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ORIGINAL ARTICLE

Exercise maintains bone density at spine and hip EFOPS: a 3-year longitudinal study in early postmenopausal women

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Abstract It is an important aim in the prevention of osteoporosis to stop or decelerate bone loss during the early postmenopausal years. Here we report on results of the 3-year EFOPS exercise trial in osteopenic women. The exercise strategy emphasized low-volume high-resistance strength training and high-impact aerobics. Forty-eight fully compliant women (55.1 ± 3.3 years) with no medication or illness affecting bone metabolism participated in the exercise group (EG); 30 women (55.5 ± 3.0 years) served as non-training controls (CG). At baseline there were no significant between-group differences with respect to physical fitness, bone mineral density, pain and nutritional status. The training consisted of two group training and two home training sessions per week. The study participants of both groups were individually supplemented with calcium and vitamin D (cholecalciferol). Bone mineral density (BMD) was measured by DXA at the lumbar spine, proximal femur and distal forearm and by QCT at the lumbar spine. Speed of sound and broadband ultrasound attenuation were determined at the calcaneus by quantitative ultrasound (QUS). Pain frequency and intensity at different skeletal sites were assessed via questionnaire. After 38 months, the following within-group changes were measured: DXA lumbar spine, EG: 0.8% n.s.; CG: −3.3% $P < 0.001$; QCT trabecular ROI, EG: 1.1% n.s; CG: −7.7% $P < 0.001$; QCT cortical ROI, EG: 5.3% $P < 0.001$; CG: −2.6% $P < 0.001$; DXA total hip: EG: −0.2% n.s; CG −1.9%, $P < 0.001$; DXA distal forearm, EG: −2.8% $P < 0.001$; CG: −3.8% $P < 0.001$; BUA, EG: −0.3% n.s; CG −5.4% $P < 0.001$; SOS, EG: 0.3% n.s; CG −1.0% $P < 0.001$. At year 3 between-group differences relative to the exercise group were: DXA lumbar spine: 4.1% $P < 0.001$; QCT trabecular ROI: 8.8% $P < 0.001$; QCT cortical ROI: 7.9% $P < 0.001$; DXA total hip: 2.1%, $P < 0.001$; DXA distal forearm: 1.0% n.s.; BUA: 5.8% $P < 0.05$; SOS: 1.3% $P < 0.001$. Pain frequency and intensity in the spine significantly decreased in the exercise group and increased in the control group, while no between-group differences were detected in the main joints. In summary, over a period of 3 years our low-volume/high-intensity exercise program was successful to maintain bone mineral density at the spine, hip and calcaneus, but not at the forearm.

Keywords Bone loss · BMD · Early menopausal women · Exercise · Osteoporosis · Resistance training

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Introduction

Because of ovarian decline most women show an accelerated bone loss during early menopause [1, 2]. So far, hormone replacement therapy (HRT) has been used as a major preventive strategy, but was questioned after the publication of the WHI study [3]. As one alternative, in particular for women that according to the WHO scheme are classified as osteopenic, increased physical activity or exercise along with adequate Ca and vitamin D supplementation is often recommended to maintain bone [4]. In elderly men and women, regular exercise maintains or even increases bone mass [5, 6, 7]. However, as discussed in a recent review [8], data from studies in early postmenopausal women are less consistent (Fig. 1). Partly this is due to the inadequate control of confounding factors such as nutritional changes or diseases and medication effecting bone metabolism, partly to the small number of subjects and partly to the short study durations of often less than 12 months. Also, the exercise regimes of the studies were rather

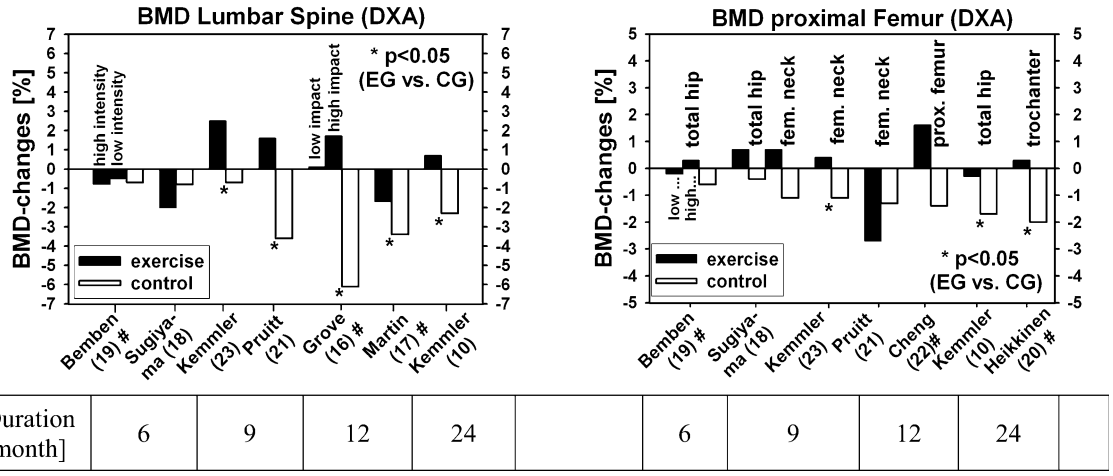

Fig. 1 BMD changes at the lumbar spine and femoral neck in women 0.5–8 years after menopause [8]. Cheng: QCT of the intertrochanteric region. #: randomized studies. Figure adopted from [8]

heterogeneous, ranging from aerobics to high-intensity resistance exercise. Furthermore, attendance rates varied severely between the studies.

To overcome some of these limitations, we designed EFOPS (Erlangen Fitness Osteoporosis Prevention Study), a long-term exercise study with low to moderate training volume, but high-resistance intensity along with high-impact aerobics and endurance for early postmenopausal women with osteopenia. These women already have an increased fracture risk, but typically still pursue an active lifestyle with regular physical activity and recreational exercise. In this contribution we specifically focus on bone mineral density changes at various skeletal sites that have been monitored over 3 years with a variety of densitometric techniques.

