Table 1 Baseline characteristics

Variable	Teriparatide group (n = 261)	Placebo group (n = 281)	p
Age (years)	75.3 (5.8)	75.4 (5.8)	0.906
Height (cm)	148.0 (6.5)	147.6 (6.3)	0.483
Weight (kg)	50.5 (7.7)	49.8 (8.0)	0.224
BMI (kg/m^2)	23.0 (3.3)	22.8 (3.4)	0.452
Prevalent vertebral fracture number	1.9 (1.4)	1.7 (1.3)	0.151
Lumbar BMD (T-score)	−2.7 (0.9)	−2.6 (0.9)	0.343
Hip total BMD (T-score)	−2.4 (0.7)	−2.4 (0.8)	0.564
Femoral neck BMD (T-score)	−2.1 (1.0)	−2.1 (0.9)	0.686
Serum osteocalcin (ng/mL)	8.2 (3.1)	8.0 (2.9)	0.837
Serum P1NP (ng/mL)	54.4 (24.8)	51.6 (20.1)	0.389
Urinary NTX (nMBCE/mM Cr)	43.9 (24.9)	42.8 (23.2)	0.739
Urinary DPD (pM/μM Cr)	4.7 (2.2)	4.6 (1.9)	0.765
e-GFR (mL/min/1.73 m^2)	70.2 (16.8)	70.7 (16.2)	0.871

Data are expressed as means (SD)

BMD bone mineral density, *PINP* procollagen type I N-terminal propeptide, *NTX* type I collagen cross-linked *N*-telopeptides, *DPD* deoxypyridinoline, *e-GFR* estimated glomerular filtration rate

Relative risk (RR) and the 95 % confidence interval (CI) of the incident vertebral fracture in the teriparatide group compared to the placebo group for each subgroup were estimated with the unadjusted Cox regression model. All analyses were conducted using a two-sided test with the significance level equal to 0.05.

Results

Subjects

Two hundred sixty-one (90.0 %) and 281 (97.6 %) of 290 and 288 subjects with osteoporosis randomized to the teriparatide and placebo groups, respectively, had radiographic evidence of vertebral fracture at baseline. The baseline subject characteristics including age, BMI, prevalent vertebral fracture number and grade, BMD at the lumbar spine, total hip, and femoral neck, bone metabolic markers, and e-GFR are presented in Table 1. There was no significant difference in any of the baseline indices between the teriparatide group and the placebo group.

The median (and the distribution range) of the study duration was 72 (2–76) weeks in the teriparatide group and 72 (3–74) weeks in the placebo group (p = 0.062).

Incident vertebral fracture

Incident vertebral fracture occurred in 2.7 % (7/261) of cases in the teriparatide group and 13.2 % (37/281) of cases in the placebo group. The distribution of incident vertebral fracture number by spinal location is shown in Fig. 1. Multiple incident vertebral fractures (two vertebral fractures) were observed in two cases in the teriparatide group. Two incident vertebral fractures occurred in four cases, three incident vertebral fractures in one case, and four incident vertebral fractures in one case in the placebo group. A total of nine incident vertebral fractures in the teriparatide group and 46 incident vertebral fractures in the placebo group were observed. A higher peak incident vertebral fracture number was observed in lower spinal locations (T11–L4). The most frequent fracture sites in the placebo group were T11, L1, and L3 (n = 7, respectively). The number of incident vertebral fractures in the teriparatide group was lower than that in the placebo group for both higher and lower spinal locations.

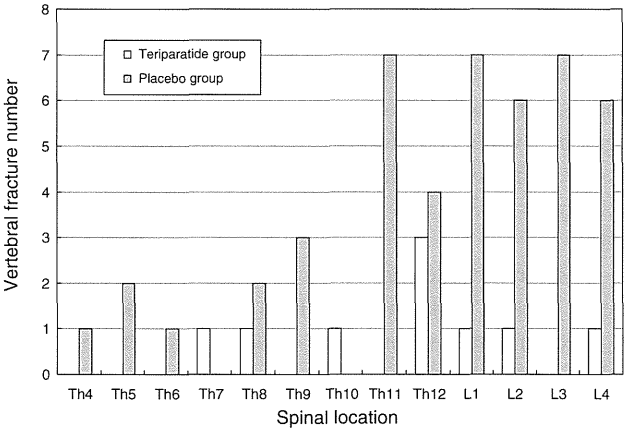

Fig. 1 Incident vertebral fracture number during the study by spinal location in the teriparatide group and placebo group

Fracture risk reductions in each subgroup

The overall RR of incident vertebral fracture between the teriparatide group compared to the placebo group selected in this subgroup analysis was 0.20 (Fig. 2). Each subgroup was divided to assess groups of all patients and exclusively female patients in order to evaluate the relationship between baseline clinical risk factors and response to treatment for each gender. Once-weekly teriparatide significantly reduced the risk of incident vertebral fracture for all patients in both the younger (<75 years: RR = 0.06, $p = 0.007$) and older (≥75 years: RR = 0.32, $p = 0.015$) patients. RR in patients without prevalent vertebral fracture was 0.00 because incident vertebral fracture was not observed in the teriparatide group. There was significant fracture risk reduction in patients with one and two or more prevalent vertebral fractures, with RRs of 0.08 ($p = 0.015$) and 0.29 ($p = 0.009$), respectively.

Patients with prevalent vertebral fracture severity grades of 0, 1, or 2 indicated no incident vertebral fracture (RR = 0.00). Once-weekly teriparatide significantly reduced the risk of incident fracture in patients with the most severe (grade 3) vertebral deformity (RR = 0.26, $p = 0.003$).

RR in patients with low lumbar BMD (<−2.5 SD) was 0.25 ($p = 0.035$), and RR with high BMD (≥−2.5 SD) was 0.00.

The teriparatide group had a significantly reduced incident fracture risk in both high bone marker turnover (≥median) and low turnover (<median) patients ($p < 0.05$) when compared with the placebo group.

In the e-GFR subgroup, significant vertebral fracture risks were observed in patients with lower renal function (<70 mL/min/1.73 m^2) and higher renal function (≥70 mL/min/1.73 m^2) (RR 0.31, $p = 0.042$, RR 0.13, $p = 0.001$, respectively).

RRs observed in the subset of exclusively female patients were similar to those observed in all patients.

Discussion

Vertebral fractures are the most common of all osteoporotic fractures, and are linked to impaired mobility, increased mortality [15, 16], and decreased quality of life (QOL) [17]. Risk factors for incident vertebral fracture, such as higher age, lower BMD, and more severe fracture grade, have been reported previously [18, 19]. Moreover, it was reported that patients with mild renal dysfunction were at increased risk for BMD decreases and vertebral fractures [20]. These studies have demonstrated that either the number or the severity of prior vertebral fractures is an individually important predictor of incident vertebral fracture risk. Because the fracture risk was different in each osteoporotic patient, the subgroup analysis between each risk factor and fracture risk reduction associated with the treatment was important to assess.

In this subgroup analysis from the TOWER trial, we demonstrated fracture risk reduction by baseline characteristics and the effect of once-weekly teriparatide treatment on incident vertebral fracture. Weekly teriparatide significantly reduced the vertebral fracture risk in patients with high fracture risk (severe) at baseline in subgroups such as age ≥75 years, prevalent vertebral fracture number ≥2, prevalent vertebral fracture grade 3, and lumbar BMD < −2.5 SD, (RR 0.25–0.32). Previous studies have shown that 20 μg and 40 μg of daily teriparatide injection reduce the risk of vertebral fractures, even in those with severe and multiple vertebral fractures at baseline when compared to other osteoporotic treatments [9].

Weekly teriparatide injections result in significant fracture risk reduction in patients with low fracture risk (mild to moderate) at baseline. The RRs were in the subgroup of age <75 years 0.06, vertebral fracture number 0 to 1: 0.0–0.08, prevalent vertebral grade 0 to 2: 0.0, and lumbar BMD ≥−2.5 SD 0.0. Moreover, significant vertebral fracture risk reductions were observed in the subgroup with lower and higher bone turn over as well as lower and higher renal function status. Once-weekly teriparatide consistently reduced incident vertebral fracture across all of the higher and lower risk patients for future fracture.

The incidence of vertebral fracture was lower in the teriparatide group than in the placebo group at the thoracic and lumbar locations. It was reported that prevalent lumbar vertebral compression fractures lead to lowered QOL and more severe pain than prevalent thoracic vertebral fractures [21, 22]. Therefore, once-weekly injection of teriparatide may prevent a reduction in QOL and health in patients with osteoporosis.

Subgroup analyses inherently have limited power to detect interactions in a small subgroup with few events [23]. This produces a statistical limitation for our study. In this analysis, statistically significant reduction was not observed in the subgroup with prevalent vertebral fracture number equal to 0, prevalent vertebral fracture grade 0–2, and lumbar BMD ≥−2.5 SD, and there may have been too few subjects in each subgroup. However, the incidence of new vertebral fracture in the teriparatide groups was 0. Therefore, we feel that these results can be generalized to the clinical setting.

In conclusion, our results indicate that once-weekly injections of 56.5 μg teriparatide reduce the vertebral fracture risk in various subgroups including: age, vertebral fracture number and grade, bone turnover level, and renal function level. These results indicate the consistent anti-fracture efficacy of teriparatide in patients with varying degrees of fracture risk.

