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Full title: The effects of aerobic and resistance exercise on markers of large joint health in stable rheumatoid arthritis patients; a pilot study

Short title: Exercise and joint health in rheumatoid arthritis

Authors:

Rebecca-Jane Law ^{a, b}

Zoe L. Saynor ^c,

Julia Gabbitas ^b,

Jeremy Jones ^{b, d},

Alexandra Kraus ^e,

Anne Breslin^d,

Peter J. Maddison^b,

Jeanette M. Thom ^{b, f*}

^aNorth Wales Centre for Primary Care Research, Bangor University; ^bSchool of Sport, Health and Exercise Sciences, Bangor University; ^cDepartment of Sport and Exercise Science, University of Portsmouth; ^dPeter Maddison Rheumatology Centre, Betsi Cadwaladr University Health Board, Llandudno; ^eRadiology Department, Betsi Cadwaladr University Health Board, Bangor; ^fSchool of Medical Sciences, University of New South Wales, Australia.

*Correspondence to: Dr. Jeanette M. Thom

School of Medical Sciences, University of New South Wales, Sydney NSW 2052, Australia

Email: j.thom@unsw.edu.au

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Abstract

Objective

Exercise is beneficial for people with rheumatoid arthritis (RA). However, patients and health professionals have expressed concern about the possible detrimental effects of exercise on joint health. This study investigates the acute and chronic effects of high-intensity low impact aerobic and resistance exercise on markers of large joint health in RA.

Methods

Eight RA patients and eight healthy, matched control (CTL) participants performed 30-minutes high-intensity low impact aerobic and lower body resistance exercise, one week apart. Primary outcome measures assessing joint health were serum cartilage oligomeric matrix protein (sCOMP) and knee joint synovial inflammation (Doppler ultrasound color fraction; CF). These measures were taken at baseline, immediately post- and 0.5, 1, 2, 6 and 24-hours post-exercise. In a separate study, 9 RA patients completed 8-weeks of progressive exercise training. The same outcome measures were re-assessed at baseline, and at 1-hour post-exercise of training weeks 0, 1, 4 and 8.

Results

RA patients showed higher overall sCOMP [(RA:1347±421, CTL:1189±562ng/ml; $p<0.05$, effect size (ES)=0.32)] and CF when scanned longitudinally (RA:0.489±0.30 $\times 10^{-3}$, CTL:0.101±0.13 $\times 10^{-3}$; $p<0.01$, ES=1.73) and transversely (RA:0.938±0.69 $\times 10^{-3}$, CTL:0.199±0.36 $\times 10^{-3}$; $p<0.01$, ES=1.33) than CTL. However, no acute effects on joint health were observed post-exercise. Similarly, no chronic effects were observed over 8 weeks of combined aerobic and resistance training in RA, with positive effects on physical fitness and function.

Conclusion

RA patients on stable treatment with low disease activity were able to perform an individually prescribed high-intensity low impact aerobic and resistance exercise without changes in markers of large joint health.

Introduction

Regular exercise training in the rheumatoid arthritis (RA) population is associated with improvements in aerobic capacity, muscle strength, functional ability, and psychological well-being (de Jong et al., 2005). Despite this recognized benefit, RA patients generally partake in insufficient levels of physical activity (Lee et al., 2012) and this physical inactivity is associated with a significantly worse cardiovascular risk profile (Metsios et al., 2009). Based on the evidence, combined aerobic and strength training is recommended as part of routine management for patients with RA (Hurkmans et al., 2009) and consequently, exercise promotion is a key role of rheumatology health professionals. However, research suggests that patients harbor concerns relating to the potentially detrimental effects of exercise on their joints (Law et al., 2010). Moreover, health professionals perceive a lack of evidence relating to exercise and joint health (Halls et al., 2012). These perceptions may not be surprising given that the underlying physiological responses to exercise in RA, and in particular relating to the large, weight-bearing joints, are not fully elucidated (Anandarajah et al., 2004).

Intensive exercise offers greater health benefit for RA patients when compared to low-intensity exercise (van den Ende et al., 1996). The intensive exercise program in the study by van den Ende (1996) consisted of dynamic weight-bearing exercises performed at a high pace such as knee bends, step-ups, fast walking, trunk exercises and exercises for the upper body. Twenty minutes of cycling exercise was also performed, whereby heart rate was maintained at 70-85% of age-predicted maximum heart rate. However, one report assessed large joint damage using X-rays and raised concerns that intensive exercise might have a detrimental effect on pre-existing damage in RA patients (de Jong et al., 2003). This was refuted in a follow-up study (de Jong et al., 2009), but because this was a cross-sectional study determining the chronic effects of training, the study was not able to determine whether exercise *per se* aggravates joint damage or inflammation.

Cartilage oligomeric matrix protein (COMP) binds and stabilizes collagen fibers in articular cartilage (Saxne et al., 1992) and has shown promise as a sensitive marker of cartilage breakdown. The measurement of COMP in the serum (sCOMP) has previously been utilized to determine the acute effects of exercise on cartilage breakdown in healthy individuals and people with osteoarthritis. Previous studies including RA patients have reported sCOMP levels ranging from 980 – 2400 ng/ml (Vilím et al. 2003; Momohara et al. 2004; Lindqvist et al. 2005; Wisłowska et al. 2005; Skoumal et al. 2006; Morozzi et al. 2007; de Jong et al. 2008; Fujikawa et al. 2009; Syversen et al. 2009; Christensen et al. 2011). Studies including healthy control participants have reported sCOMP levels within the range of 723 – 890 ng/ml (Kersting et al. 2005; Mündermann et al. 2005; Liphardt et al. 2009; Niehoff et al. 2010; Christensen et al. 2011). Based on median sCOMP levels observed at baseline in 281 patients with RA, de Jong and colleagues defined ‘high’ sCOMP as greater than 1790 ng/ml (de Jong et al. 2008).

