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Increased Bone Mineral Density and Improved Metabolic Bone Markers in Patients with Hypophosphatemic Rickets/Osteomalacia Treated with the Calcimimetic, Cinacalcet

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Abstract

Hypophosphatemic rickets/osteomalacia is a rare disorder characterized by renal phosphate wasting and low 1,25-dihydroxyvitamin D levels, leading to hypophosphatemia and abnormal bone mineralization. Patients are conventionally treated with a Vitamin D Receptor Activator (VDRA), but dosing is often limited because of side effects, such as hypercalcemia and/or hypercalciuria. This study aimed to assess the efficacy of the calcimimetic, cinacalcet, in the treatment of four adult patients with hypophosphatemic rickets/osteomalacia over a 2-year period. Patients continued VDRA (alfacalcidol) therapy, doses of which were adjusted to ensure that hypercalcemia or hypercalciuria was not present prior to cinacalcet administration. These doses were fixed for the first year but could be adjusted in the second. In the first year, cinacalcet 25 mg/day reduced serum Parathyroid Hormone (PTH) and Calcium (Ca) levels by 46% and 9%, respectively. Reduced serum PTH levels increased the tubular maximum reabsorption of phosphate to glomerular filtration rate by 112%; as a result, serum phosphorus levels increased by 38%. Reduced serum Ca levels enabled mean doses of alfacalcidol to be increased from 2.4 ± 1.3 to 3.3 ± 1.1 μg/day in the second year. Reduced serum bone-specific alkaline phosphatase levels indicated improved osteoblast maturation and bone calcification. In addition, cinacalcet administration increased bone mineral density by 26% and 16% in the lumbar spine and femur, respectively. Although the interpretation of these data is limited by the small number of participants and absence of controls, our results indicate the potential of this new therapeutic approach for patients with hypophosphatemic rickets/osteomalacia.

Keywords: Calcimimetic; Cinacalcet; Hypophosphatemic Osteomalacia; Hypophosphatemic Rickets; PTH; Vitamin D Receptor Activator

Introduction

Hypophosphatemic rickets/osteomalacia is a rare disorder characterized by renal phosphate wasting and low levels of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), leading to hypophosphatemia and abnormal bone mineralization [1]. Currently, large oral doses of a Vitamin D Receptor Activator (VDRA) and/or inorganic phosphorus (P) are the standard treatments [2]. Although these therapies are effective in raising serum P levels and resolving bone deformities and pain, dosing is often limited by nephrocalcinosis or secondary hyperparathyroidism [3] and treatment may, therefore, be inadequate. Burosumab (KRN23), a fully human monoclonal IgG1 antibody that neutralizes excess serum Fibroblast Growth Factor 23 (FGF23), has been evaluated in clinical trials of pediatric and adult patients with X-Linked Hypophosphatemic Rickets (XLH) [4,5]. In adults, burosumab treatment significantly increased the Tubular Maximum Reabsorption of Phosphate to Glomerular Filtration Rate (TmP/GFR), serum P levels, and $1,25(OH)_2D$ levels [4]. Burosumab also significantly improved patient perception of their physical functioning and stiffness scores [5]. Similar results could be expected in patients with other conditions, such as Tumor-Induced Osteomalacia (TIO); however, burosumab is currently under development and is not yet available for use in clinical practice.

Cinacalcet HCl (cinacalcet) is a calcimimetic, which acts by increasing the sensitivity of calcium (Ca) receptors on parathyroid cells to Reduce Parathyroid Hormone (PTH) levels and thereby

reduce serum Ca levels [6,7]. A single dose of cinacalcet has been shown to suppress PTH, leading to increases in serum P levels within 4 hours in eight patients with XLH [8]. Cinacalcet treatment has also been shown to result in increased TmP/GFR, allowing for a reduction in inorganic P supplementation; additional evidence of bone healing was also seen by bone scanning and biopsy in two patients with TIO [9]. While the beneficial effects of cinacalcet on phosphate metabolism in patients with hypophosphatemic rickets/osteomalacia have been reported, little is known about the effects on metabolic bone markers and Bone Mineral Density (BMD). In this study, we aimed to determine the effects of cinacalcet on metabolic bone markers and BMD in patients with hypophosphatemic rickets/osteomalacia, who were also receiving VDRA. The ability to increase VDRA dosing with concomitant cinacalcet therapy was also analyzed.

