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ORIGINAL ARTICLE

Effect of a High-Intensity Weight-Bearing Exercise Program on Radiologic Damage Progression of the Large Joints in Subgroups of Patients With Rheumatoid Arthritis

MARTEN MUNNEKE,[1] ZUZANA DE JONG,[2] AEILKO H. ZWINDERMAN,[2] H. KAREL RONDAY,[3] DIRKJAN VAN SCHAARDENBURG,[4] BEN A. C. DIJKMANS,[4] HERMAN M. KROON,[2] THEODORA P. M. VLIET VLIELAND,[2] AND JOHANNA M. W. HAZES[5]

Objective. **To investigate whether a high-intensity exercise program accelerates the rate of radiologic damage of the large joints in predefined subgroups of patients with rheumatoid arthritis.**
Methods. **The data of 277 participants in a 2-year randomized controlled trial, comparing the effects of high-intensity exercises with usual care, were used. Linear regression analysis was used to test which predefined variables at baseline (age, disease duration, disease activity, physical capacity, functional ability, joint damage) modified the effect of high-intensity exercise on the progression of radiologic damage of the large joints over 24 months.**
Results. **Baseline radiologic joint damage was the only variable associated with the effect of high-intensity exercise on joint damage progression in large joints. In a subgroup of 218 patients with no or little joint damage (defined as Larsen score ≤5; 80% of our study population) the proportions of patients with an increase in joint damage were similar for the exercise and usual-care group (35% versus 36%, risk ratio [RR] 1.0 [0.7–1.4]; P = not significant), whereas, in a subgroup of 59 patients who already had extensive damage of large joints (defined as Larsen score >5) the proportion was significantly higher in the exercise group (85% versus 48%, RR 1.8 [1.2–2.6]; $P < 0.05$).**
Conclusion. **High-intensity weight-bearing exercises appear to accelerate joint damage progression in patients with preexisting extensive damage. Patients with extensive large joint damage should, therefore, be advised to refrain from activities excessively loading the damaged joints.**

KEY WORDS. Exercise; Rheumatoid arthritis; Joint damage progression; Randomized controlled trials.

INTRODUCTION

The effectiveness and safety of exercise programs aimed at improving muscle strength and aerobic capacity (high-intensity exercise programs) in patients with rheumatoid arthritis (RA) have been investigated thoroughly. Results of several studies have shown that patients with RA were able to increase their physical capacity (muscle strength, cardiorespiratory fitness) and functional ability without detrimental effects on disease activity (1–6). It has also been shown that progression of radiologic joint damage of the hands and feet in patients with RA was not increased by long-term, high-intensity, weight-bearing exercises (7–10). Only one randomized study investigated the effects of high-intensity exercise on radiologic progression of large joints (11). The results of that study demonstrated a trend toward more joint damage within large joints in the exercise group compared with the usual-care group. Although

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[1]Marten Munneke, PhD: Leiden University Medical Center, Leiden, and Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [2]Zuzana de Jong, MD, Aeilko H. Zwinderman, PhD, Herman M. Kroon, MD, PhD, Theodora P. M. Vliet Vlieland, MD, PhD: Leiden University Medical Center, Leiden, The Netherlands; [3]H. Karel Ronday, MD, PhD: Leyenburg Hospital, The Hague, The Netherlands; [4]Dirkjan van Schaardenburg, MD, PhD, Ben A. C. Dijkmans, MD, PhD: Jan van Breemen Institute, Amsterdam, The Netherlands; [5]Johanna M. W. Hazes, MD, PhD: Leiden University Medical Center, Leiden, and Erasmus Medical Center, Rotterdam, The Netherlands.
Address correspondence to Marten Munneke, PhD, Radboud University Nijmegen Medical Centre, Department of Neurology, Internal postal code 326, PO Box 9101, 6500 HB Nijmegen, The Netherlands.
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the overall analysis demonstrated only small, nonsignificant differences, it might be questioned whether this trend is caused by subgroups of patients for whom long-term, high-intensity, weight-bearing exercise is detrimental (12). Potential risk factors for excess radiologic joint damage with high-intensity exercise are preexisting joint damage, high disease activity, older age, and lower functional ability (12–15).