Materials and methods

EFOPS is a controlled exercise trial in early postmenopausal women approved by the ethics committee of the University of Erlangen (Ethik Antrag 905) and the German and Bavarian agencies for radiation protection [Bundesamt für Strahlenschutz (S9108–202/97/1) and Bayerisches Landesamt für Arbeitsschutz (13B/3443–4/5/98)]. All study participants gave written informed consent.

Subjects

Using population registers, 137 early postmenopausal (1–8 years) women were recruited from the Erlangen area. The inclusion criterion was osteopenia at the lumbar spine or total proximal femur ($-1 >$ DXA T-score > -2.5 SD). Seven thousand five hundred women aged 48–60 were contacted by mail. From 1,100 women who responded and were contacted via telephone, 618 were excluded because of secondary osteoporosis, inflammatory diseases, known osteoporotic fractures, diseases or use of medication affecting bone within 2 years before the start of the study, cardiovascular diseases, very low physical capacity at ergometry (< 75 W) and athletic activity during the last 2 decades. Out of 494 subjects screened by DXA, 225 did not meet the inclusion criterion of osteopenia. One hundred thirty-seven of the 257 remaining women agreed to participate in the trial. Based on their own decision, 86 joined the exercise and 51 the control group. Further details of the recruitment process have been described in an earlier publication [9]. The exercise group underwent the training regime described below, while participants in the control group were requested to continue their normal lifestyle. Both groups were individually supplemented with calcium and vitamin D according to their nutritional intake.

Intervention

The intervention has been described in detail elsewhere [9, 10]. Therefore, here we present a condensed description containing in particular those details relevant for this contribution. In summary, the training consisted of two group sessions per week lasting 60–70 min each and of two home training sessions per week of 25 min each.

Group training session

The group training session consisted of four sequences.

1. Warm-up/endurance sequence. A gradually increased walking and running program was carried out during the first 3 months of the study. Running games were added to promote unusual strain distributions under weight-bearing conditions. After 3 min of running, heart rates (HR) exceeded 65% HRmax, and

remained at 70–85% HRmax during the sequence. After the initial 3 months an increasing amount of high-impact aerobics concluded the sequence (20 min). Peak reaction forces measured by force plates (Erbe Medizintechnik, Tübingen, Germany) during high-impact aerobics were 1,445 ± 232 N.

2. Jumping sequence. Six months after the start of the study, a jumping phase was introduced. After initial rope-skipping, 4 different sets of 15 simple multidirectional jumps were carried out. Subjects were asked to focus on intensive take off and soft landing. Peak ground reaction forces were 1,791 ± 344 N for take off and 2,363 ± 462 N for landing.
3. Strength-training sequence. Strength training was divided into two parts, one performed with and the other without machines. During the training with machines (Techno Gym, Gambettola, Italy), 13 exercises affecting all main muscle groups were carried out. Exercise intensity was increased slowly but progressively, beginning with 2 sets of 20 repetitions (reps.) at 50% 1 repetition maximum (1 RM). Seven months after the start of the study, the training was periodized. As illustrated in Fig. 2, 12 weeks of high-intensity training (≈70–92.5% 1 RM) were interleaved by 4–5-week periods of low training intensity (50% 1 RM). During the second part of the strength training, isometric exercises and exercises with elastic belts, dumbbells and weighted vests were performed. Two to four sets of wide bench presses, one arm dumbbell rowing and squats/deadlights with weighted vests and beverage boxes were carried out parallel to the high-intensity machine training described above.
4. Flexibility training sequence. Stretching with 1–2 sets and 30 s of passive stretching for all main muscle groups was performed before and after the strength sequence and during the rest periods.

Home training session

The 20–25-min home training session, which consisted of rope skipping, isometric and belt exercises as well as stretching, was to be carried twice per week. Every 12 weeks exercises were replaced to increase intensity and maintain compliance.

Measurements

Table 1 shows the timing of the measurements reported here.

Anthropometric data

Anthropometric data consisted of height, weight, circumference measurements of various sites and body composition. Body composition was measured using the impedance technique (Tanita BF 305, Tanita, Japan).

Bone mineral density

Dual X-ray absorptiometry (DXA) was performed at the lumbar spine (L1–L4), the proximal femur and the forearm (QDR 4500a, Hologic, Bedford, Mass.) using standard protocols. In addition, at the lumbar spine (L1–L3) quantitative computed tomography (QCT) was carried out (Somatom Plus 4, Siemens, Erlangen, Germany) using the Osteo protocol [11]. Quantitative ultrasound (QUS) parameters were measured with a Sahara machine (Hologic, Bedford, Mass.) using the protocol specified by the manufacturer.

Questionnaire

Our baseline questionnaire was subdivided into different parts: (1) well being, (2) pain frequency and intensity at the cervical, thoracic and lumbar spine and at the main joints according to the protocol proposed by the Osteoporosis Quality of Life Study Group [12], (3) pre-study exercise levels, (4) normal daily load levels due to work, household and gardening activities and (5) common osteoporotic risk factors.

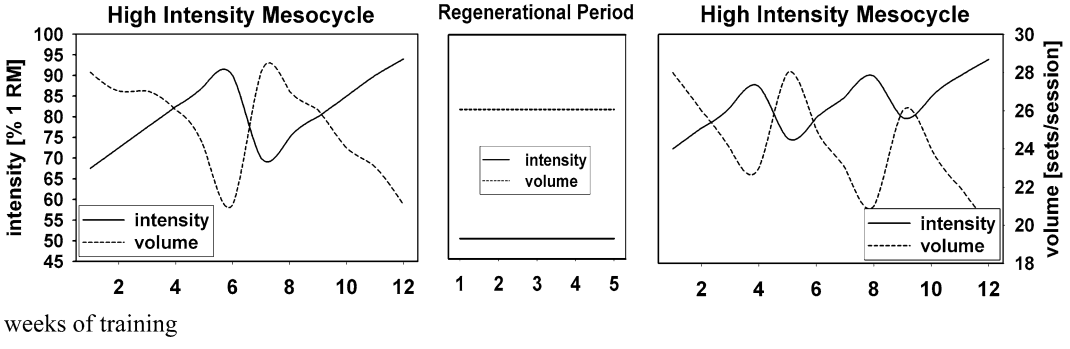

Fig. 2 Scheme of our periodized resistance protocol. Two high-intensity mesocycles (12 weeks each) were interleaved by a 5-week regeneration period with constant intensity (50% 1 RM) and volume (13 exercises with 2 sets and 20 reps)

Table 1 Timing of EFOPS measurements

	Screening	Baseline	Follow-up 1	Follow-up 2	Follow-up 3
Time to study start	−3.5 months	−2 months	14 months	26 months	38 months
Anthropometric data		X	X	X	X
DXA: PA L1–L3 and femur	X		X	X	X
DXA forearm		X		X	X
QCT L1-L3		X		X	X
Questionnaire		X	X	X	X
Nutritional analysis		X	X	X	X

During the intervention period additional questionnaires were used to track changes in diseases and medications, lifestyle and sportive activities outside the EFOPS training program. The reproducibility of the questionnaires had been tested in an earlier study [13].

