-year survivorship of 29 modular implants was 87.5 % [45]. Flint et al. reported on 44 patients after sarcoma resection from the proximal tibia and uncemented endoprosthetic reconstruction. At a mean final follow-up of 60 months, there were no cases of aseptic loosening, and it was concluded that aseptic loosening is uncommon with uncemented proximal tibia reconstruction [46]. Farfalli et al. studied the results of 50 intramedullary uncemented press-fit distal femoral stems. The overall Kaplan–Meier prosthetic survival rates were 85 % at 5 and 71 % at 10 years. They concluded that stem diameters less than 13.5 mm and a diaphyseal/stem coefficient greater than 2.5 mm were associated with decreased prosthetic survival [47]. The longevity of endoprosthetic reconstruction after bone tumor resection is largely dependent on bone-prosthesis interface and length of bone resection [48, 49]. New tumor prostheses with improved bioengineered design require fewer revisions; however, they continue to fail due to septic and aseptic loosening secondary to stress shielding and particle induced osteolysis [49].

Newer implants achieve stable prosthesis–bone fixation without using long intramedullary stems, either cemented or not. A spring-loaded prosthesis component exerts continuous high compression forces, inducing bone hypertrophy at the bone-prosthesis interface [50, 51]. These prostheses provide immediate stable fixation and avoid stress shielding [51]. A clinical review suggests these compressed implants compare favorably in the short term with cemented and uncemented prostheses [48, 52]. Mechanical failure of these systems is characterized by a lack of bone hypertrophy or even some bone resorption, with failure of the compress mechanism [48]. It seems that chemotherapy adversely affects both the absolute amount and the rate of bony hypertrophy at the prosthetic interface of massive tumor endoprosthesis secured with compressive osseointegration technology. In Avedian et al.'s study, chemotherapy delayed cortical hypertrophy compared to the no-chemotherapy group [49]. However, no differences were observed in cortical width after 12 months. An adverse effect of chemotherapy on prosthetic survival was suggested but not statistically supported.

Radiation therapy causes a wide spectrum of changes in the bone, ranging from temporary nonclinically significant alterations to radio-osteonecrosis [53, 54]. Radiation-induced bone changes are dependent on the age of the patient, location, beam energy, total dose, and fractionation. The threshold of bone cell changes is 30 Gy, with cell death and devascularization of the bone occurring at doses over 50 Gy [55, 56]. Impaired osteoblast function results in reduced osteoid production which is seen as osteopenia on plain x-rays, usually 1 year after irradiation [57]. Osteopenia due to radiation is asymptomatic, and no periosteal reaction is seen. New bone formation and deposition on unresorbed trabeculae result in a mottled appearance of the bone 2–3 years later, with osteopenia and coarse trabeculation. This radiological appearance is usually named radiation osteitis (Fig. 22.4) [55, 58]. Bonfiglio, in 1953, suggested that femoral neck fractures after irradiation are actually stress fractures as the irradiated bone is brittle and loses its ability to remodel and withstand stresses. However, as long as some bone vascularity is preserved, there is still the potential for bone healing



Fig 22.4 A 70-year-old woman sustained a subtrochanteric fracture. Twenty-five years ago, she was treated for a soft tissue sarcoma of the proximal lateral thigh with tumor resection and high-dose radiation therapy. X-ray reveals a typical image of radiation-induced bone abnormalities. The patient was treated with resection of the proximal femur and reconstruction with hemiarthroplasty proximal femur cemented mega-prosthesis. Intraoperatively the bone was very hard and brittle

[59]. Massin and Duparc reported in 1995 on 56 patients with various radiological lesions due to irradiation, including atraumatic femoral neck fracture, osteonecrosis of the femoral head or of the acetabulum, and radiation osteitis of the whole pelvis [60]. Seventy-one hips were treated by total replacement with standard cemented components for severe disability after pelvic irradiation. The rate of aseptic acetabular loosening was very high (52 % at 69 months mean follow-up). However, some of the early aseptic acetabular loosening could be attributed to the metal on metal prosthesis and large-diameter femoral heads. The authors suggested reinforcement of the acetabulum using a metallic ring when total replacement is required for an irradiated hip [60]. More recently, Kim et al. have published a series of 66 hips that had radiation therapy for prostate cancer and had subsequently undergone an elective primary uncemented total hip arthroplasty [61]. The mean duration of follow-up was 4.8 years. There was no aseptic loosening of either component in any of the hips. They concluded that osseointegration of uncemented components does not seem to be compromised in these patients in the short term.

Osseointegration processes in the oncological patient may be altered due to local and systemic factors. It seems that the biology of the tumor itself alters osteoblastic and osteoclastic pathways. Additionally, adjuvant types of treatments, including radiation therapy and chemotherapy,

can have a negative impact both systemically and locally, more or less permanent, on the osseointegration process and tissue healing. These alterations should be taken into consideration in order to make the best decision about therapeutic strategies in the oncological setting, which may be significantly different for patients with traumatic or degenerative disease.

