The New England Journal of Medicine

Volume 325 OCTOBER 24, 1991 Number 17

PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

A Comparative Study of Exercise, Calcium Supplementation, and Hormone-Replacement Therapy

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Abstract *Background.* Osteoporosis among older women is a major public health problem. We studied the effects of three approaches to the prevention of osteoporosis in women with low bone density.

Methods. One hundred twenty postmenopausal women (mean [±SD] age, 56±4) who were selected because they had low forearm bone density were enrolled in a double-blind, placebo-controlled, randomized study comparing the effects of an exercise regimen (exercise group, n = 41), exercise plus dietary calcium supplementation (exercise–calcium group, n = 39), and exercise plus continuous replacement of estrogen and progesterone (exercise–estrogen group, n = 40). Periodically during the two-year study period, we measured the women's bone density at three forearm sites, measured indexes of calcium metabolism, and recorded symptom scores. A comparison group of 42 women (mean age, 55.5±3.1) with normal bone density was also followed for two years.

Results. Significant bone loss in the distal forearm occurred in the group with normal bone density (control group) and the exercise group (change, −2.7 percent and −2.6 percent of the base-line value per year, respectively). Bone loss at the distal forearm site was significantly lower in the exercise–calcium group (−0.5 percent of the base-line value per year), and bone density increased at this site in the exercise–estrogen group (+2.7 percent of the base-line value per year). Bone loss at the median forearm site was significantly lower in the exercise–calcium group (−1.3 percent of the base-line value per year) than in the exercise group (−2.4 percent), and bone density at this site increased significantly in the exercise–estrogen group (+0.8 percent of the base-line value per year). Breast tenderness occurred in 47 percent of the women in the exercise–estrogen group but in only 20 percent in the other two treatment groups. Vaginal bleeding occurred at some time in 52 percent of the women who had not had a hysterectomy in the exercise–estrogen group, as compared with 11 percent and 12.5 percent, respectively, in the exercise and exercise–calcium groups.

Conclusions. In postmenopausal women with low bone density, bone loss can be slowed or prevented by exercise plus calcium supplementation or estrogen–progesterone replacement. Although the exercise–estrogen regimen was more effective than exercise and calcium supplementation in increasing bone mass, it also caused more side effects. (N Engl J Med 1991;325: 1189-95.)

THE high prevalence of bone fractures among women with osteoporosis makes prevention of this disease important. Bone densitometry makes it possible to quantify the risk of fracture in both the appendicular and the axial skeleton.[1-4] The forearm is a good site for bone-density screening[5] because of the ease of measurement and the relatively low cost, although the correlation coefficient for bone-density values measured at various skeletal sites is only about 0.5 to 0.7.[6,7]

We studied the effects of three approaches to the prevention of bone loss. The first was an exercise regimen that has been proved, at least in some studies,[8] to be effective in slowing bone loss. In a second regimen, calcium supplementation was added to the exercise program, since we thought the combination of these two approaches might be more effective than either alone. Calcium supplementation has also been shown to be effective in some studies[9] but not in others.[10] The third regimen combined exercise with continuous replacement of estrogen and progesterone. Hormone replacement has been shown to maintain bone mass[11,12] and, in retrospective case–control studies, to be effective in preventing fractures.[13,14] In addition to the effects of these interventions on bone density, we studied their effects on calcitropic hormones and calcium metabolism in order to elucidate their mechanisms of action. We also studied side effects, which are important in planning any community-based intervention program.

For this study we selected women who were at in-

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Supported by the National Health and Medical Research Council, the King Edward Memorial Hospital for Women Research Foundation, Sandoz Australia, and Upjohn Australia.

creased risk for fracture because their bone density was lower than a fracture threshold set close to 1 SD below the mean for premenopausal women. This level was based on previous data suggesting that bone-density values below it were associated with an increased prevalence of fracture.[15] For purposes of comparison, we also studied women with bone-density values above the fracture threshold, who did not receive any specific intervention (control group).

