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Title: A systematic review of the effects of dynamic exercise in rheumatoid arthritis

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Key words: Rheumatoid Arthritis, Exercise, Rehabilitation, Systematic Review

Abstract

Exercise is commonly used in the management of patients with rheumatoid arthritis (RA), however there is little consensus in the literature to support its use. This systemic review aimed to determine the effects of dynamic exercise on patients with RA. A systematic search of Medline (1949-2007), Cinahl (1982-2007), Embase (1974-2007) and Cochrane library was performed for randomised controlled trials using the keywords “rheumatoid arthritis” and “exercise” or “training” or “sport”. The methodological quality of studies was assessed using a ten point scale.

Eighteen papers relating to 12 different studies met inclusion criteria. The mean methodological quality score was 6.9/10. Studies using aerobic training, strength training and combinations of both were included. Patients with early, stable, and active RA were studied. A number of studies reported improvement in muscle strength, physical function and aerobic capacity with dynamic exercise. Some studies also reported improvements in disease activity measures, and small improvements in hip bone mineral density. One study reported significantly less progression of small joint radiographic damage of the feet in the dynamic exercise group. However, one study also reported worse large joint radiographic damage in patients using dynamic exercise who had pre-existing large joint damage, though this was a retrospective analysis. No studies reported worse outcomes for function, disease activity or aerobic capacity with dynamic exercise. Cardiovascular outcomes were not reported in any study, and no data were presented to assess the effect of exercise on patients with significant underlying cardiovascular disease.

This systematic review suggests that the majority of patients with RA should be encouraged to undertake aerobic and / or strength training exercise. Exercise programmes should be carefully tailored to the individual, particularly for patients with underlying large joint damage or pre-existing cardiovascular disease.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown aetiology that primarily involves joints. Patients with RA suffer increased morbidity and mortality from cardiovascular disease, largely due to accelerated atherosclerosis.^{1,2} This is not all due to traditional cardiovascular risk factors. The vascular effects of chronic systemic inflammation are thought to play a significant role.^{3,4}

Traditionally patients with active RA were advised to rest from active exercise, particularly during exacerbations.⁵ In the last two decades there has been increasing use of active exercise in patients with RA, with a number of studies looking at the effect of exercise on outcome measures as diverse as fitness, muscle strength, bone density, functional scores, disease activity and joint damage.⁶ However this remains a controversial area in rheumatology, with some clinicians discouraging active exercise for patients with RA, particularly during times of disease flare. While the benefits of exercise for healthy individuals in terms of cardiovascular health are clear, there has been little study of the cardiovascular benefits of exercise for patients with RA, who already have excess cardiovascular risk, and who have lower baseline levels of activity.

A Cochrane review of dynamic exercise therapy for treating RA concluded that dynamic exercise is effective at increasing aerobic capacity and muscle strength.⁶ No detrimental effects on disease activity and pain were observed at this time, however, the effects on functional ability and radiological progression were unclear, further there was no examination of the effect of exercise on cardiovascular outcomes. This Cochrane review⁶ published in 2000 included only six studies. In the years since this review was carried out there have been a number of studies looking at the effect of different types of exercise on a number of outcome measures in RA. The aim of this review therefore, was to determine the effectiveness of dynamic exercise in improving outcomes for patients with RA.

Methods

A systematic search of Medline (1949-2007) for randomised controlled trials using keywords “rheumatoid arthritis” and “exercise” or “training” or “sport” limited to human subjects and English language was performed in July 2007. Similar searches were also performed using the Cinahl (1982-2007), Embase (1974-2007) and Cochrane library. Abstracts were scanned and all potentially relevant papers requested for analysis. Existing reviews in the area were also scanned searching for additional references.

Inclusion criteria

All randomised controlled trials of adult patients with a confirmed diagnosis of RA, where the intervention included any form of dynamic physical exercise were examined. Primary outcome measures included radiographic damage, swollen and tender joint counts, laboratory measures of inflammation, bone density, functional scores, measures of fitness and muscle strength, and measures of cardiovascular outcomes. Studies presenting data from mixed groups of patients with different arthropathies were excluded. The analysis is qualitative rather than quantitative because of the wide variation in study subjects, interventions, and outcome measures used.

Methodological Quality

Each study was assessed for methodological quality using 10 criteria (see below and table 2). These criteria were modified from the Delphi list⁷, with reference to similar criteria published by Van den Ende et al.⁶, Van Tulder et al.⁸, and the Pedro scale.⁹ The quality criteria relating to blinding of patient and blinding of care provider were not suitable for intervention involving dynamic physical exercise and were not included in this list. Each criterion was scored yes, no, or unclear with no weighting of results giving a maximum quality score of 10/10. For the purpose of this review drop out rates of 25% or less were deemed satisfactory. Studies fulfilling seven or

more criteria are deemed high quality. Those with less than four out of 10 are deemed low quality.