Post-exercise increases in sCOMP have been shown to return to baseline (or below) by 1 hour post-exercise in these populations (Mündermann et al., 2005; Andersson et al., 2006b), however the acute response of sCOMP to exercise is yet to be investigated in RA. Following 6 months of exercise training in osteoarthritis patients, there were no significant changes in 1-hour post-exercise sCOMP when compared to pre-training levels (Andersson et al., 2006b). In RA, researchers have found no significant increases in sCOMP following 3 months of intensive exercise, but these authors acknowledged that sCOMP was not measured at a particular time post-exercise, potentially confounding their conclusions (de Jong et al., 2008).

Synovial inflammation is characteristic of RA and can be assessed through quantitative analysis of ultrasound images, termed color fraction (CF) (Terslev et al., 2003). No significant post-exercise changes in CF of the wrist joint were found following a bout of low-intensity handgrip exercise in RA (Ellegaard et al., 2009) and also when RA patients were assessed at baseline and after 8 weeks of low-intensity handgrip training (Ellegaard et al., 2013). However, the acute effects

of high-intensity exercise and the effect of exercise training upon synovial inflammation of the large, weight-bearing joints require further investigation.

Serum C-reactive protein (sCRP) levels provide an indication of systemic inflammation in RA, with levels above 40 mg/L indicating moderately active disease and levels of above 100 mg/L present in severe disease (Amos et al. 1977). sCRP has been assessed in RA patients after continued exercise training, with no significant changes from baseline observed (Neuberger et al. 2007; van den Ende et al., 1996). Disease activity has shown improvements or no change (Stenström et al. 2003) following continued training. Pain levels have also shown improvements following both aerobic (Baillet et al. 2010) and resistance (Baillet et al. 2012) training interventions. However, the acute effects of different modes of exercise on these other disease-related measures need further investigation.

This report includes two studies addressing the limitations in evidence surrounding the effects of exercise on joint health. Study 1 focuses on the acute effects of aerobic and resistance exercise on cartilage breakdown (sCOMP), synovial inflammation, systemic inflammation (sCRP) and knee joint pain. Study 2 investigates the effects of an 8-week combined aerobic and resistance exercise training intervention on these markers of joint health. The overall objective is to provide further information about the acute and chronic effects of high-intensity low impact aerobic and resistance exercise on markers of joint health in RA.

Methods

Recruitment

Participants diagnosed with RA (Arnett et al., 1988) were recruited by means of convenience sampling from outpatient clinics at the Rheumatology Department of the local hospital (Figure 1). Clearance for participation was given by a consultant rheumatologist and patients with medical conditions placing them at unacceptable risk for participation in the study were excluded (e.g.,

underlying cardiac, pulmonary, metabolic, renal, gastrointestinal or other uncontrolled medical conditions). In Study 1, RA patients were included only if they had complained of knee symptoms in the past year. In Study 2, RA patients did not need to have previous knee symptoms to be included. Healthy control participants (Study 1) were recruited from the local area by word-of-mouth and poster advertising and were excluded if they had previous knee symptoms or conditions affecting the joints. Research was carried out in compliance with the Helsinki Declaration and received full ethical approval from the North West Wales Research Ethics Committee (09/WNo01/41).