Nutritional analysis and calcium/vitamin D supplementation

Individual 5-day dietary records were used to assess nutritional intake. The analysis was performed in close relationship with the Department of Sports Medicine of the University of Bayreuth using Prodi-4.5/03 expert (Wissenschaftlicher Verlag, Freiburg, Germany). Based on the calcium and vitamin D analysis, participants in the training as well as in the control group were individually supplemented with calcium and cholecalciferol to ensure a total daily intake of 1,500 mg calcium and 500 IE vitamin D.

Statistical analysis

Normality of distribution and homogeneity of variance were determined using the Kolgomorov-Smirnov test and Levine's F -test. For normally distributed variables, paired t -tests were used to detect within-group changes; for non-normally distributed variables the Wilcoxon test was used. Differences between the exercise and control groups were analyzed using an analysis of variance (ANOVA) with repeated measurement design using absolute values of the measurements. The within-group factor was the point of measurement (baseline and14, 26 and 38 months); the between-group factor was exercise versus control. The number of years after menopause was used as covariate in all analyses where bone parameters were dependent variables. No other covariates were used. At specific time points we also compared between-group changes using paired t - or Wilcoxon tests. Here, percent changes relative to baseline were used. All tests were two-tailed; a 5% probability level was considered significant (*).SPSS 12.0 (SPSS Inc., Chicago) was used for all statistical analyses

Results

Sixty-eight women of the exercise and 36 of the control group completed the 3-year follow-up visit corresponding to drop-out rates of 21 and 29%, respectively (Table 2). Training attendance, averaged over 3 years, was 77% for the group and 61% for the home sessions, resulting in an annual weekly average of 2.4 sessions. Forty-eight women of the exercise and 30 of the control group were included in the analysis. Ten women had to

Table 2 Reasons why and times when subjects left the study or were excluded from analysis

	Exercise group	Control group
Included at baseline:	86	51
Drop-outs	18	15
Reasons for drop-out		
Occupational changes or relocation to other city	8	6
Diseases[1]	5	3
Study-related reasons	3	3
Lost interest	2	3
Time of drop-out		
During year 1	13	8
During year 2	2	3
During year 3	3	4
Invited to follow-up year 3	68	36
Excluded from follow-up analysis	20	6
Diseases with impact on bone	3	2
Medication with impact on bone	2	3
Attendance rate <2 sessions/week	15	-
Significant increment of physical activity	-	1
Included in 3-year analysis	48	30

[1]Not related to training activities

be excluded because of diseases or medication affecting bone metabolism. One woman of the control group was excluded because she had started an exercise program. According to the study protocol, 15 women of the exercise group were excluded from the analysis because of poor training compliance, defined as less than two exercise sessions per week [13] averaged over the whole study period.

The most relevant baseline measurements are given in Table 3. Mean values and variances were not significantly different between the exercise and control group. Differences remained non-significant for the 78 subjects included in the 3-year follow-up analysis. Also, when comparing the baseline data for cohorts admitted into the study with those included in the 3-year analysis, there were no significant differences for either the exercise or control group.

After 38 months of training, slight but non-significant between-group differences were observed for weight (EG: $-1.1 \pm 4.3\%$ vs. CG: $0.3 \pm 4.0\%$), %fat (EG: $-2.2 \pm 6.3\%$ vs. CG: $-0.2 \pm 6.2\%$) and LBM (EG: $-0.2 \pm 4.3\%$ vs. CG: 0.1 ± 4.3). No significant differences were observed for energy, phosphorous, calcium and vitamin D intake.

Results of various bone measurements are given in Figs. 3 and 4. After 3 years, within-group BMD changes at the lumbar spine relative to baseline in the exercise group were: DXA: $+0.8\%$, n.s.; QCT trabecular ROI: $+1.1\%$, n.s.; QCT cortical ROI: $+5.3\%$; $P < 0.001$. In the CG LS-BMD significantly decreased: DXA: -3.3%, $P < 0.001$; QCT trabecular ROI: -7.7%, $P < 0.001$; QCT cortical ROI: -2.6%; $P < 0.01$). Between-group differences as analyzed by the ANOVA with repeated measures with adjustment for years after menopause were significant ($P < 0.001$) for all spinal measurements. Significance levels of between-group differences at a given time point are indicated in the figures.

At the proximal femur, BMD was maintained (-0.2%, n.s.) in the EG, while a significant reduction occurred in the CG (-1.9%; $P < 0.001$), (Fig. 4).

Table 3 Baseline data of exercise (EG) and control groups (CG). Columns 2–4 show baseline data for the complete study population; columns 5–7 show baseline data for those subjects included in the 3-year analysis. Loss to follow-up was 41% in both groups. Neither in the exercise nor in the control group were significant differences found between the subjects included at baseline and those included in the analysis for any of the variables