Item	Category		n	RR (95% CI) p	RR (95% CI)
Total		All	542	0.20 (0.09-0.45) < 0.001	
		Female	519	0.18 (0.08-0.45) < 0.001	
Age, years	< 75	All	259	0.06 (0.01-0.48) 0.007	
		Female	252	0.06 (0.01-0.48) 0.008	
	≥ 75	All	283	0.32 (0.13-0.80) 0.015	
		Female	267	0.30 (0.11-0.81) 0.018	
Prevalent vertebral fracture number	1	All	219	0.08 (0.01-0.61) 0.015	
		Female	213	0.09 (0.01-0.67) 0.019	
	≥ 2	All	260	0.29 (0.11-0.73) 0.009	
		Female	244	0.26 (0.10-0.71) 0.009	
Prevalent vertebral fracture grade	grade 3	All	219	0.26 (0.11-0.63) 0.003	
		Female	207	0.25 (0.10-0.64) 0.004	
Lumbar BMD, T-score	< -2.5SD	All	167	0.25 (0.07-0.91) 0.035	
		Female	163	0.25 (0.07-0.92) 0.037	
Serum osteocalcin	< Med	All	265	0.11 (0.03-0.49) 0.004	
		Female	254	0.11 (0.03-0.50) 0.004	
	≥ Med	All	276	0.29 (0.11-0.79) 0.015	
		Female	264	0.26 (0.09-0.79) 0.017	
Serum PINP	< Med	All	270	0.07 (0.01-0.50) 0.009	
		Female	258	0.08 (0.01-0.59) 0.013	
	≥ Med	All	271	0.30 (0.12-0.76) 0.011	
		Female	260	0.25 (0.09-0.68) 0.006	
Urinary NTX	< Med	All	270	0.08 (0.01-0.58) 0.013	
		Female	257	0.08 (0.01-0.62) 0.015	
	≥ Med	All	271	0.28 (0.11-0.69) 0.006	
		Female	261	0.25 (0.09-0.67) 0.006	
Urinary DPD	< Med	All	266	0.07 (0.01-0.53) 0.010	
		Female	252	0.07 (0.01-0.55) 0.011	
	≥ Med	All	275	0.29 (0.11-0.72) 0.008	
		Female	266	0.26 (0.10-0.72) 0.009	
eGFR (ml/min/1.73m^2)	< 70	All	279	0.31 (0.10-0.96) 0.042	
		Female	272	0.26 (0.07-0.92) 0.036	
	≥ 70	All	263	0.13 (0.04-0.45) 0.001	
		Female	247	0.14 (0.04-0.48) 0.002	

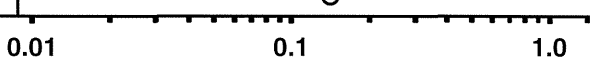

Fig. 2 Effects of once-weekly teriparatide on incident vertebral fractures risk reductions by subgroup *Solid line* (□) indicates all participants; *dashed line* (○) indicates female participants *BMD* bone mineral density, *PINP* Procollagen type I N-terminal propeptide, *NTX* type I collagen cross-linked *N*-telopeptides, *DPD* deoxypyridinoline, *e-GFR* estimated glomerular filtration rate, *RR* relative risk

Acknowledgments This study was supported by Asahi Kasei Pharma Corporation.

Conflict of interest MS received consulting fees from Chugai, Daiichi Sankyo, Asahi Kasei Pharma, Teijin, and MSD. TS received research grants and consulting fees from Asahi Kasei Pharma and Daiichi Sankyo. MI has received research grants and consulting fees or other remuneration from Chugai, Daiichi Sankyo, JT, and Asahi Kasei Pharma. MF has received consulting fees from Astellas and Asahi Kasei Pharma. HH received research grants and consulting fees from Asahi Kasei Pharma, Chugai, Astellas, Ezai, Takeda, and MSD. TN received research grants and/or consulting fees from Chugai, Teijin, Asahi Kasei Pharma, and Daiichi Sankyo. TK is an employee of Asahi Kasei Pharma Corporation. TeN, HK and TeS declare that they have no conflicts of interest.

References

1. Kanis JA, on behalf of the World Health Organisation Scientific Group (2007) Assessment of osteoporosis at the primary health care level. WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield. http://www.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf
2. Fujiwara S, Hamaya E, Goto W, Masunari N, Furukawa K, Fukunaga M, Nakamura T, Miyauchi A, Chen P (2011) Vertebral fracture status and the World Health Organization risk factors for predicting osteoporotic fracture risk in Japan. Bone 49:520–525
3. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 280:2077–2082
4. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY, Hip Intervention Program Study Group (2001) Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 344:333–340
5. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH (2001) Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441
6. Miyauchi A, Matsumoto T, Sugimoto T, Tsujimoto M, Warner MR, Nakamura T (2010) Effects of teriparatide on bone mineral density and bone turnover markers in Japanese subjects with osteoporosis at high risk of fracture in a 24-month clinical study: 12-month, randomized, placebo-controlled, double-blind and 12-month open-label phases. Bone 47:493–502
7. Yamamoto T, Tsujimoto M, Hamaya E, Sowa H (2013) Assessing the effect of baseline status of serum bone turnover markers and vitamin D levels on efficacy of teriparatide 20 μg/day administered subcutaneously in Japanese patients with osteoporosis. J Bone Miner Metab 31:199–205
8. Marcus R, Wang O, Satterwhite J, Mitlak B (2003) The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. J Bone Miner Res 18:18–23
9. Bouxsein ML, Chen P, Glass EV, Kallmes DF, Delmas PD, Mitlak BH (2009) Teriparatide and raloxifene reduce the risk of new adjacent vertebral fractures in postmenopausal women with osteoporosis. Results from two randomized controlled trials. J Bone Joint Surg Am 91:1329–1338
10. Gallagher JC, Genant HK, Crans GG, Vargas SJ, Krege JH (2005) Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. J Clin Endocrinol Metab 90:1583–1587
11. Miller PD, Schwartz EN, Chen P, Misurski DA, Krege JH (2007) Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. Osteoporos Int 18:59–68
12. Nakamura T, Sugimoto T, Nakano T, Kishimoto H, Ito M, Fukunaga M, Hagino H, Sone T, Yoshikawa H, Nishizawa Y, Fujita T, Shiraki M (2012) Randomized Teriparatide [Human Parathyroid Hormone (PTH) 1-34] Once-Weekly Efficacy Research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. J Clin Endocrinol Metab 97:3097–3106
13. Imai E, Horio M, Nitta K, Yamagata K, Iseki K et al (2007) Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol 11:41–50
14. Genant HK, Jergas M, Palermo L, Nevitt M, Valentin RS, Black D, Cummings SR (1996) Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis. The study of Osteoporotic Fractures Research Group. J Bone Miner Res 11:984–996
15. Kado DM, Duong T, Stone KL, Ensrud KE, Nevitt MC, Greendale GA, Cummings SR (2003) Incident vertebral fractures and mortality in older women: a prospective study. Osteoporos Int 14:589–594
16. Hallberg I, Bachrach-Lindstrom M, Hammerby S, Toss G, Ek AC (2009) Health-related quality of life after vertebral or hip fracture: a seven-year follow-up study. BMC Musculoskel Disord 10:135
17. Wustrack R, Seeman E, Bucci-Rechtweg C, Burch S, Palermo L, Black DM (2012) Predictors of new and severe vertebral fractures: results from the HORIZON Pivotal Fracture Trial. Osteoporos Int 23:53–58
18. Nevitt MC, Cummings SR, Stone KL, Palermo L, Black DM, Bauer DC, Genant HK, Hochberg MC, Ensrud KE, Hillier TA, Cauley JA (2005) Risk factors for a first-incident radiographic vertebral fracture in women ≥65 years of age: the study of osteoporotic fractures. J Bone Miner Res 20:131–140
19. Ross PD, Davis JW, Epstein RS, Wasnich RD (1991) Pre-existing fractures and bone mass predict vertebral fracture incidence in women. Ann Intern Med 114:919–923
20. Kaji H, Yamauchi M, Yamaguchi T, Shigematsu T, Sugimoto T (2010) Mild renal dysfunction is a risk factor for a decrease in bone mineral density and vertebral fractures in Japanese postmenopausal women. J Clin Endocrinol Metab 95:4635–4642
21. Cockerill W, Ismail AA, Cooper C, Matthis C, Raspe H, Silman AJ, O'Neill TW (2000) Does location of vertebral deformity within the spine influence back pain and disability? Ann Rheum Dis 59:368–371
22. Oleksik A, Lips P, Dawson A, Minshall ME, Shen W, Cooper C, Kanis J (2000) Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. J Bone Miner Res 15:1384–1392
23. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM (2007) Statistics in medicine-reporting of subgroup analyses in clinical trials. N Engl J Med 357:2189–2194

Osteoporos Int (2014) 25:1173–1180
DOI 10.1007/s00198-013-2516-1

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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Received: 28 January 2013 / Accepted: 4 September 2013 / Published online: 10 October 2013

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 $300\times10^4/\mu L$ 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.

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

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).

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.

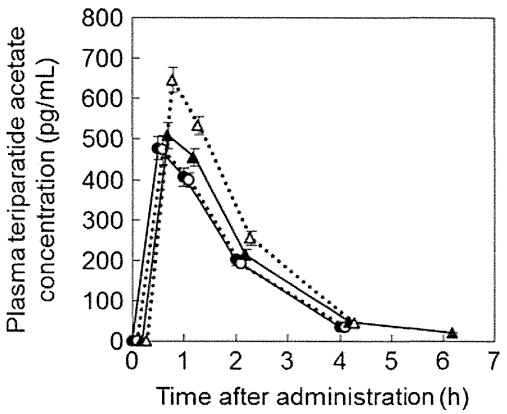

Fig. 1 Mean change over 24 h of the plasma concentration of teriparatide acetate at 0 weeks (*black circle*), 4 weeks (*white circle*), 12 weeks (*black triangle*), and 24 weeks (*white triangle*). Data are plotted as means (±SE)

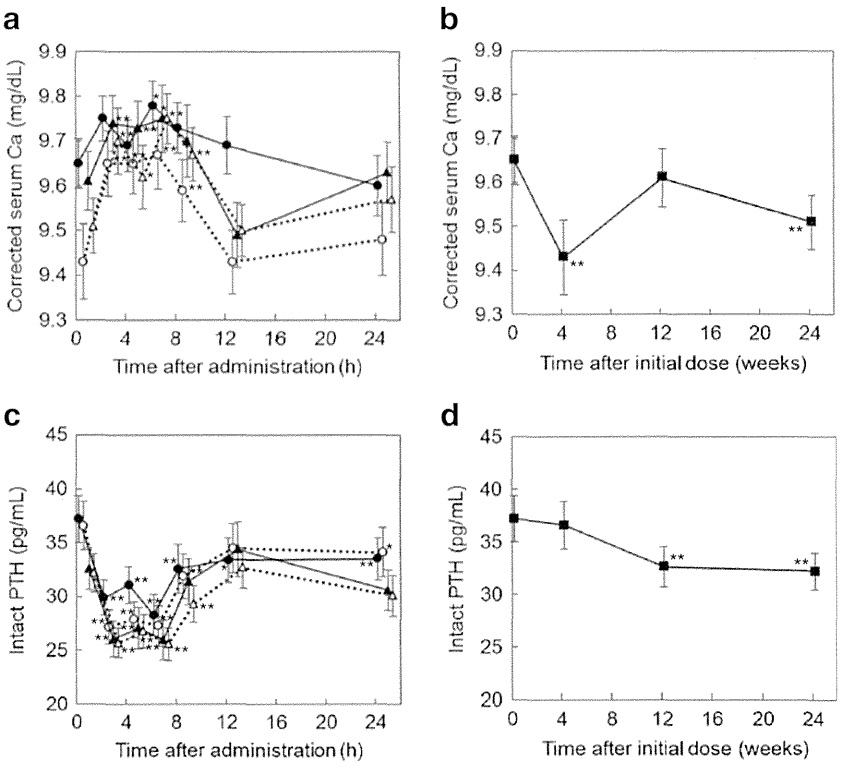

Fig. 2 Mean changes in serum calcium and intact PTH after injection of 56.5 μg. teriparatide Time courses of corrected serum calcium (**a**) and intact PTH (**c**) over 24 h at 0 weeks (*black circle*), 4 weeks (*white circle*), 12 weeks (*black triangle*), and 24 weeks (*white triangle*), and the changes 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

