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Original Article

The Effect of Low-Dose Cyclical Etidronate and Calcium on Bone Mass in Early Postmenopausal Women

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Abstract. This 2-year study was carried out in 36 healthy women of mean age 53.9 ± 3.8 (SD) years and 3.4 ± 2.3 years postmenopausal. Bone mineral density (BMD) in the spine, measured by single-energy quantitative computed tomographic scanning, gave a mean initial value of 110 ± 26 mg/ml. The women were divided randomly into group 1 (n = 11), calcium 600 mg/day; group 2 (n=15), calcium plus etidronate sodium 400 mg/day for 14 days every 3 months; and group 3 (n=10), calcium plus etidronate plus phosphate, the 14-day etidronate course being preceded by phosphate 1 g twice daily for 3 days. During the first year of the study BMD decreased by 6.0 ± 5.8% (p<0.005) in group 1 subjects and increased by 4.5 ± 7.8% (p<0.005) in the combined etidronate-treated groups (difference between control and treated p<0.001). Inclusion of phosphate in the regimen did not affect the response to etidronate. In the second year there was no significant mean change in BMD in any of the three groups. However, whilst there was little change in BMD values for most of the group 1 subjects, there was considerable variation in individual response within the etidronate-treated groups, with some subjects gaining and some losing bone. The change in BMD during the second year in the subjects as a whole was highly correlated with the change in plasma calcium after 3 months of treatment (r = 0.60, p<0.001). Low-dose cyclical etidronate prevents postmenopausal bone loss during the first year of its administration, but was no more effective than calcium supplements during the second year. The positive correlation between early change in plasma calcium and second-year change in BMD, and the reduced bone loss in the second year in the subjects having only calcium supplements, are consistent with a beneficial effect of calcium supplements.

Keywords: Bone mineral density; Calcium; Bisphosphonates; Menopause; Osteoporosis

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Introduction

Osteoporotic fractures could largley be prevented if women whose bone mass was low at the time of the menopause were identified by universal screening and treated by hormone replacement therapy. However, such screening is not recommended [1] because of uncertainty about the overall benefits and risks of hormone replacement therapy [2].

Etidronate, a non-hormonal agent that inhibits bone resorption, has been used for many years to treat Paget's disease of bone and heterotopic ossification. Recent studies have reported beneficial results in osteoporotic patients, with an increase in bone mass and a reduced fracture rate [3,4]. A related drug, tiludronate, inhibited postmenopausal bone loss in a 1-year study [5] whilst pamidronate increased spinal bone mass in patients with osteoporosis [6,7]. The present study was therefore carried out to determine whether etidronate would also prevent early postmenopausal bone loss.

Subjects and Methods

Subjects

The subjects were healthy women whose menopause (defined as the cessation of menstruation for 6 months) had occurred within the previous 7 years, and who

volunteered in response to advertisements directed to hospital staff, family planning centres and local general practitioners. Exclusion criteria included systemic illness, glucocorticoid administration, ethanol >250 g/week or cigarettes >140/week.

Thirty-six healthy women completed the 2-year study, out of an initial 46. Reasons for withdrawal were: non-compliance (4), decision to commence hormone replacement therapy (3), concern about low bone mass (1), calcium supplement thought to cause bone pain (2). The women who completed the study were aged 53.9 ± 3.8 (SD) years (range 46–63 years) and were 3.4 ± 2.3 years (range 0–7 years) postmenopausal. Their height was 163 ± 5 cm, weight 66 ± 11 kg and BMI 24.9 ± 4.4.

Methods

The women were allocated to one of three treatment groups according to computer-generated random numbers. The groups were similar as regards age, height, weight, time since menopause, biochemical variables and spinal bone mineral density (BMD) (Table 1). All subjects took a proprietary preparation (Caltrate, Lederle) containing calcium carbonate (calcium 600 mg) each day.

Table 1. Clinical, biochemical and CT data at onset of study

	Group 1	Group 2	Group 3
Age (yr)	56±4	52±3	55±3
Years since menopause	4±2	3±2	4±2
Height (cm)	162±3	163±5	163±6
Weight (kg)	67±9	63±11	70±11
Plasma calcium (mmol/l)	2.34±0.07	2.37±0.08	2.39±0.06
Plasma phosphate (mmol/l)	1.18±0.22	1.14±0.18	1.14±0.07
24-hour urinary calcium (mmol/l)	3.3±2.0	3.5±2.4	4.4±2.0
Fasting urinary hydroxyproline (mmol/mmol creatinine)	11.9±4.2	10.9±5.5	9.7±3.3
Spinal BMD (mg/cm^3)	116±39	105±17	111±22

The treatment groups were:

Group 1 (n=11): Calcium only.

