

Alendronate in Early Postmenopausal Women: Effects on Bone Mass during Long-Term Treatment and after Withdrawal*

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ABSTRACT

We studied the effect on bone mass of alendronate treatment for 5 yr and its withdrawal. Four hundred and forty-seven postmenopausal women with normal bone mass entered a 3-yr randomized trial followed by a 2-yr open label extension. Three hundred and eleven women completed the first 3 yr, and 263 consented to continue and completed the extension. We are reporting data from groups using the dose of alendronate currently approved for osteoporosis prevention (5 mg) or from the group in which alendronate treatment was withdrawn: 52 women received alendronate (5 mg) for 5 yr (group I), 56 received 3 yr of placebo followed by alendronate (5 mg) for 2 yr (group II), and 52 received alendronate (20 mg) for 2 yr followed by 3 yr off

therapy (group III). In group I, alendronate (5 mg) increased bone mineral density (BMD) at the spine and trochanter by 2.5–3.2% ($P < 0.001$ vs. baseline) and stabilized total body and femoral neck BMD (change vs. baseline, $P = \text{NS}$) over 5 yr. By the end of 5 yr, BMD was comparable at the spine, hip, and total body in groups I and III. The 3-yr decrease in BMD after withdrawal of alendronate (20 mg) in group III was 1.8–5.7% ($P < 0.01$ vs. baseline) and similar to the 3-yr decrease in BMD in group II during the initial 3 yr. In conclusion, alendronate (5 mg) for 5 yr or alendronate (20 mg) for 2 yr followed by 3 yr off therapy prevented postmenopausal bone loss. After withdrawal of alendronate (20 mg), bone loss resumed at the normal early postmenopausal rate. (*J Clin Endocrinol Metab* 85: 1492–1497, 2000)

IN THE SEARCH for potential alternatives to hormone replacement therapy for osteoporosis treatment and prevention, much attention has been drawn to the bisphosphonates. This class of drugs has its main effect through inhibition of the osteoclast-mediated resorption of bone (1).

Alendronate is a bisphosphonate, which has recently been introduced into clinical practice for treatment of osteoporosis, and results from large studies have suggested 10 mg/day oral alendronate as the optimal dose. This dose causes increases of 5–9% in spine and hip bone mineral density (BMD) over 2–3 yr (2–5) and reduces the risk of vertebral and hip fractures by up to 50% (2, 6) in women with low bone mass or osteoporosis.

In contrast to treatment of osteoporosis, the aim of osteoporosis prevention is not to markedly increase, but rather

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to stabilize BMD. A dose of 5 mg/day oral alendronate seems to be the most appropriate dose with such effect and is the recommended dose for osteoporosis prevention in countries where alendronate is approved for this indication (7, 8). The use of alendronate for osteoporosis prevention has increased the potential application in clinical settings considerably, and it becomes important to define optimal treatment regimens over the longer term.

This study investigates the effect on bone mass and bone markers of treatment with 5 mg alendronate for 5 yr in recently postmenopausal women with normal bone mass. In addition, the effect after withdrawal of 2 yr of treatment with 20 mg alendronate is studied.

Subjects and Methods

Subjects

The study recruited healthy women, aged 40–59 yr, who were 6–36 months past menopause at study entry. FSH levels had to be in the postmenopausal range (42–126 IU/L). Subjects with a spinal BMD more than 2 SD above or below the young normal mean value or a history of nontraumatic spine or hip fractures were excluded. Women with disorders of bone and mineral metabolism were also excluded, as were those with a history of major upper gastrointestinal disease within 1 yr of study entry (such as peptic ulcer, esophageal disease, or malabsorption). Other exclusion criteria included previous treatment with bisphosphonates or fluoride (>1 mg/day) or treatment with estrogen, progestin, calcitonin, glucocorticoids, anticonvulsant agents, phosphate-binding antacids, or excessive vitamin A or vitamin D. Women who regularly used (>4 times/week) any medication that had the potential to cause gastrointestinal irritation (such as aspirin), who smoked more than 20 cigarettes/day, who drank 2 or more alcohol beverages/day, or who had a body weight more than 15% below or 30% above the ideal (as defined by the Metropolitan Health Insurance Co.) were also excluded. The study was approved by the local ethics committees and institutional review boards. All participants gave informed written consent. About 80% of the participants reported themselves as Caucasian.

