ARTHRITIS & RHEUMATISM
Vol. 50, No. 4, April 2004, pp 1066–1076
DOI 10.1002/art.20117

Slowing of Bone Loss in Patients With Rheumatoid Arthritis by Long-Term High-Intensity Exercise

Results of a Randomized, Controlled Trial

Zuzana de Jong,[1] Marten Munneke,[1] Willem F. Lems,[2] Aeilko H. Zwinderman,[1] Herman M. Kroon,[1] Ernest K. J. Pauwels,[1] Annemarie Jansen,[3] Karel H. Ronday,[4] Ben A. C. Dijkmans,[5] Ferdinand C. Breedveld,[1] Theodora P. M. Vliet Vlieland,[1] and Johanna M. W. Hazes[6]

Objective. **Patients with rheumatoid arthritis (RA) are more at risk for the development of osteoporosis and osteoporotic fractures than are their healthy peers. In this randomized, controlled, multicenter trial, the effectiveness of a 2-year high-intensity weight-bearing exercise program (the Rheumatoid-Arthritis-Patients-In-Training [RAPIT] program) on bone mineral density (BMD) was compared with usual care physical therapy, and the exercise modalities associated with changes in BMD were determined.**

Methods. **Three hundred nine patients with RA were assigned to an intervention group, either the RAPIT program or usual care physical therapy. The primary end points were BMD of the hip and spine. The exercise modalities examined were aerobic fitness, muscle strength, and, as a surrogate for those effects not directly measured by the RAPIT program, attendance rate.**

Results. **The data on the 136 RAPIT participants and 145 usual care participants who completed the study were analyzed. The mean rate of decrease in hip BMD, but not in lumbar spine BMD, was smaller in patients participating in the RAPIT program when compared with that in the usual care group, with a mean decrease of 1.6% (95% confidence interval [95% CI] 0.8–2.5) over the first year and 0.5% (95% CI 1.1–2.0) over the second year. The change in hip BMD was significantly and independently associated with changes in both muscle strength (multivariate odds ratio [OR] 1.75, 95% CI 1.07–2.86) and aerobic fitness (OR 1.79, 95% CI 1.10–2.90), but not with the attendance rate (OR 1.00, 95% CI 0.99–1.00).**

Conclusion. **A long-term high-intensity weight-bearing exercise program for RA patients is effective in slowing down the loss of BMD at the hip. The exercise modalities associated with this effect are muscle strength and aerobic fitness.**

Patients with rheumatoid arthritis (RA) are, as a consequence of their disease and its treatment, more at risk of developing osteoporosis and osteoporotic fractures than are their healthy peers (1–5). Pain (due to both joint inflammation and joint damage), fatigue, and also the common advice of the attending physicians, who often advise against high-intensity weight-bearing exercises, lead to a decrease in physical activities. Consequently, aerobic fitness and muscle strength decline (6,7).

In a healthy population, long-term exercise can

Supported by the College Voor Zorgverzekeringen (the Dutch Health Care Insurance Board) grant OG-97-024 to the Rheumatoid-Arthritis-Patients-In-Training project.

[1]Zuzana de Jong, MD, Marten Munneke, MSc, Aeilko H. Zwinderman, PhD, Herman M. Kroon, MD, Ernest K. J. Pauwels, PhD, Ferdinand C. Breedveld, MD, Theodora P. M. Vliet Vlieland, MD, PhD: Leiden University Medical Center, Leiden, The Netherlands; [2]Willem F. Lems, MD: Vrije Universiteit Medical Center, Amsterdam, The Netherlands; [3]Annemarie Jansen, PhD: Jan van Breemen Instituut, Amsterdam, The Netherlands; [4]Karel H. Ronday, MD: Leyenburg Hospital, The Hague, The Netherlands; [5]Ben A. C. Dijkmans, MD: Leiden University Medical Center, Leiden and Jan van Breemen Instituut, Amsterdam, The Netherlands; [6]Johanna M. W. Hazes, MD, PhD: Leiden University Medical Center, Leiden and Erasmus Medical Center, Rotterdam, The Netherlands.

Address correspondence and reprint requests to Zuzana de Jong, MD, Department of Rheumatology C4-R, Leiden University Medical Center, Post-box 9600, 2300 RC Leiden, The Netherlands.

Submitted for publication May 27, 2003; accepted in revised form December 11, 2003.

be effective in increasing the bone mineral density (BMD) of the sites loaded. In this respect, only exercises of moderate or high intensity have been proven effective, and their effect seems to be site specific (8,9). Moreover, long-term leisure-time physical activity appears to protect against later hip fracture (10), possibly by improving balance and coordination and thereby diminishing the risk of falling.

As yet, only a limited number of trials investigating the effectiveness of exercise on BMD in RA patients have been performed. However, none of these trials has been able to demonstrate an effect (11–13). Their negative results might be due to factors such as insufficient loading of the sites measured or a low number of participants in these studies.

A recent large randomized, controlled trial (the Rheumatoid-Arthritis-Patients-In-Training [RAPIT] trial) showed that RA patients were able to improve their aerobic fitness and muscle strength by engaging in long-term, high-intensity weight-bearing exercise without experiencing detrimental effects on the disease activity or on the progression of radiologic damage of the large joints (with the exception of patients with significant radiologic joint damage) (14). In the present report, we analyzed the data from this trial to determine whether a long-term, high-intensity, weight-bearing exercise program is also able to prevent the loss of BMD. Furthermore, we examined which exercise modalities are important to the change in BMD in patients with RA.

