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# Comparison of the effects of eldecalcitol and alfacalcidol on bone and calcium metabolism☆

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ABSTRACT

Eldecalcitol [ED-71, 2β-(3-hydroxypropyloxy)-1,25-dihydroxyvitamin $D_3$] increases lumbar and hip bone mineral density (BMD) in a dose-dependent manner in osteoporotic patients with vitamin D supplementation. However, there has been no head-to-head comparison of the effects of eldecalcitol with alfacalcidol on bone and calcium metabolism in human subjects. Therefore, a randomized open-label clinical trial was conducted to compare the effect of eldecalcitol on bone turnover markers and calcium metabolism in 59 Japanese postmenopausal women. Subjects were randomly assigned to receive 1.0 μg alfacalcidol, 0.5 or 1.0 μg eldecalcitol once a day for 12 weeks. There was almost no increase in serum calcium (Ca) throughout the study period. Eldecalcitol from 0.5 to 1.0 μg increased daily urinary Ca excretion in a dose-dependent manner, and 1.0 μg eldecalcitol increased urinary Ca to a similar extent to 1.0 μg alfacalcidol. Both 0.5 and 1.0 μg eldecalcitol suppressed urinary NTX stronger than 1.0 μg alfacalcidol (−6, −30 and −35% in 1.0 μg alfacalcidol, 0.5 and 1.0 μg eldecalcitol-treated groups, respectively, at 12 weeks). In contrast, changes in serum BALP were similar among the three groups (−22, −22 and −29% in 1.0 μg alfacalcidol, 0.5 and 1.0 μg eldecalcitol-treated groups, respectively, at 12 weeks). These results demonstrate that 0.5–1.0 μg eldecalcitol can effectively inhibit bone resorption stronger than alfacalcidol with a similar effect on bone formation and a comparable effect on urinary Ca excretion, and suggest that eldecalcitol may have a better osteoprotective effect than alfacalcidol.



## 1. Introduction

In an effort to find out an analog of 1,25-dihydroxyvitamin $D_3$ [1,25$(OH)_2D_3$] with potent effects on bone, we have developed eldecalcitol [ED-71, 2β-(3-hydroxypropyloxy)-1,25-dihydroxyvitamin $D_3$]. Eldecalcitol binds to the nuclear vitamin D receptor with less affinity but to serum vitamin D-binding protein with higher affinity than 1,25$(OH)_2D$, showing a long half life in plasma [1]. Eldecalcitol has been shown to increase bone mass [2], and to have superior effects to alfacalcidol on bone strength in rodents [3]. An earlier open-labeled clinical trial in osteoporotic patients demonstrated that treatment with 0.25–1.0 μg/day eldecalcitol for 6 months increased lumbar bone mineral density (BMD) in a dose-dependent manner without causing sustained hypercalcemia or hypercalciuria [4]. Furthermore, the effect of eldecalcitol on BMD was not due to a nutritional supplementary effect of vitamin D, because our randomized, double-blind, placebo-controlled clinical trial revealed that eldecalcitol treatment for 12 months increased both lumbar and hip BMD in osteoporotic patients with vitamin D supplementation [5]. In addition, eldecalcitol increased lumbar BMD regardless of serum 25(OH)D levels in the study subjects, further supporting the notion that its effect on BMD is not a nutritional supplementary effect [6]. However, there has been no direct head-to-head comparison of the effects of eldecalcitol with alfacalcidol on bone and calcium (Ca) metabolism in postmenopausal women. Therefore, the present study was undertaken to compare the effect of eldecalcitol on bone turnover markers and Ca metabolism in postmenopausal women.

## 2. Subjects and methods

The present study is a randomized, open-label clinical trial to compare the effect of eldecalcitol with that of alfacalcidol on bone and calcium metabolism, involving 59 Japanese postmenopausal women who were at least 3 years after menopause. Subjects were randomly assigned to receive 1.0 μg alfacalcidol, 0.5 or 1.0 μg eldecalcitol once a day for 12 weeks. Subjects were excluded if they had disorders such as hyperthyroidism, hyperparathyroidism, diabetes mellitus, or a history or suspicion of active urolithiasis at any time. Subjects were also excluded if they had taken bisphospho-

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**Table 1**
Demographics and baseline characteristics of subjects. Data are means ± SD for the indicated number of subjects in each group.

