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Original article

Comparative effect of eldecalcitol and alfacalcidol on bone microstructure: A preliminary report of secondary analysis of a prospective trial

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ABSTRACT

Objectives: To compare the effect of eldecalcitol and alfacalcidol on skeletal microstructure by high-resolution peripheral QCT (HR-pQCT).
Methods: This was a substudy of a randomized, double-blind, active comparator trial. Five female osteoporotic patients with 1-year 0.75 μg/day eldecalcitol and 5 with 1-year 1.0 μg/day alfacalcidol completed HR-pQCT scans before and after treatment were enrolled.
Results: Total vBMD [1.67 ± 1.06% (mean ± SD), P = 0.043 versus baseline] and trabecular vBMD (2.91 ± 1.72%, P = 0.043) at the radius increased in eldecalcitol group, while total, trabecular, and cortical vBMD tended to decrease in alfacalcidol group, with a significant reduction in cortical vBMD at the tibia (0.88 ± 0.62%, P = 0.043). Cortical area (1.82 ± 1.92%, P = 0.043) at the radius and thickness (0.87 ± 1.12%, P = 0.043) at the tibia increased in eldecalcitol group, while these parameters decreased with alfacalcidol at the tibia (1.77 ± 1.72%, P = 0.043 for cortical area; 1.40 ± 2.14%, P = 0.042 for cortical thickness). Trabecular thickness at the radius (1.97 ± 1.93%, P = 0.042) and number at the tibia (3.09 ± 3.04%, P = 0.043) increased by eldecalcitol but did not increase by alfacalcidol. Trabecular separation decreased by eldecalcitol (2.22 ± 2.43%, P = 0.043) but tended to increase by alfacalcidol at the tibia.
Conclusions: Eldecalcitol has the greater potential to improve cortical and trabecular microstructure at the peripheral bone than alfacalcidol which needs further more studies.
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1. Introduction

Osteoporosis is defined as a systemic bone disease characterized by loss of bone mass and deterioration of microstructure, resulting in an increased risk of fracture [1]. Iliac crest biopsies showed a reduction in the amount of both cortical and trabecular bone, and the deteriorated trabecular microstructure was strongly associated with fractures [2]. With the use of high-resolution peripheral quantitative computed tomography (HR-pQCT), it has been shown that osteoporotic patients have abnormal bone microstructure at both the distal radius and tibia, with decreased bone strength [3].

Eldecalcitol is an analog of active vitamin D_3 with hydroxypropyloxy group at the 2β position of 1α,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], and has been approved for treatment of osteoporosis in Japan [4]. A 3-year, randomized, double-blind clinical trial comparing eldecalcitol with alfacalcidol in Japanese patients with osteoporosis under vitamin D supplementation revealed that eldecalcitol significantly decreased the incidences of vertebral and wrist fractures, with greater increase in lumbar spine and total hip areal bone mineral density (aBMD) and stronger suppression of bone turnover markers (BMTs) [5]. Due to the low level of calcium intake and serum 25-hydroxyvitamin D (25OHD) in China, in order to explore whether eldecalcitol is also effective in increasing aBMD of axial bone under low vitamin D status, we conducted a 1-year,

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randomized, double-blind, double-dummy multicenter study to compare the effect of eldecalcitol with alfacalcidol on aBMD of axial bone in Chinese osteoporotic patients. Consistent with the previous study, the results demonstrated that eldecalcitol treatment for 12 months could also increase lumbar spine, total hip, and femoral neck aBMD compared with alfacalcidol under low calcium intake and serum 25OHD [6].

Although aBMD detected by dual-energy X-ray absorptiometry (DXA) is associated with fracture risk, as improvements in aBMD induced by treatment leads to a reduction in fracture risk [7–9], bone quality such as bone microstructure also affects fracture risk [10–14]. HR-pQCT is a novel noninvasive technique which can separately detect trabecular and cortical vBMD and microstructure at the distal radius and the tibia in vivo. Recent studies have shown that microstructural indices measured by HR-pQCT are strong predictors of fracture independent of aBMD by DXA [10,11,14,15], and the effect of anti-osteoporosis drugs has been assessed by HR-pQCT widely [13,16,17]. However, there has been no studies assessing the microstructural changes of bone in response to eldecalcitol by HR-pQCT in osteoporotic patients.

The aim of the present study is to compare the effects of eldecalcitol and alfacalcidol treatment for 12 months on vBMD and microstructure at the distal radius and the tibia by analyzing HR-pQCT in patients with osteoporosis.

2. Methods

2.1. Study design

This was a single-center study conducted in Peking Union Medical College Hospital (PUMCH) derived from a randomized, active comparator, double-blind, double-dummy multicenter study, comparing the efficacy of eldecalcitol with alfacalcidol in Chinese osteoporotic patients (*Clinical Trial Registration number JAPIC CTI 152904*) [6]. A total of 265 patients (242 females and 7 males) aged from 48 to 83 years from 16 centers in China were enrolled between July 2015 and June 2017, and randomly assigned to receive either eldecalcitol (at a dose of 0.75 μg once a day) or alfacalcidol (at a dose of 1.0 μg once a day) for 12 months (128 for eldecalcitol, 121 for alfacalcidol) [6].

