may be required to maintain patients' QOL in osteoporosis. (*Clin Ther.* 2014;36:225–235)

Key words: 25(OH)D, fall, fracture, osteoporosis, QOL.

INTRODUCTION

Osteoporosis is characterized by deteriorated bone strength.[1] It is a national burden in an aging society such as that in Japan, because of the high susceptibility to bone fractures in patients with osteoporosis, which can result in impaired quality of life (QOL),[2–4] and is also associated with increased morbidity and mortality in both white and Asian populations.[5–11] Therefore, the prevention of osteoporotic fractures is a primary end point of treatment because of socioeconomic aspects and patient survival.

Although several kinds of drugs are available to prevent fractures,[12] sufficient prevention of osteoporotic fractures has not been achieved, and an inadequate clinical outcome of osteoporosis treatment has been associated with decreased QOL scores.[13] In this context, maintenance or improvement of patients' QOL is required in clinical practice. Recent progress in the treatment of osteoporosis has indicated that teriparatide administration improves patients' QOL.[14,15] However, the duration of teriparatide use is limited to only 2 years. Bisphosphonates or calcitonin are other options for the improvement of deteriorated QOL.[16] To achieve further improvement of deteriorated QOL, exploration of modifiable risks for the deterioration of QOL would be required.

Until now, several factors related to the deterioration of QOL or disability have been reported, such as age, number of prevalent vertebral fractures, low bone mineral density (BMD), pain, and coexisting osteoarthritis.[17–24] However, there is little known evidence regarding the specific modifiable factors that are associated with patients' QOL.

Vitamin D insufficiency and deficiency, which are common in the elderly population, are directly connected with various morbidities in elderly people.[25,26] Bone fractures, falls, immune dysfunction, and even increasing mortality have been reported to be associated with vitamin D insufficiency.[10] Moreover, the effects of vitamin D supplementation on the prevention of fractures,[27] falls,[28,29] and cancers[30,31] and on physical function[32,33] have been extensively investigated. These reports raise an expectation that serum 25(OH)D level may have an effect on individual QOL. However, little had been known regarding the relationship between serum 25(OH)D levels and QOL in osteoporosis. Our aim was to explore the role of vitamin D status on QOL score in osteoporosis with high fracture risk.

PATIENTS AND METHODS

Ethical Considerations

The present study was conducted in accordance with the Declaration of Helsinki. All of the patients provided written informed consent. The protocol was reviewed and approved by a central ethical committee (chair, Dr. Rikushi Morita) and was also reviewed by the institutional review board at each institution as necessary.

Inclusion and Exclusion Criteria

Eligible patients were outpatients with postmenopausal osteoporosis enrolled in the Japanese Osteoporosis Intervention Trial (JOINT)-02, which was conducted to verify the effect of combination therapy with alendronate and alfacalcidol compared to monotherapy with alendronate alone nationwide in Japan.[34] Patients were diagnosed based on the diagnostic criteria established by the Japanese Society for Bone and Mineral Research,[35] aged ≥70 years, and had ≥1 risk factor for incident fracture (1–4 prevalent vertebral fractures between T4 and L4, BMD ≤ percentage of the young adult mean [%YAM] −3.0 SD, or high bone turnover marker). The participants in the present study were residents of the local community without high dependency, and institutionalized patients were excluded. We also excluded patients who had metabolic bone diseases other than osteoporosis, severe degenerative deformation of the spine from T4 to L4, hypothyroidism, hyperparathyroidism, or critical illness. Patients who had received some bisphosphonates in the 6 months before enrollment were also excluded from this study because of possible modification of patients' QOL at registration. Patients with dementia were excluded because the patients were required to respond to the QOL questionnaire and to provide written informed consent. All patients were questioned carefully at baseline regarding their previous treatment for osteoporosis (*yes* or *no*) and complications such as hypertension, diabetes mellitus, dyslipidemia, rheumatoid

arthritis, or osteoarthritis. Participants were also questioned regarding history of falls.

Health-Related QOL Measurement

We used the Japanese Osteoporosis Quality of Life Questionnaire (JOQOL), which was established by the Japanese Society for Bone and Mineral Research, to measure and assess QOL in Japanese osteoporotic patients. The JOQOL instrument consists of 6 domains and 38 items, based on the Osteoporosis Assessment Questionnaire[36] and the Quality of Life Questionnaire of the European Foundation of Osteoporosis,[37] with some added questions involving Japanese lifestyle. Higher scores indicated better QOL. A validation study of the JOQOL was previously conducted and the reliability and validity of its questionnaire in Japanese osteoporotic patients were verified.[38] A patient's response to each item was scored with a points scale from 0 to 4, and the maximum total score of all the responses was 152 points. The number of items and subscale scores per domain were as follows: pain (5 items; 20 points), activities of daily living (16; 64), recreational and social activity (5; 20), general health (3; 12), posture and figure (4; 16), and fall and psychological effect (5; 20). Each patient was asked to complete a self-report questionnaire at baseline. The total score and subscale scores per domain were calculated and converted into corresponding values on a 100-point scale (0 = poor to 100 = perfect QOL) Japan Clinical Research Support Unit (Tokyo, Japan).

Diagnosis of Prevalent Vertebral Fractures

We collected anteroposterior and lateral radiographs of the thoracic and lumbar spine at baseline. Prevalent vertebral fractures were diagnosed by a central committee without any information on the patients. The diagnoses of the prevalent vertebral fractures were judged semiquantitatively using the diagnostic criteria for prevalent vertebral fractures.[39]

Measurements of Biochemical Parameters

For serum levels of 25(OH)D, intra- and interassay variance were 5.96% to 6.99% and 7.09% to 10.82%, respectively, and the minimal measurement was 3.4 ng/mL. 25(OH)D was measured by immunoassay (DiaSorin Inc, Stillwater, Minnesota) in a central laboratory (SRL, Tokyo, Japan). Serum creatinine level was measured by autoanalyzer at each institution, and estimated glomerular filtration rate (eGFR) was calculated using a formula proposed by the Japanese Society of Nephrology,[40] as follows:

$$\text{eGFR (mL/min/1.73 m}^2) = (194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287}) \times 0.739$$

The eGFR was classified into 3 categories, as follows: ≥ 90 mL/min/1.73 m^2, chronic kidney disease grade 1; 60–<90 mL/min/1.73 m^2, grade 2; and <60 mL/min/1.73 m^2, grade 3.

Measurement of BMD

BMD was measured in each institution by dual-energy x-ray absorptiometry for the lumbar spine, femoral neck, or distal site of the radius, or by microdensitometry for the left second metacarpal bone. The values were expressed in terms of %YAM.[35]

Statistical Analysis

The data for numerical variables are expressed as mean (SD) values. We assessed whether several baseline factors were associated with QOL total and subscale scores. ANOVA was performed to assess differences in continuous variables (age, BMI, eGFR, years since menopause, serum 25[OH]D level, and BMD). Mantel-Haenszel χ^2 test was used to assess differences among categorical variables (number of prevalent vertebral fractures, comorbidity, history of fall, and prior treatment). The determinants of total QOL score were analyzed using an adjusted linear regression model. Moreover, a multiple linear regression model was applied to investigate the relationship between QOL scores (total score and subscale scores) and serum 25(OH)D concentration. A category of serum 25(OH)D of ≥ 30 ng/mL was used as the reference group. This analysis was performed on a 2-step basis, as follows: first, unadjusted (model 1); second, adjusted for all confounders that had the association of P value <0.1 with total QOL score (model 2) using a multiple linear regression model. All analyses were performed using SAS release 9.1 software (SAS Institute Inc, Cary, North Carolina).

RESULTS

Background Characteristics of the Patients

A total of 1710 patients who responded to the QOL questionnaire from 186 institutions nationwide participated in the present study. The participants in whom the serum 25(OH)D levels were not measured were excluded (n = 125). Finally, a total of 1585

patients were recruited to the present study. The mean age was 76.5 years (range, 70–95 years), and the mean (SD) BMI was 23.2 (3.6) and eGFR was 68.2 (18.4) mL/min/1.73 m^2. Mean BMD (%YAM) of all measured sites was <70% of Japanese diagnostic threshold of osteoporosis. The mean (SD) total QOL score was 65.8 (15.3). About 60% of the patients had ≥1 prevalent vertebral fracture. A total of 1138 of 1585 participants (71.8%) had ≥1 comorbidity other than osteoporosis. The mean serum 25(OH)D level was 23.7 ng/mL. Serum 25(OH)D levels were divided into three categories, namely <20 ng/mL (n = 376, 23.7% as low group), 20 to 30 ng/mL (n = 982, 62.0% as moderately low group) and ≥30 ng/mL (n = 227, 14.3% as normal/reference group).

Association Between Quartiles of QOL Score and Baseline Variables

The total QOL score was classified into quartiles as shown in Table I.