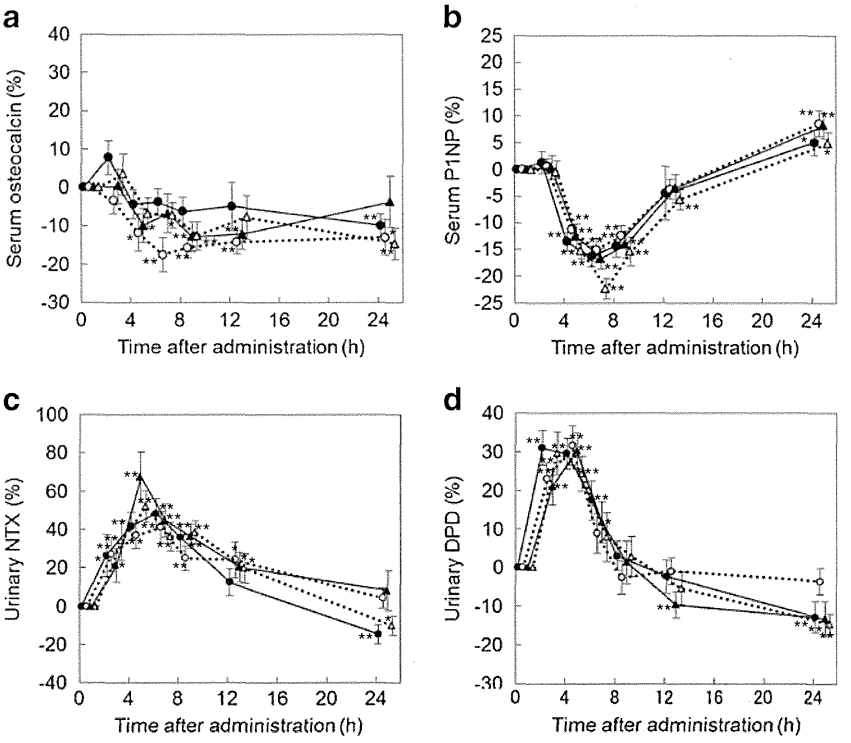

Fig. 3 Mean percent changes from 0 to 24 h for serum osteocalcin (**a**), serum P1NP (**b**), urinary NTX (**c**), and urinary DPD (**d**) at 0 weeks (*black circle*), 4 weeks (*white circle*), 12 weeks (*black triangle*), and 24 weeks (*white triangle*). Data are plotted as means (±SE) $*p<0.05$ $**p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

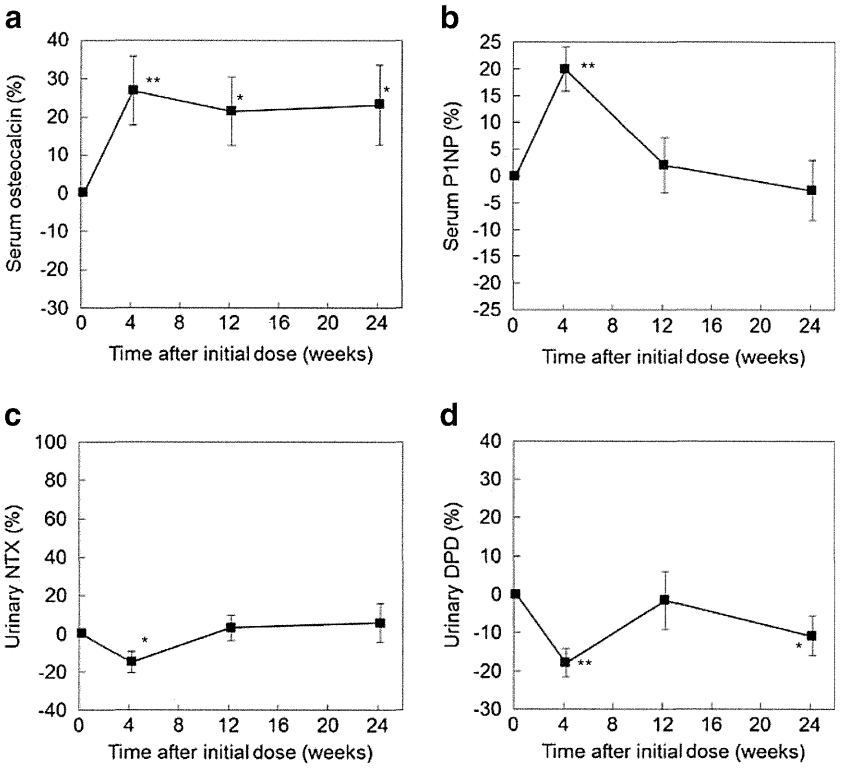

Fig. 4 Mean percent changes in 0 h values from 0 to 24 weeks for serum osteocalcin (**a**), serum P1NP (**b**), urinary NTX (**c**), and urinary DPD (**d**). Data are plotted as means (±SE) $*p<0.05$ $**p<0.01$ versus 0 week with paired t test

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.

Disclosure statement Asahi Kasei Pharma Corporation provided funding and supplied the test drugs for this study.

References

1. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH (2001) Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441
2. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman JM, Clancy AD, Gaich GA (2003) The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 18:9–17
3. Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP (2000) Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. J Clin Endocrinol Metab 85:3069–3076
4. Nakamura T, Sugimoto T, Nakano T, Kishimoto H, Ito M, Fukunaga M, Hagino H, Sone T, Yoshikawa H, Nishizawa Y, Fujita T, Shiraki M (2012) Randomized teriparatide [human parathyroid hormone (PTH) 1–34] once-weekly efficacy research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. J Clin Endocrinol Metab 97:3097–3106
5. Miyauchi A, Matsumoto T, Sugimoto T, Tsujimoto M, Warner MR, Nakamura T (2010) Effects of teriparatide on bone mineral density and bone turnover markers in Japanese subjects with osteoporosis at high risk of fracture in a 24-month clinical study: 12-month, randomized, placebo-controlled, double-blind and 12-month open-label phases. Bone 47:493–502
6. Glover SJ, Eastell R, McCloskey EV, Rogers A, Garnero P, Lowery J, Belleli R, Wright TM, John MR (2009) Rapid and robust response of biochemical markers of bone formation to teriparatide therapy. Bone 45:1053–1058
7. Shiraki M, Sugimoto T, Nakamura T (2013) Effects of a single injection of teriparatide on bone turnover markers in postmenopausal women. Osteoporos Int 24:219–226
8. Teitelbaum AP, Silve CM, Nyiredy KO, Arnaud CD (1986) Down-regulation of parathyroid hormone (PTH) receptors in cultured bone cells is associated with agonist-specific intracellular processing of PTH-receptor complexes. Endocrinology 118:595–602
9. Yamamoto I, Shigeno C, Potts JT Jr, Segre GV (1988) Characterization and agonist-induced down-regulation of parathyroid hormone receptors in clonal rat osteosarcoma cells. Endocrinology 122:1208–1217
10. Mahoney CA, Nissenson RA (1983) Canine renal receptors for parathyroid hormone: down-regulation in vivo by exogenous parathyroid hormone. J Clin Invest 72:411–421

