Effect of Teriparatide on Subsequent Fracture and Bone Mineral Density in 47 Women with Pregnancy- and Lactation-associated Osteoporosis and Vertebral Fractures

Auswirkung von Teriparatid auf nachfolgende Frakturen und Knochendichte bei 47 Frauen mit schwangerschaftsassoziierter Osteoporose und Wirbelfrakturen

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ABSTRACT

Introduction Pregnancy- and lactation-associated osteoporosis (PLO) with predominantly vertebral fractures is a rare but severe disease which can occur in the last trimester of pregnancy or postpartum. The aim of the present study was to assess the impact of teriparatide on subsequent fractures and bone mineral density (BMD) in patients with PLO.

Materials and Methods A total of 47 patients with PLO and postpartum spinal fractures (mean: 4 fractures) undergoing treatment with teriparatide were investigated. The data collection period was set between 2006 and 2018. All patients received a subcutaneous injection of 20 µg teriparatide once a day for 24 months as well as individually adapted vitamin D supplementation. After 24 months of treatment, all women received no further treatment and either had regular menstrual cycles or took oral contraceptives. Fractures were confirmed by X-ray or MRI. Changes in BMD from baseline were examined using serial DXA measurements.

Results After 24 months of teriparatide treatment, we could demonstrate an increase in BMD at the lumbar spine, femoral neck and total hip of +30.1%, +11.7% and +12.2% respectively (p < 0.001 for all). At 12 months after cessation of treatment, BMD remained stable compared to the 24-month measurements at the lumbar spine, femoral neck and total hip which showed non-significant changes of +1.4%, +2.6% and +4.1% respectively. Out of the 47 patients with PLO with a mean of 4 existing fractures, 4 patients (7.8%) sustained a subsequent fracture, two after 3–5 months of treatment and two at > 6 months of treatment.

Conclusion 24 months of treatment with teriparatide in women with PLO and multiple vertebral fractures significantly increased BMD, predominantly BMD of the spine. As patients were premenopausal, there was no significant decrease in BMD in the following 12 months after cessation of treatment.
Introduction

Osteoporosis occurs predominantly in postmenopausal woman, and osteoporosis-related spine and hip fractures are associated with increased morbidity and mortality rates [1]. Pregnancy- and lactation-associated osteoporosis (PLO) is a rare, but in most cases severe, type of premenopausal osteoporosis and was first described as a clinical syndrome in 1955 by Nordin et al. Today, the incidence is estimated to be 0.4 per 100 000 women [2, 3]. According to the World Health Organisation (WHO), osteoporosis is defined as a T-score of $-2.5$ or less at the hip or spine in postmenopausal women and men [4]. For premenopausal women, the International Society for Clinical Densitometry (ISCD) suggested using the z-score to identify patients at high risk of fracture [5]. A medical intervention should be considered in patients with a z-score of $\leq 2$ or accompanied by the fragility fractures during or after pregnancy. Most agents available to treat osteoporosis are either contraindicated or of unknown efficacy in premenopausal women, and the possible impact on the foetus is also unknown.

PLO is a rare condition which occurs predominantly in the first pregnancy (70%), occurring in the last trimester of pregnancy or immediately postpartum [6]. Pregnancy and lactation are both high maintenance periods with regard to skeletal health. Although the mechanisms of bone mineral density alteration during those periods are unknown [3], it is well documented that increased calcium requirements during foetal and neonatal development should be met by synergistically increasing intestinal calcium absorption [7]. During both pregnancy and the period of lactation, parathyroid hormone levels (PTH) increase, leading to osteoclast activation which leads to elevated serum calcium levels and a subsequent loss in bone mineral density [8]. In addition to the role of the parathyroid hormone in physiological pregnancy, it should be noted that parathyroid hormone-related peptide (PTHrP) also plays a pivotal role in calcium homeostasis during pregnancy, which is quite distinct from its pathophysiological mechanism of action in the setting of tumour-induced humoral hypercalcaemia. In contrast, serum PTH decreases during pregnancy to a low normal range during the first trimester and may increase back to midnormal ranges by the end of gestation [7]. It is unknown why most women preserve bone homeostasis while in others, pregnancy or lactation leads to fragility fractures; genetic skeletal predisposition undoubtedly contributes to this catabolic process [9, 10]. The rarity of this disease is a key issue when diagnosing PLO. PLO should be suspected in all pregnant or breastfeeding women complaining of severe, persistent and treatment-resistant back and/or lower back pain. The indistinct clinical symptoms present in pregnancy often considered to be benign antenatal discomfort, the high incidence of musculoskeletal complaints, and the hesitation to perform diagnostic imaging during pregnancy often severely delay the detection of PLO. Therefore, PLO remains under-reported and undertreated [11, 12]. If undetected and untreated, PLO can lead to an accumulation of vertebral compression fractures and subsequent fractures [13]. In addition to PLO with vertebral compression fractures, women may also be affected by transient osteoporosis of the hip, a multifactorial disease of unclear aetiology [14].

