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ORIGINAL RESEARCH

Teriparatide Treatment in Patients with Pregnancy- and Lactation-Associated Osteoporosis

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Abstract

Pregnancy- and lactation-associated osteoporosis (PLO) is a rare disease, presenting in most cases with severe back pain due to low energy vertebral fractures (VFs). Our purpose was to assess the effect of teriparatide (TPTD) *vs.* conventional management on areal bone mineral density (aBMD) and trabecular bone score (TBS) in patients with PLO. A multicenter retrospective cohort study concerning premenopausal women with PLO. Nineteen women were treated with TPTD (20 μg/day) (group A) plus calcium and vitamin D and eight women with calcium and vitamin D only (group B) for up to 24 months. The primary end-point was between group differences in lumbar spine (LS) and total hip (TH) aBMD, and TBS at 12 and 24 months. Patients in group A had sustained a median of 4.0 VFs (3–9) *vs.* 2.5 VFs (1–10) in group B ($p=0.02$). At 12 months, patients on TPTD *vs.* controls achieved a mean aBMD increase of 20.9 ± 11.9% *vs.* 6.2 ± 4.8% at the LS ($p<0.001$), 10.0 ± 11.6% *vs.* 5.8 ± 2.8% at the TH ($p=0.43$), and 6.7 ± 6.9% *vs.* 0.9 ± 3.7% in TBS ($p=0.09$), respectively. At 24 months, seven patients on TPTD and six controls achieved a mean LS aBMD increase of 32.9 ± 13.4% *vs.* 12.2 ± 4.2% ($p=0.001$). P1NP levels during the first month of TPTD treatment were positively correlated with the 1-year LS aBMD change ($r=0.68$, $p=0.03$). No new clinical fractures occurred while on-treatment. In patients with PLO, TPTD treatment resulted in significantly greater increases in LS aBMD compared with calcium and vitamin D supplementation at 12 and 24 months.

Keywords Pregnancy and lactation-associated osteoporosis · Teriparatide · Vertebral fractures · Premenopausal women

Introduction

Pregnancy- and lactation-associated osteoporosis (PLO) is a rare condition. It usually presents with multiple vertebral fractures (VFs) during the last trimester of the first pregnancy or in the early postpartum period [1–4], although fragility fractures

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at other sites (hip, pelvis, etc.) can also occur. Due to the rarity and the unawareness of the disease, delayed diagnosis is common. Previous studies reported that PLO usually does not recur in subsequent pregnancies. However, two recent studies, including a total of 107 PLO cases, reported a recurrence rate in future pregnancies of up to 20% and a short-term fracture risk of 24% [2, 5]. Apart from cases with latent inherited or secondary causes of bone fragility first emerging during this period [6–9], the pathophysiology PLO is still poorly understood. Current evidence suggests that in PLO cases the mineral and mechanical demands upon the maternal skeleton result in substantial reduction of bone strength leading to fragility fractures [1]. In most cases, areal bone mineral density (aBMD) at the lumbar spine (LS) is very low (z-score in some cases below −4.0), and the severe back pain that accompanies VFs leads to significant limitation of daily activities even to the point of inability to carry the infant.

Management of PLO is challenging and largely empirical, as large randomized-controlled studies are lacking. Adequate calcium and vitamin D intake along with stopping breastfeeding are advocated by most experts [1]. Use of spinal braces and pain management has also been implemented, especially during the first months with gradual increase of weight-bearing and resumption of daily activities. Although in most cases substantial aBMD improvement is observed with these measures, treatment with bone-protective drugs such as antiresorptive or anabolic agents to relieve the pain, accelerate the recovery and protect the patient from recurrent fractures, especially in the short term, is commonly applied. Several case reports and a small number of case series indicate that treatment with bisphosphonates (BPs) [10–12] or teriparatide (TPTD) [2, 13–18] results in additional aBMD increase, probably greater compared to the spontaneous improvement of aBMD observed 6–12 months after pregnancy and lactation have been completed. Of note, the largest study to date by Hong et al. [13] using TPTD for one year, reported substantial increase in aBMD as compared with conventional management. Unfortunately, there is not strong evidence of the efficacy of this approach, while there are important concerns about the safety of bone-protective medications, especially BPs, in women with childbearing potential, both in the short-and long-term [19–21].