PATIENTS AND METHODS

Study population. In 1997, all patients with RA who were registered in 4 outpatient rheumatology clinics and who were assumed to meet the inclusion criteria were invited by mail to participate in the trial on the effectiveness and safety of long-term, high-intensity weight-bearing exercises. To participate in the RAPIT trial, patients had to fulfill the following criteria: diagnosis of RA according to the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised classification criteria for RA (15), age between 20 and 70 years, ACR functional class of I–III (16), stable use of disease-modifying antirheumatic drugs (DMARDs) during the 3 months before inclusion, and ability to cycle on an exercise bicycle. Patients were excluded if they reported having cardiac and/or pulmonary disease precluding high-intensity exercise. Patients with prostheses of the weight-bearing joints, as well as patients with comorbidity strongly reducing their life expectancy, were also excluded. Patients willing to participate who still met the inclusion criteria after a screening by 2 trained investigators (ZdJ and AJ), and who gave their written informed consent, were subsequently randomized. The medical ethics committees of all the participating centers approved the study protocol.

Study design. Permutated blocked randomization (blocks of 4) with stratification for center, age (<50 years and >50 years), and sex, made up by a random digit generator, was used to allocate the patients to the intervention groups, consisting of either a high-intensity exercise program (RAPIT) or usual care physical therapy. An administrative assistant, who was not aware of the block size, allocated the interventions.

In March/April 1998, the patients randomized to the RAPIT group started participation in a supervised, twice-weekly, group exercise program of 1¼ hours each session. This exercise program was aimed at increasing and maintaining cardiovascular and muscle fitness (strength and endurance) and included both weight-bearing and impact-loading exercises. Overall, each session had 3 parts: bicycle training (20 minutes), exercise circuit (20 minutes), and sport or game (20 minutes). Each training component was preceded by a warm up that included impact-bearing exercises, such as stepping aside and stair walking, and ended with a cool down period.

Bicycle training started with continuous vigorous bicycling (cycling frequency 50–70 revolutions per minute) for 5 minutes. Within 6 months, the duration of vigorous bicycling was increased to 18 minutes. Bicycle load was based on 2 indicators: 1) heart rate during bicycling, and 2) rating of perceived exertion (RPE) (17). Heart rate during the bicycle training had to be between ~70% and 90% of the predicted maximal heart rate. Prediction of maximal heart rate was calculated with the formula 220 − age. A rating of 4–5 on the RPE (range 0–10) was expected to reflect an effort with enough intensity to improve cardiovascular fitness (18,19).

The exercise circuit consisted of 8–10 different exercises intended to improve muscle strength, aerobic fitness, muscle endurance, joint mobility, and activities of daily living (for example, walking, turning around in bed, getting up, lifting). Exercises were interspersed with rest. The proportions of exercise duration and rest duration changed from 90 seconds and 60 seconds, respectively, in the first weeks of the program to 90 seconds and 30 seconds, respectively, after 6 months. Each exercise was repeated ~8–15 times. The exercises within the exercise circuit were changed every 8 weeks.

The sport or game component consisted of badminton, volleyball (with a softer ball, if necessary), indoor soccer (with a low-weight ball), basketball, relay games, or pat-catch games. If necessary, the program was adapted to individual limitations to achieve the same training goals. A group of supervisors from all participating centers met every 8 weeks to evaluate the actual training circuit and to develop a new circuit and to ensure the uniformity of the exercise program in all centers.

Patients assigned to the usual care group were treated by a physical therapist only if deemed necessary by their attending physician. In both groups, the physicians had free choice with respect to medical prescriptions and any other treatment strategies, including additional individual physical therapy.

The number of RAPIT group sessions attended was recorded and expressed as a percentage of the maximum possible number of attended sessions. Attendance at any group or individual physical therapy sessions other than those of the RAPIT group was recorded in both intervention groups.

The attending physicians were informed about the treatment allocation and the results of each BMD measurement, including a suggestion for treatment with bisphospho-

nates as indicated by the current Dutch guidelines. The guidelines recommend treatment with bisphosphonates for patients with osteopenia (T score less than or equal to −1.0) who are currently taking prednisone and/or for any patient with osteoporosis (T score less than or equal to −2.5).

At baseline, sociodemographic characteristics were registered, as well as postmenopausal status (yes/no), body mass index, disease duration, presence of rheumatoid factor (yes/no), ACR functional class (16), past use of DMARDs (number) and glucocorticoids (ever/never), and current use of medication.

At baseline and every 3 months thereafter, the participants reported on their use of medication in the past 3 months, and their disease activity and physical capacity were assessed. BMD and radiologic joint damage were assessed at baseline and at 12 and 24 months.

The use of medication, such as oral glucocorticoids, hormone replacement therapy, bisphosphonates, and vitamin D and/or calcium supplementation, was expressed as the number of months that the patients reported the use of the respective drug. Since the trial lasted 24 months, the duration of use of each drug could therefore vary from 0 to 24 months. The use of DMARDs at each followup visit was compared with the use at the previous visit and coded by a clinician (ZdJ) into 3 categories: 0 = change of DMARD or change in dosage of current DMARD due to decreased disease activity, 1 = no change in DMARD or dosage of current DMARD, and 2 = change of DMARD or change in dosage of current DMARD due to increased disease activity. The numbers were summed up over the whole study period and thus could, after 2 years, vary from 16 (maximum increase due to increasing disease activity) to 0 (maximum decrease due to decreasing disease activity during the 2 years).

