ORIGINAL ARTICLE

Profile of changes in bone turnover markers during once-weekly teriparatide administration for 24 weeks in postmenopausal women with osteoporosis

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Abstract
Summary Changes in bone turnover markers with weekly 56.5 µg teriparatide injections for 24 weeks were investigated in women with osteoporosis. Changes in bone turnover markers 24 h after each injection of teriparatide were constant. During the 24 week period, bone formation markers increased and baseline bone resorption marker levels were maintained.
Introduction This study aimed to clarify the changes in bone turnover markers during 24 weeks of once-weekly teriparatide injections in postmenopausal women with osteoporosis.
Methods The 24 h changes in pharmacokinetics (PK), calcium metabolism, and bone turnover markers (serum osteocalcin, procollagen type I N-terminal propeptide (P1NP), urinary cross-linked N-telopeptide of type I collagen (NTX), deoxypiridinoline (DPD)) after each injection of 56.5 µg teriparatide at the data collection weeks (0, 4, 12, and 24 weeks) were investigated. The changes were evaluated by comparison with the data at 0 h in each data collection week.
Results Similar 24 h changes in each parameter after injection of teriparatide were observed in each data collection week. Serum calcium increased transiently, and intact PTH decreased 4–8 h after injection; serum calcium subsequently returned to baseline levels. Calcium and intact PTH levels decreased for 24 weeks. Although serum osteocalcin decreased at 24 h, it was significantly increased at 4 weeks. P1NP decreased transiently and then increased significantly at 24 h. P1NP was significantly increased at 4 weeks. Urinary NTX and DPD were significantly increased transiently and then decreased at 24 h. The urinary DPD level decreased significantly at 4 weeks.
Conclusions Twenty-four hour changes in PK, calcium metabolism, and bone turnover markers showed the same direction and level after once-weekly teriparatide injections for 24 weeks, with no attenuation of the effect over time. After 24 weeks, the bone formation marker, serum osteocalcin, increased significantly, but the serum P1NP, did not. Bone resorption markers decreased or remained the same.

Keywords Bone formation · Bone resorption · Calcium metabolism · Human · Teriparatide

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Introduction

Human parathyroid hormone (PTH) 1–34 (teriparatide) has been widely used in Japan for the treatment of osteoporosis with a high risk of fracture as a 20 µg daily regimen [1–3] and a 56.5 µg once-weekly regimen [4]. It has been reported that, with intermittent use, teriparatide has an anabolic action on the bone. The effects on bone turnover markers have been shown to differ between the 20 µg daily regimen and the 56.5 µg

once-weekly regimen [4–6]. Although daily injection increases bone formation and bone resorption, weekly injection increases bone formation moderately and decreases or maintains bone resorption. However, the effects on bone mineral density and reduction of vertebral fractures are similar.

We have previously reported changes in calcium metabolism and bone turnover markers following single injections of teriparatide (28.2 and 56.5 μg) in healthy elderly women [7]. It has been observed that a single injection of teriparatide causes an immediate, transient increase in bone resorption and a decrease in bone formation, followed by increased bone formation and decreased bone resorption for at least 1 week. These findings provide substantial proof of the effect of a once-weekly regimen of teriparatide on bone turnover. However, both repetition of the 24 h change with each injection and changes in levels of each parameter over a long period have not been evaluated in postmenopausal women with osteoporosis.

In this study, the profile of changes (0 to 24 h and 0 to 24 weeks) in pharmacokinetics (PK), calcium metabolism, and bone turnover markers during weekly injection of 56.5 μg of teriparatide for 24 weeks in postmenopausal women with osteoporosis was investigated.

Subjects and methods

Study subjects

This study was conducted at four institutes in Japan. The subjects were 28 postmenopausal Japanese women with osteoporosis, ranging in age from 60 to 79 years. The inclusion criteria included postmenopausal women without a concomitant allergic diathesis, calcium abnormalities, and drug use that may affect bone metabolism within 8 weeks prior to the study. Subjects who had taken bisphosphonates within the past 52 weeks were excluded. Women who had secondary osteoporosis, osteopenia due to a bone metabolism disorder, body weight lower than 40 kg, red blood cell number less than $300 \times 10^4/\mu L$ or hemoglobin less than 9.5 g/dL, serum calcium greater than 11 mg/dL, severe renal, liver, or heart dysfunction, a risk of osteosarcoma, or higher alkaline phosphatase levels were excluded. Osteoporosis was diagnosed by the following criteria: (1) bone mineral density (BMD) at the lumbar spine or femoral neck in less than 80 % of the young adult mean (YAM) in the Japanese population and the presence of a fragility fracture and (2) BMD at the lumbar spine or femoral neck in less than 70 % of YAM. Furthermore, as additive criteria for osteoporosis, the following items were included: age ≥65 years, previous fragility fracture at older than 50 years of age, or ≥1 pre-existing vertebral fracture.

