Benefits of 2 Years of Intense Exercise on Bone Density, Physical Fitness, and Blood Lipids in Early Postmenopausal Osteopenic Women

Results of the Erlangen Fitness Osteoporosis Prevention Study (EFOPS)

Wolfgang Kemmler, PhD; Dirk Lauber, PhD; Jürgen Weineck, PhD, MD; Johannes Hensen, MD; Willi Kalender, PhD; Klaus Engelke, PhD

Background: Growing evidence indicates that physical exercise can prevent at least some of the negative effects on health associated with early menopause. Here we determine the effects of intense exercise on physical fitness, bone mineral density (BMD), back pain, and blood lipids in early postmenopausal women.

Methods: The study population comprised 50 fully compliant women, with no medication or illness affecting bone metabolism, who exercised over 26 months (exercise group [EG]), and 33 women who served as a nontraining control group (CG). Two group training sessions per week and 2 home training sessions per week were performed in the EG. Both groups were individually supplemented with calcium and cholecalciferol. Physical fitness was determined by maximum strength and cardiovascular performance. Bone mineral density was measured at the lumbar spine (dual-energy x-ray absorptiometry [DXA] and quantitative computed tomography [QCT]), the proximal femur (DXA), and the forearm (DXA). In serum samples taken from a subset of the study participants, we determined bone formation (serum osteocalcin) and resorption (serum cross-links) markers as well as blood lipid levels. Vasomotor symptoms related to menopause and pain were also assessed.

Results: After 26 months, significant exercise effects determined as percentage changes compared with baseline were observed for physical fitness (isometric strength: trunk extensors [EG +36.5% vs CG +1.7%], trunk flexors [EG +39.3% vs CG –0.4%], and maximum oxygen consumption [EG +12.4% vs CG –2.3%]); BMD (lumbar spine [DXA L1-L4, EG +0.7% vs CG –2.3%], QCT L1-L3 trabecular region of interest [EG +0.4% vs CG –6.6%], QCT L1-L3 cortical region of interest [EG +3.1% vs CG –1.7%], and total hip [DXA, EG –0.3% vs CG –1.7%]); serum levels (total cholesterol [EG –5.0% vs CG +4.1%] and triglycerides [EG –14.2% vs CG +23.2%]); and pain indexes at the spine.

Conclusion: General purpose exercise programs with special emphasis on bone density can significantly improve strength and endurance and reduce bone loss, back pain, and lipid levels in osteopenic women in their critical early postmenopausal years.

Arch Intern Med. 2004;164:1084-1091

From the Institute of Medical Physics (Drs Kemmler, Kalender, and Engelke), and Institute of Sport Sciences (Drs Lauber and Weineck), University of Erlangen, Erlangen, Germany; and Medizinische Klinik I, Klinikum Hannover Nordstadt, Hannover, Germany (Dr Hensen). *The authors have no relevant financial interest in this article.*

REGULAR EXERCISE THAT AFfects various functions and subsystems of the human body is beneficial throughout life. There is growing evidence that exercise prevents at least some of the negative consequences of menopause such as bone loss, increased risk of coronary heart disease, or chronic diseases (eg, diabetes).[1] In particular, bone loss often accelerates significantly with the onset of menopause. Therefore, the availability of effective exercise programs for early postmenopausal women is important. However, their design is challenging as 2 different requirements compete. The multiple risk factor condition encountered in early postmenopausal women favors a general purpose exercise design. On the other hand, it is desirable to develop highly specialized training regimens dedicated to an individual risk factor such as bone loss.[2] For example, high-impact exercise should be part of a bone loss prevention program but is less relevant for general health programs.

As described in a recent review article, exercise studies in early postmenopausal women are rare.[3] Most of them target single risk factors. Follow-up times are typically around 12 months, which is very short when investigating exercise effects on bone loss. This is particularly true in studies in which exercise intensity is increased slowly to minimize the risk of training-related injuries. In this case, necessary strain levels[4] may only be applied during a short period toward the end of the study.

To overcome some of the limitations of current exercise studies, we designed the Erlangen Fitness Osteoporo-

sis Prevention Study (EFPOS), an exercise trial dedicated to early postmenopausal women. Its primary objective was to prevent menopause-induced accelerated bone loss by exercise. Secondary objectives were to improve overall fitness and quality of life.

The EFOPS is a 24-month multipurpose exercise program with specific aerobic, jumping, and muscle strength sequences dedicated to maintain bone mass at the spine and the proximal femur, which are the most important osteoporotic fracture sites. To maintain long-term training compliance, a periodic design with alternating high-impact and recreational periods was selected. The training was complemented by an extensive set of measurements in the fields of bone densitometry, physical fitness, and blood analysis as well as by detailed questionnaires. We present the most important results after 24 months; initial 1-year results have been previously published.[5]

METHODS

The EFOPS is a controlled exercise trial in early postmenopausal women approved by the ethics committee of the University of Erlangen, the Bundesamt für Strahlenschutz, and the Bayerisches Landesamt für Arbeitsschutz. All study participants gave written informed consent.

SUBJECTS

We queried population registers to contact all women of the Erlangen (Germany) area between ages 48 and 60 years by mail describing the study objectives. **Figure 1** shows an overview of the recruitment process. Inclusion criteria were a time window of 1 to 8 years after menopause and osteopenia at the lumbar spine or total hip measured by dual-energy x-ray absorptiometry (DXA) using the well-known World Health Organization T-score definition (–2.5 SD <T score ≤–1.0 SD). Exclusion criteria were known osteoporotic fractures, diseases and use of medication affecting bone metabolism, athletic activity (defined as participation in sport competitions within 2 decades before the start of the study), inflammatory diseases, history of cardiovascular disease, and very low physical capacity at ergometry (<75 W).