Design

The study was a 3-yr dose-ranging, randomized, double blind, placebo-controlled trial, followed by a 2-yr open label extension. Dose-response data for the initial 3 yr of the study were published previously (7). Of the 447 women enrolled at the original baseline, 311 women completed the initial 3 yr, 274 consented to continue in the extension, and 263 completed all 5 yr. The 11 dropouts during the extension were equally distributed across treatment groups. Here we report 5-yr data from groups using the dose of alendronate currently approved for osteoporosis prevention (5 mg) (7, 8) or the group in which alendronate treatment was withdrawn. Fifty-two women received 5 mg alendronate for 5 yr (group I), 56 received 3 yr of placebo followed by 5 mg alendronate during the extension (group II), and 52 received 20 mg alendronate for 2 yr and placebo during the third year and were observed off therapy during the extension (group III; Fig. 1).

Double-blind			Open-label	
Year 1	Year 2	Year 3	Year 4	Year 5
Placebo			5 mg ALN	
5 mg ALN			5 mg ALN	
20 mg ALN		Placebo	No treatment	

FIG. 1. Schematic presentation of the study design.

During the initial 3 yr, the participants were instructed to take the study drug at least 1 h before breakfast or, as a less desirable alternative, at least 2 h after a meal and 1 h before the next meal. During the extension, dosing was changed to at least 30 min before breakfast after an overnight fast based on consideration of data from recent bioavailability studies (9). Throughout the study, all participants received a daily supplement of calcium (500 mg) taken separately from the study drug unless daily dietary calcium intake clearly exceeded 1 g, as demonstrated by a dietary questionnaire administered at baseline. Participants were questioned about potential adverse events at each visit, which were reported regardless of assumed association with the study medication.

BMD

BMD was measured at the spine (primary end point), hip, total body, and wrist every 6 months during the double blind phase and every 12 months during the extension by dual energy x-ray absorptiometry (DXA) with a QDR-1000, 1000/W, or 2000 (Hologic, Inc., Waltham, MA; $n = 97$) or a DPX or DPX-L (Lunar Corp., Madison, WI) densitometer ($n = 60$). Total body ($n = 115$) and wrist ($n = 91$) measurements were made at centers with densitometers capable of performing these measurements. One bone densitometry quality assurance center (Oregon Osteoporosis Center), which remained blinded to treatment allocation, was responsible for the quality control of all participant and phantom scans. Phantoms were scanned daily at each center, and factors to correct for machine calibration drift were applied as necessary.

Bone markers

Fasting urinary excretion of N-telopeptide cross-links of type 1 collagen (NTX; Osteomark, Ostex International, Inc., Seattle, WA) was measured at 0, 3, 6, and 12 months and every 12 months thereafter. Fasting urinary excretion of C-telopeptides of type I collagen (CL; Urine CrossLaps enzyme-linked immunosorbent assay, Osteometer A/S, Rødovre, Denmark) was measured at baseline and every 12 months thereafter. Both NTX and CL were corrected for creatinine excretion and used as estimates of bone resorption in patients with available archived baseline urine specimens ($n = 105$ for NTX; $n = 91$ for CL). NTX and CL were analyzed centrally by Medical Research Laboratories (Heighland Heights, KY).