The aim of this study was to investigate whether high-intensity exercise accelerates the progression of radiologic damage of the large joints within subgroups of patients with older age, longer disease duration, increased disease activity, diminished muscular or cardiorespiratory fitness, worse functional ability, or preexisting structural joint damage, and if so, which specific large joints are at an increased risk for excess radiologic damage. In addition, we examined to what extent a possible excess of progression of radiologic damage in a subgroup of patients with preexisting radiologic damage was outweighed by possible larger improvement of functional ability with high-intensity exercise.

PATIENTS AND METHODS

Design. Data from the Rheumatoid Arthritis Patients In Training (RAPIT) study were used. The RAPIT study was a randomized, controlled, multicenter trial on the feasibility, effectiveness, safety, and costs of a long-term, high-intensity exercise program in patients with RA (11,16). The medical ethics committees of all participating hospitals approved the RAPIT study and all patients gave written informed consent.

Patients. The study group comprised 309 patients from the RAPIT study. Inclusion criteria for the RAPIT were as follows: a diagnosis of RA according to the 1987 revised American College of Rheumatology (ACR, formerly the American Rheumatism Association) criteria (17); age 20–70 years; receiving a stable dose of disease-modifying antirheumatic drug in the last 3 months; a functional status classification of functional class I, II, or III according to the 1991 ACR revised criteria (18); ability to cycle on a home trainer; willingness to exercise biweekly on a fixed schedule; and living in a predefined region. Exclusion criteria were inability to tolerate cardiorespiratory fitness training due to a serious cardiac or lung disease, or the presence of one or more prostheses of weight-bearing joints (ankle, knee, or hip). Patients were randomly allocated either to the exercise group or to the usual-care group with stratification for center, age ($<$50 years or $>$50 years), and sex. Nine randomized patients (1 allocated to the exercise group and 8 to the usual-care group) declined participation immediately after randomization.

Over a period of 2 years, 5 patients allocated to the usual-care group and 14 patients allocated to the exercise 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). Damage progression could be calculated in 140 completers in the usual-care group and 137 completers in the exercise group. Data for these 277 completers were therefore used for the analyses of damage progression in the current study. Patients with missing baseline or 2-year followup radiographs were not included in the analysis.

Exercise program. Patients allocated to the high-intensity exercise group were encouraged to participate in twice weekly group exercise sessions of 75 minutes each (16). The intensity of the exercise program was based on recommendations published by the American College of Sports Medicine (19) concerning the quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness and flexibility in healthy adults. The exercise program, aimed at increasing and maintaining cardiorespiratory fitness, muscle fitness (strength and endurance), and joint flexibility with the ultimate goal of improving the performance of daily activity, is described in detail elsewhere (16). Although every 8 weeks a general circuit was prescribed, each supervising therapist had the ability to adapt the circuit for each patient. If certain exercises caused too much burden (defined as too much pain during the performance, or pain lasting $>$4 hours following the exercise session in combination with additional joint swelling) the supervising therapist tried to adjust the exercise. Patients were trained in 11 exercise classes, and each class was supervised by 2 physical therapists. Depending on the exercise class, the maximum possible number of sessions in which the patient could participate was 182–192 (mean 187). Patients assigned to the usual-care group were treated by a physical therapist only if their attending physician regarded this as necessary.

Assessments. Baseline demographic and disease-related characteristics (age, sex, disease duration, functional ability, physical capacity, and disease activity) were obtained for all participants. Baseline functional ability was measured by the Dutch version of the Health Assessment Questionnaire (HAQ) (20). Physical capacity at baseline was determined by cardiorespiratory fitness and muscle strength. Cardiorespiratory fitness was measured in watts by means of a standardized incremental ergometer test (21). Muscle strength of the knee extensors was measured with an isokinetic dynamometer at an angle velocity of 60°/s and is given in Newtons (22). Disease activity was assessed with the original Disease Activity Score with 4 variables (DAS4) (23). The DAS4 ranges from 0 (no disease activity) to 10 (severe disease activity).

Radiologic damage of large joints. Radiologic damage of large joints was assessed at baseline, and at 12 and 24 months. Damage of the shoulders, elbows, hips, knees, ankles, and subtalar joints was independently scored by 2 experienced examiners (HK and ZdJ) using the method described by Larsen et al (24). The examiners were blinded to patient identity, group allocation, and time. Scores are presented as a mean of the scores of the 2 readers. The Larsen joint score ranges from 0 (no joint space narrowing, no erosions) to 5 (maximal possible damage) for each joint. For each patient a summed Larsen score was calculated by summation of all Larsen joint scores. The summed Larsen score for large joints ranges from 0 (no damage) to 60 (maximal possible damage). At baseline a Larsen score could be calculated for 145 usual-care patients and 148 high-intensity exercise group patients.

