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Effect of alendronate and exercise on bone and physical performance of postmenopausal women: a randomized controlled trial☆

K. Uusi-Rasi,[a,*] P. Kannus,[a,b] S. Cheng,[c] H. Sievänen,[a] M. Pasanen,[a] A. Heinonen,[a] A. Nenonen,[a,d] J. Halleen,[e] T. Fuerst,[f] H. Genant,[f] and I. Vuori[a]

[a] *UKK Institute for Health Promotion Research, 33501 Tampere, Finland*
[b] *Department of Surgery, Tampere University Medical School and University Hospital, 33014 Tampere, Finland*
[c] *Department of Health Sciences, University of Jyväskylä, 40014 Jyväskylä, Finland*
[d] *Department of Clinical Chemistry, Tampere University Hospital, 33014 Tampere, Finland*
[e] *Department of Anatomy, University of Turku, 20520 Turku, Finland*
[f] *University of California, Osteoporosis and Arthritis Research Group, Department of Radiology, San Francisco, CA 94105, USA*

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Abstract

In this randomized, double-blind, placebo-controlled 12-month trial we evaluated effects of weight- bearing jumping exercise and oral alendronate, alone or in combination, on the mass and structure of bone, risk factors for falling (muscle strength and power, postural sway, and dynamic balance), and cardiorespiratory fitness in postmenopausal women. A total of 164 healthy, sedentary, early postmenopausal women were randomly assigned to one of four experimental groups: (1) 5 mg of alendronate daily plus progressive jumping exercise, (2) 5 mg alendronate, (3) placebo plus progressive jumping exercise, or (4) placebo. The primary endpoint was 12-month change in bone mass and geometry (measured with dual-energy X-ray absorptiometry and peripheral computed tomography at several axial and limb sites) and physical performance; the secondary endpoint was change in biochemical markers of bone turnover. The jumping exercise was conducted an average 1.6 ± 0.9 (mean ± SD) times a week. Alendronate daily was effective in increasing bone mass at the lumbar spine (alendronate vs placebo 3.5%; 95% CI, 2.2–4.9%) and femoral neck (1.3%; 95% CI, 0.2–2.4%) but did not affect other bone sites. Exercise alone had no effect on bone mass at the lumbar spine or femoral neck; it had neither an additive nor an interactive effect with alendronate at these bone sites. However, at the distal tibia the mean increase of 3.6% (0.3–7.1%) in the section modulus (that is, bone strength) and 3.7% (0.1–7.3%) increase in the ratio of cortical bone to total bone area were statistically significant in the exercise group compared to the nonexercise group, indicating exercise-induced thickening of the bone cortex. Bone turnover was reduced in alendronate groups only. Alendronate had no effect on physical performance while the jumping exercise improved leg extensor power, dynamic balance, and cardiorespiratory fitness. As conclusion Alendronate is effective in increasing bone mass at the lumbar spine and femoral neck, while exercise is effective in increasing the mechanical properties of bone at some of the most loaded bone sites, as well as improving the participants' muscular performance and dynamic balance. Together alendronate and exercise may effectively decrease the risk of osteoporotic fractures.

Keywords: Alendronate; Exercise; Bone mass; Bone structure; Physical performance; Balance

Introduction

Osteoporosis and related fractures among elderly people are a significant public health problem, and the number of fractures is expected to rise dramatically as populations age [1,2]. Therefore, effective methods for prevention and treatment are needed. Currently, alendronate is one of the most widely used and studied drug therapies for osteoporosis. Clinical studies have confirmed that alendronate is able to inhibit bone loss [3]. Four to 6% increase in bone mass of the spine and hip with simultaneous 20 to 50% reduction in the risk of vertebral, hip, and other fractures have been reported after 2 to 3 years of alendronate treatment in elderly women with established osteoporosis [3,4]. Also, recent studies have shown that alendronate is effective in

☆ In addition to the authors, the following investigators were members of the study group: Pekka Oja, Ph.D., the UKK Institute; Kalervo Väänänen, M.D., University of Turku; and Harri Suominen, Ph.D., University of Jyväskylä, Finland.

* Corresponding author. Fax: +358-3-282-9200.
E-mail address: kirsti.uusi-rasi@uta.fi (K. Uusi-Rasi).

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preventing bone loss in younger menopausal women who are at risk of developing osteoporosis [5].

Regular exercise, in turn, seems to be effective in maintaining and even increasing bone mass and strength in pre- and postmenopausal women [6,7]. In addition, epidemiologic studies are consistent in suggesting that a higher than average level of leisure time physical activity or daily chores reduces the risk of falling and hip fractures [8,9]. The strengthening of bones seems to be obtained via high- impact, uncustomary strain-producing loading regimens, such as jumping [10–13].

However, it is not known whether exercise and antiresorptive drug therapy are able to interact in slowing the bone loss at menopause. Also, it has been hypothesized that a part of the postmenopausal bone loss is actually due to age-related reduction in physical activity and concomitant loss of muscle strength, thus resulting in increased bone resorption [14]. For all of these reasons, it is important to investigate exercise in combination with antiresorptive drug treatment for maintenance of physical fitness and prevention of osteoporosis and related fractures.

The purpose of this randomized controlled trial was to evaluate the effects of weight-bearing jumping exercise and oral alendronate (Fosamax; Merck & Co., Rahway, NJ), alone or in combination, on the mass and structure of bone in early postmenopausal women. In addition, the effects of these treatments on risk factors for falling (muscle strength and power and balance) and cardiorespiratory fitness were assessed.

Methods

Study subjects and design

The study was a 1-year double-blind, placebo-controlled (placebo pills, identical with the effective ones donated by Merck & Co), randomized intervention trial in postmenopausal women consisting of four experimental groups: (1) 5 mg of alendronate daily + exercise (Al^+Ex^+), (2) 5 mg alendronate daily (Al^+Ex^-), 3) placebo + exercise (Al^-Ex^+), 4) placebo (Al^-Ex^-). The inclusion criteria were 1–5 years postmenopause; no previous bone fractures; neither current nor previous use of estrogen, corticosteroids, bisphosphonates, and other drugs nor illness affecting bone metabolism; no contraindication to exercise or alendronate; previous regular exercise less than two times a week; femoral neck BMD ≥ 0.650 g/cm^2 (i.e., no more than 2.5 SD below the young healthy women's reference value as determined by the DXA at the UKK Institute); and an FSH level greater than 30 IU/L. The exclusion criteria were less than 1 year or more than 5 years postmenopause; history of chronic illness; evidence of metabolic bone disease or use of bone-specific medications; concurrent serious medical conditions including sepsis or disseminated cancer; abnormalities of the esophagus; inability to stand or sit upright for at least 30 min; hypersensitivity to any component of the study drug; and hypocalcemia.