1. Adequate randomisation
2. Allocation concealment
3. Groups similar at baseline
4. Eligibility criteria specified
5. Sufficient description of intervention
6. Blinding of outcome assessor
7. Co interventions avoided or similar between groups
8. Presentation of point estimates and measures of variability for primary outcome measures
9. Drop out rate described and acceptable
10. Intention to treat analysis

Results

Selection of included trials

The search strategy yielded 62 potentially relevant papers, from which a total of 46 studies were identified. Of these 18 relevant papers that met inclusion criteria were included in this review. These papers relate to 12 separate studies. All trials were prospective randomised studies, though one paper reports a retrospective subgroup analysis.¹⁰ Study characteristics and outcomes are directly compared in table 1.

Excluded papers

Excluded papers and reasons for exclusion are listed in table 3.

Intervention

A number of different exercise interventions were used in these studies, including aerobic fitness training, strength exercises, or combinations of both. With the exception of Bilberg et al.'s study¹¹, which used moderately intense pool exercise, all exercises were performed on dry land.

Aerobic exercises:

The studies by Harckom et al.²⁰ and Melikoglu et al.²⁴ used largely aerobic interventions.

Harckom et al.²⁰ studied 20 women with RA aged 27- 68 years, of ARA functional class II for 12 weeks. Four intervention groups (3 exercise, 1 control) were used. Exercises were performed on a bicycle ergometer 3 times a week for 12 weeks. Five bouts of exercise per session were performed, each separated by a one minute rest. The protocols differed in the initial length of total exercise time, the rate of progression, and the final total duration of activity achieved. The control group continued with routine daily activities. Outcome measures were aerobic capacity

(VO₂max), grip strength, 50 foot walk time, muscle strength (knee flexors and extensors), functional status index, and joint counts (combined tender/swollen score).

Melikoglu et al.²⁴ performed a prospective randomised study of short term (2 weeks) dynamic exercise therapy versus range of motion (ROM) controls in 40 female patients with non-active rheumatoid disease, functional class I or II, and on stable medication. The intervention was dynamic exercise on a treadmill to achieve 60% of age predicted maximum heart rate. Both groups exercised for five sessions per week, 20 minutes per session, for a total of 2 weeks. An additional healthy (non-RA) control group was also studied but is not included in this analysis. Primary outcome measures were levels of serum insulin-like growth factor (IGF-1), and serum insulin-like binding protein 3 (IGFBP-3). Pain VAS, HAQ, morning stiffness duration, RAI, ESR, and CRP were also recorded.

Strength training:

The studies by Hakkinen et al.^{15,16,17,18,19} and McMeekin et al.²³ used primarily strength training interventions.

Hakkinen et al published five related papers on the effect of dynamic strength training on 70 patients (44 female) with early RA.^{15,16,17,18,19} None of the patients had commenced treatment with disease modifying drugs or corticosteroids at the beginning of the study. Mean duration of symptoms was 10.5 months at the start of the study. The exercise group performed home dynamic strength training twice weekly for 12 months with rubber bands and dumbbells for upper and lower extremities, abdominal and back muscles. The exercise group is also encouraged to engage in recreational physical activities such as walking, cycling, skiing and swimming two to three times a week. The control group performs range of motion and stretching exercises. Recreational activities are allowed except for strength training of any kind. Training diaries are kept by both groups.

Hakkinen et al's first paper reports results after one year.¹⁵ Outcome measures are strength, bone mineral density at hip and lumbar spine by Lunar DEXA, disease activity score (DAS28), pain VAS and functional capacity (HAQ). Hakkinen et al's

second paper reports results after continuing the strength program for two years.¹⁶ Outcome measures reported are strength, bone mineral density at hip and lumbar spine (Lunar DEXA); disease activity (DAS28), pain VAS, functional capacity (HAQ), and also the radiographic Larsen joint score of small joints. Hakkinen et al's third paper reports a separate outcome measure (physical function as assessed by the Valpar 9 work sample test) after two years in the same group.¹⁷ Hakkinen et al's 2004 papers report five year follow up data following the initial two year exercise programme^{18,19} Both papers report muscle strength, radiological damage (Larsen small joint score of hands and feet), function (HAQ), and disease activity (DAS28). Bone mineral density (by DEXA) is reported in the Annals of Rheumatic Disease paper only.¹⁹

McMeekin et al. performed a prospective randomised six week study of knee extensor and flexor muscle training in 36 patients with RA (30 female), with a mean age 50.6 years.²³ The intervention was concentric quadriceps and hamstring training. Sessions were performed every three days for a total of six weeks, completing 14 sessions in total. Outcome measures were pain VAS, HAQ, timed up and go test (TUG), and peak torque of knee extensor and flexor muscle activity.

Aerobic / strength Combinations:

The following studies used exercise programmes with significant aerobic and strength training aspects: Bilberg et al.¹¹, the RAPIT programme studies by de Jong et al.^{12,13,14} and Munneke et al.¹⁰, Komatireddy et al.²¹, Lyngberg et al.²², Van den Ende et al.^{25,16}, and Westby et al.²⁷.