The aim of this study was to evaluate the efficacy of TPTD plus calcium and vitamin D supplementation compared with calcium and vitamin D supplementation alone in women with PLO in terms of aBMD and trabecular bone score (TBS) changes at 12 and 24 months of treatment.

Methods

Study Protocol

The study protocol was approved by the ethics committee of the KAT General Hospital and written informed consent was obtained from all participants. Among thirty-five patients with PLO presented in our institution from 2010 to 2020, those treated with TPTD or solely with calcium and/or vitamin D3 were included in this study. Nine cases were excluded due to treatment with BPs, while another three cases were excluded due to prior treatment with BPs ($n = 2$) and denosumab ($n = 1$) followed by TPTD. In addition, four patients with PLO treated with TPTD and managed in three referral centers in Thessaloniki, Greece, were also included. PLO was defined as clinical VFs during pregnancy or at the post-partum period. All VFs were confirmed with magnetic resonance imaging (MRI). VF assessment (VFA) assessed by dual-energy X-ray absorptiometry (DXA) was also obtained when possible.

Nineteen, previously treatment-naïve patients with PLO, were treated with subcutaneous injection of TPTD (20 μg/day) and calcium plus vitamin D3 supplementation (group A) for a mean period of 14.8 ± 6.1 (6.0–24.0) months based on the treating physician's choice and in accordance with the current clinical practice within the Greek health care setting. Eight age-matched women with PLO, who were treated only with calcium and vitamin D3 (group B) and followed for 37.8 ± 13.9 months, served as controls. All patients received at least 800 IU of vitamin D3, aiming at 25-hydroxyvitamin D [25(OH) D] levels > 30 ng/ml, and calcium carbonate, targeting at a total daily calcium intake of at least 1 g. Compliance with TPTD treatment was assessed at each visit. Given TPTD is not approved for patients with PLO, all patients received TPTD after approval for off-label use from the relevant committee of the Hellenic National Organization for Medicines.

Procedures

At first visit, all patients provided information on their demographics and medical history, underwent dual-energy X-ray absorptiometry (DXA) at the LS, femoral neck (FN) and total hip (TH) (all centers used Lunar Prodigy GE Lunar Corp., Madison, WI, USA) and biochemical blood tests to identify secondary causes of osteoporosis. The long-term precision (% CV) for aBMD measurements in our department was 0.7% (LS), 1.4% (FN) and 1.1% (TH). In case of vertebral fractures at the LS, fractured vertebrae were excluded from the analysis if there was more

than 1 SD difference in the z-score between two vertebrae. All patients were prospectively followed with a second aBMD measurement at 12 and 24 months, at the same DXA device and with specific blood tests according to the protocol followed by each treating physician. For patients followed up in KAT general hospital calculation of TBS (TBSiNsight, software version 3.0.3.0), VFA and measurements of serum levels of procollagen type 1 N-terminal propeptide (total-P1NP) at baseline and follow-up and C-terminal telopeptide of collagen I (CTX) at baseline were also available.

Serum PINP (reference range 15.2–58.59 ng/mL), N-MID-osteocalcin (OC) (reference range 9.7–35.1 ng/mL), CTX levels (reference range < 0.573 ng/mL) were determined with an electrochemiluminescence immunoassay (ECLIA) on Cobas e411. This method measures the total PINP. The measurement range of this assays in our laboratory is 5–1200 ng/mL and 0.010–6.00 ng/mL, with %CV of < 4.5%, < 3.5% and < 3.5%, for PINP, OC and CTX, respectively.

