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ORIGINAL ARTICLE

The Effects of Combined Treatment of Alendronate Plus Active or Plain Vitamin D on the Vitamin D Metabolism and Bone Turnover Markers in Patients with Osteoporosis

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Background: The purpose of this study was to evaluate the effects of combined treatment with alendronate plus active or plain vitamin D on the vitamin D metabolism and bone turnover markers in patients with osteoporosis.
Methods: We investigated 297 osteoporosis outpatients who were treated with Maxmarvil® (alendronate 5 mg plus calcitriol 0.5 μg) daily or Fosamax Plus® (alendronate 70 mg plus cholecalciferol 2,800 IU) weekly for 1 year. The serum levels of 25(OH)D, parathyroid hormone (PTH), calcium, phosphorus, osteocalcin and N-telopeptide were measured at baseline and after 3, 6, and 12 months of treatment.
Results: The data of 72 of the 297 patients were analyzed. In the Maxmarvil® group (n = 45), the serum PTH significantly decreased by 17% from baseline at 6 months (μd = -6.10; ± 0.85 SE; $P < 0.05$) and it remained suppressed to 12 months. The serum 25(OH)D tended to increase, but without significance. In the Fosamax Plus® group (n = 27), the serum 25(OH)D significantly increased by 77% from baseline at 3 months (μd = 9.87; ± 2.32 SE; $P < 0.05$) and it remained significantly higher than baseline at 6 months (μd = 3.49; ± 0.86 SE; $P < 0.05$) and 12 months (μd = 10.47; ± 0.71 SE; $P < 0.001$). However, the serum PTH showed no significant decrease. In the Maxmarvil® group, the serum osteocalcin significantly decreased by 26% from baseline at 12 months (μd = -5.15; ± 0.35 SE; $P < 0.05$), and in the Fosamax Plus® group, the serum osteocalcin significantly decreased by 19% from baseline at 6months (μd = -2.64; ± 0.73 SE; $P < 0.05$) and it remained suppressed to 12 months (μd = -2.99; ± 0.37 SE; $P = 0.32$) without significance.
Conclusion: Maxmarvil® and Fosamax Plus® both improved the bone metabolism in Korean osteoporosis patients. Maxmarvil® significantly lowered the serum PTH levels, whereas Fosamax Plus® significantly elevated the serum 25(OH)D levels. (*Endocrinol Metab* 25:305-309, 2010)

Key Words: Calcitriol, Cholecalciferol, Bisphosphonates, Bone metabolism

INTRODUCTION

Osteoporosis has reached pandemic levels in elderly women and has markedly increased the incidence of bone fractures and mortality [1]. Pharmacological agents have been used for the prevention and treatment of osteoporosis, such as, bisphosphonates, raloxifene, and parathyroid hormone (PTH). Nevertheless, calcium and vitamin D are still widely regarded as first-line management strategies, either alone or in combination with other therapies, because of the high prevalence of vitamin D deficiency in elderly people [2].

The major causes of vitamin D deficiency are a lack of exposure to the sun and a low dietary intake [3]. Vitamin D deficiency is usually defined as 25(OH) D level below 50 nmol/L (20 ng/mL), and according to this definition, vitamin D deficiency approaches 30%, even among postmenopausal women living in the developed countries regardless of latitude [4].

The National Osteoporosis Foundation (NOF) recommends a daily vitamin D dose of 400-800 International Units (IU) for those aged < 50 and of 800-1,000 IU for those aged ≥ 50 [5]. However, in practice many osteoporosis patients do not take these recommended amounts. Vitamin D decreases the risk of osteoporotic fracture in postmenopausal women. However, the optimal form of vitamin D remains controversial, and although some studies have shown vitamin D analogs to be advantageous in some patients, these analogs are more expensive, and in the case of calcitriol, may be more likely to cause hypercalcemia than parent compound [6].

Combining vitamin D with bisphosphonate increases calcium

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availability and stabilizes urinary calcium excretion. Furthermore, several authors have suggested that active vitamin D calcitriol and alfacalcidol [7] are interesting adjunctive partners for antiresorptive drugs like bisphosphonates [8]. This complementary effects might be due to suppressed bone turnover when administered with bisphosphonate, and the pleiotropic effects of vitamin D on calcium absorption, PTH reduction, bone mineralization and turnover, muscle function, and on the risk of falling.

The purpose of this study is to evaluate the effects of combined treatments with alendronate plus active or plain vitamin D on vitamin D status and bone turnover markers in patients with osteoporosis.