Treatment protocol

Subjects were given weekly subcutaneous injections of 56.5 μg teriparatide for 24 weeks. Teriparatide was supplied by Asahi Kasei Pharma Corporation (Tokyo, Japan). All subjects were receiving daily calcium (610 mg), vitamin D (400 IU), and magnesium (30 mg) supplements.

Data collection

Blood and urine samples were collected in weeks 0, 4, 12, and 24. In the data collection week, 0 h examinations were performed at 0800. Teriparatide was administered immediately after 0 h collection of blood and urine samples. Blood samples for PK were collected at 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 h after the injection. Serum and urine samples for measurements of bone turnover markers were collected at 0, 2, 4, 6, 8, 12, and 24 h after the injection. BMD at the lumbar spine was measured at 0 and 24 weeks.

Outcome measures

PK and changes in calcium metabolism, bone turnover markers, and BMD were measured. Plasma teriparatide concentrations were measured at Sekisui Medical Co., Ltd (Tokyo, Japan) using a rat PTH immunoradiometric assay kit (IRMA; Immutopics Inc., San Clemente, CA, USA) with a range of 10 to 1,000 pg/mL. Serum calcium (Ca) was measured at Mitsubishi Chemical Medience Co (Tokyo, Japan). Serum intact PTH levels were measured by an electrochemiluminescence immunoassay (Roche Diagnostics K.K., Tokyo, Japan). 25-hydroxy vitamin D (25(OH)D) was measured by a competitive protein-binding assay (Mitsubishi Chemical Medience Co). Serum levels of the bone turnover markers, osteocalcin and procollagen type I N-terminal propeptide (P1NP) (both bone formation markers), were measured by BGP-IRMA (Mitsubishi Chemical Medience Co) and bone radioimmunoassay (Orion Diagnostic, Espoo, Finland), respectively (the coefficients of variation were previously reported [4]). Urinary cross-linked N-telopeptide of type I collagen (NTX; Osteomark, Inverness Medical Innovations Inc, Waltham, MA, USA) was measured by ELISA, and urinary deoxypiridinoline (DPD) was measured by Mitsubishi Chemical Medience Co; both are bone resorption markers. The inter-assay coefficients of variation were described in a previous report [7]. Samples were measured at each sampling time. Lumbar BMD was measured using DXA/QDR (Hologic, Bedford, MA, USA). Adverse events (AEs) were investigated by the physicians and classified using the system organ class from MedDRA version 12.0.

Statistical analysis

The concentrations of teriparatide, calcium metabolism, and bone turnover markers are expressed as means±SE.

In the 24 h change analysis, calcium metabolism and bone turnover markers were compared to the 0 h value (paired *t* test). The bone turnover markers and lumbar BMD are expressed as the mean percent changes from corresponding week 0 values. The changes from baseline were evaluated using paired *t* test.

Ethical considerations

The protocol of the present study was approved by the Institutional Review Boards at each participating institution, and the study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice (GCP). Written, informed consent was obtained from all participants prior to their participation in the study.

Results

Subjects

Twenty-eight subjects with osteoporosis were enrolled in this study. One subject was withdrawn from the study at the first week of injection at the subject's request. The subjects' baseline characteristics are shown in Table 1. The serum 25(OH)D level was only measured at 0 weeks. One subject with a vitamin D deficiency at baseline was not included.

Pharmacokinetics

The 24 h changes in plasma teriparatide acetate concentrations were nearly equal in each data collection week (Fig. 1). No major difference was found in peak concentrations at 30 min among 0, 4, 12, and 24 weeks. The distributions of mean values of PK parameters in each sampling week were as follows: C_{max} 495.9–653.9 pg/mL, AUC_{last} 53.0–70.5 ng·min/mL, AUC_{inf} 55.5–74.1 ng·min/mL, T_{max} 34.4–41.1 min, and $T_{1/2}$ 57.4–123.4 min.