Group 2 (n=15): Etidronate sodium (Didronel, Norwich Eaton Pharmaceuticals) 400 mg/day for 14 days every 3 months.

Group 3 (n=10): Phosphate 1 g twice daily (Phosphate-Sandoz, Sandoz Pharmaceuticals) for 3 days before commencing etidronate.

Blood was taken (under non-fasting conditions) at the onset of the study and at 3, 12, 18 and 24 months (during the 14 days of etidronate administration for groups 2 and 3) for measurement of plasma urea, electrolytes, creatinine, calcium, phosphate and alkaline phosphatase, and for liver function tests. Plasma calcium level was corrected for albumin [6]. The subjects also collected a 24-hour urine sample for measurement of calcium and creatinine, and the second fasting morning urine sample for measurement of hydroxyproline and creatinine.

Plasma biochemistry was measured using a Hitachi 705 analyser. Urinary calcium was measured by atomic absorption spectrophotometry. A commercial kit method (Hypronosticon) was used to measure urinary hydroxyproline.

BMD was measured in the spine by single-energy quantitative computed tomography, using a Siemens DR3 scanner (Siemens Ltd, Erlangan, FRG) with an energy of 96 keV. The instrument was standardised by a hydroxyapatite calibration phantom supplied by the manufacturers. Measurements were taken in two vertebrae (L1 and L2) in all but one subject. In this subject a single vertebra only (L1) was measured (due to a localisation error in the initial measurement). The midplane of each vertebra was located in a lateral topogram. A representative area of cancellous bone was then defined in an 8 mm thick transverse section through this plane. The mean computed tomographic (CT) value for this volume within each vertebra was compared with the CT value from the calibration phantom; the mineral equivalent for each vertebra was then expressed as milligrams of hydroxyapatite per cubic centimetre of bone. The final reading was the average of the vertebrae measured. The reproducibility of the technique, calculated by taking duplicate non-sequential measurements in 6 normal subjects, was 2.2%.

Statistical Analysis

Statistical analysis was carried out using the Minitab Statistical package (Pennsylvania State University). Student's t-test was used for comparison of groups. Single or multiple linear regression (MLR) was used to test the significance of correlations between variables.

Results

Adverse Effects of Drugs

In the subjects who completed the trial, those taking etidronate complained of mild diarrhoea (7), nausea and heartburn (7), hip pain (1), constipation (1), leg cramps (1), or skin rash (1). The calcium supplement was said to cause indigestion (3), constipation (2), or dry mouth (1). The phosphate supplements were associated with mild nausea (3) and diarrhoea (5).

Plasma and Urine Biochemistry

There were no changes in plasma urea, creatinine or electrolytes or in liver function tests. Fig. 1 shows changes in plasma calcium, phosphate, alkaline phosphatase and urinary calcium and hydroxyproline with