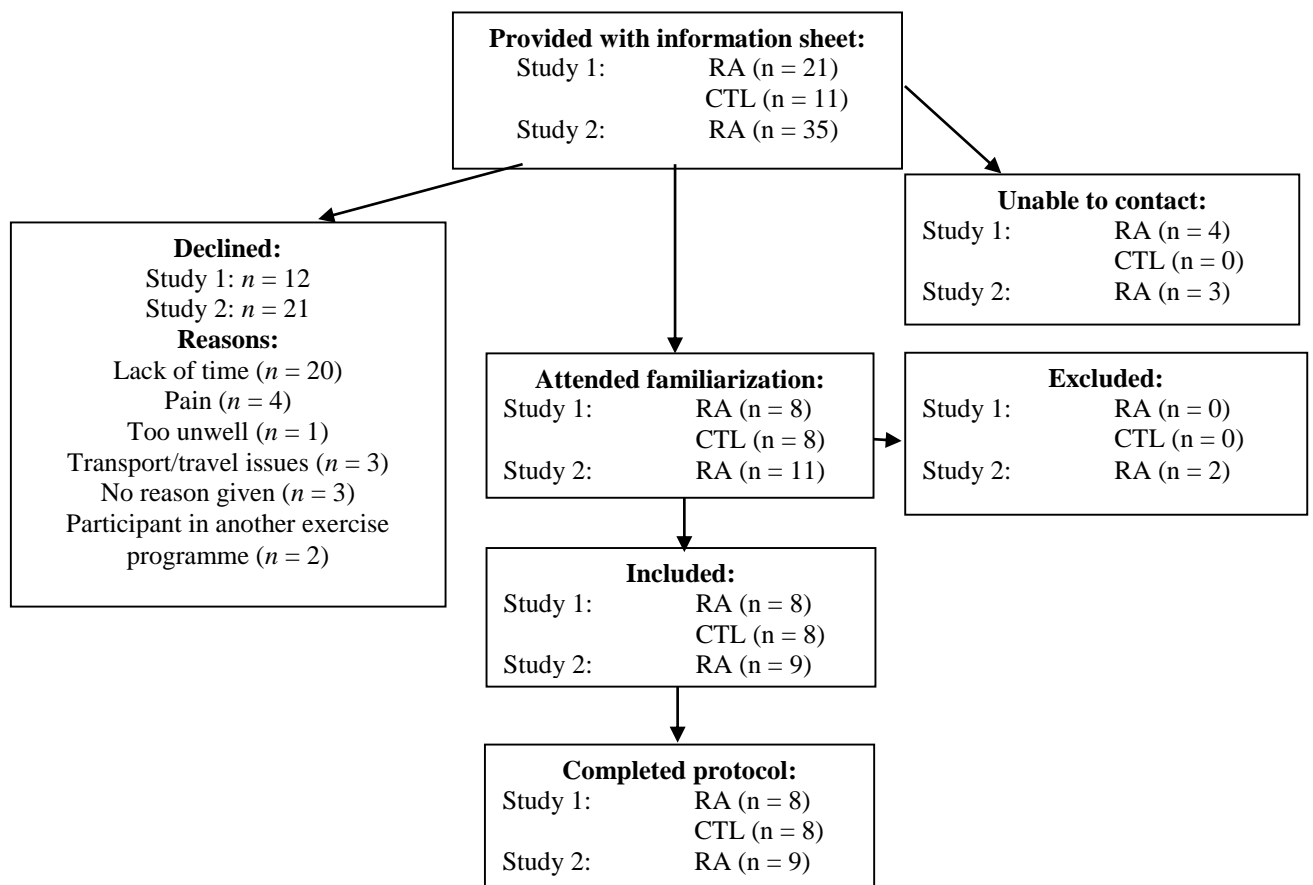


Figure 1. Flow diagram of participant recruitment, familiarization and protocol completion in Study 1 and 2 (CTL = healthy controls, RA = rheumatoid arthritis patients). Note: One of the participants included in Study 1 also participated in Study 2.

Study One:

Study Design

This randomized crossover design, with repeated measures, aimed to investigate the acute effects of exercise on joint health (Figure 2). RA patients were compared with healthy age- and gender-matched controls.

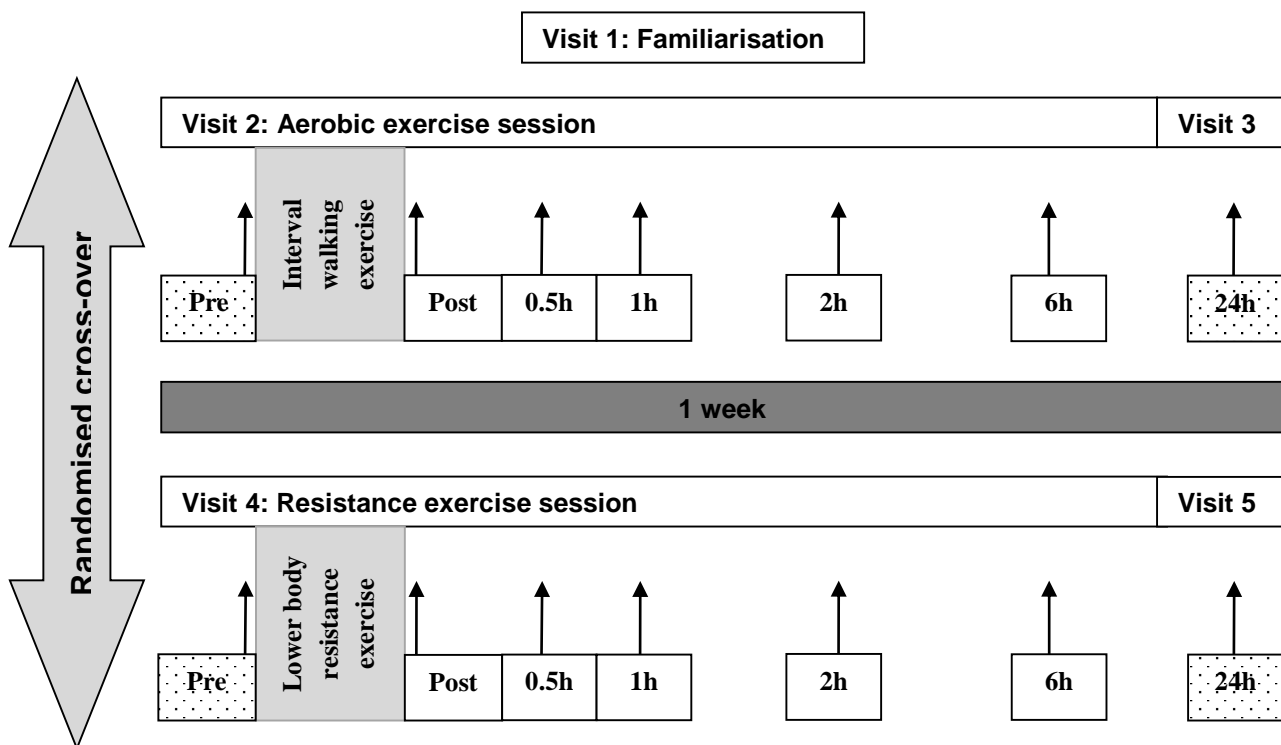


Figure 2. A schematic overview of the Study 1 protocol. Visits 2 - 3 and 4 - 5 (30 minute aerobic and resistance exercise sessions) were completed in a random order, one week apart. Vertical arrows indicate time points at which blood samples and ultrasound assessments were taken.

Outcome Variables

Serum COMP (sCOMP) and knee joint synovial inflammation were the primary outcome variables of interest. Serum C-reactive protein (sCRP), knee joint pain, peripheral and central ratings of perceived exertion (RPE; Borg, 1998) formed secondary outcome variables.

Serum samples for COMP and CRP analysis

A commercially available double monoclonal sandwich enzyme-linked immunosorbent assay (Human COMP ELISA kit KA0021, Abnova Corporation, Taiwan, detection limit < 0.4ng/ml) was used to assess sCOMP. Blood samples were allowed to clot and then centrifuged (4°C, 1500 g). Serum was frozen to -80°C and stored until analysis. For sCOMP analysis, intra-assay and inter-assay coefficients of variation (CV) were 4.9% and 6.6%, respectively and R² curve fit for all curves were > 0.97. High-sensitivity sCRP analysis was performed by the pathology department of the local hospital.

Color Fraction Ultrasonography

Synovial inflammation of the knee joint was determined by ultrasound equipped with vascular software for two-dimensional real-time imaging and color Doppler (MyLab50, Esaote, Italy). With the participant in a supine position, the synovium of both knees was examined at the suprapatellar recess of the knee, longitudinally and transversally, in 20° flexion (Kasukawa et al., 2007). The region of interest (ROI) was identified and defined as the area encompassed by the quadriceps tendon, patella and femur, with 0.5 cm of the patella visible on the screen image. Color Doppler settings were standardized for all participants, with minimal adjustments to gain to reduce artifact.