Statistical Analysis

Normality was tested using the Kolmogorov–Smirnov test. The Chi-squared test was used to evaluate differences between the two groups for categorical variables and the unpaired t-test or Mann–Whitney U test for continuous variables, as appropriate. The Wilcoxon and Friedman tests were used to evaluate differences within groups. Correlation between variables was assessed by Spearman's test. The primary end-point was the between group % difference in mean change in LS aBMD from baseline to one year. Secondary endpoints were between groups % difference in TH aBMD and within-group absolute aBMD in LS and TH from baseline to 1 and 2 years. All continuous variables were presented as mean ± standard deviation (SD) for the homogeneity of the presentation. All the statistical tests were performed using SPSS 20 statistical software (SPSS Inc, Chicago, IL). A two-sided p-value < 0.05 was considered statistically significant in all tests.

Results

Patients' Descriptive Characteristics

Patients' baseline descriptive characteristics are presented in Table 1. Twenty-five women (92.6%) were at their first pregnancy (two were twin pregnancies, one in each group) and two (7.4%) at their second. Eighteen patients (66.7%) complained of back pain during the post-partum period (mean time: 1.7 ± 2.1 months; right after delivery to seven months) and nine (33%) during the third trimester of pregnancy, at a mean time of 1.7 ± 0.9 months before delivery (three months to 15 days prior to delivery). Two patients did not breastfeed their infants.

Patients had sustained a median of 4.0 VFs (range: 1–10) [4.0 (3–9) *vs*. 2.5 (1–10), p: 0.02, for group A *vs*. group B, respectively]. Secondary causes of osteoporosis were identified in four (14.8%) patients (two cases with hyperthyroidism, one anorexia nervosa, and one inflammatory bowel disease). Nine (33.3%) women had a positive family history

Table 1 Baseline characteristics of the two groups

	Total (n = 27)	Group A (n = 19)	Group B (n = 8)	p-value
Age (years)	34.2 ± 5.4	34.7 ± 5.4	33.1 ± 5.3	0.50
Weight (Kg)	58.2 ± 7.5	58.3 ± 9.4	58.0 ± 2.1	0.95
Height (cm)	162.2 ± 6.5	161.7 ± 7.5	163.4 ± 3.5	0.56
BMI (kg/m^2)	22.0 ± 2.0	22.1 ± 2.3	21.7 ± 1.3	0.64
1st/2nd pregnancy (n, %)	25 (92.6)/2 (7.4)	18 (94.7)/1 (5.3)	7 (60)/1 (40)	0.51
Pre/Post-partum (n, %)	9 (33.3)/18 (67.7)	5 (26.3)/14 (73.7)	4 (50)/4 (50)	0.37
Duration of lactation (months)	3.9 ± 4.9	3.2 ± 2.3	5.5 ± 8.6	0.28
VFs	4 (1–10)	4 (3–9)	2.5 (1–10)	0.02
Height loss (cm)	4.2 ± 2.5	5.1 ± 2.6	3.8 ± 2.2	0.23
Secondary causes of osteoporosis (n, %)	4 (14.8)	2 (10.5)	2 (25)	0.33
Smoking (n, %)	1 (3.7)	1 (5.3)	0 (0)	0.51
Family history of osteoporosis (n, %)	9 (33.3)	7 (36.8)	2 (25)	0.55
LMWH	9 (33.3)	8 (42.1)	1(12.5)	0.14
Time from pain initiation to diagnosis (months)	3.7 ± 2.7	3.2 ± 2.2	5.0 ± 3.5	0.11

Group A: women treated with TPTD, Group B: women treated with calcium and vitamin D. Data are presented as mean ± SD, median (range) or n (%)

BMI body mass index, *LMWH* low molecular weight heparin, *VFs* vertebral fractures

of osteoporosis and nine (33.3%) had received low molecular weight heparin during pregnancy. Mean period from pain initiation to PLO diagnosis was 3.7 ± 2.7 months (range: 0–11 months, p: 0.11 between groups). Baseline aBMD and z-scores at the LS and TH, and TBS for groups A and B are presented in Table 2 and Fig. 2, while biochemical data are presented in Table 3. 42.1% of the women in Group A had aBMD LS z-score ≤ −4.0 vs. 25% in group B. In addition, 52.6% *vs*. 50% of patients had baseline 25(OH)D levels below 20 ng/ml in groups A and B, respectively.