References

1. Branemark PI. Osseointegration and its experimental studies. *J Prosthet Dent.* 1983;50:399–410.
2. Rigo ECS, Boschi AO, Yoshimoto M, Allegrini Jr S, Konig Jr B, Carbonari MJ. Evaluation in vitro and in vivo of biomimetic hydroxyapatite coated on titanium dental implants. *Mater Sci Eng C.* 2004;24:647–51.
3. Mavrogenis AF, Dimitriou R, Parvizi J, Babis GC. Biology of implant osseointegration. *J Musculoskelet Neuronal Interact.* 2009;9(2):61–71.
4. Adell R, Lekholm U, Rockler B, Brenemark PI. A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. *Int J Oral Surg.* 1981;10:387–416.
5. Linder L, Albrektsson T, Brenemark PI, Hansson HA, Ivarsson B, Jonsson U, Lundstrom I. Electron microscopic analysis of the bone-titanium interface. *Acta Orthop Scand.* 1983;54:45–52.
6. Soballe K, Hansen ES, Brockstedt-Rasmussen H, Bonger C. Hydroxyapatite coating converts fibrous tissue to bone around loaded implants. *J Bone Joint Surg Br.* 1993;75B:270–8.
7. Soballe K. Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs. *Acta Orthop Scand.* 1993;255:S1–58.
8. Davies JE. Mechanisms of endosseous integration. *Int J Prosthodont.* 1998;11:391–401.
9. Stanford CM, Keller JC. The concept of osseointegration and bone matrix expression. *Crit Rev Oral Biol Med.* 1991;2:83–101.
10. Giori NJ, Ryd L, Carter DR. Mechanical influences on tissue differentiation at bone-cement interfaces. *J Arthroplasty.* 1995;10:514–22.
11. Pilliar RM, Lee JM, Maniopoulos C. Observations on the effect of movement on bone ingrowth into porous-surfaced implants. *Clin Orthop.* 1986;208:108–13.
12. Otsuki B, Takemoto M, Fujibayashi S, Neo M, Kokubo T, Nakamura T. Pore throat size and connectivity determine bone and tissue ingrowth into porous implants: three-dimensional micro-CT based structural analyses of porous bioactive titanium implants. *Biomaterials.* 2006;27:5892–900.
13. Kudo M, Matsui Y, Ohno K, Michi K. A histomorphometric study of the tissue reaction around hydroxyapatite implants irradiated after placement. *J Oral Maxillofac Surg.* 2001;59:293–300.
14. Sumner DR, Turner TM, Pierson RH, Kienapfel H, Urban RM, Lieberman EJ, Galante JO. Effects of radiation on fixation of non-cemented porous-coated implants in a canine model. *J Bone Joint Surg Am.* 1990;72A:1527–33.
15. Sakakura CE, Marcantonio Jr E, Wenzel A, Scaf G. Influence of cyclosporin A on quality of bone around integrated dental implants: a radiographic study in rabbits. *Clin Oral Implants Res.* 2007;8:34–9.
16. Eder A, Watzek G. Treatment of a patient with severe osteoporosis and chronic polyarthritis with fixed implant-supported prosthesis: a case report. *Int J Oral Maxillofac Implants.* 1999;14:587–90.
17. McDonald AR, Pogrel MA, Sharma A. Effects of chemotherapy on osseointegration of implants: a case report. *J Oral Implantol.* 1998;24:11–3.
18. Callahan BC, Lisecki EJ, Banks RE, Dalton JE, Cook SD, Wolff JD. The effect of warfarin on the attachment of bone to hydroxyapatite-coated and uncoated porous implants. *J Bone Joint Surg Am.* 1995;77A:225–30.
19. Dahners LE, Mullis BH. Effects of nonsteroidal anti-inflammatory drugs on bone formation and soft-tissue healing. *JAAOS.* 2004;12:139–43.
20. Rosenqvist R, Bylander B, Knutson K, Rydholm U, Rooser B, Egund N, Lidgren L. Loosening of the porous coating of bicompartamental prostheses in patients with rheumatoid arthritis. *J Bone Joint Surg Am.* 1986;68A:538–42.
21. Zhang H, Lewis CG, Aronow MS, Gronowicz GA. The effects of patient age on human osteoblasts' response to Ti-6Al-4V implants in vitro. *J Orthop Res.* 2004;22:30–8.
22. Mombelli A, Cionca N. Systemic diseases affecting osseointegration therapy. *Clin Oral Implants Res.* 2006;17(S2):97–103.
23. Wong MM, Rao LG, Ly H, Hamilton L, Ish-Shalom S, Sturtridge W, Tong J, McBroom R, Josse RG, Murray TM. In vitro study of osteoblastic cells from patients with idiopathic osteoporosis and comparison with cells from non-osteoporotic controls. *Osteoporos Int.* 1994;4:21–31.
24. Martin TJ, Sims NA. Osteoclast-derived activity in the coupling of bone formation to resorption. *Trends Mol Med.* 2005;11:76–81.
25. Nakagawa N, Kinosaki M, Yamaguchi K, et al. RANK is the essential signaling receptor for osteoclast differentiation factor in osteoclastogenesis. *Biochem Biophys Res Commun.* 1998;253:395–400.
26. Takahashi N, Akatsu T, Udagawa N, et al. Osteoblastic cells are involved in osteoclast formation. *Endocrinology.* 1988;123:2600–2.
27. Papachristou DJ, Basdra EK, Papavassiliou AG. Bone metastases: molecular mechanisms and novel therapeutic interventions. *Med Res Rev.* 2012;32(3):611–36.
28. Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. *Arch Biochem Biophys.* 2008;473:139–46.
29. Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell.* 1998;93:165–76.