Statistical analysis

All participants who had a valid 3 yr and either 4 or 5 yr BMD measurement were included in the analyses. Within the double blind phase (0–3 yr) and extension (4–5 yr), missing data at a planned observation time were estimated by carrying forward the most recently observed data value. However, no data were carried forward from the double blind phase to the extension. Baseline demographic data were compared by one-way ANOVA. The changes in end-point observations from 0–5 yr were evaluated with one-sample t tests to determine whether the mean percent change was significantly different from zero. A stepwise multiple variable regression analysis was used to compare 1) the cumulative 3-yr bone loss in group III (2–5 yr), with the 3-yr bone loss in group II (0–3 yr), and 2) the cumulative 2-yr gain in bone mass in group I (0–2 yr), with the gain in bone mass in group II (3–5 yr). The percent change in BMD was the outcome variable, treatment was the main covariate, and age, years postmenopause, body mass index, and baseline BMD were additional covariates of interest. Squared terms, to test for a curvilinear relationship between response and covariates, and interaction terms, to test for treatment-related differences in the trend response over time, were evaluated and deleted from the regression model if they were not significant. Two-sample t tests were used to compare treatment means, adjusted for effects caused by age, years postmenopause, and baseline BMD. The cumulative rates of bone loss or bone gain were compared between the groups using the least significant difference (LSD) interval method. An 84% confidence interval was computed for the least squares (adjusted) mean response for each group to provide an assessment of the variability and magnitude of the mean percent change in BMD. If the groups did not overlap in confidence intervals, then the groups were different using an approximate 5% LSD test, and this implied a difference of $P < 0.05$ for between-groups test.

Results

The baseline demographic characteristics, BMD, and bone markers of the participants completing the extension were comparable across treatment groups (Table 1). There were no statistically significant differences in the baseline characteristics of the participants in the original cohort, the participants entering the extension, and the participants not entering the extension (data not shown).

In group I, BMD increased 2.5% at the spine and 3.2% at the trochanter (both $P < 0.001$ vs. baseline), whereas femoral neck and total body BMDs were stable over 5 yr (changes vs. baseline, $P = \text{NS}$; Fig. 2). Bone loss at the wrist was attenuated relative to that in the placebo group, but BMD decreased 3.4–4.8% over 5 yr at the various regions of the wrist (ultradistal, middistal, and one third distal region; all $P < 0.001$ vs. baseline). The effect of treatment with 5 mg alendronate at the spine and hip was most pronounced during the initial 1–2 yr. During the extension, decreases in BMD of 1.2% at the spine, 2.0% at the femoral neck (both $P < 0.01$ vs. 3 yr), 0.7% at the trochanter ($P = \text{NS}$ vs. 3 yr), and 0.8% at the total body were observed ($P < 0.05$ vs. 3 yr).

Upon withdrawal of alendronate (20 mg) in group III, the cumulative 3-yr bone loss during yr 2–5 ranged from 1.8–5.7% at the various skeletal regions (Fig. 3). In comparison, the cumulative 3-yr bone loss in group II during yr 0–3 was 2.3–6.3%. There were no significant differences in the cumulative bone loss rates during the respective periods between the two groups at any skeletal region after adjustment for age, years since menopause, body mass index, and baseline BMD.

BMD at the spine and trochanter was 2.5–2.8% above baseline values 3 yr after withdrawal of alendronate (20 mg) in group III ($P < 0.001$), but was not significantly different from baseline values at the femoral neck and total body (Fig. 2). Furthermore, by the end of yr 5, BMDs in groups I and III were comparable at all skeletal sites except the wrist, where BMD was 2–3% higher in group I compared with that in group III ($P < 0.01$).

After adjustment for age, years since menopause, body mass index, and baseline BMD, there were no significant differences between the 2-yr gain in BMD during yr 0–2 in group I and the 2-yr gain in BMD during yr 3–5 in group II (Fig. 3). However, group II had 2–3% lower bone mass by the end of yr 5 compared with group I ($P < 0.001$; Fig. 2).

NTX and CL decreased within the first 12 months after the

start of treatment with 5 or 20 mg alendronate to a level 70–80% below baseline values ($P < 0.001$; Fig. 4). The suppression of bone markers tended to be more pronounced during treatment with 20 mg alendronate than during treatment with 5 mg alendronate. The suppression of the markers in groups I and II was comparable during treatment with 5 mg alendronate. Upon withdrawal of alendronate (20 mg) in group III, both markers partly reversed toward baseline, but remained 40–60% below baseline values by the end of yr 5 ($P < 0.001$ for both markers). However, from 36–60 months the level of CL in group III was comparable to that in group II from 0–24 months. No consistent correlations were observed between baseline values of the bone markers and change in BMD.

No new adverse events appeared, and only 2.5% of the participants discontinued treatment due to an adverse event during the extension. One participant died of breast cancer. There were no other serious adverse events (hospitalizations) or serious upper gastrointestinal adverse events (including esophagitis or esophageal, gastric, or duodenal ulcers).

