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Exercise and joint health in rheumatoid arthritis

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EXERCISE AND JOINT HEALTH IN RHEUMATOID ARTHRITIS

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Thesis Summary

The benefits of exercise for people with rheumatoid arthritis (RA) are now well-established. However, RA patients are less active than the general population. This may result from previous negative views surrounding the effects of exercise on joint health and limitations in current empirical evidence.

The aims of this thesis were to explore patient perceptions relating to exercise and joint health, alongside determining the physiological effects of acute exercise and exercise training on novel markers of joint health.

Firstly, focus group methodology was used to collect qualitative data, offering a preliminary description of patient perceptions. This data was then used to develop a questionnaire which was distributed to a large population of RA patients. Patients showed an awareness that exercise was beneficial, but were concerned about joint health, how they should exercise and perceived uncertainty amongst health professionals. The factorial validity of the new measure was established and the quantitative data confirmed findings on a larger scale.

To enhance the information available to health professionals, and consequently RA patients, the second part of the thesis explored the effects of exercise *per se* on joint health. Intensive aerobic and resistance exercise showed no acute effect on absolute serum cartilage oligomeric matrix protein, C-reactive protein and minor effects on synovial inflammation (as assessed by colour fraction using colour Doppler ultrasound).

The third part of the thesis investigated the effects of continued intensive training on these outcome variables. Following an eight-week aerobic and resistance exercise training intervention, improvements in aerobic fitness and strength were demonstrated, with no detrimental effects on joint health.

Overall, it is anticipated that the findings from this series of studies will provide further information for health professionals when prescribing exercise and help to alleviate the fears of patients. This may well help to increase exercise participation in this population.

Authors declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

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This dissertation is the result of my own independent work/investigation, except where otherwise stated. Other sources are acknowledged giving explicit references.

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Publications

I was fully involved with all aspects of study design, data collection, data analysis and manuscript preparation for all of the chapters presented and in the following publications that have arisen from this thesis.

Full papers:

Law, R.-J., Breslin, A., Oliver, E., Mawn, L., Markland, D., Maddison, P. J. and Thom, J. (2010). 'Perceptions of the effects of exercise on joint health in rheumatoid arthritis patients.' Rheumatology **49**(12): 2444-2451.

Cooney, J. K., **Law, R.-J**., Matschke, V., Lemmey, A. B., Moore, J. P., Ahmad, Y., Jones, J. G., Maddison, P. and Thom, J. M. (2011) 'Benefits of exercise in rheumatoid arthritis.' Journal of Aging Research **2011**, DOI: 10.4061/2011/681640.

Manuscripts under review:

Law, R.-J., Markland, D., Maddison. P., and Thom, J.M. 'Perceptions of the effects of exercise on joint health in rheumatoid arthritis; a UK-based questionnaire study', Musculoskeletal Care.

Manuscripts in preparation:

Law, R.-J., Breslin, A., Kraus, A., Maddison, P., and Thom., J.M. 'The effects of acute exercise and exercise training on joint health in rheumatoid arthritis'.

Halls, S., **Law**, **R.-J.** Jones, J., Markland, D., Maddison, P., and Thom. J.M. 'Health professionals' perceptions of the effects of exercise on joint health in rheumatoid arthritis patients'.

Peer Reviewed Book Chapters:

Law, **R.-J**., Markland, D.M., Maddison, P. J., Thom, J. M. 'Perceptions relating to exercise in RA' in Rheumatoid Arthritis, Lemmey, A.B. (Ed.), InTech Open Access Publisher, 2011.

Oral conference presentations:

October 2011	**North West Rheumatology Club, Lancaster.** 'The acute effects of exercise on joint health in rheumatoid arthritis'. **Law**, **R. –J**., Thom, J., Maddison, P., Breslin, A., and Kraus, A. **North West Rheumatology Club, Lancaster.** 'Health professionals' perceptions of the effects of exercise on joint health in rheumatoid arthritis patients'. Halls, S., **Law**, **R.-J**., Jones, J., Markland, D., Maddison, P., Thom, J.

April 2011	**British Society of Rheumatology Annual conference, Brighton**. 'Perceptions of issues relating to exercise and joint health in rheumatoid arthritis; a UK-based questionnaire study' (opening plenary session, 'Jewels in the crown'). **Law**, **R.-J**., Breslin, A., Oliver, E. J., Mawn, L. Markland, D. A., Maddison, P. J., and Thom, J. M.
February 2011	**Society for Rehabilitation Research (SRR) Winter meeting, Cardiff**. 'A UK-based questionnaire study of perceptions relating to exercise and joint health among rheumatoid arthritis patients'. **Law**, **R.-J**., Breslin, A., Oliver, E. J., Mawn, L., Markland, D. A., Maddison, P., and Thom. J. M.
April 2009	**British Society for Sport and Exercise Sciences (BASES) Student conference, Hull.** 'The effects of progressive handgrip training on arteriovenous fistula maturation in chronic kidney disease – A pilot study'. **Law**, **R.-J**., MacDonald, J., Jibani, M., Bigwood, B., Williams, D., and Junglee., N.

Poster Presentations:

May 2012	**British Society of Rheumatology Annual conference, Glasgow.** **Law, R.-J**., Thom, J. M., Maddison, P., Breslin, A. and Kraus, A. (2012). 'Cartilage turnover, systemic and synovial inflammation: the acute response to high-intensity aerobic and resistance exercise.' Rheumatology **51**(suppl 3): iii52-iii92.
May 2011	**American College of Sports Medicine Conference, Denver, Colorado.** 'Issues relating to exercise and joint health among people with rheumatoid arthritis; results from a national questionnaire'. **Law**, **R.-J.** Breslin, A., Oliver, E. J., Mawn, L., Markland, D. A., Maddison, P., and Thom. J. Medicine & Science in Sports & Exercise, **43**(5) (supplement to May 2011).
April 2010	**British Society of Rheumatology Annual conference, Birmingham.** 'Exercise and rheumatoid arthritis; what's in it for us?' **Law**, **R.-J.** Breslin, A., Oliver, E. J., Mawn, L., Markland, D. A., Maddison, P., and Thom. J. 'Exercise and Rheumatoid Arthritis: What's in it for us?', Rheumatology, **49**(suppl 1): i139-i143.

Other published abstracts:

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Halls, S., **Law, R.-J**., Jones, J. G., Markland, D. A., Maddison, P. J. and Thom, J. (2012). 'Health professionals' perceptions of the effects of exercise on joint health in rheumatoid arthritis (RA) patients II; A follow-up focus group study.' Rheumatology **51**(suppl 3):iii52-iii92.

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List of abbreviations

Abbreviated words are described in full on the first occasion they appear in the manuscript. Following this, the following abbreviations are used.

ACSM	-	American College of Sports Medicine
ANOVA	-	Analysis of variance
BHPR	-	British Health Professionals in Rheumatology
BSR	-	British Society of Rheumatology
BMD	-	Bone mineral density
BMI	-	Body mass index
CF	-	Colour fraction
COMP	-	Cartilage oligomeric matrix protein
CFA	-	Confirmatory factor analysis
CRP	-	C-reactive protein
CTL	-	Control
CV	-	Coefficient of variation
CVD	-	Cardiovascular disease
DAS	-	Disease activity score
df	-	Degrees of freedom
ELISA	-	Enzyme-linked immunosorbent assay
HBM	-	Health belief model
HR	-	Heart rate
HRmax	-	Age-predicted maximum heart rate
HRR	-	Heart rate reserve
ICC	-	Intra-class coefficient
IL	-	Interleukin
IPAQ	-	International Physical Activity Questionnaire
MET	-	Metabolic equivalent
MHAQ	-	Modified health assessment questionnaire
MMP	-	Metalloproteinase
NICE	-	National Institute for Health and Clinical Excellence
NRAS	-	National Rheumatoid Arthritis Society
OA	-	Osteoarthritis
PRT	-	Progressive resistance training
PFJR	-	Patello-femoral joint reaction force
RA	-	Rheumatoid arthritis
RADAI	-	Rheumatoid arthritis disease activity score
RAPIT	-	Rheumatoid arthritis patients in training
REPS	-	Rheumatology exercise programme
RM	-	Repetition maximum
ROI	-	Region of interest
RPE	-	Rating of perceived exertion
SE	-	Standard error of the mean
SEE	-	Self-efficacy for exercise
SD	-	Standard deviation
SPSS	-	Statistical package for the Social Sciences
US	-	Ultrasound
UC	-	UC
VO_2max	-	Maximal oxygen uptake

Chapter 1. General introduction and literature review

This chapter incorporates text that has been included in the following publications:

Cooney, J. K., **Law, R.-J**., Matschke, V., Lemmey, A. B., Moore, J. P., Ahmad, Y., Jones, J. G., Maddison, P. and Thom, J. M. (2011) 'Benefits of exercise in rheumatoid arthritis.' Journal of Aging Research **2011**, DOI: 10.4061/2011/681640.

Law, **R.-J**., Markland, D.M., Maddison, P. J., Thom, J. M. ‘Perceptions relating to exercise in RA’ in Rheumatoid Arthritis, Lemmey, A.B. (Ed.), InTech Open Access Publisher, 2011.

1.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown aetiology, characterised by both synovial and systemic inflammation and the consequent destruction of bone and cartilage (Gay et al. 1993; Anandarajah et al. 2004). Joint inflammation occurs symmetrically in small and large joints causing pain, morning stiffness, tenderness, and symmetrical soft tissue swelling. When persistent, this leads to joint damage with loss of function and deformity. Extra-articular features include rheumatic nodules and presence of rheumatoid factor (Arnett et al. 1988) as well as symptoms such as fatigue having a profound impact on health-related quality of life (Rupp et al. 2004).

The modified 1987 American College of Rheumatology (ACR) classification criteria for RA is used to define RA, primarily for the purpose of clinical studies (Arnett et al. 1988). Using these criteria, the prevalence of RA has been estimated at approximately 400,000 adults in the United Kingdom population. Women are three times more likely to be affected than men and over 1% of all adult women have the disease (Symmons et al. 2002). Recently, these classification criteria have been revised to improve sensitivity in early disease and hence facilitate early diagnosis (Aletaha et al. 2010).

A prominent characteristic of RA is the extreme inflammatory response, with the synovial and cartilage cells of the joints of people with RA principally affected. The overall pathophysiology of RA involves the abnormal over-production of three main proinflammatory cytokines; interleukin-6 (IL-6), interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α). This over-production is thought to be initiated by complex immune interactions between antigen-presenting cells and T cells (Arend 1997). In the synovium, macrophage-like synovial cells are thought to lead the up regulation of proinflammatory cytokines (Scott et al. 2010). Furthermore, fibroblast-like synovial cells behave abnormally in RA, forming a layer of fibrovascular tissue (pannus) over the joint surface, which invades and destroys cartilage and bone by producing matrix-degrading enzymes (Muller-Ladner et al. 1996; Klareskog et al. 2009). These metalloproteinases (MMP's), and especially MMP1 and MMP3, play an important part in the mechanism behind cartilage destruction as they are able to degrade all important structural proteins in the extracellular matrix of cartilage (Klareskog et al. 2009).

RA is also characterised by bone erosions, osteopenia and synovial vascularisation. This is thought to be dependent on the increased osteoclastic activity brought about by stimulation from macrophage-like precursors and activated T cells. Activation of endothelial cells causes the production of adhesion molecules and also promotes the release of chemokines which act to recruit further inflammatory cells. Inflammatory cells and their products can also stimulate angiogenesis (the growth of blood vessels from the existing vasculature) which may explain the increased vascularisation of the inflamed synovium (Metsios et al. 2006). The main inflammatory cytokines also have systemic effects on the vascular and metabolic system, with persistent systemic inflammation having a potential role in the increased incidence of cardiovascular disease in RA (Kitas et al. 2003; Metsios et al. 2008). The multiple effects of activated inflammatory cells and their products may also explain the flares and chronic nature of the disease (Scott et al. 2010).

