Full Length Article

Randomized controlled trial of daily teriparatide, weekly high-dose teriparatide, or bisphosphonate in patients with postmenopausal osteoporosis: The TERABIT study

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ARTICLE INFO

ABSTRACT

Purpose: The effects of daily teriparatide (20 μg) (D-PTH), weekly high-dose teriparatide (56.5 μg) (W-PTH), or bisphosphonates (BPs) on areal bone mineral density (aBMD), bone turnover markers (BTMs), volumetric BMD (vBMD), microarchitecture, and estimated strength were investigated in postmenopausal osteoporosis patients.
Methods: The study participants were 131 women with a history of fragility fractures. They were randomized to receive D-PTH, W-PTH, or BPs (alendronate or risedronate) for 18 months. Dual-energy X-ray absorptiometry (DXA), BTMs, and high-resolution peripheral quantitative CT (HR-pQCT) parameters were evaluated at baseline and after 6 and 18 months of treatment. The primary endpoint was the change (%) in cortical thickness (Ct.Th) after 18 months' treatment compared with baseline.
Results: DXA showed that D-PTH, W-PTH, and BPs increased lumbar spine aBMD (+12.0%, +8.5%, and +6.8%) and total hip aBMD (+3.0%, +2.1%, and +3.0%), but D-PTH and W-PTH decreased 1/3 radius aBMD (−4.1%, −3.0%, −1.4%) after 18 months.
On HR-pQCT, D-PTH increased trabecular vBMD (Tb.vBMD) at the distal radius and tibia after 18 months (+6.4%, +3.7%) compared with the BPs group, decreased cortical volumetric tissue mineral density (Ct.vTMD) (−1.8%, −0.9%) compared with the other groups, increased Ct.Th (+1.3%, +3.9%), and increased failure load (FL) (+4.7%, +4.4%). W-PTH increased Tb.vBMD (+5.3%, +1.9%), maintained Ct.vTMD (−0.7%, +0.2%) compared with D-PTH, increased Ct.Th (+0.6%, +3.6%), and increased FL (+4.9%, +4.5%). The BPs increased Tb.vBMD only in the radius (+2.0%, +0.2%), maintained Ct.vTMD (−0.6%, +0.3%), increased Ct.Th (+0.5%, +3.4%), and increased FL (+3.9%, +2.8%).
Conclusions: D-PTH and W-PTH comparably increased Ct.Th, the primary endpoint. D-PTH had a strong effect on trabecular bone. Although D-PTH decreased Ct.vTMD, it increased Ct.Th and total bone strength. W-PTH had a moderate effect on trabecular bone, maintained Ct.vTMD, and increased Ct.Th and total bone strength to the same extent as D-PTH.
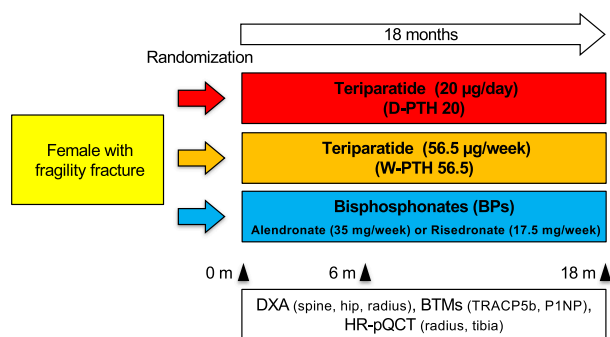
Fig. 1. Study protocol of the TERABIT study.

1. Introduction

In the current treatment strategy for osteoporosis (OP), daily teriparatide (20 μg) (D-PTH) is the main anabolic drug used for severe OP patients [1–4]. According to the concept of "goal-directed treatment" proposed in 2017, the recommendation is that initial treatment should offer at least a 50% chance of achieving a T-score > −2.5 within 3 to 5 years of starting therapy [5].

Evaluations by dual-energy X-ray absorptiometry (DXA) have shown that D-PTH greatly increases areal bone mineral density (aBMD) of vertebrae in comparison with bisphosphonates (BPs) [6]. However, another study found that it does not greatly increase the aBMD of the proximal femur, and that it may even decrease the aBMD of the radius [1].

High-resolution peripheral quantitative computed tomography (HR-pQCT) is the CT modality that provides the highest-resolution images of the peripheral bones of the living human body, enabling the longitudinal analysis of changes in the volumetric BMD (vBMD) and bone microarchitecture in OP patients [7–9]. The use of finite element analysis also enables the calculation of estimated bone strength, which reflects the vBMD and bone microarchitecture of both trabecular and cortical bones.

Previous studies using HR-pQCT found that D-PTH reduces vBMD of the cortical bone and increases cortical porosity in the distal radius and tibia [10–14], raising concerns that bone strength may decrease as a result. Due to its nature as a drug that promotes bone turnover, D-PTH increases not only bone formation, but also bone resorption. This mechanism is believed to underlie the decrease in the degree of mineralization and the increase in cortical porosity, although the details have yet to be elucidated. Few studies have investigated the effect of D-PTH on HR-pQCT; the only comparative studies are those of Hansen et al. [D-PTH vs PTH 1–84 (daily) vs zoledronic acid (ZOL) (yearly), non-randomized, controlled trial (RCT)] and Tsai et al. [D-PTH vs denosumab (once/6 months) vs D-PTH & denosumab: RCT] (DATA study) [11–13], and no studies have used the latest second-generation HR-pQCT scanners.

Daily administration of 20 μg of teriparatide increases both bone formation and resorption, generating new bone via the anabolic window. It has been found that extending the interval between teriparatide administrations enables bone formation without increasing bone resorption, and a formulation with a weekly dose of 56.5 μg has already been developed in Japan, having been available for use since 2011 [3]. No previous study has investigated the effect on bone microarchitecture of this weekly high-dose teriparatide (56.5 μg) (W-PTH) using HR-pQCT.

The objective of this study was to investigate the effects of D-PTH and of W-PTH on aBMD, bone turnover markers (BTMs), vBMD, bone microarchitecture, and bone strength in postmenopausal OP patients with a history of fragility fractures, compared with the effects of oral BPs as a control.

2. Materials and methods

2.1. Study design

This was a multicenter, open-label, randomized, controlled trial to investigate the effects of 18 months of treatment with D-PTH, W-PTH, or oral BPs in postmenopausal OP patients with a history of fragility fractures (the TERABIT Study) (Fig. 1).

This study was approved by the Ethics Committees of the institutions involved and is registered with the Japan Registry of Clinical Trials (jRCT) (jRCTs071180087) (https://jrct.niph.go.jp/latest-detail/jRCTs071180087).

2.2. Participants

The study participants were postmenopausal OP patients with a history of fragility fractures. They were recruited at 18 hospitals and clinics that cooperated with the TERABIT study.

The inclusion criteria were: age 60–89 years, female, and a history of one of the following fragility fractures: vertebral body fracture, proximal femoral fracture, distal radius fracture, proximal humerus fracture, rib fracture, pelvic fracture, or lower leg fracture.

The exclusion criteria were: serious heart disease, serious liver disease, serious renal impairment, serious diabetes mellitus, endocrine disorder affecting bone turnover, rheumatoid arthritis, motor paralysis, history of steroid use (≥5 mg for ≥3 months), history of use of OP medications (teriparatide, anti-RANKL antibody, bisphosphonate within the past 6 months, or SERM or estrogen within the past 3 months), drug hypersensitivity, and contraindications to any of the drugs used.

Written, informed consent was obtained from all participants.

2.3. Randomization and intervention

The study participants were randomly allocated to one of the three treatment groups. Allocation was performed by the stratified block method, with the stratification factors of age and femoral aBMD. Registration and allocation were conducted by our hospital's Clinical Research Center.

The treatment drugs were teriparatide 20 μg daily self-injection (Forteo Subcutaneous Injection Kit 600 μg, Eli Lilly Japan K.K., Kobe, Japan), teriparatide 56.5 μg weekly subcutaneous injection (Teribone subcutaneous injection 56.5 μg, Asahi Kasei Pharma Corporation, Tokyo, Japan), and a weekly oral BP (alendronate 35 mg or risedronate 17.5 mg). All three groups were taking 1 μg daily of oral alfacalcidol, an activated vitamin D formulation. The duration of treatment was 18 months.