Table 2 aBMD and TBS of the two groups at baseline and at 12 months

	Group A	Group B	*p*-value
aBMD LS (g/cm^2) baseline	0.745 ± 0.10 (n = 19)	0.800 ± 0.12 (n = 8)	0.25
Z-score aBMD LS baseline	− 3.46 ± 0.83	− 2.90 ± 1.01	0.15
aBMD LS (g/cm^2) at 12 months	0.885 ± 0.11 (n = 15)	0.849 ± 0.13 (n = 8)	0.51
Z-score aBMD LS at 12 months	− 2.25 ± 0.99	− 2.14 ± 0.84	0.54
aBMD LS% change from baseline to 12th month	20.9 ± 11.9	6.2 ± 4.8	< 0.001
Within group *p*-value	0.001	0.025	
aBMD FN (g/cm^2) baseline	0.684 ± 0.11 (n = 16)	0.767 ± 0.05 (n = 8)	0.027
Z-score aBMD FN baseline	− 2.31 ± 0.86	− 1.67 ± 0.29	0.032
aBMD FN (g/cm^2) at 12 months	0.726 ± 0.1 (n = 13)	0.778 ± 0.08 (n = 8)	0.27
Z-score aBMD FN at 12 months	− 1.88 ± 0.73	− 1.41 ± 0.33	0.11
aBMD FN % change from baseline to 12th month	9.6 ± 10.2	1.3 ± 7.3	0.11
Within group p-value	0.008	0.16	
aBMD TH (g/cm^2) baseline	0.673 ± 0.11 (n = 16)	0.752 ± 0.06 (n = 8)	0.09
Z-score aBMD TH baseline	− 2.59 ± 1.0	− 1.9 ± 0.4	0.07
aBMD TH (g/cm^2) at 12 months	0.720 ± 0.09 (n = 13)	0.796 ± 0.08 (n = 8)	0.08
Z-score aBMD TH at 12 months	− 2.2 ± 0.83	− 1.5 ± 0.44	0.06
aBMD TH % change from baseline to 12th month	10.0 ± 11.6	5.8 ± 2.8	0.43
Within group p-value	0.004	0.01	
TBS baseline	1.23 ± 0.09 (n = 11)	1.312 ± 0.06 (n = 5)	0.08
TBS at 12 months	1.30 ± 0.08 (n = 8)	1.323 ± 0.06 (n = 5)	0.96
TBS% change from baseline to 12th month	6.7 ± 6.9	0.9 ± 3.7	0.09
Within group p-value	0.02	0.34	

Data are presented as mean ± SD. Group A: women treated with TPTD, Group B: women treated with calcium and vitamin D

aBMD LS areal bone mineral density at the lumbar spine, *aBMD FN/TH* areal bone mineral density at the femoral neck/total hip, *TBS* trabecular bone score

Table 3 Baseline biochemical data of the two groups

	Group A	Group B	*p*-value	RR
Calcium (mg/dl)	9.45 ± 0.42	9.38 ± 0.32	0.68	8.4–10.2
Phosphate (mg/dl)	3.98 ± 0.48	4.03 ± 0.27	0.77	2.5–4.7
Creatinine (mg/dl)	0.67 ± 0.07	0.68 ± 0.06	0.83	0.6–1.1
eGFR (ml/min/1.73m^2)	112.68 ± 9.96	112.52 ± 8.76	0.96	> 90
ALP (IU/L)	86.52 ± 28.58	66.25 ± 18.08	0.07	40–150
25(OH)D (ng/ml)	23.98 ± 13.89	19.67 ± 10.56	0.44	20–50
PTH (pg/ml)	26.31 ± 13.95	30.21 ± 7.41	0.46	10–65
OC (ng/ml) (n:11/5)	31.70 ± 13.29	30.98 ± 7.59	0.91	9.7–35.1
CTX (ng/ml) (n:11/6)	0.503 ± 0.26	0.351 ± 0.14	0.21	< 0.573
PINP (ng/ml) (n:12/5)	84.26 ± 37.57	88.18 ± 32.70	0.78	15.2–58.59