ANOVA between the quartiles of total QOL score and the numerical variables indicated that the baseline age ($P < 0.0001$), BMI ($P = 0.0043$), 25(OH)D ($P < 0.0001$), and BMD at the radius ($P = 0.0027$) and metacarpal bone ($P = 0.0034$) were associated with quartiles of total QOL score (Table I). The trend analysis using Mantel-Haenszel χ^2 test between the quartiles of total QOL score and categorical variables is indicated in Table II. The baseline number of prevalent vertebral fractures ($P < 0.0001$), existing comorbidities ($P = 0.016$), especially hypertension ($P = 0.010$) and osteoarthritis ($P < 0.0001$), and history of fall ($P = 0.0003$) were associated with the quartiles of total QOL score. A history of having received any treatment for osteoporosis before enrollment was not associated with the quartile of QOL ($P = 0.10$) (Table II).

QOL Scores and 25(OH)D Level

The association between serum 25(OH)D levels and total QOL scores is shown in Figure 1. Lower serum 25(OH)D levels were associated with lower QOL score, and this trend appeared prominently in patients with levels <20 ng/mL ($P < 0.0001$) (Figure 1A). In consideration of confounding, the data were adjusted for age, BMI, BMD, number of prevalent

Table I. Association between quartiles* of JOQOL total score and baseline numerical variables (N = 1585).

	1st Quartile		2nd Quartile		3rd Quartile		4th Quartile		
Parameter	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	*P*
QOL score									
Mean ± SD	387	44.8 (10.4)	404	63.5 (3.2)	406	73.2 (2.4)	388	82.7 (3.9)	—
Range		7.9–57.2		57.9–68.4		69.1–77.0		77.6–94.7	
Age, years	387	78.1 (4.8)	404	76.9 (4.7)	406	76.0 (4.7)	388	75.0 (4.3)	<0.0001
BMI, kg/m^2	385	23.5 (4.1)	403	23.3 (3.6)	403	23.3 (3.4)	387	22.7 (3.2)	0.0043
eGFR, mL/min/1.73m^2	373	68.4 (20.9)	377	68.2 (17.5)	378	66.9 (17.3)	358	69.1 (17.4)	0.89
YSM	354	49.1 (4.8)	387	49.1 (4.1)	378	48.6 (4.7)	370	49.0 (4.3)	0.35
25(OH)D, ng/mL									
Total sample	387	22.7 (6.2)	404	23.4 (5.5)	406	24.1 (5.4)	388	24.6 (5.5)	<0.0001
Winter +	175	22.3 (6.5)	176	23.4 (5.3)	175	24.4 (4.8)	176	24.0 (5.3)	0.0003
Summer++	212	23.1 (6.0)	228	23.4 (5.6)	231	23.9 (5.8)	212	25.0 (5.6)	0.0018
BMD, %YAM									
Lumbar	116	64.2 (12.7)	115	64.1 (11.4)	101	64.3 (11.7)	105	65.6 (10.9)	0.40
Radial	113	58.6 (11.3)	151	60.9 (11.2)	185	62.8 (10.4)	179	62.2 (9.7)	0.0027
Metacarpal, Al mm equivalent	115	65.5 (10.4)	100	68.7 (10.0)	97	67.3 (9.1)	83	70.5 (11.1)	0.0034
Femoral neck	21	63.8 (9.4)	15	56.5 (10.2)	4	65.1 (10.2)	12	64.1 (3.8)	0.74
All sites	365	62.9 (11.7)	381	63.7 (11.4)	387	64.4 (10.6)	379	65.0 (10.7)	0.0061

Al = aluminum; JOQOL = Japanese Osteoporosis Quality of Life Questionnaire; Summer++ = 25(OH)D measured during April to September; Winter + = 25(OH)D measured during October to March; YSM = years since menopause.
*QOL quartiles were defined by the following QOL total score ranges: quartile 1, 7.9–57.2 (poor); quartile 2, 57.9–68.4 (fair); quartile 3, 69.1–77.0 (good); quartile 4: 77.6–94.7 (very good).

Table II. Association between quartiles* of JOQOL total score and baseline categorical variables (N = 1585). Values are number (%) of patients.

Categorical Variable	1st Quartile (n = 387)	2nd Quartile (n = 404)	3rd Quartile (n = 406)	4th Quartile (n = 388)	P
No. of prevalent vertebral fractures					<0.0001
0	118 (30.5)	145 (35.9)	184 (45.3)	201 (51.8)	
1	114 (29.5)	133 (32.9)	125 (30.8)	111 (28.6)	
≥2	154 (39.8)	126 (31.2)	97 (23.9)	74 (19.1)	
Comorbidities	295 (76.2)	286 (70.8)	296 (72.9)	261 (67.3)	0.016
Hypertension	189 (48.8)	187 (46.3)	184 (45.3)	153 (39.4)	0.010
Diabetes mellitus	46 (11.9)	31 (7.7)	36 (8.9)	37 (9.5)	0.38
Dyslipidemia	73 (18.9)	78 (19.3)	85 (20.9)	87 (22.4)	0.18
Rheumatoid arthritis	1 (0.3)	5 (1.2)	2 (0.5)	5 (1.3)	0.26
Osteoarthritis	166 (42.9)	148 (36.6)	159 (39.2)	107 (27.6)	<0.0001
History of fall	61 (15.8)	40 (9.9)	28 (6.9)	34 (8.8)	0.0003
History of pretreatment	130 (33.6)	137 (33.9)	125 (30.8)	112 (28.9)	0.10

JOQOL = Japanese Osteoporosis Quality of Life Questionnaire.
*Quartiles were defined by the following QOL total score ranges: quartile 1, 7.9–57.2 (poor); quartile 2, 57.9–68.4 (fair); quartile 3, 69.1–77.0 (good); quartile 4: 77.6–94.7 (very good).

vertebral fractures, hypertension status, osteoarthritis status, and history of fall (Figure 1B). After adjustment, although the total QOL scores for patients with levels <20 ng/mL were slightly higher, the scores consistently deteriorated in those patients compared with the group with higher serum 25(OH)D levels ($P = 0.0013$) (Figure 1B).

Determinants of Total QOL Score

The determinants of total QOL score, as analyzed using an adjusted linear regression model, are indicated in Table III. Age ($P < 0.0001$), BMI ($P = 0.0060$), low 25(OH)D (<20 ng/mL) ($P = 0.0055$), number of prevalent vertebral fractures ($P < 0.0001$), presence of osteoarthritis ($P = 0.0074$), and history of fall ($P = 0.0098$) were significant independent determinants of total QOL score, whereas the relationship between hypertension and total QOL score was not significant after adjustment for the confounding factors.

The relationship between serum 25(OH)D levels and each domain of QOL are shown in Table IV. The scores on the domains of activities of daily living and recreational and social activity domains in the patients with serum 25(OH)D levels <20 ng/mL were significantly lower compared with those in the group with serum 25(OH)D levels ≥30 ng/mL (reference group) in model 1 (unadjusted) (estimates [95% CI], –5.92 [–9.09 to –2.75] and –6.42 [–9.98, - to –2.87], respectively; $P = 0.0003$ and 0.0004). After adjustment for age, BMI, BMD, number of prevalent vertebral fractures, hypertension status, osteoarthritis status, and history of fall (model 2), the subscale scores of activities of daily living and recreational and social activity domains in the group <20 ng/mL were significantly lower compared with those in the reference group (estimates [95% CI], –3.62 [–6.61 to –0.63] and –5.59 [–9.17 to –2.01]; $P = 0.018$ and 0.0022). These findings were not observed in the other 4 domains (pain, general health, posture and figure, and fall and psychological effect). Furthermore, the subscale scores of all domains were not significantly lower in the group with serum 25(OH)D level 20 to <30 ng/mL compared with those in the reference group.