This study did not cover the treatment cost for participants, who paid for their medications themselves. Teriparatide 56.5 μg was injected weekly at a hospital or clinic. Either alendronate or risedronate was permitted because some clinics and hospitals can only prescribe either of them due to the limited number of usable oral BPs.

Participants' medication adherence was confirmed using a dedicated diary in which the date of injection was recorded and by checking the used packaging sheets for oral medication. Information was collected on all adverse events that occurred during the treatment period.

2.4. DXA and QUS

DXA and quantitative ultrasound (QUS) were performed at baseline and after 6 and 18 months of treatment. DXA (Prodigy Advance, GE, Madison, WI, USA) was used to measure the aBMD and T-score of the lumbar spine (L1–4), proximal femurs (bilateral total hip and femoral neck), and the distal third of the radius (radius 1/3).

The speed of sound (SOS) of the calcaneus was measured by QUS (CM-200, Furuno Electric Co., Ltd., Hyogo, Japan).

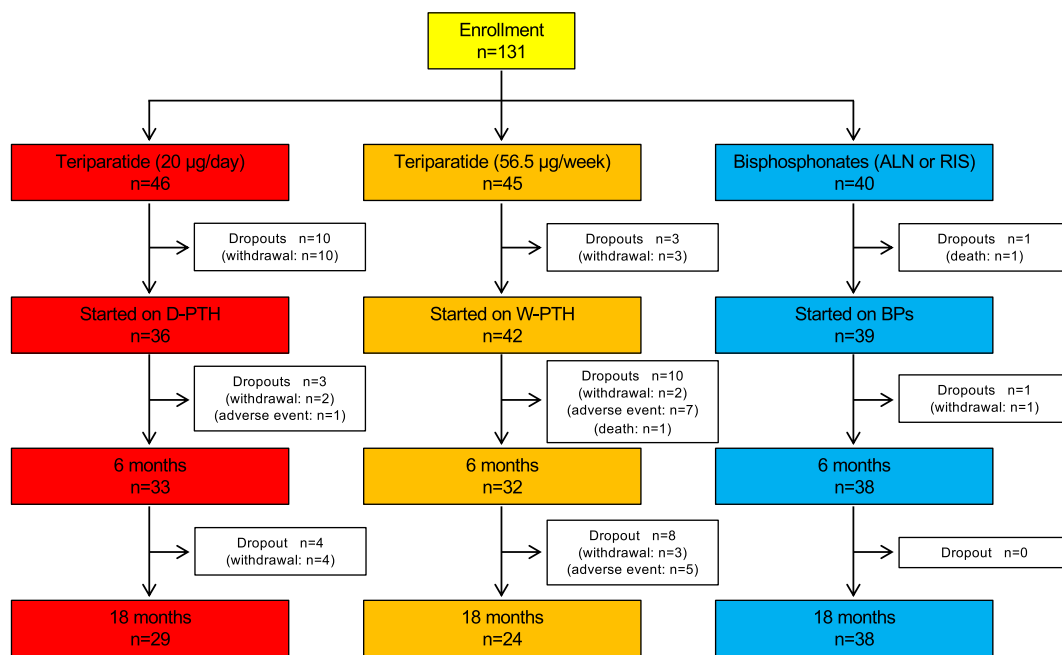In terms of measurement precision, the root mean square coefficient

Fig. 2. Consort diagram of the TERABIT study.

of variation (RMS%CV) was 0.99% for aBMD of the lumbar spine (L1–4), 0.42% for the total hip, 0.76% for the femoral neck, and 0.48% for SOS of the calcaneus.

2.5. Biochemical markers

The bone resorption marker tartrate-resistant acid phosphatase-5b (TRACP-5b) and the bone formation marker total type I procollagen-N-propeptide (total P1NP) were measured as BTMs at baseline and after 6 months and 18 months of treatment.

Biochemical tests included corrected calcium, intact parathyroid hormone (intact PTH), 25-hydroxy-vitamin D, and uric acid, as well as pentosidine, which is reportedly associated with bone collagen degradation [15].

2.6. HR-pQCT

HR-pQCT scanning was carried out at baseline and after 6 months and 18 months of treatment.

The forearm and lower leg of the participant's non-dominant arm and leg were each immobilized in dedicated casts, and the distal radius and tibia were scanned by HR-pQCT (XtremeCT II, SCANCO Medical AG, Brüttisellen, Switzerland). Following the standard scanning method, the scan sites were a 10.2-mm-wide area of the distal radius 9 mm proximal to the wrist joint and a 10.2-mm-wide area of the distal tibia 22 mm proximal to the ankle joint [16]. The scanning conditions were as follows: voltage 68 kVp, current 1470 μA, exposure time 4.3 ms, exposure count 900 projections, field of view (FOV) 140 mm, matrix 2304×2304, and voxel size 60.7 μm^3. The number of slices was 168, scanning time was 2.0 min, radiation dose was CT dose index by volume (CTDI-vol) 10.8 mGy and dose-length product (DLP) 11.0 mGycm, and the effective dose was 5 μSv.

2.7. Bone microarchitecture analysis

Bone microarchitecture was analyzed after three-dimensional (3D) registration of the data sets from baseline and after 6 months and 18 months of treatment (TRI/3D-BON, Ratoc System Engineering Co., Ltd., Tokyo, Japan) [17]. Parameters were measured in the following three categories [16–18].

1) Trabecular bone: trabecular vBMD (Tb.vBMD, mg HA/cm^3), trabecular bone volume fraction (Tb.BV/TV, %), trabecular thickness (Tb.Th, mm), trabecular number (Tb.N, 1/mm), trabecular separation (Tb.Sp, mm), star volume marrow space (V*ms) (an index that evaluates the cavitation of trabecular bone by quantifying the extent of bone marrow space) [19], connectivity density (ConnD) (an index quantifying the topographic continuity of trabeculae) [20], star volume trabeculae (V*trab) (an index that evaluates the connectivity of trabeculae by quantifying the extent of trabecular space) [19], and structure model index (SMI) (an index that quantifies the morphology of trabeculae, with plate-shaped graded as 0 and rod-shaped as 3) [21].
2) Cortical bone: cortical vBMD (Ct.vBMD, mg HA/cm^3), cortical volumetric tissue mineral density (Ct.vTMD, mg HA/cm^3), cortical porosity (Ct.Po, %), cortical thickness (Ct.Th, mm), and cortical area (Ct.Ar, mm^2).
3) Estimated bone strength: stiffness (kN/mm) and failure load (FL, kN).

The vBMD values were measured by converting X-ray attenuation values using a regression line produced with phantom scanning. Ct.vTMD was calculated only from cortical bone tissue excluding porosity.

Bone microarchitecture was analyzed on binarized images converted with a threshold of 320 mg/cm^3 for trabecular bone and 450 mg/cm^3 for cortical bone based on the guideline for HR-pQCT assessment [16]. Tb.BV/TV and Ct.Po were measured by voxel counting using their respective threshold values. Tb.Th, Tb.Sp, and Ct.Th were measured by the distance transformation method [22].

Estimated bone strength was analyzed by the finite element method (IPL, SCANCO Medical AG). Stiffness and failure load when a compression load was applied in the orientation of the bone axis were calculated with a Young's modulus of 10 GPa and a Poisson ratio of 0.3. Failure was defined as distortion of $\geq 0.7\%$ in $\geq 2\%$ of the total voxels.

In terms of measurement precision, the RMS%CVs of Tb.vBMD, Tb.BV/TV, Tb.Th, Tb.N, and Tb.Sp were 0.8%–3.3%; for V*ms, ConnD, V*trab, and SMI, they were 3.3%–5.8%; for the cortical bone parameters of Ct.vBMD, Ct.vTMD, Ct.Th, and Ct.Ar, they were 0.6%–1.4%; for Ct.

Table 1
Characteristics of the patients included in the analysis.