Blinded images were transferred to a processing program (MatLab, Massachusetts, USA) and a computer-generated box (longitudinal scans: 35 × 17mm and transverse scans: 33 × 23mm; horizontal length × vertical length) was placed on the image to contain as many of the color pixels indicating vascular flow as possible (Fukae et al., 2010). The number of color pixels in relation to the number of gray scale pixels was then expressed in order to determine CF (Terslev et al., 2003). Overall CF (left and right knee combined) obtained from longitudinal and transverse scans, at each time point, for each condition were determined quantitatively. To enable analysis of intra-rater reliability, three separate images were attained for each of the four scanning locations

(longitudinal and transverse on each knee), at each time point (RL). To assess the inter-rater reliability of image analysis, all images from 5 RA patients and 5 control participants were analyzed by another researcher (ZS) using the same methodology. Advice from a consultant radiologist with expertise in musculoskeletal sonography (AK) was sought to qualitatively assess the clinical relevance of any synovial inflammation observed.

Pain and perceived exertion

Knee joint pain was assessed using an adapted version of the Pain Intensity Scale (0 – 10; 0 = no pain at all, 10 = extremely intense pain; Cook et al., 1997) during exercise sessions. Central and peripheral RPE (Rating of Perceived Exertion; Borg, 1998) were assessed at regular intervals during exercise. This involved the patient indicating their perceived exertion on a 6 - 20 numerical scale, with different ratings given for peripheral RPE (exertion relevant to the leg muscles) and central RPE (overall feeling of exertion). A standardized set of instructions was presented to each participant prior to each experimental condition.

Study Procedures

Initial Disease Activity Assessment and Exercise Prescription

During an initial familiarization session, participants completed a standardized departmental health questionnaire, the 4-item Rheumatoid Arthritis Disease Activity Index (RADAI; Stucki et al., 1995) and the Short-Form International Physical Activity Questionnaire (IPAQ; Craig et al., 2003). A self-report questionnaire assessed pain, warmth and tenderness experienced in relation to the knee joint and also enabled patients to qualitatively describe their knee symptoms. The modified health assessment questionnaire (MHAQ) assessed participants' ability to perform activities of daily living and psychological status (Pincus et al., 1999). Exercise tests were then undertaken to individualize exercise intensities for the subsequent sessions.

For aerobic exercise, the protocol for a submaximal treadmill walking test was used as a method to determine individual exercise intensity (Ebbeling et al., 1991). Heart rate (HR) and RPE (Borg, 1998) were recorded to determine the required treadmill speed and gradient for generating high- (70-90% maximum HR; HR_{max}) and low-intensity (40-50% HR_{max}) walking exercise. For resistance exercise, an 8 repetition maximum (RM) was established for leg curl, leg extension and leg press exercises (Whaley et al., 2006). The 8-RM was then converted to 1-RM (Brzycki, 1993) and 80% of this formed the subsequent intensity of resistance exercise. The order in which the exercise bouts were completed was randomized.

Testing of outcome variables pre- and serially post-exercise

At the next testing session, baseline venous blood samples and ultrasound assessments of both knees were taken following 30 minutes of rest (Andersson et al., 2006b). A warm-up and cool-down of 5 minutes walking at a low-intensity was performed prior to and following both exercise sessions. The aerobic exercise session consisted of treadmill walking for 3 minutes at a high-intensity followed by 2 minutes walking at a low-intensity, repeated four times. For the resistance exercise session, one set of fifteen repetitions with half-load was completed before each exercise. Participants then performed three sets of eight repetitions at 80% 1-RM, with 1 minute rest between sets and the three lower body exercises.

In order to provide a suitable range of assessments to describe the post-exercise timecourse of the outcome variables and based on similar studies observing the post-exercise timecourse of sCOMP in other populations (Neidhart et al., 2000; Niehoff et al., 2010, Andersson et al., 2006b; Mündermann et al., 2005; 2009) blood sampling followed by ultrasound assessments were performed immediately and at 0.5, 1, 2 and 6-hours post-exercise. Participants rested in the laboratory in between samples and then returned home. Final assessment of the outcome variables took place in the laboratory at 24-hours post-exercise. Participants were asked to refrain from physical exercise in the intervening period and rested for 30 minutes prior to the final sample

being obtained. The remaining exercise and testing sessions as detailed above were performed the following week.

Study two

Study design

This single cohort observational study with repeated measures was used to investigate the effects of intensive exercise training on joint health. The primary and secondary outcome variables described in Study 1 above were assessed before, during and after an 8-week combined, progressive resistance and walking exercise program. Aerobic capacity, maximum strength and physical function formed additional secondary outcome variables.

Study procedures

Patients with RA visited the laboratory for a familiarization session and baseline assessments. Baseline disease activity score (DAS-28) was performed by consultant rheumatologist (JJ) to determine disease activity. Following a 30-minute rest period, blood samples and ultrasound assessments took place. The submaximal treadmill walking test (Ebbeling et al., 1991) was performed to predict maximal aerobic capacity ($\dot{V}O_{2max}$) and an 8-RM for leg press, leg extension and leg curl exercises was established (Whaley, 2006). Participants also performed two simple functional tests of the lower body; timed '8-foot-up-and-go' and a 30-second 'sit-to-stand' test (Rikli et al., 2001).

At least 2 days after familiarization, participants began the 8-week exercise program. Individually supervised sessions (~1 hour duration) took place in the exercise laboratory and occurred three times per week, with at least 48-hours between sessions. Participants performed a warm-up and cool-down of 5 minutes low-intensity walking on the treadmill and lower body flexibility exercises. The main components of the session included ~30-minutes aerobic interval-based treadmill walking exercise, followed by ~30-minutes lower body resistance exercise as described

in Study 1. During the program, exercise load was adjusted in proportion to progressive improvements in aerobic fitness and specific muscle strength. More specifically, increases in speed (whilst maintaining a walking gait), followed by gradient were used to create the desired % HR_{max} and RPE (> 13 or above; somewhat hard). For resistance exercise, if the participant was able to perform further repetitions at the current load, a 2.5-5% increase in load was attempted in the next session (Kraemer et al., 2004). Predicted $\dot{V}O_{2max}$ and 8-RM were re-assessed at 4-weeks and further guided exercise progression.