Disease activity was assessed with the original Disease Activity Score with 4 variables (DAS4). The DAS4 is a compiled index based on the number of swollen joints (maximum 44), tender joint score (Ritchie Articular Index), Westergren erythrocyte sedimentation rate, and the patient's global assessment of disease activity measured on a visual analog scale ranging from 0 (asymptomatic) to 100 (worst possible disease activity) (20). The DAS4 ranges from 0 (no disease activity) to 10 (severe disease activity). To express the change in disease activity during the 2-year study period, the area under the curve (AUC) was calculated from the combined 3-month assessments of disease activity.

Physical capacity was determined by aerobic fitness and muscle strength. Aerobic fitness was measured by a standardized ergometer test, with results expressed in watts (21). Muscle strength of the knee extensors was measured by an isokinetic dynamometer at 60°/second, with results expressed in newtons (22).

All clinical outcome assessments were done by 4 research physical therapists who were blinded to the treatment allocation and who were trained thoroughly both before the trial and after 1 year. During the study, the majority of the participants were assessed by the same assessor. A reproducibility study in 19 successive patients was performed at the last study visit and 2 weeks afterward by the same assessor, which yielded intrarater intraclass correlation coefficients (ICCs) for aerobic fitness, muscle strength, swollen joint count, and Ritchie Articular Index of 0.97, 0.98, 0.83, and 0.92, respectively.

Functional ability was assessed with the Health Assessment Questionnaire (HAQ) (23,24). The HAQ score was assessed at baseline and every 6 months thereafter. The total HAQ score ranges from 0 (no functional limitations) to 3 (serious functional limitations). The change score can thus vary from −3 (maximal improvement) to +3 (maximal deterioration).

BMD measurements of the hip (the total hip region) and of the lumbar spine (involving L1–L4) were carried out using a dual-photon X-ray absorptiometer (DXA), with results expressed in gm/cm^2. The scanning and standard quality procedures were followed. All measurements in each patient were performed using the same DXA. The in vitro reproducibility, expressed as the coefficient of variation, was 3.7% and 2.6% for the hip and 0.8% and 0.3% for the spine by Hologic QDR-2000 (Amsterdam, The Netherlands) and Hologic QDR-4500 (Leiden and The Hague, The Netherlands), respectively.

Radiologic damage of the small joints (the hands and feet) was assessed using the method devised by Larsen and modified by Scott et al (25). The following joints were assessed: the 10 proximal interphalangeal joints, the 10 metacarpophalangeal joints, the wrists (scored as one unit and multiplied by 5), the second to fifth metatarsophalangeal joints, and the first interphalangeal joints. According to this method, the Larsen score of the small joints varies from 0 (no joint space narrowing, no erosions) to 200 (maximum possible damage to the joints) and is a sum of both joint space narrowing and erosions of the hands and feet. All radiographs were scored by a single observer (AC) who was given no information about the chronology, patient's identity, and group allocation. The ICC for radiologic damage of the small joints, based on repeated readings of the 15 radiographs of the small joints by a single observer, was 0.97.

Radiologic damage of the large joints (the shoulders, elbows, hips, knees, ankles, and subtalar joints) was scored independently by 2 experienced readers (HK and ZdJ) also using the Larsen method (26). The Larsen score of the large joints ranges from 0 (no joint space narrowing, no erosions) to 60 (maximal possible damage to the large joints). The Larsen score presented is the mean of the scores of the 2 readers. The ICC for radiologic damage of the large joints, based on all readings of the 2 readers, was 0.95.

Statistical analysis. The target sample size was based on an estimated mean ± SD loss of BMD in RA patients of 4.12 ± 6.25% over 2 years (27). To demonstrate a complete inhibition of bone loss by the high-intensity exercise when compared with usual care, and based on 90% power to detect a significant difference (2-sided $P = 0.05$), a sample size of 48 patients would be required in each study group. To compensate for an expected dropout rate of ~20%, we needed to enroll at least 58 patients in each study group. However, the RAPIT study was primarily designed with the HAQ score as a primary outcome variable. To detect a difference of 0.20 in the change of HAQ score (14), the target sample size was calculated at 150 patients per group. Thus, a final cohort of 300 patients was enrolled.

Final analyses, which were based on intention to treat as initially assigned, were performed on the data from the 281

patients who completed the study (designated "completers"). At all times, measures with a Gaussian distribution are expressed as the mean and SD, and measures with a non-Gaussian distribution are the median and interquartile range (IQR). Bone mass is expressed as BMD (in gm/cm^2) and is also presented as T and Z scores. Osteoporosis was defined as a T score of less than or equal to −2.5 SD (28). Reduced bone mass was defined as a Z score of less than or equal to −1 SD.

To compare the effectiveness of the treatment over the total period of 2 years, BMD was further analyzed with a mixed-effects analysis of variance (ANOVA) model, with patient number as a random factor and treatment, time, and the treatment-by-time interaction as fixed effects. The effect analysis was performed after correction for the baseline differences.

The patient cohort was also analyzed according to individual bone loss. The individual changes in BMD values from baseline to followup (followup minus baseline) were divided in tertiles. The patients with the most BMD loss (lowest tertile) were designated as fast losers, while the patients with the least BMD loss or increased BMD (highest tertile) were gainers. The patients with slow loss (middle tertile) were designated as slow losers. Bivariate analyses (Mann-Whitney U test, Pearson's chi-square test) were used for comparisons between 2 groups, while Kruskal-Wallis test and Pearson's chi-square test were used for comparison between more than 2 groups.