30. Hofbauer LC, Khosla S, Dunstan CR, et al. The roles of osteoprotegerin and osteoprotegerin ligand in the paracrine regulation of bone resorption. *J Bone Miner Res.* 2000;15:2–12.
31. Clézardin P. The role of RANK/RANKL/osteoprotegerin (OPG) triad in cancer-induced bone diseases: physiopathology and clinical implications. *Bull Cancer.* 2011;98(7):837–46.
32. Burchardt H, Glowczewskie Jr FP, Enneking WF. The effect of Adriamycin and methotrexate on the repair of segmental cortical autografts in dogs. *J Bone Joint Surg Am.* 1983;65A:103–8.
33. Zart DJ, Miya L, Wolff DA, Makley JT, Stevenson S. The effects of cisplatin on the incorporation of fresh syngeneic and frozen allogeneic cortical bone grafts. *J Orthop Res.* 1993;11(2):240–9.
34. Cañadell J, San-Julian M, Cara J, Forriol F. External fixation in tumor pathology. *Int Orthop.* 1998;22:126–30.
35. Hazan EJ, Hornicek FJ, Tomford W, Gebhardt MC, Mankin HJ. The effect of adjuvant chemotherapy on osteoarticular allografts. *Clin Orthop.* 2001;385:176–81.
36. Friedlaender GE, Tross RB, Doganis AC, Kirkwood JM, Baron R. Effects of chemotherapeutic agents on bone. I. Short-term methotrexate and doxorubicin (adriamycin) treatment in a rat model. *J Bone Joint Surg Am.* 1984;66A:602–7.
37. Virolainen P, Inoue N, Nagao M, Frassica FJ, Chao EY. The effect of a doxorubicin, cisplatin and ifosfamide combination chemotherapy on bone turnover. *Anticancer Res.* 2002;22(4):1971–5.
38. Gravel CA, Le TT, Chapman MW. Effect of neoadjuvant chemotherapy on distraction osteogenesis in the goat model. *Clin Orthop.* 2003;412:213–24.
39. Kapukaya A, Subasi M, Kandiya E, Ozates M, Yilmaz F. Limb reconstruction with the callus distraction method after bone tumor resection. *Arch Orthop Trauma Surg.* 2000;120:215–8.
40. Tsuchiya H, Shirai T, Morsy AF, Sakayama K, Wada T, Kusuzaki K, Sugita T, Tomita K. Safety of external fixation during postoperative chemotherapy. *J Bone Joint Surg Br.* 2008;90B:924–8.
41. Capanna R, Donati D, Masetti C, Manfrini M, Panozzo A, Cadossi R, Campanacci M. Effect of electromagnetic fields on patients undergoing massive bone graft following bone tumor resection. A double blind study. *Clin Orthop.* 1994;306:213–21.
42. Virolainen P, Inoue N, Nagao M, Frassica FJ, Chao EY. The effect of multidrug chemotherapy on bone graft augmented prosthesis fixation. *J Orthop Res.* 2005;23(4):795–801.
43. Van Leeuwen BL, Verkerke GJ, Hartel RM, Sluiter WJ, Kamps WA, Jansen HW, Hoekstra HJ. Chemotherapy decreases epiphyseal strength and increases bone fracture risk. *Clin Orthop.* 2003;413:243–54.
44. Dayer R, Rizzoli R, Kaelin A, Ammann P. Low protein intake is associated with impaired titanium implant osseointegration. *J Bone Miner Res.* 2006;21(2):258–64.
45. Schwartz AJ, Kabo JM, Eilber FC, Eilber FR, Eckardt JJ. Cemented endoprosthetic reconstruction of the proximal tibia: how long do they last? *Clin Orthop.* 2010;468:2875–84.
46. Flint MN, Griffin AM, Bell RS, Ferguson PC, Wunder JS. Aseptic loosening is uncommon with uncemented proximal tibia tumor prostheses. *Clin Orthop.* 2006;450:52–9.
47. Farfalli GL, Boland PJ, Morris CD, Athanasian EA, Healey JH. Early equivalence of uncemented press-fit and Compress femoral fixation. *Clin Orthop.* 2009;467(11):2792–9.
48. Kawai A, Lin PP, Boland PJ, Athanasian EA, Healey JH. Relationship between magnitude of resection, complication, and prosthetic survival after prosthetic knee reconstructions for distal femoral tumors. *J Surg Oncol.* 1999;70:109–15.
49. Avedian RS, Goldsby RE, Kramer MJ, O'Donnell RJ. Effect of chemotherapy on initial compressive osseointegration of tumor endoprostheses. *Clin Orthop.* 2007;459:48–53.
50. Bini SA, Johnston JO, Martin DL. Compliant pre-stress fixation in tumor prostheses: interface retrieval data. *Orthopedics.* 2000;23(7):707–11.
51. Kramer MJ, Tanner BJ, Horvai AE, O'Donnell RJ. Compressive osseointegration promotes viable bone at the endoprosthetic interface: retrieval study of Compress implants. *Int Orthop.* 2008;32(5):567–71.
52. Bhangu AA, Kramer MJ, Grimer RJ, O'Donnell RJ. Early distal femoral endoprosthetic survival: cemented stems versus the Compress implant. *Int Orthop.* 2006;30(6):465–72.
53. Dawson WB. Growth impairment following radiotherapy in childhood. *Clin Radiol.* 1968;19(3):241–56.
54. Mitchell MJ, Logan PM. Radiation-induced changes in bone. *Radiographics.* 1998;18(5):1125–36.
55. Bragg DG, Shidnia H, Chu FC, Higinbotham NL. The clinical and radiographic aspects of radiation osteitis. *Radiology.* 1970;97(1):103–11.
56. Dalinka MK, Edeiken J, Finkelstein JB. Complications of radiation therapy: adult bone. *Semin Roentgenol.* 1974;9(1):29–40.
57. Howland WJ, Loeffler RK, Starchman DE, Johnson RG. Post irradiation atrophic changes of bone and related complications. *Radiology.* 1975;117:677–85.
58. Bluemke DA, Fishman EK, Scott Jr WW. Skeletal complications of radiation therapy. *Radiographics.* 1994;14(1):111–21.
59. Bonfiglio M. The pathology of fracture of the femoral neck following irradiation. *Am J Roentgenol Radium Ther Nucl Med.* 1953;70(3):449–59.
60. Massin P, Duparc J. Total hip replacement in irradiated hips. A retrospective study of 71 cases. *J Bone Joint Surg Br.* 1995;77B:847–52.
61. Kim KI, Klein GR, Sleeper J, Dicker AP, Rothman RH, Parvizi J. Uncemented total hip arthroplasty in patients with a history of pelvic irradiation for prostate cancer. *J Bone Joint Surg Am.* 2007;89A:798–805.