Baseline damage. The individual joints were classified at baseline as joints without any damage (Larsen joint score 0) and joints with any damage (Larsen joint score 1–5). The individual patients were classified as patients without joint damage (summed Larsen score 0), patients with mild joint damage (summed Larsen score 1–5) and patients with extensive damage (summed Larsen score 6–60).

Progression of damage. Progression of radiologic damage for each single joint was defined as the difference between the Larsen scores at baseline and after 24 months, and total progression of radiologic damage was defined as the difference in the summed Larsen score at 24 months and baseline. In 9 patients (3 in the usual-care group, 6 in the exercise group) missing values at 24 months were substituted by Larsen joint scores obtained at 12 months. Joints were classified as joints with no progression (change in Larsen joint score $\leq$0) and joints with progression (change in Larsen joint score 1–5). Patients were classified as patients with no damage progression (change in summed Larsen score $\leq$0), patients with mild progression (change in summed Larsen score 1–5), and patients with extensive progression (change in summed Larsen score 6–60).

Improvement of functional ability. Improvement in functional ability was assessed after 12 and 24 months by means of the McMaster Toronto Arthritis Patient Preference Interview (MACTAR). The MACTAR is used as an outcome measure because it measures patient-relevant changes in functional ability and is expected to be more responsive to changes in functional ability than the HAQ (25). The MACTAR is a semistructured interview and comprises a baseline and followup assessment (26,27). The MACTAR score was calculated for the first and the second years of study separately. The total MACTAR score was calculated as a sum of the change in scores in the first year of study and in the second year. Patients were grouped into those with improvement (MACTAR change score >0) and those without improvement (MACTAR change score $\leq$0) in functional ability.

Analysis. Measures are expressed as the median and interquartile range. Differences between the groups were analyzed by Student's unpaired *t*-test, the Mann-Whitney U test, or the chi-square test where appropriate.

Potential risk factors for excess radiologic damage progression of the large joints were identified using linear regression analysis. For each potential risk factor (age, disease duration, disease activity, muscle strength, cardiorespiratory fitness, functional ability, joint damage) a linear regression model was tested with joint damage change (change in the summed Larsen score) as the dependent variable. In each model, 3 independent variables were entered: group allocation (usual-care/high-intensity exercise), the potential risk factor, and the interaction of group allocation and the potential risk factor. If the interaction effect contributed significantly ($P < 0.05$) to the model, ad hoc subgroup analysis was performed. The interaction effect of the following predefined potential effect modifiers was tested: age (years), disease duration (years), disease activity (DAS4), muscle strength (Newtons), cardiorespiratory fitness (watt), functional ability (HAQ), and joint damage (Larsen score).

To estimate differences between the usual-care group and the high-intensity exercise group concerning the number of patients with deterioration and the number of patients with improvement in functional ability in a subgroup of patients with Larsen scores of $\leq$5 or >5, risk ratio's (RRs) with 95% confidence intervals (95% CIs) were calculated (28). Analyses were performed on patients who completed the study in the usual-care and the exercise group, and on patients in the exercise group who participated in at least 100 exercise sessions.

RESULTS

Baseline characteristics as well as changes in joint damage and in functional ability after 24 months in the usual-care and the exercise groups are presented in Table 1. At baseline, participants in the usual-care group and in the exercise group were comparable, with the exception of a slightly longer disease duration in the usual-care group than in the exercise group. A more detailed description of the overall results of the RAPIT study including other outcome measures and reasons for withdrawal is published elsewhere (11).

Potential risk factors. The results of the linear regression analysis with progression of large joint damage as the dependent variable demonstrated no significant interaction effect for exercise combined with age, disease duration, baseline disease activity, baseline functional ability, baseline muscle strength, and baseline cardiorespiratory fitness, respectively. A significant interaction effect was found, however, for exercise combined with baseline joint damage ($P < 0.01$).

Effect of exercise on the rate of radiologic progression in patients with and those without extensive baseline damage. Figure 1 illustrates the relationship between baseline radiologic damage and changes in joint damage. The lines within Figure 1 represent the best fit of the data for participants in the usual-care group and the high-intensity exercise group, respectively. The figure shows that in participants in both groups who have baseline Larsen scores $\leq$5, the slope of the lines are similar, indicating that the increase in damage is independent of participation or no participation in a high-intensity exercise program. In patients with baseline scores >5, however, the lines diverge, indicating a faster rate of damage in the high-intensity exercise group when compared with participants in the usual-care group.