Multivariate analyses were used to explore the relationships between the dependent variable, change in BMD at the total hip site, and the independent variables, the clinical characteristics that can be modified by treatment. The individual changes in muscle strength and aerobic fitness were dichotomized. Patients showing a decrease in muscle strength or aerobic fitness were designated as muscle strength or aerobic fitness losers, while patients showing an increase were gainers. The analyses were performed as a polytomous logistic regression model with BMD changes categorized in tertiles. Based on the results of the multivariate analysis and supposed clinical relevance, the variables were successively removed from the multiple regression model in a backward manner. All analyses were performed using SPSS program, version 10.0 (Chicago, IL). *P* values less than or equal to 0.05 were considered statistically significant.

RESULTS

Study participants. The recruitment procedure is shown in Figure 1. Of the 1,736 patients who were assumed to fulfill the inclusion criteria after their records were screened, and who were thus invited by mail to participate in the study (target population), 126 could not be reached and 1,219 declined participation due to reasons mainly related to required investment in time and expenses such as travel to the center. Thus, 391 patients were assessed for eligibility by the investigators, and 309 patients were then randomly assigned for participation. Nine randomized patients (1 to the RAPIT group and 8 to the usual care group) refused participation immediately after randomization. Over the period of 2 years, 5 patients allocated to the usual care group and 14 patients allocated to the RAPIT group withdrew from the trial for different reasons. There was no difference between the completers and the noncompleters of the RAPIT trial with respect to sociodemographic and disease-related characteristics (data not shown).

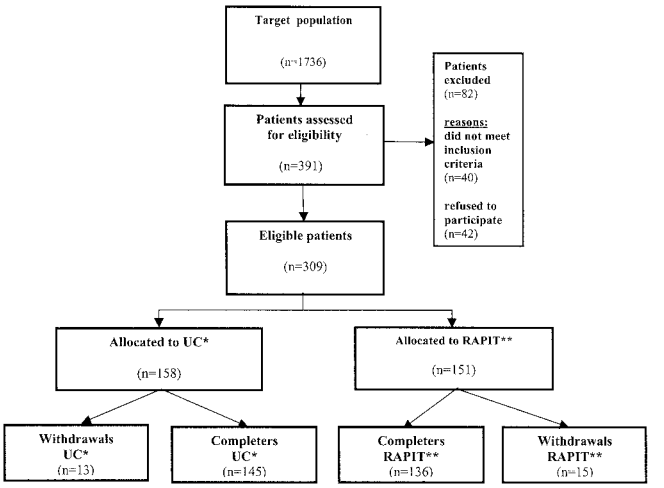

Figure 1. Recruitment procedure. * = usual care (UC) physical therapy; ** = Rheumatoid-Arthritis-Patients-In-Training (RAPIT) exercise program.

In addition to the patients who withdrew, 14 other RAPIT group participants failed to attend the exercise classes in the course of the study but were regularly evaluated with the group. The patients who withdrew from the RAPIT exercise classes did not differ in either sociodemographic or disease-related characteristics from those who did not withdraw. The median percentage of sessions attended was 74% (IQR 55%, 75%). Averaged over 2 years, 30% of all participants had a sufficient attendance rate (defined as 50–75% attendance) and 49% had a high attendance rate (defined as 75–100% attendance). After 2 years, 281 patients completed the study (completers).

Baseline characteristics. The baseline characteristics of the study completers are shown in Tables 1 and 2. At baseline, there were slight differences between the usual care and the RAPIT group participants. The disease duration in the RAPIT group participants was shorter compared with that in participants in usual care, and the RAPIT participants had less damage of the small joints.

Use of glucocorticoids and bisphosphonates. At baseline, no differences were found in the past and

Table 1. Baseline characteristics of the 281 study completers*

	Usual care (n = 145)	RAPIT (n = 136)
Demographic variables		
Age, years	54 (45, 62)	54 (46, 61)
Body mass index, kg/m^2	26.0 (23.0, 28.7)	26.0 (23.7, 29.2)
Female, no. (%)	115 (79)	110 (81)
Postmenopausal, no. (%) of females	75 (54)	63 (46)
Disease-related variables		
Disease duration, years	7.0 (3.0, 14.0)	5.0 (3, 9.5)†
Rheumatoid factor positive, no. (%)	101 (70)	96 (71)
ACR functional classes I/II/III, no. (%)	31 (21)/60 (42)/54 (37)	21 (15)/75 (55)/40 (30)
Number of DMARDs in the past	2 (1, 2)	1 (1, 2)
DAS4 (0–10)	3.36 (2.13, 4.15)	3.24 (2.64, 4.03)
HAQ score (0–3)	0.63 (0.16, 1.00)	0.63 (0.25, 1.13)
Radiologic joint damage		
Larsen score hands and feet (0–200)	37.5 (9.8, 64.3)	24.0 (2.0, 56.5)†
Larsen score large joints (0–60)	2 (0.0, 5.0)	1.5 (0.0, 4.5)
Physical capacity		
Aerobic fitness, watts	162 (126, 200)	162 (126, 200)
Quadriceps strength, newtons	83 (58, 115)	84 (64, 105)

* Except where indicated otherwise, values are the median (interquartile range [25th, 75th percentile]). RAPIT = Rheumatoid-Arthritis-Patients-In-Training; ACR = American College of Rheumatology; DMARDs = disease-modifying antirheumatic drugs; DAS4 = Disease Activity Score with 4 variables; HAQ = Health Assessment Questionnaire.
† $P < 0.05$ by Mann-Whitney U test, and chi-square test where appropriate.

current use of oral glucocorticoids and/or in the current use of bisphosphonates between the completers of the usual care and RAPIT groups (Table 2). Only 11% of the completers had ever taken glucocorticoids in the past, while 9% were currently receiving glucocorticoids and 2.5% were currently receiving bisphosphonates.

