Effects of Alendronate and Hormone Replacement Therapy, Alone and in Combination, on Bone Mass and Markers of Bone Turnover in Elderly Women with Osteoporosis

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The aim of the study was to compare alendronate, hormone replacement therapy (HRT), and their combination in treatment of osteoporosis in elderly postmenopausal women. Ninety patients, aged 65–80 yr (mean 71), with a T-score of bone mineral density (BMD) of 2.5 or less at either the lumbar spine or the femoral neck were randomized to receive daily 10 mg alendronate (n = 30), 2 mg estradiol plus 1 mg norethisterone acetate (n = 30) (HRT), or their combination (n = 30) for 2 yr. BMD of the lumbar spine and the upper femur was measured at baseline and after 1 and 2 yr of treatment. Urinary excretion of type I collagen aminoterminal telopeptide as related to creatinine and serum type I procollagen aminoterminal propeptide was assayed at baseline and after 6-month intervals thereafter. Increases of 9.1–11.2% in lumbar spine BMD at 2 yr were similar in the study groups. Only HRT increased femoral neck BMD statistically significantly (P < 0.0001 for a change from baseline) at both 1 (+4.9%; P = NS vs. the other groups) and 2 yr (+5.8%; P < 0.05 vs. the other groups). Total hip BMD increased similarly in all study groups. Percentage reductions in urinary type I collagen aminoterminal telopeptide in the HRT group (60.2–62.7%) were significantly smaller than those in the combination group (78.1–80.4%) (P < 0.0001–0.0069) and the alendronate-only group (72.4–76.1%) (P = 0.047 at 24 months). Serum type I procollagen aminoterminal propeptide decreased less in the HRT group (53.6–59.8%) than in the other groups (73.0–75.6% in the alendronate group [P < 0.001 at 12 months]; 67.0–71.5% in the combination group [P < 0.0001 at 12 months, P = 0.013 at 24 months]). We conclude that in elderly postmenopausal women with osteoporosis, the combination of HRT and alendronate did not offer an extra gain of bone mass over either treatment alone. In terms of BMD changes, the single treatments were equally effective, but the reductions in bone markers were less with HRT than with alendronate. (J Clin Endocrinol Metab 89: 626–631, 2004)

A CHRONIC IMBALANCE in the bone-remodeling process, with resorption exceeding formation, results in osteoporosis, which is characterized by reduced skeletal mass and microarchitectural deterioration of the skeleton. Consequently, skeletal fragility and risk of fracture increase (1). In the menopause, estrogen deficiency results in increased bone resorption and a reduction in bone mass; 30% of 65- to 70-yr-old women have osteoporosis. Independently of bone mineral density (BMD), advancing age is an important risk factor as regards osteoporotic fractures. Not surprisingly, according to an American cost-benefit analysis, examination and treatment of osteoporosis are most profitable when directed to 65- to 70-yr-old people (2).

Estrogen replacement therapy reduces bone resorption by decreasing serum levels of osteoclast-stimulating cytokines and up-regulating TGFβ, which inhibits bone resorption by decreasing the activity of osteoclasts and increasing their apoptosis (3). Estrogens prevent postmenopausal bone loss, improve bone density (4–8), reduce the incidence of vertebral fractures in postmenopausal women with established osteoporosis (9, 10), and according to a recent report also decrease the risk of hip fracture (11). In a cohort study, hormone replacement therapy (HRT) effectively prevented hip fractures among women older than 75 yr (12). Estrogens combined with progestins may increase vertebral BMD more than estrogens alone (13–15).

Alendronate is a potent amino bisphosphonate that inhibits osteoclast activity at sites of bone resorption. In vivo it affects the mevalonate pathway in osteoclasts (16), promotes their apoptosis, and consequently inhibits bone resorption (3). Alendronate reduces postmenopausal bone loss (17, 18) and significantly improves lumbar spine and hip BMD in osteoporotic women (18–22). In postmenopausal women with a previous vertebral fracture, alendronate approximately halved the risk of vertebral and forearm fractures and also that of hip fracture (19, 20, 23, 24).