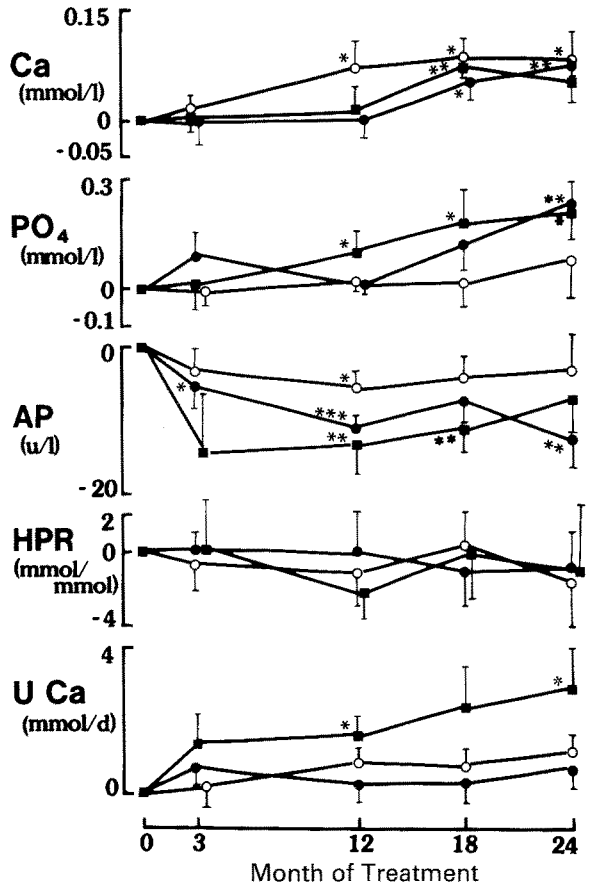

Fig. 1. Changes in biochemical values during the study. Ca, PO_4 and AP, plasma calcium, phosphate and alkaline phosphatase; HPR, fasting urinary hydroxyproline:creatinine ratio; UCa, 24-hour urinary calcium. *Open circles*, group 1; *filled circles*, group 2; *filled squares*, group 3. Different from initial value: $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

treatment. There was a small increase in mean (non-fasting) plasma calcium level, the final reading for all patients being 0.08 ± 0.09 mmol/l higher than the initial level ($p<0.001$). Plasma phosphate was not significantly changed in group 1, but increased in the etidronate-treated groups. Plasma alkaline phosphatase was decreased in all groups at 12 months and then returned to pre-treatment levels in group 1. In the etidronate-treated groups combined, the level decreased from 79 ± 22 U/l pre-treatment to 69 ± 21 U/l at 24 months ($p<0.001$). The urinary hydroxyproline:creatinine ratio was not significantly changed in any treatment group.

The final urinary calcium was increased compared with pre-treatment in group 3 (7.3 ± 3.8 vs. 4.4 ± 2.0 mmol/24 hours), in groups 1 and 2 combined (3.4 ± 2.2 vs. 4.3 ± 2.5 mmol/24 hours, $p<0.05$), and in all subjects (4.0 ± 2.2 vs. 5.3 ± 3.2 mmol/24 hours, $p<0.05$). The final urinary calcium level was higher in group 3 than in groups 1 and 2 combined ($p<0.05$). The final urinary calcium levels correlated with the pre-treatment levels ($r = 0.61$, $p<0.001$). In MLR, final urinary calcium was related to initial urinary calcium ($t = 4.05$, $p<0.001$) and phosphate treatment ($t = 2.38$, $p<0.05$) (combined $r = 0.68$, $p<0.001$) but there was no additional effect of etridronate treatment ($t = -0.33$, NS).

Spinal BMD

Mean changes in spinal BMD are shown in Table 2. In the control subjects BMD decreased in the first year of the study but was not changed in the second year. In the etidronate-treated groups BMD increased similarly in the first year (though the change was only significant in group 2) and was not changed in the second year. Fig. 2 shows changes in BMD in the individual subjects, and shows the greater variability of change in etidronate-treated groups than in the controls.

In order to evaluate the factors related to change in BMD, a correlation matrix was prepared, and the changes in BMD during the first and second years of the study were related to other variables in simple and multiple linear regression.

During the first year of the study the change in BMD was inversely related to the initial BMD in the etidronate-treated subjects ($r=-0.57$, $p<0.005$), though not in the controls ($r=0.04$, NS) or for all subjects combined ($r=-0.32$, NS) (Fig. 3).

In the second year the change in BMD was not related to etidronate treatment ($r=-0.14$, NS). However, change in BMD in the second year was highly correlated with the change in plasma calcium at 3 months ($r=0.60$, $p<0.001$) (Fig. 4). In the individual groups the cor-

Table 2. Changes in spinal BMD

	Year 0–1		Year 1–2		Year 0–2	
	mg/cm^3	%[f]	mg/cm^3	%[f]	mg/cm^3	%[f]
Group 1 (n=11)	−6.2±5.0[b]	−6.0±5.8[b]	0.9±4.7	1.3±4.2	−5.3±4.4[b]	−4.7±4.4[b]
Group 2 (n=15)	4.0±6.2[a,e]	4.4±6.6[a,e]	−2.1±8.4	−2.0±7.6	1.9±9.6[c]	2.4±9.1[c]
Group 3 (n=10)	3.9±9.1[d]	4.7±9.7[d]	0.1±7.9	−0.5±7.7	3.9±13.3	4.3±13.1
Groups 2 and 3 (n=25)	3.9±7.3[a,e]	4.5±7.8[b,e]	−1.2±8.0	−1.4±7.5	2.7±10.9[d]	3.1±10.7[d]

Significance of difference from pretreatment values: [a] $p<0.05$; [b] $p<0.005$.
Significance of difference from group 1: [c] $p<0.05$; [d] $p<0.01$; [e] $p<0.001$.
[f] Change expressed as % initial BMD.

