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TREATING BONE LOSS IN CHALLENGING SITUATIONS

Comparison of Efficacy of Pharmacologic Treatments in Pregnancy- and Lactation-Associated Osteoporosis

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Abstract
Pregnancy- and lactation-associated osteoporosis (PLO) is a rare disorder characterised by the occurrence of multiple fragility fractures, particularly at vertebral columns, in the third trimester or early postpartum period. Whether implementation for pharmacologic treatments in patients with PLO remains controversial partly due to rarity of data and known indolent recovery of bone mass after fracture, various pharmacologic treatments have been reported to effectively facilitate bone mineral density (BMD) increase in anecdotal case reports or cohorts based on individualised clinical assessment of subsequent fracture risk. In this study, we aimed to summarise pharmacologic strategies and its efficacy on BMD change and subsequent fractures using individual case data or frequency-weighted group data from available literatures. Among 2438 studies identified using PubMed and Embase until Jan 2019, 30 studies which reported pharmacologic treatment (23 studies) or observation (7 studies) were included. Reported treatment options consisted of observation with calcium/vitamin D supplements (control, $n = 32$), bisphosphonates (BP, $n = 31$), teriparatide (TPTD, $n = 40$) and other strategies (vitamin K2 and strontium; other, $n = 4$). Median treatment duration and BMD follow-up duration was 27 and 35 months, respectively. Mean lumbar spine BMD measured by dual-energy x-ray absorptiometry was increased at 3-year follow-up in all groups (control, 7.9%; BP, 18.2%; TPTD, 17.0%; other, 8.6%; $P < 0.05$ for all), with significantly higher BMD change in BP or TPTD compared to control (Bonferroni-corrected $P < 0.001$ for all). Our findings suggest the potential long-term efficacy of pharmacologic treatments in individuals with PLO with high risk of subsequent fracture.

Keywords Pregnancy- and lactation-associated osteoporosis · Premenopausal women · Vertebral fracture · Bisphosphonates · Recombinant human parathyroid hormone (1–34)

Introduction

Pregnancy- and lactation-associated osteoporosis (PLO) is a rare disorder characterised by the occurrence of fragility fractures and low bone mass most commonly at the vertebral column accompanying back pain and limited mobility in the third trimester of pregnancy or early postpartum [1–3]. Since the first description of PLO by Nordin et al. in 1955, about 150 to 200 cases have been reported from mostly anecdotal case series and uncontrolled small cohorts [3–9]. Although gradual spontaneous recovery of bone mass was observed in most of patients with PLO after weaning, the extent of BMD recovery differs substantially between individuals [3]. Although subsequent fracture risk has not been estimated in controlled trials, a retrospective, large cohort study showed that about 24% of patients with PLO had subsequent fractures during 6 years of follow-up, which was positively correlated with number of fractures at initial presentation [5]. These findings suggest important clinical implication on potential need for effective pharmacologic treatment to accelerate the BMD recovery to alleviate imminent subsequent fracture risk, in subset of patients with multiple fractures, impaired mobility and very low bone mass at initial presentation.

To date, bisphosphonates and teriparatide have been most commonly used in patients with PLO. If pharmacologic treatment in patients with PLO can yield a significant BMD gain in addition to natural recovery, this information may have clinical implication for treatment strategy based on individualised

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risk of patients with PLO. However, the efficacy of pharmacologic treatments on changes in bone mass has been rarely compared with untreated, observational groups only with nutritional support, partly due to difficulty in designing controlled trial in rare disorder. In this context, we aimed to estimate the efficacy of pharmacologic options on BMD changes in comparison with patients with PLO who did not undergo pharmacologic treatment, using extracted individual data from case series or frequency-weighted data from group studies identified by systematic review.

Data Sources, Search Strategy and Analysis

Relevant studies were identified by searching Medline via PubMed and Embase from 1994 to Jan 2019 (Fig. 1). The following words and medical subject headings were used without language restriction: 'Pregnancy', 'Lactation' and 'Osteoporosis'. Among identified 4241 studies, a total of 52 articles with available full-text remained for eligibility evaluation after excluding irrelevant or non-human studies according to predefined criteria. Data were extracted from studies with both baseline and follow-up BMD results after intervention (23 studies for pharmacologic intervention group; 7 studies for observation group). Among extracted studies, DXA-measured BMD data of 108 individuals were pooled to generate BMD changes between baseline and follow-up. Lumbar spine BMD changes was analysed as the primary outcome ($n = 107$); BMD changes at femoral neck (available in 73 subjects) and total hip (available in 69 subjects) were presented as secondary outcomes. Frequency-weighted pooled values were generated from either individual raw data extracted from case reports or representative statistics in larger case-control or cohort studies as available. Pooled mean percent BMD changes between groups adjusted for age and follow-up duration were estimated from predictions of multivariate linear regression models at fixed value of follow-up duration (36 months) and compared with Bonferroni correction, using 'margins' command of STATA 14.2 (College Station, TX, USA).