Changes in calcium metabolism

In each data collection week, the corrected serum Ca increased to a peak concentration (9.7–9.8 mg/dL) at 6 h and decreased to the baseline level at 12–24 h (Fig. 2a). During the 24 week dosage period, the serum corrected Ca level decreased significantly at 4 and 24 weeks (Fig. 2b). Serum intact PTH decreased to its minimum concentration (25.6–28.3 pg/mL) at 2 or 6 h and maintained a value lower than the 0 h level at 24 h (Fig. 2c). During the dosage period of 24 weeks, the intact PTH level decreased significantly at 12 and 24 weeks (Fig. 2d).

Table 1 Participants' baseline characteristics

Item	Mean±SD
Age (years)	71.1±3.6
Height (cm)	152.2±5.9
Weight (kg)	49.2±5.5
BMI (kg/m^2)	21.4±3.2
Lumbar BMD (g/cm^2)	0.668±0.076
Corrected serum Ca (mg/dL)	9.7±0.3
Serum P (mg/dL)	3.6±0.5
Serum intact PTH (pg/mL)	37.2±11.6
Serum 25(OH)D (ng/mL)	29.7±7.5
Serum osteocalcin (ng/mL)	7.9±3.3
Serum P1NP (ng/mL)	49.5±23.3
Urinary DPD (pmol/μmol · Cr)	5.0±2.2
Urinary NTX (nmol/mmol · Cr)	46.9±21.5

Twenty-four hour changes in bone turnover markers after each injection

The 24 h percent changes in bone turnover markers after each teriparatide injection at each data collection week are shown in Fig. 3. The serum osteocalcin level decreased to its minimum value (−9.8 to −17.5 %) at 6, 8, or 24 h (Fig. 3a). The levels at 24 h were mostly significantly lower than at 0 h. The serum P1NP decreased to its minimum value (−15.1 to −22.3 %) at 6 h and then increased significantly to about 5 % (4.9 to 8.6 %) at 24 h after the teriparatide injection (Fig. 3b). The urinary NTX increased to its maximum value (41.2 to 67.4 %) at 4 or 6 h and then decreased (Fig. 3c). The DPD increased to its maximum value (29.5 to 31.6 %) at 2 or 4 h and then decreased significantly (Fig. 3d). The profiles of the 24 h changes in each bone turnover marker were almost the same in each collection week.
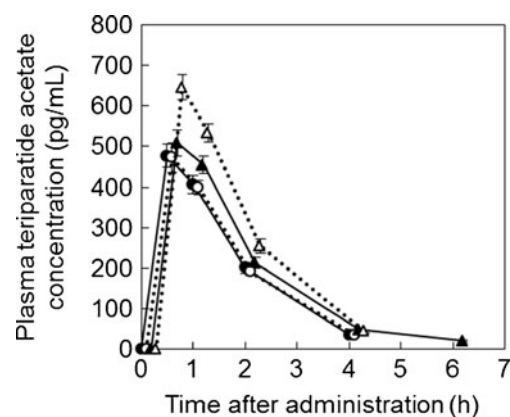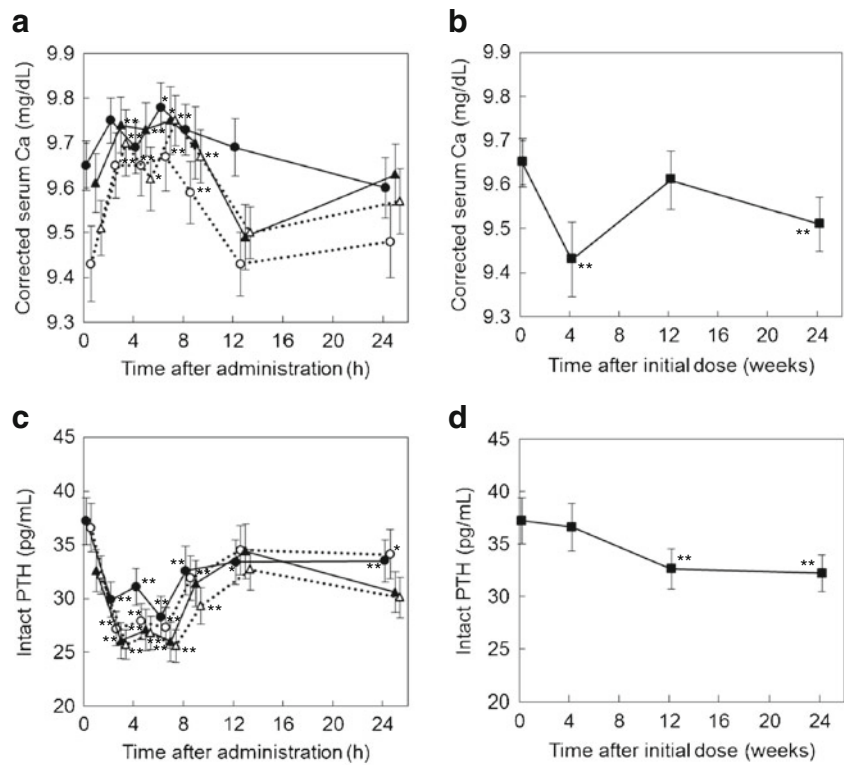