| | Reference range | Alfacalcidol | Eldecalcitol | |
|---|---|---|---|---|
| | | 1.0 μg ($n$ = 20) | 0.5 μg ($n$ = 19) | 1.0 μg ($n$ = 20) |
| Age (years) | – | 64.6 ± 2.5 | 64.6 ± 2.5 | 64.9 ± 2.8 |
| Height (cm) | – | 150.6 ± 6.2 | 151.4 ± 3.8 | 153.2 ± 5.3 |
| Body mass index (kg/m$^2$) | 18.5–25.0 | 22.3 ± 1.6 | 22.0 ± 2.0 | 22.5 ± 2.1 |
| Serum Ca (mg/dL) | 8.4–10.4 | 9.51 ± 0.38 | 9.45 ± 0.29 | 9.51 ± 0.36 |
| Daily urinary Ca (mg/day) | <200 | 137.5 ± 48.2 | 165.8 ± 51.4 | 158.5 ± 72.2 |
| Serum BALP (U/L) | 7.9–29.0[a] | 33.62 ± 6.92 | 32.36 ± 9.02 | 34.26 ± 10.64 |
| Urinary NTX (nmol BCE/mmol Cr) | 9.3–54.3[a] | 73.24 ± 32.47 | 78.95 ± 27.03 | 80.70 ± 29.11 |
| Intact PTH (pg/mL) | 14–66 | 38.2 ± 8.9 | 33.9 ± 8.4 | 37.2 ± 10.4 |
| 1,25(OH)$_2$D (pg/mL) | 16–61 | 49.4 ± 13.6 | 49.6 ± 7.7 | 49.9 ± 10.0 |
| 25(OH)D (ng/mL) | – | 29.2 ± 9.7 | 28.7 ± 8.8 | 27.6 ± 6.4 |

[a] 30–44 years, women.

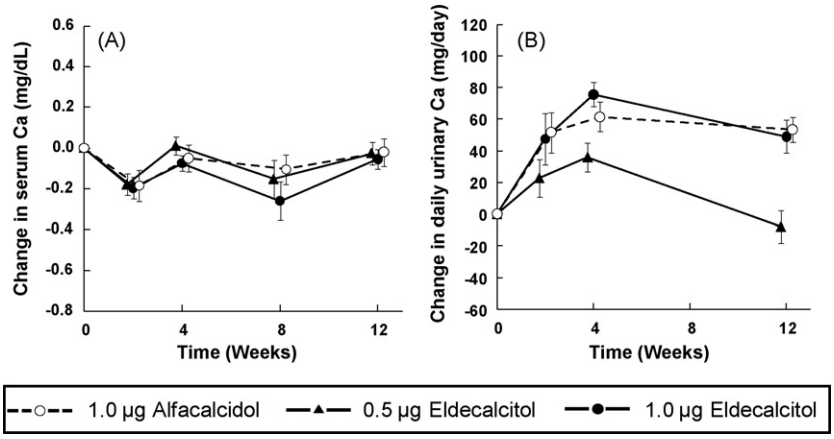


**Fig. 1.** Change in serum Ca (A) and daily urinary Ca excretion (B) in postmenoposal women given eldecalcitol or alfacalcidol for 12 weeks. Data are means ± SEM.

nates until less than 12 months before entry, taken other drugs known to have an influence on bone metabolism within the previous 2 months, had serum Ca levels above 10.4 mg/dL or urinary Ca excretion over 0.20 mg/dL glomerular filtrate, had serum creatinine levels above 1.1 mg/dL, or had clinically significant hepatic or cardiac disorders. The protocol was approved by the internal human studies review board, and informed consent was obtained from each subject.

Subjects were admitted into clinical research center 3 days before the examination to be maintained under a standard caloric and Ca intake of 600 mg/day. Serum Ca, daily urinary Ca excretion, bone-specific alkaline phosphatase (BALP) as a bone formation marker, urinary type I collagen N-terminal telopeptide (NTX) as a bone resorption marker, serum 1,25(OH)$_2$D and serum intact parathyroid hormone (PTH) levels were measured at baseline, 2, 4, 8 and 12 weeks of treatment. The efficacy end points were bone turnover markers, serum and urinary Ca.

## 3. Results and discussion

There was no significant difference in baseline demographics of enrolled subjects among the three groups (Table 1). Mean values of bone turnover markers were elevated in all three groups, and the proportion of subjects who exceeded the upper limit of the respective reference range was similar among the three groups. Serum BALP levels exceeded the upper reference limit of 29 U/L in 16 (80%), 12 (63%) and 13 (65%) subjects in 1.0 μg alfacalcidol, 0.5 and 1.0 μg eldecalcitol-treated groups, respectively. Urinary NTX levels exceeded the upper reference value of 54.3 nmol BCE/mmol in 15 (75%), 15 (79%) and 15 (75%) subjects in 1.0 μg alfacalcidol, 0.5