Women with severe osteoporosis or those who have failed to respond optimally to estrogen or bisphosphonate alone might get an additive benefit when they combine these two antiresorptive agents with different mechanisms of action. Indeed, in most previous studies, the combination produced a net excess in gain of BMD over either drug alone (25–31). However, these studies were performed in patients with the mean ages of 52–62 yr (25–31), and it is still unknown whether the efficacy of the treatments is the same in older women. In addition, the tolerability and compliance to the treatments, especially to HRT, even when nonbleeding con-
Continuous combination alternatives are used, can depend on age. For all these reasons, we designed the present study on osteoporotic women between 65 and 80 yr of age to compare the effects of alendronate, continuous combined HRT, and their combination on BMD and markers of bone turnover.

Subjects and Methods

Subjects

We enrolled 90 postmenopausal women, 65–80 yr of age (mean 71), into this double-blind, randomized, 2-yr study. The participants were required to have a BMD of the lumbar spine (n = 50) or femoral neck (n = 71) at least 2.5 σ below the mean of a reference population of young premenopausal women. Exclusion criteria included metabolic bone disease other than postmenopausal osteoporosis; general contraindications to HRT; use of bone-active agents (any previous use of bisphosphonates, concomitant use of oral glucocorticoids, or HRT use less than 6 months before the study); diseases that affect bone turnover; history of gastrointestinal mucosal disorders (erosive gastritis, gastric ulcer or esophagitis); history of a prior thromboembolic disease; liver or kidney disease; insulin-treated diabetes; history of uterine or breast cancer; or uncontrolled hypertension. Hysterectomy was not an exclusion criterion.

Study design

The women were randomized to one of three treatment regimens: continuous combined HRT [2 mg estradiol plus 1 mg norethisterone acetate orally; Kliogest; Novo Nordisk, Copenhagen, Denmark, n = 30], alendronate (10 mg Fosamax; Merck & Co. Inc., Whitehouse Station, NJ, n = 30), or HRT plus alendronate (n = 30). The principle of double dummy techniques was followed so that each regimen was similar in appearance. The women were instructed to take alendronate or its placebo in the morning, at least 30 min before the first meal of the day, with a glass of water, and to remain upright for at least 30 min after dosing.

At baseline, dietary calcium intake was assessed by using a questionnaire. On the basis of this information, the participants were instructed to take calcium supplementation (500–1000 mg/d) to assure a total intake of at least 1 g daily and vitamin D (400 IU/d) during fall and winter months from October to April. The supplements were not, however, provided by us. Calcium intake was checked at every visit. Compliance in use of the study medication was confirmed by counting the unused tablets.

Efficacy measurements

The subjects were seen at baseline and at 6, 12, 18, and 24 months. The BMD of lumbar spine, femoral neck, and total hip was measured at baseline and at 12 and 24 months by dual-energy x-ray absorptiometry (Hologic, Inc., QDR 1000W, Waltham, MA), using the same densitometer over the whole duration of the study. The precision of the method [coefficient of variation (CV)] was 0.9% at the lumbar spine, and 1.2% at the femoral neck.

Serum and second-void urine samples were obtained in the morning after an overnight fast at baseline and at 6, 12, 18, and 24 months for the assay of biochemical markers of bone turnover and serum 25-hydroxyvitamin D [5-25(OH)D]. Urinary N-telopeptide (NTX) of type I collagen related to creatinine was measured as a marker of bone resorption, using an ELISA (Osteomark NTX Test, Ostex International, Seattle, WA). The intraassay CV was 8% and the interassay CV, 13%. Serum aminoterminal propeptide of human type I procollagen (PINP) was measured as a marker of bone formation, using RIA kits (Orion Diagnostica, Espoo, Finland). The intra- and interassay CVs were 7%. S-25(OH)D was measured by RIA [Immunodiagnostic Systems Ltd., Boldon, UK]. The intra- and interassay CVs were 6%.

Statistical analysis

Data with normal distributions are expressed as means with sds; otherwise, as medians with interquartile ranges. In comparisons between the two study groups, normally distributed variables were studied using one-way ANOVA followed by Bonferroni correction in paired comparisons. Those data nonnormally distributed were tested by with Kruskal-Wallis one-way ANOVA on ranks. BMD changes were analyzed by ANOVA by using percentage changes from 0 to 12- and 24-month time points. Because the assumptions for repeated-measures ANOVA were not fulfilled for the biochemical results (even after log transformation), we used percent changes (from baseline) of each biochemical variable in the ANOVA analysis of differences between the groups. The percent changes were log transformed to meet the assumptions of this analysis. Additionally, Friedman RM ANOVA was used in the analysis of changes within a single study group. The analyses were carried out using NCSS 2000 software (NCSS Statistical Software, Kaysville, UT) or SigmaStat for Windows (version 2.0, SPSS Inc., Chicago, IL).