Fig. 1 Mean change over 24 h of the plasma concentration of teriparatide acetate at 0 weeks (*black circle*), 4 weeks (*white circle*), 12 weeks (*black triangle*), and 24 weeks (*white triangle*). Data are plotted as means (±SE)

Fig. 2 Mean changes in serum calcium and intact PTH after injection of 56.5 μg. teriparatide Time courses of corrected serum calcium (a) and intact PTH (c) over 24 h at 0 weeks (*black circle*), 4 weeks (*white circle*), 12 weeks (*black triangle*), and 24 weeks (*white triangle*), and the changes in the baseline levels of corrected serum calcium (b) and intact PTH (d) over 24 weeks. Data are plotted as means (±SE) *$p < 0.05$ **$p < 0.01$ versus 0 h or 0 weeks with paired t test

Changes in bone turnover marker levels over 24 weeks

Percent changes from baseline for 24 weeks were calculated for serum osteocalcin and P1NP and urinary NTX and DPD.

The serum osteocalcin levels before each teriparatide injection were significantly increased by 26.8 % at 4 weeks, and the levels were maintained for 24 weeks (Fig. 4a). The serum P1NP level increased significantly by 19.9 % at 4 weeks and

Fig. 3 Mean percent changes from 0 to 24 h for serum osteocalcin (a), serum P1NP (b), urinary NTX (c), and urinary DPD (d) at 0 weeks (*black circle*), 4 weeks (*white circle*), 12 weeks (*black triangle*), and 24 weeks (*white triangle*). Data are plotted as means (±SE) *$p < 0.05$ **$p < 0.01$ versus 0 h with paired t test