Bilberg et al. studied 47 (42 women, 5 men) patients with RA aged 20-65¹¹. Disease duration was one to five years, and drug therapy was stable. The intervention was pool exercise twice weekly for 12 weeks. The control group continued normal activities. Outcomes were assessed at three months. Primary outcomes were aerobic capacity and physical SF-36. Secondary outcome measures were the chair test, shoulder endurance test, index of muscle function (IMF), and hand grip force.

de Jong et al published four papers from the multicentre RA patients in training (RAPIT) programme.^{10,12,13,14} This was a two year prospective study comparing an intensive exercise programme (RAPIT) with usual care physiotherapy (UC). Three hundred patients with RA (237 women) aged 20-70 were enrolled. All patients were on stable medication, functional class I-III and with no significant cardiopulmonary disease. The RAPIT programme consisted of supervised bi-weekly group exercise of 1.25 hrs per session. Each session had three parts: bicycle training (20 minutes), exercise circuit (20 minutes), sport or game (20 minutes). Primary outcome measures¹² were divided into measures of effectiveness: functional ability as assessed by the MACTAR and HAQ scores, and safety: Larsen large joints score of radiographic damage. Secondary outcome measures were physical capacity and emotional status (effectiveness) and disease activity score (DAS4) (safety). Outcomes were assessed after 24 months.

The primary outcome measure reported in the paper published in *Arthritis and Rheumatism*¹³ was bone mineral density at the hip and spine (by DEXA) at two years. The primary outcome measure in the paper published in the *Annals of Rheumatic Disease*¹⁴ was radiological joint damage of the hands and feet. Munneke et al published a retrospective sub-group analysis of the RAPIT programme with the primary outcome measure the Larsen large joint radiographic score.¹⁰

Komatireddy et al performed a prospective randomised 12 week study of circuit based training at home.²¹ The control group had no exercise intervention. Forty nine patients with RA (37 women) were studied. The mean age was 60.5, and patients were functional class II or III. 38 patients were receiving NSAIDs, 28 oral steroids, 48 DMARDs, and 17 combination DMARDs. Home circuit training using resistive exercises and 12-15 reps per set was performed. Efficacy of the exercise programme was assessed by evaluation of changes in muscle strength, cardiopulmonary function (VO₂ max, anaerobic threshold), functional ability (50 foot walk, sit-to-stand test, HAQ, arthritis impact measurement scales -AIMS), self-reported health status (pain and fatigue VAS and self-reported joint counts) and disease activity status (physician's global assessment and tender/swollen joint counts).

Lyngberg et al performed a prospective randomised study of progressive interval training over three months in elderly patients with RA on oral steroids.²² Twenty four elderly patients who had been treated with low dose oral steroids for at least two years were studied. The mean age was 66.5 years, and mean disease duration 12 years. Patients studied had “slight or moderate” disease activity. Patients with significant heart disease were excluded. The interventions were aerobic training on an ergometer, dynamic strength training exercises, and stretching exercises. Exercises were performed for 45 minutes, twice a week. Outcomes (swollen/tender joint counts, 30 metre walk time, grip strength, stair climbing, muscle strength, aerobic capacity, and ESR) were assessed after two weeks.

In 1996 Van den Ende et al. reported a prospective randomised controlled study comparing four different exercise programmes in patients with stable RA , all lasting 12 weeks.²⁵ One hundred patients with RA (63 female), of mean age 52 yrs, and mean disease duration 10 years, were studied. Four intervention groups, each with 25 patients are described: high intensity exercise programme (HIE), low intensity group exercise (LIE-gr), low intensity individual exercise (LIE-ind), and a home exercise programme (HE)

The following outcome measures were recorded at baseline, after the 12 week exercise programme and after another 12 weeks: aerobic capacity (VO₂max), muscle strength, joint mobility (EPM-ROM score), functional ability (HAQ, Dutch-AIMS, timed 50 feet walk test, timed 10 flight up and down stair test), disease activity (0-20 swollen joint count, modified RAI 0-69, ESR, CRP), and patient VAS scores for pain, morning stiffness, and tiredness.

In 2000 Van den Ende et al. reported a prospective randomised controlled study comparing intensive and conservative exercise programs in patients admitted to hospital because of active rheumatoid disease.²⁶ This is a very different patient group to most of the other studies where patients had relatively inactive disease. Sixty four patients, of mean age 60 years were studied. Mean disease duration was eight years. Active disease was defined by six or more swollen joints and at least two of: morning stiffness greater than 45 minutes, tender joint count greater than nine, ESR greater

than 28. Patients were excluded if they had serious cardiorespiratory disease, knee arthroplasty, or were unable to walk 15 metres indoors.

All patients had conservative range of motion exercises at low pace and isometric exercises of large joints without resistance, four times a week. In addition the intensive group also had isometric and isokinetic training of knee flexors and extensors. Intensive group patients also had isometric training of shoulder girdle muscles and performed cycling three times a week for 15 minutes to 60% of maximum heart rate.