The participants were free to join the exercise group (EG) or the control group (CG). A total of 137 early postmenopausal (1-8 years) women were finally included in the study; 86 women joined the EG and 51 joined the CG. Participants of the CG were requested to continue their habitual lifestyle, while participants of the EG underwent the training regimen described in the following section. Both groups were individually supplemented with calcium and cholecalciferol according to their nutritional intake.

EXERCISE PROGRAM

The exercise program consisted of 4 sessions per week, divided into 2 supervised group sessions with 10 to 15 participants lasting 60 to 70 minutes each and 2 nonsupervised individual home training sessions of 25 minutes each. For all sessions, individual training logs were conducted, which were also used to monitor training attendance and compliance. No sanctions were imposed on participants who did not regularly exercise at home to reduce potential motivations to cheat with the training logs.

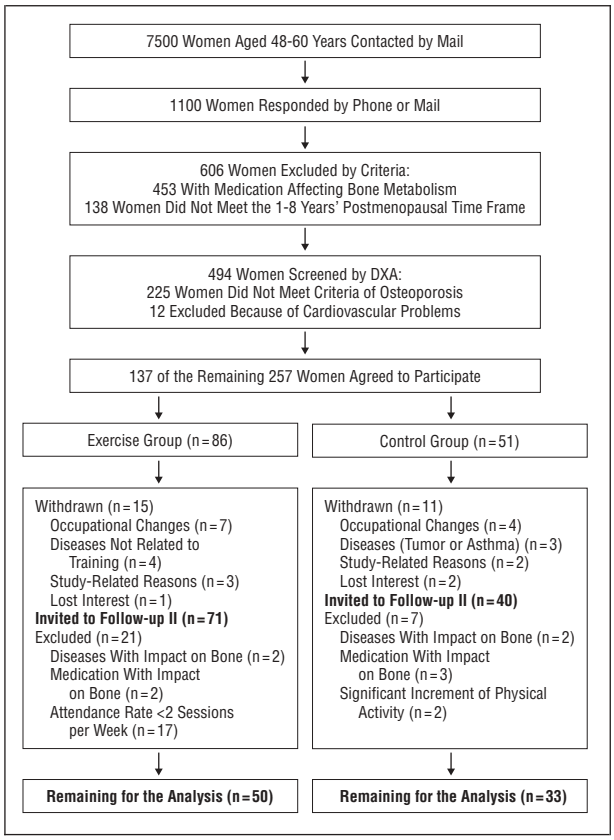

Figure 1. The Erlangen Fitness Osteoporosis Prevention Study trial profile. DXA indicates dual-energy x-ray absorptiometry.

Group Training Session

The group-training program was subdivided into warm-up/endurance, jumping, strength, and flexibility sequences. The jumping sequence started after 6 months of training.

Warm-Up/Endurance Sequence. During the first 3 study months, a gradually increasing fast walking and running program (20 minutes) was carried out to slowly accustom the participants to higher impact rates. After 3 minutes of running, heart rates (HR) exceeded 65% maximum HR (HR_{max}) and remained at 70% to 85% HR_{max} until the end of the jumping sequence. Running games were added to promote unusual strain distributions under weight-bearing conditions. After 3 months, 10 minutes of low to high impact aerobic exercise with an increasing amount of high-impact aerobic exercise concluded the sequence. Peak ground reaction forces (mean ± SD) measured by force plates (Erbe Medizintechnik; Tübingen, Germany) were 1124 ± 150 N during running and 1445 ± 232 N during high-impact aerobic exercises.

Jumping Sequence. A jumping sequence was added 5 to 6 months after the start of the study. After an introductory rope-skipping phase, 4 different sets of 15 simple multidirectional jumps (eg, closed leg jumps) were performed. Subjects were encouraged to focus on intensive takeoff and soft landing with flexed ankles and knees without heel strikes. Peak ground reaction forces (mean ± SD) were 1791 ± 344 N for takeoff and 2363 ± 462 N for landing.

Strength Training Sequence. The strength training consisted of 2 sessions, one using machines and the other isometric exercises, elastic belts, dumbbells, and weighted vests. On

the machines (TechnoGym, Gambettola, Italy), 13 exercises affecting all main muscle groups were performed. Exercise intensity was increased slowly. In the first 3 study months, 2 sets of 20 repetitions (reps) at 50% 1 rep maximum (1 RM) were performed. In the following months, the intensity was increased (after 3 months, 2 sets of 15 reps at 60% 1 RM; after 5 months, 2 sets of 12 reps at 65% 1 RM). Each rep lasted 5 seconds (2 seconds concentric/1 second static/2 seconds excentric) with 90 seconds of rest between sets and exercises. Seven months after the start of the study, the training on the machines was divided into periods: 12 weeks of periodized high-intensity training (70%-90% 1 RM) were interleaved by regenerational 4- to 5-week periods of low-intensity training (50% 1 RM).

The second strength-training session consisted of 12 to 15 different isometric exercises (2-4 sets) predominantly dedicated to the trunk and the proximal femur (6-10 seconds of maximum intensity were followed by 15-20 seconds of rest). In addition, 3 different belt exercises with 2 to 4 sets of 15 to 20 reps each were applied to the upper trunk. After the first 7 months, the belt training was replaced by dumbbell and weighted vest exercises. In parallel with the high-intensity training period described above, 10-rep maximum tests (ie, wide bench press, 1-arm dumbbell rowing, and squats/power cleans with weighted vests and beverage boxes) were conducted to individually adjust the training intensity.

Flexibility Training Sequence. Before and after the strength training and during the rest periods, a standardized stretching program (10 exercises for all main muscle groups) with 1 to 2 sets and 30 seconds of passive stretching was performed.

Home Training Session

The home training consisted of isometric, belt, and stretching exercises. An additional rope skipping program (3 sets of 20 reps) was introduced 20 weeks after the start of the study. The specific exercises were replaced every 12 weeks to increase intensity and maintain a high compliance.

MEASUREMENTS

Unless otherwise stated, all measurements detailed below were performed at baseline (2 months before the start of the exercise training) and 26 months after the start of the training.

