

Physical training preserves bone mineral density in postmenopausal women with forearm fractures and low bone mineral density

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Abstract

Summary One hundred and twelve postmenopausal women with low bone mineral density (BMD) and forearm fractures were randomized to physical training or control group. After one year the total hip BMD was significantly higher in the women in the physical training group. The results indicate a positive effect of physical training on BMD in postmenopausal women with low BMD.

Introduction The fivefold increase in hip fracture incidence since 1950 in Sweden may partially be due to an increasingly sedentary lifestyle. Our hypothesis was that physical training can prevent bone loss in postmenopausal women.

Methods One hundred and twelve postmenopausal women 45 to 65 years with forearm fractures and T-scores from -1.0 to -3.0 were randomized to either a physical training or control group. Training included three fast 30-minute walks and two sessions of one-hour training per week. Bone mineral density (BMD) was measured in the hip and the lumbar spine at baseline and after one year.

Results A per protocol analysis was performed, including 48 subjects in the training group and 44 subjects in the control group. The total hip BMD increased in the training

group $+0.005$ g/cm² (± 0.018), $+0.58\%$, while it decreased -0.003 g/cm² (± 0.019), -0.36% , ($p=0.041$) in the control group. No significant effects of physical training were seen in the lumbar spine. A sensitivity intention to treat analysis, including all randomized subjects, showed no significant effect of physical training on BMD at any site.

Conclusions The results indicate a small but positive effect of physical exercise on hip BMD in postmenopausal women with low BMD.

Keywords Bone mineral density · Forearm fracture · Physical training · Postmenopausal women

Introduction

Hip fracture, perhaps the most severe clinical manifestation of osteoporosis, is related to several sequelae, such as early death and disability. According to registry studies the incidence of fragility fractures in Sweden has more than doubled since 1950 and the incidence of hip fractures has increased even more [1]. The estimated risk for a 50-year old Swedish woman of having a hip fracture during her lifetime is presently about 23% [2]. It is uncertain whether the incidence of hip fractures will continue to rise, and data from Finland indicate that it is slowly declining [3]. The prevalence of osteoporosis increases with age. The dramatic increase in hip fractures during the last few decades, however, cannot be fully explained by an increase in the number of elderly in the population alone, but may well be due to an increasingly sedentary lifestyle [4].

The fact that mechanical loading is important for bone mineral density (BMD) has been shown in animal studies [5–7]. A drastic reduction in the physical activity of an individual will lead to a rapid and substantial decrease in

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bone mineral density and bone strength. This has been firmly shown in studies on tetraplegic patients and astronauts spending months in zero gravity [8].

Many observational cross-sectional studies indicate the beneficial effects of physical training on bone. The results of observational studies on exercising individuals show that they have higher BMD [5] and that they have lower fracture risk [7] than non-exercising individuals. The largest effects of physical activity on BMD have been reported in children and teenagers [5], but small positive effects in adults have also been observed. Several prospective randomized trials in postmenopausal women without previous fractures have looked for the effects of physical training on spine BMD [9–14] or hip BMD [15–18] or both [19–26]. In general these studies have shown an increased BMD in the physical training group compared to in the control group in the range of 1–1.5% after one year of training.

Very few studies have included women with low bone density and fragility fractures [19, 27], which is the most important population for osteoporosis intervention.

The aim of this study was to investigate whether moderate physical training of a kind that can be incorporated into daily living can prevent the expected bone loss in postmenopausal women with forearm fractures and low bone mass.

Material and methods

Patients

The ethics committee of the Karolinska Institute approved this prospective randomized controlled study. We screened postmenopausal women 45 to 65 years of age with a previous forearm fracture for enrolment in the study. Menopause was defined as one year after the last menstruation. The women were eligible if they had a BMD T-score of ≤ -1 in the total hip or spine L1–L4 and were able and willing to participate in the training. The women were excluded if they had a T-score lower than -3 at any site, had any disease known to interfere with bone metabolism, were on cortisone therapy or antiresorptive medication, including hormone replacement therapy, had a BMI lower than 19.9 or higher than 30.9, or were already training at the level of or above that of the intervention. Each subject was given a study number according to the order in which she was included in the study. This number defined which group the subject was randomized to, by use of a predefined random number table.