The mean admission length was 30 days. Patients were assessed at baseline, three, six, 12, and 24 weeks by an assessor blinded to study group. The primary outcome measure was the swollen joint count. Secondary outcome measures were tender joint count, ESR, DAS, patient pain VAS, knee extensor and flexor strength (isokinetic dynamometer), joint mobility (EPM-ROM scale), HAQ, timed 50 feet walk test, and grip strength (Martin vigorimeter).

Westby et al. performed a prospective randomised 12 month study comparing weight bearing, aerobic exercise with usual care in women with RA on low dose oral steroids.²⁷ Thirty women with RA were studied, with a mean age of 56.2 years, functional class I or II, mean disease duration 156 months, and mean oral prednisolone dose of five mg/day. Patients were excluded if they had a known history of osteoporotic fractures, significant cardiovascular disease, planned or recent surgery, previous high dose steroid use, or methotrexate use. The intervention was an aerobic, weight bearing exercise programme three times a week lasting 45-60 minutes, for 12 months. The following outcome measures were assessed by a single rheumatologist, blinded to study group, at baseline and at 12 months: 70 joint swollen and tender joint count, ESR, bone density at lumbar spine and hip (Lunar DEXA), HAQ, activity level (Caltrac accelerometer), and an aerobic fitness estimation (though this was by a self-completed questionnaire). This study had a relatively high drop out rate (21% exercise group, 38% control group). Compliance with the exercise programme was only 71% among the completers.

Methodological quality

Methodological quality of the included studies was independently evaluated by the two authors; disagreements were resolved by consensus, scores ranged between five and ten, with a mean score of 6.9. Half of the papers (9/18) had quality scores of seven or more and were deemed of high quality. According to inclusion criteria, only randomised studies were included in the review, although four papers did not describe clearly the method of randomisation in detail. Allocation concealment was either unclear or not done in eight of the papers. There were significant differences in the groups at baseline in six papers. All included papers specified inclusion criteria and described the intervention in sufficient detail. In one study²⁵ assessments were carried out by an assessor not blinded to allocation groups. In five other papers blinding of outcome assessor was not clear. Co interventions were avoided or similar between groups in 10 papers. Co interventions were significantly different between groups in four papers, and this was unclear in another four papers. All papers presented point estimates and measures of variability for primary outcome measures. The drop out rate was described and acceptable in all but one paper.²⁷ Only eight papers included an intention to treat analysis.

Effectiveness of interventions:

A summary of key outcome results is presented in table 1.

Aerobic exercises:

Harkcom et al. reported an increase in VO₂ max for the exercise groups compared with controls.²⁰ However this only reached statistical significance when the three exercise groups were combined together for analysis (p<0.01). Percentage increases in VO₂ max were 47.2%, 12.8%, and 32.9% respectively in the three exercise groups, compared with 0.5% in the control group. There was an improvement in the active joint count of 39.5% in the three combined active groups compared with 16.3% in the control group (p<0.01). No significant differences were seen in grip strength, muscle

strength or functional status index. The small group sizes (4, 3, 4, and 6 respectively) make meaningful interpretation difficult.

Melikoglu et al. reported a significant increase in the mean serum IGF-1 level in the exercise group (+25.0%) compared with the control group (-16.8%, $p < 0.001$).²⁴

This study also reported a significant improvement in the RAI in the exercise group (-27.2%) compared with controls (-9.3%, $p < 0.05$), and in the pain VAS in the exercise group (-10.7%) compared with controls (+3.8%). No significant differences were seen in IGFBP-3 levels, morning stiffness, or inflammatory markers. Further study of the effect of exercise on key cytokines such as TNF alpha would be of interest.

Strength training:

Hakkinen et al. reported significant improvements in knee extension, trunk flexion and grip strength at one and two years with persisting improvement in knee extension and trunk extension at five years in the exercise group.¹⁵⁻¹⁹

Significant differences between the exercise and control groups were seen for ESR (-59.6% versus -23.3%, $p = 0.015$), HAQ (-65.3% versus -43.7%, $p = 0.01$), and DAS28 (-48.9% versus -40.0%, $p = 0.019$) at one year, in favour of the exercise group. At two years there was persistent significant difference in HAQ and pain VAS, in favour of the exercise group. At five years the DAS28 remained significantly better in the exercise group (-47.7% versus -38.8%, $p = 0.012$), though HAQ and pain VAS were no longer different suggesting that exercise programmes need to be continued to maintain many of the beneficial effects

There was a small but statistically significant difference in hip bone mineral density at one year in favour of the exercise group (+1.1% versus -2.85%, $p = 0.024$). At five years the bone density was reasonably well maintained, but statistical significance was lost (+2.12% versus -0.45%, $p > 0.05$). Spinal bone density did not show any significant difference at any stage. Bone density by DEXA is relatively insensitive to change, and further study of the effect of exercise on bone turnover markers and ultimately fracture rates would be of interest. There was no statistical difference in Valpar 9 scores at two years, or in Larsen scores at five years.