Subjects and Methods

Study Design and Participants

The study included four patients with hypophosphatemic rickets/osteomalacia (two with XLH, one with adefovir-induced hypophosphatemic osteomalacia, and one with TIO) treated at the Osaka City University Hospital. Patients with the following comorbidities were excluded: baseline corrected Ca (cCa) levels above or below the normal range (8.5-10.4 mg/dL); urinary Ca/creatinine (Cr) ratio > 0.3 mg/mg; renal insufficiency defined as estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m^2; metabolic bone disease (e.g., Paget's disease); endocrine disorders (e.g., primary hyperparathyroidism or hyperthyroidism); poorly controlled diabetes mellitus; rheumatoid arthritis; alcohol abuse; skeletal exposure to therapeutic irradiation; symptomatic nephrocalcinosis or urolithiasis; or metastatic bone tumor. Patients were followed up for 2 years after the initiation of cinacalcet therapy.

All participants received alfacalcidol for the treatment of rickets/osteomalacia. Maximum doses were identified for each patient to ensure that they did not exhibit hypercalcemia (cCa > 10.4 mg/dL) or hypercalciuria (urinary Ca/Cr ratio > 0.3 mg/mg) prior to cinacalcet administration; these doses were then fixed for the first year of the study. Cinacalcet was administered at 25 mg/day for 2 years. In the second year, the maximum doses of alfacalcidol were determined every 3 months, while again ensuring that patients did not exhibit hypercalcemia or hypercalciuria. Metabolic bone markers and BMD were evaluated at designated periods using Dual Energy X-Ray Absorptiometry (DXA). The study protocol was approved by the institutional ethics committee (Osaka City University Graduate School of Medicine, registration number 1365). All procedures were undertaken in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants.

Biochemical Parameters

Serum and second-void urine samples were collected in the morning after overnight fasting. Serum cCa, P, Cr, and albumin (Alb) levels were determined by enzymatic methods using a Hitachi 7450 autoanalyzer (Hitachi Co., Tokyo, Japan). If the serum Alb level was < 4.0 mg/dL, the cCa level was calculated according to the following equation: cCa level (mg/dL) = serum Ca level (mg/dL) + 4.0 - serum Alb level (g/dL). To assess renal function, eGFR was calculated using the following equation [10]: eGFR (mL/min/1.73 m^2) = 175 × serum $Cre^{-1.154}$ × $age^{-0.203}$. For women, this value was multiplied by 0.742. Serum whole PTH (wPTH) was measured by immunoradiometric assay (IRMA; Scantibodies Laboratory, Inc., Santee, CA, USA) [11]. Radioimmunoassay was used to measure serum $1,25(OH)_2D$ (Immunodiagnostic Systems, Boldon Business Park, England). Serum Bone Alkaline Phosphatase (BAP) and Serum Osteocalcin (OC) were determined using Enzyme Immunoassay (EIA) kit (Alkphase-B; Metra Biosystem, Mountain View, CA, USA) and with a two-site IRMA (Mitsubishi Kagaku Bioclinical Laboratories, Tokyo, Japan), respectively. Serum FGF23 was measured using sandwich ELISA kits (Kainos Laboratories, Tokyo, Japan).

Assessment of BMD And Trabecular Bone Score

Lumber Spine (LS) and Total Hip (TH) BMD was assessed by DXA using the Hologic QDR 4500A DXA system (Hologic Inc., Marlborough, MA, USA) at the baseline and after 2 years of cinacalcet treatment. All Trabecular Bone Score (TBS) measurements were performed by DXA using TBS insight software (Med-Imaps, Bordeaux, France). The TBS was obtained by directly reanalyzing a single acquired LS-DXA image. Regions showing degenerative changes and/or vertebral fractures were excluded from the LS-BMD and TBS calculations. Vertebral fractures were assessed using a semiquantitative method [12]. At least two measurements of LS in the L1-4 region were available for all patients. The TBS was determined in the same vertebrae and regions of measurement as those used for LS-BMD, with the TBS calculated as the mean value of the individual measurements for the vertebrae as previously described [13].