The results with respect to radiologic damage in patients without extensive radiologic damage of the large joints at baseline (baseline Larsen score $\leq$5) and a subgroup of patients with extensive damage at baseline (baseline

Table 1. Baseline characteristics and summary of exercise effects*

	Usual care (n = 140)	High-intensity exercise (n = 137)	High-intensity exercise >100 sessions (n = 107)
Baseline characteristics			
Age, years (range)	54 (44–62)	54 (46–61)	55 (48–61)
Female, n (%)	112 (80)	109 (80)	88 (82)
Disease duration, years (range)	7 (3, 14)	5 (3, 9)	5 (3, 9)
HAQ functional ability, n (range)	0.6 (0.2, 1.0)	0.6 (0.3, 1.1)	0.6 (0.3, 1.0)
Muscle strength, Newtons n (range)	166 (115, 227)	165 (128, 206)	162 (128, 202)
Cardiorespiratory fitness, Watts n (range)	162 (126, 200)	162 (126, 200)	162 (126, 200)
DAS4 disease activity, n (range)	3.4 (2.1, 4.2)	3.2 (2.6, 4.0)	3.2 (2.6, 3.9)
Baseline joint damage			
Larsen score, median (range)	2 (0, 23.5)	1.5 (0, 21.5)	1.5 (0, 20.5)
Affected joints, median (range) number per patient	2 (0, 10)	2 (0, 10)	2 (0, 9)
Patients without damage, n (%)	40 (29)	39 (29)	27 (25)
Patients with mild damage, n (%)	69 (49)	70 (51)	59 (55)
Patients with extensive damage, n (%)	31 (22)	28 (22)	21 (20)
Change in joint damage			
Change summed Larsen score, median (range)	0 (−4.5, 7)	0 (−4.5, 8.5)	0.5 (−1, 8.5)
Patients without progression, n (%)	86 (61)	75 (55)	53 (50)
Patients with mild progression, n (%)	44 (31)	47 (34)	40 (37)
Patients with extensive progression, n (%)	10 (7)	15 (11)	14 (13)
Change in functional ability, MACTAR			
Patients with improvement, n (%)	74 (51)	92 (66)†	65 (69)†

* HAQ = Health Assessment Questionnaire (score range 0–3); DAS4 = Disease Activity Score with 4 variables (score range 0–10); MACTAR = McMaster Toronto Arthritis Patient Preference Interview.
† $P < 0.05$ by chi-square test compared with usual care group.

Larsen score >5) are shown in Tables 2 and 3, respectively. In the patients without extensive joint damage at baseline (Table 2, n = 218), the proportion of patients with any damage progression was similar in both the exercise and usual-care groups (35% versus 36%) with an RR of 1.0 (95% CI 0.7–1.4). The median change in the summed Larsen score was 0 in both the usual-care and exercise groups.

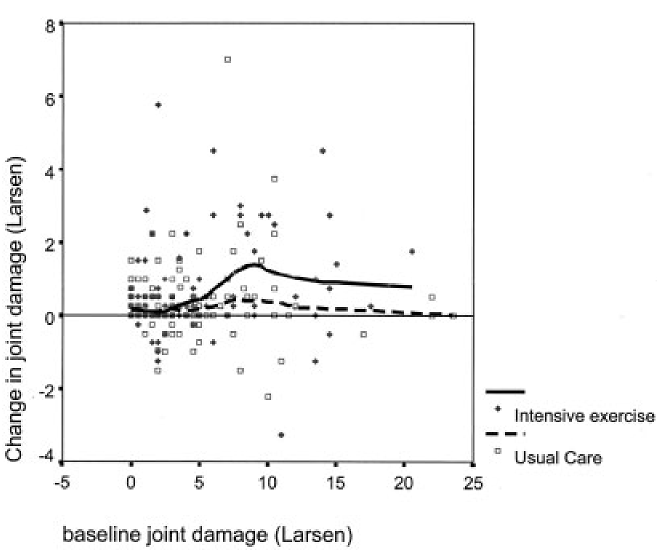

Figure 1. Association of baseline joint damage scores with joint damage change scores for both usual care and high-intensity exercise groups. The lines represent the best fit of respectively usual care data points and high intensity exercise data points.