The recruitment process is presented in Fig. 1. A questionnaire was sent to a random population sample of 3000 women representing a cohort of women born between 1942 and 1947 and living in the city of Tampere, Finland. Altogether 1098 women replied and 263 eligible women were interested in participating in the study and were subsequently invited to the screening examination. Based on the inclusion and exclusion criteria, 164 of them could be included in the study and received the baseline measurements. After randomization, 5 women were no longer willing to participate, and thus 159 women started the study.

All the women provided written informed consent prior to the study, and the study protocol was approved by the local research committee and independent medical ethics committee. The study progression was monitored and audited according to GCP instructions.

In addition to the study drugs (placebo or alendronate), all subjects received a daily supplement of calcium citrate (630 mg) and vitamin D (400 IU = 10 μg) (Citracal + D; Mission Pharmacal, San Antonio, TX). All measurements were done at baseline (before the start of the intervention) and at the end of the study, except the biochemical markers, which were also determined at 3 and 6 months. The laboratory technicians were unaware of treatment-group assignments.

Exercise program

The exercise training sessions were organized three times per week for 12 months. All sessions were supervised by experienced exercise leaders of the UKK Institute and a record of attendance of each participant was kept by these exercise leaders. Each session included 15 min of warm-up, 20 min of multidirectional jumping exercises, 15 min of calisthenics (stretching and nonimpact exercises), and 10 min cool down. The jumping part of the session consisted of either an aerobic jump program or a step program in alternative weeks. The program was progressive. In the aerobic jumping exercises, raising the height of the foam fences from 10 to 25 cm gradually increased the magnitude of the ground reaction forces. In the step exercises, the magnitude was similarly increased by increasing the number of step benches (total height from 10 to 25 cm). The pilot study showed that the peak forces varied between 2.1 and 5.6 times body weight in these described exercises [11].

The women in the nonexercising group were asked to maintain their current level of physical activity during the 12 months. Over the entire study period, all study subjects kept a continuous exercise diary with consecutive 7-day forms for type and duration of all physical activities. In addition, daily physical activity was estimated twice (once in summertime and once in wintertime) from all the subjects by measuring the daily walking distance with a step pedom-

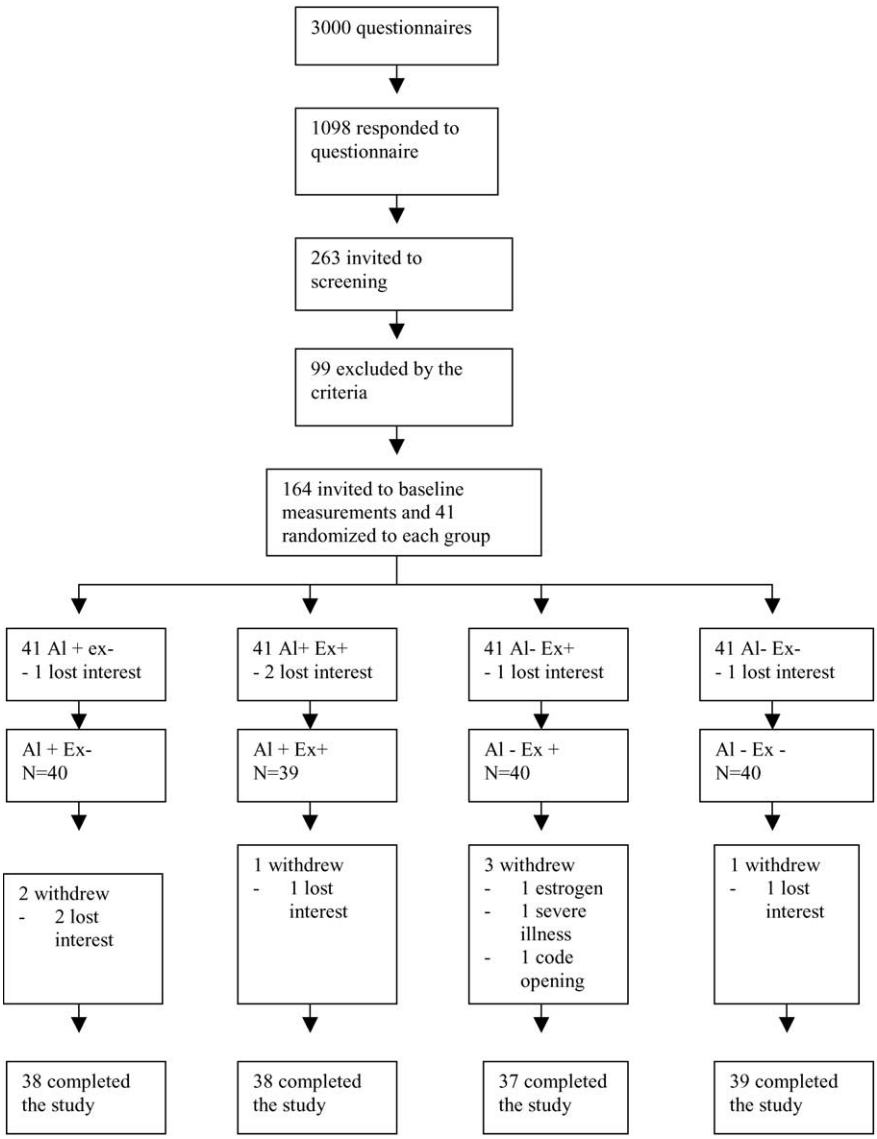

Fig. 1. Trial profile.

eter (Yamax, Digiwalker DW-700, Yamax, Japan) during 3 consecutive days.