			All (n = 103)	D-PTH 20 (n = 33)	W-PTH 56.5 (n = 32)	BPs (n = 38)
Age		(years)	72.2 ± 6.7	71.7 ± 6.9	72.9 ± 5.9	71.9 ± 7.0
Height		(m)	1.50 ± 0.06	1.50 ± 0.06	1.51 ± 0.06	1.50 ± 0.06
Weight		(kg)	51.9 ± 8.0	52.3 ± 7.3	51.2 ± 7.2	52.1 ± 9.0
BMI		(kg/m^2)	23.0 ± 3.6	23.4 ± 3.4	22.6 ± 2.9	23.1 ± 4.1
History of fragility fracture	Vertebra	(n, %)	61 (59.8)	21 (65.6)	19 (59.4)	21 (55.3)
	Proximal femur	(n, %)	12 (11.8)	6 (18.8)	2 (6.3)	4 (10.5)
	Distal radius	(n, %)	32 (31.4)	9 (28.1)	10 (31.3)	13 (34.2)
	Others	(n, %)	18 (17.6)	2 (6.3)	5 (15.6)	11 (28.9)
FRAX	Major OP fracture	(%)	25.0 (17.0, 33.0)	24.0 (15.0, 32.0)	23.5 (18.8, 35.0)	26.0 (16.3, 32.8)
	Hip fracture	(%)	7.1 (3.6, 13.0)	6.8 (3.3, 13.0)	8.0 (4.7, 14.3)	7.1 (3.7, 13.0)
DXA T-score	Lumbar spine		−2.8 (−3.5, −2.2)	−3.0 (−3.3, −2.4)	−2.8 (−3.5, −1.6)	−2.8 (−3.5, −2.2)
	Total hip		−2.1 (−2.7, −1.6)	−2.2 (−2.6, −1.6)	−1.8 (−2.7, −1.3)	−2.3 (−2.8, −1.7)
	Femoral neck		−2.7 (−3.2, −2.1)	−2.6 (−3.2, −2.2)	−2.7 (−3.3, −2.1)	−2.8 (−3.2, −2.1)
	Radius 1/3		−3.3 (−4.0, −2.7)	−3.3 (−3.8, −2.7)	−3.5 (−4.1, −3.1)	−3.3 (−4.0, −2.4)
	Osteoporosis	(n, %)	82 (79.6)	29 (87.9)	24 (75.0)	29 (76.3)
	Osteopenia	(n, %)	20 (19.4)	4 (12.1)	7 (21.9)	9 (23.7)
BTMs	TRACP-5b	(mU/dL)	548.0 (441.5, 688.5)	542.0 (479.0, 653.0)	553.5 (449.3, 689.3)	531.0 (398.5, 689.3)
	total P1NP	(µg/L)	69.1 (51.2, 88.2)	70.2 (57.3, 88.7)	66.1 (49.3, 87.1)	71.6 (50.0, 87.2)

BMI: body mass index, FRAX: fracture risk assessment tool, OP: osteoporosis, DXA: dual-energy x-ray absorptiometry, BTMs: bone turnover markers, TRACP-5b: tartrate-resistant acid phosphatase 5b, P1NP: Procollagen type 1 N propeptide, D-PTH 20: teriparatide 20 µg/day, W-PTH 56.5: teriparatide 56.5 µg/week, BPs: bisphosphonate (oral alendronate 35 mg/week or risedronate 17.5 mg/week).
Data were presented as mean ± SD, number (%), and median (25%, 75%).

Po, it was 6.0% [17].

2.8. Endpoints

The primary endpoint was the rate of change in Ct.Th after treatment for 18 months compared with baseline. The secondary endpoints were the rates of change in all other parameters evaluated after 6 and 18 months of treatment compared with baseline and the differences between the randomized groups in all parameters evaluated after 6 and 18 months of treatment.

2.9. Statistical analyses

The sample size was calculated as follows. Hansen et al. and Seeman et al. reported that the rate of change in radial Ct.Th after D-PTH for 18 months was 2.0% ± 3.8%. On this basis, to reject the null hypothesis that "the rate of change in radial Ct.Th in the group treated with D-PTH for 18 months is 0.0%" by means of Student's t-test with a significance level of 5% required a sample size of 33 to provide 85% power. Assuming drop-out rates over 18 months of 27.5% in the D-PTH and W-PTH groups and of 20% in the BPs group, the target enrollment was set at 45 patients each in the D-PTH and W-PTH groups and 40 in the BPs group, a total of 130 patients.

The analysis population was taken as study participants who took one of the study drugs at least once, and for whom valid data for at least one of the parameters evaluated at baseline and at least one time point after the start of treatment were available.

In the primary analysis, the distributions of values at each of the primary endpoints are expressed as adjusted mean and 95% confidence interval values. A robust linear regression model was used to test the null hypothesis that the mean value at the primary endpoint is 0 [23,24]. The significance level on two-sided tests was 5%. The Bonferroni correction was performed for multiple comparisons.

In the secondary analysis, the distributions of values at each of the secondary endpoints are expressed as quartiles (only median values in the main text). A robust linear regression model was used to test the null hypothesis that the mean value at the secondary endpoints is 0 [23,24]. The significance level on two-sided tests was 5%. The Bonferroni correction was performed for multiple comparisons.

Missing data after baseline were input by the last observation carried forward (LOCF) method. R version 4.0.4 was used for all analyses [25].

3. Results

3.1. Composition of the study

As shown in Fig. 2, the study enrolled 131 patients; 46 were allocated
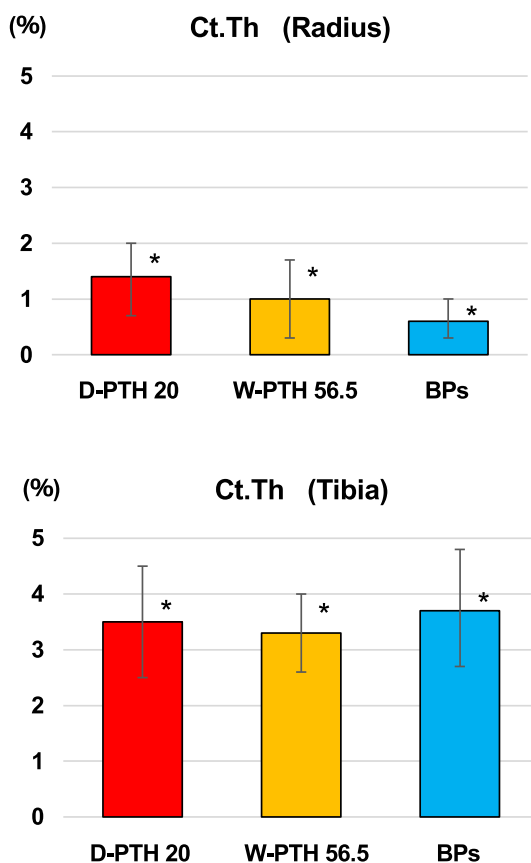

Fig. 3. Changes in Ct.Th at the distal radius and tibia after 18 months of therapy with D-PTH, W-PTH, or BPs (primary endpoint). Data are presented as adjusted averages (confidence interval). *: p < 0.05 vs baseline.

Table 2
Changes in bone turnover markers after 6 and 18 months of therapy with D-PTH, W-PTH, or BPs.

			Baseline (n = 103)	6 months (n = 103)	18 months (n = 91)
			Value	Change (%)	Change (%)
TRACP-5b	(mU/dL)	D-PTH 20	542.0 (479.0, 653.0)	0.8 (−19.5, 36.0)[a,b]	−15.9 (−24.7, 20.8)[b]
		W-PTH 56.5	553.5 (449.3, 689.3)	**−26.4 (−40.0, −12.7)[b]**	**−26.7 (−49.5, −10.9)[b]**
		BPs	531.0 (398.5, 689.3)	**−54.2 (−64.2, −42.8)**	**−53.5 (−66.6, −37.3)**
Total P1NP	(μg/L)	D-PTH 20	70.2 (57.3, 88.7)	**76.5 (41.2, 158.9)[a,b]**	**52.9 (7.9, 113.7)[a,b]**
		W-PTH 56.5	66.1 (49.3, 87.1)	−2.6 (−29.7, 32.3)[b]	−15.1 (−40.7, 25.6)[b]
		BPs	71.6 (50.0, 87.2)	**−62.8 (−71.9, −54.2)**	**−70.4 (−75.6, −52.5)**

TRACP-5b: tartrate-resistant acid phosphatase 5b, P1NP: Procollagen type 1 N propeptide, D-PTH 20: teriparatide 20 μg/day, W-PTH 56.5: teriparatide 56.5 μg/week, BPs: bisphosphonate (oral alendronate 35 mg/week or risedronate 17.5 mg/week).
Data were presented as median (25%, 75%), Bold: p < 0.05 vs baseline.
[a] p < 0.05 vs W-PTH.
[b] p < 0.05 vs BPs.