Table 2. Baseline bone mineral density (BMD) characteristics and medication of the 281 study completers*

	Usual care (n = 145)	RAPIT (n = 136)
BMD		
Hip		
BMD, gm/cm^2	0.906 (0.824, 1.011)	0.912 (0.800, 1.01)
Z score	0.06 (−0.71, 0.77)	0.03 (−0.71, 0.85)
Z score < −1.0, no. (%)	25 (17.2)	28 (20.6)
T score	−0.67 (−1.40, −0.02)	−0.72 (−0.15, 0.23)
T score < −2.5, no. (%)	6 (4.1)	8 (5.9)
Lumbar spine		
BMD, gm/cm^2	1.007 (0.882, 1.102)	0.994 (0.884, 1.110)
Z score	0.37 (−0.52, 1.05)	0.22 (−0.68, 1.23)
Z score < −1.0, no. (%)	28 (19.3)	23 (16.9)
T score	−0.44 (−1.64, 0.48)	−0.54 (−1.59, 0.51)
T score < −2.5, no. (%)	12 (8.3)	14 (10.3)
Past medication, no. (%)		
Ever used glucocorticoids	15 (10.3)	16 (11.8)
Current medication, no. (%)		
DMARD	130 (90)	111 (82)
Glucocorticoids	14 (10)	11 (8)
Vitamin D	2 (1)	2 (2)
Calcium supplements	10 (7)	11 (8)
Hormone replacement therapy	3 (2.2)	2 (1.5)
Bisphosphonates	4 (3)	3 (2)

* Except where indicated otherwise, values are the median (interquartile range [25th, 75th percentile]). See Table 1 for other definitions.

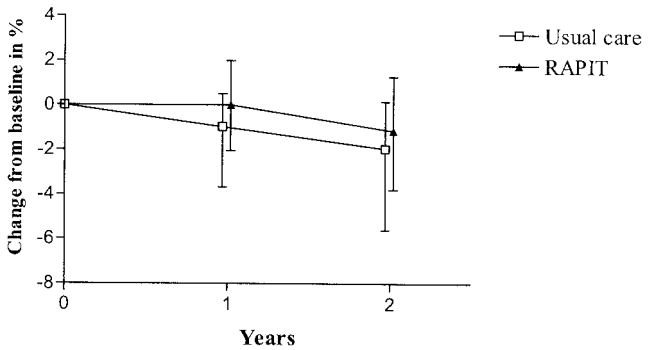

Figure 2. Percentage of change in bone mineral density of the total hip in the 2 years of the trial in patients randomized to receive either usual care physical therapy or to undergo the Rheumatoid-Arthritis-Patients-In-Training (RAPIT) exercise program. Bars show the median and interquartile range.

After 2 years of the trial, no differences were noted in the use of oral glucocorticosteroids or bisphosphonates. A long-term (>6 months) use of oral glucocorticoids and of bisphosphonates was reported by 34 completers (12%) and 19 completers (7%), respectively.

Effectiveness of the long-term, high-intensity exercise on changes in BMD. In 9 completers, the change in BMD could not be calculated due to missing values. None of the measurements were missing at baseline. At followup after 1 year, measurements were missing from 1 participant (usual care group), and after 2 years, BMD measurements were missing from 8 completers (5 in usual care and 3 in the RAPIT group).

Figure 2 demonstrates that after 1 year, the total hip BMD remained stable in the RAPIT group (median change 0.0% [IQR −2.0, 2.0]) and decreased in the usual care group (median change 1.0% [IQR −3.7, 0.5]) ($P < 0.01$). After 2 years of the trial, the hip BMD decreased by a median 1.1% (IQR −3.8, 1.3) and 1.9% (IQR −5.6, 0.2) in the RAPIT group and in the usual care group, respectively ($P = 0.06$). The mean rate of decrease in hip BMD, but not in the lumbar spine BMD, was smaller by 1.6% (95% CI 0.8–2.5) over the first year and by 0.5% (95% CI 1.1–2.0) over the second year in the RAPIT group compared with the usual care group. Furthermore, when analyzed by mixed-effects ANOVA, the mean between-group difference in change of hip BMD over the 2 years was statistically significant ($P = 0.026$).

Figure 3 demonstrates that after 1 and 2 years of the trial, the lumbar spine BMD in both the RAPIT group and the usual care group increased. After 1 year, the median increase amounted to 1.1% (IQR −0.7, 2.3) in the RAPIT group and 0.9% (IQR −1.2, 3.2) in the usual care group ($P = 0.759$). After 2 years, the median increase from baseline amounted to 0.9% (IQR −1.5, 3.1) in the RAPIT group and 0.9% (IQR −1.7, 3.2) in the usual care group ($P = 0.738$). When analyzed with mixed-effects ANOVA, the mean between-group difference in change in lumbar spine BMD over the 2 years was not statistically significant ($P = 0.697$).

The conclusions of the analysis were essentially unchanged even when the patients who reported long-term use of glucocorticoids and/or bisphosphonates (n = 48) were omitted from the analysis.