1.2 The role of exercise in the treatment of RA

Primarily, the aims of RA management include suppressing disease activity, preventing loss of function, controlling joint damage and pain, promoting self-management and enhancing self-efficacy (Luqmani et al. 2006). In established disease, the need to address likely comorbidities and evaluate the impact of the condition on the patient's quality of life are also important considerations (Luqmani et al. 2009). More specifically, in addition to the aforementioned symptoms, people with RA are at increased risk of developing cardiovascular disease (Metsios et al. 2008), cachexia (Walsmith et al. 2002) and fractures due to osteoporosis (Ekdahl et al. 1990; van Staa et al. 2006). Therefore, the benefits associated with exercise in improving cardiovascular fitness (Hurkmans et al. 2009), stimulating muscle hypertrophy (Marcora et al. 2005; Lemmey et al. 2009) and improving bone mineral density (de Jong et al. 2004b) are especially important for people with RA.

With great advances in drug treatment for RA over the past years, the characteristics of RA patients are changing (Scott et al. 2010) and it may well be that the severity of the disease is lessening (Alcorn et al. 2009). For example, hospitalisation (Ward 2004) and joint replacements (Louie et al. 2010), vasculitis (Bartels et al. 2009) and levels of inflammatory markers (Abelson et al. 2009) are all reducing in RA. Hence, nonpharmacological interventions such as exercise, can now play an important role in treatment and promoting the uptake of an active role in disease management (Scott et al. 2010; Vliet Vlieland et al. 2011). However, knowledge and consequent endorsement of the benefits of exercise for the RA population have not always been well-established. Therefore the next section describes the research advances surrounding exercise in RA, bringing the focus towards the issues associated with joint health and exercise for this population.

1.3 Historical context of exercise and joint health in RA

Historically, treatment for RA has included bed rest and sanatorium stays of up to six months, often including splinting of the affected joints. In the 1950's, Duthie (1951) concluded that pain and swelling of a joint subsided more rapidly and completely if the joint were immobilised for one to three weeks. Swanson (1956) also found that immobilisation of acutely inflamed joints for three weeks controlled symptoms, attenuated the systemic manifestations of the disease and was accompanied by increased well-being. Another trial found that those patients completely immobilised for four weeks showed similar improvements in function and range of motion, alongside greater reductions in inflammation. This was compared to a group who performed active movements daily (Partridge et al. 1963). However, the problems associated with immobilisation and inactivity (i.e. joint contractures, ankylosis, muscle wasting and reduced physical capacity) became increasingly obvious and studies involving exercise treatment began to reveal benefit (Machover et al. 1966; Ekblom et al. 1975; Nordemar et al. 1976; Nordemar 1981; Nordemar et al. 1981). Furthermore, when comparing the effectiveness of high and low intensity training in stable RA, it was observed that the former was more effective, with no detrimental effect on disease activity (van den Ende et al. 1996). The advantages of high-intensity exercise were further confirmed in a later study in patients with active RA (van den Ende et al. 2000).

Nonetheless, some research studies have provoked concern about the safety of exercise for this population. More specifically, whilst high-intensity weight-bearing exercise was shown to be safe and effective for the small joints of the hands and feet (Baslund et al. 1993; Häkkinen et al. 2001; Häkkinen et al. 2003; de Jong et al. 2004c; de Jong et al. 2005) questions were posed as to whether high-intensity weight-bearing exercise could result in further damage in those patients with significant radiologic damage of the large joints (de Jong et al. 2005). However, as will be discussed, it is now evident that regular and intensive exercise is well-tolerated by this patient group (Lemmey 2011) and improvements in fitness have been shown without increasing disease activity or joint damage (Ekdahl et al. 1990; van den Ende et al. 1996; van den Ende et al. 2000; de Jong et al. 2009; Lemmey et al. 2009). Figure 1.1 shows a timeline identifying these key, landmark studies conducted over the last decades. These are discussed further in the following section.

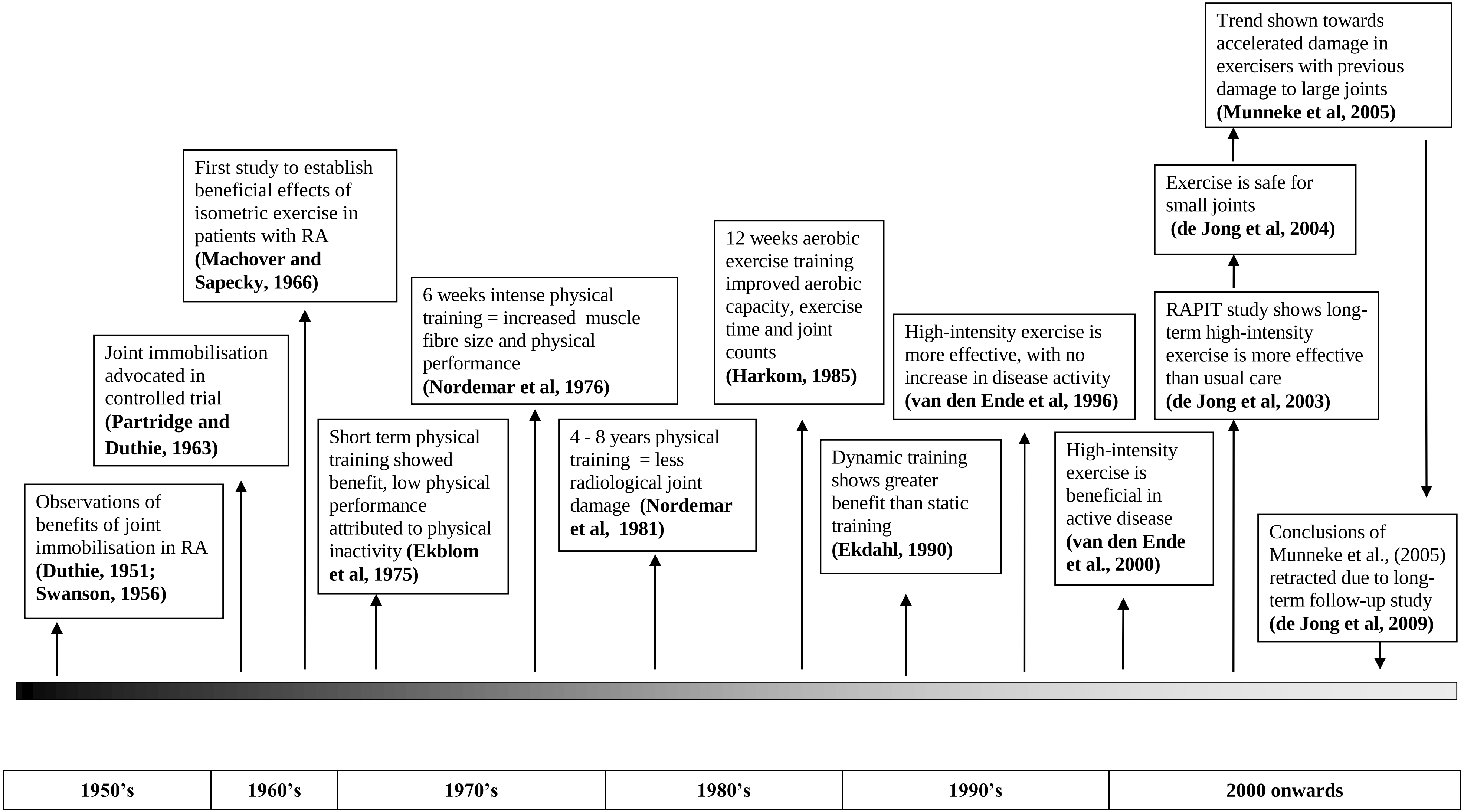

Figure 1.1 A timeline of the landmark studies in the area of exercise, joint health and RA.

1.4 Landmark exercise studies in RA

The studies advocating bed rest and immobilisation have been described in the previous section. However the first researchers to demonstrate that the effectiveness of physical training in RA were Machover and Sapecky (1966). An average strength gain of 23% was observed in eleven RA patients following a seven week resistance training programme. Participants performed maximal isometric contractions of the quadriceps three times a day for five days of the week. A variety of exercise studies conducted over the next few decades were also able to demonstrate improvements in aerobic fitness, strength, physical function and psychosocial well-being (Ekblom et al. 1975; Nordemar et al. 1976; Nordemar et al. 1981; Harkcom et al. 1985; Ekdahl et al. 1990). Furthermore, less radiological joint damage (Nordemar et al. 1981) and improved joint counts (Harkcom et al. 1985) were also observed as a result of exercise training.

The results from several larger scale randomised controlled exercise trials then transpired, with van den Ende and colleagues (1996) firstly comparing the effectiveness of high and low intensity training in RA patients with well-controlled disease. Four different twelve-week exercise interventions were compared; a) high-intensity group exercise; b) low-intensity group exercise; c) individually supervised low-intensity exercise and d) written instructions for home exercise (control group). The high-intensity exercise involved an interval programme of twelve dynamic weight-bearing exercises (e.g. knee-bending, step-ups, fast walking and strengthening exercises for the trunk and upper body), followed by bicycle exercise for 20 minutes (70 - 85% of age-predicted maximal heart rate). A warm-up and cool-down were also included. The low-intensity exercise programme was either performed as part of a group or individually with a physical therapist and involved an hour of range of motion exercises and non-weight-bearing isometric exercises of the trunk and upper and lower body. The exercises were performed at a low pace, and no resistance was applied. Those patients assigned to the home exercise programme were advised to exercise at least twice a week for fifteen minutes following written instructions. The data showed the enhanced effectiveness of dynamic weight-bearing exercise when compared to exercises traditionally recommended to RA patients. After twelve weeks of training, significantly greater improvements in maximal oxygen consumption (VO_2max), joint mobility and overall muscle strength were observed in the high-intensity exercise group (improvements of 17%, 16% and 17%, respectively). Furthermore, no deterioration of disease activity was observed (van den Ende et al. 1996).

A later study by this group (van den Ende et al. 2000) had the objective of ascertaining the effects of high-intensity exercise in RA patients with active disease. These patients had six or more swollen joints, and at least two of following criteria; a) morning stiffness lasting more than 45 minutes; b) tender joint count of more than nine; c) erythrocyte sedimentation rate of greater than 28 mm/first hour. The intervention was slightly different, with all patients following the usual conservative treatment of range of movement and isometric exercises during a period of time in hospital (mean length of hospitalisation was 30 days). Patients allocated to the intensive exercise programme were given additional exercises. Specifically, strength training exercises for the knee extensors and flexors were performed using an isokinetic dynamometer and aerobic training was performed three times per week for fifteen minutes on a cycle ergometer, with heart rate (HR) maintained at 60% of the age-predicted maximum (HRmax). In the case of excessive pain or fatigue, adjustments were made to the intensive programme and recorded accurately. Encouragingly, the authors concluded that the short term programme of intensive exercise was well-tolerated by patients with active disease. Moreover, muscle strength was significantly improved in those patients who were in the intensive exercise group. The benefits of intensive exercise for this subgroup of RA patients were further substantiated as the rate of improvement in disease activity was greater in those patients assigned to the intensive exercise group when compared to the conservative treatment group. In contrast, a steeper decline in pain (i.e. less pain) was shown in patients in the conservative exercise group during the first three weeks. Overall however, the study conclusions provided no evidence that patients with active disease should refrain from exercise due to detrimental effects. Still, the authors acknowledged that the effect of intensive exercise on erosions and cartilage damage had yet to be elucidated (van den Ende et al. 2000).