Discussion

The study demonstrated that treatment with oral alendronate (5 mg/day) for 5 yr stabilized bone mass at the spine, hip, and total body. The effect on bone mass was most pronounced during the initial 1–2 yr, during which period BMD increased steadily, consistent with a reduction in the remodeling space (10). Thereafter, BMD reached a plateau or declined slightly, but remained at or above baseline values by the end of yr 5. This is in accordance with a decrease in bone turnover to a new steady state (10) and was presently confirmed by both of the bone resorption markers remaining 70–80% suppressed throughout the 5 yr. Continuous treatment with 5 mg/day alendronate thus seems to have a persistent antiresorptive effect on the skeleton in recently postmenopausal women with normal bone mass. The present findings substantiate the results from the first 3 yr of the study (7) and the 2 yr results from another ongoing 6-yr trial (8). Similarly, the observation that bone loss at the wrist was only partly prevented has been reported in several other studies of alendronate (2–4, 6–8). Whether this implicates less protection against wrist fractures in the present study remains unanswered. However, studies have shown a 50% reduction in wrist fracture incidence even though bone loss was only partly prevented at this region (2, 8).

TABLE 1. Mean baseline characteristics (SD) in the three arms of the study

	5 mg ALN, group I (n = 52)	Placebo/5 mg ALN, group II (n = 56)	20 mg ALN/placebo/none, group III (n = 52)
Age (yr)	51.9 (2.9)	51.7 (3.5)	52.2 (3.7)
Ht (cm)	162 (5)	160 (6)	163 (8)
Wt (kg)	61.0 (9.5)	63.5 (8.9)	65.0 (9.7)
BMI (kg/m ²)	23.2 (3.2)	24.8 (4.0)	24.5 (3.9)
Calcium intake (mg/day) ^a	1192 (716)	1047 (355)	1028 (430)
Spine BMD (g/cm ² ; Hologic; n = 197)	0.93 (0.09)	0.93 (0.11)	0.95 (0.11)
Spine BMD (g/cm ² ; Lunar; n = 60)	1.05 (0.12)	1.11 (0.08)	1.05 (0.12)
NTX (nmol/mmol creatinine; n = 105)	86.9 (51.7)	69.0 (52.5)	91.6 (43.2)
CL (μg/mmol creatinine; n = 91)	275 (162)	183 (162)	265 (240)

Data are from participants completing the extension (n = 160). $P > 0.05$ for all differences between groups at baseline. BMI, Body mass index; BMD, bone mineral density; NTX and CL, urinary excretions of N- and C-telopeptides of type 1 collagen corrected for creatinine excretion. Pre- and postmenopausal mean values (±SD) are (11): NTX, 26 ± 11 nmol/mmol creatinine; 51 ± 33 nmol/mmol creatinine; and CL, 189 ± 88 μg/mmol creatinine; 266 ± 150 μg/mmol creatinine.

^a Calcium intake consisted of dietary calcium plus a 500-mg calcium supplement.