Index

A

- Abutting bone-implant interface, 296–297
- Acetabular bone grafting
 - acetabular defect classification, 203
 - CT scans, 203
 - diagnosing and assessment, 203
 - magnetic resonance imaging, 203
 - plain radiographs, 203
 - surgical management options, 203–204
- Acetabular impaction grafting
 - biology, 205
 - clinical applications and results, 206–207
 - cotyloplasty, 204–205
 - histology, 205–206
 - structural allograft, 207–208
 - surgical technique, 206
- Acrylic cement, 27
- Adverse reaction to metallic debris (ARMED), 274–275
- Anatomical medullary locking (AML) stem, 59, 60
- Anterior cruciate ligament (ACL) reconstruction, 307
 - challenges, 320
 - platelet concentrate and bone plugs, 317
 - tunnel widening, 314
- Anti-inflammatory agent, 223–224
- Arginine-glycine-aspartic acid, 18
- Arthroprosthetic cobaltism, 278
- Aseptic loosening
 - causes
 - endotoxins, 141–142
 - high fluid pressure, 141
 - micromotion, 139–140
 - particle disease, 142–143
 - particle production, 143–145
 - stress shielding, 140–141
 - cement disease, 139, 140
 - pathways
 - cathepsin, 148
 - chemokines role, 149
 - downstream pathway, 147
 - IL-6 response, 146
 - macrophages, 145–146
 - metalloproteinases, 145
 - metal-on-metal arthroplasties, 149
 - NFκB, 146
 - osteoblasts and stromal cells, 147
 - osteoclasts, 147

- osteocytes, 148
- PGE2, 146–147
- protein tyrosine kinases, 146
- pseudotumors formation, 148
- RANKL production, 146
- VEGF, 149
- treatment options
 - anti TNF- α therapy, 150
 - bisphosphonates, 150
 - cytokines circulation, 149
 - doxycycline, 150
 - erythromycin, 150
 - etanercept, 150
 - gene therapy, 150
 - osteointegration, 150
 - purinergic signaling, 151
 - RANKL-RANK-OPG axis, 150
 - sclerostin, 151
 - statins, 151
 - Wnt signaling, 151
- Aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL), 272, 274

B

- Biocoatings, 233
- Biofilm-associated bone and joint infections
 - drug delivery, 247
 - implant-related infections, pathogenesis of, 240–242
 - infection-resistant material development strategies, 247–248
 - innate immune system, 243
 - N-acetylcysteine, 248
 - osteolysis and loosening, of plate fixation, 244
 - polymorphonuclear leukocytes, 241–246
 - prevention, 246
 - quorum sensing, 246–247
 - septic interface pathology, 245–246
 - Staphylococcus* biofilms
 - macrophages, 244–245
 - neutrophils role, 243–244
 - surface cleaning, of orthopedic implants, 246
 - tissue destruction, 242–243
 - in upper extremities, 239
- Biological bone fixation, 83
- Biomechanics, 295