To standardize assessment time points, sCOMP, CF and sCRP measurements were taken 1-hour post-exercise at weeks 1, 4 and 8. Additionally, previous research (Mündermann et al. 2005; Andersson et al. 2006b; Mündermann et al. 2009) demonstrated that fluctuations in post-exercise sCOMP return to baseline (or below) by 1 hour post-exercise. Therefore, assessment of sCOMP at this time point enabled determination of the effect of exercise training on the return of sCOMP to baseline levels post-exercise. The remaining outcome variables (predicted $\dot{V}O_{2max}$, predicted 1RM for the three lower body exercises, 8 foot up-and-go, sit-to-stand, pain, DAS-28 and MHAQ) were re-assessed pre-exercise at weeks 4 and 8.

Statistical analysis

All data were analyzed using Statistical Package for the Social Sciences (SPSS, v.17.0), with significance accepted at $p < 0.05$. The Shapiro-Wilk test was used to assess normality. For Study 1, mixed-model factorial analysis of variance (ANOVA) with repeated measures was used. Due to the small dataset and because missing data values for sCOMP and CRP were assumed as missing completely at random, no data imputation was performed (West, 2009). Independent-samples t-tests were used to determine differences in exercise load and intensity between the RA and control groups. To assess intra-rater reliability when performing each ultrasound scan and also to assess inter-rater reliability in image analysis, intra-class coefficient (ICC) analysis was used. Values > 0.70 (Cronbach's α) were considered acceptable (Vincent, 1999). For Study 2,

results were analyzed using fully within-subjects repeated measures ANOVA. Independent samples Cohen's *d* was used to determine effect sizes (ES; Nakagawa et al., 2007). Data are mean \pm SD unless otherwise stated.

Results

Participant demographics

The characteristics of the participants in Study 1 and 2 are presented in Table 1. In Study 1, RA patients had low disease activity and were in a stable phase of their treatment. Those receiving systemic steroids (*n* = 3) were on low doses (< 10mg/day) and no patients had recently received an intra-articular glucocorticoid injection. One patient was taking no medication. In Study 2, medical treatment was stable with the exception of one patient who received a Rituximab infusion at week 4 and another who ceased medical treatment (Methotrexate) during the first week of the intervention and was given a preliminary corticosteroid steroid injection (120mg Depo-medrone) during week 2. This patient did not require any further treatment over the intervention period.

Characteristic	Study 1		Study 2
	RA <i>n</i> = 8	CTL <i>n</i> = 8	RA <i>n</i> = 9
Age (years)	60 \pm 12	60 \pm 14	57 \pm 14
Sex	6 F, 2 M	6 F, 2 M	8 F, 1 M
Body Mass Index (kg/m²)	24.8 \pm 4.1	27.4 \pm 3.8	26.4 \pm 3.2
IPAQ category (number of patients):			
<i>Low</i>	1	1	2
<i>Moderate</i>	5	5	5
<i>High</i>	2	2	2
Disease duration (years)	9 \pm 11	-	13 \pm 10
RADAI (0-11.5)	3.1 \pm 2.2	-	-
MHAQ (0-3)	0.6 \pm 0.4	0.1 \pm 0.1	0.5 \pm 0.6
DAS-28	-	-	2.5 \pm 1.0

Table 1. Baseline characteristics of participants in study 1 (*n* = 16) and study 2 (*n* = 9). M; Male, F; Female, IPAQ; International Physical Activity Questionnaires, RADAI; Rheumatoid Arthritis Disease Activity Index, MHAQ; Modified Health Assessment Questionnaire, DAS; disease activity score.

Study One:

Aerobic and resistance exercise

The RA and CTL groups exercised at a similar workloads during aerobic (RA: 66 ± 9 %HR_{max}, CTL: 60 ± 8 %HR_{max}; $t = 0.886$, $p = 0.392$) and resistance sessions (weight \times number of repetitions, leg press: RA: 3873.8 ± 1874.2 , CTL: 5536 ± 2637 ; leg extension: RA: 568.4 ± 303.0 , CTL: 496.5 ± 390.7 ; leg curl: RA: 165.2 ± 86.6 , CTL: 206.7 ± 122.2 , all $p > 0.01$). Central RPE was similar across both groups during aerobic (central RPE; RA: 11.8 ± 0.47 , CTL: 11.8 ± 1.2) and resistance exercise (RA: 11.8 ± 1.4 , CTL: 12.5 ± 2.2 , $F = .290$, $p = 0.599$). Peripheral RPE was significantly higher during the resistance exercise (peripheral RPE; RA: 13.5 ± 0.4 , CTL: 13.6 ± 0.8) when compared to aerobic exercise (peripheral RPE; RA: 11.05 ± 0.5 , CTL: 11.05 ± 1.2 , $F = 27.2$, $p < 0.01$).

Serum COMP

No significant interactions were observed, however RA patients had sCOMP levels which were 12% higher overall when compared to healthy controls (RA: 1347 ± 421 ng/ml, CTL: 1189 ± 562 ng/ml, $F = 4.077$ $p = 0.046$; $ES = 0.32$, Figure 3a), indicating there were no significant differences over time in either of the groups, after either type of exercise. The average CV when comparing aerobic and resistance baseline sCOMP was 8.4%.