The trial was in accordance with the 1964 Helsinki declaration and approved by the ethics committee at each study center. Informed consent was obtained from all individual participants included in the study.

2.2. Study patients and procedures

Patients were enrolled if they met the diagnostic criteria for primary osteoporosis by DXA: lumbar spine (L1-4) BMD T-score was below −1.0 SD with fragility fractures, or below −2.5 SD without fragility fractures. Women were at least 3 years after menopause or older than 60 years. Patients were excluded if they had any severe bone disorder or deformation at the lumbar spine; had primary hyperparathyroidism, hyperthyroidism, Cushing's syndrome, premature menopause due to hypothalamic, pituitary or gonadal insufficiency, poorly controlled diabetes mellitus (HbA1c $\geq$ 9%), or other causes of secondary osteoporosis; had urinary tract stones or history of urinary tract stones; had severe hepatic or cardiac disorders; had allergic history of vitamin D compounds. Patients were also excluded if they had taken any medicine which may influence bone metabolism, including active vitamin D compounds, vitamin K_2, calcitonin, selective estrogen receptor modulators, hormone replacement therapy, and glucocorticoids within the previous 2 months; taken any oral bisphosphonates more than once within 2 months before entry or more than four times within 1 year before entry, or intravenous bisphosphonates at any time; had taken parathyroid hormone, denosumab, or cathepsin K inhibitor at any time; had serum Cr above upper limit of normal range; had serum Ca above 2.59 mmol/L (10.4 mg/dL) or urinary Ca excretion of over 0.4 mg/dL glomerular filtrate (GF) (0.1 mmol/L GF); had any clinically significant hepatic or cardiac disorder; had a history of malignant tumor. Treatment was discontinued if serum calcium was > 11.0 mg/dL (2.74 mmol/L). If serum calcium was > 10.4 mg/dL (2.59 mmol/L) in 2 consecutive measurements or the urinary calcium excretion was > 400 mg/gCr in 2 consecutive measurements, and if the investigator judged that serum or urinary calcium increase was progressive, treatment was discontinued.

Eligible patients were randomly assigned to either daily eldecalcitol treatment group [eldecalcitol 0.75 μg (Fujieda Plant of Chugai Pharma Manufacturing Co., Ltd., Fujideda, Japan) + alfacalcidol placebo 1.0 μg (YaoPharma, Chongqing, China)] or daily alfacalcidol treatment group [alfacalcidol 1.0 μg (Iwakuni Factory of Teijin Pharmaceutical Manufacturing Co., Ltd. Iwakuni, Japan) + eldecalcitol placebo 0.75 μg (Fujieda Plant of Chugai Pharma Manufacturing Co, Ltd., Fujieda, Japan)] for 12 months treatment. Patients received no vitamin D or calcium supplementation during this study. Randomization was stratified by lumbar spine T-score at baseline and study site and performed by a computerized system. Patients were evaluated according to the schedule and discontinued once they reached the suspension criteria as described in a previous study [6].

2.3. High-resolution peripheral quantitative computed tomography (HR-pQCT) of the peripheral skeleton

2.3.1. HR-pQCT imaging

HR-pQCT examination was not an outcome of the original study, which was only performed on patients in our center with informed consent. HR-pQCT was performed for each enrolled patient at baseline and 12 months at the distal radius and tibia by HR-pQCT scanner (XtremeCT II, Scanco Medical AG, Bruttisellen, Switzerland) with isotropic voxel size of 61 μm. The non-dominant arm and corresponding leg of patients were scanned unless there was a prior fracture, metal shrapnel or implant, or recent non-weight bearing loads > 6 weeks at that region, in whom the dominant side was scanned. To minimize motion artifact during scanning, patient's arms and legs were fixed by dedicated casts. Reference lines were set on the distal endplate of the scanned limbs of the subjects. Then the first slice of the scan started at 9.0 and 22.0 mm from the reference line for the radius and tibia, respectively. Scanning 10.24 mm region of interest (ROI) proximally generated 168 slices, which enabled a 3D construction of the bone. Each image was carefully examined by the operator for motion artifacts and graded on a scale of 1 (no motion) to 5 (significant blurring of the periosteal surface, discontinuities in the cortical shell, or streaking in the soft tissue) using the grading method suggested by the manufacturer, and scans scored as 4 or greater were excluded from the analysis [18].