- Bisphosphonates
 - aseptic loosening, 150
 - positively affecting osseointegration, 228–230
- Bone-cement interface, 2–4
 - acetabulum, cemented fixation, 33
 - biomechanical properties, 27, 28
 - cementing technique, 28–30
 - cement mantle thickness, 30–31
 - description, 27
 - femoral component
 - shape of, 32
 - surface texture of, 31–32
 - metallurgy, 32
- Bone grafting
 - acetabular bone grafting
 - acetabular defect classification, 203
 - CT scans, 203
 - diagnosing and assessment, 203
 - magnetic resonance imaging, 203
 - plain radiographs, 203
 - surgical management options, 203–204
 - acetabular impaction grafting
 - biology, 205
 - clinical applications and results, 206–207
 - cotyloplasty, 204–205
 - histology, 205–206
 - structural allograft, 207–208
 - surgical technique, 206
 - biology
 - osteoconduction, 198
 - osteogenesis, 198
 - osteoiduction, 198
 - regeneration, 197
 - femoral bone grafting, hip surgery
 - causes, 209–210
 - clinical applications and results, 212–213
 - diagnosing and assessment, 210
 - structural and cancellous allograft, 210–212
 - surgical management options, 210
 - femoral impaction grafting
 - clinical applications and results, 215–216
 - complications, 216
 - histology, 214
 - method, 213–214
 - surgical technique, 214–215
 - healing, impairment of, 202
 - in hip surgery, 202
 - induced membrane technique, bone loss
 - reconstruction, 216–217
 - modular porous metal augments, cementless
 - reconstructions
 - cup-cage reconstruction, 209
 - ring and cage reconstruction, 209
 - trabecular metal acetabular cup and augments, 208–209
 - triflange reconstruction, 209
 - options for
 - allogenic demineralized bone matrix, 201
 - allograft, 200
 - allograft cancellous bone, 200
 - allograft cortical bone, 200–201
 - autograft, 199
 - autologous bone marrow, 199
 - autologous cancellous bone, 199
 - autologous cortical bone, 199–200
 - characteristics, 198, 199
 - incorporation, 202
 - massive osteochondral allografts, 201
 - synthetic bone substitutes, 201–202
 - vascularized autologous bone graft, 200
- Bone ingrowth
 - characteristics and interface mechanics, 175–176
 - definition, 221
 - sex and estrogen therapy, 62–63
 - success factors, in porous-coated implants, 101
 - titanium porous-coated implant-bone interface, 71
- C**
 - Calcitonin, 226–228
 - Canal-filling stem, 5
 - Cement-bone interface
 - cemented acetabular revision
 - with impaction grafting technique, 161–163
 - osteolysis, bone erosion, 159
 - technical parameters, 160
 - type I acetabular defects, 160
 - cemented femoral revision, 160–161
 - cemented fixation, revision total knee arthroplasty, 164–165
 - cement-in-cement technique
 - biomechanical study, 163
 - indications, 164
 - surgical technique, 164
 - revision total hip arthroplasty, 159
 - Cement disease, 14, 139, 140
 - Cemented acetabular revision
 - with impaction grafting technique
 - containment and impaction, 161
 - histologic evaluation, 161
 - metal mesh migration, 163
 - union of graft, 162
 - osteolysis, bone erosion, 159
 - technical parameters, 160
 - type I acetabular defects, 160
 - Cemented cups, THA, 6
 - Cemented femoral stems-cement interface. *See* Femoral stem-cement interface
 - Cemented fixation
 - of acetabulum, 33
 - of revision total knee arthroplasty, 164–165
 - titanium porous-coated implant-bone interface, 75–76
 - Cemented stems, THA, 6
 - Cemented surgical techniques, 5
 - Cement-femoral stem interface, 3–5
 - Cement-in-cement technique
 - biomechanical study, 163
 - indications, 164
 - surgical technique, 164

- Cementing technique, 28–30
- Cementless bone-implant interface
- components, 13–15
 - description, 13
 - design factors
 - coating design, 20–22
 - implant morphology, 19–20
 - fixation, 22–23
 - primary stability, 15–17
 - secondary stability, 16–19
- Cementless fully porous-coated implant-bone interface
- bone ingrowth and interface mechanics,
 - characteristics, 175–176
 - closed-cell/open-cell porosity, 172
 - complications, 177–178
 - forms and fabrication techniques
 - metallic foams, 174
 - spherical metal powders, 172–173
 - titanium-based coatings, 174–175
 - traditional metallic coatings, 173–174
 - wires/fibers, 173
 - historical overview, 169–170
 - mechanical properties, porous biomaterials,
 - 171–172
 - pore sizes, bone, 170–171
 - porosity, defined, 169
 - properties, 170
- Cementless hip stem designs, survivorship of, 19
- Cementless surgical techniques, 9
- Cementless tapered fluted implant-bone interface
- clinical results, 184–186
 - primary stability, 186–188
 - proximal femoral bone restoration, 190–191
 - secondary stability, 188–190
 - stem subsidence, 191–192
 - Wagner fluted stem, 184
- Cement mantle thickness, 30–31
- Cement pressurization, 28, 29
- Chemotherapy, 328–331
- Cobalt–chrome porous-coated implant-bone interface
- advantages, 55
 - AML stem, 59, 60
 - biocompatibility of, 58
 - cobalt–chrome alloy properties, 55, 56
 - corrosion behavior of, 61
 - forms and fabrication techniques, 56–57
 - hydroxyapatite-coated, 58
 - infection rates, 62
 - ion implantation, 57–58
 - metallic failures of, 61–62
 - metallic ions release, 60–61
 - micro-structural metal surface texture, 63
 - outcome of, 58–60
 - porous metallic coatings, 55
 - characterization of, 56
 - types of, 56, 57
 - sex and estrogen therapy on bone ingrowth, 62–63
 - sintering techniques, 61
 - stainless steel and titanium biomaterial
 - properties, 55, 56
- Cobaltism, 278
- Collared hip stem, 20
- Composite-beam fixation, 4–5
- Conforming bone-implant interface, 299
- D**
- Dual energy X-ray absorptiometry (DEXA),
 - 85, 176
- E**
- Electrochemical-deposited hydroxyapatite (EDHA)
- coated implants. *See also* Hydroxyapatite (HA)-coated implant
 - application technique, 92–95
 - clinical results, 104–112
 - vs. HA plasma-spray, 103
 - vs. titanium, 102–103
- Endotoxins, 141–142
- F**
- FE method. *See* Finite element (FE) method
- Femoral bone grafting, hip surgery
- causes, 209–210
 - clinical applications and results, 212–213
 - diagnosing and assessment, 210
 - structural and cancellous allograft, 210–212
 - surgical management options, 210
- Femoral component, bone-cement interface
- shape of, 32
 - surface texture of, 31–32
- Femoral impaction grafting
- clinical applications and results, 215–216
 - complications, 216
 - histology, 214
 - method, 213–214
 - surgical technique, 214–215
- Femoral stem-cement interface
- cement mantle, 43
 - creep, 44
 - cross-sectional shape, 36
 - non-polished stem designs, 37–38
 - rotational stability, 37
 - rough-surfaced pre-coated stem analysis, 37
 - Spectron stem size, 38
 - Exeter stem, 36, 45, 47
 - fatigue failure, 44
 - force-closed fixation design, 39
 - fretting wear, 41, 42
 - material types, 35–36
 - migration pattern, 45–49
 - porosity, 44–45
 - shape-closed fixation design, 38, 39
 - subsidence
 - Anatomic-Option stems, 45, 46
 - inside cement mantle, 47, 48
 - Lubinus SP II and Spectron EF stems, 45, 46
 - radiostereometric analysis, 49–51