Characteristics of Studies

Details of studies are summarised in Table 1. A total of 30 studies including case series, case-control studies and retrospective cohorts were reviewed. Mean age of patients with PLO was 30.6 ± 2.5 years. Although patients reported from various countries including both Caucasian and Asian population, patients had relatively lean BMI (20.9 ± 1.3 kg/m^2). Most of patients were primipara. Median fracture occurrence time was 1 month postpartum (interquartile range 1 to 2 months), ranged from 7 months earlier from partum to 6 months postpartum. Median number of fractures was 3 [2–4]. Notable medical conditions of patients included heparin use [7, 10, 11], ankylosing spondylitis [12, 13], congenital megacolon [14], twin pregnancy [15, 16] and polycystic ovarian syndrome [17]. BMD measured by DXA after diagnosis of PLO was 0.726 ± 0.106, 0.623 ± 0.074 and 0.691 ± 0.043 g/

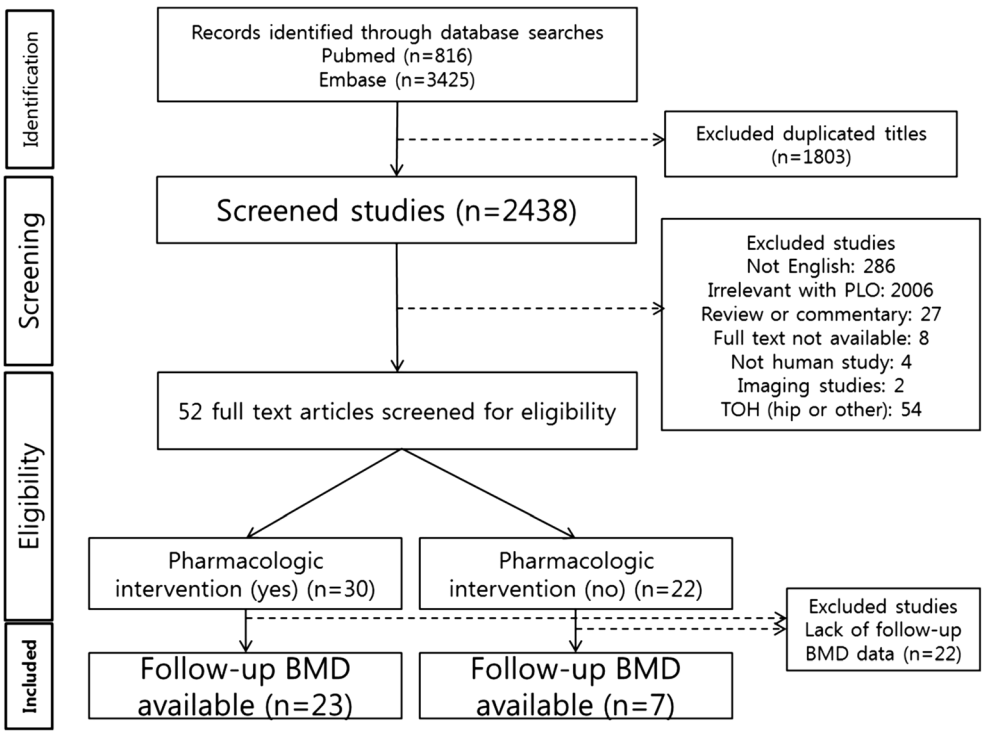

Fig. 1 Literature review and data extraction flow

Table 1 Summary of study characteristics

Study ID	Author names	Year	Country	Number	Age	BMI	Pregnancy	Fracture time from delivery (months)	Lactation (months)	Fracture site (number)	Comorbidity	Intervention	Medication duration (months)	Modality
1	Sarikaya S	2004	Turkey	1	35	18.4	G1P1	− 1	N/A	T8-L1(6)		Alendronate 10 mg/day	6	DXA
2	O'Sullivan S.M.	2006	New Zealand	10	30	21.9	8/11 G1P1	1	5.5	T-L spine(3)				
	Group 1		New Zealand	5	30							Pamidronate, alendronate, or zoledronate	24	DXA
	Group 2		New Zealand	4	30							Observation	24	DXA
3	Li L.-J., Zhang J.	2018	China	12	31	21.8	8/12 G1P1	4	4	T-L spine(4)		Alendronate 70 mg/week ($n = 5$), Zoledronic acid 5 mg/year ($n = 7$)	24	DXA