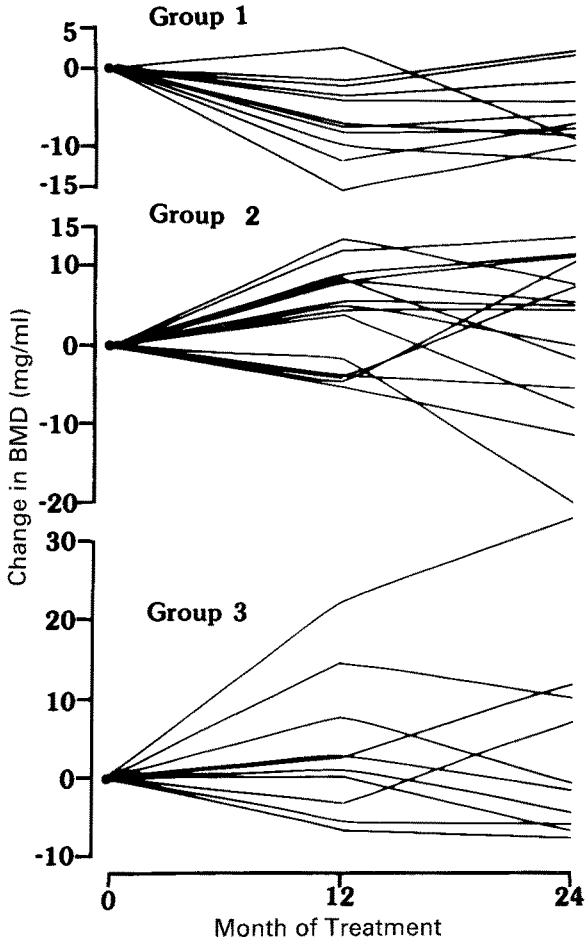

Fig. 2. Changes in spinal BMD during the study.

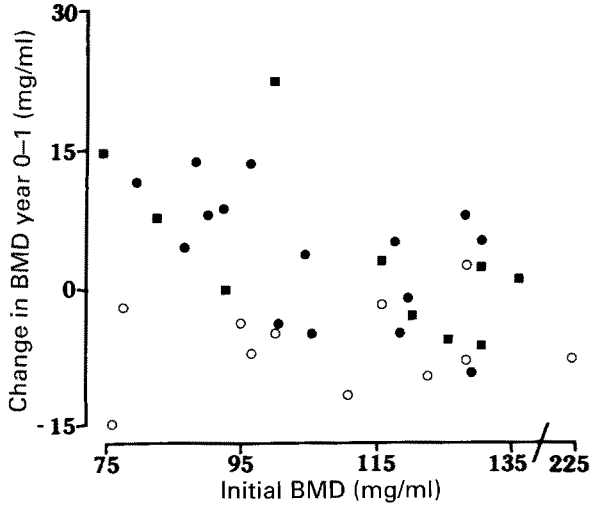

Fig. 3. Relationship between initial spinal BMD and change after 1 year. *Open circles*, group 1; *filled circles*, group 2; *filled squares*, group 3. For the etidronate-treated patients $r=-0.57$ ($p<0.005$).

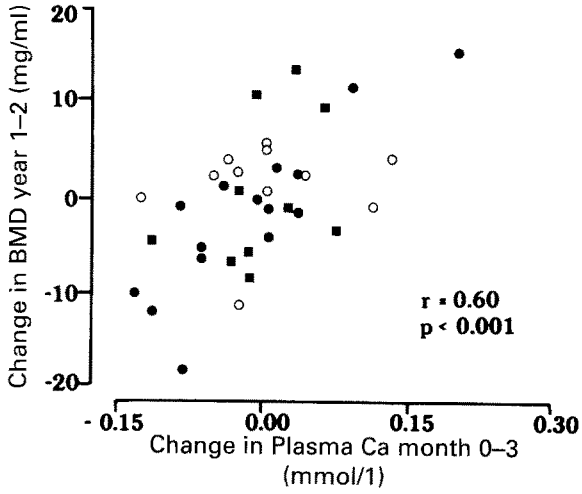

Fig. 4. Relationship between change in BMD in the second year and change in plasma calcium during first 3 months of study. *Open circles*, group 1; *filled circles*, group 2; *filled squares*, group 3.