Consequently, to address the lack of data on the safety and effectiveness of long-term intensive exercise in RA, a series of research studies were conducted. The Rheumatoid Arthritis Patients In Training (RAPIT) study (de Jong et al. 2003) was a randomised, controlled, multicentre trial involving three hundred and nine patients with RA. Patients were randomly assigned to either a two-year intensive exercise programme (RAPIT) or standard physical therapy (usual care; UC). The RAPIT intervention involved supervised, biweekly group exercise of 1.25 hours per session and was followed by participants for two years. After a warm-up, participants performed twenty minutes of bicycle training during which heart rate was maintained at ~70 - 90% of the HRmax with a rating of perceived exertion (RPE) maintained at ‘somewhat strong’ to ‘strong’ (4 - 5). Participants then completed a circuit training session which consisted of 8 - 10 different stations incorporating exercises to train muscle strength, muscle endurance, joint mobility and activities of daily living. Each exercise was repeated 8 - 15 times with a duration of ninety seconds. Rest duration was reduced from ninety to sixty seconds at six months. Following this, participants played an impact-delivering sport or game such as badminton volleyball, indoor football or basketball and then performed a cool-down. Impact loading was also applied during the warm-up and circuit session. Participants assigned to the UC group were only seen by a physical therapist if regarded as necessary by their physician (de Jong et al. 2003).

The primary RAPIT research study (de Jong et al. 2003) described the effects of treatment allocation on functional ability and radiographic progression, alongside emotional status and disease activity. It was found that functional ability and emotional status showed significantly greater improvement in the RAPIT group when compared to UC. Furthermore, radiological damage of the large joints did not increase in either group and no detrimental effects on disease activity were found. However, the authors identified a non-significant trend towards a greater increase in radiological damage to the large joints in the RAPIT group. Further analysis revealed that those patients with greater baseline damage showed a trend towards accelerate joint damage progression, a pattern that was also more obvious in the RAPIT group intervention group. Hence, the authors suggested that further research was necessary to determine the optimal frequency and intensity of loading that would promote preservation of a healthy joint. Consequently, it was recommended that RA patients with considerable damage of the large joints should be prescribed exercises to avoid high-impact on those particular joints (Finckh et al. 2003; Brosseau et al. 2004; Kettunen et al. 2004; de Jong et al. 2005; Plasqui 2008; Luqmani et al. 2009).

The next report of the RAPIT trial concentrated on the damage to the small joints of the hands and feet. This investigation (de Jong et al. 2004c) concluded that those RA patients allocated to the RAPIT intervention, showed significantly less radiological damage to the small joints of the hands and feet when compared to patients allocated to UC. Interestingly, the decrease in erosion rate of the feet was more pronounced when compared to the erosion rate of the hands. Reasoning for this has been suggested, with the hypothesis that the impact-loading associated with RAPIT programme mainly applied to the feet, and thus more advantages in terms of bone remodelling ensued.

This report also brought attention to the differences in disease duration and radiological damage at baseline (due to post-randomisation withdrawal), with the UC group characterised by a longer disease duration and more radiological damage than the RAPIT group. While this may have affected the joint damage progression observed, the authors highlighted that the rate of damage progression in RA has been found to be independent of RA disease duration (Drossaers-Bakker et al. 1999). Furthermore, disease activity or medication use did not differ between the two groups and the main inequality in baseline joint damage between the two groups was in the hands, whereas the feet appeared to benefit most from exercise. Moreover, the authors corrected for differences at baseline and were able to confirm that changes in joint damage progression were favourable for the RAPIT exercise group. In fact, decelerated joint damage has also been found by others in exercising RA patients when compared to non-exercising patients. More specifically, X-rays of the lower extremity taken before and after a mean exercise intervention time of 5.4 years, showed significantly more pronounced joint damage progression in the control group when compared to the exercise group (Nordemar et al. 1981). Overall however, this study (de Jong et al. 2004c) highlighted the need for further research to establish the effects of high-intensity, weight bearing exercise on cartilage metabolism in order to fully elucidate the pathophysioloigcal mechanisms inherent in RA (Anandarajah et al. 2004).

In 2005, Munneke and colleagues (2005) also reported data from the RAPIT study and further examined the aforementioned trend demonstrated towards more joint damage in the large joints of RAPIT participants when compared to UC. This study considered subgroups of patients of older age, longer disease duration, increased disease activity, low muscular or cardiorespiratory fitness, worse functional ability and pre-existing structural joint damage. The study investigated whether these potential risk factors for radiological joint damage were associated with accelerated joint damage as a result of exercise. Findings revealed that only baseline joint damage was found to potentially influence joint damage progression. More specifically, exercise appeared to worsen joint damage progression in patients with previous damage whereas it appeared to have no effect in patients without extensive baseline damage. Furthermore, results demonstrated that the shoulder and subtalar joint were more often deteriorated. Consequently, the authors recommended that patients with a Larsen score [1] of greater than 5 (i.e. changes where X-rays reveal that the original bony outlines have been destroyed) should avoid exercises with excessive loading of the involved joints.

[1] The use of X-ray images to assess the extent joint damage and disease progression. The Larsen scoring method includes both erosions and joint space narrowing in each joint. A single score for each joint is given on a scale of 0 to 5according to reference radiographs and written guidelines. A total score, with details of the joints assessed, forms the overall Larsen score (Larsen, 1977).

Research findings from the RAPIT study also described the effects of the exercise intervention on levels of serum cartilage oligomeric matrix protein (COMP) (de Jong et al. 2008). As later discussed, this biomarker was used as a sensitive indicator of cartilage breakdown (Wisłowska et al. 2005). It was found that there were no significant changes in serum COMP in either group following three months of the RAPIT intervention or UC. However, the authors acknowledge the salient point that they did not collect blood samples at a standardised time with respect to exercise and therefore the effects of recent activity may have influenced levels of COMP in the serum (de Jong et al. 2008).

A follow-up study in 2009 (de Jong et al. 2009), described the compliance of the RAPIT intervention group with continued exercise after the intervention. They also investigated if safety in terms of joint health and effectiveness achieved in terms of physical function was sustained. Two years after completing the RAPIT trial, 78.6% people were still participating in the group exercise sessions. In contrast to the trend initially observed, there were no significant differences in joint damage between those patients who continued exercising and those who did not. However, the authors advised caution when interpreting the results because under half (71/151) of the RAPIT participants were included in the follow-up study analysis due to logistical reasons. Furthermore, the fact that only a small number of RAPIT participants (n = 11) did not continue exercising may have reduced the overall power and applicability of the statistical analysis methods. Therefore, despite these encouraging findings, these aforementioned studies still leave unanswered questions relating to the direct physiological effects of exercise on joint health.

In overall summary, the views and opinions surrounding exercise for the patient with RA have taken somewhat of a ‘rollercoaster ride’ over previous decades. As next described however, there are clear benefits of exercise participation for this population and it is now recommended that regular exercise is incorporated into the routine care of RA patients.

1.5 The benefits of exercise in RA

There are clear and acknowledged benefits of a physically active lifestyle for the general population and there are also numerous known physiological and psychosocial advantages that are especially important for RA patients (Cooney et al. 2011b). Two Cochrane reviews have been conducted to determine the effectiveness, safety and cost-utility of dynamic exercise therapy in improving joint mobility, muscle strength, aerobic capacity and daily functioning in patients with RA (Van den Ende et al. 1998; Hurkmans et al. 2009). The reviews include only randomised, controlled trials that meet stringent inclusion criteria, with six trials included in the earlier review (Harkcom et al. 1985; Minor et al. 1989; Baslund et al. 1993; Hansen et al. 1993; Lyngberg et al. 1994; van den Ende et al. 1996) and a further two studies (Sanford-Smith et al. 1998; de Jong et al. 2003) included in the most recent (Hurkmans et al. 2009).

In the first review, the existence of possible deleterious effects of dynamic exercise therapy (i.e. an increase in pain, disease activity and radiological progression) were examined and it was concluded that there was no evidence of detrimental effects of dynamic exercise therapy on joint inflammation and disease activity (Van den Ende et al. 1998). The second review focussed on the effectiveness and safety of short-term (less than 3 months) and long-term (more than 3 months), land and water-based exercise interventions. It was concluded that short-term, land-based aerobic training had positive effects on aerobic capacity and muscle strength, when combined with strength training. Water-based exercise was also found to have a positive effect on aerobic capacity and physical function although the review was unable to conclude if these benefits are likely to be long-lasting. While the review confirmed the safety of long-term exercise in terms of radiological damage, the safety of short-term exercise remained unclear. However, long-term exercise interventions were deemed ineffective in terms of costs, whilst the cost-effectiveness of short-term exercise remained unclear. In summary, the reviews recommended that combined aerobic and strength training for RA patients should be incorporated into routine practice. However, the optimal duration of exercise intervention, mode of delivery, and the extent of supervision were highlighted as areas requiring further research.

While the Cochrane reviews described above are internationally recognised as the highest standard in evidence-based health care, there are some acknowledged limitations. Firstly, as described previously, advances in medical treatment over the years may also mean that the participants in these previous studies had different characteristics to those of current RA patients (Scott et al. 2010). Secondly, the majority of the participants were female, with low to moderate disease activity and an average disease duration of five to fourteen years. Therefore it is important to note that conclusions may not be relevant to males and those patients who have recently been diagnosed (Hurkmans et al. 2009). Thirdly, as only eight studies met the stringent inclusion criteria, other potentially relevant studies were excluded.

A wealth of additional studies provide further underlining evidence for the benefits of exercise for the cardiovascular and musculoskeletal system, physical function, disease activity and pain. Noting that these studies may have not reached the highest level of rigour and quality required for inclusion into a Cochrane review, these important studies are described in the following section. In addition, the specific benefits of exercise for the joints health of people with RA are also highlighted throughout.

1.5.1 Benefits for cardiovascular health

People with RA have a lower aerobic capacity and a significantly worse cardiovascular risk profile when compared to the general population. Hence, these patients are at increased morbidity and mortality risk from cardiovascular disease (CVD) (Eurenius et al. 2005; Metsios et al. 2008; Metsios et al. 2009). Therefore, the benefits of exercise for increasing cardiorespiratory fitness in RA are of great importance.

Studies incorporating aerobic-based exercise intervention have included cycling (Ekblom et al. 1975; Harkcom et al. 1985; Baslund et al. 1993), walking (Minor et al. 1989), dance (Perlman et al. 1990) (Noreau et al. 1995; Noreau et al. 1997) and aquatic exercise (Danneskiold-Samsoe et al. 1987; Minor et al. 1989) and have all shown improvements in parameters associated with aerobic fitness. For example, the RAPIT study showed that those patients in the exercise group showed a significantly greater improvement in aerobic capacity, whereas those patients in the UC group showed a steady decline (de Jong et al. 2003). An early study by Ekdahl et al. (1990), later confirmed by van den Ende et al. (1996), found that intense dynamic, exercises were more effective than static, low intensity exercises in increasing aerobic capacity. Furthermore, Hakkinen et al. (2003) observed significant increases in aerobic capacity in RA patients following a progressive strength and endurance training protocol. This was also confirmed in patients with both early and longstanding disease (Häkkinen et al. 2003).

As previously mentioned, the most recent Cochrane review supports the positive effect of short-term aerobic training on aerobic capacity (Hurkmans et al. 2009). However, most of the exercise studies to date have focussed on RA-related disease outcomes and improvements in functional ability, and none appear to have assessed any other risk factors for CVD. Therefore, the relationship between physical activity, aerobic fitness and CVD risk in RA requires further research (Cooney et al. 2011b). Nonetheless, the efficacy and safety of cardiorespiratory training for RA patients is evident, with likely cardioprotective benefits. Moreover, analysis of results from the RAPIT trial showed that an improvement in aerobic fitness predicted a decrease in the rate of joint damage, independent of other factors (de Jong et al. 2004c). Thus, it may be postulated that the benefits of aerobic exercise training for muscle, bone and cartilage also offer advantages for overall joint health in this population.

1.5.2 Benefits for muscle

The loss of muscle mass and corresponding increase in fat mass is common in RA and is termed rheumatoid cachexia (Roubenoff et al. 1992). Potential mediators of the phenomenon include reduced insulin action, testosterone and muscle insulin growth factor-1 (mIGF-1). Physical inactivity and the use of high-dose steroid therapy are also known contributors (Gibson et al. 1991; Walsmith et al. 2002; Cutolo 2009; Lemmey et al. 2009).