4	Vujasinovic-Stupar N.	2012	Serbia	1	30	22.5	G1P1	3.5	3.5	T-L spine(1)		Etidronate	12	DXA
5	Laroche M.	2017	France	52	32.1	22.5	35/52 G1P1	1	N/A	T-L spine, bilateral femoral neck in 1, sacral in 2, rib in 3(3.8)	Heparin use in 12 subjects			
	Group 1			7								Bisphosphonate	30	DXA
	Group 2			4								TPTD	30	DXA
	Group 3			5								Observation	30	DXA
6	Blanch J.	1994	USA	2										
	Case 1		USA	1	31		G1P1	2	2	T-L spine(not noted)		Etidronate	27	QCT
	Case 2		USA	1	28			2	2	T-L spine(not noted)		Observation		QCT
7	Tran H.A.	2002	Austrailia	3										
	Case 1			1	22	23	G1P1	3	3	T5, T6(2)	Congenital megacolon	Etidronate	24	DXA
	Case 2			1	36	18.2	G1P1	1	1	T6-T8(3)		Alendronate 10 mg/day	12	DXA
8	Reid I.R.	1992	USA	1	31		G1P1		4	T7,9,10,11(4)		Pamidronate 30 mg/month	3	DXA
9	Jang J.Y.	2009	South Korea	1	30	19.6	G1P1	2	2	L4, L5(2)	Ankylosing spondylitis	Risedronate 35 mg/week	12	DXA
10	Allali F.	2005	Morocco	1	38		G1P1	4	4	L2–4(3)	Ankylosing spondylitis	Risedronate 35 mg/week	24	DXA
11	Liel Y.	1998	Israel	1	23		G1P1	− 1.5	0.25	T8–11, L2(5)		Sodium fluoride 15–20 mg daily	18	QCT
12	Tanriover M.D.	2009	Turkey	1	23	22.8	G1P1	0.5	0.5	T8–12, L1–3(8)	PCOS, twin pregnancy	Alendronate 70 mg/week 4 month - > strontium ranelate (2 g/day)	34	DXA
13	Lampropoulou-Adamidou K.	2012	Greece	1	40	22.4	G1P1	0	2	T7,T9,T10; new T8, T12, L1 fractures 1 month later (6)	LMWH for thrombophilia in last 2 trimesters	TPTD 20 mcg/day	13	DXA
14	Choe E.Y.	2012	South Korea	3										
	Case 1			1	36	20.6	G1P1	6	6	T12, L1–3(4)		TPTD 20 mcg/day	12	DXA
	Case 2			1	32	27.1	G4P1	3	4	T12, L2(2)		TPTD 20 mcg/day	18	DXA
15	Polat S.B.	2015	Turkey	1	23	24	G1P1	2	2	T5,7,10,11,12(5)		TPTD 20 mcg/day	18	DXA

Table 1 (continued)