DISCUSSION

We investigated the determinants of QOL in osteoporotic women with high fracture risk. Age, number

Serum 25(OH)D(ng/mL)	<12	12-16	16-20	20-24	24-28	28-32	32-36	36<
n	27	95	254	376	412	304	87	30

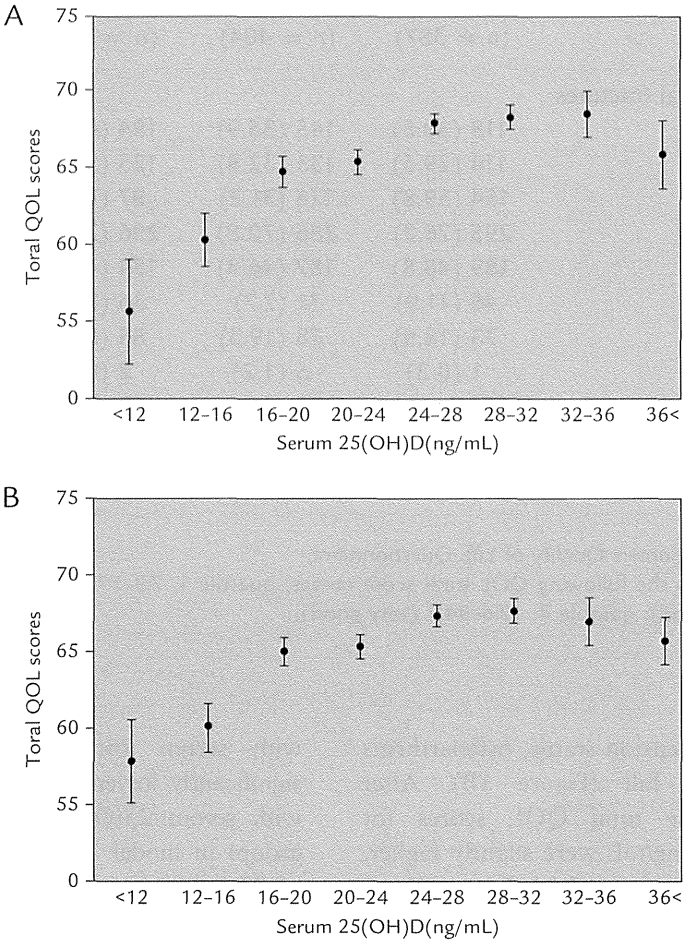

Figure 1. Relationship between total quality-of-life (QOL) scores and serum 25-hydroxyvitamin D (25[OH]D) concentrations (N = 1585). (A) Unadjusted ($P < 0.0001$); (B) Adjusted for age, number of prevalent vertebral fractures, and falls ($P = 0.0013$). The lower serum 25(OH)D levels were associated with the lower total QOL scores.

of prevalent vertebral fractures, BMI, history of fall, osteoarthritis status, and BMD were independently associated with QOL quartile in these osteoporotic patients. Number of prevalent vertebral fractures is a well-known factor of disability in osteoporotic patients.[17,18] Osteoarthritis in the vertebrae or knee joints is a risk for deteriorated QOL in the general population.[19,20] Obese patients have been reported to have impaired QOL scores,[41] and the association of osteoarthritis with obesity has been well-documented. In addition to the presence of osteoarthritis, we recently reported that obesity is a risk factor for vertebral fracture in postmenopausal women.[42] The results of the present study did not conflict with those previous data, although the present results were limited only to osteoporosis with high fracture risk.

In addition to the conventional factors known to deteriorate QOL, the present study demonstrated that low serum 25(OH)D (<20 ng/mL) was associated with QOL quartile. Wicherts et al[43] reported that serum 25 (OH)D levels were associated with physical performance in elderly people. Patients with lower vitamin D level showed poorer QOL scores in Turkish osteoporotic women.[44] The present study, together with the previous

Table III. Determinants of total QOL score (N = 1585).*

Determinant	Point Estimate	95% CI	P
Age (5-y increments)	-3.08	-3.86 to -2.30	<0.0001
BMI (5-kg/m^2 increments)	-1.50	-2.56 to -0.43	0.0060
25(OH)D, ng/mL			
<20 (low)	-3.41	-5.81 to -1.00	0.0055
20-<30 (moderately low)	0.083	-2.02 to 2.19	0.94
≥30 (normal/reference)	Reference	—	—
BMD (YAM%) (5% increments)	0.29	-0.054 to 0.62	0.10
No. of prevalent vertebral fractures	-2.98	-3.87 to -2.09	<0.0001
Hypertension	-0.76	-2.24 to 0.72	0.31
Osteoarthritis	-2.06	-3.56 to -0.55	0.0074
History of fall	-3.13	-5.51 to -0.76	0.0098

25(OH)D = 25-hydroxyvitamin D; BMD = bone mineral density; BMI = body mass index; QOL = quality of life; YAM% = percentage of the young adult mean.
*The determinants for total QOL score were analyzed by adjusted linear regression model, using the 8 baseline factors significantly associated with total QOL score.

studies, may indicate that a direct connection between the QOL and serum 25(OH)D level may exist, and therefore that the maintenance of adequate serum 25(OH)D level is important in terms of fracture prevention or maintaining better QOL. The difference in total QOL scores in the lowest and highest groups of serum 25(OH)D was ~10 points, which has been considered to have clinical and social relevance.[45]

Recent reports led us to review the biological actions of vitamin D. It has been reported that vitamin D is connected to a wide range of biological actions to regulate many activities, such as cell proliferation and activity of the immune, cardiovascular, and muscular systems.[25,26] Several observational studies have pointed to an association between serum 25(OH)D level and falls and/or frailty, mainly focused on elderly people. Among them, a prospective cohort study from Amsterdam, the Netherlands, indicated that serum levels <10 ng/mL were associated with a greater risk for falls.[46] Other observational studies have suggested that serum 25(OH)D levels <20 ng/mL are associated with greater frailty indices and likely an increased risk for falls among elderly people, with considerable heterogeneity.[47] The inconsistencies of the effects of vitamin D on frailty or falls may be related to the differences in calcium intake, assay method of 25(OH)D, or the measurements of outcomes. Although the patients in the present study were limited to osteoporotic patients with a high risk for fracture, a significant correlation between QOL quartile and serum 25(OH)D level was observed after adjustment for confounding factors. Japan is a known country, where the calcium intake is lower than the Western countries. Since low calcium intake can be facilitate the symptoms of vitamin D deficiency, it may be possible that the effect of low vitamin D exposure on QOL was more obvious in Japan than in Western people.[47]

Our baseline analysis had several limitations. First, the nutrition status of patients, sun exposure, frailty, and similar factors were not measured, despite their influence on serum 25(OH)D levels. Our results may thus have included several additional confounding factors. Second, the results of this study may not apply to the entire osteoporotic population because the inclusion criteria in this study were limited to osteoporotic patients with a high risk for fracture and aged ≥70 years. Moreover, male osteoporotic patients were excluded from the present study. Therefore, expansion of the study to a larger osteoporotic population that includes both sexes may be required in the future. However, most of the participants in the

Table IV. Association between QOL subdomain scores and serum 25(OH)D using multiple linear regression model (N = 1585).

Domain and Score (mean [SD])/ 25(OH)D Class, ng/mL	Unadjusted			Adjusted*		
	Point Estimate	95% CI	*P*	Point Estimate	95% CI	*P*
Pain (70.4 [22.2])						
<20 (low)	-1.74	-5.44 to 1.96	0.36	-1.48	-5.24 to 2.29	0.44
20-<30 (moderately low)	1.10	-2.13 to 4.33	0.50	1.28	-2.01 to 4.56	0.45
≥30 (normal/reference)	Ref			Ref		
Activities of daily living (79.9 [19.7])						
<20 (low)	-5.92	-9.09 to -2.75	0.0003	-3.62	-6.61 to -0.63	0.018
20-<30 (moderately low)	-0.74	-3.51 to 2.05	0.61	0.30	-2.31 to 2.91	0.82
≥30 (normal/reference)	Ref			Ref		
Recreational and social activity (44.3 [21.6])						
<20 (low)	-6.42	-9.98 to -2.87	0.0004	-5.59	-9.17 to -2.01	0.0022
20-<30 (moderately low)	-0.74	-3.84 to 2.37	0.64	-0.48	-3.61 to 2.64	0.76
≥30 (normal/reference)	Ref			Ref		
General health (42.8 [17.8])						
<20 (low)	-1.03	-3.98 to 1.92	0.49	-0.67	-3.69 to 2.34	0.66
20-<30 (moderately low)	1.02	-1.55 to 3.60	0.44	1.40	-1.23 to 4.03	0.30
≥30 (normal/reference)	Ref			Ref		
Posture and figure (61.3 [22.3])						
<20 (low)	-2.80	-6.49 to 0.89	0.14	-2.07	-5.74 to 1.60	0.27
20-<30 (moderately low)	-0.85	-4.08 to 2.37	0.60	-2.07	-3.47 to 2.93	0.87
≥30 (normal/reference)	Ref			Ref		
Fall and psychological effect (59.2 [20.8])						
<20 (low)	-2.86	-6.29 to 0.57	0.10	-2.48	-6.00 to 1.04	0.17
20-<30 (moderately low)	-0.13	-3.13 to 2.87	0.93	0.14	-2.93 to 3.21	0.93
≥30 (normal/reference)	Ref			Ref		
Total score (65.8 [15.3])						
<20 (low)	-4.62	-7.09 to -2.16	0.0002	-3.41	-5.81 to -1.00	0.0055
20-<30 (moderately low)	-0.47	-2.63 to 1.69	0.67	0.083	-2.02 to 2.19	0.94
≥30 (normal/reference)	Ref			Ref		

25(OH)D = 25-hydroxyvitamin D; QOL = quality of life; Ref = reference.
*Adjusted for age, body mass index, bone mineral density, number of prevalent vertebral fractures, hypertension, osteoarthritis, and history of fall.

present study were managed by a primary care clinic, and almost 70% of the patients had ≥1 comorbidity, some of which (eg, diabetes mellitus, rheumatoid arthritis, osteoarthritis) may be excluded from drug-development trials. Therefore, the evidence obtained from the present study may be more easily applicable to patients with osteoporosis with a high fracture risk visiting a general practice clinic than the evidence obtained from drug-development trials. Third, it has been well-established that serum levels of 25(OH)D show significant seasonal variation, which may have been a considerable confounder when the relationship between QOL score and serum 25(OH)D level was evaluated. In addition, latitude of the residency may also be affected by serum 25(OH)D level. However, the present study design did not include considerations of these confounders. Therefore, adjustments for these confounders on the present core results may be

insufficient. Finally, because the present study was performed with a cross-sectional design, whether a low serum 25(OH)D level is a causative factor of deteriorated QOL remains uncertain.