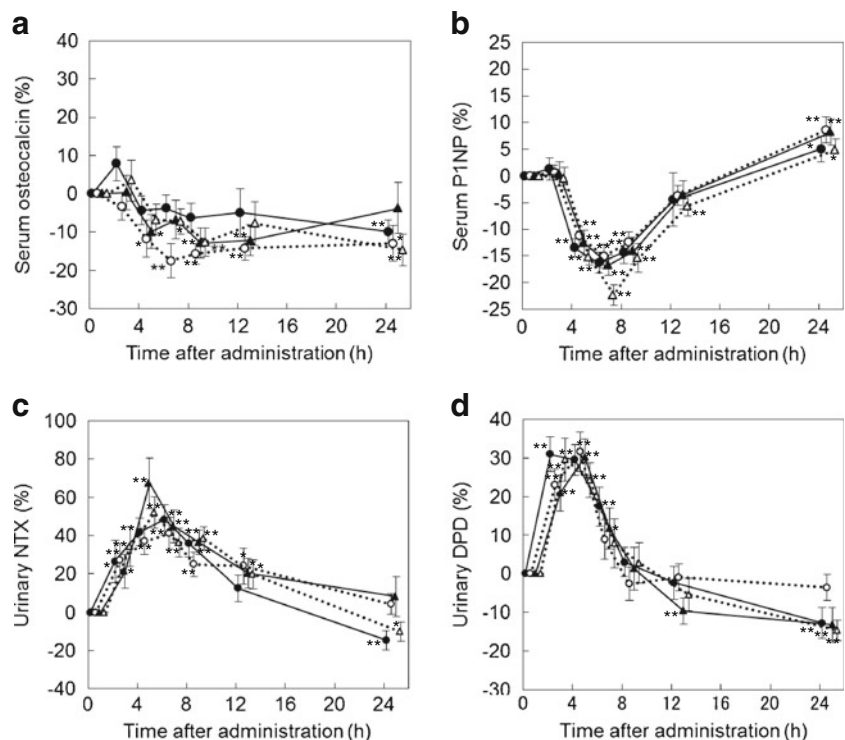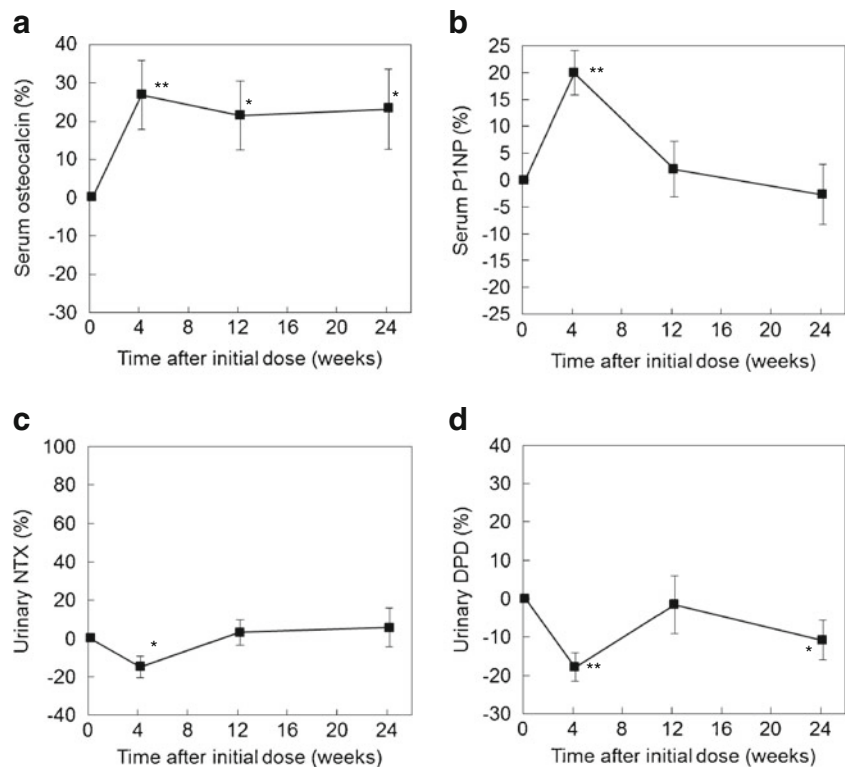
Fig. 4 Mean percent changes in 0 h values from 0 to 24 weeks for serum osteocalcin (**a**), serum P1NP (**b**), urinary NTX (**c**), and urinary DPD (**d**). Data are plotted as means (±SE) *$p < 0.05$ **$p < 0.01$ versus 0 week with paired t test

then decreased to the baseline level at 12 weeks (Fig. 4b). The urinary NTX decreased significantly by 14.8 % at 4 weeks and subsequently returned to the baseline level (Fig. 4c). The urinary DPD decreased by 17.8 % at 4 weeks and then maintained this lower level (Fig. 4d).

Lumbar bone mineral density

The percent change in lumbar BMD increased 2.6 % from baseline at 24 weeks.

Safety

No serious AEs were observed in this study. AEs occurred in 21 (75 %) subjects. The most frequent AEs were gastrointestinal disorders (14 cases, 50.0 %), and second were skin and subcutaneous tissue disorders and laboratory test abnormalities (9 cases, 32.1 %). Hypercalcemia was not observed.

Discussion

This study aimed to clarify the PK, calcium metabolism, and profile of bone turnover markers (response at 24 h after injection and changes from baseline levels during 24 weeks) with once-weekly injections of 56.5 μg teriparatide for 24 weeks. We previously reported on the response for up to 14 days after a single injection of 56.5 μg teriparatide in

healthy postmenopausal women [7], but whether this response was sustained for the long-term in women with osteoporosis was unknown.