Outcome measurements

The below-mentioned bone and physical performance measurements were the primary endpoint of the study and the secondary endpoint was the biochemical markers of bone turnover. The outcome assessors were blinded to the treatment-group assignment.

Dual-energy X-ray absorptiometry (DXA)

The bone mineral content (BMC) of the lumbar spine, right proximal femur (femoral neck and trochanter area of the femur), and nondominant distal radius were measured with DXA (Norland XR-26; Norland, Fort Atkinson, WI) at baseline and at the end of the study. At the UKK Institute, the in vivo day-to-day precision (coefficient of variation, CV%) of the DXA scanning is better than 1% [15,16].

The section modulus (Z) or "bending strength" of the femoral neck was analyzed using an algorithm described by Beck et al. [17] In this algorithm, profiles of pixel bone mass values across each region are used to drive a large number of structural variables analysis location. Measurements include cross-sectional area (CSA), cross-sectional moment of inertia (CSMI) or "bone stiffness", inner and outer cortical diameters, cortical thickness, and section moduli.

Peripheral quantitative computed tomography (pQCT)

The pQCT measurements (XCT 3000, Stratec GmbH, Germany) were performed at the midshaft (cortical bone) and distal site (trabecular bone) of the right tibia at baseline and at 12 months. The analyzed variables were the BMC,

ratio of cortical to total area of bone (CoA/ToA), and density-weighted polar section modulus (BSI) or "bending strength" for the distal tibia, and the BMC, cortical density (CoD), cortical area (CoA), and BSI for the tibial shaft. The protocol has been detailed elsewhere [18]. At the UKK Institute, the in vivo precision (CVrms) of the different pQCT variables for the tibia ranges from 0.9 to 5.9% [18].

Physical performance

The maximal isometric strength of leg extensors was measured with a leg press dynamometer (Tamtron, Tampere, Finland), and grip strength of the both arms was measured with grip strength dynamometer [19].

The leg extensor power was evaluated with a vertical countermovement jumping test, using a contact platform (Newtest, Oulu, Finland) and recording the flying time of the jump [20].

Dynamic balance (agility) was tested with a figure-eight running test [11,21]. Static postural sway was estimated with a standardized postural sway platform (Biodex Stability System, Biodex Medical Systems, New York, NY). In this system, postural sway was expressed as a stability index, a unitless measure that reflects the variance of platform displacement from a level. A high number indicates less motion control and thus poorer postural stability.

Cardiorespiratory fitness (estimated maximal oxygen uptake, VO_2max) was assessed by a standardized 2-km walk test [22].

Biochemical markers of bone turnover

Venous blood samples were obtained between 7:00 and 9:00 a.m. after 12 h fasting at baseline and at 3, 6, and 12 months. Serum was separated by centrifugation (+4°C/+15°C), aliquoted, and stored at −20°C/−70°C until the analyses. In addition to standard safety measurements, FSH and biochemical markers of bone turnover were assayed. Serum tartrate-resistant acid phosphatase isoforms 5b (TRAP 5b) [23,24] was determined as a marker of bone resorption using a commercial immunoassay (BoneTRAP; SBA-Sciences, Oulu, Finland) and serum osteocalcin as a marker of bone formation, as described previously [25]. Serum bone-specific alkaline phosphatase (BAP) was also assessed as a formation marker using immunoassay (Metra Biosystems, Mountain View, CA).

Calcium intake

Dietary food intake, including calcium intake, and the possible use of vitamin and mineral supplements were assessed by a complete 3-day (two weekdays and a Sunday) dietary record at baseline and at the end and were calculated using Micro-Nutrica software (Social Insurance Institution, Helsinki, Finland).

Statistical analysis

Means ± SD were used as descriptive statistics. Primary efficacy endpoints were changes in bone mass, bone geometry, and physical performance. Secondary endpoints were the changes in the biochemical markers of bone turnover. For the biochemical analysis, log transformation was used.

The results were first analyzed on an intention-to-treat (ITT) basis. Subjects were excluded from the ITT analysis only if endpoint data were not available. In addition to the ITT analysis, efficacy or active treatment analysis of the exercise was done for both the bone variables and physical performance, the inclusion criterion for the active exercise group being training a minimum of twice a week. The alendronate/placebo pills were taken so well that a separate efficacy analysis was not necessary (see Result).

The efficacy of the interventions and associations between the alendronate treatment and exercise were examined by an analysis of covariance using alendronate and exercise as the factor variables and the values of the baseline measurements as the covariates. The mean relative differences as results of changes between the study groups and 95% confidence intervals (CI) were presented as results of the study. When the 95% CI did not include zero, the group difference was regarded as statistically significant at $\alpha = 0.05$.

Preceding the study, the sample size and power calculations were done for selected outcome variables; that is, for the BMC of the spine and femoral neck. Using an α level of 0.05 and common standard deviation of 4% for the change, a sample size of 38 women in each group gave 90% power for the study to detect 3% BMC difference in change between the treatment groups.

Results

Basic characteristics

Characteristics of the study groups at baseline are given in Table 1. There were no clinically relevant between-groups differences nor were there statistically significant changes in body weight in any of the study groups during the trial. The mean daily dietary calcium intake in the whole study group was 956 mg at the baseline and 959 mg at the 12 months, which was considered sufficient, even without the supplements. The supplement increased calcium intake by 630 mg/day. The overall compliance for calcium supplements was 86%. Altogether 30 subjects were smokers and their number did not change during the follow-up.