Although several limitations were present in this study, our results may lead us to promote improvement of vitamin D nutrition in osteoporotic patients with a high fracture risk. Several studies have assessed the effects of vitamin D on QOL in the elderly population, using standard instruments of QOL.[48–50] However, these studies were not focused on QOL in osteoporosis. The discordant results may have been the result of different populations and different outcomes. Further prospective interventional study in osteoporosis as to whether vitamin D supplementation with or without sufficient calcium intake promotes patients' QOL will be required.

CONCLUSIONS

The present findings regarding the association of QOL score with serum 25(OH)D level may support the recommendation to measure and maintain an adequate level of serum 25(OH)D in osteoporotic patients to prevent the deterioration of QOL in addition to preventing fractures.

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CONFLICTS OF INTEREST

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ORIGINAL ARTICLE

The effects of once-weekly teriparatide on hip structure and biomechanical properties assessed by CT

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Abstract
Summary Once-weekly administration of 56.5 μg teriparatide improved cortical bone parameters and biomechanical parameters at the proximal femur by CT geometry analysis.
Introduction The aim of this study was to evaluate the effects of weekly administration of teriparatide [human PTH (1–34)] on bone geometry, volumetric bone mineral density (vBMD), and parameters of bone strength at the proximal femur which were longitudinally investigated using computed tomography (CT).
Methods The subjects were a subgroup of a recent, randomly assigned, double-blind study (578 subjects) comparing the anti-fracture efficacy of a once-weekly subcutaneous injection of 56.5 μg teriparatide with placebo (TOWER trial).
Results Sixty-six ambulatory postmenopausal women with osteoporosis were enrolled at 15 study sites having multidetector row CT, and included women injected with teriparatide (n=29, 74.2±5.1 years) or with placebo (n=37, 74.8±5.3 years). CT data were obtained at baseline and follow-up scans were performed at 48 and 72 weeks. The data were analyzed to obtain cross-sectional densitometric, geometric, and biomechanical parameters including the section modulus (SM) and buckling ratio (BR) of the femoral neck, inter-trochanter, and femoral shaft. We found that once-weekly teriparatide increased cortical thickness/cross-sectional area (CSA) and total area, and improved biomechanical properties (i.e., decreasing BR) at the femoral neck and shaft. Teriparatide did not change the cortical perimeter.
Conclusions Our longitudinal analysis of proximal femur geometry by CT revealed that once-weekly administration of 56.5 μg teriparatide improved cortical bone parameters at the femoral neck and shaft and also improved biomechanical parameters.

Keywords Once-weekly injection · Osteoporosis · Proximal femur geometry · Quantitative computed tomography · Teriparatide

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Introduction

Parathyroid hormone (PTH) stimulates bone formation and resorption and can increase or decrease bone mass, depending on the dose and timing of administration. Continuous infusions and daily subcutaneous injections of teriparatide stimulate bone formation but have distinct effects on bone

resorption and bone mass [1, 2]. Daily injections of 20 and 40 μg teriparatide increased the bone mineral density (BMD) at the lumbar spine by 9 and 13 %, and reduced the risk of incident vertebral fractures by 65 and 69 % as relative risk reduction, respectively, as compared with placebo [3].

Weekly injections of 56.5 μg teriparatide have been shown to increase BMD at the lumbar spine by 8.1 % after 48 weeks of treatment as determined by dual energy X-ray absorptiometry (DXA) [4]. Anti-fracture efficacy of once-weekly subcutaneous injection of 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 [5]. Vertebral fracture risk was reduced by 80 % as relative risk reduction.

Daily treatment with teriparatide reduced the risk of non-vertebral fractures by 35 to 40 % at the 20 and 40 μg dose, respectively, and reduced the risk of non-vertebral fragility fractures by 53 and 54 %, respectively [3]. Weekly treatment with teriparatide reduced the risk of clinical fragility fractures include non-vertebra by 67 % [5].

The bone geometry in the proximal femur is thought to be strongly related to bone strength, and our previous studies showed that proximal femur geometrical parameters could predict the incidence of neck fracture or inter-trochanter fracture [6].

The reason for reduced risk of non-vertebral fracture may be explained by changes in structure and biomechanical properties by teriparatide treatment. Therefore, it is important to evaluate changes in structure and mechanical properties in each treatment regimen of teriparatide compared to the placebo.

As a surrogate endpoint of the TOWER trial, computed tomography (CT) has been applied to evaluate and compare the effects of teriparatide versus placebo on proximal femur, since CT evaluation is considered to be a suitable cortical bone assessment. The purpose of this study was to investigate the effect of once-weekly injection of 56.5 μg teriparatide on bone geometry, volumetric bone density, and bone strength parameters of the proximal femur, using CT.

Methods

Subjects

Subjects in this study were a subset of the original TOWER trial [5], and constituted ambulatory female patients with osteoporosis enrolled at 15 study sites equipped with multidetector row CT (MDCT) to measure hip BMD, bone geometry, and biomechanical indices. All subjects in this study fulfilled the inclusion and exclusion criteria of the original TOWER trial. Subjects with one to five vertebral fractures with low BMD (T-score≤−1.67) at either the lumbar spine (L2–L4), femoral neck, total hip, or radius measured by dual-energy X-ray absorptiometry (DXA) or the right second metacarpal bone measured by radiographic absorptiometry were eligible. Subjects with diseases or using drugs affecting bone or calcium metabolism were excluded. The subjects were randomly divided into two groups, either weekly subcutaneous injection of 56.5 μg teriparatide or placebo for 72 weeks. All subjects received daily supplements of 610 mg calcium, 400 IU vitamin D_3, and 30 mg magnesium.

The original 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 written informed consent before enrollment.

CT data acquisition

CT data were obtained at baseline and follow-up scans were performed at 48 and 72 weeks of treatment, using the scanning and reconstruction protocol previously described [7]. The scanning conditions (X-ray energy, 120 to 140 kV; X-ray current, 250 mA; rotation speed, 0.8 to 1.0 s/rot; beam pitch, 0.5625 to 0.9375) and reconstruction parameters were predefined for each type of CT scanner. Beam pitch is defined as the ratio of table feed per rotation to the collimation, where collimation is the product of slice-thickness and the number of slices in each rotation. Field of View (FOV) was defined as 350 mm to cover bilateral proximal femur regions. In-plane spatial resolution of 0.625 to 0.652 mm and reconstructed slice thickness of 0.500 to 0.625 mm were adjusted according to CT scanner type. The CT values were converted to bone mineral scale by using a solid reference phantom, B-MAS200 (Fujirebio Inc., Tokyo, Japan) containing hydroxyapatite (HA) at 0, 50, 100, 150, and 200 mg/cm^3.

The MDCT scanners used in this study originally included four Asteion 4, one Aquilion 16 TSX-101A, one Aquilion 32, and three Aquilion 64 scanners (Toshiba Medical Systems Corporation); two LightSpeed Ultra_16, one LightSpeed VCT_64, and one BrightSpeed Elite_16 scanner (GE-Yokogawa Medical); and one Somatom 16, and one Somatom 64 scanner (Siemens, AG).

Scanner cross-calibration

Good linear correlations between the CT values and HA concentrations were demonstrated (r=0.993 to 1.000; p< 0.0006 to 0.0001) in all CT scanners. Differences in CT values according to X-ray energy were corrected using the reference phantom to convert CT values to HA equivalent values. However, it was necessary to confirm the longitudinal stability of the CT values of the threshold value used to define the cortical bone.

Quality assurance (QA) scans with a Type 3 Mindways Phantom (Mindways Software, Austin, TX, USA) were performed before and after study measurements took place at the individual clinical sites in order to adjust for longitudinal changes of the detector. QA measurements were evaluated according to the quantitated computed tomography (QCT)-Pro QA Guide from Mindways. There was no drift from baseline to the completion of treatment in any CT apparatus.