Methods

Subjects

We recruited subjects for the study by means of articles in the media inviting women to participate in a study of the prevention of osteoporosis. The respondents were initially screened with a short questionnaire administered over the telephone. Women were eligible for the study if they were 43 years of age or older, had been postmenopausal for 1 to 10 years, did not have hypertension or any other chronic disease, were nonsmokers, and were not taking estrogen, other steroid hormones, or anticonvulsant or thiazide diuretic drugs. The date of menopause was defined as the date of the last menstrual period. For women who had undergone hysterectomy or oophorectomy, the date of menopause was considered the date of the operation. For women who were unsure whether oophorectomy was performed at the time of hysterectomy, the date of menopause was taken as the date of onset of hot flashes. All the women had serum levels of follicle-stimulating hormone that were greater than 40 IU per liter, confirming their postmenopausal status. The 374 women who met these eligibility criteria (all of whom were white) had their forearm bone density measured. In 202 women the distal bone density was not more than 1 SD below the mean for premenopausal women (i.e., was ≥290 mg per square centimeter), and they were therefore not considered to be at high risk for osteoporotic fracture. Forty-two women selected at random from this group were designated the normal-bone-density (control) group.

The 172 women with bone-density values less than 290 mg per square centimeter at the distal forearm site were asked to attend a seminar to discuss the trial, at which 120 agreed to participate. These women were instructed on how to complete a four-day diet and exercise record, which they brought back to a morning clinic. They were then randomly assigned to one of the three study groups by being given a study number that corresponded to the number of a sealed envelope describing the treatment category. The envelopes, which had been put in random order by shuffling before the study, were kept in the hospital pharmacy and opened by the pharmacist, who was the only person who knew the women's treatment assignments. The assignments were stratified according to whether the women's distal bone density was 245 to 289 mg per square centimeter or less than 245 mg per square centimeter. There were 72 women in the higher-density stratum and 48 in the lower. The study protocol was approved by the Human Rights Committee of the University of Western Australia, and each woman gave written informed consent.

Study Protocol

The treatment regimens were as follows: exercise alone (exercise group, n = 41), exercise plus 1 g of elemental calcium nightly in the form of calcium lactate–gluconate (Sandoz, Basel, Switzerland) (exercise–calcium group, n = 39), or exercise plus 2.5 mg of medroxyprogesterone acetate (Upjohn, Sydney, Australia) nightly throughout the two-year study period and 0.625 mg of estropipate (Abbott, Sydney, Australia) nightly for one month, then 1.25 mg nightly for the remainder of the study period (exercise–estrogen group, n = 40). Identical-appearing placebo medications were made available by the three companies, so that every woman in the treatment groups took three tablets every night. Compliance was checked by counting tablets; 89 percent of the exercise–calcium group and 91 percent of the exercise–estrogen group took the assigned medication for at least 10 weeks during each 12 weeks of the study period.

The exercise regimen consisted of one weekly exercise class supervised by a trained physiotherapist and two brisk 30-minute walks per week. At the exercise classes the women participated in low-impact aerobic exercise for one hour; 30 percent of the time was devoted to arm exercises. Only 56 percent of the exercise group, 24 percent of the exercise–calcium group, and 44 percent of the exercise-estrogen group attended a minimum of 10 classes in any 12-week period. Many substituted other activities such as walking, however. The women were asked not to change their diets during the study.

Analytic Methods and Follow-up

Forearm bone density was measured every three months, and the women were examined every six months during the two-year study period. Forearm bone densitometry was performed with a Molsgaard BMA 1100 forearm bone densitometer (Molsgaard, Horsholm, Denmark), which uses a water bath to allow for differing volumes of soft tissue. Bone density was measured at three forearm sites. The distal site was defined as a site 1 cm long just distal to the point where the radius and ulna were separated by 2 mm.[15] Trabecular bone is considered to make up 60 percent of the bone mass at this site[16]; the coefficient of variation for readings at this site was 1.6 percent in 13 normal premenopausal women. The median site was defined as a site 2.6 cm long just proximal to the site at which the radius and ulna are separated by 8 mm; 15 percent of this site is made up of trabecular bone. The proximal site was defined as a site 1 cm long 63.5 mm proximal to the ulna styloid; it contains mostly cortical bone and less than 5 percent trabecular bone. The coefficients of variation for measurements at the median and proximal sites in the same 13 normal premenopausal women were 1.3 percent and 1.5 percent, respectively. At the end of the study, vertebral bone mineral density was measured by quantitative digital radiography with a QDR 1000 machine (Hologic, Waltham, Mass.).