2.3.2. Image analysis

All image analyses were performed according to standard in vivo acquisition protocols provided by the manufacturer. The fully automated segmentation method could identify the periosteal surface of the bone. All slices were examined manually and then modified manually if it was necessary to delineate the periosteal boundary. An algorithm implemented in Image Processing Language (v5.4.2, Scanco Medical, Bruttisellen, Switzerland) identified the endosteal surface and segmented the cortical and trabecular regions [19]. Total volumetric bone mineral density (Tot.vBMD),

trabecular volumetric bone mineral density (Tb.vBMD), cortical volumetric bone mineral density (Ct.vBMD), cortical perimeter (Ct.Pm), cross-sectional area of total (Tot.Ar), cortical (Ct.Ar), and trabecular (Tb.Ar) compartments could be directly measured after successful compartment segmentation. Cortical parameters included cortical thickness (Ct.Th) measured directly by distance transformation method, and cortical porosity (Ct.Po) calculated as the number of void voxels in each binary cortex image divided by the total number of voxels in the cortex. For trabecular parameters, trabecular number (Tb.N) was measured directly using a distance transformation on the binary ridge images. Trabecular thickness (Tb.Th), and trabecular separation (Tb.Sp) were obtained directly using voxel-based measurements using distance transformation [20].

2.4. Statistical analysis

Data were presented as mean ± SD for normal distribution, while non-normal distribution data were presented as median (interquartile range). Baseline characteristics were compared by Mann-Whitney *U* test. Wilcoxon's signed rank test was used to compare the parameters at baseline with 12 months. Percentage change from baseline to 12 months was calculated as (value after treatment - value at baseline)/mean value of baseline and after treatment. Analysis of covariance (ANCOVA) was used to compare HR-pQCT parameters at 12 months between the 2 groups with adjustment for corresponding parameters at baseline. $P < 0.05$ was considered statistically significant at 2-tailed tests. All statistical analyses were conducted with the use of IBM SPSS Statistical Software, version 23 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics of study subjects

A total of 16 subjects were enrolled in Peking Union Medical College Hospital (PUMCH) to complete the multicenter trial comparing the efficacy of eldecalcitol versus alfacalcidol [n = 7, eldecalcitol group (eldecalcitol 0.75 μg + alfacalcidol placebo 1.0 μg); n = 9, alfacalcidol group (alfacalcidol 1.0 μg + eldecalcitol placebo 0.75 μg)]. Among them, 10 female subjects (eldecalcitol n = 5, alfacalcidol n = 5) who completed HR-pQCT scans before and after treatment were finally included in this HR-pQCT study.

Subjects in the 2 groups shared similar baseline clinical characteristics, including demographic characteristics, BMTs, and aBMD detected by DXA (Table 1). Mean serum 25(OH)D levels were below 50 nmol/L in both the eldecalcitol and alfacalcidol groups at baseline. Baseline HR-pQCT parameters were also similar between the 2 groups except for trabecular thickness at the radius, cortical perimeter, trabecular area and thickness at the tibia (Table 2).

3.2. Changes in HR-pQCT parameters vBMD

Changes in vBMD after 12 months treatment with eldecalcitol or alfacalcidol from baseline are shown in Fig. 1. At the radius, eldecalcitol increased total vBMD by 1.67 ± 1.06% (P = 0.043 versus baseline), whereas alfacalcidol did not increase total vBMD, and there was a significant difference between the 2 groups (P = 0.028) (Fig. 1A). Similarly, trabecular vBMD increased by 2.91 ± 1.72% in the eldecalcitol group (P = 0.043 versus baseline), but did not significantly change in the alfacalcidol group, although no significant between-group difference was observed (Fig. 1B). Cortical vBMD remained stable in both the 2 groups (Fig. 1C).

At the tibia, both total vBMD (Fig. 1D) and trabecular vBMD (Fig. 1E) showed a similar tendency to those at the radius with significant difference between the 2 groups (P = 0.028 for total vBMD). Cortical vBMD decreased by 0.88 ± 0.62% in the alfacalcidol group (P = 0.043 versus baseline) but was maintained in the eldecalcitol group, and there was a significant difference between the 2 groups (P = 0.028) (Fig. 1F).

After adjustment for baseline HR-pQCT parameters, total vBMD at the radius and cortical vBMD at the distal tibia after 12 months treatment remained significantly different between the 2 groups (Table 2).

3.3. Cortical microarchitecture

Changes in cortical microarchitecture after 12 months treatment with eldecalcitol or alfacalcidol are shown in Fig. 2. At the radius, cortical area increased by 1.82 ± 1.92% (P = 0.043 versus baseline) in the eldecalcitol group but showed no change in the alfacalcidol group (Fig. 2A). Cortical thickness (Fig. 2B) and perimeter (Fig. 2D) did not significantly change in the 2 groups, but there was a tendency to increase in the eldecalcitol group and to decrease in the alfacalcidol group.

At the tibia, cortical area tended to increase in the eldecalcitol group and significantly decrease in the alfacalcidol group (−1.77 ± 1.72%, P = 0.043 versus baseline). As a result, a significant difference between the 2 groups was observed (P = 0.016) (Fig. 2E). Cortical perimeter slightly increased in both eldecalcitol (P = 0.039 versus baseline) and alfacalcidol (P = 0.038 versus baseline) groups (Fig. 2F). Cortical thickness increased by 0.87 ± 1.12% (P = 0.043 versus baseline) with eldecalcitol and decreased by 1.40 ± 2.14% (P = 0.042 versus baseline) with alfacalcidol, with significant

Table 1
Baseline clinical characteristics of subjects included in HR-pQCT analysis.