Physical activity, calcium intake, and vitamin D supplementation in combination with medical intervention play a key role in the treatment of osteoporosis [15]. Kovacs et al. addressed this and examined non-pharmacological as well as pharmacological approaches [9]. The non-pharmacological approach includes cessation of lactation as well as calcium and vitamin D supplementation. During lactation, an average of 300–400 mg of calcium is transferred daily from mother to child, which may lead to a maternal skeletal calcium loss of up to 5–10%. Remarkably, in most cases, this amount is fully regained at 6–12 months after cessa-
tion of lactation; therefore, the weaning process constitutes a ma-
jor part of treatment [16]. Teriparatide (recombinant human
parathyroid hormone, PTH) is a bone-forming agent, predomi-
nantly used in cases with severe osteoporosis [15]. Teriparatide
enhances the anabolic osteoblast process, inhibits osteoblast ap-
oposis, and is hypothesised to even accelerate fracture healing
[17]. Failure to this mechanisms causes severe back pain and facil-
itates vertebral prolapse following osteoporotic vertebral fracture,
which may lead to neurological deficits [18].

We conducted the present analysis to investigate the effect of
teriparatide on subsequent fracture risk and changes in lumbar
spine, femoral neck, and total hip bone mineral density (BMD) in
patients with PLO and at least one vertebral fracture.

Patients and Methods
We included a total of 47 patients with PLO who had suffered
spine fractures postpartum and had been referred to the German
reference centre for PLO between 2004 and 2018. This was a ret-
rospective study using data collected between 2006 and 2018.

Methodology
All patients completed a standardised questionnaire including de-
tailed history of disease and medication use known to effect bone
health. Baseline characteristics were extracted from the data in-
cluding age, height, weight, BMI, and age at menarche. We also
obtained more detailed information, such as mode of delivery,
timing of PLO in the context of the number of pregnancies, the
use of oral contraceptives and history of assisted reproductive
medicine prior to diagnosis with PLO. All BMD measurements
and changes from baseline were obtained from the German PLO
reference centre using serial dual-energy X-ray absorptiometry
(DXA) performed with the same device (Prodigy; GE/Lunar). We
have previously reported on the precision error and least signifi-
cant change (LSC) of BMD measurements using this device [19,
20]. All fractures were confirmed by X-ray or MRI. Fractured verte-
brae were excluded from BMD measurements in accordance with
our standard operating procedures. All participants ceased breastfeed-ing once vertebral fractures were diagnosed. No pre-
vious history of antiresorptive treatment had been recorded, only a few patients had been administered glucocorticoids prior to PLO
(10.6%). None of the patients had a previous history of osteopo-
rotic fracture prior to pregnancy. None of the included women
had a history of medication intake or disease that could interfere
with bone metabolism and lead to secondary osteoporosis.

The treatment regimen consisted of subcutaneous injection
with 20 µg teriparatide once daily for a total of 24 months. All pa-
tients were instructed on teriparatide administration, given die-
tary advice on improving bone health and ensuring an optimal cal-
cium intake, and were supplemented with vitamin D if necessary.
The patient’s adherence to treatment was confirmed and docu-
mented at the 12- and 24-month visits. Teriparatide treatment
was initiated immediately after the first visit to the German PLO
reference centre. Informed consent was obtained from all pa-
ients; data analysis was permitted by the ethics committee of
the University of Marburg and was conducted in accordance with
German law and the Declaration of Helsinki.