A 24-hour urine sample, a fasting 2-hour urine sample, and a fasting blood sample were collected before the study began and at intervals of six months during the study period. The urine samples were analyzed for creatinine, calcium, and phosphorus with use of a Technicon SMAC analyzer (Technicon, Tarrytown, N.Y.), and hydroxyproline was measured colorimetrically in an acid hydrolysate of the urine. Plasma creatinine, alkaline phosphatase, and phosphorus concentrations were measured with a Technicon SMAC analyzer. Dialyzable calcium was measured in serum with modification of a technique for total calcium estimation.[17] Serum calcitriol (1,25-dihydroxycholecalciferol) was measured with a column-extraction technique, followed by assay with calf-thymus cytosol-binding protein[18]; the intraassay and interassay coefficients of variation for the calcitriol assay were 21 percent and 24 percent, respectively. The serum level of intact parathyroid hormone was measured by an "immunochemiluminometric" method[19]; the intraassay and interassay coefficients of variation were 3.6 percent and 6.2 percent, respectively. Serum 25-hydroxyvitamin D (25-OH-D) was measured with an extraction technique,[20] followed by a competitive-binding assay with diluted human serum. Serum vitamin D–binding protein was measured by radioimmunoassay with use of antiserum supplied by Dr. R. Bouillon. Serum parathyroid hormone, calcitriol, vitamin D–binding protein, and 25-OH-D concentrations were measured in all base-line samples and in samples obtained at other times from 15 randomly selected women from each group. The glomerular filtration rate was calculated from the creatinine clearance. The renal phosphate threshold was calculated by the method of Bijvoet.[21]

At intervals of six months, the women recorded their physical activity for four days. From these diaries the most active two hours of the day were scored with tables of the metabolic equivalents of various activities[22] (a measure of aerobic activity) to generate a physical-activity score. One metabolic equivalent is defined as the energy consumed per minute of sitting at rest; the activities were measured in relation to this standard. At the beginning and the end of the study, the women completed four-day diet records with the assistance of a trained dietitian. The calcium content of the diet was determined by a technique that scores only foods containing high levels of calcium as determined from Australian nutritional data. This estimate correlated closely with the estimate derived from the complete coding of the four-day records.

The women were assigned a symptom score based on the frequency of eight symptoms potentially related to menopause: hot flashes, headaches, anxiety, sleeplessness, libido, dyspareunia, breast dis-

comfort, and vaginal bleeding. The scores were recorded at base line, after one month, after three months, and thereafter at intervals of three months throughout the study by the same interviewer, who did not know what medication the women were receiving. The women were asked to rate the frequency of symptoms on a three-point scale, with 0 representing the absence of symptoms, 1 monthly symptoms, 2 weekly symptoms, and 3 daily symptoms. The findings were simplified to absent or present, since the results with these two categories were similar to those derived from the analysis of weighted scores.

Statistical Analysis

Statistical analysis was conducted with use of the SPSS/PC statistical package. The base-line results were analyzed by one-way analysis of variance. If the F test was significant, Duncan's test was used to evaluate individual group differences. For the three treatment groups, the changes in bone density with time were calculated from the slope of the regression line through each woman's results, fitted by least-squares analysis, if three or more data points were available. Thus, if the woman remained in the study for at least six months, her results were included in the analysis. Differences in the rate of increase or decrease in bone density during the two years of the study were evaluated by comparing the slopes of the regression lines for the groups with analysis of variance. Interactions between categorical variables were analyzed by multivariate analysis of variance. When significant time or treatment effects were found, one-way analysis of variance and Duncan's test were performed to determine which points were significantly different from each other. Interactions between continuous variables were analyzed by linear regression analysis with use of the least-squares method and by stepwise multiple regression analysis. Only effects that were significant at the level of ≤ 0.05 in a two-tailed test are reported.

Results

The base-line data on the four groups (the three treatment groups and the control group) are shown in Table 1. The women in the normal-bone-density (control) group had a higher bone density at all three forearm sites and also had been postmenopausal for less time than the women in the other groups. The mean base-line physical-activity score was similar in the three treatment groups (Table 1), and it increased significantly in all three groups during the study (Table 2). Measured calcium intake, not including the dietary calcium supplement, was similar in the four groups (Table 2). During the course of the study eight women withdrew from the exercise–estrogen group, six from the exercise group, and three from the exercise–calcium group.