Variable	Included at baseline			Included in 3-year follow-up analysis		
	EG ($n=86$)	CG ($n=51$)	P	EG ($n=48$)	CG ($n=30$)	P
Age (years)	55.1 ± 3.3	55.8 ± 3.1	n.s.	55.2 ± 3.3	55.5 ± 3.0	n.s.
Height (cm)	163.8 ± 6.8	162.4 ± 6.6	n.s.	163.9 ± 6.6	162.7 ± 6.9	n.s.
Weight (kg)	67.6 ± 9.6	67.0 ± 13.6	n.s.	68.1 ± 9.6	67.3 ± 11.9	n.s.
Total body fat (%)	36.0 ± 5.0	35.0 ± 7.2	n.s.	36.3 ± 5.3	34.9 ± 5.6	n.s.
Waist to hip ratio	0.82 ± 0.07	0.81 ± 0.07	n.s.	0.82 ± 0.06	0.81 ± 0.07	n.s.
Age at menarche (years)	13.4 ± 1.4	13.3 ± 1.6	n.s.	13.4 ± 1.4	13.3 ± 1.5	n.s.
Age at menopause (years)	50.5 ± 3.3	50.4 ± 3.1	n.s.	50.4 ± 3.3	50.5 ± 3.4	n.s.
Years since menopause	4.6 ± 2.1	5.4 ± 2.1	n.s.	4.8 ± 2.2	5.0 ± 2.2	n.s.
Number of pregnancies	2.0 ± 1.1	1.9 ± 1.3	n.s.	2.0 ± 1.2	2.0 ± 1.3	n.s.
VO2max (l/min)[1]	1.77 ± 0.40	1.75 ± 0.31	n.s.	1.78 ± 0.45	1.73 ± 0.35	n.s.
Isometric strength trunk extensors (Nm)[3]	104.1 ± 34.9	107.4 ± 36.3	n.s.	100.2 ± 31.6	103.5 ± 39.9	n.s.
Isometric strength trunk flexors (Nm)[3]	56.6 ± 18.9	51.6 ± 19.5	n.s.	55.5 ± 18.6	50.5 ± 15.4	n.s.
Isometric strength hip flexors (Nm)[3]	37.6 ± 10.8	36.7 ± 13.4	n.s.	37.6 ± 10.8	36.7 ± 13.4	n.s.
Physical activity[2]	4.1 ± 1.3	4.0 ± 1.2	n.s.	4.2 ± 1.3	4.1 ± 1.3	n.s.
Energy intake[3](kJ/day)	7731 ± 1366	7577 ± 2143	n.s.	8164 ± 1255	7751 ± 1730	n.s.
Calcium intake[3](mg/day)	1055 ± 379	989 ± 290	n.s.	1035 ± 397	971 ± 287	n.s.
Phosphorus intake[3](mg/day)	1299 ± 368	1175 ± 338	n.s.	1311 ± 324	1220 ± 308	n.s.
Vit. D intake[3](µg/day)	5.1 ± 4.1	5.5 ± 5.3	n.s.	5.7 ± 4.5	5.5 ± 5.1	n.s.
Osteoporosis of parents or siblings (% per group)	16%	14%	n.s.	17%	20%	n.s.
Corticosteroids (>5 mg/day) or thyroxin (≥75 mg/day) for more than 6 months during lifetime (% per group)	11%	12%	n.s.	10%	13%	n.s.
Coffee intake (ml/day)	766 ± 345	815 ± 365	n.s.	753 ± 329	787 ± 312	n.s.
Smokers (% per group)	9%	10%	n.s.			n.s.
DXA PA L1-L4 (g/cm^2)	0.874 ± 0.094	0.869 ± 0.090	n.s.	0.876 ± 0.087	0.878 ± 0.098	n.s.
QCT trabecular L1-L3 (mg/cm^3)	94.0 ± 18.4	95.9 ± 12.8	n.s.	92.0 ± 18.4	96.7 ± 12.8	n.s.
QCT cortical L1-L3 (mg/cm^3)	251.7 ± 40.4	257.5 ± 40.0	n.s.	248.6 ± 42.8	260.4 ± 45.4	n.s.
DXA total Hip (g/cm^2)	0.857 ± 0.081	0.841 ± 0.070	n.s.	0.852 ± 0.078	0.847 ± 0.071	n.s.
DXA forearm (g/cm^2)	0.526 ± 0.037	0.532 ± 0.044	n.s.	0.528 ± 0.038	0.531 ± 0.036	n.s.

[1]Methods have been described extensively elsewhere [9]. [2]Based on a scale from 1 (very low) to 7 (very high) according to a subjective assessment of professional, household and recreational activities. [3]Five-day dietary analysis

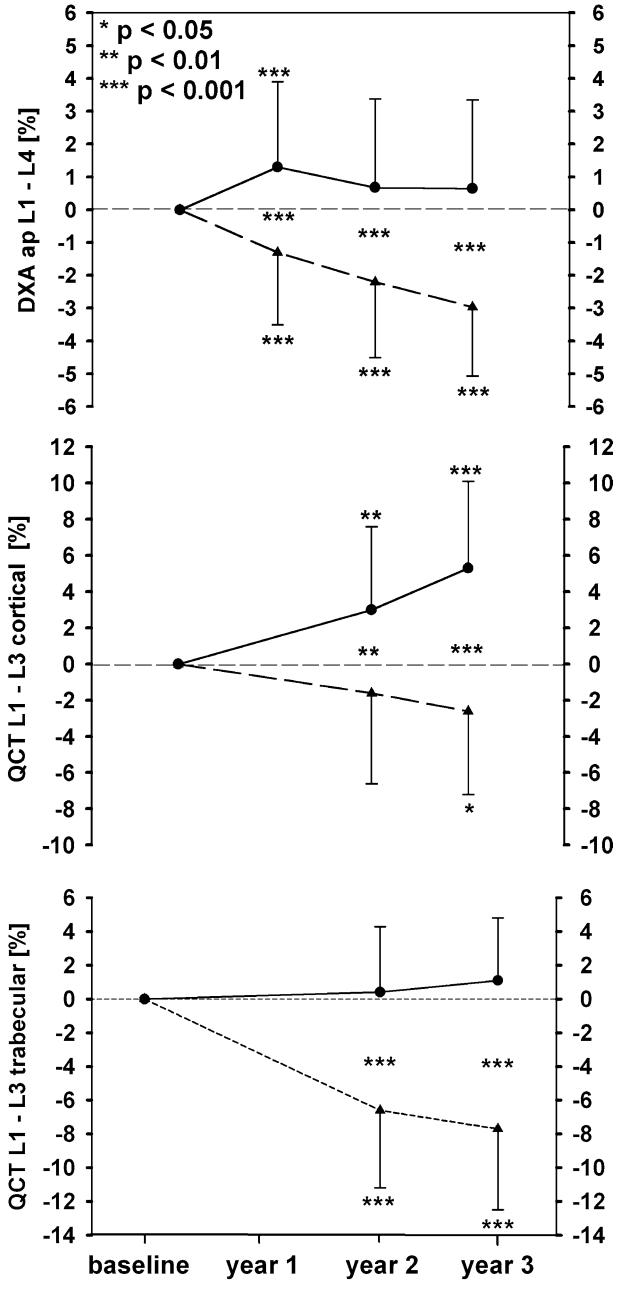

Fig. 3 Relative changes in bone mineral density at the lumbar spine. Levels of significance are indicated for within-group differences relative to baseline and for between-group differences for a given time point. QCT was not measured at the end of year one