Data are presented as mean ± SD. Group A: women treated with TPTD, Group B: women treated with calcium and vitamin D

CTX carboxyterminal crosslinking telopeptide of type I collagen, *ALP* alkaline phosphatase, *eGFR* estimated glomerular filtration rate (by CKD-EPI equation), *OC* osteocalcin, *PTH* parathyroid hormone, *PINP* procollagen type I N-terminal propeptide

Change in aBMD and TBS

At six months, 12 patients treated with TPTD achieved a mean aBMD increase of 13.6 ± 7.3% (range: 5.3–26.9%) at the LS, 6.4 ± 7.3% (range: −0.6% to 24.1%) at the FN, 7.5 ± 8.0% (range: −4.7% to 20.4%) at the TH and increase 6.1 ± 4.2 ($n=8$, range: 0.7–14.8%) in TBS. No analysis was performed for changes in aBMD at 6 months between groups since only three patients had available data in the control group. At 12 months, the aBMD % change was significantly higher in group A compared with group B at the LS (20.9% *vs.* 6.2%, $p<0.001$) (Fig. 1), but not at the FN (9.6% *vs.* 1.3%, $p=0.11$) and TH (10.0% *vs.* 5.8%. $p=0.43$). The corresponding within-group differences in aBMD were significant in both groups (Group A: LS: $p=0.001$, FN: $p=0.008$, TH: $p=0.004$, Group B: LS: $p=0.025$, FN: $p=0.16$, TH: $p=0.01$), except for FN in the control group. At 12 months 66.7%, 58.3% and 46.2% of the women in Group A had aBMD LS, FN, TH z-score ≤ −2.0 vs. 50%, 12.5% and 12.5% in group B (Fig. 2). There was no difference in % change in TBS at 12 months between groups (6.7% vs.0.9%, $p=0.09$). The corresponding within-group TBS differences were significant only in group A ($p=0.02$) (Table 2). At 24 months, mean aBMD increase was 32.9 ± 13.5% (18.8–51.1, $n=7$) *vs.* 12.2 ± 4.2% (4.9–17.5, $n=6$) at the LS ($p=0.001$), 18.6 ± 13.6% (1.5–42.6, $n=7$) *vs.* 1.25 ± 8.7% (−9.2–14.2, $n=6$) at the FN ($p=0.02$) and 18.0 ± 14.4% (5.2–43.1, $n=7$) *vs.* 8.6 ± 8.7% (−3.0–24.1, $n=6$) at the TH ($p=0.18$) in group A compared with group B; TBS was increased by 15.2 ± 15.5% (6.6–38.4, $n=4$) *vs.* 1.2 ± 2.2% (−1.0–4.1, $n=4$) ($p=0.03$) ,respectively. The corresponding within-group differences were significant over baseline (LS, FN, TH, TBS) and over 12 months (LS, FN, $p<0.05$) for group A and over baseline only (LS, TH, $p<0.05$) for group B. Absolute aBMD change at the LS was significantly higher in group A *vs.* group B at both 12 and 24 months ($p<0.001$ and $p=0.001$, respectively), indicating that the response to TPTD was not affected by baseline BMD. One woman in each group had a twin pregnancy. The observed changes in LS aBMD at one year in these two cases were 17.4% vs.

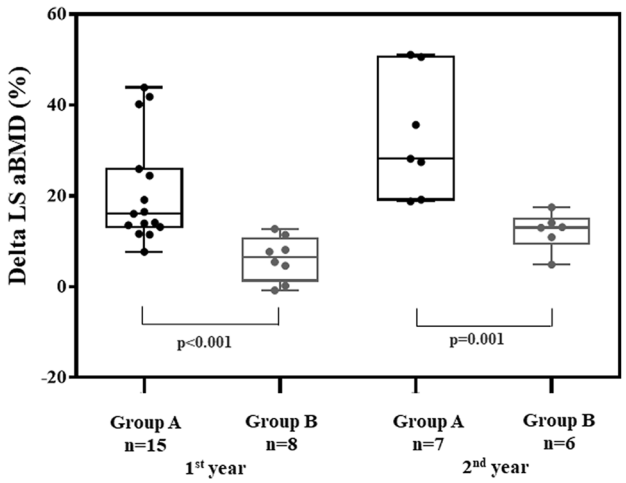

Fig. 1 Percent changes in LS aBMD in the two groups. Horizontal lines represent median values, boxes represent IQR (25–75) and bullets represent individual values