Bone Density

The changes in bone density at the distal forearm site in the three treatment groups are shown in Figure 1. The rate of bone loss in the exercise group was similar to that in the control group (Table 2). The rate of bone loss at two sites was significantly lower in the exercise–calcium group than in either the exercise group or the control group. In the exercise–calcium group, the rate of change in bone density at the distal site did not differ significantly from zero, but significant bone loss occurred at the proximal and median sites. The exercise–estrogen group had an increase in bone density at all three sites that was significantly different from the changes in the exercise–calcium group and the exercise group (Table 2 and Fig. 1). Vertebral bone mineral density measured in the women who remained in the study after two years was slightly but not significantly higher in the exercise–estrogen group than in the other two treatment groups (Table 2).

Table 1. Base-Line Characteristics of the Three Treatment Groups and the Group with Normal Bone Density (Controls).*

Characteristic	Exercise	Exercise–Calcium	Exercise–Estrogen	Controls
No. of subjects	41	39	40	42
Age (yr)	56.5±3.7	56.8±3.7	55.2±3.7	55.5±3.1
Years since menopause	5.8±2.6	5.7±2.6	5.4±2.5	4.5±2.1†
Physical-activity score (METs)‡	362±46	355±51	364±57	—
Calcium intake (mg/day)	780±293	850±344	714±265	—
Forearm bone density (mg/cm²)				
Distal	251±28	249±29	248±26	338±41†
Median	385±39	384±49	399±44	464±41†
Proximal	532±47	534±58	551±53	602±44†

*Values are means ±SD.

†$P<0.05$ for the comparisons with all the other groups.

‡The mean maximal two-hour metabolic-equivalent (MET) score. One MET is defined as the energy consumed per minute of sitting at rest.

Base-Line Determinants of the Bone-Density Response

In the exercise group, the change in distal-forearm bone density was positively correlated with the physical-activity level at base line (Fig. 2); multiple regression analysis indicated that this was the only significant determinant of change in bone density in this group (change in distal bone density = activity × 0.07 − 31.8; $r = 0.37$; $P = 0.02$). In the exercise–calcium group, the change in distal bone density was positively correlated with the base-line serum calcitriol level (Fig. 2) and the number of years since menopause, a correlation confirmed by multiple regression analysis (change in distal bone density = calcitriol × 0.10 + years since menopause × 0.25 − 15.8; $r = 0.64$; $P = 0.001$). In this group the change in bone density was not correlated with base-line dietary calcium intake. In the exercise–estrogen group, the changes in distal bone density were positively correlated with the number of years since menopause in both linear and multiple regression analyses (change

Table 2. Changes in Forearm Bone Density and Other Indexes in the Three Treatment Groups and the Group with Normal Bone Density (Controls) during the Two-Year Study Period.*

Index	Exercise	Exercise–Calcium	Exercise–Estrogen	Controls
Change in forearm bone density (% of base-line value/yr)				
Distal	−2.6±3.2	−0.5±2.4†	2.7±3.2†	−2.7±3.3
Median	−2.4±2.2	−1.3±1.8†	0.8±1.5†	−1.9±2.4
Proximal	−2.0±2.5	−1.5±2.3	0.7±1.3†	−1.5±2.1
Vertebral bone density at 2 yr (mg/cm²)	0.85±0.09	0.87±0.10	0.90±0.13	0.97±0.14†
Physical-activity score at 2 yr (METs)‡	392±41§	408±69§	418±48§	385±48
Dietary calcium intake at 2 yr (mg/day)	681±212	781±317	766±301	819±244

*Values are means ±SD.

†$P<0.05$ for the comparisons with all the other groups, as calculated from the slopes of the regression lines fitted to the data for each woman with three or more data points.

‡The mean maximal two-hour metabolic-equivalent (MET) score. One MET is defined as the energy consumed per minute of sitting at rest.

§$P<0.01$ for the comparison with the base-line value.

in distal bone density = years since menopause × 1.6 − 1.7; r = 0.51; P = 0.003). The changes in bone density at the median and proximal sites were not correlated with any base-line values.