Study ID	Author names	Year	Country	Number	Age	BMI	Pregnancy	Fracture time from delivery (months)	Lactation (months)	Fracture site (number)	Comorbidity	Intervention	Medication duration (months)	Modality
16	Stumpf U.C.	2007	Germany	2	32			6	6	T5,7,8,10,12,L2–3(7)	LWMH with coumadin for pulmonary embolism	TPTD 20 mcg/day	6	DXA
17	Coskun Benlidayi I.	2014	Turkey	1	25		G1P1	5	5	T-L spine(multiple)		TPTD 20 mcg/day	6	DXA
18	Hellmeyer L.	2010	Germany	1	40	21	G4P2	1.5	1.5	T8,10, L2–3(4)		TPTD 20 mcg/day	18	DXA
19	Hong N.	2018	South Korea	32	31	20.3	30/32 G1P1							
	Group 1			27	31	20.3		2	3			TPTD 20 mcg/day	12	DXA
	Group 2			5	32	20.2		2	2			Observation	N/A	DXA
20	Ijuin A.	2017	Japan	1	27	17.1	G1P1	0.5	0.5	L1–3(3)		TPTD 56.5 mg/week (6 months) > Dmab 60 mg (6 months)	12	DXA
21	Tsuchie H.	2012	Japan	4										
	Case 1			1	30		G1P1	1	3	T8,10,12,L1(4)		Vit K2 45 mg/day	21	DXA
	Case 2			1	23		G1P1	2	2	T7,T12,L1(3)		Vit K2 45 mg/day	11	DXA
	Case 3			1	34		G1P1	0.25	0.25	T6,8,12(3)		Vit K2 45 mg/day	9	DXA
22	Grizzo F.M.F.	2015	Brazil	1	31	20.2	G1P1	1.5	1.5	T8, L1(2)	Twin	Zoledronic acid 5 mg/year	12	DXA
23	Ofluoglu O.	2008	Turkey	1	30	21.6	G1P1	1	1	T6,T8,T10,L1–5(8)		Alendronate 70 mg/week	12	DXA
24	Zhang M.	2017	China	1	23		G1P1	2	2	T-L spine(multiple)		Observation	N/A	DXA
25	Honjo S.	2001	Japan	1	32		G1P1	5	5	L3(1)		Observation	N/A	DXA
26	Rillo O.L.	1994	Argentina	1	25	24.3	G1P1	−3	0	T-L spine(multiple)	Twin	Observation	N/A	DXA
27	Chung H.C.	1988	South Korea	1	26	18.5	G1P1	0	0	L1, L3(2)		Observation	N/A	SPA
28	Anai T.	1999	Japan	2										
	Case 1			1	24	19.7	G1P1	−3	0	T7(1)		Observation	N/A	DXA
	Case 2			1	30	19.7	Third pregnancy	2	7	T6, T8(2)		Observation	N/A	DXA
29	Phillips A.J.	2000	UK	13	29		12/13 G1P1	3	3	T-L spine(multiple)		Observation (etidronate in one)	N/A	DXA
30	Smith R., Athanasou N.A.	1995	UK	24	27									
	Case 1			1	28		G1P1	−7	N/A			Observation	N/A	DXA
	Case 2			1	28		G1P1	0.25	N/A			Observation	N/A	DXA
	Case 3			1	37		G1P1	1	N/A	T-L spine(multiple)		Observation	N/A	DXA

cm^2 for lumbar spine, femoral neck and total hip, respectively. As expected, BMD data prior to PLO diagnosis were not available in most cases. In a case series, 3 among 10 patients reported previous history of osteoporosis prior to diagnosis of PLO [9]. A case of 31-year-old women reported that intact lumbar spine BMD before pregnancy (0.947 g/cm^2) which was measured opportunistically due to other reason decreased substantially to 0.771 g/cm^2, suggesting potential rapid bone loss during pregnancy in patients with PLO [16]. Diagnosis of osteogenesis imperfecta was reported in two cases, although the data on prevalence of genetic screening were limited in most of studies [3, 18].

Natural Courses

Philips and colleagues reported 9.5% spontaneous recovery of lumbar spine BMD during 3-year follow-up (annualised 3.2% increase) in 13 subjects without any pharmacologic treatments [3]. In our cohort, we also observed similar 3.5% increase at 1-year follow-up in 5 subjects without treatment [4]. The range of spontaneous lumbar spine BMD recovery was relatively wide among studies (from annual 1.32 to 13.4%) [7, 9, 15, 19–22]. In observation group, pooled estimate of lumbar spine BMD changes from age-adjusted regression model was 7.9% (95% CI 6.0 to 10.8%, $P < 0.001$) at 3-year follow-up. In a case, lumbar spine volumetric BMD measured by quantitative computed tomography (QCT) increased by 5% at 6-month follow-up [19]. These findings support the notion that most of patients with PLO show spontaneous, gradual recovery at postpartum period up to 3 years. However, substantial heterogeneity in degree of recovery among individuals is noted. Pooled estimates for BMD changes at femoral neck and total hip at 3-year follow-up were 3.0% (95% CI 1.7 to 4.3%, $P < 0.001$) and 5.7% (95% CI 4.4 to 7.1%, $P < 0.001$), respectively.