| Table 1 Baseline characteristics. |
| --- |
| | N | Mean % | SD |
| Age (years) | 47 | 34.2 | 4.8 |
| Height (cm) | 47 | 166.3 | 5.6 |
| Weight (kg) | 47 | 62.6 | 10.1 |
| Body mass index (kg/m²) | 47 | 22.6 | 3.4 |
| Age at menarche (years) | 47 | 13.1 | 1.3 |

| Table 2 Additional baseline characteristics. |
| --- |
| Mode of delivery for PLO pregnancy | N | % |
| Normal delivery | 31 | 66.0 |
| Vaginal operative delivery | 1 | 2.1 |
| Primary caesarean section | 10 | 21.3 |
| Secondary caesarean section | 5 | 10.6 |
| Pregnancy when PLO was diagnosed | | |
| 1st | 39 | 83.0 |
| 2nd | 6 | 12.8 |
| 3rd | 1 | 2.1 |
| 1st and 2nd | 1 | 2.1 |
| Use of oral contraceptives prior to PLO | | |
| No | 5 | 10.6 |
| Yes | 42 | 89.4 |
| Use of assisted reproductive medicine prior to PLO | | |
| No | 46 | 97.9 |
| Yes | 1 | 2.1 |
| Immobilisation during pregnancy | | |
| No | 37 | 78.7 |
| Yes | 10 | 21.3 |
| Heparin during pregnancy | | |
| No | 40 | 85.1 |
| Yes | 7 | 14.9 |
| Cycle irregularities prior to PLO (%) | | |
| No | 31 | 66.0 |
| Yes | 16 | 34.0 |
| Secondary amenorrhoea (> 6 months) prior to PLO (%) | | |
| No | 39 | 83.0 |
| Yes | 8 | 17.0 |
| Use of glucocorticoids prior to PLO | | |
| No | 42 | 89.4 |
| Yes | 5 | 10.6 |
| Smoking prior to PLO (%) | | |
| No | 42 | 89.4 |
| Yes | 5 | 10.6 |
| History of lactose intolerance (%) | | |
| No | 40 | 85.1 |
| Yes | 7 | 14.9 |
| Family history of osteoporosis | | |
| no | 33 | 70.2 |
| Yes | 14 | 29.8 |
Statistical analysis

Statistical analysis was performed using IBM SPSS software, version 24.0. Statistical significance was achieved at a power of 0.8 and an α of 0.05. Spearman’s correlation coefficient was used to obtain comparative results. Wilcoxon and Mann-Whitney U test were used to evaluate group differences, and baseline characteristics were analysed for normal distribution using χ² test and Fisher’s exact test.

Results

Baseline characteristics

Our study included 47 patients with PLO and vertebral fractures. All women received 20 µg teriparatide daily over a period of 24 months shortly after being diagnosed with PLO.

Demographic characteristics showed that the mean age of our population was 34.2 years with a mean weight of 62.6 kg, height of 166.3 cm and BMI of 22.6 (▶ Table 1). ▶ Table 2 includes additional baseline characteristics such as the use of oral contraceptives, previous history of assisted reproductive medicine, immobilisation during pregnancy, etc. The mode of delivery was predominantly spontaneous vaginal delivery (66% of the study population). In 83% of cases, PLO occurred during the first pregnancy.

Follow-up data

Next, we investigated the number and distribution of fractures per patient with PLO. The mean number of vertebral fractures was 4 and the distribution of fractures is displayed in ▶ Fig. 1a. We also investigated the location of fractures. Fractures were evenly distributed between the lumbar and thoracic spine, with 72.3% of all fractures observed at the lumbar and 68.1% in the thoracic spine (▶ Fig. 1b). All patients presented with fractures after a severe episode of back pain without having suffered a traumatic accident. Most women presented with four vertebral fractures, followed by five; very few patients had ten or more fragility fractures (▶ Fig. 1b); no distal radius or hip fractures were observed.

Time-dependent changes in BMD, T-scores and z-scores in women with PLO, and teriparatide treatment are shown in ▶ Table 3. Median changes in lumbar spine, femoral neck, and total hip BMD using T-scores and z-scores were examined. (▶ Fig. 2a–c). We evaluated time-dependent changes in BMD at the lumbar spine, femoral neck and total hip at baseline, after 12 and 24 months of teriparatide treatment and after a further 12 months of follow-up (36 months after the start of treatment). We found a significant, linear increase in BMD at all visits.

The BMD increase from baseline in the lumbar spine at 12, 24 and 36 months was + 21.1%, + 31.4% and + 30.3%, respectively (p<0.001). At the femoral neck, we found a significant increase of + 9.3%, + 12.2% and + 16.3%, respectively (p<0.001), and at the total hip, we found a significant increase of + 7.7%, + 11.7% and + 13.3% for the same period (p<0.05, ▶ Fig. 3a–c). BMD gradually increased from baseline to 36 months in all groups (+ 16.3%, + 13.3% and + 31.5%), with BMD values recorded at 24 months of treatment.
Four out of the 47 patients (7.8%) suffered a subsequent fracture in the area of the lumbar spine whilst receiving teriparatide treatment. Two of these patients suffered a repeat fracture within three to five months of diagnosis and two after six months. All subsequent fractures were identified by X-ray.