Results

The baseline characteristics were similar in all treatment groups (Table 1). Twenty-one patients discontinued the study: eight (27%) in the alendronate group, seven (23%) in the HRT group, and six (20%) in the combined treatment group. Seventeen discontinued due to an adverse experience (two of them for two reasons): six with stomach problems (two in each group), five with breast tenderness with HRT, two with back and leg pains in the alendronate group, one with fear of medication in the alendronate group, two with arrhythmia (one in the HRT group and one in the combination group), one with myocardial infarction in the alendronate group, and one with a complaint of general weakness (one in each group). Twelve patients withdrew from the study: two with a fear of medication, one with a complaint of general weakness, one with leg pains in the alendronate group, one with leg pains in the HRT group, and one with a complaint of general weakness in the combined group.

TABLE 1. Baseline characteristics [mean (SD) or medians with interquartile ranges] of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Alendronate</th>
<th>HRT</th>
<th>Combination</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers (n)</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>0.19</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>70 (68–74)</td>
<td>70 (69–73)</td>
<td>72.5 (68–74)</td>
<td>0.45</td>
</tr>
<tr>
<td>Years since menopause</td>
<td>22.6 (6.5)</td>
<td>21.8 (4.9)</td>
<td>23.0 (4.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>Calcium intake (mg/d)</td>
<td>817 (434)</td>
<td>707 (321)</td>
<td>687 (257)</td>
<td>0.16</td>
</tr>
<tr>
<td>Alcohol (doses/wk)a</td>
<td>0.73 (1.3)</td>
<td>1.20 (2.7)</td>
<td>1.73 (3.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.8 (5.5)</td>
<td>158.2 (5.8)</td>
<td>160.7 (4.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.5 (55–70.3)</td>
<td>65.0 (59.8–70.3)</td>
<td>61.5 (54.8–74)</td>
<td>0.94</td>
</tr>
<tr>
<td>BMI</td>
<td>25 (22–27)</td>
<td>25 (24–28)</td>
<td>23 (22–28)</td>
<td>0.45</td>
</tr>
<tr>
<td>BMD lumbar spine (g/cm²)</td>
<td>0.740 (0.689–0.802)</td>
<td>0.741 (0.697–0.86)</td>
<td>0.771 (0.722–0.533)</td>
<td>0.44</td>
</tr>
<tr>
<td>BMD femoral neck (g/cm²)</td>
<td>0.609 (0.555–0.649)</td>
<td>0.624 (0.603–0.651)</td>
<td>0.614 (0.563–0.655)</td>
<td>0.51</td>
</tr>
<tr>
<td>BMD total hip (g/cm²)</td>
<td>0.733 (0.113)</td>
<td>0.778 (0.085)</td>
<td>0.746 (0.084)</td>
<td>0.13</td>
</tr>
<tr>
<td>Urinary NTX (nmol/mmol Crea)</td>
<td>71.5 (51.7–89.7)</td>
<td>66.9 (48.2–90.6)</td>
<td>67.1 (52.1–83.7)</td>
<td>0.92</td>
</tr>
<tr>
<td>Serum PINP (µg/liter)</td>
<td>49.5 (38.8–66.8)</td>
<td>50.0 (34.5–58.8)</td>
<td>47.0 (36.8–59.3)</td>
<td>0.76</td>
</tr>
<tr>
<td>Serum 25(OH)D (ng/ml)b</td>
<td>18.4 (15.1–26.4)</td>
<td>20.8 (15.5–26.0)</td>
<td>21.8 (11.2–26.5)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

a Alcohol dose = 12 g of absolute alcohol meaning 0.12 liter wine, 0.33 liter beer, or 0.04 liter liquor; b to convert to nmol/liter, multiply by 2.5.
nate group, one with repeated respiratory infections in the combination group, and one with night sweating in the HRT group. Two patients in the alendronate group did not want to continue the study for personal reasons, and two patients were excluded due to a protocol violation (one in the HRT group and one in the combination group). Sixty-nine patients (77%) completed the study. Reported as adverse events during the study were one hip fracture in the alendronate group, one wrist fracture in the HRT group, and one vertebral fracture in the combination group.