Within the subgroup of patients with extensive radiologic joint damage (Larsen score >5, n = 59) the proportion of patients with any damage progression was significantly higher in the exercise group then in the usual-care group (85% versus 48%; RR 1.8 [95% CI 1.2–2.6], $P < 0.05$). In addition, the median change in the summed Larsen score was also higher in the exercise group when compared with the usual-care group (1.5 versus 0, $P < 0.05$ by Mann-Whitney U test).

All analyses were repeated including only patients who participated in at least 100 exercise sessions (Tables 2 and 3). These analyses demonstrated an equal risk of damage progression in patients without extensive baseline joint damage (41% versus 36%; RR 1 [95% CI 0.8–1.5], P not significant [ns]) and an increased risk of damage progression in patients with extensive baseline damage (91% versus 48%; RR 1.9 [95% CI 1.3–2.8]).

Effects of exercise on the rate of radiologic progression of individual joints in subgroups of patients with low and extensive baseline damage. To find out whether high-intensity exercise has resulted in damage progression in specific joints, each joint was analyzed separately. For both the exercise group and the usual-care group, the number of joints with any increase in radiologic joint damage and the accompanying RRs are presented in Table 4. In joints without any damage at baseline, the risk of damage progression varied from 1% to 11%. This risk is comparable for both the usual-care group and exercise group (RR varied from 1.0 to 1.6). In joints with any damage at baseline, the risk of damage progression varied from

Table 2. Subgroup of patients without extensive baseline joint damage (summed Larsen score ≤5)*

	Usual care	High-intensity exercise	High-intensity exercise (>100 sessions)
Baseline			
Patients in subgroup, n (% of total population)	109 (78)	109 (80)	86 (80)
Age, years (range)	53 (44–62)	54 (47–61)	57 (48–63)
DAS4 disease activity, n (range)	3.3 (2.0, 4.2)	3.2 (2.6, 4.0)	3.1 (2.6, 3.8)
HAQ functional status, n (range)	0.50 (0.13, 1.0)	0.63 (0.3, 1.0)	0.63 (0.3, 1.0)
Larsen score, median (range)	1 (0, 5)	1 (0, 5)	1 (0, 5)
Affected joints, median number (range)	1 (0, 7)	1 (0, 5)	1.5 (0, 5)
Patients without damage, n (%)	40 (37)	39 (36)	27 (31)
Patients with mild damage, n (%)	69 (63)	70 (64)	59 (69)
Change in joint damage following 24 months			
Larsen score, median change (range)	0 (−1.5, 3)	0 (−2, 8.5)	0 (−1, 8.5)
Patients without progression, n (%)	70 (64)	71 (65)	51 (59)
Patients with mild progression, n (%)	34 (31)	34 (31)	31 (36)
Patients with extensive progression, n (%)	5 (5)	4 (4)	4 (5)
Change in functional ability			
Patients with improvement, n (%)	56 (50)	73 (66)†	61 (67)†

* DAS4 = Disease Activity Score with 4 variables (score range 0–10); HAQ = Health Assessment Questionnaire (score range 0–3).
† $P < 0.05$ by chi-square test compared with usual care group.

4% to 40%. With the exception of shoulder and subtalar joints this increase was comparable for the usual-care group and exercise group (RR varied from 1.0 to 1.7). However, in the exercise group, the relative risk of developing additional damage in the shoulder joints and subtalar joints increased to 2.7 and 10.0, respectively.

Effect of exercise on changes in functional ability in subgroups of patients with or without extensive baseline damage. In patients with no extensive joint damage as well as in patients with extensive joint damage, the proportion of patients with improvement of functional ability was higher in the high-intensity exercise group than in the usual-care group. However, in patients without extensive joint damage the difference between the exercise and the usual-care groups was more evident (66% versus 50%; RR 1.3 [95% CI 1.1–1.7], $P < 0.05$) than in the patients with extensive joint damage (66% versus 55%; RR 1.2 [95% CI 0.8–1.8], *P* not significant).