METHODS

This study was based on a retrospective chart review of medical records in the Endocrinology Clinic in the Ajou University Hospital. Total 297 patients from January 1, 2005 to September 15, 2008 who treated with combined agent of alendronate 5 mg and calcitriol 0.5 μg (Maxmarvil®, Yuyu Co., Korea) daily or alendronate 70 mg and cholecalciferol 2,800 IU (Fosamax Plus®, MSD Co., Korea) weekly were evaluated. The patients with concomitant diseases or those taking medications affecting vitamin D metabolism were excluded. Finally 72 patients were included in this study.

Serum 25(OH)D, parathyroid hormone (PTH), calcium, phosphorus, osteocalcin and N-telopeptide levels were measured at 0, 3, 6, and 12 months of treatment. Serum 25(OH)D levels were measured by radioimmunoassay using DiaSorin 25(OH)D ^{125}I RIA kits (detecting total D_2 and D_3 25OHD, inter-assay coefficient of variation 11.7%) (DiaSorin, Stillwater, MN, USA). Serum parathyroid hormone levels were measured by radioimmunoassay using ELSA-PTH kit (inter-assay coefficient of variation 6.8%) (CIS Bio International, Gif Sur Yvette, Cedex, France). Serum calcium and phosphorus were measured by automatic analyzer TBA, 200FR, (Toshiba, Japan). Osteocalcin was measured by radioimmunoassay using OSTEO-RIACT kit (inter-assay coefficient of variation 5.2%) (CIS Bio International, Gif Sur Yvette, Cedex, France). N-telopeptide type I collagen was measured by Vitros Enhanced Chemiluminescence Immunoassay (Ortho-Clinical Diagnostics, Amersham, UK). Finally, lumbar spine and total hip BMD were measured at baseline by dual-energy X-ray absorptiometry (DXA, Prodigy Advance, GE Lunar Co., Madison, WI, USA).

Table 1. Baseline characteristics of subjects

Variables	Maxmarvil® group	Fosamax Plus® group	*P*-value
Age (years)	60.1 ± 0.4	65.7 ± 0.7	< 0.05
Male:Female	6:39	1:26	
25(OH)D (ng/mL)	11.9 ± 0.3	12.9 ± 0.4	NS
PTH (pg/mL)	35.9 ± 0.9	42.6 ± 1.7	NS
Calcium (mg/dL)	9.25 ± 0.02	9.16 ± 0.03	NS
Phosphorus (mg/dL)	3.51 ± 0.03	3.62 ± 0.05	NS
Osteocalcin (ng/mL)	20.2 ± 0.4	14.1 ± 0.4	< 0.05
NTx (nM/mM Cr)	45.7 ± 1.1	31.9 ± 1.1	< 0.05
BMD, L-spine (g/cm^2)	0.897 ± 0.006	0.880 ± 0.013	NS
BMD, femur total (g/cm^2)	0.796 ± 0.006	0.763 ± 0.011	NS

Values are mean ± SE; Maxmarvil® group, Alendronate 5 mg and calcitriol 0.5 μg (Maxmarvil®) daily (n = 45); Fosamax Plus® group, Alendronate 70 mg and cholecalciferol 2,800 IU (Fosamax Plus®) weekly (n = 27); 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; NTx, N-telopeptide of type I collagen; BMD, bone mineral density.

The follow-up data of the two treatment groups were analyzed with ANOVA repeated measure. The statistical differences between the two groups at baseline were examined with *t*-test. The μd is the statistical term which denotes the mean difference between groups.

RESULTS

The baseline characteristics of two groups were similar (Table 1). In both the Maxmarvil® (alendronate and calcitriol) and Fosamax Plus® (alendronate and cholecalciferol) group, there was no significant change in serum calcium, phosphorus and N-telopeptide levels during 3, 6, and 12 months, respectively.

In the Maxmarvil® group, serum 25(OH)D showed no significant change. In the Fosamax Plus® group, serum 25(OH)D increased by 77% from baseline at 3 months (μd = 9.87; ± 2.32 SE; $P < 0.05$) and remained significantly higher than baseline at 6 months (μd = 3.49; ± 0.86 SE; $P < 0.05$) and 12 months (μd = 10.47; ± 0.71 SE; $P < 0.001$) [9] (Fig. 1).

In the Maxmarvil® group, serum PTH significantly decreased by 17% from baseline at 6 months (μd = -6.10; ± 0.85 SE; $P < 0.05$) and remained suppressed at 12 months (μd = -3.34; ± 0.95 SE; $P = 0.54$) without significance. However, in the Fosamax Plus® group, serum PTH showed no significant change (Fig. 2).