Subject adherence

Seven of 159 women did not reach the endpoint measurements. One woman was found to have breast cancer just at the start, and one subject started estrogen-replacement therapy; three lost interest during the first 3 months, and one

Table 1
Baseline characteristics of the randomized groups

Characteristic	Al^+Ex^- ($n = 41$)	Al^+Ex^+ ($n = 41$)	Al^-Ex^+ ($n = 41$)	Al^-Ex^- ($n = 41$)
Age (y)	54.2 ± 2.4	53.0 ± 2.8	53.3 ± 2.2	53.2 ± 2.1
Height (cm)	164.1 ± 5.2	164.1 ± 5.7	164.0 ± 4.6	162.5 ± 6.2
Weight (kg)	71.7 ± 10.6	70.9 ± 9.4	73.8 ± 10.8	71.4 ± 10.8
BMI	26.7 ± 3.6	26.3 ± 3.5	27.4 ± 4.1	27.0 ± 3.7
Menopause age (y)	50.9 ± 3.3	49.6 ± 3.3	50.0 ± 3.1	49.8 ± 3.1
Years since menopause	4.0 ± 2.4	2.9 ± 2.7	4.0 ± 2.5	4.1 ± 2.9
Number of smokers	5	9	8	8
Dietary calcium intake	953 ± 301	1059 ± 433	939 ± 309	868 ± 306

Note. Values are means ± SD. Al^+Ex^+, 5 mg of alendronate daily + exercise; Al^+Ex^-, 5 mg alendronate daily, Al^-Ex^+, placebo + exercise; Al^-Ex^-, placebo; BMI, body mass index (kg/m^2).

during the first half a year, and one's code had to be broken after 10 months (due to suspicion of gastrointestinal bleeding). Seventy-five women in the exercise group and 77 women in the nonexercise group completed the study (Fig. 1). The final sample size for the ITT analysis was thus 152 women.

Mean (±SD) compliance in the exercise group, defined as attendance in the training sessions, was 1.6 ± 0.9 times per week. Four women from the exercise group did not attend a single training session, and six other women attended less than 10 times during the study year. One of them, however, did the exercises at home after moving away from the study area. All these women were included into the intention-to-treat analysis. For the active treatment analysis of the exercise, 33 of the total number of 82 women randomized to the exercise groups were included (each of them having average training frequency two times per week or more).

The reported mean compliance for taking alendronate/placebo pills, defined as the percentage of all available pills, was 94%. The mean daily physical activity as measured by a pedometer was 9285 ± 2824 steps per day in the training group (including one training session) and 8503 steps ± 3488 per day in the nontraining group and this did not change during the study. Neither training nor nontraining subjects reported changes in habitual activity during the study except for the given exercise program in the training group.

Adverse events

In general, alendronate was well tolerated. The overall numbers of patients reporting any upper gastrointestinal symptom (also including all the symptoms that were considered to be related to the study drug) were 16 (21%) and 27 (35%) in the alendronate and placebo groups, respectively. The drug therapy was discontinued for one subject and the code was opened because of an adverse event (severe abdominal pain with suspicion of gastrointestinal bleeding). She belonged to the placebo group. One subject required medical consultation due to a mild allergic-type skin reaction at the lower limbs and the study drug (alendronate) was discontinued for 2 weeks. In addition, two other women contacted the physician due to abdominal pain (both from the placebo group).

Exercise-related musculoskeletal symptoms

During the study period, 19 subjects from the exercise group consulted the attending physician (P.K.) due to musculoskeletal injuries or symptoms; 1 subject had an acute severe ankle sprain requiring surgical treatment. The rest were mild overuse symptoms; 1 subject with a mild knee distortion injury; 5 subjects with an overuse problem at the knee joint (3 with chondromalacia patellae and 2 with unspecific knee pain); 4 with an overuse problem at the foot (2 with an insertional tendinopathy of the Achilles tendon and 2 with unspecific foot pain); 2 with low back pain (1 sciatica, 1 unspecific); 2 with hip pain (1 trochanteric bursitis, 1 unspecific); 2 with shoulder pain (both supraspinatus tendinitis); and 2 with unspecific fibromyalgia (tension neck symptoms).

Bone mass (BMC)

The mean percentage changes in the bone mass from baseline to 12 months are shown in Table 2. Alendronate and exercise showed no statistically significant interaction effect on any of the outcome variables, and therefore, the between-group differences are described separately for alendronate and exercise (Table 2, Fig. 2). At 12 months, a statistically significant difference in change between the alendronate and placebo groups was seen for BMC of the lumbar spine and femoral neck, 3.5% (95% CI, 2.2–4.9%) and 1.3% (95% CI, 0.2–2.4%), respectively. There were no similar between-groups differences in the exercise vs nonexercise groups.

Although alendronate increased bone mass at the femoral neck, the section modulus of the neck did not change (Table 3, Fig. 3). Neither alendronate nor exercise had an effect on radial BMC. However, at the distal tibia, the only group losing bone mass was Al^-Ex^- group (Table 2, Fig. 2). Efficacy analyses did not change the BMC results of the exercise group (Table 4).

Bone structure

The mean percentage changes and effects of the alendronate and exercise treatments on the bone structure are given

Table 2
Mean values of bone mass in study groups and mean percent differences in the alendronate and exercise treatments

Variable	Baseline[a]	End[a]	Alendronate effect (%)	Exercise effect (%)
Lumbar spine, BMC[b]				
Al^+Ex^- (n = 38)	4.23 ± 0.78	4.38 ± 0.76	3.5 (2.2–4.9)	0.9 (−0.4–2.2)
Al^+Ex^+ (n = 38)	4.18 ± 0.63	4.35 ± 0.66		
Al^-Ex^+ (n = 37)	4.20 ± 0.56	4.26 ± 0.64		
Al^-Ex^- (n = 39)	4.06 ± 0.76	4.06 ± 0.77		
Femoral neck, BMC				
Al^+Ex^-	3.02 ± 0.54	3.05 ± 0.51	1.3 (0.2–2.4)	−0.2 (−1.3–0.9)
Al^+Ex^+	2.91 ± 0.42	2.92 ± 0.42		
Al^-Ex^+	2.96 ± 0.38	2.95 ± 0.39		
Al^-Ex^-	2.92 ± 0.44	2.91 ± 0.47		
Distal radius, BMC				
Al^+Ex^-	0.966 ± 0.24	0.961 ± 0.23	0.5 (−2.1–3.1)	0.0 (−2.6–2.7)
Al^+Ex^+	0.970 ± 0.22	0.970 ± 0.19		
Al^-Ex^+	1.024 ± 0.17	1.001 ± 0.17		
Al^-Ex^-	0.947 ± 0.21	0.958 ± 0.20		
Distal tibia, BMC				
Al^+Ex^-	650.3 ± 95.7	651.8 ± 91.1	1.1 (0.2–2.1)	1.0 (0.0–2.0)
Al^+Ex^+	629.7 ± 80.2	632.3 ± 74.8		
Al^-Ex^+	644.3 ± 92.9	646.9 ± 84.0		
Al^-Ex^-	645.3 ± 97.2	634.5 ± 97.1		
Tibial shaft, BMC				
Al^+Ex^-	765.0 ± 94.7	760.8 ± 93.6	0.2 (−0.6–1.0)	0.7 (−0.1–1.5)
Al^+Ex^+	757.5 ± 64.0	756.4 ± 63.9		
Al^-Ex^+	767.0 ± 89.7	766.0 ± 84.7		
Al^-Ex^-	767.5 ± 82.2	759.9 ± 84.4		

Note. BMC, bone mineral content; Al^+Ex^+, 5 mg of alendronate daily + exercise; Al^+Ex^-, 5 mg alendronate daily; Al^-Ex^+, placebo + exercise; Al^-Ex^- = placebo.