Table 3
Changes in aBMD after 6 and 18 months of therapy with D-PTH, W-PTH, or BPs.

			Baseline (n = 103)	6 months (n = 103)	18 months (n = 91)
			Value	Change (%)	Change (%)
Lumbar spine aBMD	(g/cm²)	D-PTH 20	0.745 (0.672, 0.823)	**7.5 (3.3, 12.9)**	**12.0 (7.3, 17.3)[b]**
		W-PTH 56.5	0.758 (0.660, 0.935)	**3.4 (1.8, 5.0)**	**8.5 (4.8, 12.9)**
		BPs	0.737 (0.642, 0.835)	**4.8 (1.2, 7.9)**	**6.8 (2.3, 11.6)**
Total hip aBMD	(g/cm²)	D-PTH 20	0.676 (0.617, 0.749)	**1.8 (0.7, 3.0)**	**3.0 (0.5, 5.1)**
		W-PTH 56.5	0.732 (0.611, 0.791)	**1.2 (0.6, 2.1)**	**2.1 (0.9, 3.6)**
		BPs	0.664 (0.601, 0.744)	**1.8 (0.6, 3.0)**	**3.0 (1.1, 3.9)**
Femoral neck aBMD	(g/cm²)	D-PTH 20	0.641 (0.573, 0.686)	1.5 (−0.6, 3.3)	**2.5 (0.1, 5.9)**
		W-PTH 56.5	0.639 (0.565, 0.700)	0.4 (−0.7, 2.1)	1.1 (−0.8, 3.7)
		BPs	0.625 (0.570, 0.703)	**1.5 (0.5, 3.5)**	**2.3 (0.6, 5.0)**
Radius 1/3 aBMD	(g/cm²)	D-PTH 20	0.556 (0.511, 0.610)	−0.1 (−3.4, 1.6)	**−4.1 (−6.8, −1.0)[b]**
		W-PTH 56.5	0.536 (0.485, 0.579)	−1.5 (−3.2, 2.5)	**−3.0 (−6.1, −0.6)**
		BPs	0.562 (0.498, 0.635)	0.2 (−2.5, 2.3)	−1.4 (−3.2, 1.3)

aBMD: areal bone mineral density, D-PTH 20: teriparatide 20 μg/day, W-PTH 56.5: teriparatide 56.5 μg/week, BPs: bisphosphonate (oral alendronate 35 mg/week or risedronate 17.5 mg/week).
Data were presented as median (25%, 75%), Bold: p < 0.05 vs baseline.
[a] p < 0.05 vs W-PTH.
[b] p < 0.05 vs BPs.

to D-PTH, 45 to W-PTH, and 40 to BPs. In the D-PTH group, 10 dropped out after the allocation, 7 by 18 months; the dropout rate was 37%. In the W-PTH group, 3 dropped out after the allocation, 18 by 18 months; the dropout rate was 47%. In the BPs group, 1 dropped out after the allocation, 1 by 18 months; the dropout rate was 5%.

The reasons for dropping out of the D-PTH group were an adverse event (ovarian cancer) in 1 case and refusal to self-inject or the cost of treatment in 16. In the W-PTH group, the reasons were adverse events (nausea, general malaise, headache) in 12 cases, death from lung cancer in 1 case, and either difficulty in visiting the hospital every week or treatment cost in 8. In the BPs group, the reasons were sudden death in 1 case (before the start of BP treatment), and unwillingness to undergo testing in 1 case.

3.2. Baseline characteristics

The analysis population was a total of 103 patients, with 33 in the D-PTH group, 32 in the W-PTH group, and 38 in the BPs group (Fig. 2). Of the 38 patients in the BP group, 20 were prescribed alendronate (35 mg/w) and 18 risedronate (17.5 mg/w).

As shown in Table 1, the mean age of the analysis population was 72.1 years. 59.8% of them had a history of a vertebral fracture, 31.4% a distal radius fracture, and 11.8% a proximal femoral fracture. The median time from fracture to study enrollment was 2.7 months (82.0 days),
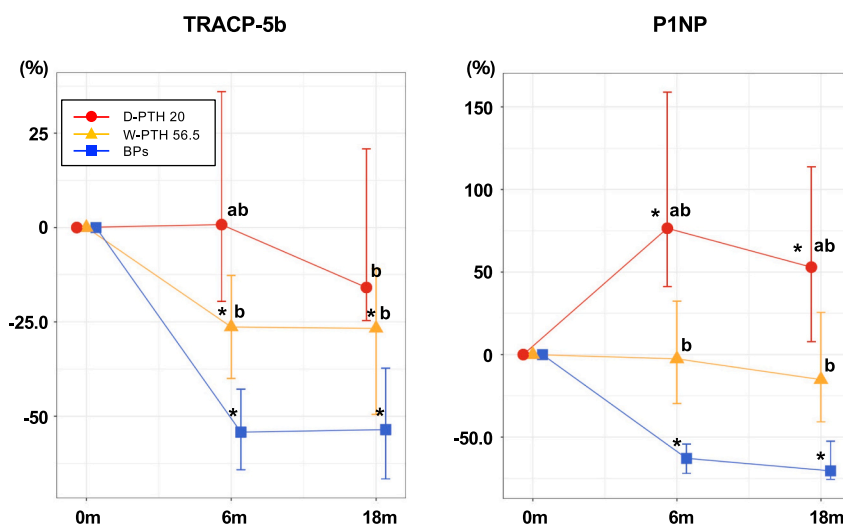

Fig. 4. Changes in TRACP-5b and total P1NP after 6 and 18 months of therapy with D-PTH, W-PTH, or BPs. Data are presented as medians (25%, 75%). *: p < 0.05 vs baseline, †: p < 0.05 vs 6 months, a: p < 0.05 vs W-PTH, b: p < 0.05 vs BPs.
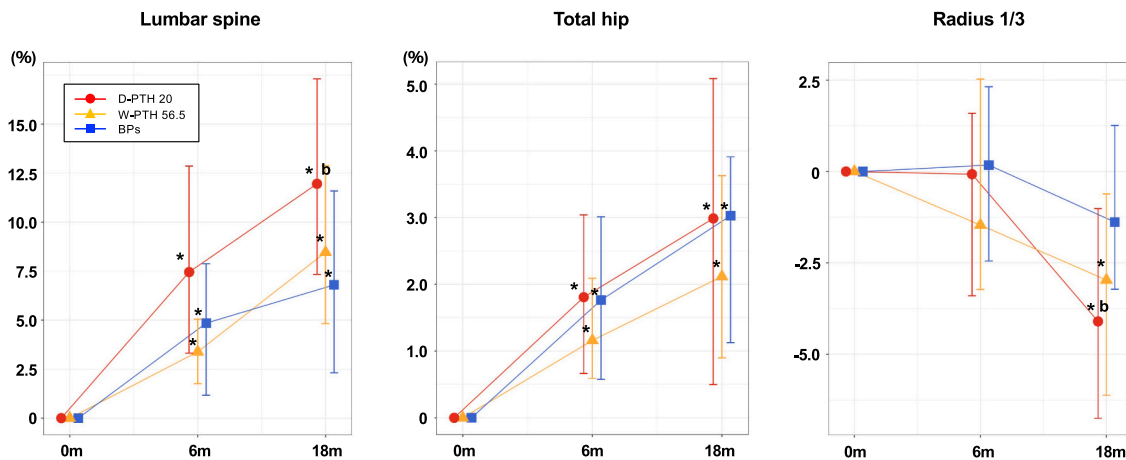
Fig. 5. Changes in aBMD at the lumbar spine, total hip, and radius 1/3 after 6 and 18 months of therapy with D-PTH, W-PTH, or BPs. Data are presented as medians (25%, 75%). *: p < 0.05 vs baseline, †: p < 0.05 vs 6 months, a: p < 0.05 vs W-PTH, b: p < 0.05 vs BPs.

and 69% (71/103) enrolled within 6 months of the fracture.