In the Maxmarvil® group, serum osteocalcin significantly decreased by 26% from baseline at 12 months (μd = -5.15; ± 0.35 SE; $P < 0.05$), and in the Fosamax Plus® group, serum osteocalcin significantly decreased by 19% from baseline at 6 months (μd = -2.64;

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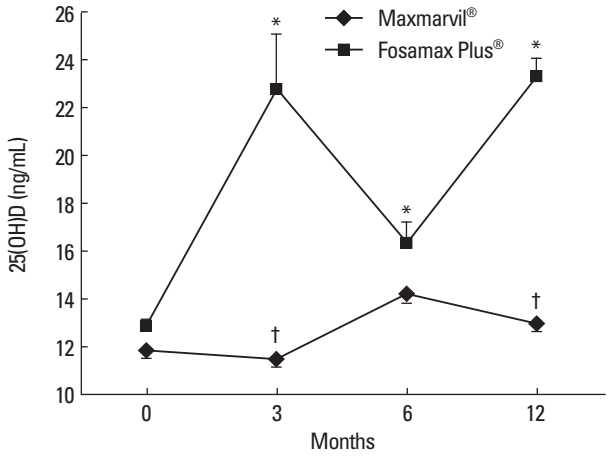

Fig. 1. The effect of combined treatment of alendronate and active or plain vitamin D on serum 25(OH)D. In the Maxmarvil® group, serum 25(OH)D showed no significant change. However, in the Fosamax Plus® group, serum 25(OH)D increased by 77% from baseline at 3 months (μd = 9.87; ± 2.32 SE; $P < 0.05$) and remained significantly higher than baseline at 6 months (μd = 3.49; ± 0.86 SE; $P < 0.05$) and 12 months (μd = 10.47; ± 0.71 SE; $P < 0.001$).
*$P < 0.05$ vs. baseline value; †$P < 0.05$ vs. Fosamax Plus® group.

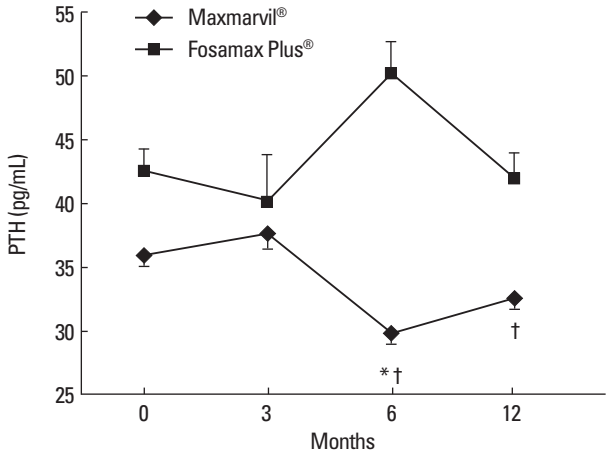

Fig. 2. The effects of combined treatment of alendronate and active or plain vitamin D on serum PTH. In the Maxmarvil® group, serum PTH decreased by 17% from baseline at 6 months (μd = -6.10; ± 0.85 SE; $P < 0.05$) and remained suppressed at 12 months (μd = -3.34; ± 0.95 SE; $P = 0.54$) without significance. In the Fosamax Plus® group, serum PTH showed no significant change.
*$P < 0.05$ vs. baseline value; †$P < 0.05$ vs. Fosamax Plus® group.

± 0.73 SE; $P < 0.05$) and remained suppressed at 12 months (μd = -2.99; ± 0.37 SE; $P = 0.32$) without significance (Fig. 3).