Statistical Analysis

Data are expressed as the number (%) or mean ± Standard Deviation (SD). Mean differences in clinical parameters from baseline following cinacalcet treatment were compared using one-way repeated-measures Analysis of Variance (ANOVA) followed by Dunnett's test. The changes in administered doses of alfacalcidol, LS-BMD, TH-BMD, and TBS were analyzed by Mann-Whitney's U test. P-values < 0.05 were considered to be statistically significant. All statistical analyses were performed using JMP software version 11.2.0 (SAS Institute, Cary, NC, USA).

Results

Participants

Patient baseline characteristics are summarized in (Table 1).

	Case 1	Case 2	Case 3	Case 4	Mean ± SD
Diagnosis	Rickets	Rickets	Osteomalacia	Osteomalacia	
Gender	Female	Female	Female	Male	
Age, years	40	56	62	66	56 ± 10
cCa, mg/dL	9.8	10.2	9.5	9.8	9.8 ± 0.2
P, mg/dL	1.7	2.6	2.2	1.6	2.0 ± 0.1
TmP/GFR, mg/dL	0.92	0.89	1.10	1.53	1.11 ± 0.30
wPTH, pg/mL	19.4	82.5	20.2	20.2	35.6 ± 31.3
BAP, µg/L	34.3	77.9	151.0	299.9	140.8 ± 116.5
LS-BMD, g/cm^2	1.093	0.709	0.511	1.123	0.859 ± 0.299
TH-BMD, g/cm^2	0.698	0.602	0.339	0.779	0.601 ± 0.191
TBS	1.414	1.182	1.120	1.265	1.245 ± 0.077

cCa, corrected calcium; P, phosphorus; TmP/GFR, tubular maximum reabsorption of phosphate per glomerular filtration rate; wPTH, whole parathyroid hormone; BAP, bone-specific alkaline phosphatase; LS-BMD, lumbar spine bone mineral density; TH-BMD, total hip bone mineral density; TBS, trabecular bone score.

Table 1: Patient baseline characteristics.

Two participants were diagnosed with hypophosphatemic rickets in infancy and treated with alfacalcidol. Both patients exhibited elevated serum FGF23 levels at baseline. Participants 3 and 4 were cases of adult-onset hypophosphatemic osteomalacia. Case 3 exhibited osteomalacia with suppressed serum FGF23 levels (2.9 pg/mL) after receiving adefovir (for the treatment of mild but incurable chronic hepatitis B), suggesting a diagnosis of adefovir-induced hypophosphatemic osteomalacia. More than 2 years' VDRA treatment stabilized their metabolic bone markers and BMD; serum FGF23 level increased during VDRA (1.5 µg/day alfacalcidol) treatment to 300 pg/mL at the start of this study. Adefovir therapy continued during the study period at a stable dose. Case 4 exhibited adult-onset hypophosphatemic osteomalacia with elevated serum FGF23 levels, suggesting TIO; however, no causative tumor was identified.