Between-groups differences again were significant. At the distal forearm (EG: −2.8%; CG: −3.8%; both $P < 0.001$) (Fig. 4) as well as on the ultra distal forearm (EG: −4.0; CG: −4.6; both $P < 0.001$), both groups lost BMD significantly. The ANOVA analysis did not result in any significant between-group differences.

Results of the BUA and SOS measurements at the calcaneus are presented in Fig. 5. After 3 years of exercise, SOS and BUA were maintained in the EG, while significant ($P < 0.001$ and $P < 0.01$) reductions of −0.9% for SOS and −5.4% for BUA were observed in the CG. Annual changes for BUA and SOS within both groups were rather heterogeneous during the study course. The ANOVA analysis resulted in significant between-group differences ($P < 0.001$).

In the spine, pain frequency and intensity significantly decreased in the EG and increased in the CG. Table 4 shows for all time points the significance levels relative to baseline. For the main joints there were no within-group changes in pain. Consistent with this basic analysis, the ANOVA showed significant between-group differences ($P < 0.001$) for the lumbar spine pain intensity and frequency, but not for the main joints.

Discussion

In this contribution we demonstrated the positive long-term effect of a combined endurance, jumping and high-intensity resistance training on bone density in early postmenopausal women. The negative effect of ovarian failure on BMD was compensated. This is highly important because early postmenopause is characterized by an accelerated bone loss [1]. It is still speculative whether our program was successful, because after hormonal depletion higher strains may be needed to stimulate bone [14, 15].

In contrast to most of the other exercise studies in early postmenopausal women [16, 17, 18, 19, 20, 21, 22, 23] (Fig. 1), our study possesses several strengths: (1) The study duration (3 years) was longer, and the number of subjects analyzed ($n = 78$) was higher than in other exercise studies [7]. (2) Disease incidence and changes of medication, nutrition or life style were extensively monitored during the 3-year period. Menopausal age was included in the analysis as a covariate. (3) Training contents and exercise intensities were periodized and individually adapted. (4) There was a long (6–7 months) phasing-in period to adapt the participants to the more strenuous exercises. (5) Exercise attendance and compliance during the study were high [24, 25]; based on the results of a previous study [13], we excluded subjects with low training frequencies (less than two sessions/week). (6) Bone mineral density was measured at different sites and with different techniques. (7) All study subjects were optimally supplemented with calcium and vitamin D according to their nutritional intake.

Two potential limitations of our study are the lack of randomization and a relatively large (early) postmenopausal age range of 1–8 years. The design of a non-blinded randomized study is difficult because subjects may refuse to participate in the arm to which they are randomized. This effect will generate a bias. Also, in particular in long-term exercise studies where cross-over designs cannot be used, participants may drop out early; even worse, subjects randomized to exercise may not exercise properly and subjects willing to exercise but randomized to the control group may exercise without reporting. Of course, a comparison of the bias

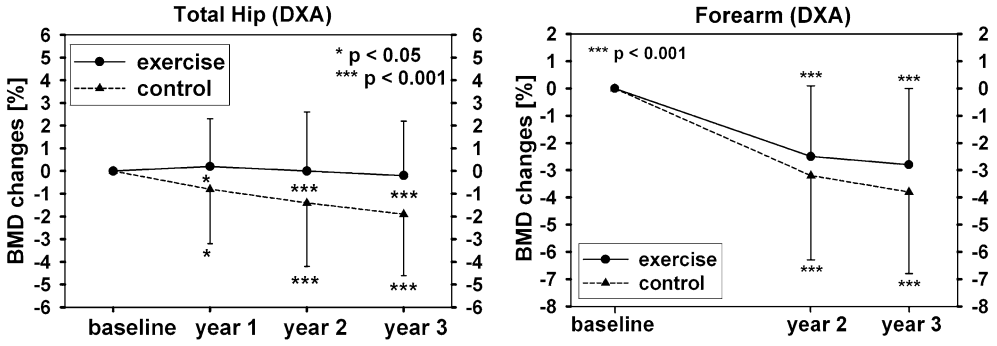

Fig. 4 Relative changes in bone mineral density at the proximal femur and the forearm. Levels of significance are indicated for within-group differences relative to baseline and for between-group differences for a given time point. Forearm was not measured after year one

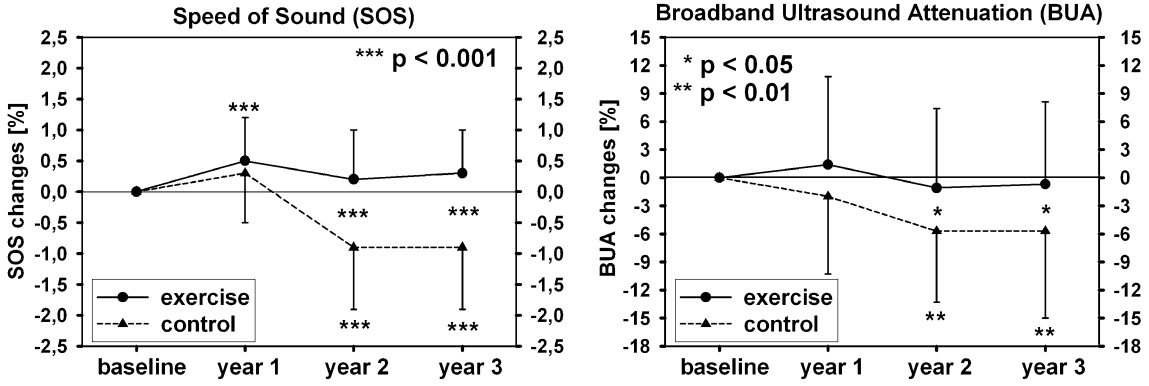

Fig. 5 Relative changes of speed of sound (SOS) and broadband ultrasound attenuation (BUA) at the calcaneus. Levels of significance are indicated for within-group differences relative to baseline and for between-group differences for a given time point