DISCUSSION

The results of this planned subgroup analysis show that the association between high-intensity exercise and joint damage progression might be influenced by baseline joint damage but not by age, disease duration, physical capacity, functional ability, or disease activity. In patients with extensive baseline damage, high-intensity exercise appears to aggravate joint damage progression, whereas in patients without extensive baseline damage, high-intensity exercise does not result in more joint damage progression in comparison with usual care. In addition, analysis showed that the shoulder and subtalar joints were more

Table 3. Subgroup of patients with extensive baseline joint damage (summed Larsen score > 5)*

	Usual care	High-intensity exercise	High-intensity exercise (>100 sessions)
Baseline			
Patients in subgroup, n (% of total population)	109 (78)	109 (80)	86 (80)
Age, years (range)	56 (46, 61)	54 (43, 59)	54 (44, 59)
DAS4 disease activity, n (range)	3.5 (2.4, 4.3)	3.4 (2.4, 4.5)	3.3 (2.7, 4.5)
HAQ functional status, n (range)	0.88 (0.5, 1.4)	0.94 (0.38, 1.2)	1.0 (0.38, 1.2)
Larsen score, median (range)	8 (5.5, 23.5)	9.5 (5.5, 20.5)	9.5 (5.5, 20.5)
Affected joints, median number (range)	5 (2, 10)	6 (2, 9)	6 (4, 9)
Change following 24 months			
Larsen score, median change (range)	0 (−4.5, 7)	1.5 (−4.5, 6.5)	2 (−0.5, 6.5)
Patients without progression, n (%)	16 (52)	4 (14)	2 (10)
Patients with mild progression, n (%)	10 (32)	13 (46)	9 (43)
Patients with extensive progression, n (%)	5 (16)	11 (39)†	10 (48)†
Change in functional ability			
Patients with improvement, n (%)	18 (55)	19 (66)	14 (67)

* DAS4 = Disease Activity Score with 4 variables (score range 0–10); HAQ = Health Assessment Questionnaire (score range 0–3).
† $P < 0.05$ by chi-square test compared with usual care group.

Table 4. Radiologic deterioration of joints of patients allocated to the usual care group and the high-intensity exercise group*

Joint	Evaluated joints, n (%)	Incidence of deterioration: Usual care group, %	Incidence of deterioration: High-intensity exercise group, %	RR (95% CI)
Shoulder				
Without damage	457 (81)	5	5	1.0 (0.4, 2.2)
With damage	107 (19)	10	27	2.7 (1.1, 7.0)
Elbow				
Without damage	413 (72)	4	6	1.6 (0.7, 3.8)
With damage	157 (28)	16	20	1.3 (0.6, 2.5)
Hip				
Without damage	479 (83)	1	2	1.5 (0.3, 6.4)
With damage	95 (17)	11	20	1.8 (0.6, 4.7)
Knee				
Without damage	372 (65)	10	11	1.1 (0.6, 1.9)
With damage	201 (35)	19	24	1.3 (0.7, 2.1)
Ankle				
Without damage	472 (83)	4	4	1.1 (0.5, 2.6)
With damage	100 (17)	19	19	1.0 (0.4, 2.3)
Subtalar				
Without damage	537 (94)	1	2	1.2 (0.3, 4.6)
With damage	35 (6)	4	40	10 (1.3, 79)

* A distinction is made between joints without radiologic damage (Larsen score 0) and with radiologic damage (Larsen score 1–5) at baseline. Deterioration is defined as any increase in joint damage. RR = relative risk; 95% CI = 95% confidence interval.

often deteriorated in patients participating in intensive exercise.

Based on our results, it can be concluded that for patients with no or little joint damage (Larsen score ≤5) high-intensity exercise is safe. This subgroup includes ~80% of our study population. Analysis of participants and nonparticipants of our study (29) demonstrated that participants adequately reflect the total population of patients with RA fulfilling the inclusion criteria. Therefore we estimate that the majority of patients with RA fulfilling the inclusion criteria (most important criteria: age between 20 and 70 years, no arthroplasty of weight-bearing joints, and able to cycle on a bicycle) can safely participate in high-intensity exercise programs. The results, however, do suggest an unfavorable outcome of high-intensity exercise on joint progression in the remaining 20% of our study population, namely, the patients with extensive joint damage in large joints at baseline (defined as summed Larsen score >5). The median difference in the summed Larsen score for change between usual-care and high-intensity exercise in this subgroup is, however, relatively small (median change in Larsen score 0 versus 1.5). In contrast, 2 years is a short period for a chronic disease. Performing high-intensity exercise over a more prolonged period (10 years or more) may eventually result in relevant joint damage and accompanying disability (30,31).