**Discussion**

We demonstrated a linear increase of lumbar spine, femoral neck, and total hip BMD after 24 months of treatment with teriparatide. After 24 months of teriparatide treatment, the increase seems to be most pronounced in lumbar spine BMD, with only rare cases of further subsequent fractures occurring in women with PLO and existing vertebral fractures. Long-term follow-up data [21] including subsequent fracture risk from our German reference centre (n = 107 over 6 years) showed that almost one quarter of patients with PLO sustained a subsequent fracture. This fracture risk correlated with the number of fractures at diagnosis. These findings were recently confirmed in a review by Qian et al. [22] and were congruent with other 338 cases from 65 included papers.

Pregnancy- and lactation-associated osteoporosis is an infrequent but severe condition that is often misdiagnosed. Its aetiology is only partly understood but risk factors such as poor nutrition, insufficient calcium and vitamin D levels, high BMI, physical inactivity, smoking, first degree relative with a history of PLO, and corticosteroid intake have been identified [23]. Hadji et al. [24] identified pregnancy-associated diseases which require immobilisation as the highest impact risk for PLO in a large study with 102 PLO patients and 102 controls. Recently, Butscheidt et al. [25, 26] reported on three monogenic mutations in *LRP5*, *COL1A1* and *COL1A2* which may play a role in the aetiopathogenesis of PLO. As such, pregnancy was found to be a skeletal risk factor promoting the initial onset of previously unrecognised monogenic bone disorders.

Today, there is no generally accepted treatment guideline for patients with PLO, and treatment protocols are controversially discussed. There is an undoubtedly consensus that treatment should aim to prevent further fractures by increasing BMD, especially at the most vulnerable fracture site.

| Time (months) | 0 | 12 | 24 | 36 |
|---------------|---|----|----|----|
| **Femoral neck (g/cm²)** | | | | |
| N | 37 | 21 | 26 | 16 |
| Mean | 0.73 | 0.79 | 0.83 | 0.83 |
| SD | 0.09 | 0.11 | 0.10 | 0.12 |
| **Femoral neck T-score** | | | | |
| N | 36 | 21 | 27 | 16 |
| Mean | −2.01 | −1.59 | −1.17 | −1.26 |
| SD | 0.73 | 0.92 | 0.75 | 0.93 |
| **Femoral neck z-score** | | | | |
| N | 34 | 20 | 24 | 16 |
| Mean | −1.84 | −1.42 | −0.97 | −1.05 |
| SD | 0.80 | 1.02 | 0.80 | 0.97 |
| **Total hip (g/cm²)** | | | | |
| N | 36 | 20 | 25 | 14 |
| Mean | 0.76 | 0.81 | 0.85 | 0.82 |
| SD | 0.10 | 0.08 | 0.10 | 0.07 |
| **Total hip T-score** | | | | |
| N | 38 | 19 | 26 | 14 |
| Mean | −1.98 | −1.58 | −1.22 | −1.46 |
| SD | 0.82 | 0.66 | 0.85 | 0.57 |
| **Total hip z-score** | | | | |
| N | 33 | 19 | 25 | 14 |
| Mean | −1.80 | −1.45 | −1.08 | −1.30 |
| SD | 0.87 | 0.78 | 0.80 | 0.65 |
| **Lumbar spine (g/cm²)** | | | | |
| N | 40 | 23 | 27 | 15 |
| Mean | 0.800 | 0.941 | 1.022 | 0.954 |
| SD | 0.128 | 0.108 | 0.112 | 0.091 |
| **Lumbar spine T-score** | | | | |
| N | 40 | 23 | 29 | 17 |
| Mean | −3.02 | −1.83 | −1.40 | −1.76 |
| SD | 0.95 | 0.90 | 1.08 | 0.73 |
| **Lumbar spine z-score** | | | | |
| N | 38 | 22 | 26 | 17 |
| Mean | −2.96 | −1.67 | −1.31 | −1.60 |
| SD | 1.03 | 1.00 | 1.14 | 0.84 |
Fig. 2  

- **a** Distribution of lumbar spine T-scores in women with PLO at baseline.
- **b** Distribution of femoral neck T-scores in women with PLO at baseline.
- **c** Distribution of total hip T-scores in women with PLO at baseline.