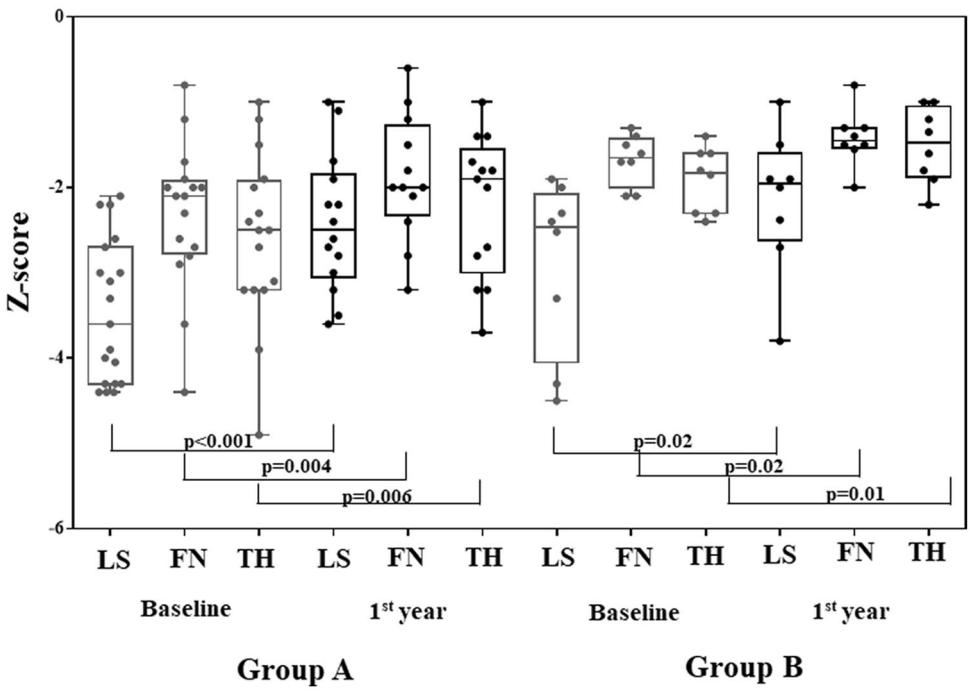

Fig. 2 Z-score at the LS, FN and TH at baseline and 12 months in the two groups. Horizontal lines represent median values, boxes represent IQR (25–75) and bullets represent individual values

4.6%, in the TPTD vs. control group, respectively. Exclusion of these two cases did not alter the results.

Following TPTD treatment PINP levels increased (Friedman test: $p < 0.05$), remained elevated over baseline at six months ($n = 12$) and returned to baseline levels at 12 months ($n = 6$) (Fig. 3). PINP levels during the first month of TPTD treatment ($n = 12$) increased by 82.5% (range: 14.7–273.2) and were positively correlated with aBMD % change during the first 12 months of treatment ($r = 0.68$, $p = 0.03$ and $r = 0.71$, $p = 0.02$, for LS and TH, respectively). Furthermore, baseline CTX was associated with the LS aBMD % change at 12 months ($r = 0.61$, $p = 0.02$). Age, BMI, baseline PINP concentrations, height loss and duration of lactation were not associated with aBMD % change at any site.

Treatment with TPTD was generally well-tolerated, apart from mild nausea and dizziness reported by two women. One patient developed mild hypercalcemia (Ca: 10.6 mg/dl), that resolved with reduction of the dose of calcium carbonate. No new clinical fractures were observed while on-treatment. In group A, two patients had a second pregnancy after stopping TPTD treatment, without the occurrence of new fracture(s). In group B, two patients had a second pregnancy; one presented back pain with concomitant bone oedema at the same vertebra (L1) that had fractured after the previous pregnancy.