At data collection during the 24 week observation period, the changes in PK, calcium metabolism, and bone turnover markers at 24 h after injection repeatedly showed the same direction and level of response. It has been reported that, with PTH administration, PTH/PTHrP receptors are down-regulated, the receptor number decreases [8–10], and the receptor decrease is also regulated at the gene expression level [11, 12]. However, based on the results of the responses in the present study, even if PTH/PTHrP receptors are transiently down-regulated by PTH administration, the response was repeatedly sustained with once-weekly injections of 56.5 μg teriparatide. This is the first evidence in humans that the response at 24 h after injection of teriparatide is repeated without attenuation during weekly administration. The transient decrease followed by an increase in bone formation markers and the transient increase followed by a decrease in bone resorption markers at 24 h after injection of 56.5 μg teriparatide were repeated each time at the same levels for up to 24 weeks.

PTH is reported to increase RANKL expression on osteoblast lineage cells and to trigger osteoclast differentiation and activation. Ma et al. reported that, 1 h after PTH administration in mice, RANKL increased and OPG decreased at the mRNA level, and after 3 h, they returned to baseline levels [13]. This response after teriparatide injection, in which bone resorption increased transiently and then returned to basal

levels after 24 h, was also confirmed in humans in the present study.

Meanwhile, PTH in vitro has been reported to inhibit bone formation, such as collagen synthesis [14], osteocalcin production [15], and calcified bone-like nodule formation in primary osteoblast cultures [16]. However, Bellows and our group found that when PTH is removed from culture, the osteoblast function that was inhibited was restored [15, 16]. In addition, PTH stimulates the proliferation and differentiation of osteoprogenitor cells and pre-osteoblasts [15, 17], inhibits apoptosis [18, 19], and acts to gradually increase the osteoblast number.

Based on these findings, the 24 h responses in osteocalcin and P1NP with injection of 56.5 μg teriparatide are explained by inhibition of bone formation while teriparatide is present in the blood and a subsequent return in osteoblast function with elimination of teriparatide from the blood.

As a change from baseline levels at 24 weeks with once-weekly injection of 56.5 μg teriparatide, a significant decrease in intact PTH was observed. We previously reported that intact PTH was decreased even after 7 days with a single-dose injection of 56.5 μg teriparatide [7]. The significant decrease in baseline intact PTH after 12 and 24 weeks with repeated administration in the present study is probably due to these accumulated decreases at 7 days after teriparatide injection. Moreover, the significant decreases after 4 and 24 weeks in corrected serum Ca are similar to the results with long-term administration of teriparatide by Fujita et al. [20] and our group [4]. Changes in baseline levels of bone turnover markers with once-weekly injection of 56.5 μg teriparatide included increases in bone formation markers (serum osteocalcin and P1NP) and decreases in bone resorption markers (urinary NTX and DPD), particularly at week 4. These baseline changes can be explained from the results of single-dose injection of 56.5 μg teriparatide. On day 7 after injection of 56.5 μg teriparatide, osteocalcin and P1NP increased by 5 and 10 %, respectively, and NTX decreased by 10 % [7]. With repeated administration of teriparatide once-weekly, the increases in bone formation markers and decreases in bone resorption markers with each previous injection accumulated. As a result, a significant change in bone turnover markers was observed after 4 weeks in the present study.

Moreover, the direction and level of changes in these bone turnover markers were similar to previously reported results with once-weekly administration of teriparatide. Fujita et al. [20] reported that serum bone-type alkaline phosphatase (serum BAP) increased and peaked at 4 weeks, but it decreased to baseline levels by 24 weeks, and urinary DPD continued to decrease. Similar patterns of changes in bone turnover markers were also observed in our previous trial [4]. In the present study as well, serum P1NP increased and peaked at 4 weeks, but subsequently decreased, and urinary

DPD and urinary NTX remained the same or tended to decrease over the 24-week period. Thus, the changes in bone turnover markers with once-weekly teriparatide injection were reproduced in each report, and the level of increase in bone formation markers in each was about 20 %. Furthermore, with weekly teriparatide, serum osteocalcin increased significantly after 24 weeks, but serum P1NP did not increase significantly. Osteocalcin is produced by mature osteoblasts, but P1NP, a collagen synthesis marker, is produced by premature osteoblasts [21]. Therefore, the changes in serum P1NP and serum osteocalcin with once-weekly injection of teriparatide may indicate early stimulation of collagen production, followed later by long-term stimulation of collagenous matrix mineralization.