Anthropometric Data

We measured height, weight, body composition, and waist-hip ratio. Body composition was determined using the impedance technique (Tanita BF 305, Tanita, Japan).

Physical Fitness Tests

Maximum isometric strength was measured with a dynamometer (Schnell M3; Schnell, Peutenhausen, Germany). We used the test protocol by Tusker[6] consisting of 2 maximum efforts lasting 5 seconds each with a 40-second rest period in between. The higher of the 2 values was used for data analysis.

Endurance was assessed using a stepwise treadmill test up to a voluntary maximum. Starting with 6 km/h (0° slope), velocity was increased every 3 minutes by 1 km/h. Maximum oxygen uptake ($\dot{V}O_{2max}$), maximum carbon dioxide output ($\dot{V}CO_{2max}$), and ventilation (VE) were determined breath by breath using a Zan 600 open spirometric system (Zan Meßgeräte GmbH, Oberthulba, Germany). Subjects who could not achieve a minimum HR_{max} of 155 beats/min were excluded from the analysis.

Bone Mineral Density

Bone mineral density (BMD) was measured by DXA and quantitative computed tomography (QCT) —DXA (QDR 4500A; Hologic Inc, Bedford, Mass) was performed at the lumbar spine (L1-L4), the proximal femur, and the forearm using standard protocols specified by the manufacturer; QCT (Somatom Plus 4; Siemens, Erlangen, Germany) was performed at the lumbar spine (L1-L3) using the Osteo protocol.[7] For baseline DXA data, measurements of the screening visit taken 3.5 months before the start of the training program were used.

Serum Markers of Bone Turnover and Blood Lipids

Blood was sampled from an antecubital vein in the morning after an overnight fast. Serum samples were frozen at –70°C after being centrifuged at 3000 rpm for 20 minutes. Markers of bone turnover and lipid levels were analyzed in a subset of the study participants. We randomly (separate for the EG and CG) selected 34 women of the EG and 24 women of the CG for this analysis.

Bone formation was determined from serum osteocalcin (N-mid Osteocalcin One Step ELISA [enzyme-linked immunosorbent assay]; Osteometer BioTech A/S, Herlev, Denmark) and bone resorption from serum cross-links (CrossLaps One Step ELISA; Osteometer BioTech A/S). Interassay (intra-assay) variation was 2.8% to 6.5% (5.4%-6.8%) for the N-mid Osteocalcin One Step ELISA and 5.4% to 8.1% (5.0%-5.4%) for the CrossLaps One Step ELISA. Sensitivity was 0.5 ng/mL for the N-mid Osteocalcin One Step ELISA and 94 pmol/L for the CrossLaps One Step ELISA.

With regard to blood lipids, levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, glucose, uric acid, and apolipoproteins A-I and B were determined.

Questionnaire

A detailed questionnaire was used to assess (1) pain frequency and grade at various skeletal sites, (2) historical and immediate prestudy exercise levels, (3) normal daily load levels associated with work, household, and gardening activities, and (4) common osteoporotic risk factors. At 26 months, we additionally asked for changes that had occurred during the intervention period, particularly for (5) diseases and medication affecting bone metabolism, (6) vasomotor symptoms, and (7) additional sport activities outside the EFOPS training program. The reproducibility of the questionnaires had been evaluated in an earlier study.[8] A random sample of 10 women had answered the questionnaires twice within 2 weeks. The mean difference between the first and second scores was less than 5%.

NUTRITIONAL ANALYSIS AND CALCIUM AND CHOLECALCIFEROL SUPPLEMENTATION

The individual dietary intake was assessed by a 5-day protocol completed by each study participant. The consumed food was weighted precisely. The analysis of the protocols was performed using Prodi-4,5/03 Expert software (Wissenschaftlicher Verlag, Freiburg, Germany), which extracts 1500 different basic nutritional ingredients. Based on the calcium and vitamin D results from this analysis, all study participants were individually supplemented with calcium and cholecalciferol to ensure a total daily intake of 1500 mg of calcium and 500 IU of cholecalciferol.

STATISTICAL ANALYSIS

Baseline measurements are reported as mean±SD. Results of the follow-up visit at 26 months are reported as percentage

changes compared with baseline. The Kolgomorov-Smirnov test was used to check for normal distribution. Homogeneity of variance was investigated using the Levine F test. For normally distributed variables, differences within and between groups were assessed with paired and unpaired *t* tests; otherwise, the Wilcoxon or Mann-Whitney test was used. All tests were 2-tailed; $P<.05$ was considered significant. All statistical analyses were performed with SPSS 10.08 (SPSS Inc, Chicago, Ill).

RESULTS

Of 86 women who had started in the EG, 71 completed the 26-month follow-up visit. In the CG, 40 of 51 women completed the visit (Figure 1). For the 71 women of the EG, training attendance averaged over 26 months was 79% for group sessions and 61% for home sessions. After the analysis of the questionnaires, 50 women of the EG and 33 of the CG were included in the data analysis presented in this article. Seventeen women were excluded from the analysis because of poor training compliance (defined as <2 sessions per week on average over the complete course of the study). In the CG, 2 participants were excluded because they had significantly increased their physical activity by starting weight-training exercises. Also, subjects with diseases or taking medication affecting bone metabolism were excluded.

Table 1 and **Table 2** summarize the most important baseline measurements of the 83 women included in the analysis. There were no significant differences between the EG and CG for any of the variables for mean ± SD values.

Follow-up measurements at 26 months showed no significant changes for the anthropometric variables. Also, after excluding the subjects described above (Figure 1) there were no significant changes for the lifestyle parameters given in Table 1 after 26 months. Most of the other results are presented in **Figures 2**, **3**, **4**, and **5**, which share the same design in showing percentage changes over the complete 26-month period. Significance levels between baseline and follow-up measurements are shown separately for the EG and CG. Figures 2 through 5 also include the significance levels of the difference of the changes between the EG and CG.