Recruitment procedures and participant flow

Three hundred and seventy-seven women contacted the clinic after they had read our advertisements in a newspaper

and six were referred from the orthopaedic emergency unit after a forearm fracture within the last five years. All women were subjected to a preliminary telephone interview by the study nurses. Prior to the DXA, 216 women were possibly eligible. All of these were invited for bone densitometry. One hundred and ninety-one women turned up. Forty of these women had normal bone mineral density, 11 had a T-score below -3.0 , and 19 were ineligible due to other causes, such as significant disease, medication or withdrawal of consent. We aimed at an inclusion of 154 women. However, after three years the inclusion was stopped due to a low inclusion rate, and the inclusion target was not reached.

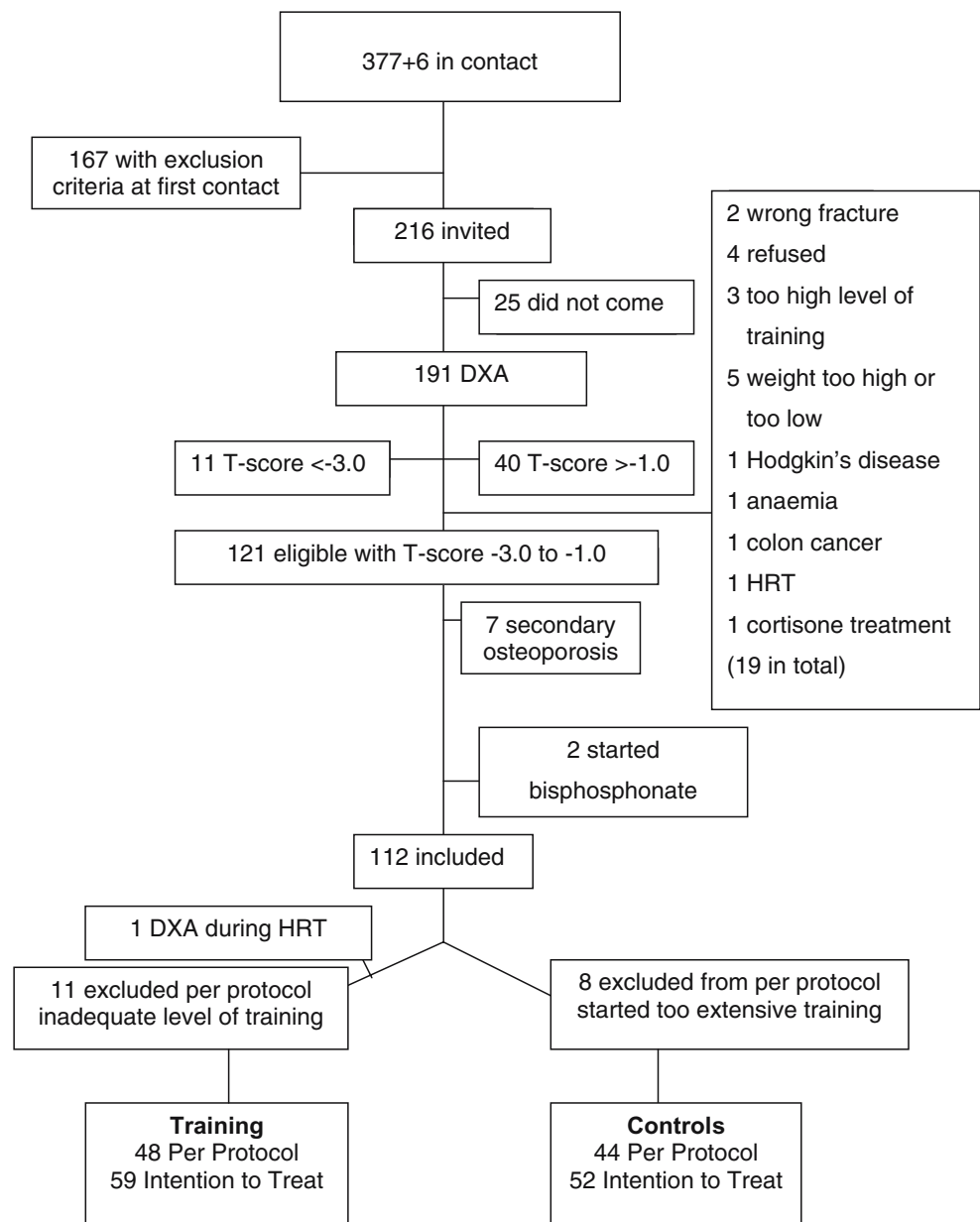
One hundred and twenty-one women fulfilled the BMD inclusion criteria and were called for inclusion. They had routine blood tests performed: blood count, sedimentation rate, serum levels of creatinine, calcium, phosphate, alkaline phosphatase, free T4 and TSH. A urine sample was taken for glucose and albumin. Vitamin D levels were not analysed. Each participant was seen by a doctor and her medical history was taken. A medical examination was performed. When appropriate, additional laboratory tests were taken to rule out secondary osteoporosis. Seven were diagnosed with primary hyperparathyroidism. All women suitable for antiresorptive therapy were offered this treatment as an alternative to inclusion in the study. Two were started on bisphosphonates and were excluded before randomization. Thus a total of 112 women were randomized (see Fig. 1 for participant flow).