Subject positioning for CT scanning

Subjects were scanned in the supine position with the reference phantom beneath them and placed so as to cover a region from the top of the acetabulum to 4 cm below the bottom of the lesser trochanter in each hip joint (average slice number was 298). Buffer material to protect artifact, such as a bolus bag or blanket, were placed between the subject and the CT calibration phantom. The subject's hands and arms were placed over their head or as high on the chest as was comfortable to avoid interfering with the scan area. The CT scanner table height was set to the center of the greater trochanter.

Analysis of BMD, bone geometry, and biomechanical properties obtained by CT

Subject data were evaluated with QCT-Pro software v4.1.3 with the QCT-Pro Bone Investigational Toolkit v2.0 (BIT) (Mindways Software) for the femoral neck, inter-trochanter, and femoral shaft regions. All measurements were analyzed by a radiologist (M. Ito) blinded to treatment-group assignment.

QCT-Pro CTXA proximal femur exam analysis

The exact 3D rotation of the femur and the threshold setting for defining the bone contours appeared to be the two most critical steps for achieving accuracy and reproducibility in the automated procedures performed by QCT-Pro [7, 8]. The outer cortical margin was defined using uniform HA equivalent BMD values.

The femoral neck axis was identified visually and also automatically with the "Optimize FN Axis" algorithm. Using the eccentricity registration method, a series of 10 reformatted 1-mm slices was positioned perpendicularly to the neck axis. The definitions of inter-trochanter and femoral-shaft cross-section are consistent with the DXA-based hip structure analysis methods developed by Tom Beck [9]. All steps were compared visually across all visits and repeated if the positioning did not appear to be accurate.

The eccentricity registration method was applied to define the volume of interest (VOI) consisting of six reformatted 1-mm slices oriented perpendicular to the neck axis. QCT BIT processing was then performed with a fixed-bone threshold for cortical separation set to 350 mg/cm^3 for all subjects and visits. This application was used to measure hip axis length (HAL), femoral neck angle (FNA), and neck width, vBMD, cross-sectional area (CSA), and cross-sectional bone mass of the femoral neck, inter-trochanter, and femoral shaft (total and cortical regions). Cortical thickness and perimeter were also measured. Biomechanical properties were also derived from the cross-sectional parameters of the femoral neck, inter-trochanter, and shaft.

Analysis of cross-sectional bone geometry and volumetric BMD

The cross-sectional femoral neck data were based on the geometrical axis to calculate cortical CSA (in square centimeter), total CSA (in square centimeter), volumetric cortical BMD (cortical vBMD; in milligram per cubic centimeter), total volumetric BMD (total vBMD; in milligram per cubic centimeter), total bone mass (in gram), and cortical bone mass (in gram). In this study, total CSA was defined as the estimated total mineralized area. Cortical thickness (in millimeter) and cortical perimeter (in centimeter) were also derived.

Biomechanical parameters

Because biomechanical parameters were determined on the principal axis, the cross-sectional moment of inertia (CSMI; in millimeters to the fourth power), the section modulus (SM; in cubic millimeter) and the buckling ratio (BR) were calculated from bone density and geometrical data. The CSMI is defined by the integration of the products of incremental CSA and the square of their distance from the center of mass (centroid). The SM is the ratio of CSMI to the maximal distance of the material from the centroid, which is directly related to strength with respect to a corresponding bending stress. Due to local buckling, failure occurs on the compressive surface, and BR was calculated in this study as the maximal distance from the centroid divided by the average cortical thickness [9].

Reproducibility of the analysis done by the QCT-Pro program was calculated by using five repeated measurements with visual matching each time from CT data sets without visible artifacts from seven healthy subjects. The coefficient of variation, as determined by the root mean square standard deviation divided by the mean, was 1.49 % for total vBMD, 2.63 % for cortical vBMD, 1.12 % for total mass, 1.71 % for total CSA, 2.11 % for cortical CSA, 2.11 % for cortical perimeter, and 3.58 % for cortical thickness at the femoral neck [10].

Statistics

All statistical analyses were performed on subjects who had been randomized and had evaluable observations for QCT

assessment both at baseline and post-dose (48 or 72 weeks). Paired and Student's t tests, and chi-square test were used and Pearson's correlation coefficients are shown. All p values calculated in the analysis were two-sided and were not adjusted for multiple testing. Statistical analyses were done with SAS version 9.1 (SAS Institute, Cary, USA).

Results

A total of 66 subjects were enrolled and randomly assigned to two treatment groups. There were 29 in the teriparatide group (age 66 to 83 years; mean ± SD, 74.2±5.1 years) and 37 in the placebo group (age 66 to 88 years, 74.8±5.3 years). Table 1 shows the background of subjects and bone 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 bone geometry parameters

Baseline and the observed change of bone geometry parameters are shown in Table 2. There were no significant differences at baseline for any bone geometry parameter at the femoral neck, inter-trochanter, and femoral shaft between the teriparatide and placebo groups. Compared to baseline, weekly teriparatide significantly increased cortical thickness at the femoral neck (3.5 %, 48 weeks) and shaft (2.6 %, 72 weeks). Cortical CSA increased at the inter-trochanter (3.8 %, 48 weeks) and femoral shaft (2.7 %, 72 weeks). Total CSA increased at the inter-trochanter (3.8 % at 48 weeks; 4.7 %, 72 weeks) and femoral shaft (2.5 %, 72 weeks). Cortical vBMD decreased at the femoral neck (1.2 %, 72 weeks) and inter-trochanter (1.5 %, 72 weeks). BR was also decreased at the femoral shaft (3.3 %, 72 weeks). There was no change in cortical perimeter at any site. There were no significant changes observed in the placebo group except for an increase in BR at the inter-trochanter (4.3 %, 48 weeks).

Table 1 Subject baseline demographics and bone characteristics

	Teriparatide (n=29)	Placebo (n=37)
Age (years)	74.2±5.1	74.8±5.3
Body height (cm)	147.8±5.1	147.5±5.5
Body weight (kg)	50.9±8.4	49.1±8.5
Body mass index (BMI) (kg/m^2)	23.3±3.5	22.5±3.5
Years after menopause (years)	24.6±6.5	25.2±6.6
Bone mineral density (T-score)		
Lumbar spine (L2–4)	−2.6±1.0	−2.8±0.8
Femoral neck	−2.4±0.7	−2.6±0.7
Femoral total hip	−2.0±1.0	−2.5±1.2
Number of prevalent vertebral fractures	1.6±1.1	1.3±1.3

Bone mineral density was measured by dual X-ray absorptiometry

Data are mean ± SD

Two subjects who were diagnosed with a BMD evaluation at the radius or metacarpal bone in the teriparatide group and one subject evaluated at the metacarpal bone in the placebo group were included

Effect of teriparatide on cortical thickness, cortical and total CSA, and cortical perimeter compared to placebo

Comparisons of cortical thickness, CSA, and perimeter between the two groups are shown in Fig. 1. Significantly higher cortical thickness was observed in the teriparatide group at the femoral neck (48 and 72 weeks) and shaft (72 weeks) (Fig. 1a). Significantly higher cortical CSA at the inter-trochanter (at 48 weeks) and at the femoral neck (72 weeks) were observed in the teriparatide group (Fig. 1b). Significantly higher total CSA at the inter-trochanter (48 and 72 weeks) and the femoral shaft (72 weeks) were observed in the teriparatide group (Fig. 1c). No significant differences were observed in the cortical perimeters between the teriparatide and placebo groups at any measurement site (Fig. 1d).

In summary, both cortical thickness and CSA increased in all three regions following treatment with teriparatide and decreased in the placebo group. In contrast, there was no change in cortical perimeter following once-weekly injections of teriparatide.

Effect of teriparatide on cortical and total vBMD compared to placebo

The comparison of cortical and total vBMD between the teriparatide and placebo groups is shown in Fig. 2. No significant differences in cortical vBMD were observed between the groups. A significant higher total vBMD in the teriparatide group was observed at the inter-trochanter (Fig. 2b).

Effect of teriparatide on biomechanical parameters compared to placebo

The differences in biomechanical parameters are shown in Fig. 3. SM changes in the teriparatide group at the three measurement sites were positive but not significant (Fig. 3a). BR values in the teriparatide group at the femoral neck (48 and 72 weeks) and shaft (72 weeks) were significantly lower compared to placebo (Fig. 3b).