11. González EA, Martin KJ (1996) Coordinate regulation of PTH/PTHrP receptors by PTH and calcitriol in UMR 106–01 osteoblast-like cells. Kidney Int 50:63–70
12. Jongen JW, Willemstein-van Hove EC, van der Meer JM, Bos MP, Jüppner H, Segre GV, Abou-Samra AB, Feyen JH, Herrmann-Erlee MP (1996) Down-regulation of the receptor for parathyroid hormone (PTH) and PTH-related peptide by PTH in primary fetal rat osteoblasts. J Bone Miner Res 11:1218–1225
13. Ma YL, Cain RL, Halladay DL, Yang X, Zeng Q, Miles RR, Chandrasekhar S, Martin TJ, Onyia JE (2001) Catabolic effects of continuous human PTH (1–38) in vivo is associated with sustained stimulation of RANKL and inhibition of osteoprotegerin and gene-associated bone formation. Endocrinology 142:4047–4054
14. Dietrich JW, Canalis EM, Maina DM, Raisz LG (1976) Hormonal control of bone collagen synthesis in vitro: effects of parathyroid hormone and calcitonin. Endocrinology 98:943–949
15. Isogai Y, Akatsu T, Ishizuya T, Yamaguchi A, Hori M, Takahashi N, Suda T (1996) Parathyroid hormone regulates osteoblast differentiation positively or negatively depending on the differentiation stages. J Bone Miner Res 11:1384–1393
16. Bellows CG, Ishida H, Aubin JE, Heersche JN (1990) Parathyroid hormone reversibly suppresses the differentiation of osteoprogenitor cells into functional osteoblasts. Endocrinology 127:3111–3116
17. Nishida S, Yamaguchi A, Tanizawa T, Endo N, Mashiba T, Uchiyama Y, Suda T, Yoshiki S, Takahashi HE (1994) Increased bone formation by intermittent parathyroid hormone administration is due to the stimulation of proliferation and differentiation of osteoprogenitor cells in bone marrow. Bone 15:717–723
18. Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC (1999) Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. J Clin Invest 104: 439–446
19. Tobimatsu T, Kaji H, Sowa H, Naito J, Canaff L, Hendy GN, Sugimoto T, Chihara K (2006) Parathyroid hormone increases beta-catenin levels through Smad3 in mouse osteoblastic cells. Endocrinology 147:2583–2590
20. Fujita T, Inoue T, Morii H, Morita R, Norimatsu H, Orimo H, Takahashi HE, Yamamoto K, Fukunaga M (1999) Effect of an intermittent weekly dose of human parathyroid hormone (1–34) on osteoporosis: a randomized double-masked prospective study using three dose levels. Osteoporos Int 9:296–306
21. Wang YH, Liu Y, Buhl K, Rowe DW (2005) Comparison of the action of transient and continuous PTH on primary osteoblast cultures expressing differentiation stage-specific GFP. J Bone Miner Res 20:5–14
22. McClung MR, San Martin J, Miller PD, Civitelli R, Bandeira F, Omizo M, Donley DW, Dalsky GP, Eriksen EF (2005) Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med 165:1762–1768
23. Stepan JJ, Burr DB, Li J, Ma YL, Petto H, Sipos A, Dobnig H, Fahrleitner-Pammer A, Michalská D, Pavo I (2010) Histomorphometric changes by teriparatide in alendronate-pretreated women with osteoporosis. Osteoporos Int 21:2027–2036
24. Rubin MR, Bilezikian JP (2003) The anabolic effects of parathyroid hormone therapy. Clin Geriatr Med 19:415–432
25. Bilezikian JP, Rubin MR, Finkelstein JS (2005) Parathyroid hormone as an anabolic therapy for women and men. J Endocrinol Invest 28:41–49
26. Saito M, Marumo K, Kida Y, Ushiku C, Kato S, Takao-Kawabata R, Kuroda T (2011) Changes in the contents of enzymatic immature, mature, and non-enzymatic senescent cross-links of collagen after once-weekly treatment with human parathyroid hormone (1–34) for 18 months contribute to improvement of bone strength in ovariectomized monkeys. Osteoporos Int 22:2373–2383
27. Chen P, Miller PD, Delmas PD, Misurski DA, Krege JH (2006) Change in lumbar spine BMD and vertebral fracture risk reduction in teriparatide-treated postmenopausal women with osteoporosis. J Bone Miner Res 21:1785–1790
28. Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD (2002) Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. J Bone Miner Res 17:1–10
29. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, Black DM (2002) Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med 112:281–289
30. Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, Barton IP, van Staa TP, Adachi JD (2004) Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. J Clin Densitom 7:255–261
31. Austin M, Yang YC, Vittinghoff E, Adami S, Boonen S, Bauer DC, Bianchi G, Bolognese MA, Christiansen C, Eastell R, Grauer A, Hawkins F, Kendler DL, Oliveri B, McClung MR, Reid IR, Siris ES, Zanchetta J, Zerbini CA, Libanati C, Cummings SR, FREEDOM Trial (2012) Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. J Bone Miner Res 27: 687–693
32. Jacques RM, Boonen S, Cosman F, Reid IR, Bauer DC, Black DM, Eastell R (2012) Relationship of changes in total hip bone mineral density to vertebral and nonvertebral fracture risk in women with postmenopausal osteoporosis treated with once-yearly zoledronic acid 5 mg: the HORIZON-pivotal fracture trial (PFT). J Bone Miner Res 27:1627–1634

Bone 64 (2014) 75–81

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

The effects of once-weekly teriparatide on hip geometry assessed by hip structural analysis in postmenopausal osteoporotic women with high fracture risk

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ARTICLE INFO

Article history:
Received 20 December 2013
Revised 14 March 2014
Accepted 1 April 2014
Available online 13 April 2014

Edited by: Sharmila Majumdar

Keywords:
Teriparatide
Weekly injection
Hip geometry
Hip structural analysis
Osteoporosis

ABSTRACT

Weekly administration of teriparatide has been shown to reduce the risk of vertebral and non-vertebral fractures in patients with osteoporosis at higher fracture risk in Japan. However, its efficacy for hip fracture has not been established. To gain insight into the effect of weekly teriparatide on the hip, hip structural analysis (HSA) based on dual-energy X-ray absorptiometry (DXA) was performed using the data of 209 postmenopausal osteoporotic women who had participated in the original randomized, multicenter, double-blind, placebo-controlled trial assessing the effects of once-weekly 56.5 μg teriparatide for 72 weeks. The DXA scans, obtained at baseline, 48 weeks and 72 weeks, were analyzed to extract bone mineral density (BMD) and cross-sectional geometrical indices at the narrowest point on the neck (NN), the intertrochanteric region (IT), and the proximal shaft. Compared with placebo after 72 weeks, the teriparatide group showed significantly higher BMD, average cortical thickness, bone cross-sectional area, and section modulus, and lower buckling ratio at both the NN and IT regions. No significant expansion of periosteal diameter was observed at these regions. There were no significant differences in BMD and HSA indices at the shaft region. The results indicate that overall structural strength in the proximal femur increased compared to placebo, suggesting that once-weekly teriparatide effectively reverses changes in hip geometry and strength with aging.

Introduction

Intermittent administration of teriparatide (human parathyroid hormone: PTH 1–34) increases bone mineral density (BMD) and improves microarchitecture through its anabolic effect on bone [1–5]. Once-weekly teriparatide injection at a dose of 56.5 μg and daily teriparatide injection at 20 μg are currently available for the treatment of primary osteoporosis with high fracture risk in Japan. In both teriparatide treatment regimens, marked reduction in fracture risk has been demonstrated at the spine, whereas their efficacy has not been established for hip fracture. Of the common osteoporotic fracture sites, hip fractures present the greatest risk of morbidity and mortality, but hip fractures are far less frequent than vertebral fractures, and most clinical trials are insufficiently powered to show a comparable reduction in hip fractures.

The anti-fracture efficacy of once-weekly 56.5 μg teriparatide for 72 weeks was evaluated in 578 postmenopausal women and older men with primary osteoporosis by a randomized, controlled trial, the Teriparatide Once-Weekly Efficacy Research (TOWER) trial [6]. Teriparatide administration increased BMD by 6.4%, 3.0%, and 2.3% at the lumbar spine, total hip, and femoral neck, respectively, compared

Abbreviations: HSA, hip structural analysis; DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; NN, narrowest point on neck; IT, intertrochanteric region; Teriparatide, human parathyroid hormone: PTH 1–34; TOWER trial, Teriparatide Once-Weekly Efficacy Research trial; CSMI, cross-sectional moment of inertia; SM, section modulus; OD, outer diameter; ED, endocortical diameter; CoTh, average cortical thickness; CSA, total mineralized bone area in cross-section; BR, buckling ratio; ROI, region of interest; BMI, body mass index; QCT, quantitative computed tomography.

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http://dx.doi.org/10.1016/j.bone.2014.04.004

Table 1
Baseline demographics and clinical characteristics of the teriparatide and placebo groups.

	Teriparatide group (n = 98)	Placebo group (n = 111)
Age (years)	73.9 ± 5.4	74.1 ± 5.4
Body height (cm)	148.3 ± 5.4	147.7 ± 5.6
Body weight (kg)	51.0 ± 7.5	51.4 ± 7.8
Body mass index (BMI) (kg/m^2)	23.2 ± 3.3	23.5 ± 3.1
Years after menopause (years)	24.4 ± 6.5	24.4 ± 6.6
Bone mineral density (T-score)		
Lumbar spine (L2–4)	−2.7 ± 1.0	−2.6 ± 1.0
Femoral neck	−2.5 ± 0.8	−2.4 ± 0.8
Total hip	−2.2 ± 1.0	−2.1 ± 0.9
Number of prevalent vertebral fractures	1.9 ± 1.4	1.7 ± 1.1

Data are mean ± SD.
Hip bone mineral densities are data at conventional DXA regions.

with placebo. Incident vertebral fracture risk was reduced by 80% (relative risk reduction) compared to placebo. In addition to its antifracture efficacy at the spine, once-weekly treatment with teriparatide reduced the risk of clinical fragility non-vertebral fractures by 67% compared to placebo. Although the increase of hip BMD was significant, the magnitude of the percent increase was less than half that of lumbar BMD. The reduced risk of non-vertebral fracture may be partially due to the changes in long bone geometry caused by teriparatide treatment.

Bone geometry refers to bone tissue distribution and alignment, which are critical for both the structural and biomechanical properties of bone [7]. In this context, the hip structural analysis (HSA) algorithm was developed for noninvasive clinical evaluation of dual-energy X-ray absorptiometry (DXA) of the proximal femur [8]. Prospective epidemiological studies demonstrated the ability of this method to predict hip fracture using indices of hip geometry. In a prospective case–control study of 71 women and 25 men more than 60 years old [9], the femoral neck diameter and section modulus (SM) were identified as independent predictors of hip fracture risk after adjustment for BMD in both women and men. Recent prospective studies of large epidemiologic cohorts have shown that certain geometric properties, particularly buckling ratio, cortical thickness, and outer diameter, predict incident hip fracture as well as conventional BMD at the proximal femur [10–12].

HSA is considered to be a suitable technique for geometrical assessment. Although one must be cautious about the methodological limits of measuring geometry from two-dimensional DXA scans, HSA could provide critical insights into the mechanisms of the therapeutic efficacy of anti-osteoporotic agents. The purpose of this study was to investigate the effect of once-weekly injection of 56.5 μg teriparatide on proximal femoral geometry using HSA.

Subjects and methods

Subjects

The subjects in this analysis were a subgroup of the original TOWER trial [6], and they included 209 ambulatory female patients with osteoporosis (>65 years old) enrolled at 25 sites equipped with DXA systems to measure hip BMD, bone geometry, and biomechanical indices. The inclusion and exclusion criteria of the original TOWER trial were fulfilled [6]. Subjects with 1 to 5 vertebral fractures with low BMD (T-score ≤ −1.67) were eligible. Subjects with diseases or using drugs affecting bone or calcium metabolism were excluded. The subjects were randomly allocated to either weekly subcutaneous injection of 56.5 μg teriparatide (teriparatide group) or placebo (placebo group) for 72 weeks. All subjects received daily supplements of calcium (610 mg), vitamin D_3 (400 IU), and magnesium (30 mg).

The original TOWER trial was conducted in compliance with the ethical principles stated in the Declaration of Helsinki and Good Clinical Practice. The trial was approved by the institutional review boards at each site, and all subjects provided their written, informed consent before enrollment.

Methods

The subjects were measured for bone parameters by DXA at baseline and after 48 and 72 weeks of treatment. All DXA devices were of the Hologic system (Hologic Inc., Waltham, MA), and each machine was

Table 2
Baseline HSA measurements and percent changes at 48 and 72 weeks.