Parameters related to physical fitness (Figure 2) significantly increased in the EG and remained either constant or decreased in the CG, resulting in overall significant differences when comparing the changes after 26 months between the EG and CG.

At the lumbar spine and the proximal femur, parameters of bone densitometry were stable in the EG with the exception of a relative large increase (+3.1%) for cortical BMD of the spine and a small decrease of –1% for BMD of the femoral neck (Figure 3). At the same time, the CG showed significant decreases at these sites, resulting in significant differences when comparing the changes after 26 months between the EG and CG. Results are very different for the forearm: BMD decreased up to 4% in the ultradistal region of interest in the EG as well as in the CG.

Serum markers of bone turnover did not show significant changes for either group. With respect to blood lipids, significant differences between the EG and CG were measured for total cholesterol and triglycerides but not for HDL-C (Figure 4).

Table 1. Baseline Data of Exercise and Control Groups for Anthropometric Variables and Osteoporotic and Coronary Heart Disease Risk Factors*

Variable	Exercise Group (n = 50)	Control Group (n = 33)
Age, y	55.5 ± 3.2	55.9 ± 3.1
Height, cm	164 ± 6	162 ± 7
Weight, kg	67.6 ± 9.7	64.8 ± 13.6
BMI	25.1 ± 3.3	24.7 ± 3.9
Total body fat, %	35.9 ± 4.9	33.6 ± 7.2
Waist circumference, cm	76.9 ± 7.9	75.6 ± 8.4
Waist-hip ratio	0.80 ± 0.08	0.78 ± 0.08
Age at menarche, y	13.4 ± 1.3	13.3 ± 1.6
Age at menopause, y	50.4 ± 3.2	50.4 ± 3.1
Irregular menstrual cycle for more than a year during lifetime, % group	16	15
No. of pregnancies	2.0 ± 1.1	1.9 ± 1.3
Low physical activity, % group	52	55
$\dot{V}o_{2max}$, L/min	1.79 ± 0.43	1.75 ± 0.36
Energy intake, kcal/d	1923 ± 319	1859 ± 512
Protein intake, g/d	70.5 ± 11.9	69.1 ± 15.9
Calcium intake, mg/d	1127 ± 371	1055 ± 265
Phosphorus intake, mg/d	1344 ± 317	1251 ± 338
Vitamin D intake, µg/d	5.3 ± 4.4	5.6 ± 5.3
Osteoporosis of parents or siblings, % group	16	14
Use of oral contraceptives, % group	78	82
Use of corticosteroids (>5 mg/d) or thyroxin (≥75 mg/d) for >6 mo during lifetime, % group	10	12
Coffee intake, mL/d	788 ± 329	827 ± 357
Smoker, % group	8	12

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); $\dot{V}o_{2max}$, maximum oxygen uptake.
*Data are mean ± SD value unless otherwise specified. All nutritional intake parameters were assessed for 49 women in the exercise group and 31 women in the control group. The difference between the groups was nonsignificant ($P\geq.05$) for all variables.

Table 3 contains the results of the pain assessment from the questionnaires. Pain intensity and frequency were graded from 1 (very weak/very seldom) to 7 (very heavy/very often). In the EG, pain intensity as well as frequency decreased significantly at the spine, resulting in significant differences between the 2 groups in the cervical and thoracic sections. Despite high-intensity/high-impact exercise, no changes were reported for the main joints. Improvements or deteriorations of vasomotor symptoms also assessed by questionnaire using grades from –3 to +3 are summarized in Figure 5. There was an overall tendency toward improvement in both groups, with the exception of insomnia and mood.

COMMENT

In this study we showed that a long-term multipurpose exercise program with emphasis on bone density not only offsets bone loss but also improves physical fitness and lower back pain and reduces some coronary heart disease risk factors in early postmenopausal women. The EFOPS

exercise design is practicable, attractive, and safe. Within the 26-month period, 1 fall with a hairline fracture of the os pubis during the aerobic sequence occurred. Dropout (17%) and attendance rates (71%) are reasonable and comparable with short-term exercise studies.[3]

Our study has several strengths: (1) We specifically targeted osteopenic early postmenopausal women, a population for which a stoppage or at least a reduction of bone loss is highly relevant. (2) The 2-year study duration was long, and the number of subjects included in the analysis (n=83) was high compared with most other similar studies. (3) A large variety of physical fitness parameters was investigated. (4) Bone density was measured at multiple sites and with different modalities. (5) We showed that benefits from exercise could be achieved in addition to those caused by an offset of calcium and vitamin D deficits. And (6) covariates such as diseases, medication, nutrition, or lifestyle changes affecting bone or muscle metabolism were strictly controlled for throughout the study. Significant changes resulted in an exclusion of the corresponding subject from the analysis. Based on the results of a preceding study,[8] we also excluded from the data analysis 17 subjects with an average attendance of less than 2 sessions per week.

A limitation of the study is its nonrandomized design. However, randomization of exercise trials is much more difficult compared with placebo-controlled pharmaceutical studies because exercise studies cannot be blinded. Therefore, in exercise studies participants often refuse to be randomized to the study arm they do not prefer. People who do not want to exercise will drop out immediately. Even worse, those subjects randomized to the CG who initially wanted to exercise may exercise without reporting, causing a bias. In particular, in long-term studies such as the EFOPS program it is difficult to convince these subjects not to take up exercise for another couple of years, which also may be ethically questionable. Even in our controlled design in which participants could select whether to exercise, 2 subjects of the CG started a weight-training program at a local fitness center.