McMeekin et al. reported significant improvements in the timed up and go test (TUG) (-11.1% versus -3.2%, $p=0.005$), pain VAS (-4.9% versus -44.2%, $p=0.031$), and HAQ (-30.0% versus +14.3%, $p=0.036$) all in favour of the strength training intervention.²³ She also reports significant improvements in knee flexor and extensor torque in the exercise group compared with the controls.

Aerobic / strength Combinations:

Bilberg et al. reported no significant differences in aerobic capacity or the physical component of the SF-36 with moderately intensive pool-based exercises.¹¹ The index of muscle function (IMF) however did show significant improvement in the exercise group compared with controls (-59.3% versus -4.3%, $p=0.006$), and the chair test was also significantly improved in the intervention group (+15% versus -4.3%, $p=0.005$). There were also some significant differences in favour of the intervention for a number of muscle endurance outcomes, though the benefits were less marked than in some of the more intensive programmes in this review.

Outcomes from the RAPIT study are reported in four papers.^{10,12,13,14} The mean difference in change in function as measured by the MACTAR score was significantly different and in favour of the exercise group at 12, 18 and 24 months (RAPIT 6.8% improvement v usual care 1.3% improvement, $p=0.017$ at 24 months). There was no significant difference in function as measured by the HAQ score. The authors comment that the MACTAR score may be more relevant here because of its assessment of endurance and ability to perform repetitive complex tasks.

The RAPIT group had significantly more improvement in aerobic capacity (mean change +8.2W versus -6.7W, $p<0.001$) and muscle strength (mean change 26.1N versus 9.6N, $p<0.001$) at two years compared with the control group, in keeping with outcomes from other studies in this review. The mean difference in emotional status as measured by the HADS score was also significantly different and in favour of the RAPIT group at 12 and 24 months (-10% versus +0.9%, $p=0.007$ at 2 years).

Disease activity as measured by DAS4 (RAI and number of swollen joints) decreased in both groups throughout the study with no significant difference between the groups. There was no difference between the groups in terms of ESR or general health.

In the two years of the study the median radiographic damage of large joints did not increase in either group. However it was noted that the mean difference in change of the large joint Larsen score between the groups showed a non significant trend towards more damage in the RAPIT group. Patients with more baseline damage showed slightly more progression in damage, and this was more obvious in the RAPIT group.

This trend was felt to be difficult to interpret by the authors and a retrospective subgroup analysis of the progression of large joint radiologic damage was undertaken.¹⁰ In this paper 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 large joints over 24 months. Baseline radiographic joint damage was the only variable associated with the effect of the RAPIT programme on large joint damage progression. In patients with pre-existing extensive damage of large joints (Larsen score >5, n=59) 85% of the RAPIT group had progression of damage compared with 48% of the usual care group (p<0.05). There was no significant difference in patients without pre-existing extensive large joint damage (Larsen score <5, n=218). In the subgroup with extensive baseline damage, a significantly higher percentage of shoulders and subtalar joints deteriorated in the RAPIT group compared with the usual care group when joints were analysed individually (no significant differences were noted for elbows, hips, knees or ankles). The authors propose that biomechanical instability may be particularly prevalent in these joints in RA, but these findings should be interpreted with caution, as this study was not powered to assess radiological damage.

In terms of bone loss there were only small changes in bone mineral density at the spine and hip over the two years in both groups.¹³ There was a non-significant trend to

less bone loss at the hip in the RAPIT group versus usual care (-1.1% versus -1.9%, $p=0.06$), and no difference between the groups for bone density in the spine (+0.9% versus +0.9%, $p=0.697$). However when analysed by mixed-effect ANOVA, the mean between-group difference in change of hip BMD over the 2 years was statistically significant ($p=0.026$) in favour of the RAPIT group. The change in hip bone mineral density was significantly and independently associated with changes in both muscle strength and aerobic fitness.

de Jong et al. reported the outcomes of small joint damage (Larsen score hands and feet) from the RAPIT study in 2004.¹⁴ The usual care group had slightly more baseline radiological damage than the RAPIT group. There was no significant difference in radiological progression of hands between the groups (12.2% versus 13.0% increase – RAPIT versus usual care), however there was significantly less progression in feet in the RAPIT group (6.5%) compared with the usual care group (11.5%), $p=0.047$.

Multivariate subgroup analysis demonstrated that a higher rate of joint damage was independently predicted by higher baseline damage (unstandardised regression coefficient (standard error) 0.04 (0.02), $p<0.005$), more frequent use of glucocorticoids (0.17 (0.09), $p<0.05$), and a decrease in aerobic fitness (-0.01(0.02), $p<0.05$). Further long term study, powered to detect bony changes, using high resolution ultrasound or MRI scanning would be of interest.