Synovial inflammation

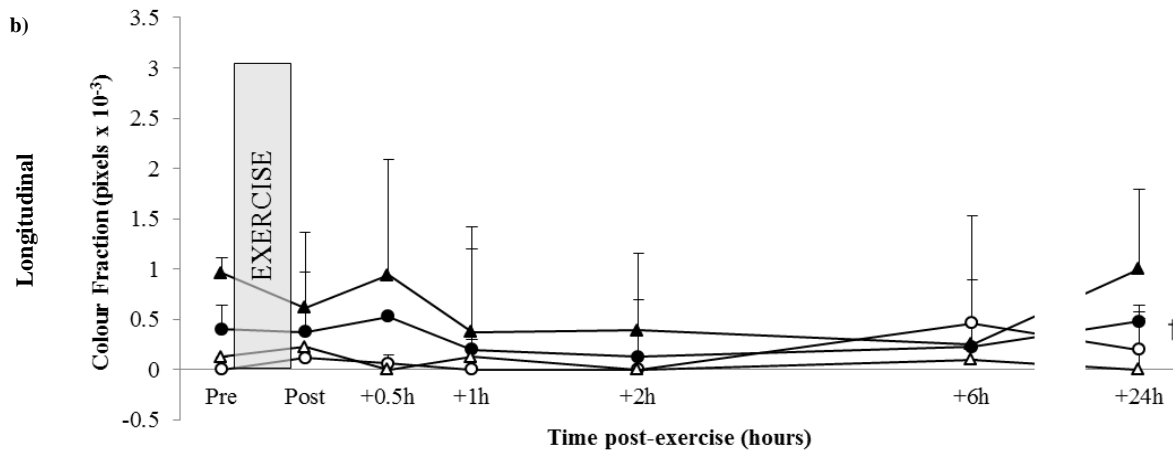
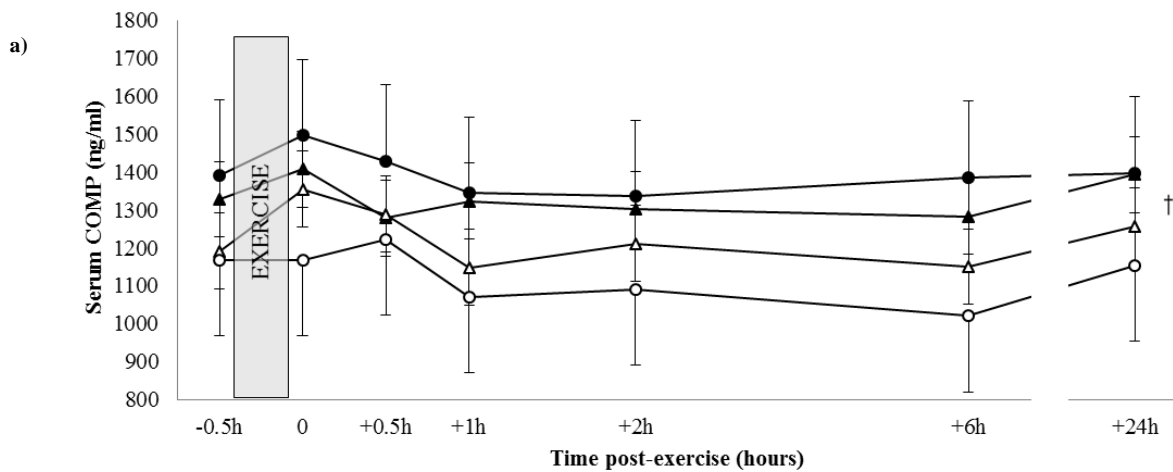
There were acceptable ICC's when examining the inter-rater and intra-rater reliability (Cronbach's $\alpha = 0.80-0.82$). No significant interactions were observed, however the RA group had higher CF overall when considering both longitudinal (mean \pm SD; RA: $0.489 \pm 0.30 \times 10^{-3}$, CTL: $0.101 \pm 0.13 \times 10^{-3}$; $p < 0.01$, $F = 12.323$, $ES = 1.73$, Figure 3b) and transverse scans (RA: $0.938 \pm 0.69 \times 10^{-3}$, CTL: $0.199 \pm 0.36 \times 10^{-3}$; $p < 0.01$, $F = 13.00$, $ES = 1.33$, Figure 3c). Despite differences in CF, the inflammatory blood flow observed at all time points in both RA and CTL

groups were considered very mild and unlikely to be associated with detrimental effects on the synovial joint.

Systemic inflammation and pain

sCRP levels were higher overall in participants with RA when compared to healthy control participants (RA: 14.3 ± 2.1 mg/L, CTL: 1.3 ± 1.9 mg/L; $F = 67.7, p < 0.01, ES = 9.2$), however there were no significant interactions, indicating no worsening of systemic disease activity in the period following exercise.

No pain during either forms of exercise was reported in the control group. The RA group experienced some knee pain during aerobic (0.5 ± 0.7) and resistance exercise (2.2 ± 3.0 ; on a 1–10 scale).