Intervention

The physical training consisted of three fast 30-minute walks and one or two sessions of one-hour training per week in a training centre, separate from the hospital. The fact that the training sessions were given at several different time-points every day of the week gave the subjects excellent accessibility to the training. The physical training consisted of a 5-minute warm-up, 25 minutes of strengthening exercises for the arms, legs, back and stomach, 25 minutes of aerobic exercise, and 5 minutes of stretching. The individuals chose their own level and intensity of training and were encouraged to increase the level if possible. The women recorded each training episode. Attendance was controlled by the study nurses for each subject after 3, 6 and 12 months (compliance was 95%). All patients were given a supplement of vitamin D and calcium.

Bone mineral density measurements

The main endpoints of the study were the changes in bone mineral density of the total hip and the lumbar spine. BMD was measured in each subject at baseline and after one year,

Fig. 1 Participant flow

using the dual X-ray absorptiometry scans (DXA) (Lunar Prodigy 10631 GE Medical Systems). Throughout the study automatic calibration checks were performed daily. Three times a week calibration using a spine phantom provided by the manufacturer was performed. The left hip was scanned in all patients and the lumbar spine was measured by scanning from the fourth to the first lumbar vertebra. The precision was about 1%.

Leg muscle performance test

The timed-stand test is a performance-based measure that records the time in seconds needed to stand up ten times

from a standard chair [28]. A shorter time indicates better performance.

Statistical methods and power calculations

A power calculation was performed based on results from other studies [11, 24]. With a sample size of 64 in each group, we had a 80% power to detect a difference in means of 3%, assuming that the standard deviation was 6% and using a two group t-test with a 0.05 two-sided significant level. With a dropout frequency of 20%, we calculated that a total of 154 subjects would be needed. Our choice to study women with a Colles fracture increased the likelihood

of a fairly homogenous cohort and increased the chance of detecting subjects with low bone mass, thus reducing the number of subjects that would have to be screened in order to reach the targeted number.

The data were analysed using basic descriptive statistics and repeated measurement ANOVA with the Statistica 7.0 software. The two groups (control and training) were the between-factor and the time (0 and 12 months) was the within-factor. The proportional differences over time in each group were calculated and compared. In both groups there were technical measurement problems in the DXA in the hip of one patient. Three timed-stand tests, including subjects from both groups, were not performed at the correct time and were, therefore, excluded. The missing values in the data set were supposed to be at random [29].

Results

One hundred and twelve women were randomized.

In the training group 11 patients were excluded, because they did not start training or trained less than 1/2 year. In the control group eight were excluded, since they trained with intensity equal to or higher than the training group. In addition, one woman on HRT randomised into the training group was excluded, due to failure to attend the DXA measurement at the designated time. The baseline data are presented in Table 1. The groups were similar in age, body mass index, smoking status and BMD of the hip. A small random difference between the groups was observed in the BMD of the spine.

All women received oral and written information by the investigator and a signed consent was obtained.