Biochemical Results

There was a significant positive correlation between the base-line serum levels of parathyroid hormone and calcitriol in the 120 women with low bone density (r = 0.28, P = 0.05). The ratio of urinary hydroxyproline to creatinine, a measure of bone resorption, decreased in both the exercise–calcium and exercise–estrogen groups (Fig. 3). Urinary calcium excretion decreased after six months in the exercise–estrogen group to a greater extent than could be accounted for by the decrease in filtered calcium load, measured by the dialyzable calcium concentration (Fig. 3). The

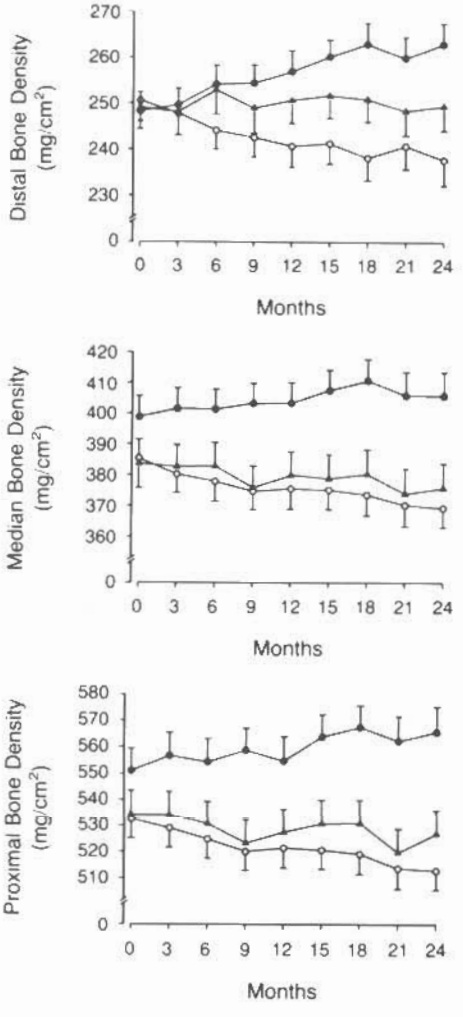

Figure 1. Effects of the Three Interventions on Bone Density at Distal, Median, and Proximal Forearm Sites during the Two-Year Study Period.

The exercise group is represented by open circles, the exercise–calcium group by solid triangles, and the exercise–estrogen group by solid circles. The values shown are means ±SE for all women remaining in each group at the time indicated. After two years there were 35 women remaining in the exercise group, 36 in the exercise–calcium group, and 32 in the exercise–estrogen group.

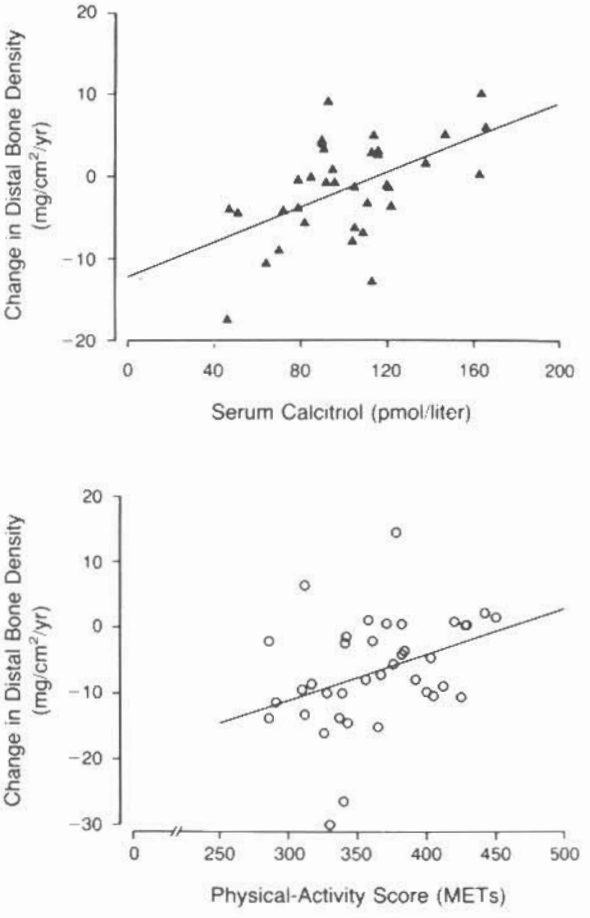

Figure 2. Relation of Physical Activity and Calcitriol Level to Changes in Distal-Forearm Bone Density.