Progressive resistance training (PRT) has been shown to successfully reverse rheumatoid cachexia. In a pilot study by Marcora and colleagues (2005), ten patients with well-controlled RA completed a twelve-week exercise intervention which consisted of eight resistance exercises (leg press, leg extension, leg curl, standing calf raise, seated row, chest press, triceps push down, biceps curl), performed three times per week. The authors observed significant increases in both arm and leg lean mass when assessed post-intervention. This formed the first study to demonstrate the effectiveness of high-intensity PRT as an adjunct treatment for rheumatoid cachexia. A randomised controlled trial from the same group confirmed that twenty-four weeks of PRT effectively restored lean mass and physical function in patients with RA, with no detrimental effect on disease activity (Lemmey et al. 2009). Furthermore, mIGF-1 was found to be significantly elevated following the 24 week training period. This is an important finding as this hormone is thought to regulate the adaptation of skeletal muscle to loading (i.e. muscle hypertrophy) (Adams 2002).

In addition to an increase in muscle mass, the associated improvement in muscle strength is also an important benefit of exercise for the RA patient. Despite earlier views that RA patients may be resistant to the anabolic effects of exercise (Rall et al. 1996), there is now evidence that this patient group are able to achieve similar increases in muscle strength and favourable changes in body composition (i.e. increased quadriceps femoris thickness and decreases in subcutaneous fat thickness) when compared with age-matched healthy controls (Häkkinen et al. 2005). Furthermore, equivalent muscle quality parameters (muscle-specific force and activation) were observed in cachectic RA patients and healthy controls (Matschke et al. 2010a; Matschke et al. 2010b). In fact, the only studies to find no changes in body composition (Rall et al. 1996) or muscle strength (Komatireddy et al. 1997) as a result of PRT have been deemed somewhat insufficient in terms of training volume (i.e. number of exercises and sessions per week) and intensity (Marcora et al. 2005; Lemmey 2011).

Numerous studies involving a combination of aerobic and strength based exercise training have also demonstrated increased muscle strength (Lyngberg et al. 1994; van den Ende et al. 1996; Häkkinen et al. 1999; McMeeken et al. 1999; van den Ende et al. 2000; Häkkinen et al. 2001; de Jong et al. 2003). Furthermore, the most recent meta-analysis of ten randomised controlled trials concluded that resistance exercise training significantly improved isokinetic, isometric and grip strength (Baillet et al. 2012). Taken together, these findings highlight the importance of including PRT of a sufficient intensity as part of the routine management of RA.

Further advantages of resistance training that are specific to the joints of people with RA have also been proposed. More specifically, the enhanced strength and endurance of the musculature surrounding the joint structure has been suggested to promote joint stabilisation, alignment and attenuation of impact and compressive forces (Bland 1988; Minor 1991). Researchers have also speculated that improved muscle function and joint stabilisation as a result of exercise training has a positive effect on joint inflammation. However, these links are not well-understood (van den Ende et al. 2000).

1.5.3 Benefits for bone mineral density

One of the predominant radiological changes in rheumatoid arthritis (RA) is a loss of peripheral bone. This is thought to be due to the systemic inflammation associated with the disease, treatment with high-dose oral glucocorticoids and a sedentary lifestyle. Consequently, people with RA have a lower bone mineral density (BMD) and are therefore at increased risk of fracture due to osteoporosis (Sinigaglia et al. 2006; van Staa et al. 2006; Franck et al. 2009). Hence, the known physiological benefits of exercise for increasing BMD are extremely important (American College of Sports Medicine 2010).

Data from the RAPIT study (de Jong et al. 2003), demonstrated that participants in the exercise intervention group showed reduced losses in BMD at the hip. Aerobic fitness and muscle strength were also significantly and independently associated with this change. Interestingly however, this was not the case for the lumbar spine BMD, explained by an overall increase in lumbar spine BMD over time (apparent in both groups) and a lack of loading specific to the lumbar spine. These phenomena may offer explanation as to why the intervention did not affect spinal BMD in the same way as the hip (de Jong et al. 2004b). Previous studies have also found positive trends towards improved BMD as a result of exercise training (Häkkinen et al. 1999; Westby et al. 2000; Häkkinen et al. 2001). For example, in a randomised controlled trial evaluating the impact of a two year home-based programme of strength training, changes in BMD were favourable for the exercise group and losses were observed in the control group. However, while these changes did not reach significance over the exercise intervention and follow-up period (apart from changes in the femoral head at 2 years; $p = 0.024$), the authors highlighted that the majority of patients had normal BMD at baseline and that this was maintained, hence disease-related bone loss was potentially avoided (Häkkinen et al. 2001).

Taken together however, the above findings suggest that exercise has an overall advantageous effect for the BMD of RA patients. Furthermore, in terms of benefits for the rheumatoid joint, it appears that adaptation to loading occurs in a site-specific manner (de Jong et al. 2004b) and therefore it may be postulated that increased bone deposition local to the large synovial joints could have important benefits for the overall strength of the joint structure.

1.5.4 Benefits for physical function, disease activity and pain

Loss of physical function is an overall consequence of the joint pain and deformity, muscle weakness and aerobic deconditioning associated with RA (Ekblom et al. 1974; Escalante et al. 2002). Despite the powerful effects of current medications, some patients still suffer from functional limitations that often lead to work disablement. Unfortunately, studies have shown that 20% – 35% of patients with RA stop working within two to three years after disease onset (Jacobs et al. 2011). However, exercise has been shown to significantly improve many of the symptoms associated with reduced physical functioning (e.g. (Ekdahl et al. 1990; Häkkinen et al. 1994; van den Ende et al. 1996; Komatireddy et al. 1997; McMeeken et al. 1999; de Jong et al. 2003; Marcora et al. 2005; Brorsson et al. 2009; Lemmey et al. 2009). Furthermore, a recent systematic review also concluded that both aerobic and resistance exercise interventions reduce the fatigue that commonly limits physical functioning in RA (Mayoux-Benhamou 2006; Neill et al. 2006).

Most studies have utilised subjective assessments of physical functioning such as the Health Assessment Questionnaire (HAQ) (Fries et al. 1980) and its derivatives; the modified HAQ (Pincus et al. 1983) and Multidimensional HAQ (Pincus et al. 1999). These self-report questionnaires involve the patient evaluating their own ability to perform a number of everyday tasks. Encouragingly, a meta-analysis of the effects of cardiorespiratory aerobic exercise, revealed small but significant improvements in the HAQ. However, it was apparent that this improvement was to a lesser extent in those patients with more severe functional status (Baillet et al. 2010). Whilst these self-report measures provide an easy to administer, non-invasive method of assessing physical function, the limitations of the HAQ for detecting improvements in function have been highlighted. For example, in a randomised controlled trial of high-intensity resistance training, significant improvements in objective measures of physical function were observed with 30%, 25%, 23% and 17% improvements in 30 second chair stand test, knee extensor strength, 30-second arm curl test and 50 foot walk test, respectively. However, no change in Multidimensional HAQ was observed (Lemmey et al. 2009). It has been suggested that this is probably due to the inability of the measure to detect smaller changes in mildly disabled patients, such as those often volunteering to be participants in exercise studies (Lemmey 2011). Hence, the use of objective physical measures that reflect activities of daily living are now advocated (van den Ende et al. 1997) and have been used to assess physical function as described in Chapter 6. Furthermore, the most recent meta-analysis of resistance training intervention studies included studies utilising objective measures of physical function and concluded that resistance training is efficacious in reducing functional capacity impairment (Baillet et al. 2012).

In terms of disease activity and pain, a review of the evidence for the benefit of aerobic and resistance training in RA reported that six of the fourteen randomised controlled trials included demonstrated improvements in disease activity, with the others reporting no change (Stenström et al. 2003). Furthermore, in two recent meta-analyses, both aerobic (Baillet et al.

2010) and resistance (Baillet et al. 2012) training has been found to improve post-intervention pain levels. Taken together, these findings suggest that there are no detrimental effects, and often a positive effect, of continued exercise training on physical function, disease activity and pain in RA.

1.5.5 Benefits for the rheumatoid joint

The specific benefits of exercise for the rheumatoid joint are of great importance, especially as this is the most pronounced and invariant element of the RA disease pathology (Maini et al. 2004). As discussed previously, it has been demonstrated that the aforementioned benefits of exercise in terms of improved cardiorespiratory fitness, muscular strength and bone mineral density, also have benefits for the structure and function of the rheumatoid joint (van den Ende et al. 2000; de Jong et al. 2004b; de Jong et al. 2004c). The effects of exercise on the tendons, ligaments and lubrication of the joint also offer important advantages for people with RA.

Recent research has revealed that tendon stiffness, and consequently the efficiency of force production, is reduced in the RA population (Matschke et al. manuscript in preparation). It is thought this is due to the effect of elevated levels of inflammatory cytokines on collagen, leading to damage and disruption of tendon structure. Furthermore, advancing age and physical inactivity are also associated with reduced tendon stiffness (Reeves et al. 2005; Onambele et al. 2006; Reeves et al. 2006). However, in the general population, regular exercise increases the strength of tendons and connective tissue, thus increasing joint stability (Fentem 1994). More specifically, resistance and endurance training has been shown to improve tendon stiffness (Buchanan et al. 2002; Reeves et al. 2006). Therefore, whilst currently unknown, it may be that the potential benefits of exercise training for tendon stiffness may be of increased importance for people with RA. Similarly, it is known that exercise strengthens ligaments and even short periods of immobilisation weakens them (Benjamin et al. 1996; Benjamin et al. 1997). Hence, the potential for exercise to enhance the ability of the ligament to stabilise and guide the joint through its normal range of motion may also be of increased benefit to the RA population (Frank 2004; Cooney et al. 2011b).

The protein responsible for joint lubrication is known as lubricin and it has been noted that RA patients have reduced levels in the synovial fluid. Hence, it has been speculated that this may contribute to the increased friction and cartilage breakdown that occurs in RA (Jay et al.

2004; Elsaid et al. 2007). While it is known that lubricin is secreted by synovial fibroblasts, whether exercise increases lubricin expression in RA is yet to be determined (Jay et al. 2001). However, a process termed film fluid lubrication occurs as a result of exercising the joint, as the movement brought about by exercising the joint causes synovial fluid to be squeezed out between the two joint surfaces (Scholes et al. 2004). Analogous to this, study findings have revealed that joint range of movement is improved with continued exercise training (van den Ende et al. 1996).

It appears that the mechanical loading aspect of exercise may be another mechanism by which exercise exerts a protective effect at the local tissue level (Leong et al. 2011). For example, Ferritti et al. (2005; 2006) have demonstrated that the mechanical signals generated by exercise may also have anti-inflammatory effects, with potentially beneficial consequences for joint tissues. It is thought that these mechanical signals may act to prevent or suppress pro-inflammatory molecule expression. Furthermore, upregulation of anti-inflammatory cytokines IL-4 and IL-10 have been observed *in vitro* and *in vivo* with moderate loading (Millward-Sadler et al. 2004; Ferretti et al. 2005). Furthermore, in osteoarthritis (OA), increased levels of the anti-inflammatory cytokine IL-10 have been found in the intra-articular and synovial spaces after acute resistance exercise (Helmark et al. 2010). In RA patients with moderate disease activity, a reduction in the number of clinically active joints following vigorous exercise interventions has also been observed (Minor et al. 1989; van den Ende et al. 1996).

In summary, despite previously highlighted concerns surrounding the effects of exercise on joint health (de Jong et al. 2003), a growth in evidence supporting the important benefits of exercise for this population has occurred. Consequently, guidelines for use by health professionals when advocating exercise to people with RA have been developed. These recommendations and their limitations will be discussed in the following section.