BMD in spine L1–L4

The mean (SD) BMD for the control group was 1.021 g/cm² (0.107) at baseline and 1.014 g/cm² (0.108) at 12 months. The mean BMD for the training group was 0.960 g/cm² (0.077) at baseline and 0.957 g/cm² (0.077) at

Table 1 Baseline data for the control and training groups

	Control (N=44)	Training (N=48)
Age, years	59.6 (3.6)	58.9 (4.3)
BMI, kg/m ²	24.9 (2.3)	24.4 (2.6)
Smokers	2	3
Muscle strength, seconds	18.8 (5.6)	18.7 (4.5)
BMD, spine L1–L4, g/cm ²	1.021 (0.107)	0.960 (0.077)
BMD, spine L2–L4, g/cm ²	1.049 (0.115)	0.984 (0.079)
BMD, hip total, g/cm ²	0.869 (0.080)	0.873 (0.071)
BMD, femoral neck, g/cm ²	0.826 (0.085)	0.829 (0.078)
Mean (SD)		

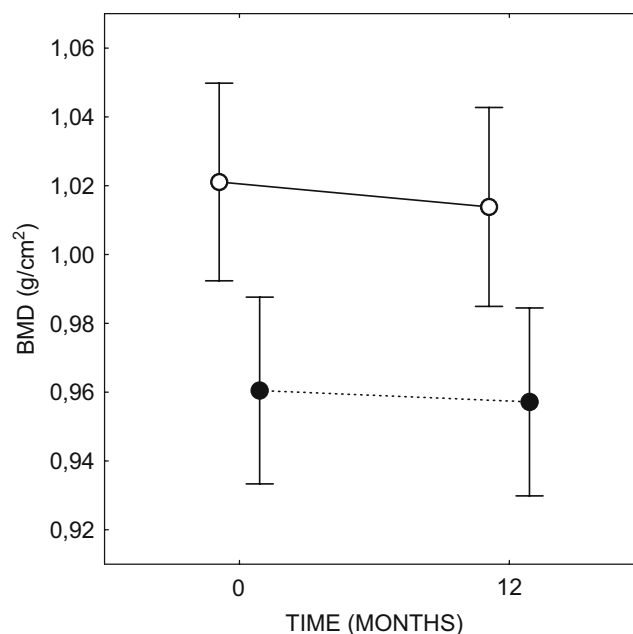


Fig. 2 The patients' total bone mineral density of the spine, L1–L4, was measured at baseline and at 12 months as described in material and methods. There was no significant increase in BMD in the training group compared to the control group after 12 months when calculated with repeated measurement ANOVA, $p=0.608$. Legends: open circles, control group; filled circles, training group. Vertical bars denote 95% confidence interval

12 months (Fig. 2). Thus, BMD decreased in both groups during the 12-month study period equalling -0.003 g/cm² (0.031) ($p=0.475$) in the training group and -0.007 g/cm² (0.039) ($p=0.247$) in the control group. The interaction for the group*time variables was not significant (repeated measurement ANOVA, $F=0.265$, $p=0.608$) for the BMD in spine L1–L4.

BMD in total hip

The mean (SD) BMD for the control group was 0.869 g/cm² (0.080) at baseline and 0.866 g/cm² (0.083) at 12 months. The mean BMD for the training group was 0.873 g/cm² (0.071) at baseline and 0.878 g/cm² (0.073) at 12 months (Fig. 3). The increment in BMD during 12 months in training group was $+0.005$ g/cm² (0.018) ($p=0.066$) while the control group decreased their BMD with -0.003 g/cm² (0.019) ($p=0.283$). The interaction for the group*time variables was significant, $F=4.33$ ($p=0.040$) for the BMD in total hip. The mean proportional change in BMD over time was $+0.58\%$ for the training group and -0.36% for the control group.

Intention to treat analysis

We also carried out an intention-to-treat analysis, including all 112 randomised subjects in the calculations, to evaluate