Discussion

The decision to start anti-osteoporosis therapy in women suffering from PLO, especially in cases with childbearing potential, carries several challenges due to the heterogeneity of the underlying bone disease, the limited data on short-and long-term fracture risk, the safety of anti-osteoporosis medications and the possible loss of the therapeutic effect after completion of treatment. In the case of TPTD another concern is the safety restriction of "once a lifetime use". Thus, although PLO was first described by Nordin et al. in 1955 [22], given the rarity of the disease, there are still no formal guidelines on its management.

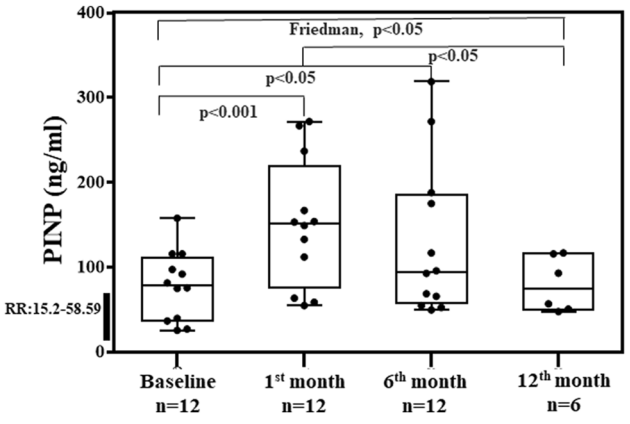

Fig. 3 PINP levels at baseline and follow-up in patients treated with TPTD. Horizontal lines represent median values, boxes represent IQR (25–75) and bullets represent individual values. *RR* reference range

Our study extends the results of Hong et al. [13] that reported the effect of TPTD on aBMD and bone markers for one year, in 27 cases with PLO and five cases on calcium and vitamin D. In the present study, TPTD treatment for up to two years resulted in substantial, early and gradual improvement of aBMD at the LS and hip, as well as in trabecular microarchitecture, as assessed by TBS, which was significantly higher, concerning LS and TBS, than that with calcium and vitamin D only supplementation. Notably, a wide heterogeneity in treatment response was observed, ranging in increases from 7.71% to 43.8% at the LS, similarly with prior studies. In particular, Hong et al. [13], reported a 16.2% (4.5–34.3%) increase in LS aBMD after one year of TPTD treatment, significantly higher as compared with conventional treatment. Choe et al. [18], in three patients with PLO reported a 19.5% (14.5–25%) increase in LS aBMD after 18 months of TPTD. Similar responses (8–21% increase in LS aBMD) were reported in case reports [14–17]. Furthermore, the present study showed an increase in FN and TH aBMD by 9.6% and 10%, respectively, higher than the 5.4% and 5.2% reported by Hong et al. [13]. This difference might be related to the higher baseline BMD and the previous treatment with BPs in 22% of cases in their study.

Moreover, TBS, a new index of trabecular microarchitecture [23] also improved with TPTD treatment by 6.7% (4.5%, if we exclude one outlier) and 15.2% in the first and second year of treatment, respectively. Thus, after 12 months of TPTD treatment, 77.8% of patients presented normal or partially degraded TBS (> 1.35 and 1.2–1.35, respectively) [24] as compared with 58.3% at baseline. This effect is considerably higher as compared with other conditions treated with TPTD, such as 2% in premenopausal idiopathic osteoporosis (IOP) [25], 2.7% in postmenopausal osteoporosis [26] and 3.7% in glucocorticoid-induced osteoporosis [27]. However, the observed changes in aBMD and TBS under treatment with TPTD should probably be considered as additive upon the spontaneous recovery following weaning and resumption of menses. In the present study, women managed conservatively had a significant increase in aBMD at both LS (6.18% and 12.2%) and TH (5.8% and 8.62%) at the first and second year, respectively. Similar increase of 7.5% and 5% at the LS and TH, respectively, was reported by Hong et al. [13] in five cases with PLO. However, recent studies questioned the full reversibility of the bone structural defects caused by prolonged lactation, at least at the appendicular skeleton [28, 29].