Relationship between changes in cortical thickness and other parameters

In order to understand the relationships between the parameters, the correlations between the percent changes in cortical

Table 2 Baseline QCT measurements and the percent changes at 48 and 72 weeks

Site	Parameter	Teriparatide			Placebo		
		(n=29)			(n=37)		
		Baseline	48 weeks	72 weeks	Baseline	48 weeks	72 weeks
Femoral neck	Cortical thickness (mm)	1.47±0.24	3.5±7.1*	3.6±9.0	1.52±0.26	−0.5±6.8	−0.9±5.1
	Cortical CSA (cm^2)	0.86±0.15	2.8±7.6	2.2±7.9	0.90±0.15	−0.6±6.1	0.0±5.2
	Total CSA (cm^2)	1.22±0.21	2.2±7.1	3.2±7.3	1.28±0.19	−0.2±5.1	0.6±4.8
	Cortical perimeter (cm)	10.96±0.97	−1.6±4.4	−1.4±5.9	10.96±0.93	0.2±3.8	0.1±3.5
	Cortical vBMD (mg/cm^3)	667.00±52.57	−0.6±2.7	−1.2±2.3*	676.84±46.65	−0.2±4.3	−0.8±3.1
	Total vBMD (mg/cm^3)	221.77±31.77	1.0±3.4	0.0±3.8	227.98±35.35	−0.7±4.4	−1.2±3.3
	SM (cm^3)	0.38±0.1	3.4±8.2	2.3±8.8	0.38±0.1	−0.3±8.2	0.6±7.5
	BR	13.96±2.32	−3.2±7.4	−3.0±8.3	13.44±3.22	1.3±6.2	1.8±6.1
Inter-trochanter	Cortical thickness (mm)	1.43±0.26	0.9±5.9	0.7±6.4	1.51±0.29	−2.3±6.6	−0.8±7.7
	Cortical CSA (cm^2)	1.38±0.29	3.8±7.4*	2.9±8.6	1.54±0.33	−1.6±5.6	−0.6±5.5
	Total CSA (cm^2)	2.38±0.45	3.8±8.8*	4.7±9.4*	2.59±0.5	−1.8±5.6	−0.6±4.8
	Cortical perimeter (cm)	16.76±1.15	0.2±3.3	−0.6±2.0	17.12±1.18	0.6±2.4	0.0±2.1
	Cortical vBMD (mg/cm^3)	638.96±48.01	−0.4±2.4	−1.5±2.1**	646.03±44.09	−0.3±2.9	−0.6±2.4
	Total vBMD (mg/cm^3)	186.13±35.97	1.1±3.3	0.7±4.7	196.1±35.7	−1.5±4.5	−1.5±4.8
	SM (cm^3)	0.67±0.18	5.0±15.8	4.1±11.8	0.73±0.18	2.4±12.0	1.8±10.2
	BR	19.71±3.6	2.1±10.2	1.8±10.7	19.26±4.41	4.3±9.5*	2.1±10.1
Femoral shaft	Cortical thickness (mm)	3.71±0.62	0.7±5.1	2.6±4.5*	3.91±0.62	−0.7±4.6	−1.3±3.9
	Cortical CSA (cm^2)	2.22±0.39	1.7±5.2	2.7±3.6*	2.35±0.39	−0.6±4.1	−0.5±3.0
	Total CSA (cm^2)	2.38±0.38	1.7±5.0	2.5±3.4*	2.5±0.39	−0.5±4.0	−0.1±3.0
	Cortical perimeter (cm)	10.27±0.6	0.4±3.8	−0.7±2.5	10.3±0.7	0.2±4.3	0.5±3.2
	Cortical vBMD (mg/cm^3)	879.65±70.77	0.4±2.7	0.1±3.6	892.97±59.03	0.3±4.1	−0.9±3.1
	Total vBMD (mg/cm^3)	461.36±77.37	0.7±5.1	1.1±5.7	482.05±74.95	−0.2±5.2	−1.4±4.3
	SM (cm^3)	0.88±0.18	1.3±5.9	2.7±7.2	0.93±0.2	−0.8±5.2	0.3±4.8
	BR	3.67±0.88	−0.4±7.7	−3.3±5.4*	3.39±0.75	0.9±6.7	1.9±5.3

Data are mean ± SD

QCT quantitated computed tomography, *CSA* cross-sectional area, *vBMD* volumetric bone mineral density, *SM* section modulus, *BR* buckling ratio

* $p<0.05$; ** $p<0.01$ compared with baseline

thickness and those in the other parameters at the femoral neck at 72 weeks were analyzed, since cortical thickness was most significantly improved following once-weekly teriparatide treatment. Percent changes in cortical thickness at the femoral neck had significant positive correlations with percent change of cortical CSA ($r=0.612$, $p<0.0001$), total CSA ($r=0.389$, $p=0.0062$), total vBMD ($r=0.546$, $p<0.0001$), and SM ($r=0.523$, $p=0.0001$) in the teriparatide group. Negative correlations were found between percent changes of cortical thickness and cortical perimeter ($r=-0.561$, $p<0.0001$) or BR ($r=-0.905$, $p<0.0001$) in teriparatide group. The same trends in the correlation between cortical thickness and the other parameters were observed in placebo group. The correlation between percent change in cortical thickness and BR at the femoral neck was higher in the teriparatide group ($r^2=0.82$) than in the placebo group ($r^2=0.54$). There was no significant correlation between the percent change in cortical thickness and that of cortical vBMD in either group.

To visualize the relationships of multiple parameters at the individual level, the percent change in cortical thickness at the femoral neck was plotted on the horizontal axis of each panel in Fig. 4 versus the percent changes in cortical CSA (Fig. 4a), perimeter (Fig. 4b), SM (Fig. 4c), and BR (Fig. 4d), separately for the teriparatide (solid lines) and placebo (dashed lines) groups. Each panel of Fig. 4 is divided into four quadrants and the percentages of closed circles (teriparatide) and open circles (placebo) included in each quadrant are provided in the figure. The linear regression lines are basically the same between the teriparatide and placebo groups. Further, with respect to parameters with positive correlations (Fig. 4a, c), the distribution of individual data in the teriparatide group is significantly different from placebo (cortical CSA: $p=0.0111$, SM: $p=0.0250$); weighted distribution of closed circles (teriparatide) in the first quadrant is high, while the open circles (placebo) are highly distributed in the third quadrant. Similarly, in the case of parameters with negative correlations (Fig. 4b, d), the

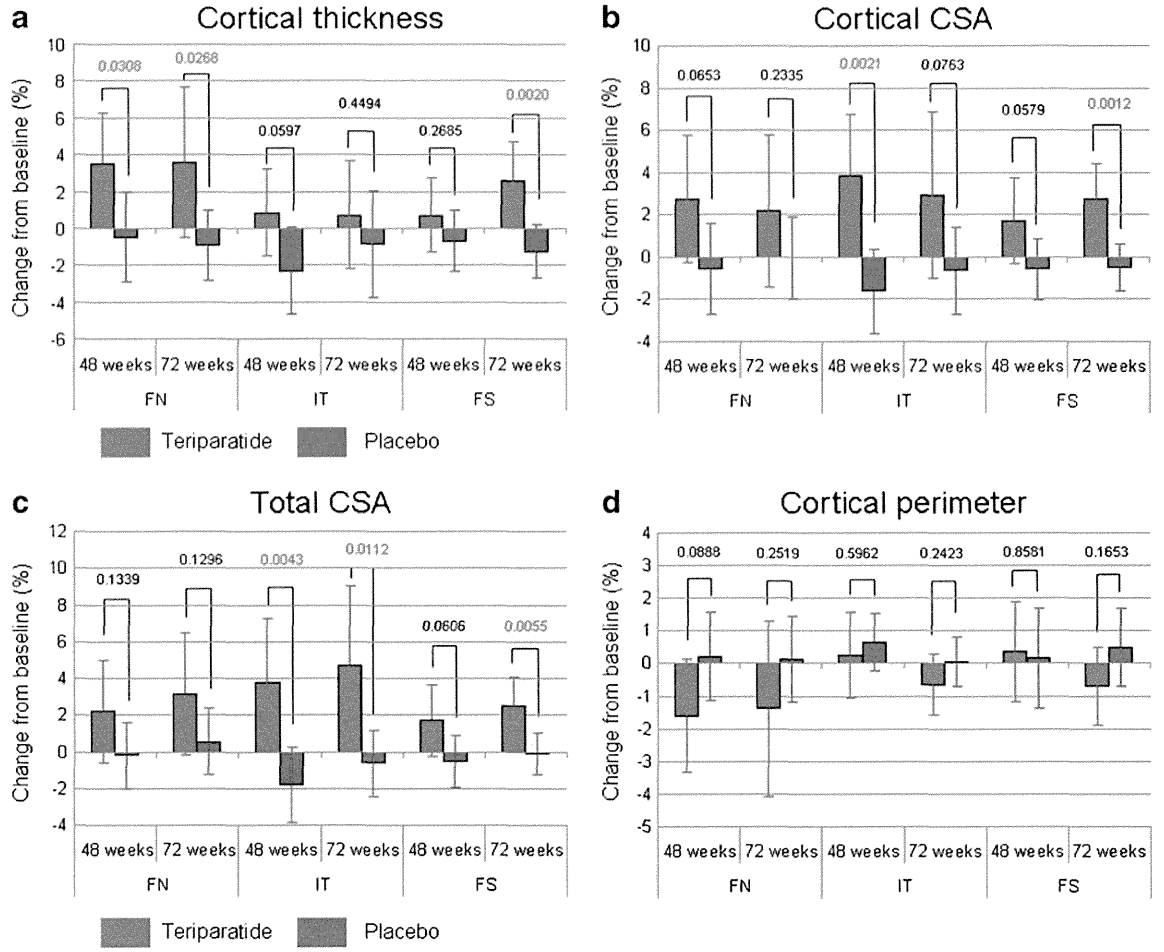

Fig. 1 Mean percent changes and 95 % confidence interval from baseline in cortical thickness (**a**), cortical cross-sectional area (*CSA*) (**b**), total CSA (**c**), and cortical perimeter (**d**) at 48 and 72 weeks of treatment with teriparatide and placebo. Changes at the femoral neck (*FN*), inter-trochanter (*IT*), and femoral shaft (*FS*) are shown. *Values on top of each panel* indicate *p* values (between teriparatide and placebo group). *Red* and *blue bars* correspond to teriparatide and placebo groups, respectively. To compare the difference between the two groups, the percent changes from baseline in QCT parameters were analyzed using the Student's *t* test