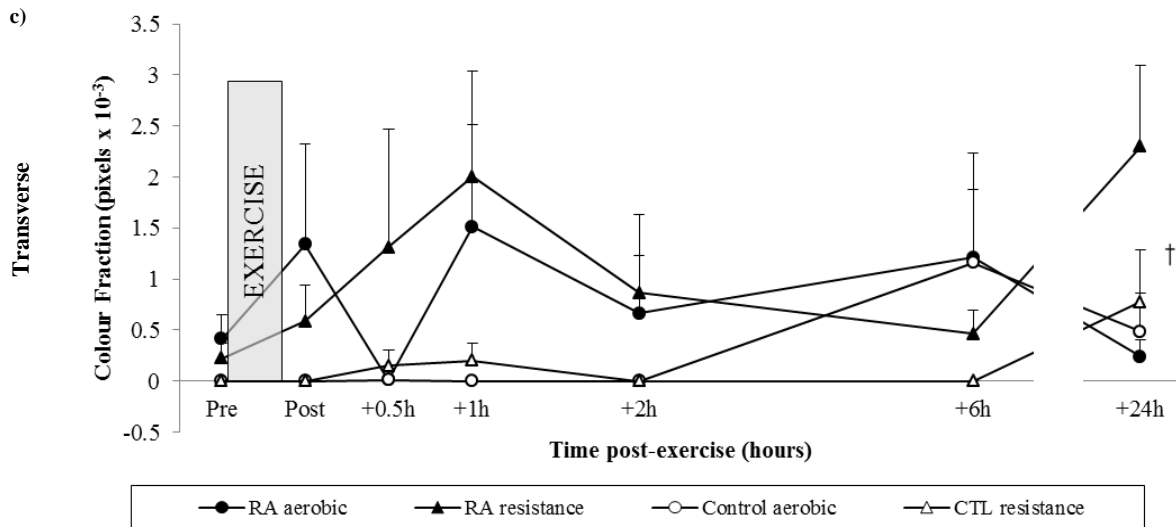


Figure 3. a) The post-exercise time course of absolute sCOMP over time and exercise condition in the RA and CTL group. † = significant main effect for group ($p < 0.05$). Missing values were replaced with individual mean for graphical representation. b) CF response over time and exercise condition in the RA and CTL group for longitudinal scans. c) CF response over time and exercise condition in the RA and CTL group for transverse scans. Data for (a) and (b) are mean CF ($\times 10^{-3}$) of the left and right knee combined. All data are means \pm standard error.

Study 2:

Of a maximum 24 exercise sessions, total attendance was 21.8 ± 3.0 sessions, with the majority of patients ($n = 6$) completing the full number of sessions. However, during the final four weeks, one patient attended only two exercise sessions due to a reaction to a Rituximab infusion.

Over the 8 week training period, average walking speed increased significantly by 14% ($F = 4.69$; $p = 0.049$) and average weight lifted increased by 13%, 37% and 35% for the leg press ($F = 4.09$, $p = 0.04$), leg extension ($F = 4.18$, $p = 0.035$) and leg curl, ($p > 0.05$) respectively. Predicted $\dot{V}O_{2\max}$ improved by 3% ($F = 7.6$, $p = 0.005$), with predicted 1RM increasing by 18% for the leg press ($F = 17.762$, $p < 0.01$), 52% for the leg extension ($F = 12.787$, $p < 0.01$) and 55% for the leg curl ($F = 3.332$, $p = 0.09$). Physical function also improved, with a 9.5% decrease in 8 foot up-and-go time ($F = 4.522$, $p = 0.002$) and a 30.5% increase in sit-to-stand performance ($F =$

13.579, $p = 0.003$). No changes in sCOMP, synovial inflammation, sCRP, pain, disease activity and disability were observed over course of the intervention (Table 2).

	Week 0	Week 1	Week 4	Week 8
<i>Training protocol</i>				
Walking speed (km/h)	-	4.8 ± 1.1	5.1 ± 0.7	5.5 ± 0.6*
Gradient (%)	-	0.81 ± 0.9	1.46 ± 0.8	2.0 ± 1.3**
Leg press weight lifted (kg)	-	127.7 ± 29.3	132.6 ± 29	143.6 ± 31.4*
Leg extension weight lifted (kg)	-	15.0 ± 5.1	15.8 ± 4.5	20.5 ± 7.5*
Leg curl weight lifted (kg)	-	5.8 ± 3.6	6.8 ± 3.9	7.8 ± 3.3
<i>Physical performance</i>				
Predicted VO ₂ max (ml/kg/min)	29.8 ± 8.4	-	32.5 ± 8.3	30.7 ± 7.6 **
Leg press predicted 1RM (kg)	166.2 ± 27.9	-	184.7 ± 36.6	196.9 ± 38.8**
Leg extension predicted 1RM (kg)	21.3 ± 7.9	-	33.6 ± 19.8	32.4 ± 10.2
Leg curl predicted 1RM (kg)	8.1 ± 4.8	-	11.5 ± 5.9	12.8 ± 6.3**
8 foot up-and-go (seconds)	4.2 ± 1.0	-	4.1 ± 1.1	3.8 ± 0.7**
Sit-to-stand (repetitions)	14.4 ± 2.9	-	17.1 ± 3.6	18.8 ± 3.2**
<i>Disease-related variables</i>				
RA-related pain (1-10)	1.4 ± 1.7	-	1.4 ± 1.9	1.3 ± 1.9
Disease activity (DAS-28 score)	2.5 ± 1.0	-	2.6 ± 1.1	2.5 ± 1.1
MHAQ	0.5 ± 0.6	-	0.4 ± 0.6	0.4 ± 0.6
sCOMP (ng/ml)	806.7 ± 258.1	822.5 ± 236.4	748.6 ± 265.9	778.4 ± 283.4
CRP (mg/L)	3.1 ± 1.9	3.2 ± 2.4	5.0 ± 5.2	3.1 ± 2.2
Color Fraction (CF) x 10 ⁻³	0.00	0.00	0.00	0.00

Table 2. Exercise and disease-related variables over the 8-week training intervention. sCOMP, sCRP and CF assessments at weeks 1, 4 and 8 were taken 1-hour post-exercise. * = main effect of time ($p < 0.05$); ** = main effect of time ($p < 0.01$).

Discussion

This study provides new information regarding the acute effects of 30-minutes aerobic and resistance exercise in RA patients and healthy controls (Study 1), alongside the effects of regular high-intensity low impact exercise training (Study 2) on cartilage breakdown, synovial inflammation, systemic inflammation and pain in RA patients. Encouragingly, the main findings demonstrate that despite higher sCOMP observed in the RA group, there were minimal effects on sCOMP over the 24-hour period following both types of exercise. Moreover, participants who completed the 8-week exercise intervention demonstrated improvements in aerobic fitness, lower body strength and physical function, with sCOMP levels remaining similar to baseline. In both studies, synovial inflammation observed at baseline and at all time points post-exercise was very mild. Exercise was not associated with any changes in sCRP, DAS-28 or pain. Following previous concerns relating to the effect of exercise on the health of large weight-bearing joints such as the knee (de Jong et al., 2003), these findings suggest welcome reassurance for patients with stable RA and low disease activity.