There are conflicting data of the effect of the bias introduced by different levels of motivation or other variables in nonrandomized controlled exercise studies. With respect to bone density, Wolff et al[9] reported in their recent meta-analysis that nonrandomized exercise studies show an effect almost twice as high as randomized studies. However, in another meta-analysis of exercise studies with men, Kelley et al[10] observed the opposite effect (effect size: 1.08 [randomized] vs 0.44 [nonrandomized]). To minimize potential bias in our study, we controlled for many variables at baseline. The measurements for which the 2 groups were matched at the start of the study are given in Tables 1 and 2.

One of the main objectives of our study was to stop or reduce bone loss in early postmenopausal women. Similar exercise programs in this population report ambiguous results. Some failed to demonstrate significant BMD effects,[11-14] while others found positive effects of exercise on bone density.[15-17] To show a significant impact on bone density, the exercise intensity (strain magnitude) must be higher than the minimum effective strain threshold of bone.[18] Therefore, our program not only promotes high-strain rates but also unusual strain distributions[19] through a variety of movements during running, gaming, aerobics, jumping, and resistance and stretching sequences. Furthermore, the women in our study exercised with a reasonable training frequency of 2 to 4 ses-

Table 2. Baseline Data for Exercise and Control Groups*

Variable	Exercise Group (n = 50)	Control Group (n = 33)
DXA PA L1-L4, g/cm^2	0.874 ± 0.094	0.869 ± 0.090
DXA total hip, g/cm^2	0.857 ± 0.081	0.841 ± 0.070
DXA femoral neck, g/cm^2	0.715 ± 0.069	0.713 ± 0.070
DXA ultradistal radius, g/cm^2	0.421 ± 0.052	0.408 ± 0.050
DXA forearm, g/cm^2	0.526 ± 0.037	0.532 ± 0.044
QCT trabecular L1-L3, mg/cm^3	94.0 ± 19.9	95.9 ± 17.8
QCT cortical L1-L3, mg/cm^3	252 ± 40	258 ± 40
Osteocalcin, µg/L	24.9 ± 11.9	29.7 ± 17.4
CrossLaps, pmol/L	3224 ± 2153	3232 ± 1384
Total cholesterol, mg/dL	234 ± 39	242 ± 43
Triglycerides, mg/dL	86.5 ± 32.1	88.3 ± 33.0

Abbreviations: CrossLaps, urinary collagen type 1 cross-linked C-telopeptide; QCT, quantitative computed tomography; DXA, dual-energy x-ray absorptionmetry; PA, posterior-anterior.

SI conversion factors: To convert osteocalcin to nanomoles per liter, multiply by 0.171; to convert cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

*Data are mean ± SD unless otherwise specified. Blood samples were obtained for 34 women in the exercise group and 24 women in the control group. The difference between the groups was nonsignificant ($P \geq .05$) for all variables.

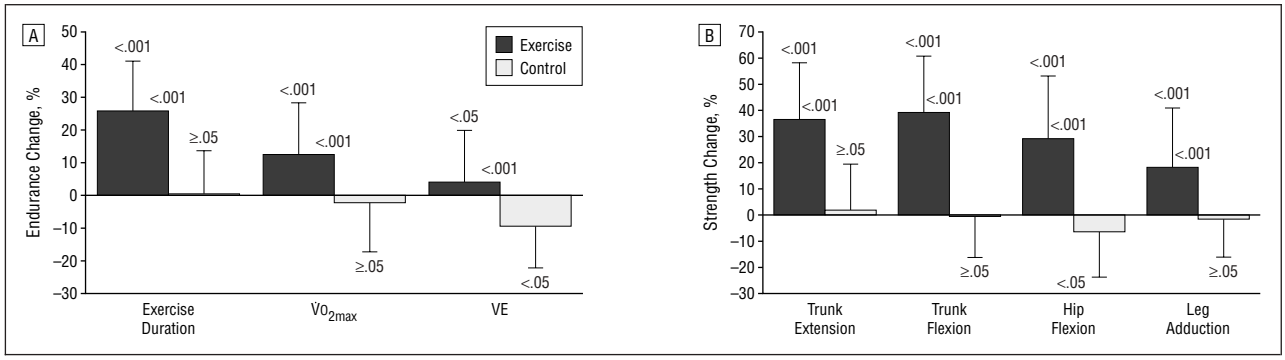

Figure 2. Changes of endurance (A) and strength (B) parameters after 26 months of intervention in the exercise and control groups. *P* values centered with respect to each bar indicate significant changes from baseline; *P* values between the bars indicate significant differences between exercise and control groups after 26 months. $\dot{V}O_{2max}$ indicates maximum oxygen uptake; VE, ventilation.