The median level of TRACP-5b was 548.0 mU/dL (reference range 120–420 mU/dL), and that of total P1NP was 69.1 μg/L (reference range 16.8–70.1 μg/L), both of which were high because the patients were all postmenopausal and had suffered a recent fracture.

There were no significant differences in baseline characteristics among the three groups.

3.3. Primary endpoint

As shown in Fig. 3, Ct.Th of the distal radius, expressed as adjusted averages (confidence interval), increased significantly after 18 months, +1.4% (+0.7, +2.0%) in the D-PTH group (P = 0.001), +1.0% (+0.3%, +1.7%) in the W-PTH group (P = 0.016), and + 0.6% (+0.3%, +1.0%) in the BP group (P = 0.005). Ct.Th of the distal tibia increased significantly, +3.5% (+2.5%, 4.5%) in the D-PTH group (P < 0.001), +3.3% (+2.6%, +4.0%) in the W-PTH group (P < 0.001), and + 3.7% (+2.7%, +4.8%) in the BP group (P < 0.001).

3.4. Biochemical markers

As shown in Table 2 and Fig. 4, in the D-PTH group, TRACP-5b did not change after 6 and 18 months, maintaining the high level at baseline (542.0 mU/dL), while P1NP increased significantly after 6 and 18 months. In the W-PTH group, TRACP-5b decreased significantly after 6 and 18 months, bringing it down to within the reference range, whereas P1NP did not change after 6 and 18 months, maintaining the high value at baseline (66.1 μg/L). In the BPs group, both TRACP-5b and P1NP decreased significantly after 6 and 18 months.

3.5. DXA

As shown in Table 3 and Fig. 5, in the D-PTH group, lumbar spine aBMD increased significantly after 18 months compared to the BPs group, total hip aBMD increased to the same extent as the BPs group, and radius 1/3 aBMD decreased significantly compared to the BPs group. In the W-PTH, lumbar spine aBMD increased, showing an intermediate increase between the D-PTH and BPs groups. Total hip aBMD increased to the same extent as the BPs group. Radius 1/3 aBMD decreased, showing an intermediate decrease between the D-PTH and BPs groups.

3.6. HR-pQCT

As shown in Tables 4 and 5 and Fig. 6, in the D-PTH group, Tb.vBMD increased significantly after 6 and 18 months in the radius and tibia. In

particular, the connectivity index V*trab increased significantly after 6 and 18 months compared to the BPs group in the radius and tibia. In the W-PTH group, Tb.vBMD and V*trab increased significantly after 18 months in the radius and tibia, showing an intermediate increase between the D-PTH and BPs groups. In the BP group, Tb.vBMD increased significantly after 18 months only in the radius, and there was no change in V*trab.

In the D-PTH group, Ct.vTMD decreased significantly after 6 and 18 months in the radius, showing a significant decrease compared to the W-PTH and BPs groups after 18 months. In the W-PTH group, Ct.vTMD decreased slightly in the radius, but it was comparable to the BPs group. Although not significant, similar trends were observed in the tibia. Regarding Ct.Po, no significant change was observed in all groups in this study.

FL increased significantly after 6 and 18 months in the radius and tibia in all groups. The rate of change in FL was comparable between the D-PTH and W-PTH groups.

Regarding the comparison between D-PTH and W-PTH, there were no significant differences of DXA and HR-pQCT parameters after 18 months with the sample size of this study except for Ct.vTMD at the radius, which decreased more with D-PTH than with W-PTH (Table 4 and Fig. 6).

Data on the other biochemical markers (corrected calcium, intact PTH, 25-hydroxy-vitamin D, pentosidine, and uric acid), QUS, and HR-pQCT parameters (Tb.BV/TV, V*ms, Conn.D, SMI, Ct.Ar, and Stiffness) are listed in Supplementary Tables 1–4, and p-values of comparisons between time points and treatment groups are listed in Supplementary Tables 5–8.

4. Discussion

4.1. Effects on vBMD, bone microarchitecture, and estimated bone strength

The increase rate in Tb.vBMD was high in both the D-PTH and W-PTH groups in this study (Fig. 6), reconfirming that teriparatide has a strong effect on trabecular bone. To investigate the mechanism of this effect, various microstructural parameters of trabecular bone were analyzed (Tables 4 and 5, and Supplementary Tables 3 and 4). The parameter that exhibited the greatest change induced by teriparatide was V*trab, as shown in Fig. 6. V*trab is a parameter that quantifies the extent of trabecular space and is greatly increased by a rise in connectivity or a change in a plate-like structure.

The decrease rate in Ct.vTMD was greater in the D-PTH group than in the other groups. The reason for the decrease in Ct.vTMD is generally

Table 4

Changes in trabecular and cortical bone parameters and estimated bone strength at the distal radius after 6 and 18 months of therapy with D-PTH, W-PTH, or BPs.

Distal radius				Baseline (n = 99)	6 months (n = 99)	18 months (n = 88)
				Value	Change (%)	Change (%)
Trabecular bone	Tb.vBMD	(mg/cm³)	D-PTH 20	46.6 (39.3, 54.7)	**3.8 (1.4, 6.3)[b]**	6.4 (3.7, 13.9)
			W-PTH 56.5	47.7 (36.2, 57.0)	1.8 (−1.3, 3.4)	**5.3 (2.5, 6.9)**
			BPs	50.2 (34.8, 60.5)	0.6 (−1.2, 3.3)	**2.0 (−0.6, 4.9)**
	Tb.Th	(μm)	D-PTH 20	194.2 (185.3, 201.2)	**1.0 (−0.3, 1.8)[b]**	2.3 (0.4, 2.9)
			W-PTH 56.5	192.2 (182.9, 197.5)	−0.2 (−0.7, 0.8)	0.4 (−0.5, 2.0)
			BPs	194.7 (186.6, 204.7)	−0.1 (−1.1, 0.7)	0.0 (−0.7, 1.3)
	Tb.N	(1/mm)	D-PTH 20	0.95 (0.85, 1.07)	0.2 (−2.4, 2.2)	0.9 (−1.3, 2.3)
			W-PTH 56.5	1.01 (0.91, 1.07)	0.3 (−1.4, 1.7)	**1.0 (0.0, 3.9)**
			BPs	0.98 (0.86, 1.07)	0.3 (−1.3, 2.9)	0.5 (−0.7, 3.4)
	Tb.Sp	(μm)	D-PTH 20	857.2 (743.0, 974.7)	−0.6 (−2.8, 2.3)	−1.1 (−3.2, 1.0)
			W-PTH 56.5	806.3 (747.0, 906.0)	−0.3 (−2.3, 1.5)	**−2.1 (−4.8, −0.4)**
			BPs	813.6 (719.1, 961.6)	−0.4 (−3.2, 1.6)	−0.5 (−4.3, 1.1)
	V*trab	(mm³)	D-PTH 20	0.34 (0.28, 0.47)	**6.9 (0.7, 11.6)[a,b]**	**12.8 (8.5, 18.7)[b]**
			W-PTH 56.5	0.31 (0.26, 0.46)	0.7 (−3.7, 5.1)	**7.2 (−0.3, 11.1)**
			BPs	0.39 (0.28, 0.49)	1.5 (−1.4, 3.1)	2.8 (−2.2, 9.0)
Cortical bone	Ct.vBMD	(mg/cm³)	D-PTH 20	887.0 (857.0, 920.0)	**−0.9 (−1.5, −0.4)**	**−1.8 (−3.6, −1.0)**
			W-PTH 56.5	879.6 (862.4, 913.2)	**−0.5 (−1.0, −0.2)**	**−0.6 (−1.3, −0.1)**
			BPs	890.1 (861.0, 910.7)	**−0.5 (−0.8, −0.1)**	**−0.6 (−1.0, −0.2)**
	Ct.vTMD	(mg/cm³)	D-PTH 20	890.8 (867.4, 926.4)	**−0.9 (−1.6, −0.4)**	**−1.8 (−3.7, −0.8)[a,b]**
			W-PTH 56.5	883.4 (866.6, 917.5)	**−0.5 (−1.0, −0.2)**	**−0.7 (−1.3, −0.1)**
			BPs	895.9 (870.4, 915.8)	**−0.5 (−0.9, −0.1)**	**−0.6 (−1.0, −0.1)**
	Ct.Po	(%)	D-PTH 20	0.9 (0.7, 1.1)	3.4 (−4.3, 9.8)	4.2 (−2.3, 18.8)
			W-PTH 56.5	0.8 (0.7, 1.1)	1.2 (−5.1, 6.0)	1.2 (−6.6, 7.2)
			BPs	0.9 (0.6, 1.1)	3.2 (−0.6, 9.0)	5.0 (−4.9, 17.1)
	Ct.Th	(μm)	D-PTH 20	813.5 (676.0, 875.7)	**1.4 (0.9, 1.9)**	**1.3 (0.1, 2.3)**
			W-PTH 56.5	761.2 (670.4, 805.3)	**0.8 (0.4, 1.8)**	**0.6 (0.2, 2.4)**
			BPs	782.8 (668.6, 865.9)	**1.0 (0.3, 1.6)**	**0.5 (0.0, 1.4)**
Estimated bone strength	FL	(kN)	D-PTH 20	2.04 (1.81, 2.31)	**2.5 (1.2, 4.6)**	**4.7 (1.8, 5.6)**
			W-PTH 56.5	1.93 (1.75, 2.38)	**1.4 (−0.7, 5.1)**	**4.9 (3.0, 8.5)**
			BPs	2.14 (1.79, 2.39)	**2.0 (−0.2, 3.5)**	**3.9 (0.3, 6.2)**