Table 4 Baseline and follow-up data for pain frequency and intensity at the lumbar spine and the main joints in the EG and CG. Pain scale ranged from 1 (very seldom/very low) to 7 (very often/very heavy)

Variable/time course	EG ($n=48$)	CG ($n=30$)
Pain frequency LS baseline	3.04 ± 1.99	2.24 ± 1.97
Pain frequency LS year 1	2.36 ± 2.06*	2.94 ± 2.12*
Pain frequency LS year 2	1.91 ± 1.85***	3.15 ± 2.06*
Pain frequency LS year 3	2.00 ± 1.80***	3.13 ± 2.05*
Pain intensity LS baseline	3.21 ± 1.80	2.24 ± 1.90
Pain intensity LS year 1	2.45 ± 2.04*	2.94 ± 2.12*
Pain intensity LS year 2	1.96 ± 1.78***	3.06 ± 1.87*
Pain intensity LS year 3	2.19 ± 1.83***	3.03 ± 1.92*
Pain frequency main joints[1] baseline	2.81 ± 1.88	2.22 ± 1.58
Pain frequency main joints[1] year 1	2.98 ± 1.91	2.61 ± 1.88
Pain frequency main joints[1] year 2	2.60 ± 2.04	2.91 ± 1.91
Pain frequency main joints[1] year 3	3.04 ± 1.87	2.83 ± 1.82
Pain intensity main joints[1] baseline	2.70 ± 1.76	2.55 ± 1.84
Pain intensity main joints[1] year 1	2.43 ± 1.93	2.76 ± 1.95
Pain intensity main joints[1] year 2	2.57 ± 1.96	2.64 ± 2.04
Pain intensity main joints[1] year 3	2.42 ± 1.94	2.80 ± 2.01

* $P < 0.05$; *** $P < 0.001$. [1]Main joints: ankle, knee, hip, shoulder, elbow and hand. Significant levels apply to within-group changes relative to baseline

introduced by either design, randomized or not, has not been published so far, but two independent meta-analyses came to opposite conclusions. Wolff et al. [7] report that non-randomized exercise studies showed positive changes twice as high as randomized studies; Kelley et al. [5] showed the opposite effect. For EFOPS we selected a non-randomized design, but at baseline there were no significant differences between control and exercise groups with respect to physical fitness, bone mineral density, pain and nutritional status (Table 3).

The early postmenopausal age range of 1 to 8 years used as an inclusion criterion includes the phase of rapid bone loss immediately after menopause and the transition to the subsequent period of lower bone loss rates. Exercise effects may be different in these two phases; however, we selected this age range in accordance with

other authors [26, 27, 28]. Although there were no differences in postmenopausal age between the exercise and the control group, we included this parameter as a covariate in the ANOVA.

In the spine we observed increasing between-group differences with increasing study duration. This was caused by stabilization of BMD in the exercise group and a continued loss in the control group. However, the BMD loss in the CG was slightly smaller than expected from the literature. Typical averaged values for 1–8-year postmenopausal women range from −1.5 to −2.0% p.a. [1, 2] at the LS. However, one must consider that our participants were optimally supplemented with calcium and vitamin D.

In the exercise group, trabecular BMD changes measured by QCT were similar to those measured by DXA, but were twice as high (7.7 versus 3.0%) in the control group. The higher sensitivity of spinal QCT is also underscored by the cortical measurement where actually an increase of BMD was observed in the exercise group. One should caution that due to the limited spatial resolution of the CT technique, a measured increase in cortical BMD can also be caused by an increase in cortical thickness [29]. However, BMD and thickness contribute to bone strength.

The proximal femur was only measured by DXA. The results show the same tendency as those in the spine, BMD stabilization in the exercise and significant loss in the control group, with a significant between-group difference. As expected, the loss in the control group is about 50% of that in the spine. We also observed positive exercise effects on the calcaneus. To our knowledge, long-term QUS results from exercise studies have not been reported so far. In a 12-month study. Jones et al. [30] demonstrated significant BUA increases relative to sedentary controls in their brisk walking group. In accordance with the set point theory, positive changes in their postmenopausal exercise group were lower than in pre- and perimenopausal women.

The picture is very different in the forearm, where no training effects were observed. Detailed results were given for the total forearm, but there were no differences for the other ROIs (1/3, mid- and ultradistal). It is known that under pharmaceutical treatment BMD changes at the forearm are often negligible and are not in agreement with those at the spine and hip. Nevertheless, we had expected between-group differences because the exercise strategy was comparable for the upper extremities and the axial skeleton. The intensity and volume of the resistance sequence did not differ. One potential explanation surfaced during a retrospective review after 2 years. Most exercises for the upper extremities focused on axial extension, bending and torsion, while only one exercise (bench press) promoted direct axial compression. A volume increase for this exercise by 50–75% during the third training year had no significant effect, however. But one has to consider that compared to the axial skeleton, direct axial compression with high strain rates (i.e., jumping) was not applied at the upper extremities.

A review of the literature [6, 24, 25] shows that with some exceptions [31, 32, 33, 34, 35, 36, 37] the majority of studies in postmenopausal women also failed to demonstrate significant positive effects at the forearm. The exercise regimes of those studies that did show positive results varied widely from Tai Chi [31, 36] via non-site-specific resistance training [33, 34, 35] to site-specific resistance training [32, 37, 38]. Thus, it is difficult to draw final conclusions with respect to exercise protocol optimization for the forearm.