		Teriparatide group (n = 98)			Placebo group (n = 111)		
Site	Parameter	Baseline	48 weeks	72 weeks	Baseline	48 weeks	72 weeks
Narrow neck	BMD (g/cm^2)	0.63 ± 0.10	2.4 ± 7.1[a]	3.4 ± 6.9[a]	0.63 ± 0.09	−0.7 ± 5.0	−0.5 ± 4.8
	CoTh (cm)	0.12 ± 0.02	2.8 ± 8.9[a]	3.8 ± 8.2[a]	0.12 ± 0.02	−0.4 ± 6.3	0.1 ± 6.4
	CSA (cm^2)	1.88 ± 0.29	1.9 ± 5.7[a]	2.2 ± 5.6[a]	1.90 ± 0.27	−1.1 ± 4.4[a]	−1.1 ± 4.3[a]
	OD (cm)	3.15 ± 0.22	−0.3 ± 3.8	−1.1 ± 3.3[a]	3.16 ± 0.20	−0.4 ± 3.2	−0.6 ± 2.8[a]
	ED (cm)	2.92 ± 0.24	−0.5 ± 4.5	−1.4 ± 4.0[a]	2.92 ± 0.21	−0.4 ± 3.7	−0.6 ± 3.3
	SM (cm^3)	0.90 ± 0.16	1.3 ± 8.0	2.6 ± 7.5[a]	0.90 ± 0.16	−0.2 ± 7.1	−0.8 ± 7.3
	BR	15.89 ± 3.48	−2.6 ± 11.5	−4.5 ± 10.1[a]	15.77 ± 3.20	0.3 ± 8.3	−0.3 ± 8.1
Intertrochanteric region	BMD (g/cm^2)	0.62 ± 0.12	2.3 ± 4.7[a]	3.1 ± 5.0[a]	0.63 ± 0.10	−0.8 ± 4.1[a]	−1.4 ± 4.6[a]
	CoTh (cm)	0.26 ± 0.05	1.8 ± 4.5[a]	2.1 ± 4.7[a]	0.27 ± 0.05	−1.0 ± 4.8	−0.9 ± 0.1[a]
	CSA (cm^2)	3.03 ± 0.56	1.6 ± 3.9[a]	2.6 ± 4.1[a]	3.10 ± 0.49	−0.6 ± 4.2	−0.9 ± 4.5
	OD (cm)	5.14 ± 0.30	−0.4 ± 2.2	−0.3 ± 2.2	5.20 ± 0.28	0.3 ± 1.9	0.4 ± 2.1
	ED (cm)	4.62 ± 0.33	−0.6 ± 2.5[a]	−0.5 ± 2.6	4.67 ± 0.31	0.4 ± 2.1[a]	0.6 ± 2.4[a]
	SM (cm^3)	2.52 ± 0.59	0.9 ± 6.5	3.3 ± 7.4[a]	2.63 ± 0.60	0.9 ± 7.4	−0.0 ± 7.6
	BR	12.20 ± 3.11	−2.2 ± 5.4[a]	−2.3 ± 5.8[a]	11.88 ± 2.60	1.2 ± 5.7[a]	2.0 ± 5.9[a]
Shaft	BMD (g/cm^2)	1.23 ± 0.21	0.1 ± 3.8	0.3 ± 3.8	1.24 ± 0.19	−0.3 ± 3.7	−0.5 ± 3.9
	CoTh (cm)	0.45 ± 0.10	−0.1 ± 5.1	−0.2 ± 5.0	0.46 ± 0.09	0.5 ± 4.9	−0.8 ± 5.0
	CSA (cm^2)	3.19 ± 0.53	−0.1 ± 3.3	1.0 ± 3.6[a]	3.24 ± 0.47	0.0 ± 3.4	−0.1 ± 3.8
	OD (cm)	2.74 ± 0.20	−0.0 ± 2.2	0.9 ± 1.7[a]	2.75 ± 0.19	−0.3 ± 2.0	0.4 ± 2.0[a]
	ED (cm)	1.84 ± 0.33	−0.0 ± 5.7	1.6 ± 4.4[a]	1.83 ± 0.32	−0.8 ± 5.0	1.3 ± 5.2[a]
	SM (cm^3)	1.68 ± 0.32	−0.0 ± 4.6	1.4 ± 5.1[a]	1.69 ± 0.26	−0.8 ± 4.9	1.0 ± 5.5
	BR	3.33 ± 0.97	−0.0 ± 7.2	1.2 ± 6.9	3.25 ± 0.83	−0.8 ± 6.7	1.5 ± 7.0[a]

Data are mean ± SD.
SM, section modulus; BR, buckling ratio; CSA, total mineralized bone area in cross-section; OD, outer diameter; ED, endocortical diameter; CoTh, cortical thickness.
[a] $p < 0.05$, compared with baseline.

adjusted for differences by calibration with standard phantoms to verify the reproducibility of the measurements within ± 1.5% during the study period. DXA scan data for the proximal femur were analyzed using APEX 3.0 software (Hologic, Inc.), and all analyses were conducted by the same technician (TT) in the Department of Radiological Technology, Kawasaki College of Allied Health Professions.

The HSA algorithm is based on a principle first articulated by Martin and Burr [13], who demonstrated that mineral profiles created during single photon absorptiometry are a projection of the corresponding bone cross-section and can be used to define its geometry. As described previously [8,14,15], the HSA algorithm derives the conventional BMD (g/cm^2), the outer diameter (OD, cm), the endocortical diameter (ED, cm), the average cortical thickness (CoTh, cm), the total mineralized bone area in the cross-section (CSA, cm^2), the cross-sectional moment of inertia (CSMI, cm^4), and the section modulus (SM, cm^3) directly from the mass profiles. SM is computed as CSMI / d_{max}, where d_{max} (cm) is the maximum distance between the center of the mass (centroid) and the outer cortex. Another parameter, the buckling ratio (BR), is estimated as the ratio of d_{max} to the estimated average CoTh derived from an annulus model of the cross-section using the measured OD, assuming that a fixed proportion of CSA is in the cortex. CSA and SM are indices of resistance to axial compressive and bending loads, respectively, and BR is a crude index of susceptibility to local buckling under bending loads.

The HSA software generates profiles of pixel values traversing the proximal femur at three locations: the narrow neck (NN) across the femoral neck at its narrowest point, the intertrochanteric region (IT) along the angle bisector defined by the neck and shaft axes, and across the shaft at 30 mm below the most prominent portion of the lesser trochanter. To avoid variation in the visualization of the lower border of the lesser trochanter depending on the inner rotation of the hip joint, the distance from the highest part of the lesser trochanter was made constant to improve the reproducibility of bone shaft regions and to correctly determine the region of interest (ROI). At each of these locations, five parallel profiles were generated, spaced one pixel apart, proximal and distal to the three defined locations. The five profiles were averaged within each region, and the BMD, CSA, OD, ED, CoTh, SM, and BR were reported.

Statistics

All statistical analyses were performed on subjects who had been randomized and had evaluable observations for HSA assessment at baseline and at 48 and 72 weeks. Paired and unpaired Student's *t*-tests were used. All *p* values calculated in the analysis were two-sided and were not adjusted for multiple testing. Statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

Background characteristics

A total of 209 subjects were analyzed by the HSA program. There were 98 subjects in the teriparatide group (mean age ± SD: 73.9 ± 5.4 years) and 111 subjects in the placebo group (74.1 ± 5.4 years). Table 1 shows the subjects' background characteristics at baseline in both groups. There were no significant differences between the two groups in age, height, weight, body mass index (BMI), years after menopause, BMD at the spine and hip, or the number of vertebral fractures ($p > 0.05$).

Effect of teriparatide on BMD

Percentage changes in BMD of individual femoral regions from baseline are shown in Table 2. There were no significant differences at baseline for BMD at the NN, IT, and shaft between the teriparatide and placebo groups. Compared to baseline, weekly teriparatide significantly increased BMD at the NN (2.4%, 48 weeks, $p = 0.01$; 3.4%, 72 weeks, $p < 0.01$) and IT (2.3%, 48 weeks, $p < 0.01$; 3.1%, 72 weeks, $p < 0.01$). No significant increase was observed at the shaft (0.1%, 48 weeks, $p = 0.87$; 0.3%, 72 weeks, $p = 0.55$).

Effects of teriparatide on bone geometry parameters

Baseline and percent changes in bone geometry parameters are shown in Table 2. There were no significant differences at baseline for any bone geometry parameter at the NN, IT, and shaft between the teriparatide and placebo groups. Compared to baseline, weekly teriparatide significantly increased: CoTh at the NN (2.8%, 48 weeks, $p = 0.03$; 3.8%, 72 weeks, $p < 0.01$) and IT (1.8%, 48 weeks, $p < 0.01$; 2.1%, 72 weeks, $p = 0.01$); CSA at the NN (1.9%, 48 weeks, $p = 0.02$; 2.2%, 72 weeks, $p = 0.02$), IT (1.6%, 48 weeks, $p < 0.01$; 2.6%, 72 weeks, $p < 0.01$), and the shaft (1.0%, 72 weeks, $p = 0.03$); OD at the shaft (0.9%, 72 weeks, $p < 0.01$); and ED at the shaft (1.6%, 72 weeks, $p = 0.04$). Teriparatide treatment also decreased OD at the NN (−1.1%,

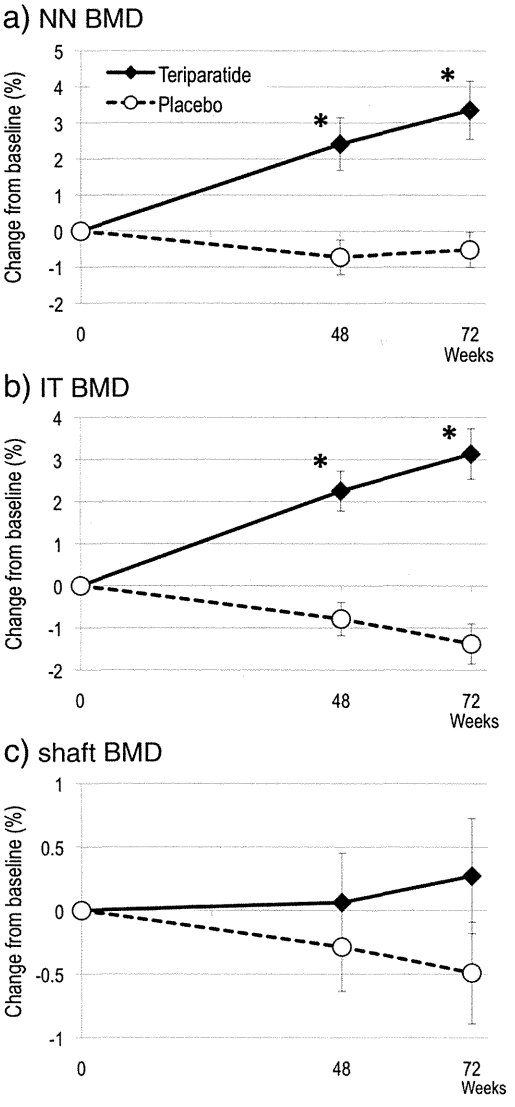

Fig. 1. Mean ± standard error (SE) and percent changes from baseline in narrow neck (NN, 1a), intertrochanteric region (IT, 1b), and shaft (1c) bone mineral density (BMD) at 48 weeks and 72 weeks of treatment with teriparatide and placebo. Solid and broken lines correspond to teriparatide and placebo groups, respectively. To compare the difference between the two groups, the percent changes from baseline in hip structural analysis (HSA) parameters were analyzed using Student's *t*-test. *$p < 0.05$, compared with placebo.