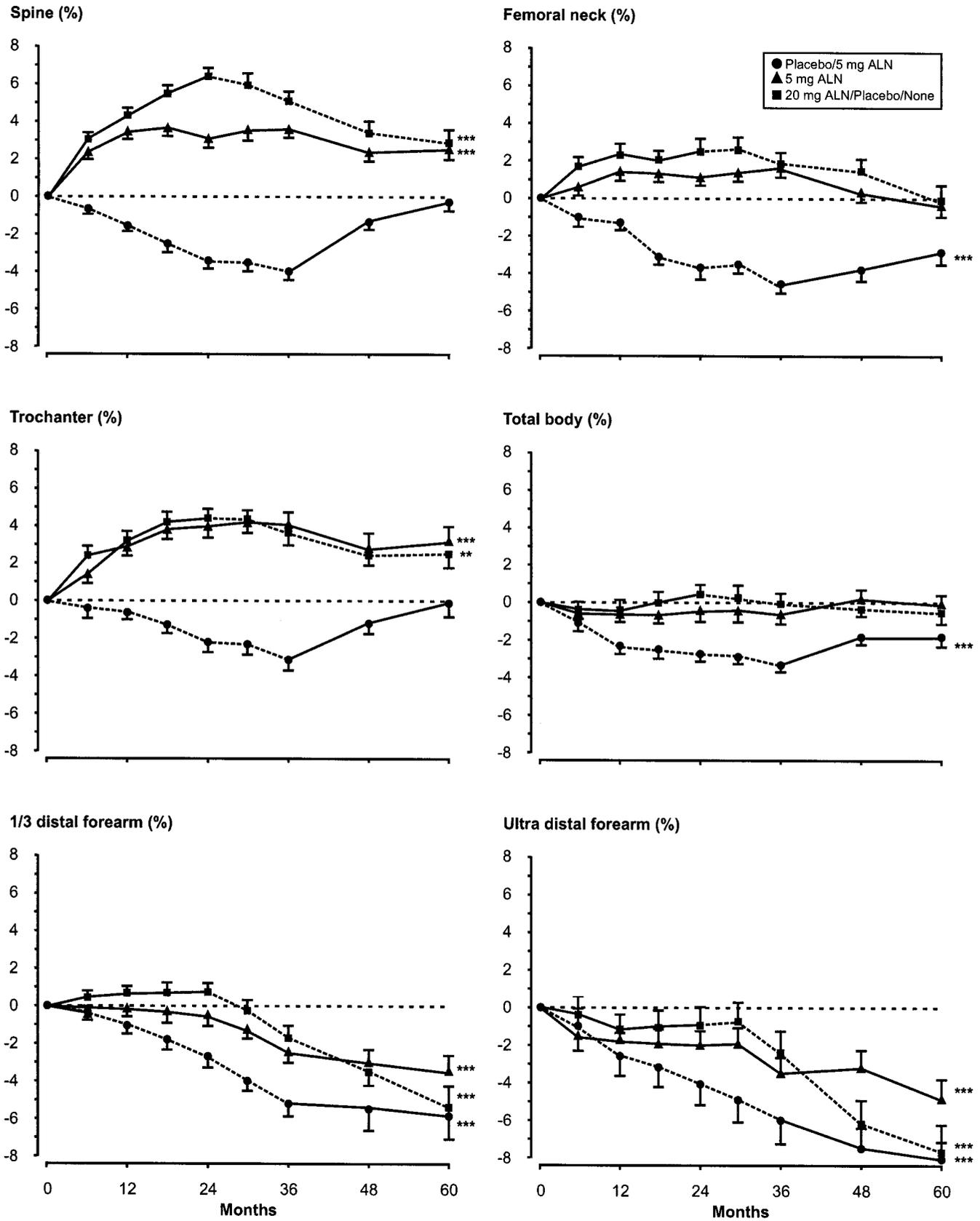


FIG. 2. Percent change in BMD at different skeletal sites as a function of time and treatment [mean (SEM)]. Solid lines represent alendronate treatment. Dashed lines represent placebo or no treatment. **, P < 0.01; ***, P < 0.001 (compared with baseline).