Characteristics	Eldecalcitol (n = 5)	Alfacalcidol (n = 5)	P-value
Age, yr	65.2 ± 5.9	64.6 ± 5.6	0.310
BMI, kg/m^2	21.9 ± 1.5	24.2 ± 2.8	0.151
25OHD, nmol/L	34.5 ± 12.7	28 ± 18.7	0.421
sP1NP, ng/mL	59.0 ± 22.6	63.2 ± 27.9	0.690
sBAP, U/L	52.2 ± 9.7	51.2 ± 26.3	0.548
sCTx, ng/mL	0.463 ± 0.171	0.591 ± 0.146	0.221
uNTx/Creatinine, nM/mM	46.3 ± 20.9	58.3 ± 34.5	0.690
Total hip aBMD, g/cm^2	0.768 ± 0.096	0.765 ± 0.089	0.841
Femoral neck aBMD, g/cm^2	0.731 ± 0.119	0.711 ± 0.065	0.421
L1-4 BMD, g/cm^2	0.786 ± 0.022	0.793 ± 0.091	0.841

BMI, body mass index; 25OHD, 25-hydroxyvitamin D, sCTx, serum C-terminal telopeptide of type I collagen, uNTx, urinary N-terminal telopeptide of type I collagen, sBAP, serum bone-specific alkaline phosphatase, sP1NP, serum procollagen type I N-terminal propeptide. aBMD, areal bone mineral density.
Reference range, 25OHD ≥ 10 nmol/L, sP1NP 15–60 ng/mL, sBAP 11.6–29.6 U/L, sCTx 0.025–0.573 ng/mL, uNTx/Creatinine 14–74 nmol BCE/mmol·Cr.
Data are presented as mean ± SD.

Table 2
HR-pQCT Measures at Baseline and at 12 Months and comparison of change of HR-pQCT parameters after treatment in two groups.

	Eldecalcitol			Alfacalcidol			P-value for baseline	P-value for 12 months
	Baseline	12 months	P-value	Baseline	12 months	P-value		
Radius								
Tot.vBMD, mgHA/cm^3	208.2 ± 48.2	211.4 ± 47.3	0.043*	199.1 (197.6, 225.1)	201.90 (194.0,222.5)	0.144	1.000	0.025*
Tb.vBMD, mgHA/cm^3	71.2 ± 18.5	73.4 ± 18.9	0.043*	71.1 ± 17.0	70.0 ± 18.2	0.500	0.841	0.080
Ct.vBMD, mgHA/cm^3	876.9 ± 38.5	871.0 ± 44.1	0.138	876.6 ± 32.8	871.8 ± 38.3	0.225	1.000	0.778
Tb.Ar, cm^2	217.5 ± 39.1	216.8 ± 38.5	0.068	208.2 ± 10.7	208.1 ± 10.4	0.686	0.841	0.544
Ct.Ar, cm^2	45.3 ± 6.2	46.1 ± 6.0	0.043*	44.9 ± 1.9	44.8 ± 1.8	0.854	0.690	0.200
Tb.N, mm-1	1.025 ± 0.160	1.005 ± 0.183	0.225	0.899 ± 0.137	0.906 ± 0.182	0.893	0.222	0.029*
Tb.Th, mm	0.198 (0.198, 0.203)	0.204 ± 0.005	0.042*	0.218 ± 0.006	0.217 ± 0.005	0.102	0.008*	0.574
Tb.Sp, mm	0.981 ± 0.144	1.017 ± 0.179	0.223	1.123 ± 0.170	1.139 ± 0.228	0.686	0.222	0.030*
Tb.BV/TV, %	9.85 (9.7, 10.5)	11.1 ± 2.2	1.000	12.04 ± 1.46	11.9 ± 1.5	0.197	0.310	0.370
Ct.Th, mm	0.792 ± 0.146	0.797 ± 0.139	0.581	0.777 ± 0.062	0.777 ± 0.062	0.892	0.690	0.497
Ct.Pm, mm	65.9 ± 4.6	66.2 ± 4.8	0.080	67.9 ± 1.8	67.5 ± 1.2	0.144	0.548	0.121
Ct.Po (%)	0.92 ± 0.46	0.60 (0.50,0.60)	0.109	0.54 ± 0.34	0.52 ± 0.22	0.705	0.151	0.488
Tibia								
Tot.vBMD, mgHA/cm^3	174.6 ± 31.9	176.4 ± 32.3	0.136	192.3 ± 14.9	182.3 (179.1201.6)	0.138	0.151	0.059
Tb.vBMD, mgHA/cm^3	90.5 ± 17.1	90.6 ± 16.2	0.715	88.3 ± 22.5	87.3 ± 20.2	0.500	0.841	0.313
Ct.vBMD, mgHA/cm^3	815.3 ± 51.4	819.7 ± 57.9	0.225	842.5 ± 77.3	835.4 ± 80.1	0.043*	0.421	0.005*
Tb.Ar, cm^2	680.6 ± 98.3	679.8 ± 98.6	0.080	552.8 ± 42.3	554.4 ± 43.4	0.043*	0.016*	0.019*
Ct.Ar, cm^2	90.4 ± 17.1	91.1 ± 17.4	0.080	91.1 ± 9.8	89.5 ± 9.7	0.043*	0.841	0.025*
Tb.N, mm-1	1.039 ± 0.118	1.074 ± 0.148	0.043*	0.830 ± 0.173	0.825 ± 0.177	0.500	0.056	0.405
Tb.Th, mm	0.227 ± 0.010	0.228 ± 0.009	0.102	0.252 ± 0.011	0.251 ± 0.010	0.492	0.016*	0.979
Tb.Sp, mm	0.966 ± 0.107	0.946 ± 0.119	0.043*	1.278 ± 0.349	1.297 ± 0.387	0.500	0.056	0.760
Tb.BV/TV, %	15.60 ± 1.90	15.48 ± 1.71	0.581	15.92 ± 2.86	15.74 ± 2.67	0.223	0.690	0.854
Ct.Th, mm	0.989 ± 0.227	0.998 ± 0.228	0.043*	1.133 ± 0.089	1.117 ± 0.081	0.042*	0.310	0.138
Ct.Pm, mm	107.3 ± 5.9	107.5 ± 5.9	0.039*	98.6 ± 4.4	98.7 ± 4.4	0.041*	0.032*	0.703
Ct.Po, %	3.44 ± 1.00	3.06 ± 1.29	0.197	3.18 ± 1.88	3.50 ± 2.45	0.465	0.548	0.062