[a] Values are means ± SD

[b] Values in parentheses are 95% CIs.

in Table 3 and Fig. 3. Exercise improved the polar section modulus (BSI) of the distal tibia by 3.6% (95% CI, 0.3–7.1%). There was no such effect due to alendronate treatment. At the tibial shaft, both alendronate and exercise were ineffective. In the exercise group, the efficacy analysis did not change the results concerning the bone structure (Table 4).

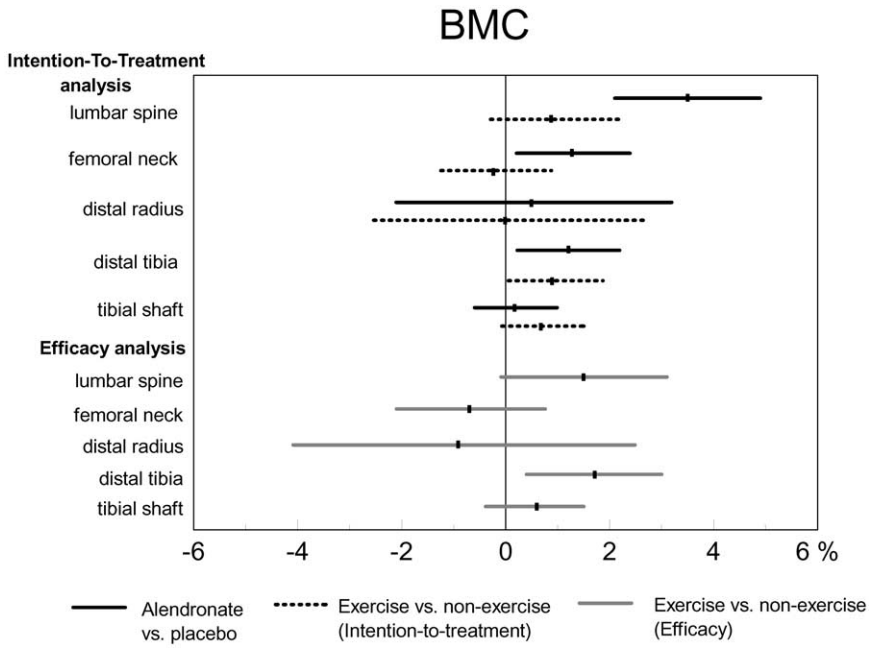

Fig. 2. Means and 95% confidence intervals of the group differences (%) in the bone mineral content (BMC) between the alendronate groups (black lines) and between the exercise groups (dotted lines for ITT analysis and grey lines for efficacy analysis).

Table 3
Mean values of the bone strength variables of the study groups and mean differences in the alendronate and exercise treatments

Variable	Baseline[a]	End[a]	Alendronate effect[b] (%)	Exercise effect[b] %
Femoral neck, Z				
Al^+Ex^- (n = 38)	1497.8 ± 312.2	1529.4 ± 301.4	1.1 (−0.7–2.9)	−0.5 (−2.2–1.3)
Al^+Ex^+ (n = 38)	1415.6 ± 248.3	1428.8 ± 252.0		
Al^-Ex^+ (n = 37)	1501.8 ± 245.4	1475.8 ± 240.2		
Al^-Ex^- (n = 39)	1446.6 ± 260.8	1429.1 ± 273.3		
Distal tibia, TrD				
Al^+Ex^-	225.3 ± 27.3	225.2 ± 26.4	0.6 (−0.1–1.2)	0.5 (−0.2–1.1)
Al^+Ex^+	229.0 ± 34.2	229.3 ± 32.0		
Al^-Ex^+	216.0 ± 33.9	216.2 ± 33.6		
Al^-Ex^-	229.1 ± 34.7	227.3 ± 34.9		
Distal tibia, ToA				
Al^+Ex^-	894.8 ± 119.9	884.3 ± 120.3	0.5 (−0.6–1.6)	−0.4 (−1.5–0.6)
Al^+Ex^+	915.6 ± 113.9	915.9 ± 114.0		
Al^-Ex^+	957.1 ± 130.9	947.5 ± 130.6		
Al^-Ex^-	903.3 ± 144.9	890.6 ± 138.5		
Distal tibia, CoA/ToA				
Al^+Ex^-	15.2 ± 3.5	15.5 ± 3.4	0.9 (−2.6–4.4)	3.7 (0.1–7.3)
Al^+Ex^+	14.9 ± 3.3	15.8 ± 3.3		
Al^-Ex^+	14.5 ± 2.9	15.4 ± 3.1		
Al^-Ex^-	15.4 ± 3.9	15.5 ± 3.7		
Distal tibia, BSI				
Al^+Ex^-	928.3 ± 280.1	942.3 ± 279.0	1.8 (−1.5–5.2)	3.6 (0.3–7.1)
Al^+Ex^+	865.9 ± 226.8	917.2 ± 238.9		
Al^-Ex^+	913.8 ± 279.1	943.2 ± 269.9		
Al^-Ex^-	922.6 ± 302.3	922.7 ± 302.9		
Tibial shaft, CoD				
Al^+Ex^-	1093.0 ± 23.1	1095.3 ± 22.0	0.5 (0.2–0.9)	−0.3 (−0.6–0.1)
Al^+Ex^+	1102.4 ± 27.1	1099.9 ± 29.2		
Al^-Ex^+	1097.7 ± 28.4	1091.0 ± 29.4		
Al^-Ex^-	1093.8 ± 28.3	1089.2 ± 26.5		
Tibial shaft, CoA				
Al^+Ex^-	279.9 ± 33.3	277.7 ± 32.6	−0.3 (−1.2–0.6)	1.0 (0.1–1.9)
Al^+Ex^+	274.8 ± 21.6	275.1 ± 22.4		
Al^-Ex^+	279.2 ± 30.9	280.7 ± 30.9		
Al^-Ex^-	280.6 ± 28.8	279.0 ± 29.3		
Tibial shaft, BSI				
Al^+Ex^-	1664.6 ± 292.3	1664.5 ± 289.5	0.1 (−1.3–1.6)	0.1 (−1.3–1.6)
Al^+Ex^+	1626.4 ± 222.1	1620.6 ± 224.0		
Al^-Ex^+	1701.7 ± 243.9	1701.3 ± 246.0		
Al^-Ex^-	1612.2 ± 232.5	1604.1 ± 236.0		