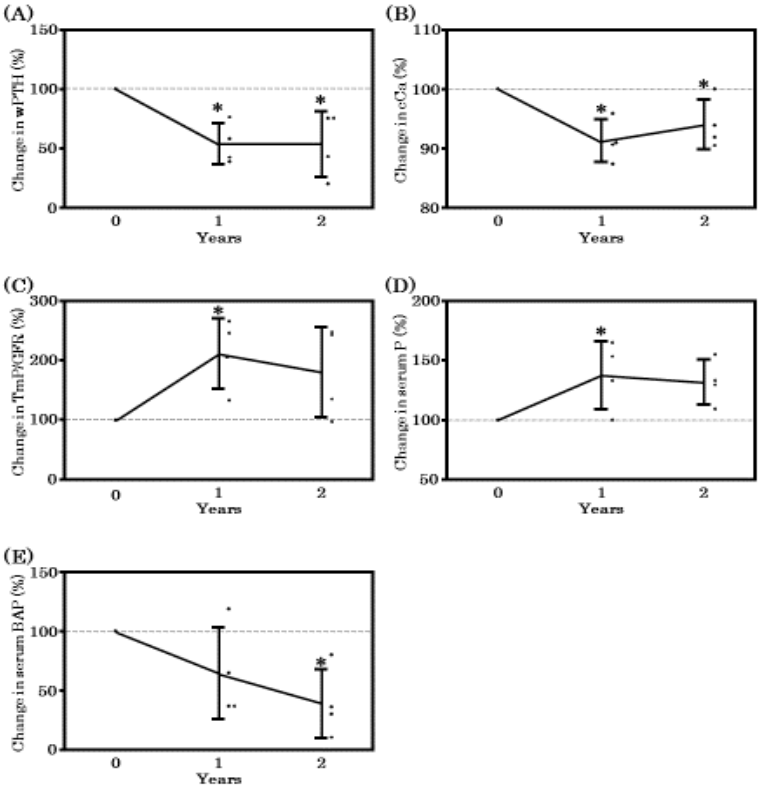
Changes in Serum and Urinary Parameters

Cinacalcet 25 mg/day was associated with a significant reduction in serum wPTH and cCa levels in the first year (46% and 9% reduction, respectively, $P < 0.05$); (Figure 1A and 1B). Urinary Ca/Cre ratio decreased in the first year but did not reach statistical significance (Table 2). Reduced serum wPTH resulted in increased P reabsorption, as shown by an increase in TmP/GFR of 112% ($P < 0.05$; Figure 1C). As a result, serum P levels increased by 38% ($P < 0.05$; Figure 1D), which is beneficial for bone calcification. Serum $1,25(OH)_2D$ levels increased in the first year, but these changes did not reach statistical significance (Table 2).

	Baseline	1 year	2 years
Alb, g/dL	4.1 ± 0.5	4.4 ± 0.3	4.3 ± 0.1
Cr, mg/dL	0.53 ± 0.06	0.57 ± 0.08	0.58 ± 0.10
eGFR, mL/min/1.73 m^2	97.8 ± 2.5	92.0 ± 14.3	90.8 ± 18.7
ALP, IU/L	952 ± 662	553 ± 236	419 ± 256
OC, U/L	7.2 ± 1.3	7.6 ± 2.9	7.3 ± 5.4
CTX, ng/mL	1.042 ± 0.367	1.029 ± 0.499	1.113 ± 0.634
FGF23, pg/mL	346 ± 128	276 ± 118	328 ± 94
25OHD, ng/mL	12.7 ± 5.8	12.5 ± 4.9	14.0 ± 5.0
$1,25(OH)_2D$, pg/mL	56.3 ± 18.7	76.8 ± 32.3	88.0 ± 31.1
U-Ca/Cr, mg/mgCr	0.22 ± 0.20	0.17 ± 0.07	0.25 ± 0.09

Alb, albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; OC, osteocalcin; CTX, collagen C-terminal telopeptide; FGF23, fibroblast growth factor 23; 25OHD, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; U-Ca/Cr, urinary calcium/creatinine ratio. No significant change was observed in these parameters by repeated-measures one-way ANOVA.

Table 2: Changes in clinical parameters during cinacalcet treatment.



Figures 1(A-E): Changes in clinical parameters after the initiation of cinacalcet. **A**) wPTH, **B**) cCa, **C**) TmP/GFR, **D**) serum P, and **E**) serum BAP. Data are presented as mean ± SD. Changes in all parameters were statistically significant by repeated-measures one-way ANOVA. *P < 0.05 vs baseline by Dunnett's test. wPTH, whole parathyroid hormone; cCa, corrected calcium; TmP/GFR, tubular maximum reabsorption of phosphate per glomerular filtration rate; P, phosphate; BAP, bone-specific alkaline phosphatase.

The observed reductions in cCa enabled mean alfacalcidol dosing to be increased from 2.4 ± 1.3 to 3.3 ± 1.1 μg/day in the second year ($P < 0.05$; Figure 2). Although increased alfacalcidol doses in the second year were accompanied by increased cCa, $1,25(OH)_2D$, and urinary Ca/Cre ratio, these changes were not statistically significant (Table 2). No notable changes in eGFR and 25OHD were seen during the study. Cinacalcet treatment was well tolerated, with no patients experiencing side effects.