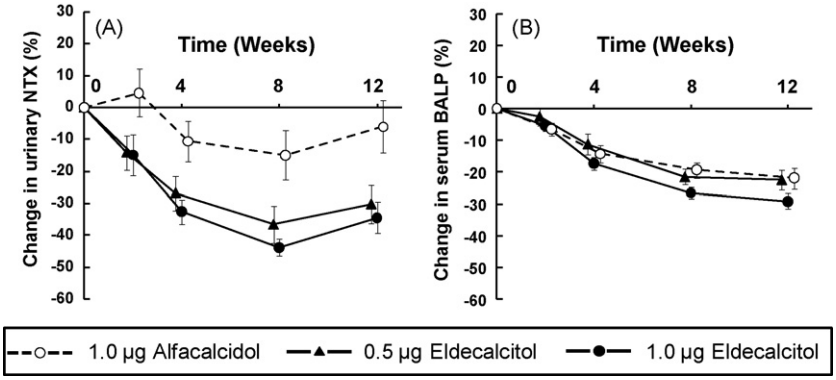


**Fig. 2.** Change in urinary NTX (A) and BALP (B) in postmenoposal women given eldecalcitol or alfacalcidol for 12 weeks. Data represent mean percent changes from baseline. Data are means ± SEM.

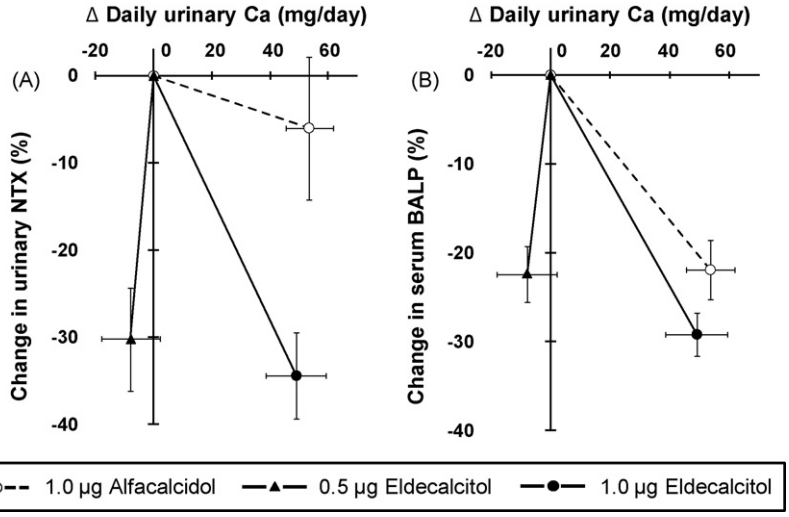


**Fig. 3.** Relationship between the change in daily urinary Ca and urinary NTX (A) or serum BALP (B) in postmenoposal women treated with eldecalcitol or alfacalcidol for 12 weeks. Data are means ± SEM.

and 1.0 μg eldecalcitol-treated groups, respectively. Thus, most of the enrolled postmenopausal women were at high bone turnover state.

There was almost no increase in serum Ca levels in all the treatment groups throughout the study period (Fig. 1A). Daily urinary Ca excretion increased in all the groups, reached the peak at 4 weeks, and remained elevated in 1.0 μg alfacalcidol and eldecalcitol groups. In 0.5 μg eldecalcitol-treated group, daily urinary Ca level at 4 weeks was significantly lower than the other two groups, and gradually decreased thereafter to reach an almost similar level to that at baseline (Fig. 1B). These results demonstrate that eldecalcitol from 0.5 to 1.0 μg increases urinary Ca excretion in a dose-dependent manner, and suggest that 1.0 μg alfacalcidol and eldecalcitol enhance intestinal Ca absorption to a similar extent. There is also a possibility that the lower increase in urinary Ca excretion in eldecalcitol group may be due in part to the lack of the effect of eldecalcitol in the suppression of serum intact PTH level (Fig. 4A). The present results also demonstrate that daily administration of eldecalcitol within this dose range does not cause sustained hypercalcemia in postmenopausal women with high bone turnover.

Suppression of urinary NTX was much stronger in both 0.5 and 1.0 μg eldecalcitol-treated than in 1.0 μg alfacalcidol-treated subjects, and urinary NTX decreased by −6, −30 and −35% in 1.0 μg alfacalcidol, 0.5 and 1.0 μg eldecalcitol-treated groups, respectively, at 12 weeks (Fig. 2A). In contrast, changes in serum BALP were similar among the three groups at 12 weeks (−22, −22 and −29% in 1.0 μg alfacalcidol, 0.5 and 1.0 μg eldecalcitol-treated groups, respectively) (Fig. 2B). Thus, there is a stronger suppression of bone resorption with a similar suppression of bone formation by eldecalcitol compared with alfacalcidol.