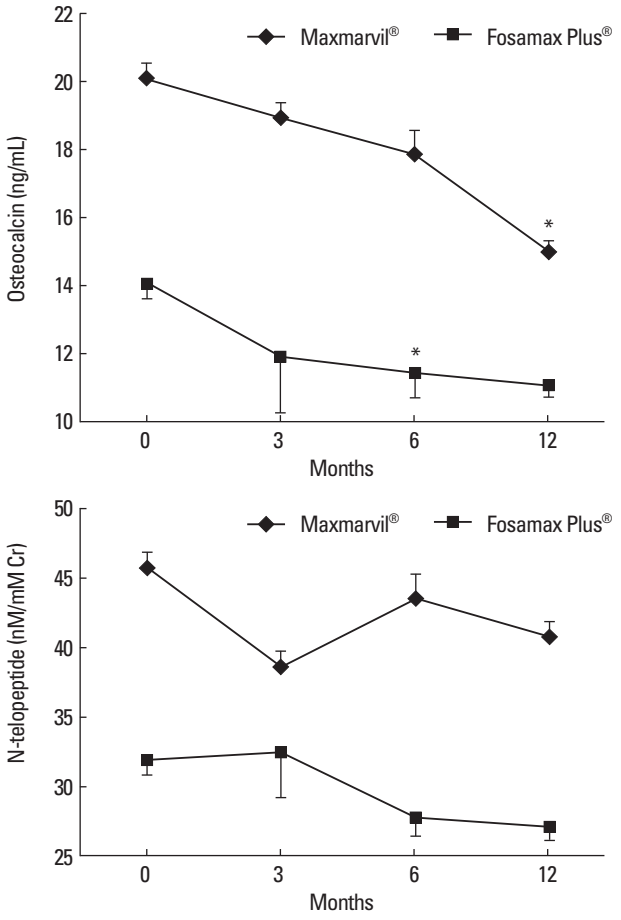

Fig. 3. The effects of combined treatment of alendronate and active or plain vitamin D on serum bone turnover markers. In the Maxmarvil® group, serum osteocalcin decreased by 26% from baseline at 12 months (μd = -5.15; ± 0.35 SE; $P < 0.05$). In the Fosamax Plus® group, serum osteocalcin decreased by 19% from baseline at 6 months (μd = -2.64; ± 0.73 SE; $P < 0.05$) and remained suppressed at 12 months (μd = -2.99; ± 0.37 SE; $P = 0.32$) without significance. In both group, N-telopeptide showed no significant change.
*$P < 0.05$ vs. baseline value.

DISCUSSION

Bisphosphonates act on osteoclasts to induce apoptosis, and thus, decrease bone resorption. Accordingly, bisphosphonate therapy increases bone mineral density and reduces fracture risk [10]. In particular, alendronate is a potent inhibitor of bone resorption, and causes sustained reductions in the biochemical markers of bone remodeling and produces consistent dose-related increases in bone mineral density regardless of age and gender. Furthermore, these effects of alendronate have been associated with a substantially reduced risk of vertebral and non-vertebral fractures [11].

In primary osteoporosis (postmenopausal or senile), the supplementation of vitamin D has a role because the interaction between $1,25(OH)_2D_3$ and vitamin D receptor increases the efficiency of intestinal calcium and phosphorus absorption [12]. Primary vitamin D deficiency is caused by an inadequate supply of the precursors. In $1,25(OH)_2D_3$ deficiency or resistance, plain vitamin D cannot correct the defect. Accordingly active vitamin D (alfacalcidol or cal-

citriol) can overcome the limit of plain vitamin D in those conditions. Furthermore active vitamin D analogs can bypass the feedback regulation that controls renal $1,25(OH)_2D_3$ synthesis, thus, active vitamin D increases serum $1,25(OH)_2D_3$ and correct the vitamin D deficiency and improves the calcium absorption more effectively than plain vitamin D [13].

The Fosamax Plus® has been reported to provide the same antiresorptive benefit as Fosamax® and to improve vitamin D status. In addition, Fosamax Plus® was not found to be associated with hypercalcemia, hypercalciuria, or other adverse effects [14].

There are recent studies reporting that active vitamin D is more effective in osteoporosis treatment than plain vitamin D. Francis et al. [15] directly compared the effect of alfacalcidol and vitamin D_2 on calcium absorption, serum PTH, and bone turnover in 46 women with postmenopausal osteoporosis in one randomized, single-blinded, controlled study. They showed that the 6-month alfacalcidol (0.5 μg/day) treatment improved calcium absorption, suppressed secondary hyperparathyroidism, and reduced bone turnover. In contrast, daily treatment with 500-1,000 IU vitamin D for the same time period had no significant effect on any of the measured parameters [15]. Ringe et al. [16] showed that alendronate plus alfacalcidol was better than alendronate plus plain vitamin D or alfacalcidol alone in terms of increasing vertebral and femoral BMDs and reducing back pain and fractures. Furthermore, no negative interactions between alendronate and alfacalcidol have been reported, whereas a reduction in alfacalcidol-induced hypercalcuria has been reported for this combination [16]. Richy et al. [17] conducted a meta-analysis study of the effects of plain vitamin D versus active vitamin D (alfacalcidol and calcitriol). All randomized, controlled, double-blinded trials that compared oral plain and active vitamin D to placebo were included. It was concluded that alfacalcidol and calcitriol possibly are more effective at preventing spinal bone loss in primary osteoporosis than plain vitamin D [17]. In the present study, we compared the effects of calcitriol versus cholecalciferol with combination of alendronate in Korean osteoporotic patients. Serum vitamin D status and bone turnover markers were followed-up for 12 months (relatively long duration) in a real world clinical practice setting. The limitations of our study are that was based on a retrospective chart review, subjects were not randomized, the sample size was relatively small, patient compliance was not checked, and some data were missing.

In conclusion, alendronate 5 mg and calcitriol 0.5 μg (Maxmarvil®) daily or alendronate 70 mg and cholecalciferol 2,800 IU (Fosamax Plus®) weekly both improved bone metabolism in Korean osteoporosis patients. Maxmarvil® was found to have a significant effect on lowering serum PTH levels, whereas Fosamax Plus® significantly elevated serum 25(OH)D levels.

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