The long-term changes in bone turnover markers with daily teriparatide administration have been fully reported. Daily teriparatide markedly and quickly increased a bone formation marker by 105 % after 1 month and 218 % after 6 months, and a bone resorption marker increased by 58 % after 6 months [22]. Serum P1NP has been established as the most specific marker for PTH action at the osteoblastic level. In addition, a clinical study of daily teriparatide reported that early changes in serum P1NP can predict future increases in BMD [22] and bone architecture [23]. The time interval and the differences in the levels of the increases in bone formation markers and bone resorption markers are called the "anabolic window" [24, 25].

However, the direction and level of changes in bone turnover markers in the present study differed from those with daily teriparatide administration. Namely, with daily administration, bone formation markers increased greatly (serum PINP 218 %), and then bone resorption markers increased (urinary NTX 58 %) [22]. In contrast, with once-weekly injection of teriparatide, bone formation markers increased and bone resorption markers decreased, although these changes were small. This difference may be due to the timing of administration (once-weekly vs. daily) and the doses of teriparatide (56.5 vs. 20 μg). Once-weekly teriparatide treatment may provide a beneficial window based on the difference between the small increase in bone formation and the small decrease in bone resorption. Nevertheless, the effects on fracture risk reduction were similar with the once-weekly and daily regimens (relative risk reduction in vertebral fractures: once-weekly teriparatide 80 % [4], daily teriparatide 65 % [1]), the anabolic window proposed with daily teriparatide alone may not explain the effects of weekly teriparatide on reducing fracture risk. Therefore, explanatory factors for fracture reduction other than the amount of change in bone turnover markers may also exist. The small increase in bone formation and decrease in bone resorption with once-weekly injection of teriparatide may affect the balance and regulation of bone metabolism. With once-weekly teriparatide in ovariectomized monkeys, Saito et al. explained the effects on increasing bone strength as an improvement in bone structure

and bone quality [26]. In addition, increased lumbar spine BMD with daily teriparatide injection accounts for 30–41 % of vertebral fracture reduction [27], which is higher than that with antiresorptive agents [28–30]. Therefore, an increase in lumbar spine BMD with once-weekly teriparatide injection may contribute to some extent to vertebral fracture reduction. In fact, Fujita reported that incident vertebral fractures were observed in the low- or middle-dose weekly teriparatide group, but a greater increase in vertebral BMD, and no incident vertebral fractures were observed in the high-dose (56.5 μg as in the present study) group [20]. Moreover, the contribution of the change in vertebral BMD to incident vertebral fracture with weekly teriparatide treatment in our previous study [4] was higher (unpublished data) than that with daily teriparatide treatment [27]. Namely, with once-weekly teriparatide, bone density increases, collagen enzymatic cross-links increase, and non-enzymatic cross-links decrease. This results in a highly effective increase in bone strength. Therefore, the marked fracture prevention effects with once-weekly administration may at least be partially explained by the difference in stimulation of bone formation and inhibition of bone resorption as well as improvement in bone quality.

Moreover, although non-vertebral fragility fracture risk reduction did not differ significantly with once-weekly teriparatide injection because of the small sample size, there tended to be a reduced risk (relative risk, 0.67; 95 % CI, 0.24–1.84; $p = 0.43$) [4]. Increased femoral BMD explained 87 % of the reduction in non-vertebral fracture risk for denosumab [31] and 61 % of the reduction for zoledronic acid [32]. This was reported to be relatively high compared to the vertebral fracture risk reduction. Once-weekly teriparatide injection may also reduce non-vertebral fracture risk, mainly by increasing total hip BMD [4].

The present study did have some limitations. First, only a single-dose regimen (once-weekly 56.5 μg teriparatide) was used without a control group. However, regarding comparisons with other administration regimens, a full comparison with the daily administration regimen was performed. Second, the treatment evaluation period was 24 weeks (one third of the full treatment regimen). However, the repeated responses were sustained for at least 24 weeks, and no decreases in the response levels were observed. In addition, the changes from baseline levels of the bone turnover markers seen in this study were similar to the results of the TOWER trial with a 72-week treatment period. Thus, the responses may be sustained for up to 72 weeks.

Conclusions

In conclusion, the present study evaluated the profile of bone turnover markers with once-weekly injection of 56.5 μg teriparatide for 24 weeks. Changes in PK, calcium metabolism,

and bone turnover markers at 24 h after teriparatide injection continued in the same direction and at the same level for 24 weeks. No loss of responsiveness was observed. After 24 weeks, the bone formation marker serum osteocalcin increased significantly, but serum P1NP did not increase significantly. Bone resorption markers decreased or remained the same.

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