When bone turnover markers are plotted against daily urinary Ca excretion, there was a much stronger suppression of urinary NTX by 0.5 and 1.0 μg eldecalcitol than by 1.0 μg alfacalcidol, with a similar increase in urinary Ca excretion by 1.0 μg eldecalcitol and alfacalcidol (Fig. 3A). In contrast, the suppression of serum BALP was similar among the three groups (Fig. 3B). These results demonstrate that eldecalcitol suppresses bone resorption stronger than alfacalcidol with similar effects on bone formation, and that these effects of eldecalcitol on bone can be observed with a similar or less increase in urinary Ca excretion compared to alfacalcidol.

Finally, the effects of alfacalcidol and eldecalcitol on serum intact PTH and $1,25(OH)_2D$ levels were examined. As reported previously [5,7], while 1.0 μg alfacalcidol suppressed intact PTH by approximately 20%, 0.5 or 1.0 μg eldecalcitol showed almost no suppressive effect on serum intact PTH level, despite the fact that these doses of eldecalcitol exhibited potent effects on bone turnover markers (Fig. 4A). Because alfacalcidol can be converted to $1,25(OH)_2D$, serum $1,25(OH)_2D$ increased slightly and peaked at 4 weeks after alfacalcidol treatment, with 3% increase at 12 weeks.

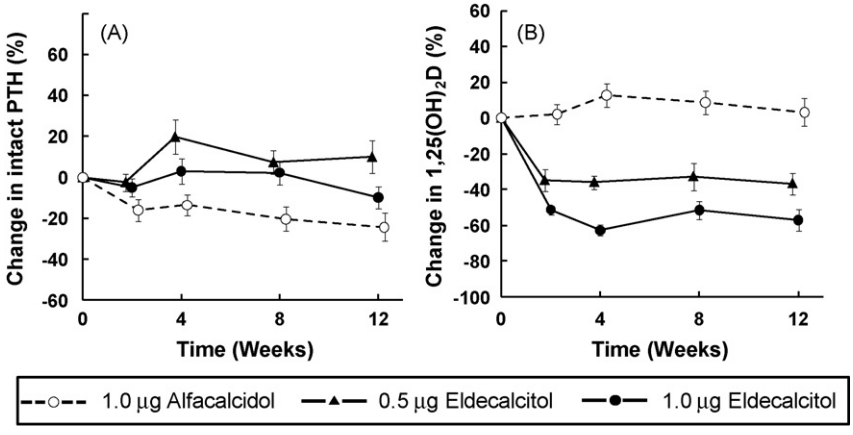


**Fig. 4.** Change in serum intact PTH (A) and $1,25(OH)_2D$ (B) in postmenoposal women given eldecalcitol or alfacalcidol for 12 weeks. Data are means ± SEM.

In contrast, endogenous serum $1,25(OH)_2D$ was robustly suppressed by 37% in 0.5 μg eldecalcitol-treated and by 57% in 1.0 μg eldecalcitol-treated groups at 12 weeks (Fig. 4B). Because eldecalcitol suppresses *CYP27B1* gene expression and enhances *CYP24* gene expression, The marked suppression of serum $1,25(OH)_2D$ by eldecalcitol treatment can be due to either or both of these effects of eldecalcitol. These results suggest that eldecalcitol has little suppressive effect on PTH secretion, and that the suppression of endogenous $1,25(OH)_2D$ production by eldecalcitol is not dependent upon a suppression of PTH secretion.

The results presented herein are consistent with the notion that the doses of eldecalcitol between 0.5 and 1.0 μg can effectively inhibit bone resorption stronger than alfacalcidol with a comparable effect on urinary Ca excretion, and may have a better osteoprotective effect than alfacalcidol. We have previously performed a randomized, double-blind, placebo-controlled dose-finding study in osteoporotic patients, and found that 0.75 μg eldecalcitol can effectively and safely increase lumbar and hip BMD in osteoporotic patients with vitamin D supplementation without causing sustained hypercalcemia [5]. Based upon those and the present studies, a randomized, active comparator, double-blind study was performed to compare the anti-fracture efficacy of eldecalcitol with that of alfacalcidol. In this study, osteoporotic patients under vitamin D supplementation were randomly assigned to receive either 1.0 μg alfacalcidol or 0.75 μg eldecalcitol once a day for 36 months. After 36 months of treatment, eldecalcitol-treated group exhibited a lower incidence of new vertebral fractures compared with the alfacalcidol group, especially in subjects with BMD T-score below −2.5 and those with multiple vertebral fractures (unpublished). Taken together, the accumulated evidence so far indicates that eldecalcitol has osteoprotective effects better than alfacalcidol, and suggests that eldecalcitol may serve as a new generation of active vitamin D with anti-fracture efficacy in osteoporotic subjects.

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