Pharmacologic Interventions

Bisphosphonates

Bisphosphonates have been used in PLO with various types (alendronate, risedronate, zoledronic acid, etidronate and pamidronate) and treatment duration (from 6 to 30 months) [6, 7, 13, 14, 16, 23–25]. Age-adjusted pooled estimates for BMD changes at 3-year follow-up from our regression models were 18.2% (95% CI 15.3 to 21.1%, $P < 0.001$), 4.3% (95% CI 3.4 to 5.2%, $P < 0.001$) and 9.1% (95% CI 7.4 to 10.9%, $P < 0.001$) at lumbar spine, femoral neck and total hip, respectively. In a case report, bisphosphonate use increased QCT-based lumbar spine volumetric BMD by 29% for 24 months [19]. These data align the well-known efficacy bisphosphonates for preventing bone loss or increasing BMD in premenopausal women with various conditions such as glucocorticoid exposure or adjuvant endocrine therapy in breast cancer, which have important clinical implication for efficacy of bisphosphonates on BMD improvements in patients with PLO [26, 27]. However, two major concerns need to be noted regarding bisphosphonate therapy in premenopausal women with PLO. First, bisphosphonates are category C drug for fetal safety because of a rat model data showing toxic effects due to accumulation of bisphosphonate in fetal skeleton, although many human case reports suggested no excess adverse maternal or fetal outcomes regarding bisphosphonates [28, 29]. Second, although one can expect favourable short-term BMD outcomes with bisphosphonates therapy in patients with PLO, efficacy on fracture prevention and long-term risks by bisphosphonate exposure remain unclear yet [30].

Teriparatide

Given the potential fetal toxicity from long-term residual effects of bisphosphonates, teriparatide, a recombinant human parathyroid hormone 1–34, has been considered as a potential therapeutic agent for premenopausal women with PLO. Previous clinical trials showed substantial efficacy of teriparatide for preventing bone loss and improving BMD in premenopausal women with idiopathic osteoporosis or osteoporosis due to anorexia nervosa [31, 32]. In reviewed PLO studies, treatment duration of teriparatide varied from 6 to 30 months [4, 7, 10, 11, 33–37]. In our previous study, the mean BMD increase at lumbar spine after 12 months of teriparatide therapy was 16.2% in patients with PLO [4]. However, the response varied substantially (with the standard deviation of 8.1%) among individuals. In accordance with the finding, reviewed studies also showed wide spectrum of BMD increase (annualised 3.0 to 33.4%), which suggest that PLO might be heterogeneous disorder with different etiologies. Bone biopsy from a case showed osteoblast failure, which may partly explain the differences in responsiveness to anabolic agent [18]. Nevertheless, when the BMD responses were pooled into a single estimate using regression model with adjustment for age and follow-up duration, teriparatide treatment was associated with BMD increases of 16.9% (95% CI 13.7 to 20.1%, $P < 0.001$), 5.3% (95% CI 4.4 to 6.2%, $P < 0.001$) and 10.6% (95% CI 8.4 to 12.8%, $P < 0.001$) at lumbar spine, femoral neck and total hip, respectively, at 3-year follow-up. Although the short-term result on BMD changes seems promising, long-term fracture prevention efficacy and risk profiles regarding teriparatide use in premenopausal women remain unclear [30]. In addition, the need for maintenance of anti-resorptive therapy after teriparatide cessation is still controversial in premenopausal women [38]. Given the limited data on long-term use of teriparatide in premenopausal women, use of teriparatide can be reserved for patients sustaining multiple, recurrent fractures with high risk of subsequent fracture.

Other Agents

Use of vitamin K2 was reported in 3 Japanese subjects, which showed 2.2% for 9 months to 5.0% for 21 months increases in lumbar spine BMD [39]. Weekly oral alendronate (4 months) followed by strontium ranelate (30 months) yielded substantial increase in lumbar spine BMD up to 40% during 34 months in a case report, although the results need to be validated in larger samples [17]. Pooled BMD changes could not be estimated due to small sample size and heterogeneity of data.