Factors associated with change in hip BMD after 2 years. Since no differences between the RAPIT and usual care groups were found in changes of the lumbar spine BMD, only the changes in hip BMD after 2 years were further analyzed. The individual changes in hip BMD from baseline were categorized in 3 groups (tertiles), with 91 patients in each tertile. The fast losers of hip BMD lost a median of −6.3% (IQR −8.4, −4.3), the slow losers lost −1.6% (IQR −2.3, −0.9), and the gainers gained 2.1% (IQR 0.7, 3.8).

Table 3 shows the distribution of the demographic and disease-related characteristics at baseline among the fast losers, slow losers, and gainers of BMD at the hip. Except for sex, no statistically significant associations were present between these characteristics and the changes in BMD. Female sex was most frequent in the fast losers group ($P < 0.05$). In addition, fast losers of BMD were slightly more often participants in the usual care physical therapy, were older, had somewhat more disease activity (higher DAS4), more damage of the small and large joints, lower hip BMD, and the

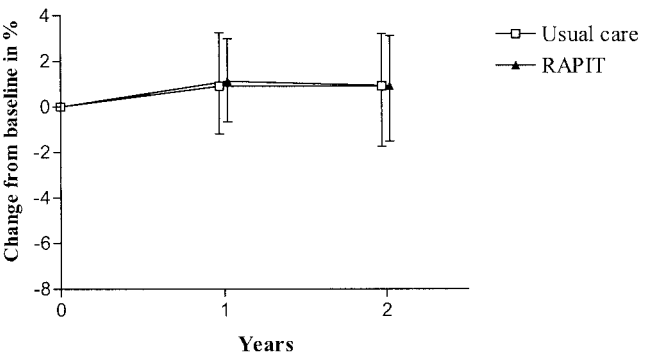

Figure 3. Percentage of change in bone mineral density of the lumbar spine in the 2 years of the trial in patients randomized to receive either usual care physical therapy or to undergo the Rheumatoid-Arthritis-Patients-In-Training (RAPIT) exercise program. Bars show the median and interquartile range.

Table 3. The distribution of the demographic and disease-related baseline characteristics within completers with fast loss, slow loss, and gain in bone mineral density (BMD) of the hip after 2 years*

	No. of patients in each tertile	Fast losers BMD	Slow losers BMD	Gainers BMD
Participants in RAPIT/UC group, no. (%)	91/91/91	37 (41)/54 (59)	45 (50)/46 (50)	51 (56)/40 (44)
Age, years, median (IQR)	91/91/91	55 (48, 61)	54 (43, 62)	53 (41, 61)
Body mass index, kg/m^2, mean ± SD	91/91/91	26.6 ± 4.1	26.2 ± 5.3	27.2 ± 5.4
Female, no. (%)	91/91/91	79 (87)	75 (82)	66 (73)†
Duration of RA, years, median (IQR)	90/90/89	5 (3, 13)	7 (3, 12)	6 (3, 9)
Baseline DAS4, mean ± SD	90/91/91	3.4 ± 1.1	3.1 ± 1.2	3.3 ± 1.3
Baseline Larsen score small joints, median (IQR)	89/89/89	32.0 (0.0, 62.0)	32.0 (7.0, 71.5)	29.0 (9.5, 60.0)
Baseline Larsen score large joints, median (IQR)	89/91/88	2.0 (0.0, 5.0)	1.5 (0.0, 4.5)	1.5 (0.0, 4.5)
Baseline muscle strength, newtons, median (IQR)	91/90/89	77.5 (56.0, 102.0)	86.8 (64.4, 112.4)	84.0 (61.0, 109.0)
Baseline aerobic fitness, watts, median (IQR)	87/91/91	161.9 (125.8, 199.7)	161.9 (125.8, 199.7)	180.4 (125.7, 218.9)
Baseline hip BMD, gm/cm^2, median (IQR)	91/91/91	0.884 (0.813, 1.002)	0.906 (0.815, 0.994)	0.937 (0.804, 1.022)

* RAPIT = Rheumatoid-Arthritis-Patients-In-Training; UC = usual care physical therapy; IQR = interquartile range (25th, 75th percentile); RA = rheumatoid arthritis; DAS4 = Disease Activity Score with 4 variables.
† $P < 0.05$ by Kruskal-Wallis test.

worst physical capacity at baseline, but these differences did not reach statistical significance.

Table 4 shows the distribution of the change characteristics in fast losers and slow losers of hip BMD. It demonstrates that an increase in physical capacity is associated with an increase in hip BMD ($P < 0.05$). Although the differences between the groups were not statistically significant, fast losers appeared to be patients who had a lower attendance rate, who had more active disease, who were taking glucocorticoids more frequently but bisphosphonates and vitamin D less frequently, and who acquired more radiologic damage of the small joints.

Factors associated with change in hip BMD after 2 years that can be responsive to an intervention. In order to establish which factors might be responsive to an intervention, we performed univariate analysis to explore the factors possibly predicting change in BMD. The following factors were explored: disease activity (defined by the AUC DAS4), frequency of medication use during the study (DMARDs, glucocorticoids, bisphosphonates, as well as calcium and vitamin D supplementation), and change in aerobic fitness and in muscle strength. To account for possible independent effects of the training program on BMD that would not translate into a change in muscle strength and/or aerobic fitness, such as impact loading, the percentage of sessions attended (attendance rate) was also included in the model. Univariate analyses (Table 5) showed that the following factors predicted BMD: the AUC DAS4, use of bisphosphonates, use of vitamin D, and physical capacity.