Tot.vBMD, total volumetric BMD; Tb.vBMD, trabecular volumetric BMD; Ct.vBMD, cortical volumetric BMD; Ct.Ar, cortical area; Ct.Th, cortical thickness; Ct.Pm, cortical perimeter; Ct.Po, cortical porosity; Tb.Ar, trabecular area; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation.
Data are presented as mean ± SD for normal distribution, median (interquartile range) for non-normal distribution data.
P-value for comparison of HR-pQCT parameters 12 months between 2 groups was adjusted for baseline HR-pQCT parameters.
* indicates statistically significant (P < 0.05).

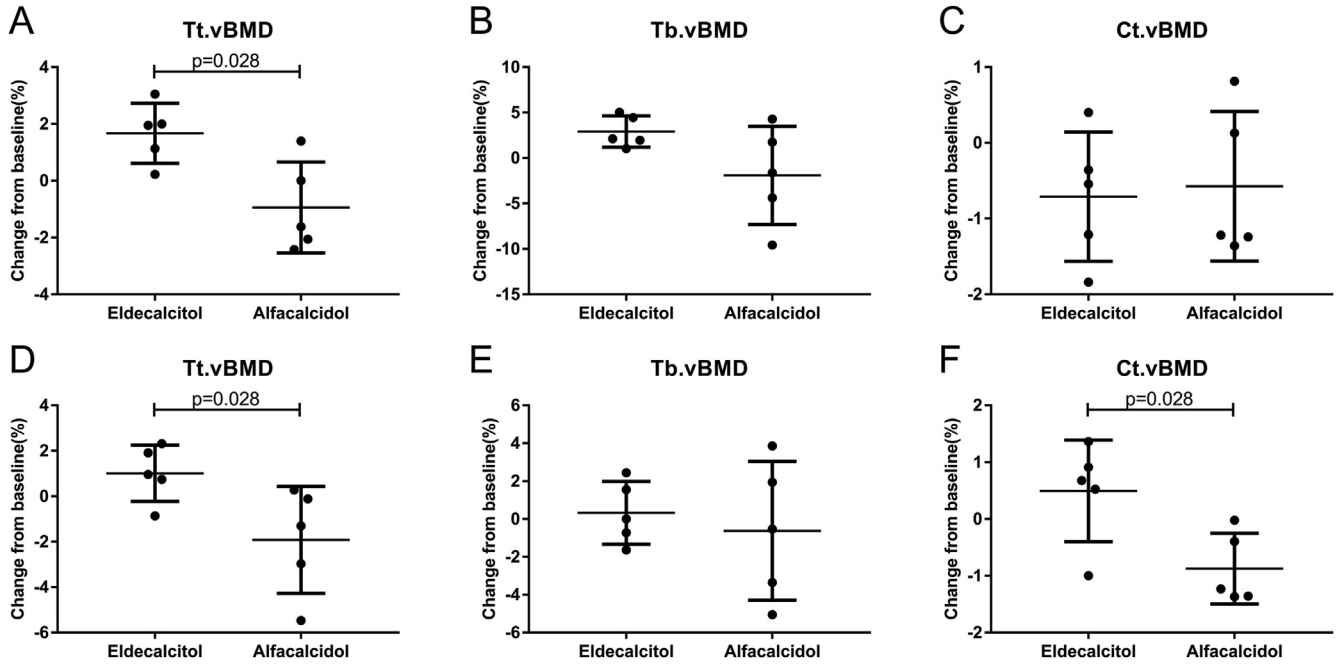

Fig. 1. Mean percent change from baseline at distal radius and tibia in Tt. vBMD, Tb. vBMD, and Ct. vBMD treated with eldecalcitol and alfacalcidol at the distal radius (A–C) and tibia (D–E). Tt. vBMD, total volumetric bone mineral density; Tb. vBMD, trabecular volumetric bone mineral density; Ct. vBMD, cortical volumetric bone mineral density. Bars represent P value < 0.05 between groups.

between-group difference (P = 0.047) (Fig. 2H). These results demonstrate that both cortical area and thickness were increased or maintained by eldecalcitol but not changed or decreased by alfacalcidol at both the radius and tibia. In addition, cortical porosity tended to decrease with eldecalcitol but to increase with alfacalcidol treatment at both the radius and the tibia (Fig. 2C and