72 weeks, $p = 0.01$) and ED at the NN (−1.4%, 72 weeks, $p = 0.01$) and IT (−0.6%, 48 weeks, $p = 0.02$). In the placebo group, CoTh at the IT (−0.9%, 72 weeks, $p < 0.01$), CSA at the NN (−1.1%, 48 weeks, $p = 0.01$; −1.1%, 72 weeks, $p = 0.02$), and OD at the NN (−0.6%, 72 weeks, $p = 0.04$) decreased significantly, whereas OD at the shaft (0.4%, 72 weeks, $p = 0.04$) and ED at the IT (0.4%, 48 weeks, $p = 0.04$; 0.6%, 72 weeks, $p = 0.01$) and shaft (1.3%, 72 weeks, $p = 0.02$) increased significantly.

Effects of teriparatide on bone strength indices

Baseline and percent changes in bone strength indices are shown in Table 2. There were no significant differences at baseline for any bone strength indices at the NN, IT, and shaft between the teriparatide and placebo groups. Teriparatide treatment also decreased BR at the NN (−4.5%, 72 weeks, $p < 0.01$) and IT (−2.2%, 48 weeks, $p < 0.01$; −2.3%, 72 weeks, $p < 0.01$). In the placebo group, BR at the IT (1.2%, 48 weeks, $p = 0.03$; 2.0%, 72 weeks, $p < 0.01$) and shaft (1.5%, 72 weeks, $p = 0.04$) increased significantly.

Effect of teriparatide on BMD compared to placebo

The comparison of BMD between the teriparatide and placebo groups is shown in Fig. 1. No significant differences in BMD were observed at the shaft between the groups. Significantly greater increases in BMD were observed in the teriparatide group (48 and 72 weeks) at the NN and IT (Figs. 1a and b).

Effects of teriparatide on bone geometry parameters compared to placebo

Comparisons of CoTh, CSA, OD, and ED between the two groups are shown in Fig. 2. Significantly greater increases in CoTh at the NN (48 weeks, $p < 0.01$; 72 weeks, $p < 0.01$) and IT (48 weeks, $p < 0.01$; 72 weeks, $p < 0.01$) were observed in the teriparatide group (Figs. 2–1a and b). There was no significant difference in CoTh at the shaft (Fig. 2–1c). Significantly greater increases in CSA values were observed at the NN (48 weeks, $p < 0.01$; 72 weeks, $p < 0.01$) and IT (48 weeks, $p < 0.01$; 72 weeks, $p < 0.01$) in the teriparatide group (Figs. 2–2a and b). There was no significant difference in CSA at the shaft (Fig. 2–2c). A significantly greater decrease in OD was observed at the IT

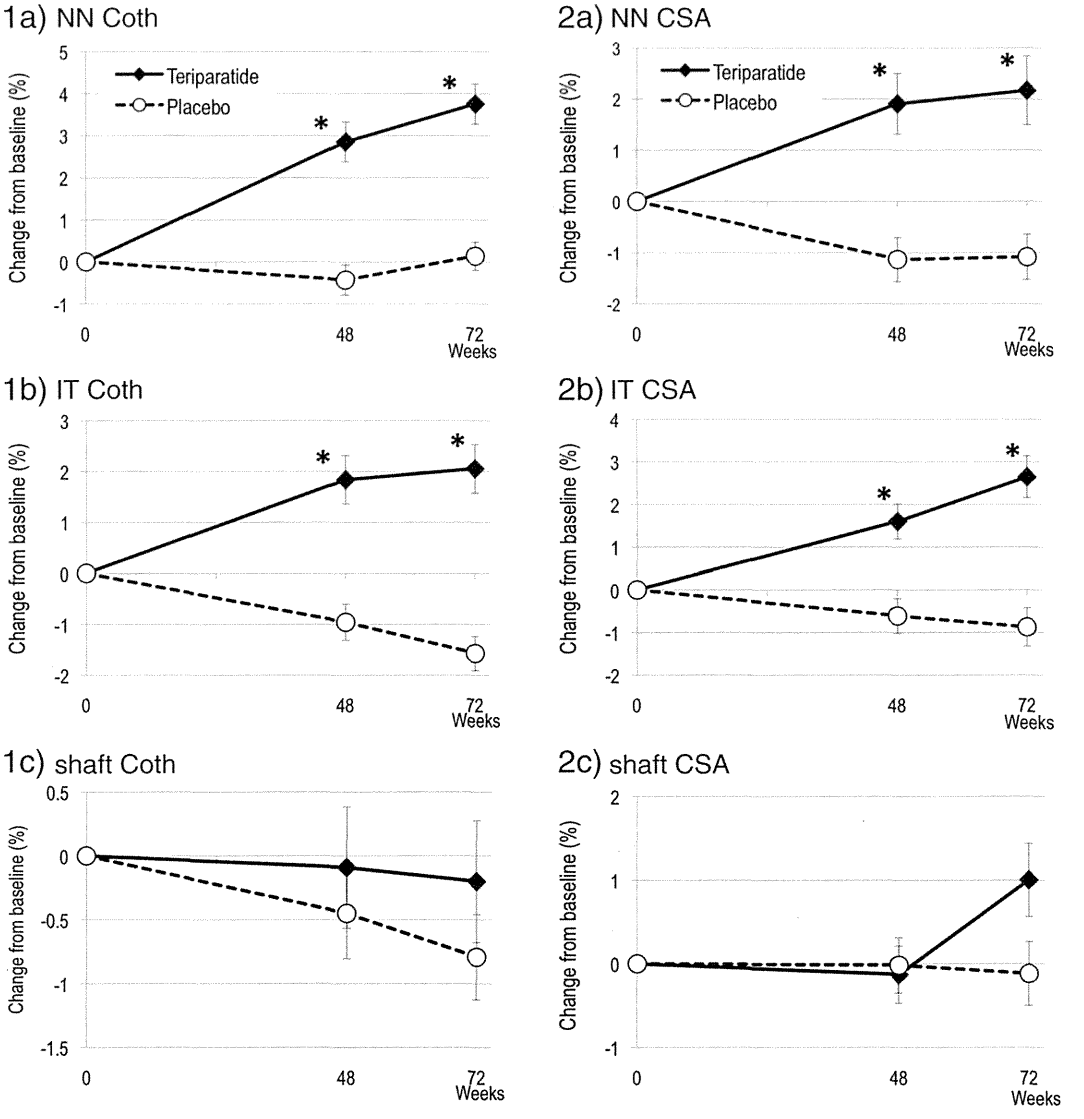

Fig. 2. Mean ± SE and percent changes from baseline in cortical thickness (CoTh) in NN (1a), IT (1b), and shaft (1c); total mineralized bone area in the cross-section (CSA) in NN (2a), IT (2b) and shaft (2c); outer diameter (OD) in NN (3a), IT (3b), and shaft (3c); and endocortical diameter (ED) in NN (4a), IT (4b), and shaft (4c) at 48 weeks and 72 weeks of treatment with teriparatide and placebo. Solid and broken lines correspond to the teriparatide and placebo groups, respectively. To compare the difference between the two groups, the percent changes from baseline in HSA parameters were analyzed using Student's *t*-test. *$p < 0.05$, compared with placebo.