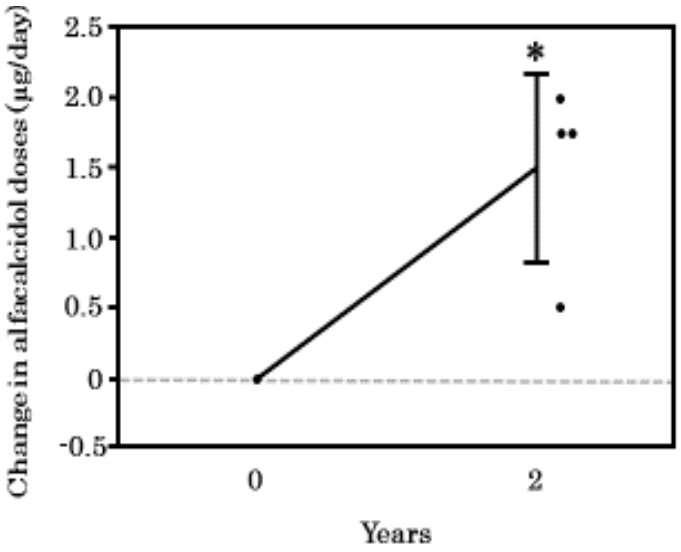


Figure 2: Alfacalcidol dosing over the study period. Alfacalcidol dose was fixed for the first year of cinacalcet administration; in the second year, the maximal doses of alfacalcidol were determined every 3 months for each participants, while ensuring that patients did not exhibit hypercalcemia (cCa > 10.4 mg/dL) or hypercalciuria (urinary calcium/creatinine ratio > 0.3 mg/mg). Data are presented as mean ± SD. *$P < 0.05$ vs baseline by Mann-Whitney's U test.

Changes in Metabolic Bone Markers and Bone Architecture

Cinacalcet treatment and increased alfacalcidol dosing resulted in reduced serum BAP levels in the second year, suggesting improved maturation of osteoblasts and bone calcification status ($P < 0.05$; Figure 1E). No notable changes were seen in terms of OC and collagen C-Terminal Telopeptide (CTX). Cinacalcet therapy reduced serum FGF23 levels in the first year, and increased alfacalcidol dosing resulted in increased levels in the second year, although these changes were not statistically significant (Table 2). Treatment increased BMD in the lumbar spine by 26% and in the femur by 16%, but no significant effects were seen on TBS (Figure 3).

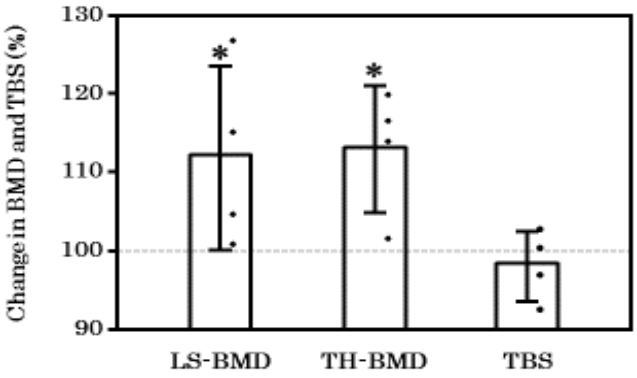


Figure 3: Change in BMD and TBS after the initiation of cinacalcet. Changes in Lumber Spine (LS) BMD, Total Hip (TH) BMD, and TBS were observed after 2 years' cinacalcet therapy. Data are presented as mean ± SD. *$P < 0.05$ vs baseline by Mann-Whitney's U test.

Discussion

This study assessed the efficacy of cinacalcet for the treatment of hypophosphatemic rickets/osteomalacia in four patients who also received conventional VDRA therapy with alfacalcidol. Alfacalcidol dose was adjusted to ensure that patients did not exhibit hypercalcemia and/or hypercalciuria prior to receiving cinacalcet. These doses were then fixed for the first year but could be adjusted in the second. The addition of cinacalcet reduced serum PTH and Ca levels; the reduced serum PTH resulted in increased phosphate reabsorption, as indicated by increased TmP/GFR. In addition, the decreased serum PTH reduced serum Ca levels and urinary Ca excretion, enabling higher doses of alfacalcidol to be administered. As a result, serum phosphate levels increased, which is beneficial for bone calcification in hypophosphatemic patients. Serum 25OHD levels were low and stable during the study, suggesting that the nutritional vitamin D status of the participants was poor and not improved by cinacalcet treatment. An increase in serum $1,25(OH)_2D$ levels was seen with higher alfacalcidol doses, but this change was not statistically significantly.