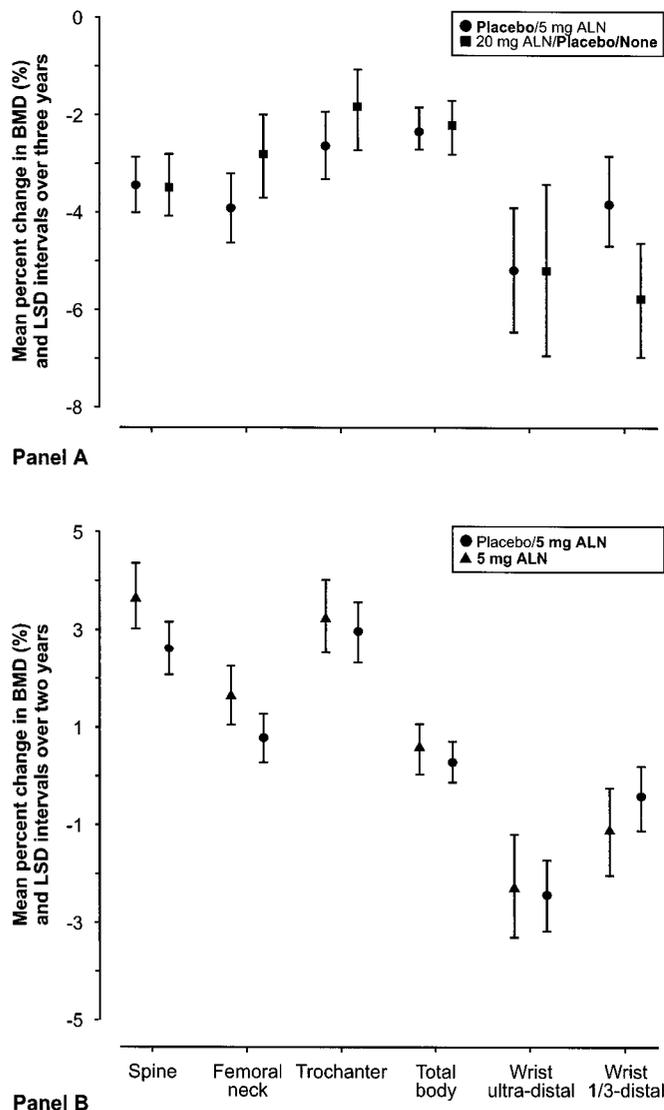


FIG. 3. Cumulative 3-yr decrease in BMD and corresponding LSD intervals at various skeletal regions in group III (2–5 yr) and group II (0–3 yr; A), and cumulative 2-yr increase in BMD and corresponding LSD intervals in group I (0–2 yr) and group II (3–5 yr; B). Overlapping LSD intervals implies $P > 0.05$ for between-groups test.

This indicates that protection against fractures during alendronate treatment is not completely explained by increases in BMD (11). Furthermore, the high content of cortical bone at the wrist (12) may blunt the BMD response to antiresorptive treatment at this region (13).

Upon withdrawal of 2 yr of treatment with 20 mg/day alendronate, bone loss resumed at a yearly rate of 0.5–2%, which was comparable to the bone loss observed in the group initially taking placebo. Both markers of bone resorption partly reversed after withdrawal of alendronate, but remained below baseline values by the end of 5 yr. Because of the lack of a placebo group during the extension, the small number of urine specimens, and a relatively wide range of test results, the possibility remains that the persistent suppression of the markers in this group was at least partly caused by artifacts. However, alendronate is expected to

have some long term effect on bone turnover after treatment withdrawal. Alendronate buried within the mineralized matrix of bone (14) is pharmacologically inactive (15). However, as bone resorption resumes after treatment withdrawal, alendronate is exposed on the resorption surfaces. Furthermore, consistent findings of bone loss despite suppression of the bone turnover markers have been reported previously. During the first 3 yr of the present study, a bone loss of about 1–2% was observed in the group treated with 1 mg/day alendronate, although NTX was suppressed by 40% (7). This indicates that complete prevention of bone loss only occurs once bone turnover is suppressed to premenopausal levels.

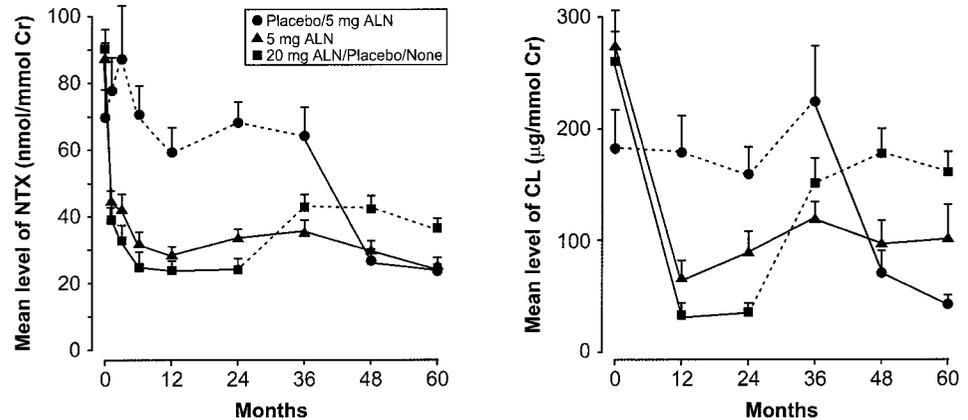
The study indicated that bone loss resumes at a normal postmenopausal rate after withdrawal of alendronate treatment. The stepwise multiple variable regression analysis, where age and years post menopause were covariates of interest, was used to compare bone loss in the group withdrawn from alendronate and the group taking placebo. The analysis compensated at least partly for a difference between the groups of 2 yr past menopause. However, because of the lack of a placebo group during the extension, we cannot rule out that natural slowing of bone loss during the withdrawal period partly explained the normal rate of bone loss observed after withdrawal of alendronate.