Femoral stem-cement interface (*cont.*)
 scientific hip stems, 45, 47
 Tifit stem, 45, 46
 surface roughness, 39–41
 wear and migration, 41–43
 Finite element (FE) method, 15–16
 Flat-faced interbody cage implants, 297
 Force-closed fixation, 3–4, 39
 French paradox principle, 30, 31

G

Gripping bone-implant interface, 298–299
 Grit-blasted implant bone interface
 acetabulum
 press-fit technique, 86
 radiological analysis of, 85
 Bicon cup, 87
 Cox multivariate regression analysis, 85
 DEXA, 85
 femoral cortical thickening, 85
 ingrowth fixation, 83
 ongrowth fixation, 83
 proximal radiolucent, 88
 SL-Plus stem, 87–88
 tapered implants, 87
 Ti6Al4V and Ti6Al7Nb alloys, 84
 Wolff's law, 83, 84

H

HA-coated implant. *See* Hydroxyapatite (HA)-coated implant
 High fluid pressure, aseptic loosening, 141
 Hydroxyapatite (HA)-coated implant
 bone formation, 91
 calcium and phosphate ions, release, 92
 clinical results, 103–104
 EDHA
 application technique, 92–95
 clinical results, 104–112
 vs. HA plasma-spray, 103
 vs. titanium, 102–103
 on metallic substrates, 91
 osteoconductive property, 91
 plasma-sprayed HA-coated implants
 animal model, 96
 bone and implant, gap effect, 99
 bone grafting effect, implant fixation, 99–100
 clinical motivation, experimental studies, 95–96
 evaluation, 97–99
 HA coating effect, implant fixation, 101–102
 implantation models, 96–97
 implants and surface coatings, 96
 magnitude of motion, 101
 micromotion effect, implant fixation, 100–101
 Hyperbaric oxygen (HBO) treatment, 315

I

Implant-graft interface. *See* Bone grafting
 Innate immune system, 243
 Integrins, 18
 Ion implantation, 57–58

K

Kroll process, 67

L

Loaded-taper fixation, 3–4
 Low-intensity pulsed ultrasound (LiPUS), 315, 316
 Lytic lesions
 metastatic renal cell carcinoma, 328
 osteoclastic activity, 327

M

Metal augmentation devices, 263
 Metallic wear particles
 aseptic loosening, 276–277
 biological responses
 cytotoxicity, 271
 immunologic response, 271–272
 mutagenesis, 272–273
 carcinogenesis, 283–285
 cardiovascular system, 279–280
 developmental toxicology, 282–283
 endocrine and reproductive effects, 280–281
 hematopoietic tissues, 277–278
 hepatobiliary system, 278
 infection, 277
 musculoskeletal system, 282
 nervous system, 278–279
 origin and composition, 270
 osteolysis, 276–277
 pseudotumors, 274–275
 renal system, 278
 respiratory system, 279
 skin sensitivity, 281–282
 soft tissue reactions, 274–276
 visual and auditory systems, 280
 Metallosis, 274
 Metallurgy, bone-cement interface, 32
 Metal-on-metal (MoM) bearings, 144, 269, 270, 276, 277, 285
 Micromotions
 implant fixation, 100–101
 measuring techniques, 15
 radiostereometric analysis, aseptic loosening, 139–140
 Micro-structural metal surface texture techniques, 63
 Modular acetabular components, 256–257
 Modular interfaces
 acetabular components, 256–257
 assembling process, 261
 clinical advantages and disadvantages, 257–258

- corrosion, 259–260
- cracking mechanism, 259
- debris and wear, 260
- fretting, 257–258
- shoulder arthroplasty
 - advantages, 263–264
 - disadvantages, 264
 - humeral head components, 264
 - metal-backed glenoid components, 264–265
- stress distribution and micromotion, 260–261
- total hip replacement, 256–257
- total knee replacement
 - metal augmentation devices, 263
 - press-fit stem, 263
 - tibial inserts, 261–263
- Modularity, 255

- N**
- Neck-stem modularity, 255
- Nonspecific immune system, 243

- O**
- Omnifit stem, 9
- Orthopedic implant, mechanical stability of, 13
- Osseointegration, 68
 - chemotherapy, 331–332
 - definition, 221
 - inhibiting factors, 327
 - malnutrition, 330
 - patients with neoplastic disease, 327
 - pharmacological agents (*see* Pharmacological agents, bone-implant interface)
 - radiation therapy, 331–332
- Osteoconduction, 18, 198
- Osteogenesis, 198
- Osteoinduction, 17, 198
- Osteointegration, 19
- Osteolysis
 - cemented acetabular revision, 159
 - definition, 221
 - metallic wear particles, 276–277
 - particle disease, 143