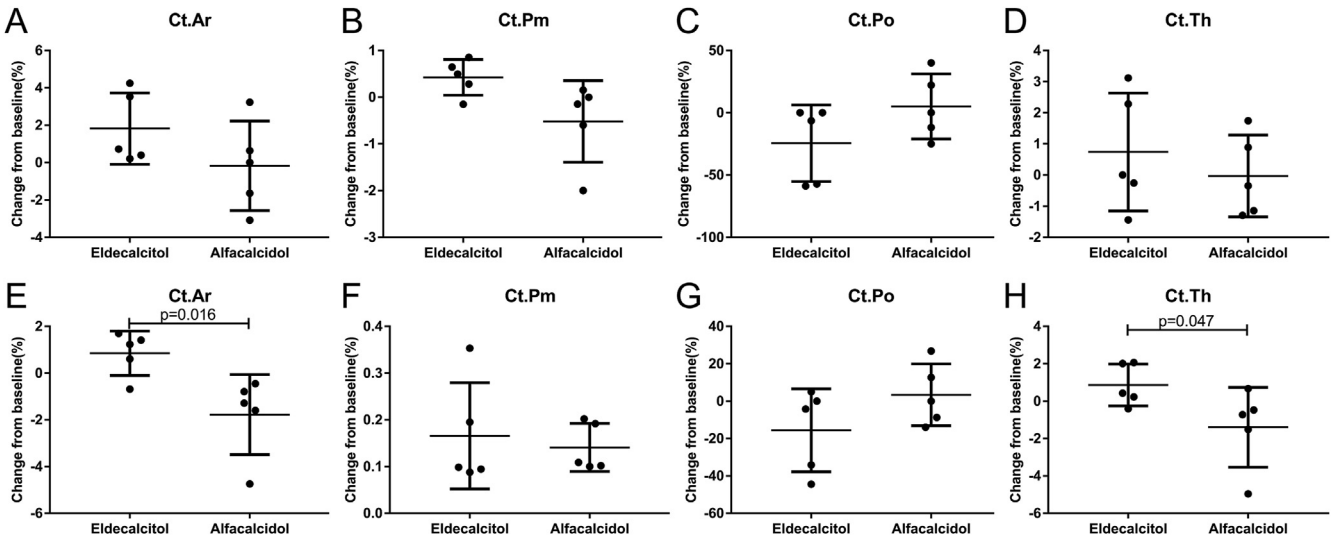

Fig. 2. Mean percent change from baseline at distal radius in Ct. Ar, Ct.Pm, Ct. Po, Ct. Th treated with eldecalcitol and alfacalcidol at the distal radius (A–D) and tibia (E–H). Ct. Ar, cortical area; Ct.Pm, cortical perimeter; Ct. Po, cortical porosity; Ct. Th, cortical thickness. Bars represent P value < 0.05 between groups.

G).

After adjustment for baseline HR-pQCT parameters, only the cortical area at the distal tibia after 12 months treatment remained significantly different between 2 groups (Table 2).

3.4. Trabecular microarchitecture

Changes in trabecular microarchitecture after 12 months treatment with eldecalcitol or alfacalcidol from baseline are shown in Fig. 3. At the radius, trabecular area or number did not change significantly in either eldecalcitol or alfacalcidol groups (Fig. 3A and B). Trabecular thickness increased by 1.97 ± 1.93% with eldecalcitol (P = 0.042 versus baseline) but tended to decrease with alfacalcidol, and there was a significant difference between 2 groups (P = 0.008) (Fig. 3C). There was a large variation in the measurement of trabecular separation (Fig. 3D), and no significant change from baseline or between-group difference were observed in the eldecalcitol and alfacalcidol groups.