The top panel shows the correlation between the base-line serum calcitriol concentration and the change in distal-forearm bone density in the exercise–calcium group during the two-year study period (y = 0.11x − 12.19; r = 0.54; P = 0.001). The bottom panel shows the correlation between the base-line level of physical activity and the change in distal-forearm bone density in the exercise group during the two-year study period. Physical activity was measured in metabolic equivalents (METs) (y = 0.07x − 32; r = 0.37; P = 0.02). One MET is defined as the energy consumed per minute of sitting at rest.

women in the exercise–estrogen group also had a significant increase in the serum calcitriol level (Fig. 3) with no change in the levels of 25-OH-D or vitamin D–binding protein (Table 3). The increase in the calcitriol level at six months was correlated with the decrease in the plasma phosphorus concentration (r = −0.53, P = 0.02) but not with the decrease in renal phosphate threshold or serum levels of parathyroid hormone or dialyzable calcium.

Symptoms

There were significant effects of treatment, time, or both, according to multivariate analysis of variance, on the frequency of hot flashes, vaginal bleeding, breast discomfort, sleeplessness, and dyspareunia, whereas the frequency of headache, anxiety, and libido did not change during the study (data not shown). Fewer women in the exercise–estrogen group

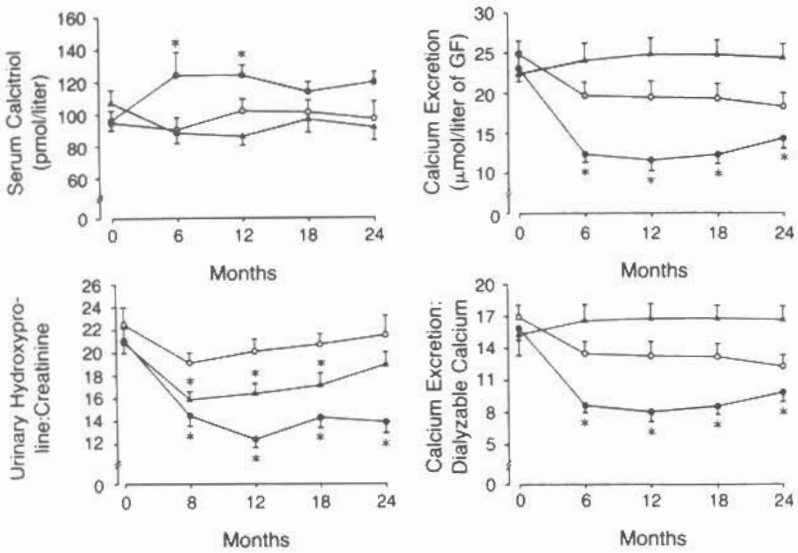

Figure 3. Effects of Exercise (Open Circles), Exercise plus Calcium Supplementation (Solid Triangles), and Exercise plus Hormone Replacement (Solid Circles) on the Serum Calcitriol Level, Calcium Excretion, the Hydroxyproline:Creatinine Ratio, and the Ratio of Calcium Excretion to the Serum Level of Dialyzable Calcium during the Two-Year Study Period.

The values shown are means ±SE. The asterisks indicate $P<0.05$ for the comparison with the base-line value. GF denotes glomerular filtrate. Urinary hydroxyproline was measured in millimoles per liter, and creatinine in micromoles per liter.

had hot flashes than in the exercise–calcium and exercise groups after three months of treatment (Fig. 4), but the proportion of women with hot flashes in the exercise and exercise–calcium groups decreased significantly during the study. In the exercise–estrogen group, sleeplessness also improved (from 38 percent at base line to 25 percent at two years, $P = 0.001$), as did dyspareunia (from 38 percent at base line to 9 percent at two years, $P = 0.004$). There was no change in the frequency of these symptoms in the other two groups. The proportion of women who had vaginal bleeding during the study was higher in the exercise–estrogen group than in the other two groups (Fig. 4). Altogether 52 percent of the 30 women who had not undergone hysterectomy in the exercise–estrogen group had vaginal bleeding at some time during the study, as compared with 11 percent of the 30 women without hysterectomy in the exercise group and 12.5 percent of the 34 in the exercise–calcium group. Seven women in the exercise–estrogen group required dilation and curettage. The proportion of women who had breast discomfort after one month and thereafter was higher in this group than in the other two groups (Fig. 4); four women in the group withdrew because of this symptom. Altogether, 47 percent of the women in the exercise–estrogen group had breast discomfort, as compared with 20 percent in the other two groups; in 28 percent in the exercise–estrogen group the breast discomfort persisted for more than six months, as compared with 8 percent in the exercise group and 12 percent in the exercise–calcium group.