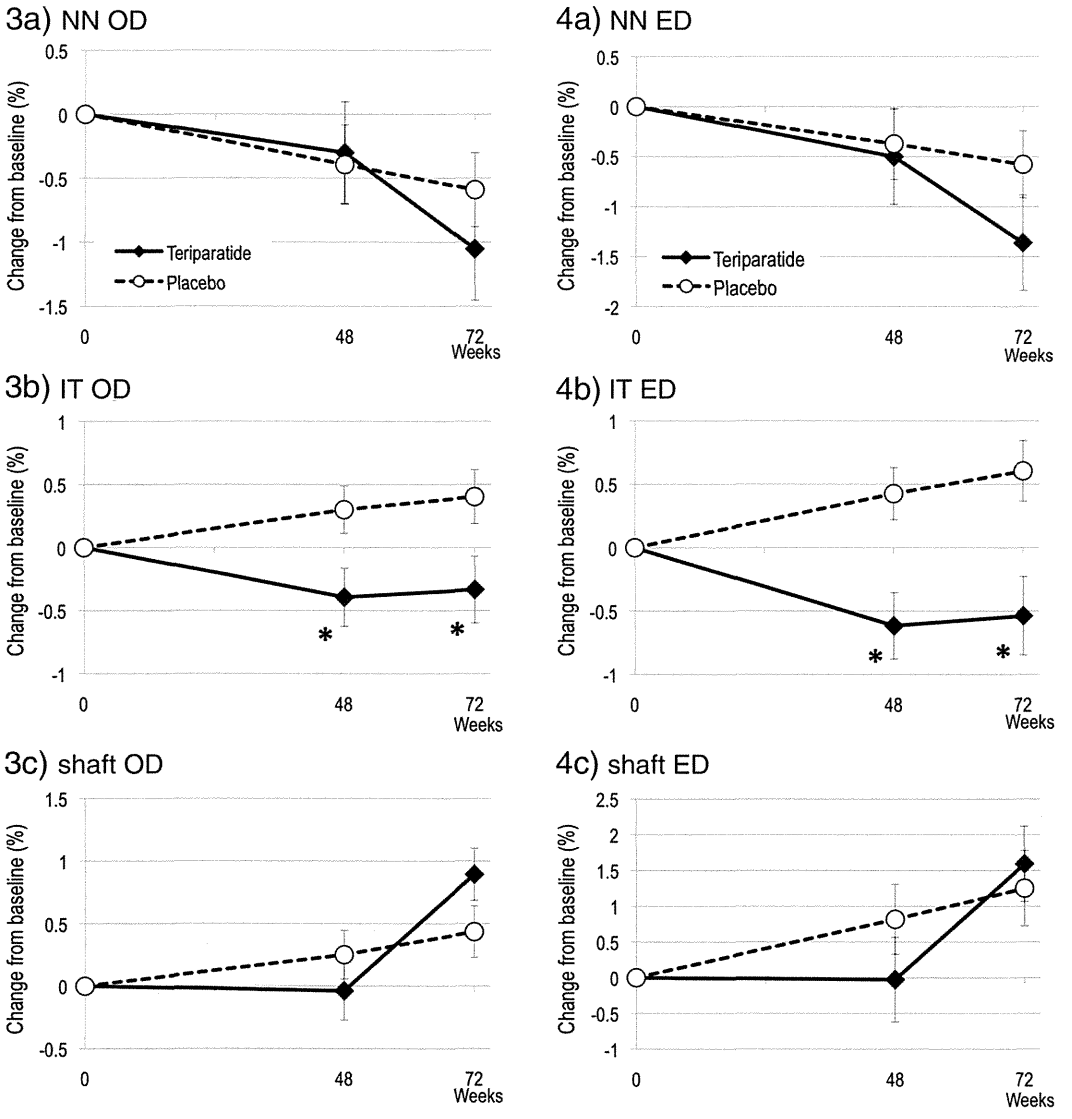

Fig. 2 (*continued*).

(48 weeks, $p = 0.02$; 72 weeks, $p = 0.03$) in the teriparatide group (Fig. 2–3b). There were no significant differences in OD at the NN and shaft (Figs. 2–3a and c). A significantly greater decrease in ED at the IT (48 weeks, $p < 0.01$; 72 weeks, $p < 0.01$) was observed in the teriparatide group (Fig. 2–4b). There were no significant differences in ED at the NN and shaft (Figs. 2–4a and c). In summary, both CoTh and CSA increased in the NN and IT regions following treatment with teriparatide; both OD and ED decreased in IT regions following treatment with teriparatide compared to placebo.

Effects of teriparatide on bone strength indices compared to placebo

Percent changes in bone strength indices are shown in Fig. 3. SM showed significantly greater increases compared to placebo in the teriparatide group at the NN (72 weeks, $p < 0.01$) and IT (72 weeks, $p < 0.01$) (Figs. 3–2a and b). There was no significant difference in SM at the shaft (Fig. 3–2c). BR values showed significantly greater decreases in the teriparatide group at the NN (48 weeks, $p = 0.04$; 72 weeks, $p < 0.01$) and IT (48 weeks, $p < 0.01$; 72 weeks, $p < 0.01$) compared to placebo (Figs. 3–3a and b). There was no significant difference in BR at the shaft (Fig. 3–3c).

Discussion

This subgroup study using HSA demonstrated the changes of BMD, bone geometry, and mechanical properties at the proximal femur with once-weekly injection of 56.5 μg teriparatide for 72 weeks. This is the first longitudinal HSA study of weekly teriparatide including comparison with a placebo group. Previous studies have evaluated the effects of daily teriparatide on hip geometry and its biomechanical properties using HSA [16]. The effects of once-weekly teriparatide injection on hip geometry in this study are roughly similar to the results with daily teriparatide injection.

In this study, CoTh and CSA increased, while OD and ED remained unchanged or decreased at the NN and IT over 72 weeks of once-weekly teriparatide treatment. The results suggest that bone formation took place at the endosteal and trabecular bone surfaces and not at the periosteal surface. Previous reports suggested that daily treatment with teriparatide stimulates new bone formation on both the periosteal and endosteal surfaces [5,17]. The difference may be explained by the dose of teriparatide or the timing of injection (daily versus weekly). Generally, the diameter of bone expands with age to compensate for the decrease in bone strength due to age-related bone loss [18–21]. Once-weekly teriparatide treatment increased CoTh without an

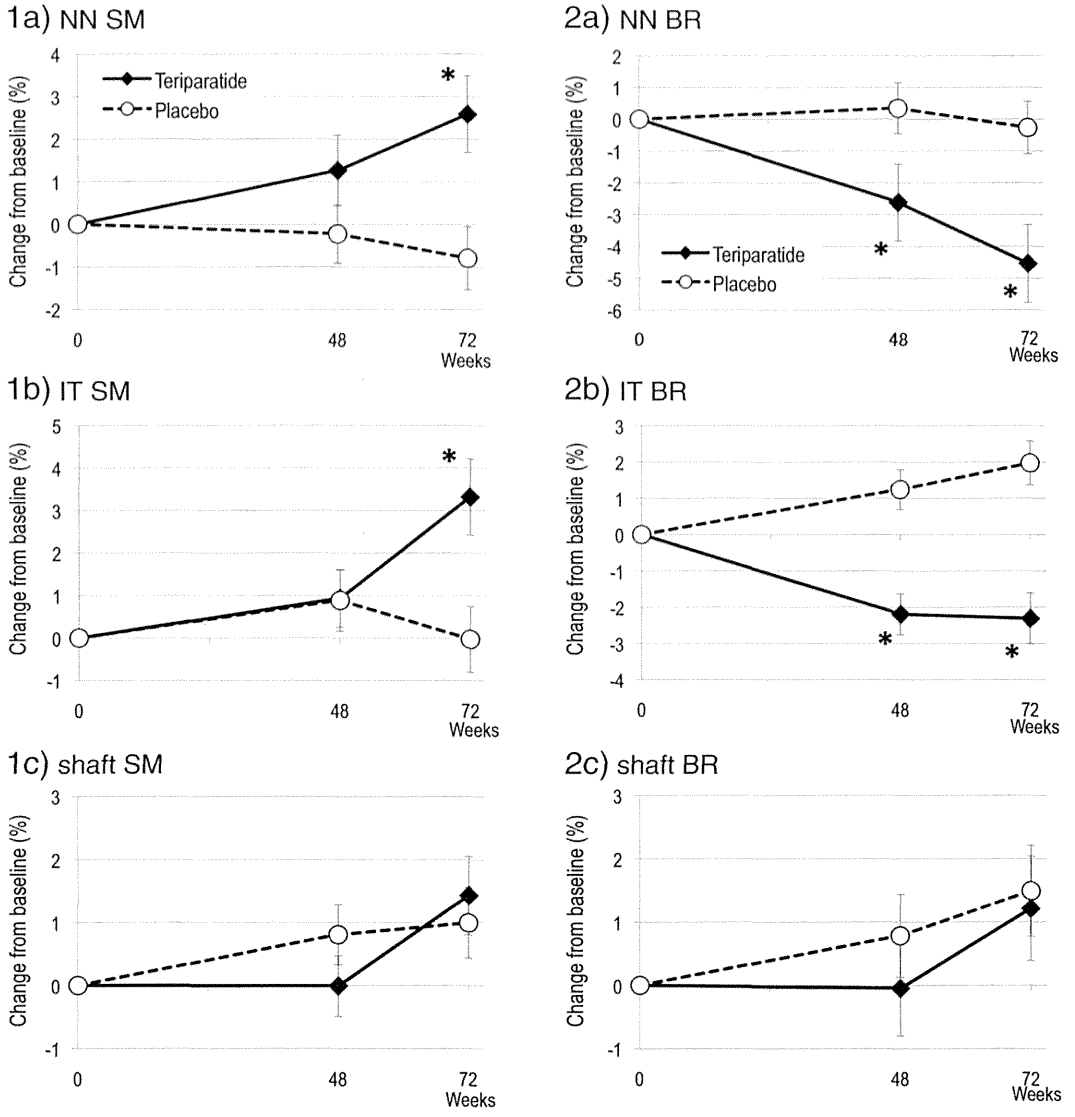

Fig. 3. Mean ± SE and percent changes from baseline in section modulus (SM) in NN (1a), IT (1b), and shaft (1c), and buckling ratio (BR) in NN (2a), IT (2b), and shaft (2c) at 48 and 72 weeks of treatment with teriparatide and placebo. Solid and broken lines correspond to teriparatide and placebo groups, respectively. To compare the difference between the two groups, the percent changes from baseline in HSA parameters were analyzed using Student's *t*-test. $^{*}p < 0.05$, compared with placebo.

increase in cortical perimeter at the NN and IT. This phenomenon may indicate anti-aging effects of teriparatide treatment. Reflecting the increase in CoTh, a significant decrease in BR was also observed in the teriparatide group.

Contrary to our expectations, OD at the NN showed a small but significant decrease compared with baseline in the placebo group, although it showed an increase both at the IT and shaft. The decrease in OD at the NN in the placebo group is not consistent with previous reports that showed a significant age-related increase in OD by HSA [20,22]. At a region of very thin cortex, such as the upper border of the femoral neck, the edge detection error in DXA analysis due to the partial volume effect may become evident, resulting in the apparent decrease in OD. Such an error in edge detection would be exaggerated by the increase in cortical porosity and the decrease in mineralization density of bone tissue. In this context, the decreased tendency in OD in the teriparatide group compared with the placebo group at the NN and IT may be an artifact of edge detection error.

In contrast to the changes at the NN and IT with teriparatide treatment, no significant differences were observed at the shaft in HSA indices between the teriparatide and placebo groups. Similar results have been reported in a study with daily teriparatide injection [22].

The present HSA study results are consistent with the three-dimensional assessment of proximal femoral geometry by quantitative computed tomography (QCT) using a small sample of the TOWER trial [23]. The present study confirmed the results of the QCT study using a larger sample from the same trial. Taken together with the results of the QCT study, once-weekly teriparatide injection appears to reverse age-related deteriorations in bone structural strength by increasing CoTh, CSA, and BMD, while not increasing cortical perimeter at the NN and IT. Thus, once-weekly injection of 56.5 μg teriparatide may have the potential to reduce the risk of hip fracture.