Komaitreddy et al. reported the outcome of a 12 week study of resistive circuit training exercises in patients with RA.²¹ Of note, in pre study screening the authors identified two cases of asymptomatic ischaemic heart disease, underlining the importance of coronary artery disease in this population. Significant improvements in the exercise group compared with the control group were reported for self-reported joint count (-13.9% versus +36.2%, $p=0.02$), sit to stand time (-23.4% versus -3.9%, $p=0.02$), night time pain (-20.6% versus +8.1%, $p=0.05$), and time to anaerobic threshold (-35.1% versus +10.1%, $p=0.02$). No significant between group differences were noted for morning stiffness, hours before fatigue, isokinetic strength, grip

strength, self reported pain and fatigue, physicians joint count, 50 foot walk time, AIMS, HAQ, treadmill time, peak heart rate, time to anaerobic threshold, or VO_2 max.

Lyngberg et al. reports outcomes of progressive interval training over three months in “elderly fragile patients” with RA on low dose oral steroids.²² There were no significant differences between groups for swollen/tender joints, ESR, morning stiffness, grip strength, 30m walk time or VO_2 max. There was a small statistical difference in favour of the exercise group for left ankle plantar flexion torque (-7.1% versus -53.6%, $p=0.04$) though the clinical significance of this is unclear. No significant differences for muscle torque of right ankle or either knee was noted, however, the study was limited by low numbers, short duration and relatively low intensity intervention. The study did note a doubling of the work capacity of the trained patients but this was not recorded for the control group.

In Van den Ende et al’s first paper, the outcomes of four different exercise programmes (1.high intensity exercise, 2.low intensity exercise in a group, 3.low intensity individual exercise, and 4.home exercise) on 100 stable patients with RA from an outpatient population over 12 weeks are presented.²⁵

The high intensity exercise group (group 1) had significantly more improvement in aerobic capacity ($p<0.001$), muscle strength ($p=0.02$), range of movement (EPM-ROM) ($p<0.001$) and the walk test ($p<0.001$) at 12 weeks than the other three exercise groups. The swollen joint count improved by 32.7% in group 1, when the swollen joint count either worsened or did not change in the other groups ($p<0.001$). It should be noted however that the baseline swollen joint count was higher in this group (5.2) than in the others (3.0, 4.4, and 3.6 respectively), with a wide standard deviation (3.2), so this finding should be interpreted with caution.

The exercise programmes lasted 12 weeks. The assessments were also completed after 24 weeks. All significant differences between groups were lost at 24 weeks with the exception of muscle strength ($p<0.001$), underlining the importance of continuing regular exercises. There were no significant between group differences at any time for HAQ, Dutch-AIMS, RAI, pain VAS, global disease activity VAS or ESR. Of note,

the assessments in this study were performed by a single observer not blinded to treatment group.

In Van den Ende et al's second paper the outcomes of a dynamic intensive exercise regimen on hospital inpatients with very active rheumatoid disease (baseline DAS 7.0) are presented.²⁶ Medical treatment was similar in both groups, and both groups had a gradual decline in disease activity throughout the 24 week study. No significant differences in disease activity were observed between the groups. At 24 weeks significantly more patients in the intensive group met modified ACR response criteria than in the conservative group (12 versus 3, $p=0.04$). Joint mobility, the 50 foot walk test and HAQ improved in both groups without significant differences between groups. Measures of muscle strength were significantly better in the intensive group than the conservative group at 24 weeks – (isokinetic extension +36.8% versus +0%, $p<0.05$; isometric extension +51.2% versus +4.2%, $p<0.05$). This study suggests that a short term programme of intensive exercises is well tolerated by inpatients with active disease, resulting in significant improvements in muscle strength without worsening of disease activity. However this study did not assess long term structural changes.

Westby et al. present results of a 12 month weight bearing aerobic exercise program on disease activity, physical function and bone mineral density in women with RA taking low dose prednisolone.²⁷ There were no significant differences in disease activity, physical function or bone density between the groups at the end of the study. There was a significant improvement in fitness estimation (though this was by questionnaire) in the exercise group (+87.1% versus -12.1%, $p=0.001$).

Limitations

A number of the studies included in this review had relatively small numbers of patients. Power calculations to determine sample size are only presented for the RAPIT study group of papers,¹²⁻¹⁴ and for the two studies by Van den Ende et al.^{25,26} increasing the risk of statistical type two error in the other studies. Many of the papers included in this review present a large number of outcome variables. In only a small

number of papers is any statistical allowance made for this in the analysis^{16,24,25} increasing the risk of statistical type one error in the other studies.

The search strategy used in this review deliberately excluded studies that were not randomised controlled trials. Also some studies were excluded because patients with different arthropathies were analysed together. No quality assessment criteria specific to exercise intervention in RA have been validated though the quality assessment score used in this review is a modification of the Delphi list⁷, and similar to that used in the Cochrane review.⁶ It was not possible to perform a quantitative review of the outcomes of these studies because of the widely different patient characteristics, study design and outcome measures used in the different studies.