Discussion

Both exercise plus calcium supplementation and exercise plus hormone replacement were effective in slowing or stopping bone loss in women considered to be at increased risk of osteoporotic fracture on the basis of a low base-line bone density. Thus, bone-density screening and intervention may be effective in preventing osteoporosis.

Although physical activity increased 8 percent in the exercise group, on average the exercise program alone was ineffective in preventing bone loss. There was a relation, however, between the base-line level of physical activity and the subsequent effect of the intervention on distal-forearm bone density; thus, if the women had a metabolic-equivalent score equal to moderate-to-brisk walking for two hours per day there was no bone loss. Not surprisingly, few women were this active.

Two recent studies have suggested an effect of dietary calcium supplementation on forearm bone den-

Table 3. Serum and Urinary Biochemical Indexes in the Three Treatment Groups before and after 24 Months of Treatment.*

Index	Exercise		Exercise–Calcium		Exercise–Estrogen	
	base line	24 mo	base line	24 mo	base line	24 mo
Serum dialyzable calcium (mmol/liter)	1.47±0.05	1.47±0.06	1.47±0.05	1.47±0.07	1.46±0.04	1.45±0.05
Plasma phosphorus (mmol/liter)	1.04±0.10	1.07±0.13	1.05±0.12	1.03±0.10	1.04±0.12	0.99±0.09†
Renal phosphate threshold (mmol/liter of glomerular filtrate)	0.94±0.20	1.02±0.19†	0.98±0.17	1.00±0.18	0.97±0.17	0.91±0.12†
24-hr urinary calcium (mmol/day)	3.9±1.7	3.5±1.5	4.1±1.8	4.9±1.9†	3.5±1.1	3.3±1.2
24-hr urinary phosphorus (mmol/day)	24.9±6.6	26.0±4.3	27.5±7.7	24.1±7.5†	24.2±6.6	26.0±8.2
Plasma alkaline phosphatase (U/liter)	72±12	77±14	76±23	76±22	80±22	62±19
Serum 25-OH-D (nmol/liter)	81±30	75±41	64±18	ND	69±24	61±13
Serum vitamin D–binding protein (μmol/liter)	5.4±1.4	6.2±1.3	6.7±3.0	ND	4.6±1.5	4.9±2.6
Serum parathyroid hormone (pmol/liter)	2.8±0.8	2.8±0.6	3.4±0.9	2.8±1.4	1.7±0.8	2.5±1.2†

*Values are means ±SD. Only women who completed 24 months of study are included in the base-line results: 35 in the exercise group, 36 in the exercise–calcium group, and 32 in the exercise–estrogen group. ND denotes not determined.

†$P<0.05$ for the comparison with the base-line value

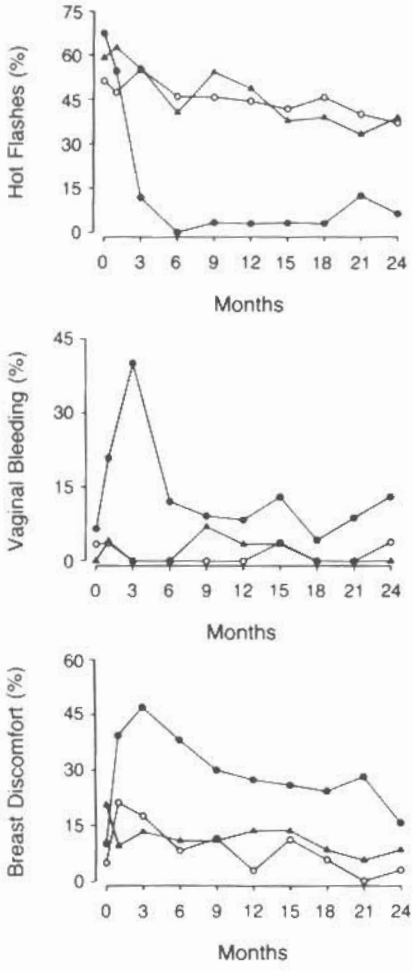

Figure 4. Percentage of Women in Each Group Who Had Hot Flashes, Vaginal Bleeding, and Breast Discomfort during the Two-Year Study Period.