1.7 Guidelines for exercise in RA

Clinical guidelines have been developed and published for use by health professionals as tools for reducing variation in health care, lowering costs and improving the quality of patient care (Rashidian et al. 2008). Alongside medical treatment recommendations, these guidelines include exercise recommendations for people with RA and, in line with research development, have shown considerable changes over the years.

In 2002, the American College of Rheumatology (American College of Rheumatology Subcommittee on Rheumatoid Arthritis 2002) recommended 'instruction in a home programme of joint range of motion and strengthening exercises'. Furthermore, they advocated 'regular participation in dynamic and even aerobic conditioning exercise programmes'. The Ottawa Panel (Brosseau et al. 2004) also supported the benefits of therapeutic exercise interventions for people with RA and highlighted improvements in overall function, and the reduced number of sick leave observed as a result of exercise participation. However, with a view that high-intensity exercise may exacerbate the inflammatory process and risk joint damage, low-intensity exercise programmes were seen as favourable in terms of pain control and improving functional status.

More recently, the American College of Sports Medicine (ACSM) recommended low-impact and functional exercises and stretching whenever possible. They also advised that stair climbing, contact sports, one-legged stance and rapid stop-and-go actions, should be avoided in those with knee involvement. Furthermore, it was recommended that patients avoid activities that cause increased joint pain and that post-exercise soft-tissue discomfort should be expected (Minor et al. 2009).

Later recommendations by the ACSM highlighted that although exercise should be advocated, specific guidelines regarding type, frequency and intensity of exercise have not been addressed. However, based on the evidence from fifteen randomised clinical trials (Stenström et al. 2003), the ACSM recommend aerobic exercise (i.e. walking, aquatics, bicycling) at an intensity of 60 - 85% of age-predicted (220 - age) maximum HR (HRmax), performed three times per week, alongside resistance training (i.e. use of weight machines, dumbbells, elastic bands) at an intensity of 50 - 80% of one repetition maximum (1RM; see Chapter 5 for definition), 2 - 3 times per week. They also advise that modifications of intensity based on previous activity levels, joint range of movement and potential flare-ups should be made where necessary (Millar 2010).

The European League Against Rheumatism guidelines (Combe et al. 2007) offer similar exercise guidance and recommend that non-pharmaceutical interventions such as dynamic exercises, occupational therapy and hydrotherapy can be applied as an adjunct treatment to pharmaceutical interventions in patients with early arthritis. However, they also state that the optimal exercise programme is yet to be determined and that their recommendations relating to early RA are based upon the extrapolated results of randomised controlled trials in patients with established RA.

The guidelines from the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) for the management of RA have issued two separate guidelines; one for application during the first two years (Luqmani et al. 2006), and one for application after two years of disease onset (Luqmani et al. 2009). The former recommends that 'aerobic exercise should be encouraged to help combat the adverse effects of rheumatoid disease on muscle strength, endurance and aerobic capacity.' They specify the benefits of range of movement, strengthening and aerobic exercises have important benefits for reducing stiffness, improving flexibility, strength, cardiovascular fitness, physical function and weight control. They also highlight that dynamic aerobic exercise can be undertaken without exacerbation of disease activity. However, the guidelines also acknowledged that the long-term effects were unknown. The BSR and BHPR guidelines for 'after the first two years' highlighted that exercise was effective in improving function and reducing the rate of bone loss (Luqmani et al. 2009). However, attention was again drawn to the studies that urged caution of the use of high-intensity weight-bearing exercises for fear of detrimental effects for the rheumatoid joint. These guidelines also state that increasing the knowledge surrounding attitudes towards physical activity in RA was also necessary in order to establish the factors that would encourage people to exercise. This will be further discussed later in this chapter as part of Chapters 3 and 4 of this thesis.

The current guidelines published by the National Institute for Health and Clinical Excellence (NICE) are the most recent guidelines for the management of RA in adults (National Collaborating Centre for Chronic Conditions 2009). The NICE guidelines consist of recommendations on the most effective ways to diagnose, treat and prevent disease and ill health and are based on systematic reviews of best available evidence (Deighton et al. 2009;

NICE 2011). They state that exercise is beneficial for most people with RA and recommend that patients should have access to specialist, periodically reviewed physiotherapy, in order to encourage exercise and hence improve general fitness. Furthermore, NICE highlights that it is important for patients to learn exercises to help with the management of functional impairments, enhance joint flexibility and increase muscle strength (National Collaborating Centre for Chronic Conditions 2009). However, they also note the lack of cost-effectiveness of interventions such as the RAPIT programme when compared to usual care (de Jong et al. 2003). Concordance with exercise was highlighted as a particular problem and that it is important for all members of the multidisciplinary team to provide a consistent and supportive message regarding the benefits of exercise. Finally, corresponding with others, NICE also recommends that further research should take place with regards to the best methods of delivery, the optimal mode and level of activity, and methods of maximising long-term concordance (National Collaborating Centre for Chronic Conditions 2009).

1.7.1 Summary and perspective

Despite the aforementioned advantages of exercise, alongside established guidelines recommending exercise for this population, RA patients are significantly less active than the general population (Sokka et al. 2008), with worrying evidence that over two in five (42%) RA patients (n = 176) performed no ten minute bouts of moderate-to-vigorous activity during a week of monitoring (Lee et al. 2012).

This lack of physical activity is likely due to the barriers that exist in relation to exercise, with numerous barriers existing within the general population (Trost et al. 2002). However, there are additional barriers that are specific to the RA population, arising as a result of the local and systemic characteristics of the disease. It may also that people with arthritis are attitudinally different from other clinical and healthy populations and that factors which commonly deter people from exercise may not be the same for people with arthritis (Gecht et al. 1996). Hence, as beliefs have been shown to be related to the adoption of health behaviours such as exercise (Janz et al. 1984), previous research has explored the perceptions of RA patients in relation to exercise. The next section of this Chapter focuses on this important area.

1.8 Perceptions of RA patients in relation to exercise

The perceptions of people with RA are important for health professionals to consider when talking about exercise as part of the consultation. Due to the previous views surrounding the safety of exercise for people with RA, limitations within the current empirical evidence and a lack of specific exercise recommendations in the current guidelines, negative perceptions about exercise may still exist in the RA population and amongst health professionals. This issue may well form an important contributing factor to the high levels of inactivity observed in this patient population (de Jong et al. 2004a; Lee et al. 2012). As later discussed, previous researchers have investigated generalised perceptions and barriers relating to exercise in people with various forms of arthritis and have used both qualitative and quantitative methodologies to explore this area and generate data.

1.8.1 Qualitative and quantitative methods of assessing patient perceptions

Qualitative research attempts to interpret phenomena in terms of the meaning that people bring to them (Denzin et al. 2005). Qualitative research methods allow the researcher to gather rich, plentiful data and enables an in-depth description of experiences, thought-processes and beliefs (Kitzinger 1995; Ong et al. 2006). Focus groups are often used as an exploratory means of generating qualitative data and can be defined as ‘a carefully planned discussion designed to obtain perceptions relating to a defined area of interest in a non-threatening environment, where participants share and respond to comments and ideas’ (Litosseliti 2003). This method involves the researcher creating groups that are similar enough to enable comparison but diverse enough to stimulate discussion and is known as purposeful sampling (Barbour 2007). In comparison with one-to-one interview approaches, focus groups encourage interaction amongst participants, challenging views and stimulating new ideas. Furthermore, grouping individuals associated by a common theme (i.e. having RA) often works to facilitate openness in discussion (Kitzinger 1995; Ong et al. 2006).

Focus groups can also be helpful in facilitating the development of useful and valid research tools to collect quantitative data (McLeod et al. 2000). This methodology has been used by several researchers during the initial phase of studies to develop questionnaire items (Lineker et al. 1996; McKinley et al. 1997; Eys et al. 2009). The role of focus groups in such an approach is to ensure that the questions being asked are contextually relevant, appropriate and easily understood by respondents (Dumka et al. 1998; McLeod et al. 2000). In comparison to qualitative research techniques, questionnaire-based studies allow the collection of larger amounts of quantitative data. One of the limitations of questionnaire studies is that they are typically deductive in nature and rely on keeping to a pre-planned research design (Gray et al. 2007). However, this systematic collection of large amounts of data allow the use of statistical techniques to determine the reliability and validity of the instrument developed (Floyd et al. 1995). Both focus groups (Hill et al. 1991; Scharloo et al. 1998; Ahlmen et al. 2005; Coenen et al. 2006) and questionnaires (de Jong et al. 2004a; Eurenius et al. 2005; Ehrlich-Jones et al. 2011) have been used by previous researchers to explore the perceptions of people with various forms of arthritis.

1.8.2 Perceptions relating to exercise and joint health

Previous researchers have investigated the views and beliefs of people with arthritis in relation to exercise and have highlighted numerous barriers and facilitators. Physical barriers have included limited physical ability, pain and fatigue. Medications and complications associated with additional co-morbidities alongside environmental barriers such as a lack of time and transportation are also commonly highlighted. Psychological aspects including a lack of enjoyment, motivation and confidence have also been identified as additional barriers. On the other hand, receiving assistance from instructors and the opportunity for social interaction are established factors that encourage patients with arthritis to exercise (Schutzer et al. 2004; Wilcox et al. 2006; Neuberger et al. 2007; Gyurcsik et al. 2009; Hutton et al. 2009). Encouragingly however, research has also revealed that people with arthritis believe exercise to be an important factor in treatment (Lambert et al. 2000).

With specific relevance to perceptions relating to exercise and joint health, joint pain has been highlighted as a definitive barrier to exercise and has also been perceived as a prominent factor in determining patients' exercise behaviour (der Ananian et al. 2006; Wilcox et al. 2006; Gyurcsik et al. 2009; Hutton et al. 2009). Researchers have also explored differing perceptions according to the type and intensity of exercise performed by people with arthritis, with the least positive beliefs reported for aerobic exercise (Iversen et al. 1999). More recently, Munneke et al. (2004) administered an expectancy-value questionnaire consisting of two negative (joint damage and increased inflammation) and two positive outcomes (improved fitness level and ‘feel better’) to which participants indicated their level of agreement in relation to a conventional and a high-intensity exercise programme. They found that the outcome expectations of RA patients, rheumatologists and physiotherapists for high-intensity exercise were significantly less positive than those for a conventional exercise programme. This was despite the common belief that this type of exercise was attainable for the majority of patients. Of further interest, a qualitative study by Hendry et al. (2006) investigated the perceptions of OA patients regarding exercise and identified four patient typologies; 'long-term sedentary', 'long-term active', 'exercise converted' and 'exercise retired'. Interestingly, the latter group had previously exercised but had stopped because of their symptoms and because they believed exercise was damaging their joints. It is possible that similar perceptions exist within the RA population and hence this area requires further exploration.

1.8.3 The effects of exercise perceptions on exercise behaviour

In terms of the effect of perceptions about exercise on exercise behaviour, the Health Belief Model (HBM) (Janz et al. 1984) is widely accepted as an organising framework for explaining and predicting the acceptance of health and medical care recommendations. The model suggests that behaviour is based on a desire to get well and the belief that a specific health action will have a positive impact on disease. In arthritis, Gecht et al. (1996) used this model as a framework to investigate patient beliefs associated with self-efficacy, barriers to exercise, the benefits of exercise and the impact of exercise on arthritis. With guidance from a focus group including RA patients who were currently exercising, a questionnaire designed to assess exercise beliefs was developed. The authors concluded that belief in the benefits of exercise was a strong and significant predictor of participation and consequently suggested that a positive mindset may be necessary to overcome the longstanding opinion that exercise exacerbates arthritic disease. Correspondingly, it may be that if the perception of exercise as a positive feature of RA treatment is to supersede any negative connotations, continual emphasis and education of the benefits is critical (de Jong et al., 2004, Gecht et al., 1996; Neuberger et al., 2007).