To analyze the relationship between the outcome variable (total hip BMD) and these factors simulta-

Table 4. Relationship between mean change in disease-related characteristics within completers and fast loss, slow loss, and gain in BMD of the hip after 2 years*

	No. of patients in each tertile	Fast losers BMD	Slow losers BMD	Gainers BMD
AUC DAS4	91/91/91	23.1 ± 7.6	21.0 ± 8.1	20.1 ± 8.1
Use of DMARDs (0–16)	91/91/91	0.4 ± 0.4	0.4 ± 0.4	0.3 ± 0.4
Use of glucocorticoids (0–24), months	91/91/91	3.0 ± 7.5	2.1 ± 5.7	2.4 ± 6.0
Use of bisphosphonates (0–24), months	91/91/91	0.6 ± 2.1	0.9 ± 3.3	2.4 ± 6.0
Use of calcium supplements (0–24), months	91/91/91	2.7 ± 6.3	2.7 ± 5.7	3.3 ± 6.6
Use of vitamin D supplements (0–24), months	91/91/91	0.6 ± 2.4	0.9 ± 2.7	1.5 ± 4.2
Change in Larsen score small joints (0–200), median (IQR)	89/88/89	2.0 (0.0, 7.5)	1.5 (0.0, 8.0)	1.0 (0.0, 6.5)
Change in Larsen score large joints (0–60), median (IQR)	88/89/88	0.0 (0.0, 0.5)	0.0 (0.0, 1.0)	0.0 (0.0, 0.9)
Change in muscle strength, newtons, median (IQR)	85/86/87	2.5 (−7.3, 20.2)	3.0 (−16.5, 22.1)	16.5 (−2.5, 31.0)†
Change in aerobic fitness, watts, median (IQR)	83/83/84	−0.1 (−34.6, 17.6)	0.0 (−33.2, 19.2)	17.8 (−18.8, 38.3)†
Attended sessions (%), mean ± SD	91/91/91	30 ± 38	34 ± 37	36 ± 37

* Except where indicated otherwise, values are the mean ± SD. AUC = area under the curve (see Tables 1 and 3 for other definitions).
† $P < 0.05$ by Kruskal-Wallis test.

Table 5. Univariate and multivariate odds ratios of risk factors for increase in hip BMD in completers of the RAPIT exercise program (n = 281)*

	Column 1 univariate	Column 2 multivariate	Column 3 stepwise (backward) selected
AUC ESR	1.00 (1.00–1.00)	1.00 (0.99–1.00)	
AUC DAS4	0.97 (0.94–1.00)†	0.98 (0.95–1.01)	
Use of DMARDs	0.85 (0.48–1.49)	1.11 (0.59–2.10)	
Use of glucocorticoids	0.99 (0.95–1.02)	0.98 (0.94–1.02)	
Use of bisphosphonates	1.10 (1.03–1.16)‡	1.26 (1.01–1.57)†	1.09 (1.02–1.16)†
Use of calcium supplements	1.02 (0.98–1.05)	0.98 (0.93–1.03)	
Use of vitamin D supplements	1.08 (1.01–1.17)†	1.07 (0.96–1.12)	
Change in muscle strength§	1.70 (1.08–2.67)†	1.75 (1.07–2.86)†	1.78 (1.11–2.86)†
Change in aerobic fitness§	1.89 (1.19–2.99)‡	1.79 (1.10–2.90)†	1.73 (1.08–2.77)†
Attendance rate	1.00 (0.99–1.00)	1.00 (0.99–1.00)	

* Values are odds ratios (95% confidence intervals). AUC = area under the curve; ESR = erythrocyte sedimentation rate (see Tables 1 and 3 for other definitions).
† $P < 0.05$.
‡ $P < 0.001$.
§ Change in muscle strength and aerobic fitness is dichotomized into losers versus gainers of muscle strength and aerobic fitness, respectively.

neously, a multivariate analysis was performed. In this analysis, more frequent use of bisphosphonates (odds ratio [OR] 1.26, 95% CI 1.01–1.57), increase in muscle strength (OR 1.75, 95% CI 1.07–2.86), and increase in aerobic fitness (OR 1.79, 95% CI 1.10–2.90) were found to be associated with an increase in hip BMD (Table 5). In the backwards stepwise selection of significant covariates, use of bisphosphonates, change in muscle strength, and change in aerobic fitness remained in the model (Table 5). Even when age and sex were included in the analyses, the results were similar (data not shown). Furthermore, exclusion of patients who reported use of bisphosphonates (n = 34) from the analysis did not change the outcome (data not shown).

DISCUSSION

Exercise is important in the prevention of osteoporosis and osteoporosis-related fractures, and hip fractures generate the most morbidity and mortality and the highest costs (10,29) in the general population. Exercise has also been found to be important in reducing the risk of falling by improving balance and coordination (30).

This study shows that RA patients are able to perform, during prolonged periods of time, exercises of sufficient intensity and adequate build-up to slow down the age-related decrease in BMD of the hip. The risk of fractures could not be estimated due to the relatively short duration of the study. Our results demonstrate that the effectiveness of these exercises with respect to BMD is significantly and independently associated with changes in both muscle strength and aerobic fitness, with odds ratios comparable with those associated with the use of bisphosphonates. No statistically significant effects on the course of BMD of the spine were found, and therefore, the conclusions of this study cannot be extended to BMD of the spine.