The exercise group is represented by open circles, the exercise–calcium group by solid triangles, and the exercise–estrogen group by solid circles. For hot flashes, significant effects of time and treatment and a significant time–treatment interaction ($P<0.001$ for all tests), ascribable to the reduction in hot flashes in the exercise–estrogen group, were found by two-way analysis of variance. For vaginal bleeding, a significant effect of treatment ($P<0.001$) and a significant time–treatment interaction ($P = 0.002$), ascribable to the increase in vaginal bleeding in the exercise–estrogen group, were found by two-way analysis of variance. For breast discomfort, significant effects of time and treatment and a significant time–treatment interaction ($P<0.001$ for all tests), ascribable to the increase in breast discomfort in the exercise–estrogen group, were found by two-way analysis of variance.

sity. In one, an effect on cortical bone was found only in women who had been postmenopausal for more than five years and who had a base-line calcium intake of less than 400 mg per day.[9] In the other, the effects of calcium supplementation on forearm cortical bone were more marked than its effects on vertebral bone.[12] We found that calcium supplementation had an effect on trabecular and cortical bone (in the median forearm) but a stronger effect on trabecular bone (in the distal forearm). This may be so because the trabecular bone in women with low bone mass was more responsive to the beneficial effect of dietary supplementation and exercise. Alternatively, the effect of exercise on trabecular bone found in the exercise group suggests the possibility of synergism between the exercise and calcium components of the regimen, as has been suggested in premenopausal women.[23] The relation we observed between the effectiveness of calcium supplementation and the number of years since menopause supports previous data.[9] We found no relation with base-line calcium intake, however, perhaps because the mean base-line calcium intake was much higher in this population than in the other study.[9]

The biochemical data provide insights into the causes of postmenopausal bone loss and the mode of action of calcium supplementation. The positive correlation between serum calcitriol and parathyroid hormone levels in these women at base line suggests an ongoing stimulus to the production of these hormones, which in the normal course of events should achieve a homeostatically mediated steady state. We previously found that the deprivation of dietary calcium stimulated the secretion of both parathyroid hormone and calcitriol in postmenopausal women.[24,25] Therefore, the women in this study who had high serum concentrations of parathyroid hormone and calcitriol may have been calcium-deficient. Certainly dietary calcium supplementation reduced bone loss and urinary hydroxyproline excretion, a measure of bone resorption. Interestingly, the efficacy of calcium supplementation was dependent on serum calcitriol levels. Because the active transport of calcium across the gut is dependent on calcitriol,[2] the calcitriol level probably determines the effectiveness of oral calcium supplementation by determining the fraction absorbed.

The exercise–estrogen regimen also reduced bone resorption and increased bone mass, presumably by a direct effect on bone. However, the kidney, like bone, contains estrogen receptors,[27] so that the reduction in urinary calcium excretion independent of changes in the serum level of dialyzable calcium and the filtered calcium load may indicate a direct effect of estrogen on renal calcium handling. The recent documentation of increased urinary calcium excretion in postmenopausal women[28] suggests that the loss of calcium in urine could be an important factor in postmenopausal bone loss.

The 5.4 percent increase in bone density in the distal forearm in the exercise–estrogen group was encouraging, although it did appear to plateau at about 18 months. These data clearly indicate that the continuous combined estrogen–progesterone regimen can induce an increase in bone density. However, many women treated with hormone replacement to prevent bone loss are asymptomatic. Thus, the incidence of deleterious side effects of medication is important; in this regard, the group of women we studied differs from those who have menopausal symptoms as a primary problem. Our double-blind treatment format allowed the objective evaluation of side effects of continuous estrogen–progesterone therapy. Vaginal

bleeding was an important problem; nevertheless, the incidence was much lower than with cyclical progesterone administration. Breast tenderness was another important problem, which might be alleviated by introducing estrogen more slowly or at a lower final dose. In considering the acceptability of estrogen, the beneficial effects of a reduction in hot flashes, dyspareunia, and sleeplessness must not be neglected.

These results have important implications for preventing osteoporosis. It may be appropriate to advise women with intermediate bone-density values to adopt the exercise and calcium regimen and to reserve estrogen for women with low bone density. Thus, an intervention based on bone-density screening may prove to be cost effective. The alternative approach, that of using a common intervention for all women, may be more cost effective but would have to rely on increasing dietary calcium intake and exercise rather than the administration of estrogen, because of the need for medical supervision with hormone-replacement therapy.

We are indebted to the pharmacy of Sir Charles Gairdner Hospital, which kindly dispensed the drugs.

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