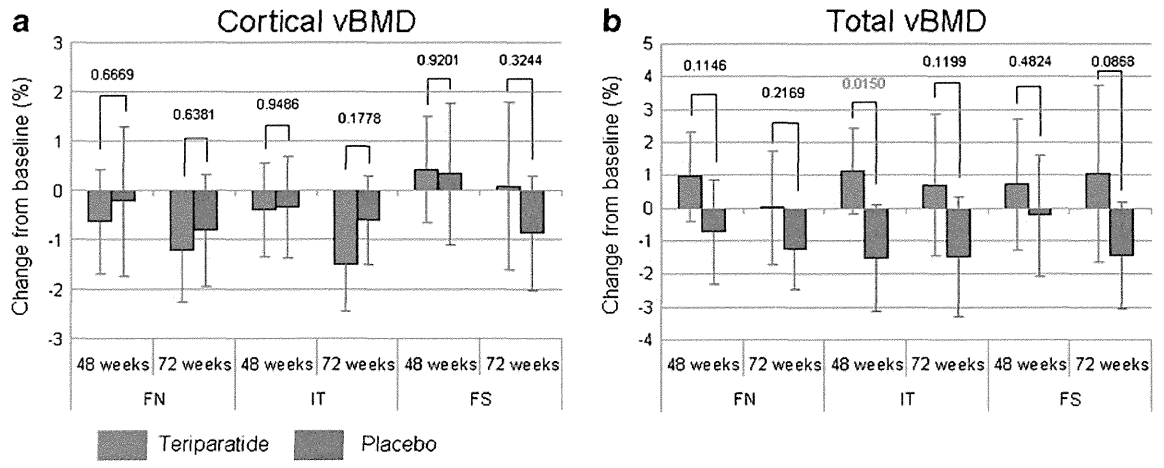

Fig. 2 Mean percent changes and 95 % confidence interval from baseline in cortical volumetric bone mineral density (vBMD) (**a**) and total vBMD (**b**) at 48 and 72 weeks of treatment with teriparatide and placebo. Changes at the femoral neck (*FN*), inter-trochanter (*IT*), and femoral shaft (*FS*) are shown. *Values on top of each panel* indicate *p* values (between teriparatide and placebo group). *Red* and *blue bars* correspond to teriparatide and placebo groups, respectively. To compare the difference between the two groups, the percent changes from baseline in QCT parameters were analyzed using the Student's *t* test

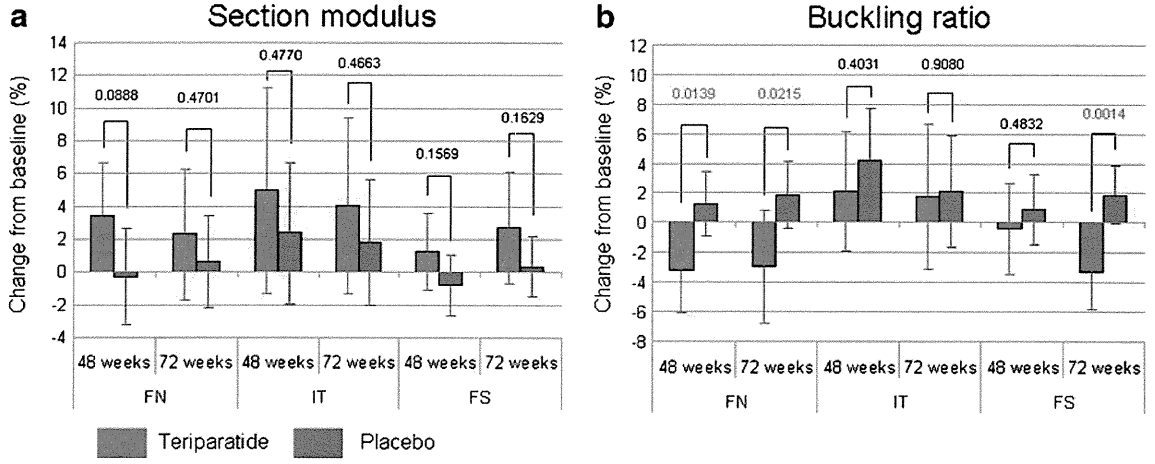

Fig. 3 Mean percent changes and 95 % confidence interval from baseline in SM (**a**) and BR (**b**) at 48 and 72 weeks of treatment with teriparatide and placebo. Changes at the femoral neck (*FN*), inter-trochanter (*IT*), and femoral shaft (*FS*) are shown. *Values on top of each panel* indicate *p* values (between teriparatide and placebo group). *Red and blue bars* correspond to teriparatide and placebo groups, respectively. To compare the difference between the two groups, the percent changes from baseline in QCT parameters were analyzed using the Student's *t* test

distribution of closed circles (teriparatide) in the fourth quadrant is high, while the open circles (placebo) are highly distributed in the second quadrant. The difference between teriparatide and placebo is significant for BR ($p=0.0274$). These results suggest that changes in the placebo group with natural aging (i.e., age-related deteriorations in proximal femur geometry and biomechanical properties) are reversed at least partially by once-weekly teriparatide treatment.

Discussion

This longitudinal assessment by CT demonstrates the changes in bone geometry, vBMD, and mechanical properties at the proximal femur by once-weekly injection of 56.5 μg teriparatide for 72 weeks. This is the first longitudinal CT study to include comparison with a double-blinded placebo group. Previous studies have evaluated the effects of teriparatide on proximal femur geometry and its biomechanical properties using CT [8], but they did not include a placebo group.

Generally, the effects of once-weekly teriparatide injection on proximal femur geometry in this study are similar to results with daily teriparatide injections reported in a subgroup of the EUROFORS study (EU-CT study) [8]. The same analysis software program was employed and the main effects included increases in cortical thickness/CSA as well as total vBMD. Cortical thickness/CSA increasing while bone perimeter remained unchanged over 72 weeks of once-weekly teriparatide, suggests that cortical bone formation took place at the endosteal surface resulting in an increase in cortical thickness with a significant decrease in BR.

One difference observed between the weekly and daily treatment regimens is the effect on cortical vBMD. Although only eight patients were included in the treatment-naïve group in the EU-CT study, daily teriparatide decreased cortical vBMD at the femoral neck after 6 months of treatment (~3.0 % from baseline), which was consistent with the results of a previous large clinical trial [11]. Moreover, a decrease in cortical BMD at the femoral neck with 12 months of daily teriparatide treatment [12] and a decrease in cortical BMD at the distal radius and tibia were reported [13]. In contrast, our results showed that once-weekly teriparatide maintained cortical vBMD at the femoral neck (−0.6 %, 48 weeks and −1.2 %, 72 weeks). This difference may be due to distinct patterns of bone remodeling between daily and weekly teriparatide treatment given that weekly teriparatide caused an increase in serum osteocalcin (bone formation marker) and a decrease in urinary NTX (bone resorption marker) [5]. Other factors such as cohort effects, differences in CT acquisition or the software may also have had an effect and help to explain the differences.

The question of whether or not teriparatide stimulates periosteal apposition has been raised. In the EU-CT study, total CSA (cortical CSA plus marrow area) did not change significantly throughout the study period and the authors concluded that there was no detectable periosteal apposition. DXA-based hip structure analysis (HSA), conducted as a subgroup of the Fracture Prevention Trial (DXA-HSA study) [9], also showed that periosteal apposition appeared to be reduced in patients receiving daily teriparatide in comparison with a placebo-treated group. On the other hand, some studies reported daily treatment with teriparatide seemed to stimulate new bone formation on the periosteal and endosteal surfaces [14, 15]. Thus, periosteal and endosteal apposition may be stimulated within a certain time window or may vary depending on skeletal sites, such as weight bearing or non-weight bearing bone [13].