Note. Al^+Ex^+, 5 mg of alendronate daily + exercise; Al^+Ex^-, 5 mg alendronate daily; Al^-Ex^+, placebo + exercise; Al^-Ex^-, placebo; Z, section modulus at the femoral neck; TrD, trabecular density; ToA, total area; CoA/ToA, ratio of cortical to total area of bone; BSI, section modulus at the tibia; CoD, cortical density; CoA, cortical area.

[a] Values are means ± SD

[b] Values in parentheses are 95% CI.

Physical performance

The absolute values of the physical performance at baseline and after 12 months are described in Table 5. From the physical performance parameters, leg extensor power, dynamic balance, and cardiorespiratory fitness (VO_2max) improved statistically significantly in the exercise group compared to the nonexercise group, the differences being 8.5% (95% CI, 4.7–12.3%), 1.5% (0–3.0%), and 3.1% (0.9–5.3%), respectively. Alendronate treatment had no effect on any of the performance parameters. In the efficacy analyses of the exercisers, the above-noted improvements in the performance were greater than those in the ITT analysis (Fig. 4). In addition, improvement in the exercises' leg extensor strength was significant (3.4%, 95% CI, 0.4–6.5%).

Biochemical markers of bone turnover

A significant reduction in the bone formation markers BAP and OC and the bone resorption marker TRAP 5b were seen in the alendronate groups at 3 months, after which they remained stable. At the end of the 12-month intervention, the mean differences between the Al^+ and Al^- groups were 30% (95% CI, 24–35%) for BAP, 40% (33–47%) for OC, and 38% (33–42%) for TRAP 5b. There was no statistically significant exercise effect on any of the biomarkers.

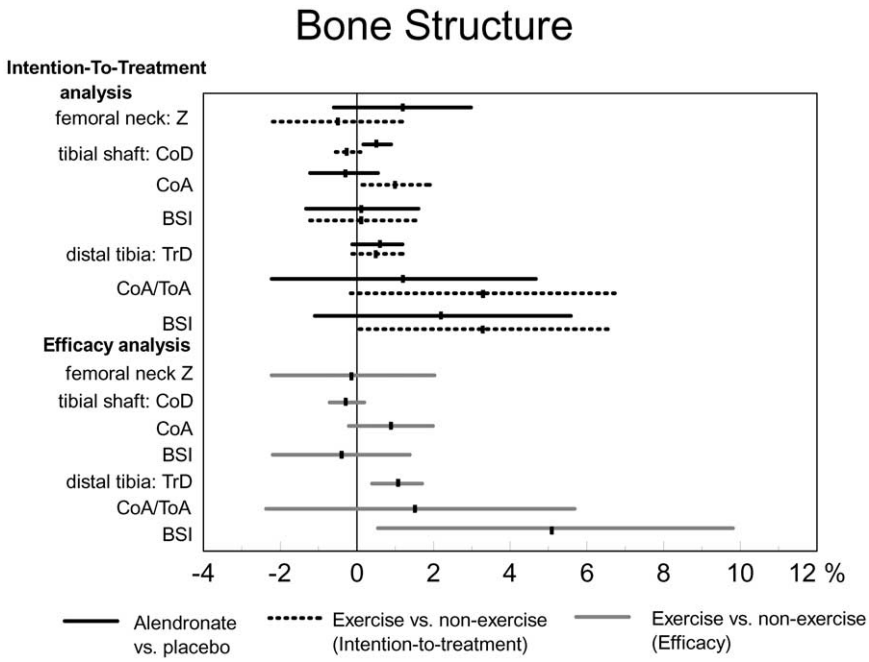

Fig. 3. Means and 95% confidence intervals of the group differences (%) in the bone structure between the alendronate groups (black lines) and between the exercise groups (dotted lines for ITT analysis and grey lines for efficacy analysis). Z, section modulus at the femoral neck; CoD, cortical density; CoA, cortical area; BSI, section modulus at the tibia; TrD, trabecular density; CoA/ToA, ratio of cortical to total area.

Discussion

This 12-month randomized, placebo-controlled trial showed significant increases in the bone mass of the lumbar spine and femoral neck of early postmenopausal healthy women in response to a 5-mg daily dose of alendronate. Exercise alone did not affect vertebral or femoral neck bone mass; it had neither an additive nor interactive effect with alendronate. However, at the distal tibia, both alendronate and exercise increased bone mass. In addition, exercise improved estimated bone strength of the distal tibia by increasing the polar moment and ratio of cortical to total area at this site. Exercise also improved physical performance of the subjects by improving dynamic power of the lower limbs, dynamic balance, and cardiorespiratory fitness. The above-noted bone results are consistent with the biochemical findings of the study and the literature, the alendronate treatment leading to overall suppression of bone remodeling and a decrease of bone turnover to a new steady- state level [26,27].