At the tibia, trabecular area did not change with eldecalcitol but increased slightly with alfacalcidol (P = 0.013 for between-group comparison) (Fig. 3E). Trabecular number increased by 3.09 ± 3.04% in the eldecalcitol group (P = 0.043 versus baseline) but did not change in the alfacalcidol group (P = 0.047 for between-group comparison) (Fig. 3F). Trabecular thickness tended to increase in the eldecalcitol group and to decrease in the alfacalcidol group (Fig. 3G). Trabecular separation decreased by 2.22 ± 2.43% in the eldecalcitol group (P = 0.043) but tended to increase in the alfacalcidol group (P = 0.028 for between-group comparison) (Fig. 3H). Overall, the change in trabecular microarchitecture was less consistent between radius and tibia, but a similar tendency was observed in trabecular thickness with an increase by eldecalcitol and a slight decrease by alfacalcidol.

After adjustment for baseline HR-pQCT parameters, only the trabecular area at the distal tibia after 12 months treatment remained significantly different between the 2 groups. At the same time, trabecular number was higher and separation was lower at

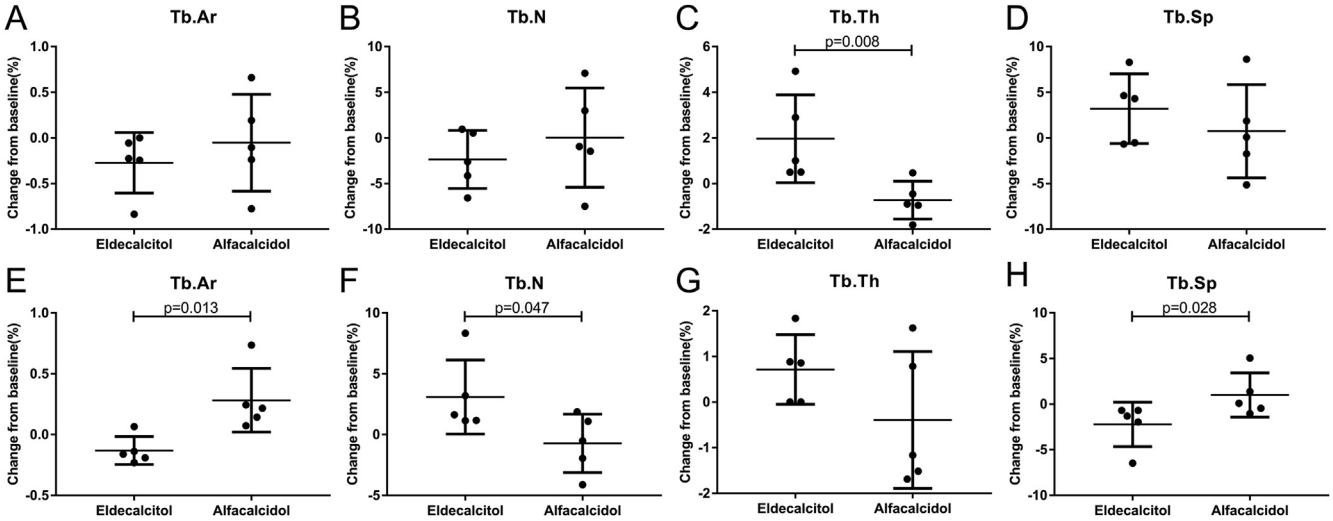

Fig. 3. Mean percent change from baseline in Tb.Ar, Tb.N, Tb.Th, Tb.Sp treated with eldecalcitol and alfacalcidol at the distal radius (A-D) and tibia (E-H). Tb.Ar, trabecular area; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation. Bars represent p value <0.05 between groups.

the distal radius in the eldecalcitol group than those in the alfacalcidol group (Table 2).

4. Discussion

This is the first study to explore the comparative effect of eldecalcitol and alfacalcidol on peripheral bone microstructure by HR-pQCT. This study extends our previous reports demonstrating superior efficacy of eldecalcitol on increasing aBMD compared with alfacalcidol [6], and in reducing vertebral and wrist fractures [5].

In the current study, total and trabecular vBMD increased in the eldecalcitol group at either the radius or the tibia, while cortical vBMD decreased in the alfacalcidol group at the tibia. Cortical area and thickness increased in the eldecalcitol group at either the radius or the tibia, while these parameters decreased with alfacalcidol at the tibia. Trabecular number and thickness increased by eldecalcitol at either the radius or the tibia, but did not increase by alfacalcidol. Trabecular separation decreased by eldecalcitol but tended to increase by alfacalcidol at the tibia. After 12 months treatment, patients in the eldecalcitol group had higher total vBMD and trabecular number with lower separation at the distal radius, and higher cortical vBMD, trabecular and cortical area at the distal tibia, than those in the alfacalcidol group. Thus, both cortical and trabecular microstructures were improved more by eldecalcitol at either the radius or the tibia than alfacalcidol.