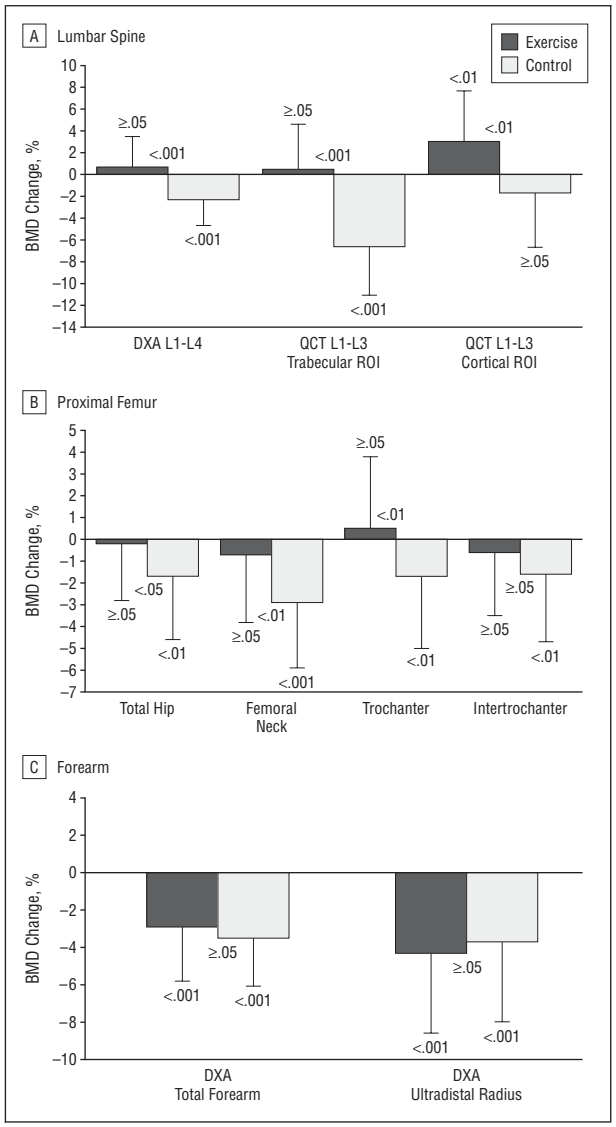

Figure 3. Changes of bone parameters for lumbar spine (A), proximal femur (B), and forearm (C) after 26 months of intervention in the exercise and control groups. *P* values centered with respect to each bar indicate significant changes from baseline; *P* values between the bars indicate significant differences between exercise and control groups after 26 months. BMD indicates bone mineral density; DXA; dual-energy x-ray absorptiometry; QCT, quantitative computed tomography; and ROI, region of interest.

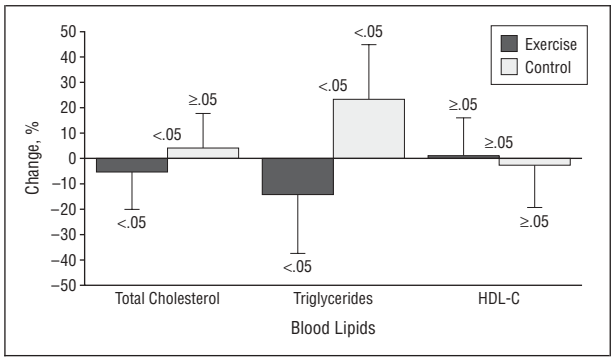

Figure 4. Changes of blood lipid levels after 26 months of intervention in the exercise and control groups. *P* values centered with respect to each bar indicate significant changes from baseline; *P* values between the bars indicate significant differences between exercise and control groups after 26 months. HDL-C indicates high-density lipoprotein cholesterol.

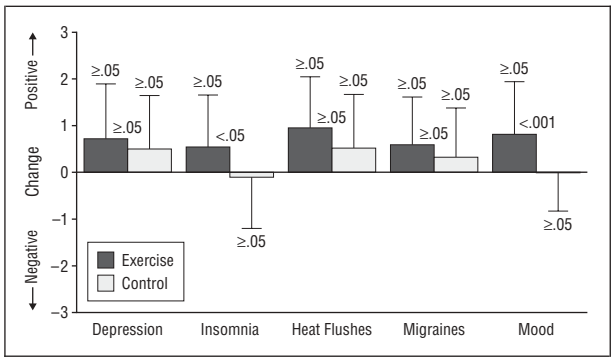

Figure 5. Changes of vasomotor symptoms related to menopause after 26 months of intervention in the exercise and control groups. *P* values centered with respect to each bar indicate significant changes from baseline; *P* values between the bars indicate significant differences between exercise and control groups after 26 months.

sions per week. Due to this mixture of training stimuli, additional benefits such as the reduction of coronary heart disease risk factors and pain were achieved simultaneously.

Endurance and strength are central parameters of physical fitness, influencing general health, falls, independence, and quality of life. Of course, these are also the primary target variables of an exercise program. In our study, isometric strength measured at various sites (Figure 2A) increased from 13.1% to 39.3% in the EG and did not significantly change in the CG, demonstrating the effectiveness of the selected training regimen. Although it is often difficult to compare exercise studies because of differing intervention periods and test protocols, our results are 15% to 25% higher than those reported by some other long-term studies (24 months) in postmenopausal women.[20,21]

A central parameter characterizing the efficacy of the cardiovascular system, $\dot{V}O_{2max}$ significantly increased in the EG (+12.4%) and nonsignificantly decreased (–2.3%) in the CG (Figure 2B). Exercise duration even increased by 25% in the EG. These results are comparable with exercise studies (≥12 months) in postmenopausal women that specifically focus on endurance[22-26] but not on bone density. This fact again highlights the versatility of the EFOPS program.

The bone density measurements further demonstrate the effectiveness of our program. The large variety of techniques and anatomical sites allowed for a detailed differentiation of the exercise effects. At the spine (Figure 3), DXA showed a 2.3% decrease in the CG, whereas BMD in the EG was stable. A differential analysis of trabecular and cortical compartments using QCT revealed that the loss in the CG was caused predominantly by the large density decrease of the metabolically more active trabecular bone (–6.6%), while BMD in the cortical region of interest did not significantly change. It must be pointed out that the cortical region of interest analyzed by QCT contains the vertebral cortex as well as some subcortical trabecular components. A change of the density measured in this region of interest can actually be caused by a true change in density but can also be caused by a change in cortical thickness or a combination of both. In the lumbar spine, exercise effectively

Table 3. Baseline and Training Effects on Pain Frequency and Intensity at Various Sites in the Exercise and Control Groups*