The confidence that patients have in their own ability to exercise (i.e. self-efficacy for exercise), was significantly associated with exercise behaviour ($p = 0.047$). This association is consistent in both the general population and those with a chronic illness (Kaplan et al. 1984; McAuley et al. 2000). The study by Gecht and colleagues (1996) also demonstrated that disease severity was the most important factor in determining whether participants in this study exercised or not. Overall, they concluded that targeted interventions designed to strengthen belief in the benefits of exercise and self-efficacy for exercise among people with arthritis were necessary, particularly in people with moderate to severe disease-related limitations (Gecht et al. 1996). More recently, Ehrlich-Jones et al. (2011) investigated the relationship between physical activity levels and beliefs, motivation and worries about physical activity in people with RA. They found that people with more positive beliefs about physical activity and an increased motivation towards physical activity were more physically active. This was independent of age, sex, race, body mass index and disease severity (Ehrlich-Jones et al. 2011).

Whilst studies in this area have yielded interesting results, there are various limitations inherent to the focus and design of previous investigations. In the study by Gecht and colleagues (1996), only one focus group was conducted with a small number of participants, all of whom were attendees of a low-impact aerobics programme for people with RA. Furthermore, this research used concepts of the HBM as a framework for content analysis of the focus group data and the creation of questionnaire items. Hence, the analysis was not fully inductive and therefore alternative perceptions may have been 'missed'. Furthermore, 52% of the patients completing the questionnaire developed by Gecht et al. (1996) had OA or 'unknown arthritis', without distinction between the views of the various types. The findings from the study by Hendry and colleagues (2006) also only included people with OA. However, it may be that differences in the manifestation of RA (such as inflammatory flares and fatigue), alongside the previous concerns about the effects of exercise on joint health for this population also affect the perceptions of RA patients. Therefore, the perceptions specific to this patient group and particularly in relation to effects of exercise on joint health, are important to explore.

1.8.4 Summary and perspective

Overall, the studies investigating perceptions relating to exercise have included people with various forms of arthritis. The perceptions specific to RA patients, particularly in relation to exercise and joint health, are yet to be fully explored and hence require further investigation.

The concerns amongst RA patients regarding exercise and joint health described in Chapters 3 and 4 of this thesis also highlight the importance of establishing the physiological effects of exercise specific to the rheumatoid joint. Moreover, the control of joint damage and inflammation are salient aspects of treatment and therefore it is of paramount importance to determine if these characteristics of the disease are worsened by exercise. However, knowledge surrounding the *direct* effects of exercise *per se* on the health of the rheumatoid joint is an under-researched area. The following sections of this chapter will discuss the literature available regarding the physiological effects of exercise on joint health, specifically focussing on cartilage breakdown and synovial inflammation.

1.9 Joint health, cartilage breakdown and exercise

Joint damage accounts for approximately one quarter of disability in established RA, with strong and potentially causal relationship between joint damage and disability also evident, particularly in late RA (Scott et al. 2000). RA-related damage to the joints is routinely assessed using X-ray methodology to detect bony erosions. Whilst these methods (e.g. Larsen scoring) are viewed as the gold standard for assessing joint damage, these are insensitive to subtle changes in joint destruction (de Jong et al. 2005). Additionally, a recent study examined the differential effects of cartilage damage and bone destruction on physical disability in a large cohort of RA patients (n = 748). This study used joint space narrowing scores to assess cartilage damage, and erosion scores to assess bone destruction and found that cartilage damage was more clearly associated with irreversible physical disability. The authors also suggested that because relatively little cartilage degradation appears to be necessary to cause impaired physical function, the importance of preventing this form of joint destruction is of increased importance (Aletaha et al. 2011). Therefore, enhanced knowledge relating to the effects of exercise on cartilage, specific to the joints of people with RA is essential.

Physiological loading of cartilage tissue is required to maintain tissue homeostasis and cartilage integrity (Leong et al. 2011). However, both reduced loading and overloading can cause cartilage degradation. Excessive mechanical stress can directly damage the extracellular matrix of cartilage, shifting the balance in cartilage cells (chondrocytes) from increased anabolic to catabolic activity (Sun 2010). On the other hand, the detrimental effects of reduced loading have also been demonstrated. Animal studies have shown that prolonged immobilisation is associated with cartilage thinning (Jurvelin et al. 1986; Haapala et al. 1999) and tissue softening (Jurvelin et al. 1986; Haapala et al. 2000). Furthermore, immobilisation has been associated with reduced proteoglycan[2] content (Haapala et al. 1996; Haapala et al. 1999; Roughley 2006) and cartilage matrix fibrillation, ulceration and erosion (Evans et al. 1960; Hagiwara et al. 2009). In addition, a study of twenty patients with ankle fractures, magnetic resonance imaging revealed a significant degree of cartilage thinning in all components of the knee after a seven week period of partial weight-bearing at the knee (Hinterwimmer et al. 2004). This cartilage degradation associated with reduced loading may

[2] Proteoglycans are essential for cartilage structure and function, creating the turgid nature and provide the osmotic properties needed to resist compressive loads (Roughley, 2006).

well also occur in response to the low levels of physical activity characteristics of the RA population.

Whilst there are postulated effects of activity and inactivity, knowledge relating to cartilage metabolism and exercise in RA is limited. Therefore, the utilisation of a marker specific to cartilage breakdown is essential to advance the understanding of the effects of exercise. This is particularly important to establish in relation to the large joints of people with RA. As later discussed, previous researchers have utilised the biomarker serum COMP to determine the effects of exercise on cartilage breakdown in healthy individuals and people with OA and RA (Mündermann et al. 2005; Andersson et al. 2006b; de Jong et al. 2008).

1.9.1 Cartilage Oligomeric Matrix Protein (COMP)

The function of COMP is to bind to collagen fibres and stabilise the collagen fibre network in the articular cartilage (Saxne et al. 1992). Figure 1.2 shows the collagen components of a cartilage fibril and the association between the fibril and noncollagenous components of cartilage (i.e. COMP).

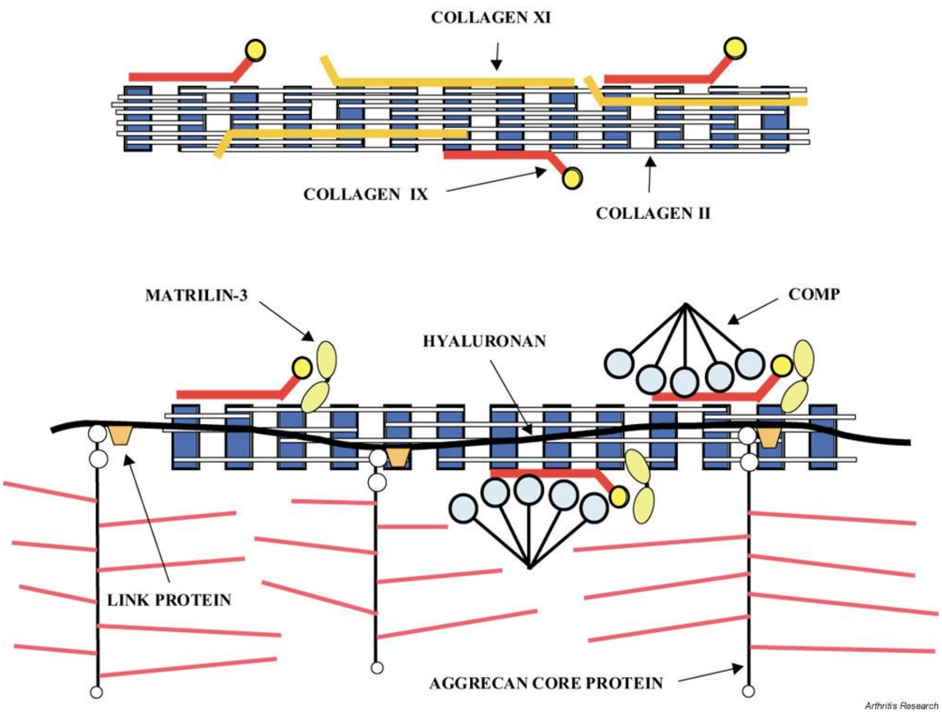

Figure 1.2 The association of COMP with the collagen components of a cartilage fibril. The collagen components of a cartilage fibril (top) and the association between the fibril and non-collagenous components of cartilage (bottom) (Reginato et al. 2002).

Occurring mainly in articular cartilage, COMP is first released into synovial fluid and then into the blood. Serum COMP has been used to provide an indication of destructive changes in cartilage, with high levels correlating with destructive changes in joints (Wisłowska et al. 2005). Christensen et al. (2011) found that serum COMP was significantly higher in RA patients (n = 160) when compared to healthy controls (n = 90). However, contrasting results have been demonstrated by Vilim et al. (2003) who found that the serum COMP of healthy controls (n = 15), RA patients (n = 10) and OA (n = 11) patients were not significantly different. Previous studies including RA patients have reported serum COMP 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 serum COMP 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 serum COMP levels observed at baseline in 281 patients with RA, de Jong and colleagues defined 'high' serum COMP as greater than 1790 ng/ml (de Jong et al. 2008). In terms of diurnal variation, it appears that serum concentrations of serum COMP are stable during the daytime in patients with RA and OA (Andersson et al. 2006a). However, significant decreases in serum COMP were apparent during overnight bed rest. These researchers also found no differences in diurnal variation between those patients treated with and without low-dose prednisolone treatment (Andersson et al. 2006a).

Researchers have also investigated the acute and long-term effects of exercise on serum COMP in athlete populations and people with OA. Following a review of the available literature, the next sections will describe and discuss these research studies investigating the effects of exercise on this biomarker.

1.9.2 The acute effects of exercise on serum COMP

Determining the acute effect of exercise on COMP is important in order to establish the effect of exercise *per se*. The research investigating the acute effects of exercise on COMP in healthy populations and people with OA is summarised in Table 1.1.

Author, year	Participants	Design: Exercise	COMP assessments	Change in serum COMP	Main conclusions
Niedhart et al. (2000)	8 endurance runners	Cross-sectional: Marathon running	31km, 43km, 2h-post, 1d-post, 2d-post	15.5 % ↑ at 31km * 23.9 % ↑ at 43km * 28.2 % ↑ at 2h post * Elevated until 24-48h post	**Significant increase in serum COMP post-marathon**
Kersting et al. (2005)	18 healthy adults	Cross-sectional: 1h training run (maximum sustainable speed)	25 mins post-run 2.5 h post-run	14.8% ↑ 25 mins post (n.s.)	**No acute effect of exercise on serum COMP observed.** Significant positive relationship between serum COMP and cartilage volume decrease.
Mundermann et al. (2005)	10 healthy, physically active adults	Cross-sectional: 30mins walking on level track at self-selected speed	Immediately post, 30 mins post, 1.5h post, 3.5h post, 5.5h post	9.7% ↑ immediately-post ** Returned to baseline at 30 mins post 8.2% ↑ 5.5h post **	**Thirty minutes walking caused significantly elevated serum COMP levels.** There may be a 5-6h metabolic delay in COMP. Resting control group serum COMP ↓ significantly over same time period.
Andersson et al. *(*2006)	7 patients with knee OA	Cross-sectional:1h supervised high-intensity circuit exercise session (lower body weight-bearing exercises > 60% HRmax)	Pre, immediately post, 30mins post, 60 mins post, 2h post, 3h post, 4h post, 5h post	14% ↑ immediately- post* Returned to baseline after 30 mins rest and continued to decrease.	**Serum COMP increased significantly in response to 1h HI exercise.** Serum COMP decreased to baseline during rest.
Kim et al. (2009)	10 male marathoners 10 male ultra-marathoners	Cross-sectional: Marathon race	1-2h pre-marathon, 0km, 10km, 20km, 30km, 42.2km, 6d recovery	1.6-fold ↑ at 10km**. No further change during race or after 1h recovery. Returned to baseline 48h-post.	**Running distance may affect serum COMP response and recovery time.**
		Ultramarathon race	6-10h pre, 100km, 200km, 6 days of recovery	1.9-fold ↑ at 200km ** Remained ↑ until 4d recovery. Returned to baseline at 6d-post.	