Table 4
Mean percentage changes from baseline to 12 months at different skeletal sites (efficacy analysis)

Variable	Al^+Ex^+ (n = 14)	Al^+Ex^- (n = 38)	Al^-Ex^+ (n = 19)	Al^-Ex^- (n = 38)
Lumbar spine BMC	4.7	3.7	2.1	0.2
Femoral neck BMC	−0.2	1.2	−0.8	−0.6
Distal radius BMC	0.3	−0.7	−1.6	0.8
Distal tibia				
BMC	1.1	0.5	1.1	−1.6
CoA/ToA	4.7	2.8	3.9	1.3
TrD	0.5	0.1	0.8	−0.6
BSI	7.5	1.7	6.3	0.3
Tibial shaft				
BMC	−0.5	−0.5	0.0	−1.1
CoD	−0.1	0.2	−0.8	−0.5
CoA	−0.4	−0.9	0.8	−0.6
BSI	−0.7	0.0	−0.7	−0.7

Note. Al^+Ex^+, 5 mg of alendronate daily + exercise, Al^+Ex^-, 5 mg alendronate daily; Al^-Ex^+, placebo + exercise; Al^-Ex^-, placebo; BMC, bone mineral content; CoA/ToA, ratio of cortical to total area of bone; TrD, trabecular density; BSI, section modulus at the tibia; CoD, cortical density; CoA, cortical area.

The BMC results of the alendronate are also consistent with earlier findings [5,27–30] and show conclusively that alendronate therapy is effective in preventing bone loss in the early postmenopausal period, with the greatest effect being at the lumbar spine, but with protection also being conferred at the clinically important femoral neck. More specifically, this effect may be due to uniformity of mineralization in cancellous bone [31].

With a higher dose of alendronate some studies have shown a small increase at the radial bone mass [26,29]. However, with a daily dose of 5 mg of alendronate, radial bone loss seems to be attenuated rather than increased [5,28,29,32]. Our results show similarly that alendronate alone was ineffective to increase radial bone mass, but in the exercise group it was able to attenuate bone loss at the distal radius. Exercise with placebo appeared to increase slightly the radial bone loss. Some of these differences may be due not only to different dose of drug but to different cortical to trabecular bone ratios at the measured bone site. Trabecular proportion of the distal radius in the present study was some

Table 5
Mean values of the performance variables of the study groups and the mean differences in the alendronate and exercise treatments

Variable	Baseline[a]	End[a]	Alendronate effect[b]	Exercise effect[b]
Leg extensors strength (kg)				
Al^+Ex^- (n = 38)	141.4 ± 27.0	146.7 ± 27.1	0.4 (−2.7–3.5)	1.7 (−1.4–5.0)
Al^+Ex^+ (n = 38)	141.5 ± 29.7	150.0 ± 35.2		
Al^-Ex^+ (n = 37)	146.6 ± 28.9	155.5 ± 36.8		
Al^-Ex^- (n = 39)	138.4 ± 27.8	142.6 ± 27.4		
Leg extensor power[c] (cm)				
Al^+Ex^-	19.5 ± 3.6	20.5 ± 3.8	−0.6 (−4.0–3.0)	8.5 (4.7–12.3)
Al^+Ex^+	19.5 ± 3.2	21.9 ± 3.7		
Al^-Ex^+	20.1 ± 5.0	22.9 ± 4.9		
Al^-Ex^-	20.1 ± 3.7	20.8 ± 3.9		
Dynamic balance[d] (s)				
Al^+Ex^-	16.4 ± 1.5	16.2 ± 1.5	−0.3 (−1.8–1.3)	1.5 (0.0–3.0)
Al^+Ex^+	16.3 ± 1.4	15.9 ± 1.5		
Al^-Ex^+	16.4 ± 1.3	16.0 ± 1.5		
Al^-Ex^-	16.4 ± 1.2	16.1 ± 1.2		
Postural sway				
Al^+Ex^-	2.1 ± 0.9	2.1 ± 0.6	3.1 (−6.0–11.4)	2.5 (−6.6–10.8)
Al^+Ex^+	2.0 ± 0.7	2.0 ± 0.8		
Al^-Ex^+	1.8 ± 0.7	2.0 ± 0.9		
Al^-Ex^-	1.9 ± 0.6	2.1 ± 0.9		
Grip strength (kg)				
Al^+Ex^-	29.1 ± 5.4	29.2 ± 5.7	1.3 (−2.0–4.8)	0.6 (−2.8–3.9)
Al^+Ex^+	28.9 ± 4.3	28.7 ± 4.8		
Al^-Ex^+	30.4 ± 4.5	30.4 ± 4.8		
Al^-Ex^-	29.5 ± 5.2	28.5 ± 5.3		
VO_{2max}[e] (ml · /kg/min)				
Al^+Ex^-	30.7 ± 4.2	30.7 ± 4.2	1.7 (−0.4–3.9)	3.1 (0.9–5.3)
Al^+Ex^+	32.2 ± 4.4	32.2 ± 4.8		
Al^-Ex^+	30.7 ± 4.4	31.0 ± 4.1		
Al^-Ex^-	31.4 ± 4.3	30.7 ± 4.6		

[a] Values are means ± SD.
[b] Values in parentheses are 95% CIs.
[c] The height of the jump was calculated from the flying time as follows: $h = gt^2/8$, where g is 9.81 m/s^2 and t is the flying time in seconds.
[d] Negative number indicates improved balance.
[e] VO_{2max}, estimated maximal oxygen uptake.

50%, this site having greater metabolic activity than the cortical bone site. It has been shown that even radial regions rich in trabecular bone have a poor response to alendronate treatment, suggesting that changes in bone mass at the forearm may not correlate with the hip and spine changes [32].

Currently, it is well accepted that neither bone mass nor bone density are the sole determinants of bone strength nor are they the only factors determining bone fractures [2,8,9,11]. Despite this, very few studies have evaluated the effects of alendronate on bone structure. In their 1-year study, Schneider et al. [30] reported increased trabecular density and bone strength at the ultradistal site of the radius in the alendronate group compared to the placebo group. At the radial shaft, however, the estimated bone strength parameters did not change in response to alendronate, a finding we made at the femoral neck.

In women, some exercise studies have reported changes or maintenance of bone mass at the hip and spine. Kerr et al. [33,34] reported an increase at the trochanteric site but no change at the femoral neck, and Nelson et al. [35] and Kohrt et al.[36] reported increases of bone mass both at the femoral neck and the lumbar spine. Welsh and Rutherford [37] found an increase at the proximal femur but no change at the spine. Heinonen et al. [12] found an endurance type of exercise effective in maintaining femoral neck bone mass, while the training effect of calisthenics was ineffective.