There is already evidence of the positive effects of exercise on BMD in several patient populations having an increased risk of developing osteoporosis, such as patients with Down's syndrome (31), Crohn's disease (32), cardiac patients following heart transplantation (33), and patients with juvenile RA (34). The data on RA patients are scarce (11–13), and until now, the positive effects of exercise on BMD have not been demonstrated.

In a randomized, controlled trial, Häkkinen et al followed up 65 patients with early RA who, for 1 year, performed twice a week either home-based dynamic strength training or range of motion movements (11). Although the strength training resulted in a significantly greater improvement in muscle strength in the exercise group than in the control group, the detected annual changes in BMD in both groups were minor. Moreover, no statistically significant differences in change of BMD of the spine or hip between the groups were found. In their later study, Häkkinen et al (12) followed up for 2 years 70 patients with recent-onset RA. The patients were randomized to perform either twice a week home-based strength training or range of motion movements. The changes in muscle strength were measured by

means of a dynamometer. Although muscle strength improved more in the exercise group than in the control group, no statistically significant differences in BMD of the spine or of the hip (femoral neck) were found.

Westby et al (13) studied 53 women with long-term RA who were followed up during 1 year; 14 of the women performed home-based aerobic dances and a strengthening program. The effectiveness of the exercises on the aerobic fitness was monitored by means of a questionnaire, and changes in activity level were monitored by means of an accelerometer. No measures of muscle strength changes were used. Although significant improvements in fitness and activity levels were measured in the exercise group and not in the control groups, the investigators found no significant differences in change of BMD of the spine or of the hip (femoral neck).

The discrepancy between the results of these studies and the current study could be due to several factors. First, the number of participants in the studies mentioned was probably too small. Second, the fact that the (minimally supervised) exercises were primarily aimed at improvement of muscle strength and were not designed as impact-loading or aerobic exercises is of importance. We can speculate that the quality and intensity of exercise was insufficient to produce a detectable effect on the BMD.

The present study demonstrates that changes in BMD of the hip are associated with changes in muscle strength and aerobic fitness, and that the increase in hip BMD is independently predicted by the changes both in muscle strength and in aerobic fitness. We found no significant association between the hip BMD and attendance rate, which we included as a surrogate for other, not directly measured, effects of the RAPIT program not associated with changes in muscle strength or aerobic fitness.

In cross-sectional studies with RA patients, a positive relationship between muscle strength and BMD has been described by other authors (35–37); however, no data are available on a relationship with aerobic fitness. In healthy populations, with regard to the association between muscle strength and aerobic fitness and BMD, exercises aimed specifically at the improvement of muscle strength (11,12) or aerobic fitness without weight- or impact-bearing components (38) did not prove to be effective in improving BMD, while a combined regimen was shown to be beneficial (39). These findings suggest an essential role for weight- and impact-bearing exercises in improving BMD.

Several mechanisms have been suggested to explain the effects of diverse exercise modalities on BMD. Dynamic and repetitive exposure of the skeleton to external impact-loading and muscular-loading forces of sufficient intensity were hypothesized to contribute to the development and maintenance of the load-bearing capacity of the bone (40). Important components of osteogenic stimulus are high strain rates and high peak forces in versatile movements (41,42). Adaptation to loading seems to occur in a site-specific manner, by gross geometric changes, structural and architectural changes, or both.

The current study was not primarily designed to investigate the effects of different exercise modalities such as the training of the muscle strength, aerobic fitness, or impact-generating exercises on the BMD. For example, the training of muscle strengths (measured as a strength of the extensors of the knee) and of aerobic fitness took place practically throughout the entire exercise session, including bicycling and impact-delivering activities such as stepping. Therefore, no conclusion can be attached to this study as to the optimal quality, quantity, or combination of exercise modalities to reach the maximum effectiveness.

In contrast to BMD of the hip, we found no beneficial effects of the long-term, high-intensity exercise program on BMD of the spine. This might be due to insufficient quality or quantity of the loading of the spine to produce measurable changes in BMD in this region. Specific exercises directed at strengthening of back muscles, which in the study by Sinaki et al (43) resulted in a long-term reduction of the incidence of vertebral fractures in postmenopausal women but not in an increase of BMD of the spine (probably due to insufficient loading), were not included in the program. In fact, in the current study, an increase in lumbar spine BMD with time was found in both the usual care and RAPIT groups. This phenomenon has also been encountered by others and attributed to several processes associated with aging (such as spondylarthrosis and atherosclerosis of the aorta), to limited decrease of the height of vertebras, and to difficulties with positioning of the vertebral column (44). Due to these problems and also the high morbidity, mortality, and costs generated by hip fractures when compared with vertebral fractures, recent recommendations for assessment of BMD prefer the measurement of the hip to other sites (45).

In conclusion, a long-term, high-intensity exercise program for RA patients, which has been proven to be safe and beneficial in several different aspects of health including aerobic fitness, muscle strength, functional ability, and emotional status (14), is also effective

in slowing down the rate of systemic bone loss. Rheumatologists who prescribe long-term exercises for their RA patients should keep in mind that patients participating in programs that result in increased aerobic fitness and muscle strength are more likely to have stable or improved BMD.

ACKNOWLEDGMENTS

We gratefully acknowledge the patients for their trust and participation. We thank the assessors I. Perquin, B. Oud, M. Fluit, and M. van Gulijk for performing the clinical assessments, and Prof. A. Cats for reading the radiographs. We also thank Dr. J. D. Macfarlane for the critical review of the manuscript.

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