Table 1.1 A summary of studies investigating the acute effects of exercise on serum COMP. (COMP = cartilage oligomeric matrix protein, km = kilometres, h = hour, d = day, min = minutes, OA = osteoarthritis, IL-10 = interleukin-10, ↓ = decrease, ↑ = increase, * = $p < 0.05$, ** = $p < 0.01$.

Author, year	Participants	Design: Exercise	COMP assessments	Change in serum COMP	Main conclusions
Mundermann et al. (2009)	42 patients with knee OA, 41 healthy age-matched controls	Cross-sectional: 30 mins walking on level track at self-selected speed	Immediately post, 30 mins post, 1.5h post, 3.5h post, 5.5h post	~5.9 % ↑ COMP immediately post-exercise in controls and OA**. COMP returned to baseline at 30 min post-walk, continued ↓ up to 5.5h post-walk. Change in COMP n.s. between groups.	**Walking can significantly increase serum COMP in OA patients and healthy controls. Serum COMP change not related to ambulatory load.** Similar serum COMP concentrations and changes in OA and controls.
Niehoff et al. (2010)	5 healthy males	Randomised, cross-over design: a) High-impact running b) Slow, deep knee bends c) Lymphatic draining d) Rest (all 30 mins)	Pre-exercise, immediately post, 5, 10, 15, 20, 30, 50, 70, 90, 120, 150, 210, 240, 270, 300, 330, 360, 390, 420 mins post.	a) 39% ↑ ** immediately-post, remained ↑ up to 90 min-post, then returned to pre-exercise b) No change c) No change d) 19% ↓ **	**Impact-based cyclic mechanical loading is most influential on serum COMP, increase may depend on loading characteristics.**
Helmark et al. (2010)	29 females with knee OA	2 randomly assigned groups: a) No exercise b) Resistance exercise: Leg extensions - 25 sets of 10 repetitions starting every 1.5 minutes (~ 50 min)	a) 30 min after arrival, after 4h microdialysis. b) 30 minutes post-ex, after 4h microdialysis.	↓ in serum COMP over time* in both groups, regardless of exercise. ↓ in intra-articular COMP over time* in exercise group but not no-exercise group.	**Effect of rest on COMP confirmed but no effect of exercise observed.** A significant increase in chondroprotective IL-10 was shown in the exercise group but not in the non-exercising group.
Niehoff et al. (2011)	7 male, 7 female healthy sedentary participants	Randomised, cross-over design: a) 100 vertical drop-landings (30 min) b) Running at 4.9mph (30 mins) c) 30 min resting in chair	Pre-exercise, immediately post, 30 min post, 1h post, 2h post and 3h post.	a) 32% ↑** immediately post b) 31% ↑** immediately post Returned to baseline at 2h post-exercise.	**No difference between magnitude and duration of serum COMP elevation between modes of exercise.** Cartilage deformation more pronounced after running compared to drop-jumps.
Helmark et al. (2012)	11 OA patients	30 min one-legged knee-extension exercise	Pre-exercise, 15-30 min post-exercise	No significant change	**No significant changes in serum COMP post-exercise.** Concentration of COMP in the synovial fluid reduced significantly.

Table 1.1 A summary of studies investigating the acute effects of exercise on serum COMP. (COMP = cartilage oligomeric matrix protein, km = kilometres, h = hour, d = day, min = minutes, OA = osteoarthritis, IL-10 = interleukin-10, ↓ = decrease, ↑ = increase, * = $p < 0.05$, ** = $p < 0.01$.

It appears that intensive exercise provokes significant and immediate increases in serum COMP in healthy individuals (Neidhart et al. 2000; Kim et al. 2007; Niehoff et al. 2010; Niehoff et al. 2011) and individuals with OA (Andersson et al. 2006b). This offers support for the sensitivity of the marker to exercise. Evidence also suggests that as little as thirty minutes of walking can cause significant serum COMP elevations in healthy and OA populations (Mündermann et al. 2005; Mündermann et al. 2009). In contrast, a non-significant increase in serum COMP was observed following a one hour training run when assessed twenty-five minutes post-exercise (Kersting et al. 2005). Similarly, in a study investigating the effects of approximately fifty minutes of lower body resistance exercise, no post-exercise differences were observed when COMP was assessed following twenty to thirty minutes of rest (Helmark et al. 2010). Similarly, in OA, no changes in serum COMP were observed following 30 minutes of knee extension exercise, despite a significant decrease in synovial fluid COMP concentrations (Helmark et al. 2012). However, studies have demonstrated that post-exercise serum COMP consistently returns to baseline following thirty minutes of rest (Mündermann et al. 2005; Mündermann et al. 2009), thus offering potential reasoning for the non-significant increases observed.

Following equivalent findings in a sample of OA patients after a one-hour high-intensity exercise, Andersson et al. (2006b) recommended that baseline blood samples for serum COMP analysis should be taken after at least 30 minutes of rest in order to avoid the influence of acute variations in serum COMP occurring as a result of exercise. In fact, four of the studies also showed significant reductions in serum COMP as a result of inactivity, with decreases from baseline by as much as 19% after resting in a seated position for thirty minutes (Mündermann et al. 2005; Andersson et al. 2006b; Helmark et al. 2010; Niehoff et al. 2010). Despite this recommendation, it is important to note that whilst in five of the nine studies participants fulfilled some reduction in general physical activity levels before the laboratory session, only one of these followed this recommendation fully (Mündermann et al. 2009) and one incorporated a fifteen minute rest period before the first sample (Mündermann et al. 2005). Therefore, the findings from these studies may be somewhat compromised in terms of validity due to the potential effect of unknown prior physical activity.

Interestingly, in the study by Mündermann et al. (2005), a second increase in serum COMP was observed five and a half hours post-exercise. Combining this finding with the significant increase following thirty minutes of exercise, the authors postulated a diffusion time of COMP fragments to the blood of thirty minutes or less and a metabolic delay of between five and six hours following the walking exercise protocol (Mündermann et al. 2005). However, the existence of such a metabolic delay has not been confirmed by any further studies.

1.9.3 The effects of joint loading on serum COMP

A preliminary description of the effect of joint loading on serum COMP is provided in a study by Mündermann et al. (2009). They used activity monitoring (step number, distance, walking speed and cadence) and gait analysis (knee, ankle and hip moment) to describe ambulatory load and assessed serum COMP levels following thirty minutes of walking exercise. However, they found that serum COMP concentration was not related to lower extremity joint loading in participants with OA and healthy controls. Along similar lines, Niehoff and colleagues (2010) recently investigated the effects of different mechanical loading protocols on the serum COMP of five healthy males. They observed that running significantly increased serum COMP concentration by approximately 39% ($p < 0.001$), while slow knee-bends did not induce any changes. They suggested that this finding may indicate that the elevation of serum COMP concentration depends on the force rate or frequency of the applied loads. In another study by the same authors (7 healthy, sedentary males and females; $n = 14$), no difference was observed in absolute increase or duration of increase in serum COMP when comparing 30 minutes of vertical drop-jumps with 30 minutes of running at 4.9 miles per hour (Niehoff et al. 2011).

The study by Helmark and colleagues (2010) attempted to determine the potentially differential response of serum COMP to resistance exercise. However, alongside the limitations associated with the timing of blood samples, the authors also acknowledged that the exercise protocol may not have been strenuous enough to induce systemic changes (Helmark et al. 2010). Nevertheless, this study revealed interesting findings in relation to the intra-articular levels of COMP. A significant decrease in intra-articular COMP was observed in the exercise group but not in the non-exercising group. Similarly, significant increases in chondroprotective IL-10 were also observed in the exercise group only. This suggests that COMP is cleared quickly from the intra-articular space following exercise and also indicates a potentially protective effect of exercise on chondrocytes.

In summary, it appears that the assessment of serum COMP provides a sensitive outcome measure with the ability to detect acute changes in cartilage breakdown as a result of exercise.

Still, researchers have not yet investigated the acute effects of exercise on serum COMP in RA or the potentially distinct effects of various modes of exercise in this population. The effect of continued exercise training on serum COMP is also important to establish and the current literature in this area is discussed in the following section.

1.9.3 The effects of exercise training on serum COMP

Joint damage progression over the course of an exercise intervention such as the RAPIT study (de Jong et al. 2003) is typically assessed radiologically using X-rays, with Larsen scores forming the main outcome variable. However, there are limitations associated with X-rays as they change slowly in most people with RA, with six months to a year often needed to capture changes in an individual patient (Sokka 2008). Furthermore, modern RA treatment now aims to treat people before radiological damage becomes apparent (Sokka 2008). On the other hand, serum COMP provides a sensitive method of measuring changes in joint destruction, with the potential to establish the effect of exercise programmes of a shorter duration (i.e. less than 3 months). The safety of such short-term exercise interventions on the joints of people with RA is currently unclear (Hurkmans et al. 2009) and whether continued exercise training affects the acute response to exercise is also currently unknown.

In terms of the effect of exercise training on serum COMP, it appears that only five studies have been conducted (Table 1.2). One study investigated the effects of vibration training in healthy individuals (Liphardt et al. 2009), three studies have included people with OA (Andersson et al. 2006b; Chua et al. 2008; Petersen et al. 2010), and there is currently only one study that has investigated the effects of long-term training in RA (de Jong et al. 2008). In summary, these studies indicated no effect of continued high-intensity aerobic and resistance training on serum COMP, with intervention periods ranging from six weeks to two years. However, as previously discussed, the authors of the RAPIT study acknowledged that they did not collect the blood samples at a standardised time with respect to exercise (de Jong et al. 2008). Similarly, limited control over previous activity is also apparent in the other studies described (Chua et al. 2008; Liphardt et al. 2009; Petersen et al. 2010), with the exception of the study by Andersson et al. (2006b). This well-controlled study assessed the serum COMP of 58 patients with OA who had been randomly assigned to a six-week training intervention group or a control group who maintained their normal activities. Serum COMP was assessed at predefined time points before and after exercise or rest and as expected, serum COMP increased immediately following 60 minutes of exercise ($p < 0.001$). However, no changes were observed between the start and end of the study, despite the progressive nature of the programme. An interesting finding was revealed by Liphart and colleagues (2009), who found that vibration training twice per day did not prevent the reductions in serum COMP associated with rest and immobilisation, leading to the suggestion that increases in serum COMP require motion as well as loading.

Overall however, little is known about the effects of short-term exercise training on the release of COMP into the serum. Furthermore, it is unclear if exercise training alters the post-exercise time course of serum COMP. Whilst limited data exists in the OA population, it is important to establish if these effects are different in RA, as this particular group of patients have additional inflammatory symptoms, manifesting both systemically and locally at the synovial joint. The research relating to the effects of exercise on these inflammatory aspects of RA are further discussed in the following sections.