Tb.vBMD: trabecular volumetric bone mineral density, Tb.Th: trabecular thickness, Tb.N: trabecular number, Tb.Sp: trabecular separation, V*trab: star volume trabeculae, Ct.vBMD: cortical volumetric bone mineral density, Ct.vTMD: cortical volumetric tissue mineral density, Ct.Po: cortical porosity, Ct.Th: cortical thickness, FL: failure load, D-PTH 20: teriparatide 20 μg/day, W-PTH 56.5: teriparatide 56.5 μg/week, BPs: bisphosphonate (oral alendronate 35 mg/week or risedronate 17.5 mg/week).

Data were presented as median (25%, 75%). Bold: p < 0.05 vs baseline.

[a] p < 0.05 vs W-PTH.

[b] p < 0.05 vs BPs.

thought to be that D-PTH enhances bone turnover and replaces old bone with new bone composed of low-calcified tissue. The change in Ct.vTMD in the W-PTH group was similar to that in the BP group. Because W-PTH does not increase bone resorption, unlike D-PTH (Fig. 4), Ct.vTMD was thought to be maintained despite W-PTH being a teriparatide preparation.

Ct.Th, the primary endpoint of this study, increased in all groups, particularly in the tibia. Fig. 7 shows 2D and 3D images of the distal tibia of a patient treated with W-PTH. It can be seen that the increase in Ct.Th is due to new bone formation on the surface of the cortical bone endosteum.

The failure load increased in all groups, with the increase rate exceeding 4% in both the D-PTH and W-PTH groups. Failure load reflects the strength of both trabecular and cortical bone, and the decrease in Ct.vTMD caused by D-PTH may be compensated by the increases in Tb.vBMD and Ct.Th.

Although D-PTH and W-PTH have similar effects on bone strength, D-PTH has the advantage of a strong effect on trabecular bone, being suitable for OP patients with vertebral fracture. W-PTH has the advantage of a moderate effect on trabecular bone without decreasing cortical mineral density and may be suitable for OP patients with thin and low-density cortical bone.

Regarding different effects on weight bearing and non-weight bearing bone, the tibia exhibited a smaller decrease in Ct.vTMD and a larger increase in Ct.Th than the radius in all three groups. This may have been because the improvement in activity levels of the patients after a fragility fracture may have exerted a protective effect on the cortical bone of the tibia. Conversely, the increase in Tb.vBMD was greater in the radius than in the tibia. This may have been because the measured value of Tb.vBMD in the radius was lower than that in the tibia, making the rate of change (%) greater.

Table 5
Changes in trabecular and cortical bone parameters and estimated bone strength at the distal tibia after 6 and 18 months of therapy with D-PTH, W-PTH, or BPs.

Distal tibia				Baseline (n = 103) Value	6 months (n = 103) Change (%)	18 months (n = 91) Change (%)
Trabecular bone	Tb. vBMD	(mg/cm^3)	D-PTH 20	95.6 (80.9, 104.7)	**2.9 (1.2, 3.7)**	**3.7 (0.6, 5.1)**[b]
			W-PTH 56.5	96.0 (69.5, 113.3)	**1.3 (0.0, 3.7)**	**1.9 (−0.2, 3.7)**
			BPs	93.3 (76.1, 123.5)	0.8 (−1.3, 3.6)	0.2 (−2.3, 3.5)
	Tb.Th	(μm)	D-PTH 20	217.0 (209.1, 231.8)	**0.7 (0.1, 1.9)**	**1.2 (0.3, 2.7)**
			W-PTH 56.5	214.1 (206.9, 218.5)	0.3 (−0.8, 1.6)	1.0 (−0.4, 1.8)
			BPs	220.8 (208.8, 233.4)	0.1 (−0.4, 0.9)	0.2 (−0.7, 1.1)
	Tb.N	(1/mm)	D-PTH 20	1.00 (0.94, 1.12)	−0.5 (−1.8, 1.4)	−0.9 (−3.3, 0.7)
			W-PTH 56.5	1.05 (0.93, 1.14)	−0.8 (−2.6, 0.7)	−1.5 (−3.9, 1.2)
			BPs	1.04 (0.95, 1.16)	−0.6 (−2.3, 1.6)	**−1.7 (−4.0, −0.3)**
	Tb.Sp	(μm)	D-PTH 20	781.6 (681.8, 828.3)	0.3 (−1.7, 1.6)	0.7 (−0.7, 4.1)
			W-PTH 56.5	730.0 (656.4, 835.9)	1.3 (−1.6, 3.0)	1.5 (−2.2, 4.3)
			BPs	749.0 (652.5, 844.9)	0.8 (−2.5, 2.6)	**2.3 (0.4, 5.3)**
	V*trab	(mm^3)	D-PTH 20	1.31 (1.08, 1.70)	**7.7 (0.5, 12.7)**[b]	**11.6 (4.0, 15.6)**[b]
			W-PTH 56.5	1.18 (0.94, 1.55)	**4.1 (−0.7, 7.8)**	**8.4 (0.3, 13.2)**
			BPs	1.47 (0.92, 1.67)	1.5 (−2.1, 6.0)	2.1 (−2.2, 8.4)
Cortical bone	Ct. vBMD	(mg/cm^3)	D-PTH 20	837.0 (797.4, 867.0)	−0.1 (−1.0, 0.6)	−0.7 (−2.2, 0.8)
			W-PTH 56.5	833.0 (799.5, 862.9)	0.5 (−0.2, 0.9)	0.1 (−0.2, 1.0)
			BPs	825.2 (761.0, 868.4)	0.2 (−0.5, 0.9)	0.3 (−0.5, 1.8)
	Ct. vTMD	(mg/cm^3)	D-PTH 20	848.0 (809.4, 881.6)	−0.2 (−1.2, 0.5)	−0.9 (−2.3, 0.4)
			W-PTH 56.5	842.5 (815.4, 874.7)	0.2 (−0.2, 0.6)	0.2 (−0.2, 0.8)
			BPs	843.2 (776.0, 880.9)	0.2 (−0.4, 0.9)	0.3 (−0.5, 1.6)
	Ct.Po	(%)	D-PTH 20	2.4 (1.9, 2.9)	−4.4 (−10.7, 2.4)	−3.4 (−9.4, 6.6)
			W-PTH 56.5	2.3 (2.0, 3.0)	−0.2 (−8.7, 2.1)	−2.1 (−8.9, 6.0)