Summary

The aim of this review was to evaluate the effect of dynamic exercise on patients with RA. With the above caveats, improved outcomes with dynamic exercise in terms of muscle strength, physical function and aerobic capacity were reported in a number of studies. No studies reported worse outcomes for function, disease activity or aerobic capacity with dynamic exercise. Some studies also reported improvements in disease activity measures^{15,19,20,25}, and small improvements in hip bone mineral density.^{13,16} One study reported significantly less progression of small joint radiographic damage of the feet in the dynamic exercise group.¹⁴

However, one study also reported worse large joint radiographic damage in patients using dynamic exercise who had pre-existing large joint damage¹⁰, though this was a retrospective analysis. This is the only paper in this review to report a significantly worse outcome in any group performing dynamic exercise. This was seen only in shoulder and subtalar joints when joints were analysed individually. The reasons for this are not clear. This does deserve recognition, and the use of caution in recommending high impact exercise to some patients, particularly those with high levels of baseline joint damage. Further study to address this issue, using more sensitive imaging techniques are clearly required.

Perhaps the most surprising aspect of this review is that no studies addressed the effect of dynamic exercise on cardiovascular outcomes in terms of coronary artery disease or stroke, or major risk factors for these such as hypertension, dyslipidaemia, obesity or diabetes. Because excess cardiovascular mortality is the main cause of reduced life expectancy in RA, interventions to reduce cardiovascular disease or its risk factors are of vital importance.¹⁻³ It should also be noted that all of these studies excluded patients with significant pre-existing cardiovascular or other serious disease.

Because these studies were of very different designs it is not possible to be definite about which forms of exercise should be encouraged. However when different intensities of exercise were compared²⁵, more benefits were seen with high intensity exercise compared with low intensity. Less intensive pool exercises did not result in any improvements in aerobic capacity.¹¹ Improvements in aerobic capacity were reported by a number of the aerobic and combined exercise programmes^{12-14, 20, 25}, but not by the pure strength training programmes.^{16-19, 25} Conversely the strength training programmes report significant increases in muscle strength but not in aerobic capacity.

It seems sensible therefore, to suggest combined training programmes to address both aerobic fitness as well as strength training. It may be prudent to avoid sports and games involving twisting and rapid joint loading or unloading activities as described in the RAPIT programme¹²⁻¹⁴ for patients with pre-existing large joint damage, pending further study. Exercise programmes should be individualised as much as possible taking into account individual patient and joint factors.

Table 1. Study Characteristics and Outcomes

Study	Participants	Intervention	Primary outcomes	Positive outcomes for exercise group	Quality score / 10
Bilberg et al. ¹¹	47 stable RA	Moderately intense pool exercises Duration: 12 weeks	VO ₂ max, physical SF-36	Index of muscle function, chair test, muscle endurance	9
de Jong et al. ¹²	300 stable RA	RAPIT: cycling, circuits, game Duration: 2 years	MACTAR, HAQ, Large joint Larsen	MACTAR score, V02max, muscle strength, HADS score	9
de Jong et al. ¹³	281 stable RA	RAPIT: cycling, circuits, game Duration: 2 years	Bone density	Hip bone density	9
de Jong et al. ¹⁴	281 stable RA	RAPIT: cycling, circuits, game Duration: 2 years	Larsen score (hands & feet)	Larsen score (feet)	9
Hakkinen et al. ¹⁵	70 early RA	Home dynamic strength training Duration: 12 months	Muscle strength, bone density, DAS28, HAQ	Muscle strength, ESR, HAQ, DAS28,	6
Hakkinen et al. ¹⁶	70 early RA	Home dynamic strength training Duration: 2 years	Muscle strength, bone density, DAS28, HAQ, Larsen (hands/feet)	Hip bone density, HAQ, pain VAS	6
Hakkinen et al. ¹⁷	70 early RA	Home dynamic strength training Duration: 2 years	Valpar 9	None	6

Hakkinen et al. ^{18,19}	70 early RA	Home dynamic strength training Duration: 2 years (5 year follow up)	Muscle strength, bone density, DAS28, HAQ, Larsen (hands/feet)	Muscle strength, DAS28	6
Harckom et al. ²⁰	20 stable RA	Cycling Duration: 12 weeks	Vo2 max, muscle strength, joint counts, functional status	V02 max, joint count	5
Komatireddy et al. ²¹	49 stable RA	Circuits Duration: 12 weeks	Muscle strength, Vo2 max, functional status, joint counts	Self reported joint count, night pain, sit-to-stand time, anaerobic threshold	6
Lyngberg et al. ²²	24 elderly fragile RA on steroids	Cycling and dynamic strength training Duration: 3 months	Joint counts, walk times, muscle strength, Vo2 max, ESR	Left ankle strength	10
McMeekin et al. ²³	36 stable RA	Concentric quad/hamstring training Duration: 6 weeks	Muscle strength, HAQ, pain VAS, TUG	Peak muscle torque, TUG, pain, HAQ	9
Melikoglu et al. ²⁴	40 stable RA	Treadmill Duration: 2 weeks	IGF-1, IGFBP-3, pain VAS, HAQ, RAI, ESR, CRP	IGF-1 level	6