Comparison of Efficacy Between Groups

Comparison of changes in BMD according to treatment groups were presented in Fig. 2. Baseline lumbar spine areal BMD did not differ significantly between bisphosphonates vs. observation (0.799 vs. 0.750 g/cm^2, $P = 0.999$) and teriparatide vs. observation groups (0.680 vs. 0.750 g/cm^2, $P = 0.265$). However, compared to observation group, both bisphosphonate (18.2% vs. 7.9%, $P < 0.001$) and teriparatide (16.9% vs. 7.9%, $P < 0.001$) yielded significantly higher pooled estimates for BMD changes 36-month follow-up in lumbar spine DXA. Pooled lumbar spine BMD changes between bisphosphonate and teriparatide did not differ significantly ($P = 0.999$). BMD changes at total hip showed similar patterns (bisphosphonate vs. observation, 9.1% vs. 5.7%, $P = 0.001$; teriparatide vs. observation, 10.6% vs. 5.7%, $P < 0.001$). For femoral neck area, only differences in BMD changes between teriparatide vs. observation reached statistical significance (10.6% vs. 5.7%, $P = 0.017$). These results suggest that either bisphosphonate or teriparatide therapy has favourable effect on BMD improvement in patients with PLO, in addition to spontaneous recovery up to 3 years.

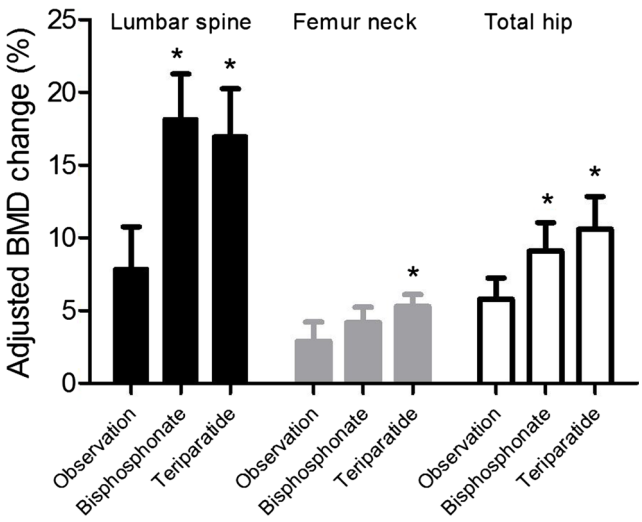

Fig. 2 Pooled estimates of relative changes in DXA-based BMD at lumbar spine, femoral neck and total hip at 36-month follow-up by treatment groups in patients with pregnancy- and lactation-associated osteoporosis. Pooled percentage changes in BMD were estimated from multivariate linear regression models with the adjustment for age and follow-up duration as fixed to 36 months. Asterisk indicates statistically significant differences compared to observation group as reference ($P < 0.05$ after Bonferroni correction for multiple comparisons). Changes in BMD between bisphosphonates and teriparatide groups did not differ significantly for any regions

Subsequent Fractures

Data on long-term subsequent fracture risk are limited in patients with PLO. In a French cohort, new vertebral, tibia or humerus fracture occurred after 4–36 months in 10 among 52 patients (3 treated; 7 untreated). Among untreated 7 patients, 2 subjects sustained repeat fracture during second pregnancy. Another study also reported that among 9 subjects (5 treated, 4 untreated), one patient sustained fracture in subsequent pregnancy in bisphosphonate non-user group. However, Anai reported a case study that the patient had uneventful second pregnancy despite of PLO with low bone mass. Long-term follow-up data with adequate controls are needed to assess the efficacy of pharmacologic treatment on fracture prevention.

Strength and Limitations

To our knowledge, this study is the first to report pooled estimates for BMD changes at various sites according to treatment modalities in patients with PLO. Our results may provide important clinical insight for weighing the balance between the risk and benefit of pharmacologic intervention. Our study is limited by retrospective observational nature, which is inevitable due to scarcity of data and rarity of the PLO. Although we tried to search all the relevant studies as possible, our study may not be free from selection bias due to excluding studies because we only included studies with quantifiable DXA values (either in baseline and follow-up value or percent change value at any region of interest). The possibility of underestimation of variances for pooled estimates cannot be excluded due to incomplete collection of the individual-level data.

Conclusion

In conclusion, bisphosphonate or teriparatide therapy may have favourable impact on BMD increase over spontaneous recovery in patients with PLO. Indications for pharmacologic treatment have not been established yet. Bisphosphonates or teriparatide can be reserved for patients with very severe symptoms, multiple fractures at initial presentation and with high risk of imminent fractures, with the careful consideration

for lack of long-term risk-benefit profiles. Efficacy of pharmacologic treatments on subsequent fracture risk remains as unmet need, which need to be investigated in future studies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Not applicable.

Informed Consent Not applicable.

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