Bone turnover markers (BTMs), especially PINP, may help to predict the response of aBMD in patients treated with TPTD [30]. In the present series, PINP concentrations during the first month of treatment positively correlated with the increase in aBMD at 12 months. Similar findings were reported by Hong et al. [13] with osteocalcin at three months, and by Cohen et al. [25] with PINP and osteocalcin at three months in women with IOP. In addition, in the present study, higher baseline CTX levels were associated with a better aBMD response. However, in the study by Hong et al. [13], there was no correlation between baseline values of BTMs with the annual increase of aBMD. This finding contrasts with the results from the Fracture Prevention Trial [31] in postmenopausal women, where baseline PINP and PICP levels modestly correlated ($r=0.43$ and $r=0.36$, $p<0.05$, respectively) with LS aBMD response under TPTD. This finding might be related to the relatively small number of patients, the confounding effect of the recent fracture(s) and the dynamic changes of bone remodeling during the postpartum period. Thus, although it appears that BTMs, especially the bone formation markers PINP and osteocalcin, might serve as predictors of aBMD response during treatment with TPTD in cases with PLO, more data are certainly needed, especially specific cut-offs under standardized conditions, to guide clinical decisions.

The substantial variability in the response of aBMD both with TPTD treatment and conventional management in the present study, should be also underscored. Although 93.3% of our patients treated with TPTD demonstrated an aBMD response higher than that of the controls, there was some overlap between the two groups. Hong et al. [13] reported that younger age was the only independent predictor of the response in aBMD, suggesting an attenuated age-related osteoblast response to TPTD, as a possible mechanism in poor responders. Other possible explanations might include previous treatment with bisphosphonates that might attenuate the subsequent response to TPTD and differences in the background bone disease, such as the presence of monogenic bone disorders or relevant genetic variants associated with low bone formation as reported by Butscheidt et al. [6], that determine the severity of the disease and might also have an impact on the response to specific treatment. This finding is supported by recent data in patients with IOP [25], where the rate of bone formation assessed by quadruple-labeled transiliac bone biopsy was 44 to 58% lower, albeit not significantly, in non-responders to TPTD. In any case, given that low bone remodeling at a tissue-level seems to be a cardinal feature in patients with PLO [32], treatment with an anabolic agent appears the most reasonable approach. In the case of TPTD, until more data become available, treatment should probably be offered to severe cases, e.g., with multiple VFs.

Our study has several limitations, such as the retrospective design and the small number of patients. However, post-hoc power analysis indicated that our study had 95% probability of detecting the observed between groups difference in the 12 months' % change at LS aBMD, with a two tailed significance of $p<0.05$. Although patients treated with TPTD had more VF(s) than controls, which might represent a bias towards treating more severe cases with TPTD, the rest of the demographics and baseline BMD were comparable. Another limitation is the fact that we did not perform genetic testing for inherited metabolic bone disease, such as the several forms of osteogenesis imperfecta that might first present as PLO. Furthermore, it should be mentioned that DXA scans and biochemical tests were not performed in the same facilities in all patients and the effect of TPTD on back pain was not formally assessed.

Conclusions

This study showed a substantial improvement in aBMD and trabecular microarchitecture, as assessed by TBS, in patients with PLO treated with TPTD compared with conventional management with weaning and calcium and/or vitamin D supplementation. Spontaneous recovery with conventional treatment may occur for some patients with PLO, while treatment with TPTD may be required in severe cases with multiple VFs. In any case, further randomized-controlled studies are needed to establish optimal therapeutic strategy in patients with PLO.

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Data Availability Yes, upon a reasonable request by the requestors.

Declarations

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Ethical approval The study was approved by the ethics committee of KAT General Hospital. All procedures were conducted according to

the recommendations of Good Clinical Practice and all other applicable local regulatory and ethical requirements and the Declaration of Helsinki (revised edition, Tokyo 2004).

Consent to participate Written informed consent was obtained from all patients.

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