Munneke et al. ¹⁰	281 stable RA	RAPIT: cycling, circuits, game Duration: 2 years (retrospective subgroup analysis)	Large joint radiographic change	None. <i>* More progression of large joint Larsen score in patients with pre-existing damage in exercise group</i>	9
Van den Ende et al. ²⁵	100 stable RA	4 groups: High intensity exercises/cycling; low intensity group exercise; low intensity individual exercise, home ROM Duration: 12 weeks	VO ₂ max, muscle strength, HAQ, joint counts, pain VAS, ESR/CRP	VO ₂ max, joint mobility, muscle strength, swollen joint count	7
Van den Ende et al. ²⁶	64 active RA inpatients	Isometric/isokinetic exercises and cycling Duration: 30 days	Swollen joint count	Muscle strength	8
Westby et al. ²⁷	30 stable RA	Aerobic dance & low load strengthening exercise Duration: 12 months	Swollen/tender joint count, ESR, bone density, HAQ, fitness estimation	Fitness by questionnaire	6

Table 2. Methodological Quality of Studies

Study	Adequate randomisation	Allocation concealment	Groups similar at baseline	Eligibility criteria specified	Description of intervention	Blinding of outcome assessor	Co-intervention avoided	Presentation of point estimates and measures of variability	Drop out rate	ITT analysis
Bilberg et al. ¹¹	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
de Jong et al. ¹²	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
de Jong et al. ¹³	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
de Jong et al. ¹⁴	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Hakkinen et al. ¹⁵	Y	U	Y	Y	Y	U	N	Y	Y	N
Hakkinen et al. ¹⁶	Y	U	Y	Y	Y	U	N	Y	Y	N
Hakkinen et al. ¹⁷	Y	U	Y	Y	Y	U	N	Y	Y	N
Hakkinen et al. ^{18,19}	Y	U	Y	Y	Y	U	N	Y	Y	N
Harckom et al. ²⁰	Y	U	N	Y	Y	U	Y	Y	Y	U
Komatireddy et al. ²¹	U	U	Y	Y	Y	Y	U	Y	Y	N
Lyngberg et al. ²²	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
McMeekin et al. ²³	U	Y	Y	Y	Y	Y	Y	Y	Y	Y
Melikoglu et al. ²⁴	U	U	Y	Y	Y	Y	U	Y	Y	U
Munneke et al. ¹⁰	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Van den Ende et	U	U	Y	Y	Y	N	Y	Y	Y	Y

al ²⁵										
Van den Ende et al. 26	Y	Y	N	Y	Y	Y	U	Y	Y	Y
Westby et al. ²⁷	U	U	Y	Y	Y	Y	U	Y	N	Y

Table 3. Excluded Studies

Study	Reason for exclusion
Baslund et al. ²⁸	Study group with mixed types of inflammatory arthritis
Bearne et al. ²⁹	Control group of healthy subjects
Bell et al. ³⁰	Details of intervention not given
Brighton et al. ³¹	Non-dynamic hand exercises only
Brus et al. ³²	Intervention is education; outcome is compliance with treatment
Buljina et al. ³³	Non-dynamic hand exercises only
Daltroy et al. ³⁴	Pooled data of patients with RA and SLE
Ekdahl et al. ³⁵	Baseline and final data not presented numerically
Eversden et al. ³⁶	Not dynamic exercise (hydrotherapy)
Hakkinen et al. ³⁷	Mixed groups with RA and psoriatic arthritis
Hakkinen et al. ³⁸	Healthy control group
Hakkinen et al. ³⁹	Mixed groups with RA and psoriatic arthritis
Hall et al. ⁴⁰	Not dynamic exercise (hydrotherapy)
Hansen et al. ⁴⁰	Exercise programme not clearly described
Lineker et al. ⁴²	Details of intervention not given (follow up study of Bell et al. ³⁰)
Lyngberg et al. ⁴³	Numerical values, estimates of variability and p values not given for outcome measures

Marcora et al. ⁴⁴	Not randomised
Minor et al. ⁴⁵	Mixed RA / osteoarthritis groups
Minor, Hewett ⁴⁶	Not randomised
Moffet et al. ⁴⁷	Observational study (no control group)
Nordemar ⁴⁹ Nordemar et al. ⁴⁸	Not randomised
Noreau et al. ⁵⁰	Not randomised
Neuberger et al. ⁵¹	Observational study (no control group)
Stenstrom et al. ⁵²	Not randomised
Stenstrom et al. ⁵³	Intervention compared is cognitive therapy
Stenstrom et al. ⁵⁴	Study group with mixed types of inflammatory arthritis
van den Berg et al. ⁵⁵	Internet study; primary outcome measure is physical activity

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