Treatment was seen to reduce serum BAP levels, a metabolic bone marker for immature osteoblasts, indicating improved maturation of osteoblasts and bone calcification status. Increased serum P levels is beneficial for osteoblast maturation in the hypophosphatemic patient. Serum OC levels, a metabolic bone marker for mature osteoblasts, were stable during the study. FGF23 levels and urinary Ca/Cre ratios decreased in the first year, although not significantly. As PTH stimulates osteocyte production

and secretion of FGF23 [14,15], the decrease in PTH levels as a result of cinacalcet treatment resulted in decreased FGF23 levels in the first year. Urinary Ca/Cre decreased in accordance with the reduction in serum Ca levels in the first year. In the second year, increased alfacalcidol dosing resulted in higher FGF23 levels and increased urinary Ca/Cre ratios. Hyp is a mouse model of XLH, in which high levels of osteocyte FGF23 expression are seen, leading to hypophosphatemia and ricketic bone abnormalities. Deletion of FGF23 in osteoblasts and osteocytes resulted in reduced serum FGF23 levels, increased serum P levels, and normalized ricketic bone abnormalities in the mice [16], indicating the importance of bone FGF23 expression in XLH. In addition, bone-derived FGF23 regulates osteocyte function as an autocrine/paracrine factor [17]. Alfacalcidol stimulates FGF23 secretion *in vivo* [18] and also in CKD patients [19]. In this study, although increased doses of alfacalcidol also resulted in higher serum FGF23 levels, this was outweighed by the beneficial effects in terms of osteoblast maturation and BMD.

CTX, a marker of bone resorption, remained stable during the study, suggesting that cinacalcet and/or additional alfacalcidol administration did not affect osteoclast function. Levels of another osteoclast marker, urinary N-telopeptide of collagen type I, were reported to be within normal ranges in patients with XLH and TIO treated with conventional therapy [20]. Although serum PTH levels were reduced by cinacalcet, this did not appear to impact on osteoclast function.

Cinacalcet administration resulted in improvements in BMD of more than 10% in both the lumbar spine and femur. By contrast, a 6-year prospective study failed to demonstrate BMD improvement in patients treated with conventional therapy (alfacalcidol) and inorganic phosphate, in comparison with no treatment [21]. The calcimimetic R568 also failed to increase BMD in the Hyp mouse model [22]. In the present study, cinacalcet itself and/or increased alfacalcidol dosing as a result of cinacalcet administration was seen to be beneficial in terms of BMD. Impaired trabecular microarchitecture has been shown in the distal radius and distal tibia using high-resolution peripheral quantitative computed tomography in patients with XLH [23]. In the present study, TBS was not affected by treatment, and trabecular microarchitecture in the LS in all participants assessed by TBS was better than the age-matched mean reported in the Japanese Population-Based Osteoporosis (JPOS) baseline study [24]. Therefore, while increases in serum P levels seen in this study may improve calcification in osteomalacic bone, improvement in trabecular microarchitecture was not seen. Further investigation is required to clarify these mechanisms.

The main limitations of this study are the small number of participants, absence of control subjects, and retrospective study design. In addition, three of the participants (cases 1, 2, and 4) were cases of FGF23-related hypophosphatemic rickets/osteomalacia, while case 3 was not. Although the cause of rickets/osteomalacia differed among the participants, all responded to treatment in a similar manner, suggesting that cinacalcet could be beneficial to patients who are not suitable for burosumab therapy, such as those with non-FGF23-related hypophosphatemic rickets/osteomalacia. In conclusion, the addition of cinacalcet to conventional treatment was beneficial in patients with hypophosphatemic rickets/osteomalacia. Cinacalcet increased serum P levels and enabled increased dosing of VDRA. Cinacalcet treatment improved BMD in the LS and femur, possibly by accelerating bone calcification as a result of increased serum P levels.

Acknowledgments

NH contributed to the acquisition, analysis, and interpretation of the data. YI, ME, and MI contributed to the conception and design of the study. NH, YI, MO, DM, and YN contributed to the acquisition of the data. DM was responsible for the integrity of the data analysis. All authors participated in drafting or revising the manuscript and approved the final version of the manuscript for submission.

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