- P**
- Parathyroid hormone (PTH), 232–233
- Particle disease
 - alumina wear debris, 145
 - aseptic loosening, 142–143
 - ceramic-on-ceramic prostheses, 145
 - macrophage, 143
 - metal ions, 145
 - metal-on-metal bearing, 144
 - metal sensitivity, 145
 - osteolysis, 143
 - pathogenesis, 142
 - polyethylene wear, 144
 - pre-coated/blasted stem implants, 144
 - pro-inflammatory factors, 142
 - vacuum mixing, 143–144
 - Vit E addition, 144
- Passivation, 71
- Penetrating bone-implant interface, 297–298
- Pharmacological agents, bone-implant interface
 - indomethacin administration, 233
 - osteolytic response, 222
 - positively affecting osseointegration
 - antibiotics, 223
 - anti-inflammatory agent, 223–224
 - biocoatings, 233
 - bisphosphonates, 228–230
 - calcitonin, 226–228
 - PTH and teriparatide, 232–233
 - RANK/RANKL/OPG system, 224–225
 - simvastatin, 225–226
 - statins, 225–226
 - strontium ranelate, 231–232
 - selection criteria, 222
 - warfarin administration, 233
- Plasma-sprayed hydroxyapatite-coated implants.
 - See also* Hydroxyapatite (HA)-coated implant
 - animal model, 96
 - bone and implant, gap effect, 99
 - bone grafting effect, implant fixation, 99–100
 - clinical motivation, experimental studies, 95–96
 - evaluation, 97–99
 - HA coating effect, implant fixation, 101–102
 - implantation models, 96–97
 - implants and surface coatings, 96
 - magnitude of motion, 101
 - micromotion effect, implant fixation, 100–101
- Plasma-spraying process, 20, 21, 68
- Polymethylmethacrylate (PMMA), 2, 4, 13–14, 27, 28, 45, 47, 49, 143, 145, 146, 147, 223, 224, 247, 248, 300
- PolyWare method, 136
- Porosity, defined, 169
- Porous-coated implants. *See* Cobalt–chrome porous-coated implant–bone interface
- Porous metallic coatings, 55–56
 - characterization of, 56
 - types of, 56, 57
- Primary stability, implants, 15–17
- Pro-inflammatory factors, 142
- Prosthesis infection
 - cationic antimicrobial peptides, 248
 - ^{99m}Tc-labeled annexin V, pain after TJA, 135
- PTH. *See* Parathyroid hormone (PTH)
- Pullout method, 15
- Pullout resistance, of screws, 298

- Q**
- Quorum sensing, 246–247

R

- Radiation therapy, 331
- Radiostereometric analysis (RSA), 16, 76
 - micromotion measurement, 139–140
 - stem-cement interface, 49–51
- RANK/RANKL/OPG system, 224–225, 327–328
- Revision total joint arthroplasty. *See* Cementless tapered fluted implant-bone interface
- Round-faced interbody cage implants, 297
- RSA. *See* Radiostereometric analysis (RSA)

S

- Screw's insertional torque, 298
- Secondary stability
 - cementless tapered fluted implant-bone interface, 188–190
 - implants, 16–19
- Section modulus, 295
- Septic interface pathology, 245–246
- Shape-closed fixation design, 38, 39
- Shock-wave treatment, 315
- Shoulder arthroplasty, modular implants
 - advantages, 263–264
 - disadvantages, 264
 - humeral head components, 264
 - metal-backed glenoid components, 264–265
- Simvastatin, 225–226
- Sintered beads, 6, 7
- Sintered porous coatings, 57
- Spinal surgery
 - biomechanics, 295
 - bone-implant interface
 - abutting, 296–297
 - conforming, 299
 - description, 296
 - gripping, 298–299
 - osseointegration process, 299–300
 - penetrating, 297–298
 - flat-faced interbody cage implants, 297
 - graft end-plate interface, 302–303
 - implant size, 301–302
 - implant stiffness, 295–296
 - intact vs. burned end plate
 - endurance, 302–303
 - machine screws, 297
 - principles, 295–296
 - pullout resistance, of screws, 298
 - screw's insertional torque, 298
 - section modulus, 295
 - self-tapping machine screws, 297
 - total disc replacement, 302
 - triangulation effect, 300–301
 - wood screws, 297
- Staphylococcus* biofilms
 - macrophages, 244–245
 - neutrophils role, 243–244
- Statins, 225–226
- Stress shielding, 140–141

- Strontium ranelate, 231–232
- Surface cleaning, of orthopedic implants, 246

T

- Tendon-to-bone surface healing
 - double-row technique, 318
 - rehabilitation regimens, 318–319
 - rotator cuff repair
 - acellular dermal matrix grafts, 319
 - growth factors, 319
 - LiPUS treatment, 320
 - mesenchymal stem cells, 319
 - platelet-rich plasma, 319–320
 - shock-wave treatment, 320
 - xenografts, 319
- Tendon-to-bone tunnel healing
 - enhancement of
 - artificial tissue engineering, 317–318
 - biomaterials, 314
 - bone morphogenetic protein-2, 316, 317
 - calcium phosphate cement, 314
 - cell therapy, 317
 - chemical and biological agents, 314–315
 - cost-effectiveness issues, 320
 - gene therapy, 316–317
 - growth factors, 316–317
 - HBO treatment, 315
 - hydroxyapatite, 314
 - limitations, 320
 - LiPUS treatment, 315, 316
 - magnesium-based bone adhesive, 314
 - mesenchymal stem cells, 317
 - shock-wave treatment, 315
 - tricalcium phosphate, 314
 - spatial variations within bone tunnels, 314
 - tibial vs. femoral tunnel healing, 313
- Teriparatide, 232–233
- THA. *See* Total hip arthroplasty (THA)
- Third-generation cementing technique, 6, 28, 29
- Titanium porous-coated implant-bone interface
 - bone ingrowth, 71
 - classification, 68
 - coating types, 68–69
 - factors affecting bone fixation, 70
 - fiber–metal composite, 69
 - fiber–titanium composite, 69
 - history, 67
 - hydroxyapatite titanium porous-coated acetabular implants, 70
 - material property, 67–68
 - osseointegration, 68
 - plasma spraying method, 68
 - porous-coated femoral prostheses, 69
 - total hip arthroplasty
 - acetabulum, 75
 - cemented fixation, 75–76
 - femoral components, 71–75
 - total knee arthroplasty, 76