Table 5 (*continued*)

Distal tibia				Baseline (n = 103) Value	6 months (n = 103) Change (%)	18 months (n = 91) Change (%)
			BPs	2.5 (2.1, 2.9)	−3.0 (−12.6, 1.0)	−4.9 (−15.9, 4.8)
	Ct.Th	(μm)	D-PTH 20	881.8 (810.9, 1027.3)	**3.4 (2.1, 4.2)**	**3.9 (1.7, 5.3)**
			W-PTH 56.5	873.7 (816.0, 972.9)	**3.0 (2.0, 3.9)**	**3.6 (2.1, 4.4)**
			BPs	877.6 (771.1, 1007.3)	**3.1 (2.0, 5.8)**	**3.4 (1.9, 6.7)**
Estimated bone strength	FL	(kN)	D-PTH 20	5.90 (5.37, 6.40)	**2.3 (0.7, 4.9)**	**4.4 (2.0, 6.7)**
			W-PTH 56.5	5.84 (5.34, 6.62)	**2.3 (0.5, 5.4)**	**4.5 (2.0, 8.4)**
			BPs	6.08 (5.06, 6.86)	**1.8 (0.2, 3.7)**	**2.8 (0.1, 5.7)**

Tb.vBMD: trabecular volumetric bone mineral density, Tb.Th: trabecular thickness, Tb.N: trabecular number, Tb.Sp: trabecular separation, V*trab: star volume trabeculae, Ct.vBMD: cortical volumetric bone mineral density, Ct. vTMD: cortical volumetric tissue mineral density, Ct.Po: cortical porosity, Ct.Th: cortical thickness, FL: failure load, D-PTH 20: teriparatide 20 μg/day, W-PTH 56.5: teriparatide 56.5 μg/week, BPs: bisphosphonate (oral alendronate 35 mg/week or risedronate 17.5 mg/week).
Data were presented as median (25%, 75%). Bold: p < 0.05 vs baseline.
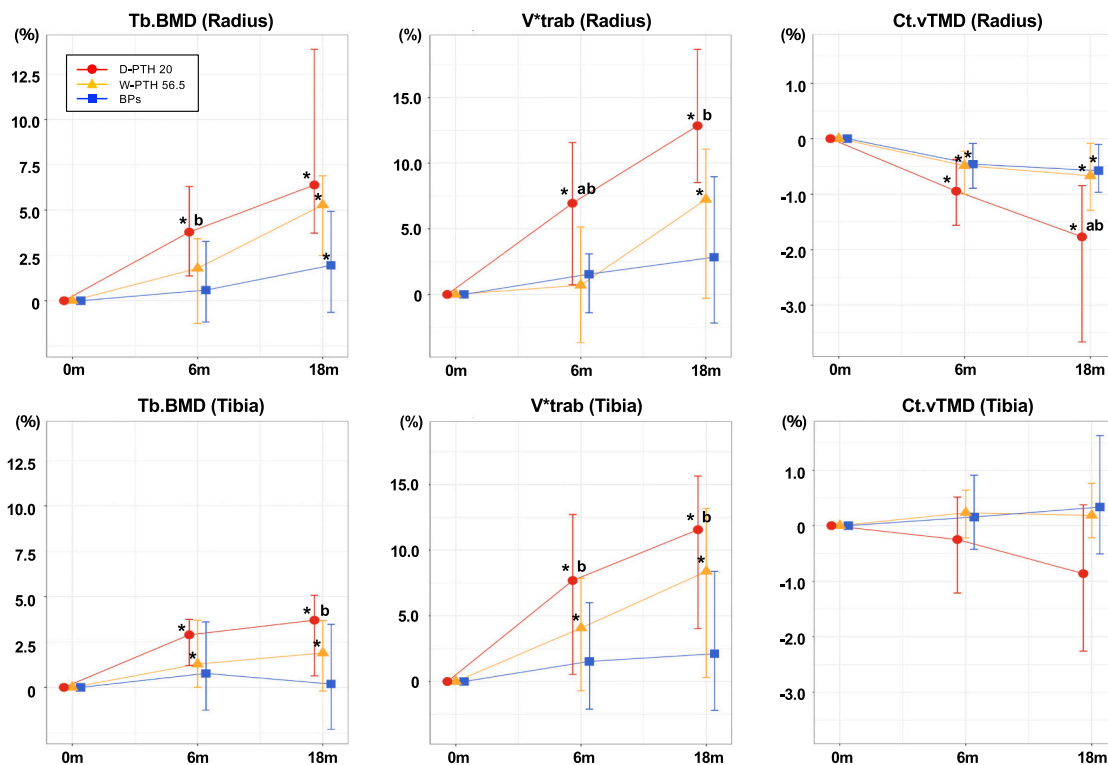[a] p < 0.05 vs W-PTH.
[b] p < 0.05 vs BPs.

4.2. Comparisons with previous studies

Four previous studies evaluated the effects of D-PTH using HR-pQCT in postmenopausal OP patients [10–14]. Macdonald et al. reported that Ct.vBMD decreased in 11 women treated with D-PTH for 18 months [10]. Hansen et al. reported that, when 18 women were treated with D-PTH for 18 months, although Ct.vBMD decreased and Ct.Po increased, failure load was preserved because Ct.Th and Tb.BV/TV increased [11]. Tsai et al. treated 27 women with D-PTH for 24 months, and they reported that Ct.vBMD decreased, Ct.Po increased, and stiffness decreased in the tibia, although it was preserved in the radius [12,13]. Paggiosi et al. reported that they treated 20 women with D-PTH for 24 months, resulting in decreased Ct.vBMD and increased Ct.Po [14].

In all those studies, Ct.vBMD decreased, and this was also the case in the present study. With respect to other parameters, however, the results from the previously reported studies are inconsistent. Ct.Po increased in three of the four previous studies, but it did not increase significantly in one, and in the present study, it also did not show a significant increase. The results for Ct.Th varied: it increased in two, was unchanged in one, and decreased in one, and it increased in the present study. The results for Tb.vBMD and Tb.BV/TV were similarly varied: they increased in two, were unchanged in one, and decreased in one, and showed significant increases in the present study. Variation of the results was also evident for FL and stiffness, which were unchanged or tended to increase in two, were unchanged or tended to decrease in one, and were not investigated in one, but showed significant increases in the present study.

The variation in these results may have been due to multiple factors, including the mean age of the study participants (65–72 years) and their attributes (severity of OP, period from fractures), the duration of treatment (12–24 months), the HR-pQCT device used (first-generation or
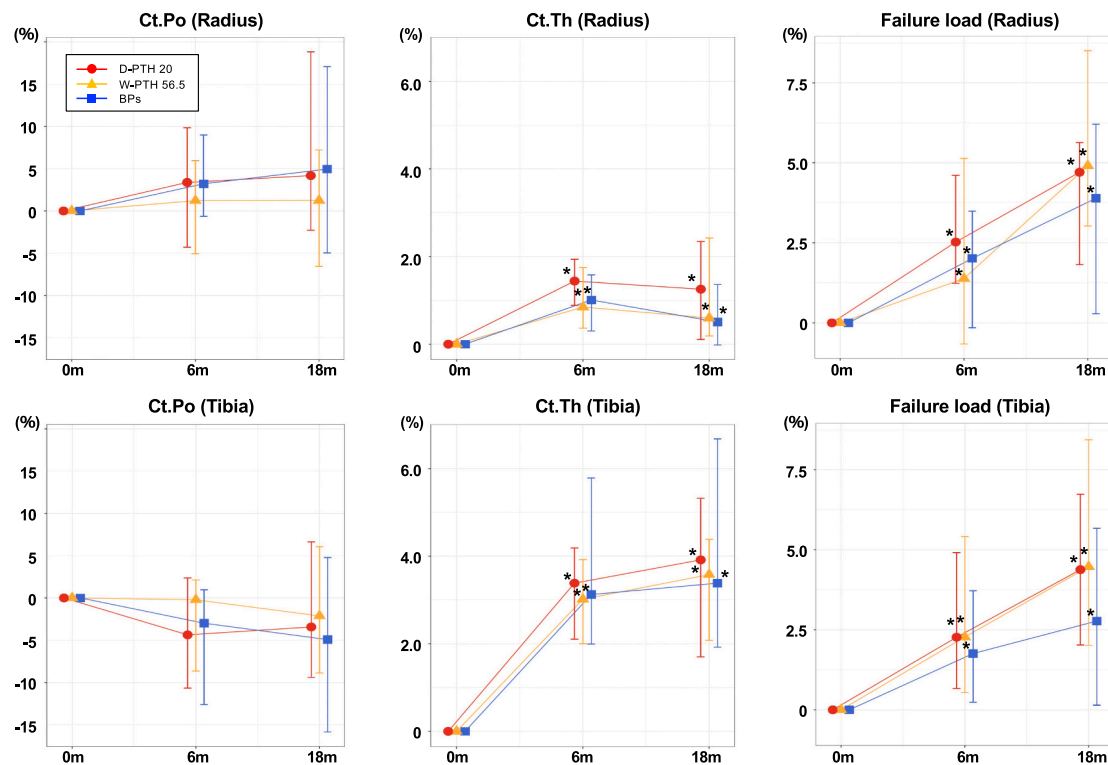
a