In contrast to previous investigations (de Jong et al., 2008), the current study assessed sCOMP at a predefined time in relation to exercise and rest. Although some researchers have found no differences in sCOMP between RA and healthy controls (Christensen et al., 2011), our findings correspond with others who found that sCOMP was significantly higher in RA patients when compared to healthy controls (Skoumal et al., 2004). As one of the functions of COMP is to stabilize the collagen fiber network in articular cartilage and levels in the serum reflect its release from the cartilage, it may be that destructive changes in the joints of people with RA contribute to the higher level of COMP present in the serum (Saxne et al. 1992, Tseng et al., 2009).

As shown in healthy and OA populations (Mündermann et al., 2005; Andersson et al., 2006b), sCOMP in the current study tended to increase post-exercise in both populations, returning to

baseline levels 30-60 minutes post-exercise. Additionally, sCOMP in both the RA and control groups tended to show further decreases following rest (Andersson et al., 2006b; Mündermann et al., 2009). The second increase in sCOMP at five and a half hours observed by Mündermann *et al* (2005), was not observed in the current study.

When considering differences in exercise type, Niehoff and colleagues (2010) observed that in five healthy males, slow knee-bends did not induce any changes in sCOMP whereas running significantly increased levels by approximately 39%. When comparing the walking and resistance exercise in the current study however, there were no significant changes from baseline for either type of exercise, suggesting that the walking and resistance exercise in the current study may not have been as diverse or intense in terms of musculoskeletal load and repetitive impact. Nonetheless, as shown in Study 2 this type of exercise still offered benefits in terms of physical fitness and function when performed regularly.

The effect of exercise training interventions on sCOMP incorporating varying levels of impact have been explored in a healthy cohort, with exercise of a higher intensity resulting in lower post-exercise sCOMP after 12 weeks (Celik et al., 2013). Significant reductions in sCOMP have also been observed in osteoarthritis patients completing 10 weeks of lower-body strengthening exercise when compared to a non-exercising control group (Hunt et al., 2013). In the current study, anticipated improvements in aerobic capacity, muscle strength and physical function were observed (Bilberg et al., 2005; van den Ende et al., 2000; Marcora et al., 2005; Lemmey et al. 2009; Ekdahl et al., 1990; Rall et al., 1996). Importantly however, sCOMP assessed pre-exercise at week 0 was similar to sCOMP assessed 1-hour post-exercise at weeks 1, 4 and 8. This suggests that whilst no decrease in sCOMP was observed following exercise training, continued exercise training in RA does not appear elevate sCOMP levels.

Synovial inflammation of the wrist joint has been assessed quantitatively following low-intensity handgrip exercise (Ellegaard et al., 2009) and the current study addresses limitations in the literature by exploring the effects of intensive exercise and by assessing synovial inflammation of the large, weight-bearing knee joint. In study 1, CF was higher overall in the RA group compared to the control group. However, in response to both types of exercise, and continued exercise training, synovial inflammation was clinically evaluated as very mild and color signal presence was not associated with clinical features such as joint pain or swelling, indicating that any minor fluctuations in CF when quantitatively assessed were not suggestive of pathological changes.

In terms of other RA-related markers, sCRP levels characteristic of the RA population were evident in the current study (Amos et al., 1977). However, there were no significant changes in sCRP or knee joint pain in the immediate time period following either mode of exercise (Study 1). Also of importance for this population, sCRP, DAS-28 and pain remained similar to baseline over the 8-week training period (Study 2).

The current study incorporates a strong research design and the findings offer encouraging information for patients and health professionals regarding the safety of exercise for the large joints of people with RA. However, there are also limitations that should be considered. Firstly, the study findings require further confirmation in a larger population and varying disease states. Secondly, despite showing promise as a marker of cartilage breakdown, questions still remain as to whether an increase in sCOMP indicates breakdown, synthesis, or modification in clearance (Tseng et al., 2009). Furthermore, as COMP is produced and released from other tissues (Di Cesare et al., 2000) the exact origin of COMP detected in the serum is unknown. Despite these limitations, a lack of diurnal variation in sCOMP has been previously observed (Andersson et al., 2006a) and the low CV observed in the current study indicates low within-participant day-to-day

biological variability, thus supporting the stability of sCOMP as a biomarker. Thirdly, evidence of synovial inflammation was minimal in the present cohort and therefore we were unable to determine the effect of exercise in the presence of meaningful synovial inflammation. It is a positive finding however, that despite the increased exercise intensity when compared to previous studies (Ellegaard et al., 2013), high-intensity low impact exercise does not appear to stimulate synovial inflammation. Finally, it is also important to note that whilst clinical remission is now a realistic goal for many RA patients (Jayakumar et al., 2012), application of the current study findings are limited to patients with well-controlled disease.

Further research is required to determine the mechanism of COMP metabolism and the effect of continued, high-intensity exercise on sCOMP levels of patients with active disease and patients with 'high' sCOMP levels (>1790 ng/ml; de Jong et al., 2008). Additionally, identifying patients with overt synovial inflammation would allow the effects of exercise on this outcome to be more comprehensively explored. The effect of long-term exercise programs (i.e. > 3 months) on these outcomes and the best mode of exercise intervention for the diverse subgroups existing in the RA population also warrants further investigation.

Conclusion

This study investigated the effects of high-intensity low impact exercise on markers of joint health in patients with stable RA and low disease activity. Findings showed that whilst absolute sCOMP and CF was higher in RA, the responses to aerobic and resistance exercise were similar in RA and healthy control participants, indicating that having RA does not significantly alter the response to exercise. Similarly, both types of exercise do not appear to adversely affect disease activity or knee joint pain. Similar findings were also illustrated in RA patients over an 8-week combined exercise program, during which significant improvements in aerobic capacity, strength and functional physical capacity were observed, without effects on sCOMP, CF, sCRP or pain.

Given the well-known benefits of exercise and the harmful effects of inactivity, it is anticipated that these findings, alongside those from subsequent research, will help to improve understanding of the acute and chronic response to exercise and potentially alleviate concerns amongst patients and health professionals regarding exercise and joint health.

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