Bone mineral density

The baseline values of BMD were similar in all treatment groups (Table 1). Mean percentage changes in BMD relative to baseline after 12 and 24 months of treatment are shown in Fig. 1. Lumbar spine BMD increased similarly in all treatment groups ($P < 0.0001$ vs. baseline). The increases ranged from 6.8% to 8.4% at 12 months and from 9.1% to 11.2% at 24 months. Only HRT increased femoral neck BMD statistically significantly at both 12 (+4.9%; $P < 0.0001$) and 24 months (+5.8%; $P < 0.0001$). At the latter time point, the HRT group differed from the other groups ($P < 0.05$), of which the alendronate group exhibited a significant increase of +3.3% from baseline at 12 months ($P < 0.05$), and the combination treatment group showed an increase of +2.7% at 24 months ($P < 0.05$). Total hip BMD increased in all study groups ($P < 0.05–0.0001$ for differences from baseline at 12 months; $P < 0.0001$ at 24 months), with no significant differences between the treatments.

Biochemical markers of bone turnover

The baseline values for the markers were similar in all treatment groups (Table 1). Significant reductions from baseline were seen in all treatment groups from 6 months onward ($P < 0.001$) in both urinary NTX and in serum PINP (Fig. 2). Percentage decreases in urinary NTX ranged from 60.2% to 62.7% in the HRT group, which were significantly smaller than those of 78.1–80.4% in the combination treatment group ($P < 0.0001–0.0069$). The respective decreases in the alendronate group were 72.4–76.1%, which differed from the HRT group at 24 months ($P = 0.047$) and the combination group at 12 months ($P = 0.002$). Serum PINP decreased less in the HRT group (53.6–9.8%) than in the other groups [73.0–75.0% in the alendronate group ($P < 0.001$ at 12 months); 67.0–71.5% in the combination treatment group ($P < 0.0001$ at 12 months, $P = 0.013$ at 24 months)].

Relationship between changes in BMD and bone markers

In the whole study population, the maximum reduction in serum PINP levels correlated with the increase in lumbar spine BMD at both 12 ($r = 0.34, P = 0.004$) and 24 months ($r = 0.24, P = 0.04$). Respectively, the maximum drop from baseline in urinary NTX correlated with the increases in lumbar spine BMD at both time points ($r = 0.32–0.40, P < 0.001–0.007$) and in total hip BMD at 24 months ($r = 0.27, P = 0.02$). However, as calculated from these poor correlations ($r^2$ values) the marker changes explained only 10–15% of the BMD changes.
Serum 25-hydroxyvitamin D

The three study groups had similar S-25(OH)D levels at baseline (Table 1) and at 6, 12, 18, and 24 months (data not shown). Hypovitaminosis D, determined as a S-25(OH)D level of less than 15 ng/ml (32) was found in 18.9%, 12.9%, and 17.2% of the whole study population at baseline and at 12 and 24 months, respectively.

Discussion

In this study of elderly women with osteoporosis, the combination of alendronate and HRT did not offer an extra benefit over either treatment alone in terms of increases in BMD at any measurement site, and alendronate and HRT appeared to be equally efficient in preserving or increasing bone mass. However, reductions in the levels of bone markers indicated alendronate or the combination to be superior to HRT alone.

In terms of BMD changes, our results deviate from those of previous studies, which mostly have favored the combination of HRT and bisphosphonate (alendronate, etidronate, or risedronate) over at least HRT alone (25–31). This deviation is not explained by estrogen dose because equivalent treatments (2 mg estradiol or 0.625 mg conjugated equine estrogen) were used in previous studies (25–31). As a progestin component of HRT, we used norethisterone acetate, which is known to increase bone mass (14), but the same regimen was used by Tirasa et al. (29). In two studies (27, 31), medroxyprogesterone acetate was used, and in two others (28, 30), no progestin at all was employed. Most importantly, however, our study was aimed at studying the effects of treatment of osteoporosis in elderly women with a mean age of 71 yr, which is 10–20 yr higher than in earlier studies (25–31). It can be reasoned that our elderly subjects represented a group with lower bone turnover rate that was sufficiently suppressed with one drug alone. Consequently, the combination did not offer any extra benefit. It is well known that after the first postmenopausal years, bone turnover rate goes down before increasing again in late senescence (33, 34). Recently it was demonstrated that the lower the endogenous estradiol level, the higher is the response of BMD to HRT in elderly women (35). Because serum estradiol concentration is inversely related to age (36), it can be anticipated that estrogen levels are lower in late than in early postmenopausal women.