- Titanium porous-coated total knee arthroplasty, 76
- Toe-in placement, 300
- Toe-out placement, 300
- Total hip arthroplasty (THA)
 - acetabulum, 75
 - aseptic loosening, 269
 - bearing surfaces, 269
 - bone-cement interface, 2–4
 - bone-implant interface, 6–8
 - cause of failure, 269
 - cemented cups, 6
 - cemented fixation, 75–76
 - cemented stems, 6
 - cemented surgical techniques, 5
 - cement-femoral stem interface, 3–5
 - cementless surgical techniques, 9
 - description, 1–2
 - evidence-based data, 9
 - femoral components
 - electrochemically deposited HA coatings, 72–73
 - hydroxyapatite coatings, 72–73
 - osseointegration, in stem revision, 74–75
 - passivation, 71
 - Ti-6Al-4V alloy, 71, 72
 - implant-cement interface (*see* Femoral stem-cement interface)
 - implant-related parameters, 5, 7
 - initial fixation, 2, 3
 - lifetime of, 2
 - long-term survival affecting parameters, 1
 - metal allergy, 281
 - metal-on-metal bearings, 269–270
 - Sikomet and Metasul, 276
 - tri-spike acetabular component, 75
- Total hip replacement, modular implants, 256–257
- Total joint arthroplasty (TJA)
 - bone-cement interface
 - acetabulum, cemented fixation, 33
 - biomechanical properties, 27, 28
 - cementing technique, 28–30
 - cement mantle thickness, 30–31
 - description, 27
 - femoral component, 31–32
 - metallurgy, 32
 - cementless bone-implant interface
 - components, 13–15
 - description, 13
 - design factors, 19–22
 - fixation, 22–23
 - primary stability, 15–17
 - secondary stability, 16–19
 - Co-Cr implant-bone interface (*see* Cobalt–chrome porous-coated implant-bone interface)
 - failures, painless, 127, 128
 - grit-blasted implant bone interface
 - acetabulum, 85, 86
 - Bicon cup, 87
 - Cox multivariate regression analysis, 85
 - DEXA, 85
 - femoral cortical thickening, 85
 - ingrowth fixation, 83
 - ongrowth fixation, 83
 - proximal radiolucent, 88
 - SL-Plus stem, 87–88
 - tapered implants, 87
 - Ti6Al4V and Ti6Al7Nb alloys, 84
 - Wolff’s law, 83, 84
 - pain after
 - arthrography, 133
 - aspiration technique, 130, 133
 - cemented acetabular components, 131–132
 - cemented components, 130–131
 - cementless acetabular components, 132
 - cementless stems, 131
 - 3 DeLee acetabular zones, 130
 - diagnosis, 127
 - dynamic computed tomography scanning, 135
 - evaluation, 128
 - fluoroscopic imaging, 133
 - 7 Gruen femoral zones, 130
 - imaging with investigational agents, 134–135
 - indication, thigh pain, 128–129
 - indium-111-labeled leukocytes scintigraphy, 134
 - interleukin-6 level, 130
 - in vivo wear measurements, bearing surfaces, 135
 - laboratory test, 129–130
 - ^{99m}Tc-labeled annexin V, 135
 - musculoskeletal examination, 129
 - PET findings, 135
 - radiographic evaluation, 130
 - serum metal ion levels, 136
 - triple-phase bone scanning, 133–134
 - wound healing, delayed, 128, 129
 - titanium porous-coated implant-bone interface
 - bone ingrowth, 71
 - classification, 68
 - coating types, 68–69
 - factors affecting bone fixation, 70
 - fiber–metal composite, 69
 - fiber–titanium composite, 69
 - history, 67
 - hydroxyapatite titanium porous-coated acetabular implants, 70
 - material property, 67–68
 - osseointegration, 68
 - plasma spraying method, 68
 - porous-coated femoral prostheses, 69
 - total hip arthroplasty, 71–76
 - total knee arthroplasty, 76
 - trabecular metal
 - acetabular component, 123
 - animal studies, 121–122
 - clinical studies, 122–125
 - description, 121
 - histological evaluation, 122
 - Monoblock TMT cup, 123
 - retrieval studies, 122

Total joint arthroplasty (TJA) (*cont.*)
 strain adaptation, 124
 structure, 121, 122
 vs. titanium tibia, 124

Total knee replacement, modular implants
 metal augmentation devices, 263
 press-fit stem, 263
 tibial inserts, 261–263

Trabecular metal (TMT)
 acetabular component, 123
 animal studies, 121–122
 clinical studies, 122–125
 description, 121
 histological evaluation, 122
 Monoblock TMT cup, 123

 retrieval studies, 122
 strain adaptation, 124
 structure, 121, 122
 vs. titanium tibia, 124
Triangulation effect, 300–301

V

Vroman effect, 18

W

Wagner fluted stem, 184
Wolff's law, 84