There are also findings that are more consistent with our current results [38–40]. In a study among postmenopausal women, Bassey et al. [41] showed no change in bone mineral density of the spine and femoral neck despite the jumping program including daily vertical jumps and despite that similar exercise improved femoral bone density of premenopausal women by 2–3%. Goto et al.[42] reported in a 4-year follow-up study that a high level of physical activity was able to increase the mass and estimated strength of bone in athletic young women, while similar training was ineffective to prevent bone loss after menopause.

There are many possible explanations for the inconsistent bone results of the above-noted exercise studies. They may be due to differences regarding the training program itself (type, frequency, duration, and intensity) or due to differences related to the subjects (such as age, race, menopausal status, nutrition, and basic physical fitness). It is also

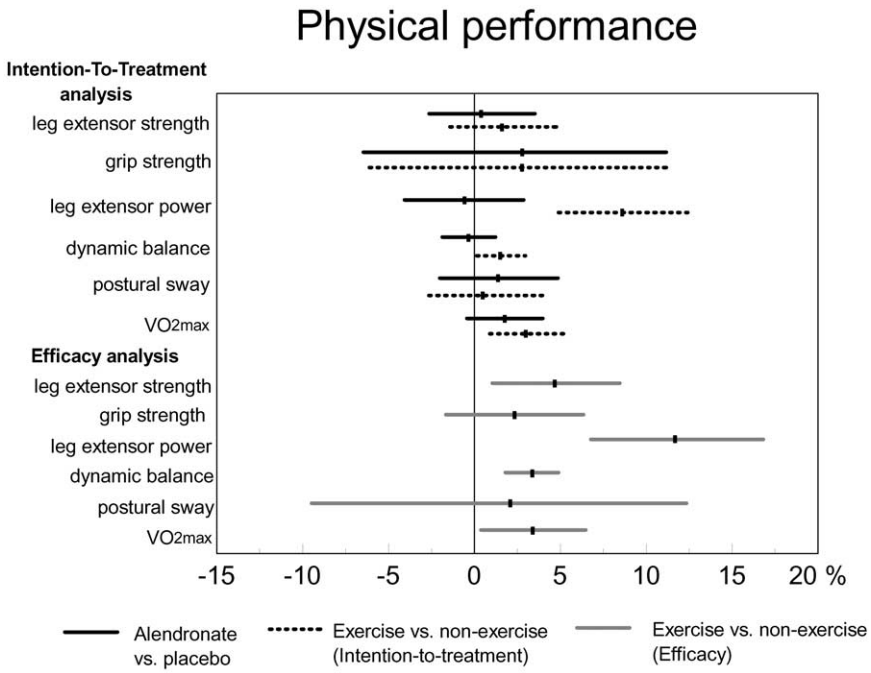

Fig. 4. Means and 95% confidence intervals of the group differences (%) in the physical performance between the alendronate groups (black lines) and between the exercise groups (dotted lines for ITT analysis and grey lines for efficacy analysis). VO_2max, estimated maximal oxygen uptake.

possible that the lack of osteogenic effect is due to relatively high bone mass at baseline: the strain due to the loading will stimulate an osteogenic response until the bone is strong enough to bear the load, and if the bone is strong enough already at baseline, the exercise would not produce effective new strains [43]. However, in our study, at the distal tibia, a highly loaded bone site, exercise was effective to create structural changes. Since the exercise was indeed able to increase mass and estimated strength of bone at the distal tibia, the lack of effect at the lumbar spine and proximal femur suggests that insufficient loading may have occurred at these bone sites. It has been shown that exercise can improve bone strength despite no effect on BMC, and although BMD and BMC are related to bone strength at the group level, inferring an individual's bone strength solely from these variables may be misleading [38]. At the lumbar spine, we were able to measure DXA-based BMC only and exercise showed no effect on this variable. At the femoral neck, there was no exercise-induced change in either the BMC or the section modulus, suggesting no change in bone strength. Perhaps the magnitude of our loading regimen and the corresponding strains did not sufficiently exceed the usual strain levels at these sites.

Not only bone mass but also the material properties geometry and tissue quality have an effect on the ability of bones to resist fractures. It is also well accepted that bone is dynamically remodeled throughout the life, and it is unlikely that bone geometry would remain static. Geometric and structural properties are often underestimated due to, for example, practical problems in measurements. The very first study evaluating the training effects on bone structure (measured by the pQCT technique) was by Adami et al. [38] They showed that, although the bone mass or bone density did not change, a distinct reshaping of bone structure and geometry took place. Our results, comparable with those of Adami et al.[38] indicated that, in addition to maintenance of bone mass, a remarkable reshaping of its structure and geometry took place at the most loaded site of the skeleton. The change in cortical-to- trabecular bone ratio may play an important role in determining the strength of bone, since changes in bone cortex are responsible for the improved bending strength. We were not, however, able to show any reshaping in the other parts of the skeleton. The estimated section modulus of the femoral neck showed no structural changes at this site, neither due to exercise nor to alendronate, even though the alendronate treatment increased bone mass.

Despite small or no effects on bone mass, exercise an average 1.6 times a week was effective in improving leg extensor power, dynamic balance, and cardiorespiratory fitness. When regarding the efficacy analyses (including those subjects participating at least twice a week in the training), the between-groups differences in the physical performance were even larger than those in the ITT analysis, thus demonstrating that the training program was effective.

With age, not only deterioration in bone mass and quality, but also deterioration in muscular performance, balance, and coordination increase the risk of bone fracture [8]. In prevention of fractures, the importance of balance and postural stability can not be overemphasized: in addition to increasing or maintaining bone mass, exercise regimens have a great value in prevention of falls of the older adults [8,44]. Our current results were in line with these observations; in addition to improving the mechanical competence

of bone at the loaded sites, exercise provided valuable fracture-preventing benefits by increasing muscular performance, balance, and functional capacity of the postmenopausal women.

In conclusion, alendronate is effective in increasing bone mass at the lumbar spine and femoral neck, while exercise is effective in increasing the mechanical properties of bone at some of the most loaded bone sites, as well as the participants' muscular performance and balance. Together alendronate and exercise may effectively decrease the risk of osteoporotic fractures.

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