b

Fig. 6. Changes in Tb.vBMD, V*trab, Ct.vTMD, Ct.Po, Ct.Th, and FL at the distal radius and tibia after 6 and 18 months of therapy with D-PTH, W-PTH, or BPs. Data are presented as medians (25%, 75%). *: $p < 0.05$ vs baseline, †: $p < 0.05$ vs 6 months, a: $p < 0.05$ vs W-PTH, b: $p < 0.05$ vs BPs.
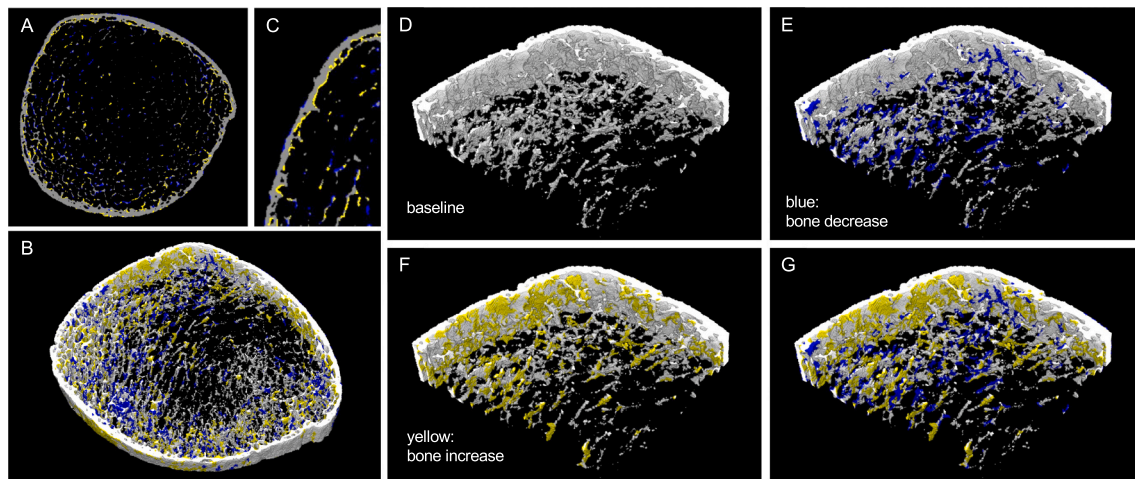
Fig. 7. HR-pQCT images of the left distal tibia of a 72-year-old woman treated by weekly high-dose teriparatide (56.5 μg/week) for 18 months. Bone increased (yellow) and decreased (blue) regions are shown in 2D and 3D images (A and B). 3D magnified images (C, D, E, and F) show that bone increase has occurred on the surfaces of endocortical bone, while both bone decrease and increase are observed in the trabecular bones. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

second-generation/resolution), and the analytical algorithm used (indirect or direct measurements/threshold values). In the present study, all patients were older women with fractures, with a median time from fracture to enrollment of 2.7 months, and the fact that their activity levels improved during the subsequent 18 months of OP treatment may have contributed to the good results seen for both trabecular and cortical bone.

4.3. Cortical porosity

In terms of the absence of a significant increase in Ct.Po, the difference in resolution between first-generation and second-generation HR-pQCT devices (82 μm vs 61 μm) and the different thresholds used in the analytical algorithm for cortical bone may have contributed to it [26,27]. Manske et al. compared first-generation and second-generation HR-pQCT and found that, because the second-generation uses lower threshold values for cortical bone, the measurement values of Ct.Po in second-generation HR-pQCT are smaller compared with the values measured by first-generation HR-pQCT (x0.31 for the radius and x0.42 for the tibia) [27]. All four of the previous studies mentioned above used first-generation HR-pQCT devices, and newly generated bone with a low calcification and/or microporosity may have been apparent as increased Ct.Po. Conversely, in the second-generation HR-pQCT used in the present study, newly generated bone with a low calcification and/or microporosity may have been apparent as a decrease in Ct.vTMD rather than as an increase in Ct.Po.

4.4. Strengths & limitations

The strength of this study was its nature as an RCT comparing three groups of patients taking D-PTH, W-PTH, and BPs using HR-pQCT. Of the four previous studies that investigated patients taking D-PTH using HR-pQCT, two were single-arm studies, one was non-randomized (D-PTH vs PTH 1–84,100 μg/day vs zoledronate 5 mg/year), and only one was an RCT (D-PTH vs denosumab 60 mg/6 months vs combination therapy) [10–14].

The first limitation of this study is the high dropout rate because of patients' refusal of allocated treatment or side effects (Fig. 2). Although D-PTH has few side effects, many patients were reluctant to perform daily self-injections and dropped out before the start. W-PTH is not self-injected, but many patients dropped out because of its side effects. In addition, the participants in this study had to pay for their medications themselves, and the costs of D-PTH and W-PTH were about 10 times

higher than of BPs. D-PTH was self-injected, W-PTH needed weekly hospital visits, and BPs were oral medications. These different costs and efforts required of each allocation group caused many withdrawals in the D-PTH and W-PTH groups. The second limitation is that the small sample number may have prevented the detection of significant differences among the different treatment groups. The third limitation is that W-PTH is not a standard treatment except in Japan, and that the BPs included two types of oral bisphosphonates, and the doses for oral alendronate and risedronate in Japan are lower than in other countries due to their higher absorption rates from the intestinal tract.

5. Conclusions

The different effects of D-PTH, W-PTH, and BPs were investigated. BTMs showed that D-PTH maintained the high bone resorption of baseline while increasing bone formation, and W-PTH maintained the high bone formation of baseline while decreasing bone resorption.

DXA showed that D-PTH, W-PTH, and BPs all increased the aBMD of the lumbar spine and proximal femur, whereas D-PTH and W-PTH decreased radius 1/3 aBMD.

On HR-pQCT, D-PTH increased Tb.vBMD and trabecular bone connectivity (V*trab) significantly compared to BPs. Although it decreased Ct.vTMD in comparison with the W-PTH and BPs, it increased Ct.Th and estimated bone strength. W-PTH increased Tb.vBMD and trabecular bone connectivity moderately. Although it is a teriparatide preparation, it maintained Ct.vTMD at a level equivalent to that of BPs, and it increased Ct.Th, increasing estimated bone strength to the same extent as D-PTH.

CRediT authorship contribution statement

Study design: KC, AK, SS, SN, MO.
Data acquisition: KC, NO, AK, TW, AM, MS, KA, ME, KY, TI, YY, KF, CK, and KT.
Data analysis: KC, SO, YI, and SM.
Data management: ST.
Statistical analysis: SM and SS.
Data interpretation: KC.
Drafting of the manuscript: KC.
Revision of the manuscript content: AY, MT, and MO.

Declaration of competing interest

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2022.116416.

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