Variable	Exercise Group (n = 50)	Control Group (n = 33)	Difference
Pain frequency CS			
Baseline	2.36 ± 1.81	2.58 ± 1.99	≥.05
Follow-up	1.40 ± 1.84	2.67 ± 2.02	<.05
Change	<.001	≥.05	
Pain intensity CS			
Baseline	2.32 ± 1.78	2.48 ± 2.07	≥.05
Follow-up	1.36 ± 1.73	2.73 ± 2.02	<.05
Change	<.001	≥.05	
Pain frequency TS			
Baseline	1.54 ± 1.51	1.64 ± 1.87	≥.05
Follow-up	0.60 ± 1.22	1.58 ± 1.84	<.05
Change	<.001	≥.05	
Pain intensity TS			
Baseline	1.36 ± 1.40	1.55 ± 1.80	≥.05
Follow-up	0.72 ± 1.45	1.48 ± 1.77	<.05
Change	<.01	≥.05	
Pain frequency LS			
Baseline	2.74 ± 1.91	2.12 ± 1.92	≥.05
Follow-up	1.66 ± 1.78	2.82 ± 2.09	≥.05
Change	<.001	<.05	
Pain intensity LS			
Baseline	3.08 ± 1.80	2.21 ± 1.83	≥.05
Follow-up	1.72 ± 1.65	2.79 ± 2.04	≥.05
Change	<.001	≥.05	
Pain frequency main joints			
Baseline	2.98 ± 1.87	2.15 ± 1.48	≥.05
Follow-up	2.54 ± 1.84	2.64 ± 1.86	≥.05
Change	≥.05	≥.05	
Pain intensity main joints			
Baseline	2.86 ± 1.87	2.64 ± 1.83	≥.05
Follow-up	2.54 ± 1.84	2.72 ± 2.04	≥.05
Change	≥.05	≥.05	

Abbreviations: CS, cervical spine; LS, lumbar spine; TS, thoracic spine.
*Frequency and intensity data are mean ± SD; change and difference data are *P* value.

stops the decrease of trabecular BMD and significantly strengthens the cortex by thickening bone or increasing of BMD. Differential effects could not be adequately determined in the femur and the distal forearm since only DXA was available.

At the proximal femur (Figure 3), a similar trend was observed, although it was less pronounced compared with the spine. Losses in BMD in all femoral regions in the CG of up to 2.9% in the neck must be compared with small (<1%) but insignificant losses in the EG. In the trochanter, even a small increase of 0.5% was detected. These results are in line with expectations because in early postmenopausal women the femur responds more slowly to interventions compared with the spine.

At the forearm site, significant BMD reductions were observed in the EG and CG (Figure 3). This may have a number of reasons. The specific strength exercises of the EFOPS program are more tailored for the hip and the spine than for the forearm. Also, the jumping sequences primarily induce axial loads that obviously affect the forearm to a lower degree compared with the spine and hip. Nevertheless, we did not neglect the forearm. Isometric strength of the arm flexors and extenders increased significantly in the EG by 20.6% and 24.2%, respectively, compared with losses of 11.6% and 0.5% (nonsignificant) in the CG (data not included in the Figure 3). Thus, it is not entirely obvious why forearm BMD in the EG is reduced as much as in the CG.

Our exercise regimen further significantly reduced total cholesterol levels by 5% and triglyceride levels by 14% compared with an increase of 4% and 23%, respectively, in the CG. According to the 5-day nutritional analyses, it can be concluded that these changes are not caused by changes in dietary intake during the study. Changes for HDL-C and LDL-C levels as well as the apolipoproteins A and B levels were not significant in either group during the 26 months. Similar investigations in exercise studies are rather heterogeneous and depend on exercise intensity, duration, and frequency.[27,28] Most studies in postmenopausal women failed to demonstrate positive effects on total cholesterol or triglycerides.[27] Increases in HDL-C levels were observed if regular exercise intensity levels exceeded 80% HR_{max}[29] but not at lower intensity levels.[27]

Back pain is a common problem in Western civilizations. Raspe and Kohlmann[30] report back pain prevalence rates of 35% to 40% in German women between the age of 50 and 59 years, which we also found in our cohort. Thus for many people, pain reduction is high on their agenda to improve quality of life. As stated recently by Vuori,[31] physical (interventional) activity can be effective in preventing low back pain, but on the other hand, prolonged heavy loading may actually cause low back pain. In the EFOPS program, pain was not increased despite many high-impact exercises. On the contrary, pain was significantly reduced in the spine, with the highest reduction in the lumbar part (Table 3). This confirms our view that a carefully increased exercise regimen with an adequate number of recreational periods can reduce low back pain despite prolonged heavy loading. Contrary to the apprehension by Turner,[32] we also did not observe a pain increase in the knee, hip, or elbow. We attribute this positive effect in particular to the slow impact and intensity increases of the training regimen during the first months.

Finally, overall positive trends were reported with regard to the reduction of vasomotor symptoms (Figure 5); however, significant differences between the EG and CG were only found for mood and, to a lesser degree, insomnia. We have to consider that the severity of vasomotor symptoms typically decreases with time after the onset of menopause. Thus, it is understandable that we observed positive trends also in the CG. For example, 42% of the participants in the EG and 36% in the CG reported reductions of heat flushes during the intervention period.

In summary, our results demonstrate that the EFOPS design, a general purpose exercise program with special emphasis on bone density, fulfills the main objectives in preventing bone loss in early postmenopausal women, improving physical fitness, and reducing lipid levels, which are an important coronary heart disease risk factor. It also demonstrates that long-term exercise pro-

grams can be maintained with reasonable dropout and attendance rates.

Accepted for publication June 30, 2003.

We gratefully acknowledge the support of Henning Ber-Sanofi Synthelabo (Berlin, Germany) who supplied calcium and cholecalciferol for all study participants. We also acknowledge the supply of the Therabands by Thera-Band GmbH (Hadamer, Germany) and support of the Uni-Bund Erlangen.

Preliminary 26-month results of this study have been presented at the IOF World Congress on Osteoporosis; May 10-14, 2002; Lisbon, Portugal.

Corresponding author and reprints: Wolfgang Kemmler, PhD, Institute of Medical Physics, University of Erlangen, Krankenhausstr 12, 91054 Erlangen, Germany (e-mail: wolfgang.kemmler@imp.uni-erlangen.de).