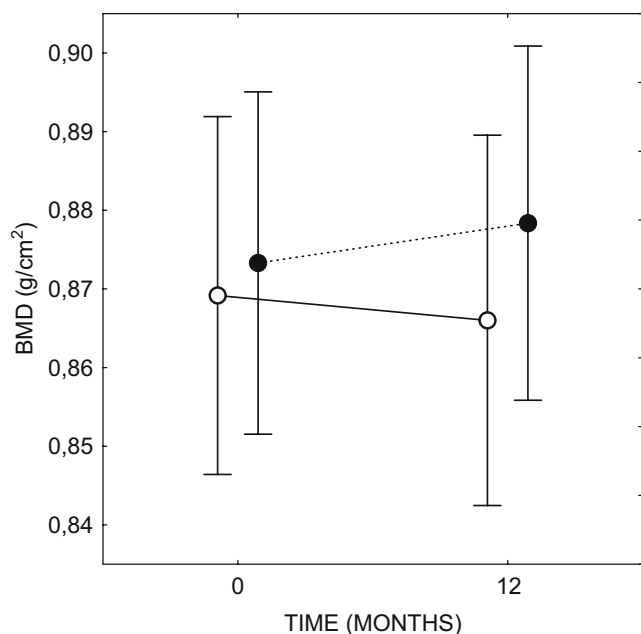


Fig. 3 The patients' total bone mineral density of the hip was measured at baseline and at 12 months as described in material and methods. There was a significant increase in BMD in the training group compared to the control group after 12 months when calculated with repeated measurement ANOVA, $p=0.040$. Legends: open circles, control group; filled circles, training group. Vertical bars denote 95% confidence interval

the effect of physical training on hip BMD. The mean (SD) for the control group was 0.875 g/cm^2 (0.080) at baseline and 0.874 g/cm^2 (0.083) at 12 months. The mean BMD for the training group was 0.876 g/cm^2 (0.067) at baseline and 0.878 g/cm^2 (0.070) at 12 months. The interaction for the group*time variables was not significant (repeated measurement ANOVA, $F=0.732$, $p=0.394$) (data not shown).

Leg muscle performance test

The effects of the prescribed physical activities on leg muscle strength were assessed by the subjects' performance in the timed-stand test at base line and after one year (Fig. 4). The control group had a mean time (SD) of 18.8 seconds (5.6) at baseline and 16.8 s (5.1) at 12 months. The corresponding data for the training group was 18.7 (4.5) and 14.1 (3.5) seconds, respectively. There was a significant increased performance in the training group compared to in the control group after 12 months when calculated with repeated measurement ANOVA, $F=9.69$ ($p=0.003$). In post hoc testing, both groups significantly improved their results in comparison to their baseline performance after one year ($p<0.005$ for both group comparisons). The results were similar in leg performance when it was evaluated according to the intention-to-treat protocol. The group*time interaction was significant in the ANOVA analysis ($p=0.003$).

Discussion

In the present study a positive effect on total hip BMD after one year of physical training was observed. Our results confirm those of predominantly smaller studies [21, 23, 24], showing a 1% increase in hip BMD after one year of training. Although an overall treatment effect of 1% over one year is numerically small, it might have a significant impact on the number of osteoporotic fractures in a large population [30]. Also other determinants involved in fracture risk, such as muscle strength, coordination and balance, are affected positively by physical training [5]. In this study the leg muscle performance significantly improved in the training group as measured with the timed-stands test from a mean for 65-year-olds to a mean of 40-year-olds. This indicates high compliance among the subjects that continued to train for the duration of the study.

Strain is a measure of bone deformation and generates the adaptive response to loading [31]. When the skeleton is subjected to *loading*, and as a result of that *strain* over a certain threshold, it will respond by inducing bone formation. The bone will adapt to these increased demands of tenacity. After the adaptation to a certain load, this load will induce a lower level of strain and bone formation will not be induced by it. This is the mechanism by which physical training may increase BMD and bone strength [5]. Animal experiments show that bone cells respond the most to high

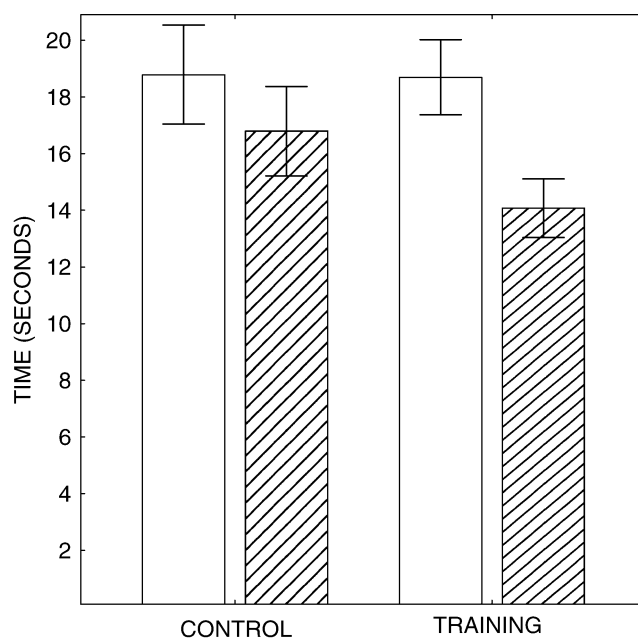


Fig. 4 A leg muscle performance test, the timed stand test was performed at baseline and after 12 months. There was a significant increased performance in the training group (fewer seconds) compared to the control group after 12 months when calculated with repeated measurement ANOVA, $p=0.003$. Open circles, control group; filled circles, training group. Vertical bars denote 95% confidence interval

levels of strain from different directions, changing at fast rates [31].