The EFOPS exercise strategy is rather pragmatic. Under the premise that early postmenopausal woman are usually unwilling to spend a large amount of time for prevention, the available time should be used most effectively. Therefore, the training volume of our approach was low to moderate ($\leq$ 3 h/week), but subjects exercised with moderate to high intensity (i.e., high-strain magnitude and rate). The exercise regimen should affect bone along multiple pathways. During the initial warm-up sequence (running and games), exercise intensity was moderate [39, 40], but cycle number ($>$ 1,000 cycles) and strain frequency (2–4 Hz) were high. According to Cullen et al. [41], high cycle numbers compensate for strain magnitudes that are slightly below the adaptive threshold of bone. Furthermore, within the range of deliberate motion ($<$ 4 Hz.), Turner et al. [42] demonstrated significantly higher bone formation rates after higher strain frequencies (2 Hz) compared with lower frequencies ($<$ 0.5 Hz).

High-impact aerobics and jumping as performed in our first and second training sequence produced high-strain magnitudes and rates [39, 40] along with unusual strain distributions [43], factors that positively affect bone. The resistance training was characterized by high strain magnitudes, low strain rates, low cycle numbers, low strain frequencies ($\approx$0.25 Hz) and long rest periods (2–3 min) between the loading blocks. These rest periods may be important to prevent short-term desensitization [44, 45, 46]. Turner et al. [47] reported higher increments of bone strength exercising 2×5 weeks with an intermittent 5-week rest period than with 15 weeks of continuous exercise. Although our ''regenerational exercise periods'' do not promote full recovery, exercise intensity during these periods was rather low compared to the high-intensity periods ($\approx$50% 1 RM vs. $\approx$70–92.5% 1 RM, Fig. 2). Thus, long-term desensitization could be prevented by our training protocol embedded in periodized meso- and macrocycles.

The EFOPS exercise protocol was also designed to activate large muscle groups with sufficient volume and intensity, factors that may increase the concentration of hormones [48] that are important for bone metabolism and calcium homeostasis. Indeed, after monitoring a typical EFOPS training session, we could demonstrate significant serum concentration increases of DHEAS, estradiol, free testosterone, hGH and IGFBP-3 [49].

It is very important that despite the high-intensity strategy, pain did not increase in the exercise group. In contrast, a recent study [6] cautioned against the application of prolonged heavy loading. Our results do not support the statement, ''what is good for the bones is bad for the joints'' [50]. We attribute our positive findings to several factors: (1) the slow increment of exercise intensity and impact during the first study months; (2) complete exhaustion of the participants by maximizing the number of repetitions at a given load was not a training aim; (3) ''recreational exercise periods'' interrupted the heavy-loading periods (Fig. 2); (4) the intensity and volume within the heavy-loading periods varied.

In summary, our results show that dedicated exercise programs can maintain bone mineral density at the axial skeleton even during the early postmenopausal years. If we add the positive exercise effects on other (early) postmenopausal risk factors [51] and consider that pain was not increased, we recommend dedicated long-term exercise programs as a potential alternative to hormone replacement therapy.

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References

1. Okano H, Mizunuma H, Soda M, Kagami I, Miyamoto S, Ohsawa M, Ibuki Y, Shiraki M, Suzuki T, Shibata H (1998) The long-term effect of menopause on postmenopausal bone loss in Japanese women: results from a prospective study. J Bone Miner Res 13:303–309
2. Shipman AJ, Guy GW, Smith I, Ostlere S, Greer W, Smith R (1999) Vertebral bone mineral density, content and area in 8,789 normal women aged 33–73 years who have never had hormone replacement therapy. Osteoporos Int 9:420–426
3. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, LeBoff M, Lewis CE, McGowan J, Pettinger M, Stefanick ML, Wactawski-Wende J, Watts NB (2003) Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 290:1729–1738
4. Burghardt M (1999) Exercise at menopause: a critical difference. Medscape Womens Health 4:1
5. Kelley GA, Kelley KS, Tran ZV (2000) Exercise and bone mineral density in men: a meta-analysis. J Appl Physiol 88:1730–1736
6. Vuori IM (2001) Dose-response of physical activity and low back pain, osteoarthritis, and osteoporosis. Med Sci Sports Exerc 33:S551–S586
7. Wolff I, van Croonenborg JJ, Kemper HC, Kostense PJ, Twisk JW (1999) The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. Osteoporos Int 9:1–12
8. Kemmler W, Engelke K (2004) A critical review of exercise training effects on bone mineral density (BMD) in early postmenopausal women. Int Sportmed J 5:67–77
9. Kemmler W, Engelke K., Lauber D, Weineck J, Hensen J, Kalender WA (2003) The Erlangen Fitness Osteoporosis Prevention Study (EFOPS)—a controlled exercise trial in early postmenopausal women with low bone density: first year results. Arch Phys Med Rehabil 84:673–683
10. Kemmler W, Engelke K, Lauber D, Weineck J, Hensen J, Kalender WA (2004) Impact of intense exercise on physical fitness, quality of life, and bone mineral density in early postmenopausal women. Year 2 results of the Erlangen Fitness Osteoporosis Prevention Study (EFOPS). Arch Int Med 164:1084–1091
11. Kalender WA, Klotz E, Süss C (1987) Vertebral bone mineral analysis: an integrated approach with CT. Radiology 164:419–423
12. Investigators (1997) Measuring quality of life in women with osteoporosis. The Osteoporosis Quality of Life Study Group. Osteoporos Int 7:478–487
13. Kemmler W, Riedel H (1998) Körperliche Belastung und Osteoporose—Einfluß einer 10 monatigen Interventionsmaßnahme auf ossäre und extraossäre Risikofaktoren einer Osteoporose. Dtsch Z Sportmed 49:270–277
14. Turner CH (1991) Homeostatic control of bone structure: an application of feedback theory. Bone 12:203–217
15. Frost HM (1992) The role of changes in mechanical usage set points in the pathogenesis of osteoporosis. J Bone Miner Res 7:253–261
16. Grove KA, Londeree BR (1992) Bone density in postmenopausal women: high impact vs low impact exercise. Med Sci Sports Exerc 24:1190–1194
17. Martin D, Notelovitz M (1993) Effects of aerobic training on bone mineral density of postmenopausal women. J Bone Miner Res 8:931–936
18. Sugiyama T, Yamaguchi A, Kawai S (2002) Effects of skeletal loading on bone mass and compensation mechanism in bone: a new insight into the ''mechanostat'' theory. J Bone Miner Metab 20:196–200
19. Bemben DA, Fetters NL, Bemben MG, Nabavi N, Koh ET (2000) Musculoskeletal responses to high- and low-intensity resistance training in early postmenopausal women. Med Sci Sports Exerc 32:1949–1957
20. Heikkinen J, Kyllönen E, Kurttila-Matero E, Wilén-Rosenqvist G, Lankinen KS, Rita H, Väänänen HK (1997) 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 26:139–149
21. Pruitt LA, Jackson RD, Bartels RL, Lehnhard HJ (1992) Weight-training effects on bone mineral density in early postmenopausal women. J Bone Miner Res 7:179–185
22. Cheng S, Sipila S, Taaffe DR, Puolakka J, Suominen H (2002) Change in bone mass distribution induced by hormone replacement therapy and high-impact physical exercise in postmenopausal women. Bone 31:126–135
23. Kemmler W (1999) Einfluß unterschiedlicher Lebensabschnitte auf die belastungsabhängige Reaktion ossärer Risikofaktoren einer Osteoporose. Dtsch Z Sportmed 50:114–119
24. Kelley GA (1998) Exercise and regional bone mineral density in postmenopausal women: a meta-analytic review of randomized trials. Am J Phys Med Rehabil 77:76–87
25. Wallace BA, Cumming RG (2000) Systematic review of randomized trials of the effect of exercise on bone mass in pre- and postmenopausal women. Calcif Tissue Int 67:10–18
26. Bailey DA, McCulloch RG (1990) Bone tissue and physical activity. Can J Sport Sci 15:229–239
27. Birkhäuser M (1991) Postmenopausale Osteoporose: Pathophysiologie und Prophylaxe. Schweizerische Rundschau Medizin (Praxis) 80:418–422
28. Ettinger B (1988) Prevention of osteoporosis: treatment of estradiol deficiency. Obstet Gynecol 72:1–6
29. Prevrhal S, Engelke K, Kalender WA (1999) Accuracy limits for the determination of cortical width and density: the influence of object size and CT imaging parameters. Phys Med Bio 44:751–764
30. Jones PRM, Hardmann AE, Hudson A, Norgan NG (1991) Influence of brisk walking on the ultrasonic attenuation of the calcaneus in previously sedentary women aged 30–61 years. Calcif Tissue Int 49:112–115