REFERENCES

1. Burghardt M. Exercise at menopause: a critical difference. *Medscape Womens Health.* 1999;4:1.
2. Marcus R. Exercise: moving in the right direction. *J Bone Miner Res.* 1998;13: 1793-1796.
3. Wallace BA, Cumming RG. Systematic review of randomized trials of the effect of exercise on bone mass in pre- and postmenopausal women. *Calcif Tissue Int.* 2000;67:10-18.
4. Frost HM. The role of changes in mechanical usage set points in the pathogenesis of osteoporosis. *J Bone Miner Res.* 1992;7:253-261.
5. Kemmler W, Engelke K, Lauber D, Weineck J, Hensen J, Kalender WA. Exercise effects on fitness and bone mineral density in early postmenopausal women: 1-year EFOPS results. *Med Sci Sports Exerc.* 2002;34:2115-2123.
6. Tusker F. *Bestimmung von Kraftparameter eingelenkiger Kraftmessungen.* Aachen, Germany: Shaker Verlag; 1994.
7. Kalender WA, Klotz E, Süss C. Vertebral bone mineral analysis: an integrated approach with CT. *Radiology.* 1987;164:419-423.
8. Kemmler W, Riedel H. Körperliche Belastung und Osteoporose—Einfluß einer 10-monatigen Interventionsmaßnahme auf ossäre und extraossäre Risikofaktoren einer Osteoporose. *Dtsch Z Sportmed.* 1998;49:270-277.
9. Wolff I, van Croonenborg JJ, Kemper HC, Kostense PJ, Twisk JW. The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporos Int.* 1999;9:1-12.
10. Kelley GA, Kelley KS, Tran ZV. Exercise and bone mineral density in men: a meta-analysis. *J Appl Physiol.* 2000;88:1730-1736.
11. Bassey EJ. Exercise in primary prevention of osteoporosis in women. *Ann Rheum Dis.* 1995;54:861-862.
12. Bassey EJ, Rothwell MC, Littlewood JJ, Pye DW. Pre- and postmenopausal women have different bone mineral density responses to the same high-impact exercise. *J Bone Miner Res.* 1998;13:1805-1813.
13. Bemben DA, Fetters NL, Bemben MG, Nabavi N, Koh ET. Musculoskeletal responses to high- and low-intensity resistance training in early postmenopausal women. *Med Sci Sports Exerc.* 2000;32:1949-1957.
14. Maddalozzo GF, Snow CM. High intensity resistance training: effects on bone in older men and women. *Calcif Tissue Int.* 2000;66:399-404.
15. Revel M, Mayoux-Benhamou MA, Rabourdin JP, Bagheri F, Roux C. One-year psoas training can prevent lumbar bone loss in postmenopausal women: a randomized controlled trial. *Calcif Tissue Int.* 1993;53:307-311.
16. Pruitt LA, Jackson RD, Bartels RL, Lehnhard HJ. Weight-training effects on bone mineral density in early postmenopausal women. *J Bone Miner Res.* 1992;7: 179-185.
17. Kemmler W, Riedel H. Körperliche Belastung und Osteoporose—Einfluß unterschiedlicher Lebensabschnitte auf die Reaktion ossärer Risikofaktoren. *Dtsch Z Sportmed.* 1999;50:114-119.
18. Turner CH. Homeostatic control of bone structure: an application of feedback theory. *Bone.* 1991;12:203-217.
19. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. *J Bone Joint Surg Am.* 1984;66:397-402.
20. Heikkinen J, Kyllönen E, Kurttila-Matero E, et al. HRT and exercise: effects on bone density, muscle strength and lipid metabolism: a placebo controlled 2 year prospective trial on two estrogen-progestin regimens in healthy postmenopausal women. *Maturitas.* 1997;26:139-149.
21. Sinaki M, Wahner HW, Offord KP, Hodgson SF. Efficacy of nonloading exercises in prevention of vertebral bone loss in postmenopausal women: a controlled trial. *Mayo Clin Proc.* 1989;64:762-769.
22. Blumenthal JA, Matthews K, Fredrikson M, et al. Effects of exercise training on cardiovascular function and plasma lipid, lipoprotein, and apolipoprotein concentrations in premenopausal and postmenopausal women. *Arterioscler Thromb.* 1991;11:912-917.
23. Chow R, Harrison JE, Notarius C. Effect of two randomised exercise programmes on bone mass of healthy postmenopausal women. *BMJ.* 1987;295: 1441-1444.
24. Dalsky GP, Stocke KS, Ehsani AA, Slatopolsky E, Lee WC, Birge SJ Jr. Weight-bearing exercise training and lumbar bone mineral content in postmenopausal women. *Ann Intern Med.* 1988;108:824-828.
25. Martin D, Notelovitz M. Effects of aerobic training on bone mineral density of postmenopausal women. *J Bone Miner Res.* 1993;8:931-936.
26. Nelson ME, Fisher EC, Dilmanian FA, Dallal GE, Evans WJ. A 1-y walking program and increased dietary calcium in postmenopausal women: effects on bone. *Am J Clin Nutr.* 1991;53:1304-1311.
27. Haddock BL, Hopp Marshak HP, Mason JL, Blix G. The effect of hormone replacement therapy and exercise on cardiovascular disease risk factors in postmenopausal women. *Sports Med.* 2000;29:39-49.
28. Lokey EA, Tran ZV. Effects of exercise training on serum lipid and lipoprotein concentrations in women: a meta-analysis. *Int J Sports Med.* 1989;10:424-429.
29. Durstine JL, Haskell WL. Effects of exercise on plasma lipids and lipoproteins. *Exerc Sport Sci Rev.* 1994;22:477-521.
30. Raspe H, Kohlmann T. Rückenschmerzen—eine Epidemie unserer Tage. *Dtsch Arztebl.* 1993;90:B2165-B2169.
31. Vuori IM. Dose-response of physical activity and low back pain, osteoarthritis, and osteoporosis. *Med Sci Sports Exerc.* 2001;33(6, suppl):S551-S586.
32. Turner CH. Exercise as a therapy for osteoporosis: the drunk and the street lamp, revisited. *Bone.* 1998;23:83-85.