relation was strong in groups 2 ($r = 0.85$, $p<0.001$) and not significant in group 1 ($r=0.12$, NS) or group 3 ($r=0.42$, NS). In MLR the change in BMD in the second year of the study correlated with the change in plasma calcium at 3 months ($t=5.28$, $p<0.001$), the number of years since the menopause ($t=2.84$, $p<0.01$) and the alkaline phosphatase at 2 years ($t=-2.72$, $p<0.02$) (combined correlation coefficient 0.74, $p<0.001$).

There was no relationship between the level of plasma phosphate or the change in its level at any time during the study and either the 1-year or 2-year change in BMD.

Discussion

During the first year of the study spinal BMD decreased by 6% in the subjects taking only calcium, and increased by 4.5% in the etidronate-treated groups. During the second year, though the benefit of etidronate treatment was maintained, there was no significant mean change in any group. However, while the BMD response in the control subjects was relatively uniform during the second year, there was considerable variation in response in the etidronate-treated groups. The 1-year results in our study are similar to those found using tiludronate in postmenopausal women [5], given the different techniques used to measure bone mass. The other longer-term studies using bisphosphonates have been in women with established osteoporosis [3,4,6,7]. The studies using etidronate differed from our study in finding a continuing increase in bone mass during the second year of etidronate treatment [3,4].

The near cessation of bone loss in the calcium-treated group during the second year of the study suggests that calcium supplementation reduces postmenopausal bone loss, most probably by reducing parathyroid hormone secretion [9], but that this effect is not evident until the

second year of treatment. However, in the absence of a control group not taking calcium, no conclusion can be reached about this.

The increase in spinal BMD occurring in the first year in the etidronate-treated patients was more marked in patients having a low initial BMD. There was no detectable influence of the time since menopause. It was not demonstrably influenced by the inclusion of phosphate in the regimen, in keeping with the finding of other workers [3,4]. However, unlike the findings in their studies, the increase in BMD in our subjects did not continue during the second year of the study, and the striking feature in this group was the considerable variation in response.

The relationship between the early change in plasma calcium and change in BMD in the second year was unexpected. The strength of the correlation in such that it is unlikely to be a random phenomenon, though this remains a possibility. The increase in plasma calcium could reduce bone loss by reducing the parathyroid hormone level and hence bone resorption, the effect taking a considerable time to become manifest. Such a mechanism is consistent with the reduction in bone loss during the second year in subjects taking calcium. A much less likely mechanism is a direct effect of the change in blood calcium level on osteoblasts. Calcium deficiency in rats reduces bone formation [10], and the converse of this might apply in the present study. The relationship is not proven to be one of cause and effect, but does suggest that the effects of etidronate treatment, at least in the second year of its administration, might be augmented by agents that elevate the plasma calcium level. This could be achieved by increasing the intake of oral calcium or by adding either vitamin D or thiazide diuretic.

Second-year bone loss also tended to be less with increasing years since the menopause and with decreasing 2 year plasma alkaline phosphatase level. These relationships were as expected, and were probably obscured during the first year by the etidronate effects.

Etidronate increases renal tubular phosphate reabsorption [11] and so the plasma phosphate level increased in the etidronate-treated groups. However, there was no relationship between this increase and subsequent changes in BMD. Thus measurement of plasma phosphate level does not appear to be a useful early predictor of a good BMD response to etidronate.

The calcium supplement induced hypercalciuria in some subjects, who would thus be at increased risk of kidney stone formation. Post-treatment urinary calcium correlated with the pre-treatment level, suggesting that urinary calcium levels should be checked periodically in patients given calcium supplements if the baseline urinary calcium is near the upper limit of normal. The higher level of urinary calcium in patients taking phosphate is not readily explicable. It could theoretically result from increased secretion of parathyroid hormone [12] with consequent increased synthesis of calcitriol. However the administration of phosphate supplements to patients with idiopathic hypercalciuria reduced their urinary calcium levels [13].

Our study thus indicates that etidronate inhibits postmenopausal bone loss at least during the first year of its administration and appears to be more effective when the initial BMD is low. However, there was no overall increase in bone mass with etidronate during the second year. Continued benefit might be dependent on an early increase in the plasma calcium level.

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