Bone generally expands in diameter with age [16, 17], as less bone density requires a wider bone to maintain bending strength. It has been speculated that expansion is a

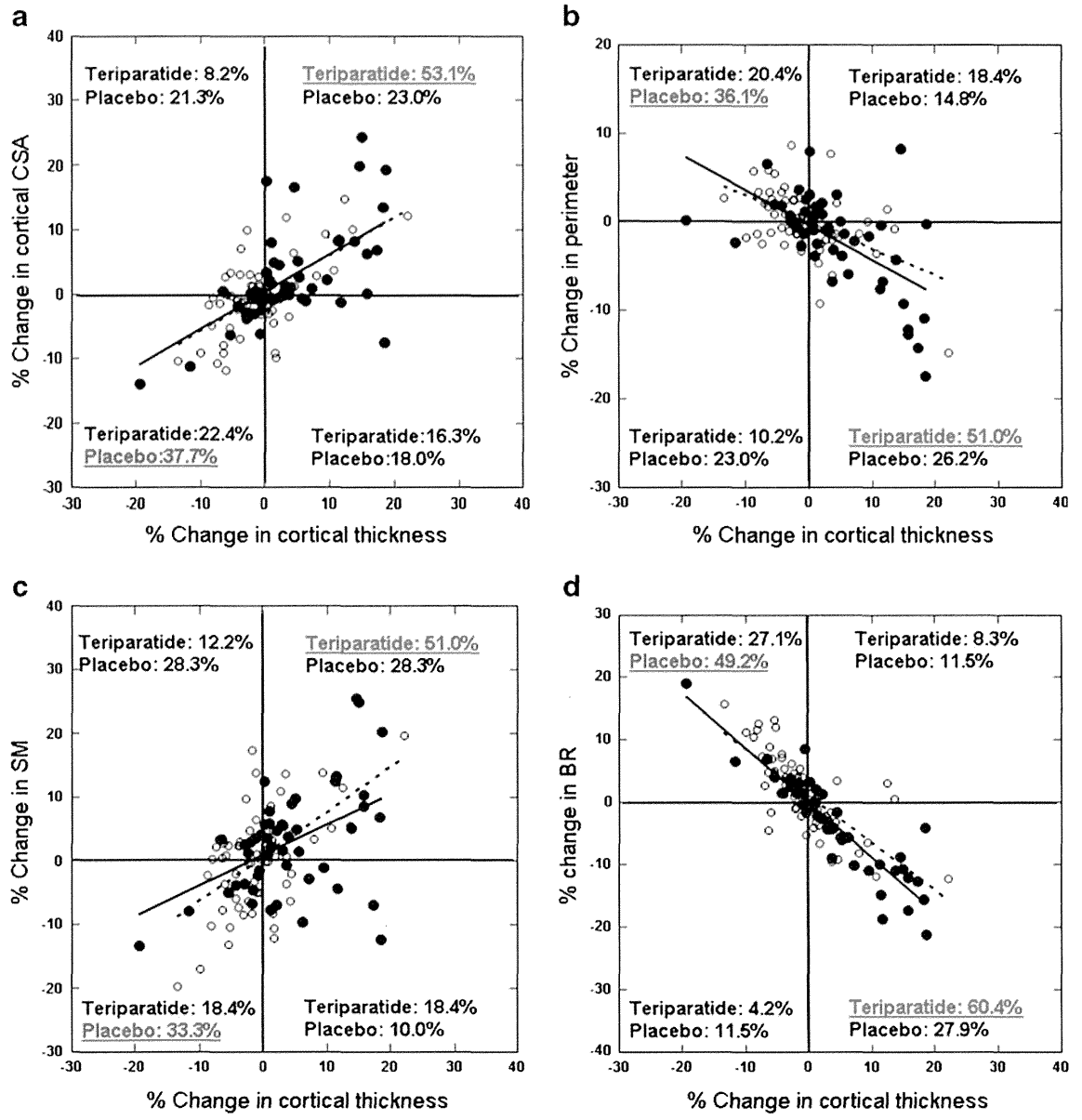

Fig. 4 Weekly administration of teriparatide reverses age-related changes at 72 weeks in cortical geometry and biomechanical properties at the femoral neck. Relationships between percent changes in cortical thickness versus those in cortical cross-sectional area (*CSA*) (**a**), perimeter (**b**), SM (**c**), or BR (**d**) are shown. *Solid circles* and *open circles* correspond to percent changes of individuals in the teriparatide and placebo groups, respectively. Note that linear regression lines for teriparatide (*solid lines*) and placebo (*dashed lines*) showing the relationship between the percent change in cortical thickness and those in other parameters, are almost identical regardless of whether the correlation is positive (**a** and **c**) or negative (**b** and **d**). The distribution of *closed* and *open circles* in each quadrant is shown in percentages. Note that with respect to the parameters with positive correlations (**a** and **c**), the relative distribution of *open circles* (for placebo) in the third quadrant is shifted to the first quadrant by weekly teriparatide (*closed circles*). Similarly, in the case of the parameters with negative correlations (**b** and **d**), relative distribution of *open circles* (for placebo) in the second quadrant is shifted to the fourth quadrant by weekly teriparatide (*closed circles*), suggesting that weekly teriparatide reversed age-related changes in proximal femur geometry and biomechanical properties

homeostatic adaptation to a net bone loss in order to maintain bone strength [18, 19]. This age-related adaptive response was not seen in the placebo group of the current study. Once-weekly injection of teriparatide increased cortical thickness with no change in cortical perimeter at the femoral neck. Thus, it is tempting to speculate that as a result of increased cortical thickness (which improves bone strength), periosteal apposition may not be required under once-weekly teriparatide treatment. Actually, a change in BR based upon improvement in cortical thickness was observed in the teriparatide group. The r^2 between percent change of cortical thickness and that of BR in the teriparatide group was higher than the placebo group.

As illustrated in Fig. 4, teriparatide improved all geometry and biomechanical parameters, while maintaining their relationships with changes in cortical thickness (as in the placebo

group). However, the distribution patterns of their relationships indicate that the effect of teriparatide is in the exact opposite direction of age-related skeletal changes. It is suggested, therefore, that compared with the changes in the placebo group, once-weekly teriparatide injection reverses age-related deteriorations in bone structure and strength by increasing cortical thickness/CSA and total vBMD, not increasing cortical perimeter, and improving biomechanical parameters.

In our previous study which characterized femoral neck geometry in patients with hip versus trochanteric fractures and compared them with age-matched controls [7], patients with femoral neck fracture had a significantly longer hip axis length (HAL), lower cross-sectional moment of inertia (CSMI), and higher BR, while those with trochanteric fractures had a smaller cortical CSA of the femoral neck. Once-weekly teriparatide may improve all these geometric changes. Taken together with the present results that SM (calculated as CSMI) divided by the maximal distance to center of the bone mass (centroid) increased by approximately 4 %, and BR decreased approximately 4 % compared to placebo, once-weekly injection of 56.5 μg teriparatide may have the potential to reduce the risk of hip fracture.

In the current longitudinal study, we also analyzed the geometry and biomechanical properties at the inter-trochanter and shaft regions in addition to those at the femoral neck. The percent changes in several parameters at the femoral neck and inter-trochanter were greater at 48 weeks compared to 72 weeks, while at the femoral shaft, the changes were greater at 72 weeks compared to 48 weeks, suggesting that the effects of teriparatide at the shaft take place in a later phase than those at the femoral neck and inter-trochanter. Endosteal bone formation might appear later at the purely cortical site, such as femoral shaft. Similar results were observed in the DXA-HSA study [9], in which teriparatide seemed to have no significant effects on femoral shaft geometrical parameters.

A limitation of our study was the small number of subjects; since all the participating institutes in the TOWER trial were not equipped with MDCT scanners, the number of subjects with CT scans was limited. We paid careful attention, for example, to the CT images and those with artifacts were excluded from the study. However, the results of this study were proved by comparison with the placebo group. Another limitation was that we had no confirmation on the event of hip fracture, since no new hip fracture was reported in either group. As an additional limitation, Mindways software was used for analyzing the geometry of inner and outer surfaces of the cortex and this method may not currently be the best available technology for this evaluation. However, we carefully applied this program to define the same region of an individual subject for analysis, using the "Optimize FN Axis" algorithm. When this algorithm did not work well and different regions were obtained, we carefully manually adjusted both the axis of the femoral neck and the axis of the femoral shaft, visually comparing the baseline CT image and the treatment image. In addition, we improved the reproducibility using the eccentricity registration method for measurement of the femoral neck.

In conclusion, we have demonstrated (using CT and 3D analysis) that once-weekly teriparatide increased cortical thickness and cortical and total CSA, and improved biomechanical indices. Moreover, once-weekly teriparatide did not increase cortical perimeter but seemed to effectively reverse changes in proximal femur geometry with aging. Taken together with its anti-fracture efficacy in the spine [5], once-weekly 56.5 μg teriparatide administration may have the potential to prevent hip fracture.

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