Histomorphometric analysis in ovariectomized cynomolgus monkeys and rats demonstrated similar results to the present study that eldecalcitol increased cortical area and width in cortical bone, increased trabecular bone volume and thickness, and reduced trabecular separation by inhibiting bone turnover in trabecular bone [21,22]. These results indicate that eldecalcitol reduces bone resorption to maintain trabecular vBMD, cortical area and thickness more strongly than alfacalcitol. Age-related cortical bone loss is associated with trabecularization of the inner cortex due to enhanced bone resorption [3,23]. Since trabecularization of endocortical bone leads to increased trabecular bone marrow cavity and trabecular area, as well as decreased cortical thickness, cortical area and cortical vBMD, it is plausible to assume that the inhibitory effect of eldecalcitol on bone resorption was able to increase or maintain cortical thickness, cortical area and cortical vBMD. In contrast, alfacalcidol was unable to maintain cortical area and thickness, and slightly increased trabecular area at the tibia, suggesting that alfacalcidol could not counteract enhanced endocortical resorption in these patients.

In addition to the prevention of endocortical bone resorption and the maintenance of cortical compartment, there was a consistent tendency in both the radius and tibia that eldecalcitol, but not alfacalcidol, decreased cortical porosity, although the changes were not significant because of the small sample size and short treatment period. A previous study demonstrated that eldecalcitol reduced cortical porosity in ovariectomized cynomolgus monkeys [21]. Taken together, these results are consistent with the assumption that eldecalcitol can inhibit not only endocortical but also intracortical bone resorption to decrease cortical porosity, while alfacalcidol is unable to show such an effect.

Eldecalcitol slightly increased cortical perimeter at both the tibia and radius. Although aging is known to increase periosteal apposition, the result is congruent with the effect of eldecalcitol in CT-based assessment of bone geometry at the femoral shaft [22,24] and histomorphometric analysis of the tibial diaphysis in rats [22,24]. A study conducted on senescence-accelerated mouse strain P6 (SAM/P6) also demonstrated that eldecalcitol improved mechanical strength of the femoral diaphysis by enhancing periosteal bone formation [25]. The present results showing a slight increase in cortical perimeter may reflect those effects of eldecalcitol in the periosteal surface of cortical bones, which may play a role in maintaining bone strength [26]. Further study is needed to clarify the effect of eldecalcitol on periosteal bone formation.

Along with these changes in cortical bone, eldecalcitol, but not alfacalcidol, improved trabecular microstructure. Eldecalcitol increased trabecular thickness at the radius and trabecular number at the tibia without deteriorating cortical thickness at both sites. Trabecular separation decreased significantly with eldecalcitol at the tibia. It is important to note that eldecalcitol can improve trabecular bone microstructure without sacrificing cortical bone, and that these protective effects were not observed in the alfacalcidol group.

In the present study, there were more improvements in trabecular and cortical microstructure at the tibia than the radius, with more significant effect of eldecalcitol at the tibia. This discrepancy between the radius and the tibia may be related to the load-bearing nature of tibia. It was reported that eldecalcitol enhanced the cortical bone response to mechanical loading in rats, and that the interaction between loading and eldecalcitol increased bone formation rate at the endocortical surface [27]. Previous clinical studies with teriparatide and denosumab combination as well as parathyroid hormone (1–84) and ibandronate combination treatment also demonstrated more favorable effect at the tibia than the radius [28,29]. Thus, it is suggested that the advantage of weight-bearing bone is expected to amplify the skeletal response to therapeutic agents for osteoporosis including eldecalcitol. In addition, less motion artifact during HR-pQCT scan at the tibia may lead to greater precision than the radius, and mild improvement of bone microstructure could be detected [30].

Our study has limitations. First, as a preliminary report, our sample size was small, which may explain for the inconsistent results when we used different statistical analyses. Larger studies are needed to verify these results. Second, the parameters measured represent bone microstructure of the distal radius and the tibia. It is unclear whether these observations can be extrapolated to bone microstructure of the proximal part of limbs and axial skeleton. Thirdly, although we used second-generation HR-pQCT with partially reduced scan time, and repeated scanning to exclude images of poor quality, motion artifact due to the long scan time could not be totally eliminated, and may have affected the measurement precision [31].

5. Conclusions

In conclusion, eldecalcitol had the potential to exert positive effects on cortical and trabecular microstructure at peripheral bones, which can be explained by the suppression of high bone turnover. In addition, greater improvement of microstructure at the distal tibia than radius in the eldecalcitol group suggests that exercise may enhance the efficacy of eldecalcitol in load-bearing bones.

CRediT author statement

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Conflicts of interest

Weibo Xia and Toshio Matsumoto serve as consultants for Chugai Pharmaceutical Co., Ltd. Xiaolin Ni, Juan Feng, Yan Jiang, Li Zhang, Wei Yu, Ou Wang, Mei Li, Xiaoping Xing declare that they have no conflict of interest.

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