31. Chan K, Qin L, Lau M, Woo J, Au S, Choy W, Lee K, Lee S (2004) A randomized, prospective study of the effects of Tai Chi Chun exercise on bone mineral density in postmenopausal women. Arch Phys Med Rehabil 85:717–722
32. Kerr D, Morton A, Dick I, Prince R (1996) Exercise effects on bone mass in postmenopausal women are site-specific and load-dependent. J Bone Miner Res 11:218–225
33. McMurdo ME, Mole PA, Paterson CR (1997) Controlled trial of weight bearing exercise in older women in relation to bone density and falls. BMJ 314:569
34. Preisinger E, Alacamlioglu Y, Pils K, Saradeth T, Schneider B (1995) Therapeutic exercise in the prevention of bone loss. Am J Phys Med Rehabil 74:120–123
35. Preisinger E, Alacamlioglu Y, Pils K, Bosina E, Metka M, Schneider B, Ernst E (1996) Exercise therapy for osteoporosis: results of a randomised controlled trial. Br J Sports Med 30:209–212.
36. Qin L, Au S, Choy W, Leung P, Neff M, Lee K, Lau M, Woo J, Chan K (2002) Regular Tai Chi Chuan exercise may retard bone loss in postmenopausal women: a case-control study. Arch Phys Med Rehabil 83:1355–1359
37. Simkin A, Ayalon J, Leichter I (1987) Increased trabecular bone density due to bone-loading exercises in postmenopausal osteoporotic women. Calcif Tissue Int 40:59–63
38. Adami S, Gatti D, Braga V, Bianchini D, Rossini M (1999) Site-specific effects of strength training on bone structure and geometry of ultradistal radius in postmenopausal women. J Bone Miner Res 14:120–124
39. Burr DB, Milgrom C, Fyhrie D, Forwood M, Nyska M, Finestone A, Hoshaw S, Saiag E, Simkin A (1996) In vivo measurement of human tibial strains during vigorous activity. Bone 18:405–410
40. Milgrom C, Miligram M, Simkin A, Burr D, Ekenman I, Finestone A (2001) A home exercise program for tibial bone strengthening based on in vivo strain measurements. Am J Phys Med Rehabil 80:433–438
41. Cullen DM, Smith RT, Akhter MP (2001) Bone-loading response varies with strain magnitude and cycle number. J Appl Physiol 91:1971–1976
42. Turner CH, Forwood MR, Otter MW (1994) Mechanotransduction in bone: do bone cells act as sensors of fluid flow? Faseb J 8:875–878
43. Rubin CT, Lanyon LE (1984) Regulation of bone formation by applied dynamic loads. J Bone Joint Surg Am 66:397–402
44. Robling AG, Burr DB, Turner CH (2001) Recovery periods restore mechanosensitivity to dynamically loaded bone. J Exp Biol 204:3389–3399
45. Srinivasan S, Gross TS (2000) Intermittend rest enhances osteoblastic activation induced by mechanical loading. Trans Orthop Res Soc 25:628
46. Umemura Y, Sogo N, Honda A (2002) Effects of intervals between jumps or bouts on osteogenic response to loading. J Appl Physiol 93:1345–1348
47. Turner CH, Robling AG (2004) Exercise as an anabolic stimulus for bone. Curr Pharm Des 10:2629–2641
48. Kraemer WJ (1992) Endocrine responses and adaptions to strength training. In: Komi V (ed) Strength and power in sport. Blackwell, Oxford, pp 291–304
49. Kemmler W, Wildt L, Engelke K, Pintag P, Pavel M, Bracher B, Weineck J, Kalender W (2003) Acute hormonal responses of a high impact physical exercise session in early postmenopausal women. Eur J Appl Physiol 90:199–209
50. Turner CH (1998) Exercise as a therapy for osteoporosis: the drunk and the street lamp, revisited. Bone 23:83–85
51. Kemmler W, Lauber D, von Stengel S, Weineck J, Kalender WA, Engelke K (2005) Exercise effects on risk factors in early postmenopausal women: 3y EFOPS results. Med Sci Sports Exerc 37:194–203