Fig. 3  

- **a** Increase of lumbar spine BMD in relation to duration of teriparatide treatment. 24 months of treatment with teriparatide significantly increased BMD, predominantly at the spine. As all patients were premenopausal, there was no significant decrease of BMD in the 12 months after cessation of treatment.
- **b** Increase of femoral neck BMD in relation to duration of teriparatide treatment.
- **c** Increase of total hip BMD in relation to duration of teriparatide treatment.
The pharmacological approach includes various antiresorptive agents such as bisphosphonates and denosumab as well as bone anabolic treatments such as teriparatide [27]. In the past, the use of bisphosphonates as a pharmacological treatment option for PLO has been the subject of a few studies. Unfortunately, as bisphosphonates persist for a long time in bone, are able to cross the placental barrier, and may accumulate in the foetal skeleton, their use is controversially discussed [23]. In contrast to bisphosphonates, teriparatide has a low half-life of only a few hours; it does not accumulate inside the bone matrix and thus poses no threat to subsequent pregnancies if administration is discontinued early enough [12, 28]. The data of Cohen et al. [29] showing low bone remodelling rates at the tissue level in women with PLO provides the pathophysiological rationale for the use of teriparatide in the setting of PLO. In a recent report, Hellmeyer et al. emphasised the positive effects of teriparatide over 18 months [30]. Soon afterwards, Lampropoulou-Adamidou et al. were also able to demonstrate the positive effects of teriparatide treatment without any serious adverse foetal effects [28, 31]. Choe et al. supported this hypothesis and examined the effect of teriparatide over 18 months of continuous administration [32]. Finally, Winarno et al. examined the use of teriparatide after unsuccessful therapy with bisphosphonates in a complex case of pregnancy-related osteoporosis [33].

Altogether only six case reports of teriparatide treatment have been published, all showing a substantial increase in BMD [34]. Previously, O’Sullivan et al. reported that the increase in BMD is greater at the lumbar spine than at the femoral neck and total hip which is in agreement with our own findings [23]. Similarly, Hong et al. [35] concluded that lumbar spine BMD increased irrespective of baseline values after treatment with teriparatide. Importantly, the increase in BMD was sustained for a period of 12 months after discontinuation of teriparatide without any further medical treatment in patients using oral contraceptives or with a regular menstrual cycle. It is important to emphasise that after stopping lactation, patients with PLO regain normal endogenous oestrogen levels, thereby normalising bone turnover and perhaps also BMD. This approach may have an important clinical impact on the course of PLO and should be included in the follow-up strategy [36].

Our study has several limitations that should be addressed. The retrospective nature of our single treatment arm study could indicate confounders, although we included all patients who received teriparatide in the given timeframe for whom BMD measurements at baseline and after 12, 24 months and 36 months were available. The demographic heterogeneity within the treatment group is a potential source of selection bias, but this is a problem for all studies of rare diseases. A placebo-controlled randomised study would certainly best address the research question, but because of the rarity of PLO, it is highly unlikely that such a RCT will ever be performed. It is also unlikely that a patient with PLO and 4 or more vertebral fractures would agree to receive placebo over the course of 24 months. We were unable to distinguish between the increase in BMD due to the cessation of lactation and the resumption of regular menstrual cycles and the increase due to teriparatide treatment, as all studied patients stopped lactation and started teriparatide treatment.

We did not collect serum levels to measure levels of reproductive hormones and vitamin D, PTH or markers of bone turnover, which would have been interesting to compare with the increase in BMD. Finally, we also did not examine sequential treatment with teriparatide and bisphosphonates or denosumab, which would also deliver interesting results. Due to the infrequency of PLO, we wanted to focus on a single treatment regimen and avoid decreasing the number of patients per group.

To our knowledge, this is the largest study to include a substantial number of cases for the purpose of investigating and demonstrating the positive effects of teriparatide on subsequent fracture risk and bone mineral density in women with pregnancy- and lactation-associated osteoporosis (PLO) with vertebral fractures.

### Conclusion

In conclusion, with regard to early diagnosis, it is crucial that physicians are cautious when pregnant or lactating women report treatment-resistant back pain. Early diagnosis is of the utmost importance. Even in pregnancy, MRI is an optional possible diagnostic tool to identify fractures which may influence the delivery mode as well as to propose primary weaning. If treatment is indicated in patients with PLO and several vertebral fractures, our results indicate that teriparatide treatment is effective at substantially increasing BMD and perhaps reducing the subsequent risk of fracture.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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