The present study has some limitations based on the methodological assumptions in HSA. First, since HSA assumes a fixed proportion of cortical and cancellous bone mass to calculate ED, the estimate of ED and its derived measurements such as CoTh and BR are influenced when bone mass changes in cortical and cancellous bone are not proportional. It has been suggested that the increased bone mass with daily teriparatide treatment predominantly involves cancellous bone [24,25]. However, the QCT study using a small sample of the TOWER trial also showed a significant increase in CoTh, as well as in CSA [23]. Thus, we think that the differential effect on bone mass between cortical and cancellous bone would be small with weekly teriparatide treatment.

Another limitation is the possible error due to the assumption of fixed bone mineralization density in HSA. Given that teriparatide tends to decrease the mean mineralization density of bone tissue, the increases in CSA, CoTh, and SM with treatments would be underestimated.

In conclusion, HSA showed that once-weekly teriparatide increased CoTh and CSA and improved biomechanical indices. Moreover, once-weekly teriparatide did not increase OD and ED, but seemed to effectively reverse changes in hip geometry and strength with aging. Taken together with its anti-fracture efficacy in the spine [6], once-weekly 56.5 μg teriparatide administration is an option for the prevention of spinal fractures and may have the potential to prevent hip fractures.

Disclosure

This study was jointly designed by all authors and the sponsor (Asahi Kasei Pharma Corporation). Funding for this study was provided by Asahi Kasei Pharma Corporation. The sponsor of the study participated in the study design, data analysis, and writing of the report, and had responsibility for quality control. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit the manuscript for publication.

TSo has received research grants and consulting fees from Astellas Pharma, Daiichi-Sankyo, Pfizer, and Takeda Pharmaceutical. MI has received research grants and consulting fees or other remuneration from Chugai Pharmaceutical, Daiichi Sankyo, Ono Pharmaceutical, and Asahi Kasei Pharma. MF has received consulting fees from Astellas Pharma and Asahi Kasei Pharma. TT has nothing to disclose. TSu has received research grants and consulting fees from Asahi Kasei Pharma and Daiichi Sankyo. MS has received consulting fees from Asahi Kasei Pharma, Daiichi Sankyo, Chugai Pharmaceutical, and Teijin Pharma. TY is an employee of Asahi Kasei Pharma. TN has received research grants and/or consulting fees from Chugai Pharmaceutical, Teijin Pharma, Asahi Kasei Pharma, and Daiichi Sankyo. TN is a counselor for hospital administration and social medical insurance with the Japan Ministry of Health, Labour and Welfare.

Acknowledgments

The authors would like to thank the doctors who participated in the clinical trial. English editing was performed by FORTE Science Communications.

References

[1] Miyauchi A, Matsumoto T, Sugimoto T, Tsujimoto M, Warner MR, Nakamura T. Effects of teriparatide on bone mineral density and bone turnover markers in Japanese subjects with osteoporosis at high risk of fracture in a 24-month clinical study: 12-month, randomized, placebo-controlled, double-blind and 12-month open-label phases. Bone 2010;47:493–502.
[2] Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. J Bone Miner Res 2001;16:1846–53.
[3] Hodsman AB, Kisiel M, Adachi JD, Fraher LJ, Watson PH. Histomorphometric evidence for increased bone turnover and cortical thickness without increased cortical porosity after 2 years of cyclical hPTH (1–34) therapy in women with severe osteoporosis. Bone 2000;27:311–8.
[4] Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksen EF. Recombinant human parathyroid hormone (1–34) [teriparatide] improves both cortical and cancellous bone structure. J Bone Miner Res 2003;18:1932–41.
[5] Zanchetta JR, Bogado CE, Ferretti JL, Wang O, Wilson MG, Sato M, et al. Effects of teriparatide [recombinant human parathyroid hormone (1–34)] on cortical bone in postmenopausal women with osteoporosis. J Bone Miner Res 2003;18:539–43.
[6] Nakamura T, Sugimoto T, Nakano T, Kishimoto H, Ito M, Fukunaga M, et al. Randomized teriparatide [human parathyroid hormone (PTH) 1–34] Once-Weekly Efficacy Research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. J Clin Endocrinol Metab 2012;97:3097–106.
[7] Yoshikawa T, Turner CH, Peacock M, Slemenda CW, Weaver CM, Teegarden D, et al. Geometric structure of the femoral neck measured using dual-energy X-ray absorptiometry. J Bone Miner Res 1994;9:1053–64.
[8] Beck TJ, Ruff CB, Warden KE, Scott Jr WW, Rao GU. Predicting femoral neck strength from bone mineral data. A structural approach. Invest Radiol 1990;25:6–18.
[9] Ahlborg HG, Nguyen ND, Nguyen TV, Center JR, Eisman JA. Contribution of hip strength indices to hip fracture risk in elderly men and women. J Bone Miner Res 2005;20:1820–7.
[10] Rivadeneira F, Zillikens MC, De Laet CE, Hofman A, Uitterlinden AG, Beck TJ, et al. Femoral neck BMD is a strong predictor of hip fracture susceptibility in elderly men and women because it detects cortical bone instability: the Rotterdam Study. J Bone Miner Res 2007;22:1781–90.
[11] Kaptoge S, Beck TJ, Reeve J, Stone KL, Hillier TA, Cauley JA, et al. Prediction of incident hip fracture risk by femur geometry variables measured by hip structural analysis in the study of osteoporotic fractures. J Bone Miner Res 2008;23:1892–904.
[12] LaCroix AZ, Beck TJ, Cauley JA, Lewis CE, Bassford T, Jackson R, et al. Hip structural geometry and incidence of hip fracture in postmenopausal women: what does it add to conventional bone mineral density? Osteoporos Int 2010;21:919–29.
[13] Martin RB, Burr DB. Non-invasive measurement of long bone cross-sectional moment of inertia by photon absorptiometry. J Biomech 1984;17:195–201.
[14] Beck TJ. Extending DXA, beyond bone mineral density: understanding hip structure analysis. Curr Osteoporos Rep 2007;5:49–55.
[15] Beck T. Measuring the structural strength of bones with dual-energy X-ray absorptiometry: principles, technical limitations, and future possibilities. Osteoporos Int 2003;14:S81–8.
[16] Uusi-Rasi Kirsti, Semanick Lisa M, Zanchetta Jose R, Bogado Cesar E, Eriksen Erik F, Sato Masahiko, et al. Effects of teriparatide [rhPTH (1–34)] treatment on structural geometry of the proximal femur in elderly osteoporotic women. Bone 2005;36:948–58.
[17] Lindsay R, Zhou H, Cosman F, Nieves J, Dempster DW, Hodsman AB. Effects of a one-month treatment with PTH(1–34) on bone formation on cancellous, endocortical, and periosteal surfaces of the human ilium. J Bone Miner Res 2007;22:495–502.
[18] Seeman E. Pathogenesis of bone fragility in women and men. Lancet 2002;359:1841–50.
[19] Seeman E. Periosteal bone formation—a neglected determinant of bone strength. N Engl J Med 2003;349:320–3.
[20] Beck TJ, Oreskovic TL, Stone KL, Ruff CB, Ensrud K, Nevitt MC, et al. Structural adaptation to changing skeletal load in the progression toward hip fragility: the study of osteoporotic fractures. J Bone Miner Res 2001;16:1108–19.
[21] Feik SA, Thomas CD, Bruns R, Clement JG. Regional variations in cortical modeling in the femoral mid-shaft: sex and age differences. Am J Phys Anthropol 2000;112:191–205.
[22] Uusi-Rasia K, Semanicka LM, Zanchettab JR, Bogado CE, Eriksenc EF, Sato M, et al. Effects of teriparatide [rhPTH (1–34)] treatment on structural geometry of the proximal femur in elderly osteoporotic women. Bone 2005;36:948–58.
[23] Ito M, Oishi R, Fukunaga M, Sone T, Sugimoto T, Shiraki M, et al. The effects of once-weekly teriparatide on hip structure and biomechanical properties assessed by CT. Osteoporos Int 2014;25:1163–72.
[24] Sato M, Westmore M, Ma YL, Schmidt A, Zeng QQ, Glass EV, et al. Teriparatide [PTH(1–34)] strengthens the proximal femur of ovariectomized nonhuman primates despite increasing porosity. J Bone Miner Res 2004;19:623–9.
[25] Keaveny TM, McClung MR, Wan X, Kopperdahl DL, Mitlak BH, Krohn K. Femoral strength in osteoporotic women treated with teriparatide or alendronate. Bone 2012;50:165–70.

Serum 25-Hydroxyvitamin D Level as an Independent Determinant of Quality of Life in Osteoporosis With a High Risk for Fracture

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ABSTRACT

Background: Deteriorated quality of life (QOL) is a major problem in osteoporotic women. However, little is known regarding the determinants of QOL in patients with osteoporosis.

Objective: Our aim was to explore the role of vitamin D status on QOL score in osteoporosis with high fracture risk.

Methods: Patients were osteoporotic women aged ≥70 years and with ≥1 risk factor for incident fracture, namely prevalent osteoporotic fracture, bone mineral density (BMD) >−3.0 SD of young adult mean, or high bone turnover marker. Health-related QOL was assessed using the Japanese Osteoporosis Quality of Life Questionnaire (JOQOL). When patients were classified into quartiles by total QOL score). Serum 25-hydroxyvitamin D (25[OH]D) level was measured by immunoassay.

Results: A total of 1585 osteoporotic women were included in the study (age range, 70–95 years). Age, body mass index, serum 25(OH)D status (low, normal, or high), bone mineral density, number of prevalent vertebral fractures, presence of hypertension, presence of osteoarthritis, and history of falls were significantly correlated with QOL quartile. Multivariate liner regression analysis indicated that low serum 25(OH)D level (<20 ng/mL) was an independent determinant of total QOL score quartile ($P = 0.0055$). The conventional determinants of QOL—age ($P < 0.0001$), body mass index ($P = 0.0060$), number of prevalent vertebral fractures ($P < 0.0001$), presence of osteoarthritis ($P = 0.0074$), and history of fall ($P = 0.0098$)—were also independent determinants of total QOL score.

Conclusions: These results strongly suggest that low serum 25(OH)D level was a significant determinant of QOL in these osteoporotic women, independently of the conventional factors that reduce QOL. Maintenance of serum 25(OH)D levels >20 ng/mL

*Members of the A-TOP Research Group are listed in the Acknowledgments.

Accepted for publication December 7, 2013.
http://dx.doi.org/10.1016/j.clinthera.2013.12.007