Several experimental studies have shown that in order to obtain maximum stimulation of bone formation, training programs should, in theory, be designed to generate high levels of strain from unusual directions, changing in fast rates [31, 32] and also continually increased. Tennis and squash are examples of sports that may induce this type of strain. In observational studies, for example, tennis players have higher bone mineral density than age-matched controls [33]. Training based on weight bearing activities, such as walking and jogging, have been shown to increase BMD although to a lesser extent [10, 13, 19, 21]. Endurance training involving strengthening exercises may also create the necessary osteogenetic stimuli and has been reported to increase BMD in studies on postmenopausal women [11, 12, 17, 18, 22, 25]. Unfortunately, invasive in nature, measurements of strain are very difficult to perform in humans [5]. Lanyon, however, once showed in one man that loading creates strain in the human skeleton as well [34]. The present study included one to two hours of aerobic training, strength training and three brisk walks every week. The training program incorporated movements that could create high strain from unusual directions and the subjects had the opportunity to choose the intensity and the magnitude of the exercise. The training was sufficient to induce a small but significant change in the total hip BMD.

In some studies showing positive effect of physical activity on BMD, the training programs have consisted of supervised, pre-decided, progressively increased training [22, 23]. In this study, we investigated the effects of an intervention possible to incorporate into daily life. This type of training should be applicable in a broad population. The patients in the present study decided their own level of training and were encouraged to increase their level of physical activity when possible. The training was not supervised. Although this may be a limitation of the study, it reflects the real life situation. Some of the individuals in the control group started high activity training, and some in the training group never commenced or ended the training program prematurely. These were all excluded from the main per protocol analysis. This reflects the compliance problems generally observed in physical training studies. To our knowledge only one previously published randomised study on physical training in postmenopausal women used the intention-to-treat analysis (ITT) and did not show any significant effects on BMD. However a significantly positive effect in bone mineral content of the trochanter could be observed [17]. In all other published studies per protocol analysis was used [9–16, 18–26].

One could argue that the results based on physical training studies have generally been biased by having

excluded the “best” subjects in the control groups and the “worst” subjects in the training groups. For several reasons the populations in lifestyle intervention trials are much more difficult to control than those in pharmaceutical trials. As the study is not blinded, some of the patients randomized to controls feel disappointed and, therefore, have a tendency to administer the active intervention themselves. As the intervention is demanding, some patients in the intervention group are not compliant. This is evident also in other lifestyle interventions, for example in trials on diet and weight reduction [35]. In a placebo-controlled drug trial, the dropouts are often similar in both groups and a self-administration of the intervention in the placebo group is not possible. In a drug trial one would probably exclude patients randomized to placebo if they, by mistake, had received the intervention for the duration of the study. We, therefore, think that although our per protocol analysis may induce a positive bias favouring, the effect of the physical training, the design of lifestyle interventions generally favour the null hypothesis if ITT analysis is used. The fact that not all subjects are able to comply with a training intervention could perhaps be overcome by selecting the subjects for randomization more carefully based on their willingness to train. This would, however, hamper the generalisability of the results and make the recruitment of subjects even more difficult.

Also other factors in our study may have favoured the null hypothesis. At this time point we felt obliged to treat all the subjects with calcium and vitamin D due to a general recommendation of supplementation in postmenopausal women with low bone mass. Calcium and vitamin D have been shown to increase BMD [36] and the supplementation may have slowed down the bone loss in both groups.

Conclusion

The study indicates a small but significantly positive effect of aerobic training and walking in combination on total hip BMD and muscle performance in postmenopausal women with low bone mass. Our certainty of the results is hampered by the need for a per protocol analysis in order to show a significant effect. Larger randomised studies taking into account the large dropout numbers often seen in these trials may overcome some methodological problems. However, even then the general tendency of a fairly large number of subjects in either group not to comply with the protocol will have to be addressed properly in order to ensure good study quality. The informed consent procedure will have to stress the importance of the subjects' adherence to the protocol regardless of the result of the randomization procedure.

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