The present reductions in bone markers were of the same magnitude as published earlier. Urinary NTX, a marker of bone resorption, decreased by 60–70% during the first year of HRT or alendronate treatment (34, 37), and serum PINP, a marker of bone formation, decreased by 40% over 6 months in responders to HRT (38). On the basis of the marker data, the combination treatment appeared to be more efficient than HRT alone. However, it is not known to what extent bone turnover rate can be safely suppressed by antiresorptive agents. The possibility exists that too extensive suppression of bone turnover leads to skeletal microdamage and an increase in bone fragility. Thus, the role of drug combinations in the treatment of osteoporosis will finally be resolved by studies with fracture as an end point. Unfortunately, such data are not yet available.

The results of a recent meta-analysis of randomized trials (39) suggest that among postmenopausal women, the relative impact of hormone use in reducing the incidence of skeletal fracture declines with increasing age. In terms of a surrogate marker of fracture, BMD, the elderly women in the present study responded to HRT similarly as to alendronate. Importantly, HRT was able to increase femoral BMD significantly, which is compatible with the ability of HRT to prevent hip fractures (39), as recently ascertained in the Women’s Health Initiative Study (11). However, increases in BMD may account for only a third of the reductions in fracture risk.

![Fig. 2. Mean (SEM) percentage changes from baseline in bone turnover markers, urinary NTX (A), and serum PINP (B). Changes from baseline were significant in all three study groups (P < 0.001, Friedman RM ANOVA). †, P < 0.001 for the difference between the HRT and combination groups; ‡, P = 0.002 for the difference between the alendronate and combination groups; #, P < 0.001 for the difference to the other two groups; *, P = 0.047 for the difference between the HRT and alendronate groups and P = 0.0069 for the difference between the HRT and combination groups; $, P = 0.013 for the difference between the HRT and combination groups.](image-url)
in response to antiresorptive treatments (40, 41), and our study did not have power to address this risk. In addition to BMD, a potential contributor to a reduction in fracture risk is a reduction in bone turnover (42, 43), and in this respect alendronate was superior to HRT.

All the treatments were well tolerated in the present study. Gastrointestinal complaints were evenly distributed in the three study groups. Breast tenderness led to discontinuation by five women, two in the HRT group and three in the combination group. Possibly this could have been prevented by using a lower dose (1 mg) of estradiol. The present HRT regimen with 2 mg of estradiol and 1 mg of norethisterone acetate was used because at the beginning of the study, there was no commercial source of continuous combined HRT with 1 mg of estradiol available in Finland. In this age group, a regimen with 1 mg estradiol may be recommended because compliance and tolerability is better and efficacy in terms of preservation of bone mass is the same as with higher doses of estrogens. In early postmenopausal women (mean age 51 yr), of three doses of esterified estrogens (0.3 mg/d, 0.625 mg/d, and 1.25 mg/d) administered without progesterin for 2 yr, the highest one was most effective in increasing lumbar BMD, but with the lower doses, there was no difference (44). In older women (mean age 73 yr), continuous estradiol at 0.3 mg/d with 2.5 mg medroxyprogesterone acetate for 3.5 yr increased lumbar spine BMD by 4.0%, total body BMD by 3.1%, and forearm BMD by 1.2% in comparison with placebo; the increase in femoral neck BMD was not statistically significant (4). In postmenopausal women aged 45–65 yr, combinations containing either 1 or 2 mg estradiol valerate together with 2.5 or 5 mg medroxyprogesterone acetate for 4 yr were equally effective in increasing lumbar and femoral neck BMD (45).

Approximately a fifth of the present subjects had hypovitaminosis D, which is compatible with the relatively poor vitamin D state of the Finnish population (46). Serum 25(OH)D levels remained stable during the study, and there were no differences in S-25(OH)D levels between the study groups throughout the study. In addition, all the participants were instructed to take at least 1 g of calcium daily, which intake was checked at every visit. Therefore, it is unlikely, that the heterogeneity in intakes of calcium and vitamin D contributed to the results.

In conclusion, the combination of HRT and alendronate did not offer an extra gain of bone mass over either treatment alone in elderly postmenopausal women with osteoporosis. Bone mass increased equally with alendronate and HRT alone, but in terms of reductions in bone markers, alendronate appeared to be superior to HRT.

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