Part of joint damage progression in the large joints of patients with RA might be attributed to secondary osteoarthritis. The influence of exercise and physical activity on the risk of osteoarthritis is a matter of debate. Epidemiologic studies have demonstrated that participation in several competitive sports increases the risk of osteoarthritis. In particular, those activities that demand high-intensity, acute, direct joint impact as a result of contact with other participants, playing surfaces, or equipment increase the risk of osteoarthritis (15,32). In general, aerobic exercises as performed by our participants do not increase the risk of osteoarthritis in healthy individuals (33). However, individuals with abnormal joint anatomy or alignment, previous significant joint injury, osteoarthritis, joint surgery, joint instability, disturbances of joint or muscle innervation, or inadequate muscle strength have increased risk of joint damage during participation in athletics (33). Our results demonstrated that in particular the shoulder and subtalar joints deteriorated more often in patients participating in high-intensity exercise. Although the numbers are small and conclusions should be drawn with caution, it might be hypothesized that changed biomechanical characteristics are, at least partly, responsible for the negative impact of high-intensity exercise in these joints. Arm movements are accompanied by large net joint moments resulting in high compression forces within the glenohumeral joint (34). Rotator cuff muscles have to stabilize the glenohumeral joint during arm movements. In RA patients with glenohumeral joint involvement, however, the humeral head is usually migrated upward and the rotator cuff is often weakened or damaged (35). This can lead to lack of stabilization of the shoulder joint during exercise, resulting in overloading and accelerated joint destruction.

Woodburn et al (36) observed altered kinematics of the ankle joint complex in patients with RA, resulting in excessive eversion during walking. These changes in kinematics might also lead to accelerated joint deformity and joint damage progression. It is therefore plausible that joint instability rather than radiologic joint damage has to be considered as a risk factor for performing high-intensity exercises in RA.

To minimize the possible negative impact of high-intensity exercise programs, Finckh et al (12) suggest involving modalities that do not load the joint, such as water walking, swimming, biking, rapid walking, or exercises directed primarily at improvement of muscle strength. Dynamic loading of arthritic joints, however, seems to be an important element of exercise (37,38) and might even protect the small joints from damage (7). In addition, de Jong et al hypothesize that joint loading improves the bone quality and as a consequence protects the bone from the action of osteoclasts (7).

Our study has several limitations. Although participants in our study form a representative sample of the RA population fulfilling the inclusion criteria (11), the number of included patients with preexisting extensive joint damage of large joints was limited, partly because of the inclusion criteria (no arthroplasty of a weight-bearing joint). Furthermore, the followup duration of the study was only 2 years. Finally, we are aware that, although subgroup analysis is considered an excellent method for generating reasonable hypotheses for testing in future studies, these analyses can in general not lead to definitive conclusions concerning the effect of an intervention in subsets of patients (39–41). Despite these limitations, our study results provide useful information that might be important for both clinical decision making and future research efforts.

The RAPIT exercise program as evaluated in this study can be considered a step beyond current treatment policy. Most previously evaluated exercise programs seem to be less intensive, especially with respect to the weight-bearing component. An important remark must be made, however, concerning the term high-intensity exercise program. This term suggests a standard intervention that is well described and completely developed. Indeed, in this report and elsewhere (16) we described the content of our exercise program. It is, however, very important to realize that the description concerns only the most important variables (e.g., frequency of exercise sessions, duration and kind of exercises). A number of other variables that might enhance or decrease the effectiveness and safety of an exercise program are not described (e.g., quality of performance of exercises, range of joint motion during exercises). The impact of many of these variables on the effectiveness and safety of exercises is still unknown. Future research needs to identify these variables in order to maximize the effectiveness and safety of exercise programs. In addition, the effects of exercise on joint damage progression in subgroups of patients have to be confirmed by additional research. In future trials, joint deformities, joint instability, and joint damage at baseline should be documented in detail for each joint to be able to conclude for which involved joints exercise results in acceleration of joint damage progression. In the mean time, rheumatologists and physiotherapists should advise patients with RA to be cautious with excessive loading of extensively damaged joints. In particular in patients with RA with already extensively damaged large joints, an individualized exercise program should therefore be designed. This underscores the need for close cooperation between rheumatologists and qualified physiotherapists with specific skills in the treatment of patients with RA (42).

In conclusion, the majority of patients with RA can be safely advised to participate in a high-intensity exercise program while the design of exercises for a small minority of patients with extensive joint damage needs special attention. This subgroup of patients should be advised to perform exercises without excessive loading of involved joints.

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