Several studies have investigated the effect on bone mass and bone turnover after withdrawal of alendronate or other bisphosphonates, but mostly in elderly postmenopausal women with osteoporosis. The studies have reported a partial or complete reversal of bone turnover and stable spine and hip BMD after withdrawal of 0.5–2 yr of treatment with oral alendronate (5–40 mg) or pamidronate (150 mg/day) (4, 16–19). The results thus indicate that in elderly postmenopausal women with osteoporosis, the bone mass gained during bisphosphonate treatment is largely sustained even several years after treatment withdrawal. The sustained effect on bone mass observed in these studies might, however, also be partly explained by the continuous administration of calcium supplementation after withdrawal of the bisphosphonate (20).

In contrast, the few studies that have addressed withdrawal of bisphosphonates in younger postmenopausal women with normal bone mass have shown normalization of bone turnover and resumption of bone loss at a normal postmenopausal rate shortly after withdrawal of the bisphosphonate (21–23). These results are consistent with our present findings and indicate that the underlying natural bone turnover and resulting bone loss are greater in more recently postmenopausal women (24), thus resulting in an earlier reversal of bone turnover and bone loss after withdrawal of the antiresorptive agent. The implications may be that alendronate is more effective in recently postmenopausal women when administered continuously compared with a discontinuous administration.

Importantly, the present study also revealed that a comparable effect on bone mass at the spine, hip, and total body could be achieved by applying a higher dose of alendronate (20 mg) for a shorter period (2 yr) followed by a period off therapy (3 yr). However, because bisphosphonates are known to cause gastrointestinal side-effects at higher doses, 20 mg/day alendronate for 2 yr might present long term compliance problems (3, 4, 7). Long term randomized trials,

FIG. 4. Absolute change in urinary excretions of NTX and CL corrected for creatinine excretion as a function of time and treatment [mean (SEM)]. *Solid lines* represent alendronate treatment. *Dashed lines* represent placebo or no treatment. **, $P < 0.05$; ***, $P < 0.001$ (compared with baseline).



which include arms with continuous and discontinuous treatments with standard accepted doses of alendronate, are still needed to elucidate these questions further and optimize treatment strategies for long term prevention of bone loss in recently postmenopausal women. This is being studied in the ongoing Early Postmenopausal Intervention Cohort study of oral alendronate (8, 23).

The gain in BMD during the initial 2 yr was similar in participants allocated to 5 mg/day alendronate at the original baseline and in participants switched to this dose after 3 yr of placebo treatment. This suggested that the effect on bone mass was independent of previous bone loss and is consistent with reports of a similar effect on BMD of 5 mg/day alendronate in elderly women with osteoporosis (25). However, participants who received placebo during the initial 3 yr had 2–3% lower bone mass by the end of 5 yr relative to those treated with 5 mg/day alendronate during all 5 yr. This indicates that the sooner alendronate treatment is instituted after the menopause, the greater the amount of premenopausal bone mass preserved.

In conclusion, 20 mg/day alendronate for 2 yr followed by 3 yr off therapy prevented postmenopausal bone loss in women with normal bone mass. In comparison, a 60% cumulative dose of alendronate administered as continuous alendronate (5 mg/day) for 5 yr had a comparable effect on spine, hip, and total body BMD, but a significantly greater effect on BMD at the wrist. The bone loss, which resumed after withdrawal of alendronate (20 mg), was comparable to normal early postmenopausal bone loss.

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