Author, year	Participants	Design: Exercise	COMP assessments	Change in serum COMP	Main conclusions
Andersson et al. (2006)$^{\$}$	58 OA patients	RCT with 6 week intervention: EG - 1h supervised x2 sessions per week (5 HI stations of weight-bearing exercises at > 60% HRmax and 30mins home-based exercises x5 sessions per week. CG - Usual activities with no restrictions.	Before and after 60 mins exercise/rest at -3 weeks, 0 weeks, 6 weeks (during intervention) and 24 weeks (18 weeks post-intervention)	-3 weeks: ↓ COMP in both groups after 1h rest** Weeks 0 and 6: ↑ COMP post-exercise in EG ** ↓ COMP post 60mins rest in CG ** Week 24: ↓ COMP in both groups after 1h rest**	**Serum COMP increased significantly as a result of exercise and rest caused a decrease. No changes in serum COMP over 24-week period so appears to be no long-term influence of training.**
de Jong et al. (2008)	281 RA patients	RCT - RAPIT study$^{\#}$	Baseline, 3 months, 2 years	Slight COMP ↑ in EG, slight COMP ↓ in CG (n.s.)	**Exercisers did not have significantly higher COMP at 3 months or 2 years.**
Chua et al. (2008)	193 overweight adults with knee OA	RCT with 18 month intervention: 4 groups - Healthy lifestyle, diet, exercise, diet and exercise. EG: x3 sessions per week of 15mins aerobic (50-75% HRR), 15 min lower-body RT (2 x 12 reps of 4 exercises), 15 min cool-down.	Baseline, 6 and 18 months	No significant changes in serum COMP over time	**COMP levels remained stable across all intervention groups.**
Liphardt et al. (2009)	8 healthy males	Randomised cross-over design: a) 14d bed rest and VT twice per day b) 14d bed rest and immobilisation	3d and 1d pre-intervention, days 2, 6, 8, 11, 13, 14 of intervention. Days 2, 3, 5 of recovery.	14.8% ↓* COMP in control condition, 10.1% ↓* COMP in VT condition after 24h treatment. N.s. difference in COMP change between treatments. After re-mobilisation COMP returned to baseline after 1d recovery.	**VT did not prevent significant reduction in COMP as a result of bed rest. COMP returned to baseline after re-mobilisation.**
Petersen et al. (2009)	36 elderly patients with knee OA	RCT with 12 week intervention: RT 3 sessions per week – warm-up, leg press, leg extension exercises (15-8RM, 4 x 12-8 reps progressing to 8RM, 4 – 5 x 8 reps and supplementation with a) glucosamine b) ibuprofen or c) placebo.	Before and after 12 week intervention	13% ↓* COMP in glucosamine group but no change with placebo/ibuprofen.	**Training per se did not induce changes in COMP but glucosamine appeared to modify the effect of RT.**

Table 1.2 A summary of studies investigating the effects of continued exercise training on serum COMP. ($^{\$}$ = see also acute study, $^{\#}$ = described elsewhere, RCT = randomised controlled trial, EG = exercise group, CG = control group, HI = high-intensity, HRmax = age-predicted maximum heart rate, HRR = heart rate reserve, RT = resistance training, VT, vibration training, reps = repetitions, RM = repetition maximum, h = hour, d = day, n.s. = non-significant↓ = decrease, ↑ = increase, * = $p < 0.05$, ** = $p < 0.01$).

1.10 Systemic inflammation (C-reactive protein) and exercise in RA

C-reactive protein (CRP) is an acute phase protein synthesised by the liver which rises in response to inflammation. It is measured in the serum and is an acknowledged and regularly assessed marker of systemic inflammation and disease activity in RA patients. Typically, serum CRP levels in the range of 30 – 40 mg/L indicate moderate disease activity, but may reach levels of above 100 mg/L in severe disease (Amos et al. 1977). Alongside a 28 swollen and tender joint count and global assessment of disease using a visual analogue scale, serum CRP also forms part of the Disease Activity Score-28 (DAS-28) (Black et al. 2004; Scott et al. 2010). As a marker of the inflammatory status of an RA patient, the effects of exercise on systemic inflammation are important to establish.

1.10.1 Serum CRP and the acute response to exercise

In healthy individuals, research findings suggest that high-intensity exercise provokes a short-term, transient increase in serum CRP that is maximal at 24 hours post-exercise. It is thought that this increase results from an acute-phase response induced by exercise, mediated by the cytokine system and mainly IL-6 (Kasapis et al. 2005). However, most studies that have investigated these acute post-exercise changes in serum CRP have examined trained, male athletes. In the study by Neidhart and colleagues (2000), no significant increases were found immediately post-marathon, but similar late elevations were observed twenty-four and forty-eight hours following marathon completion. Furthermore, the serum CRP of seven male and three female trained runners, was assessed before and after a five kilometre run. There were no significant changes in serum CRP concentration immediately after or three hours after the race. However, a small but significant rise was observed at twenty-four hours post-run, returning to baseline at forty-eight hours post-run (Drenth et al. 1998).

Of further interest, the acute response of CRP to exercise appears to be proportional to the amount of activity performed and the occurrence of muscle damage. This was demonstrated in a study of thirty-eight trained runners who competed in races between 15 and 88 kilometres. Serum CRP levels increased with increasing race duration and creatine kinase levels[3] (Strachan et al. 1984; Ebbeling et al. 1989). In addition, research also appears to suggest that the acute response of serum CRP may also depend on the type of exercise and muscle mass involved. For example, Nosaka and Clarkson (1996) assessed the serum CRP of

[3] Creatine Kinase has been identified as a marker of post-exercise muscle damage (Ebbeling, 1989).

healthy subjects (n = 14) who had not previously been involved in a resistance training programme. Following twenty-four maximal eccentric actions of the elbow flexors, no significant changes in serum CRP levels were found before, immediately after and during the five days after the exercise, despite significant changes in markers associated with muscle damage. Together, these findings suggest that resistance exercise may not stimulate such a marked serum CRP response.

Despite its potential importance, there does not appear to be any investigation of the acute response to high-intensity aerobic or resistance exercise in people with RA. Similarly, the limited evidence pertaining to the effects of exercise training on serum CRP in RA is discussed in the following sections.

1.10.2 The effects of exercise training on serum CRP

Most research examining the effects of exercise training on serum CRP has measured this acute phase protein in order to incorporate it into a DAS and hence serum CRP has not been reported separately. However, in the study by Baslund et al. (1993), those RA patients assigned to an eight-week intensive cycling training programme showed no significant changes in serum CRP over the training period. Van den Ende et al. (1996) also observed no change in serum CRP following twelve weeks of either intensive exercise, range of motion exercises or isometric exercises. Additionally, serum CRP was assessed in two hundred and twenty adults with RA following random assignment to class exercise, home-based exercise or a control group for twelve weeks. The researchers found there were no significant changes in serum CRP over the intervention period in either of the groups (Neuberger et al. 2007).

It has also been observed that exercise training reduces the acute response of CRP to strenuous activity (Liesen et al. 1977). Whilst limited to three male participants, researchers observed that after nine weeks of endurance training, serum CRP levels assessed one day following a two hour run were 40% lower than when assessed one day post-run at baseline. This was despite the participants running longer distances at the end of the training period. This potential effect of continued exercise training on the acute-phase response is also important to establish in RA. Furthermore, as discussed in the next section, the effects of exercise on localised inflammation of the synovial joints is also salient in order to further enhance the information pertaining to exercise and joint health for this population.

1.11 Synovial inflammation and the use of ultrasound

Synovial inflammation is a major feature of RA and is characterised by increased blood flow and vascularisation of the synovium. These phenomena also appear to be crucial in subsequent joint destruction (Rooney et al. 1988; Carotti et al. 2002) and therefore the effects of exercise on localised joint inflammation in RA are important to establish.

With the advantages of being a readily accessible, non-invasive and low-cost method of assessing synovial inflammation, the use of ultrasound (US) for assessing inflammatory disease activity in patients with RA has increased considerably in the last decade (Kasukawa et al. 2004). As previously discussed, conventional X-ray methods offer only late signs of inflammatory disease activity by revealing the resulting cartilage and bone destruction. Other assessment methods (i.e. serum CRP and erythrocyte sedimentation rate) are limited to indirect, systemic aspects of inflammation. However, colour Doppler ultrasonography forms a sensitive method of visualising the localised blood flow occurring in the small vessels of inflamed joints (Taylor 2005; Ellegaard et al. 2009b). Exercise is known to increase blood flow and consequently researchers have utilised ultrasound to assess the localised inflammatory hyperaemic response to exercise (Ellegaard et al. 2009a).

The colour Doppler signals observed on an ultrasound scan are a reflection of the number and speed of the red blood cells passing the transducer. As colour pixels are rarely seen in normal joints, the appearance of colour pixels in synovial tissue indicates the presence of synovial inflammation that is characteristic of RA (Terslev et al. 2003). Researchers have used this method to assess synovitis of the knee joint, using a semi-objective scoring system based on the number of colour flow signals observed (Kasukawa et al. 2004; Sato et al. 2005; Kasukawa et al. 2007). Figure 1.3 shows the knee joint of an RA patient with > 9 colour flow signals, indicating high levels of synovial inflammation (Sato et al. 2005). However, a quantitative analysis of the number of pixels with inflammatory activity has been proposed. Expressing the number of colour pixels in relation to the total number of pixels in the investigated area offers a quantitative measure of synovial inflammation, known as the colour fraction (CF) (Terslev et al. 2003). The clinical relevance of this methodology has been indicated by its correlation with systemic measures of inflammation (erythrocyte sedimentation rate and CRP), swollen joint count (Ellegaard et al. 2009a), subjective pain evaluation and morning stiffness (Qvistgaard et al. 2001). Furthermore, a decrease in colour fraction and synovial volume has been shown in response to glucocorticosteroid injection (Terslev et al. 2003).

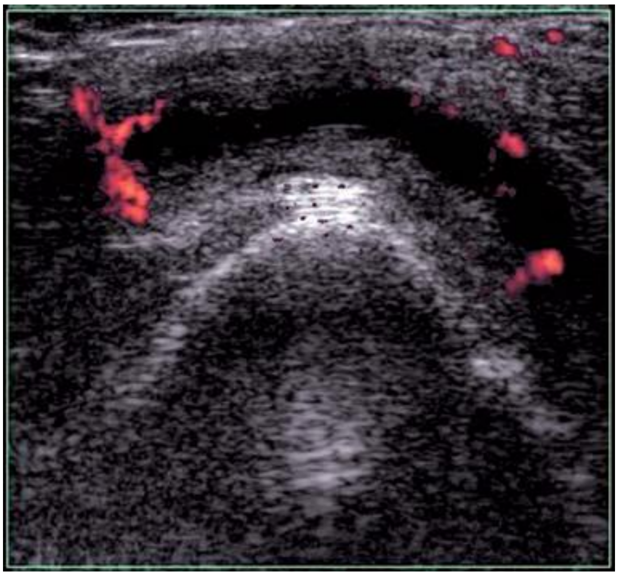

Figure 1.3 Ultrasound (transverse) image to demonstrate the appearance of colour pixels in a knee joint with high levels of synovial inflammation (Sato et al. 2005).

The quantitative US analysis method has been used extensively in RA to assess synovitis of the wrist (Terslev et al. 2003; Ellegaard et al. 2009b). However, whilst the aforementioned semi-quantitative US measures have been widely used to assess synovial inflammation of the knee joint, the use of fully quantitative methodology (i.e. CF) to assess synovial inflammation of any the large joints has not been explored. Furthermore, as discussed in the following sections, the effect of exercise on synovial inflammation has received limited research attention.

1.11.1 The effects of exercise on synovial inflammation

The acute effect of handgrip exercise on synovial inflammation has recently been investigated in RA (Ellegaard et al. 2009a). In this study, twenty-six RA patients with synovial inflammation and consequent US activity in the wrist performed five maximum handgrip contractions on a digital hand dynamometer. US scans were taken immediately before and immediately after the five exercises and a non-significant increase in CF of 0.22% from baseline was observed (p = 0.49). Recently, the same research group conducted a case-control study (n = 42) to investigate the effects of an eight-week handgrip training intervention programme on CF observed in the wrist. Twenty-four patients with colour Doppler ultrasound activity in the wrist joint but with otherwise stable RA formed the exercise group and 18 age-matched RA patients formed the non-exercising control group. The authors found that there was a modest decrease in the CF after the 8 week training period (1.86%; $p = 0.08$). However, there was no difference in CF between the training and control groups, at baseline or post-intervention ($p = 0.82$ and $p = 0.48$). These results suggest that synovial blood flow, when using CF to analyse the US images, was not affected by regular grip strength training.

It is important to acknowledge three main limitations of the studies mentioned above (Ellegaard et al. 2009a; Ellegaard et al. 2012). Firstly, low participant numbers may have limited the power of the studies to detect a significant effect. A second limitation relates to the intensity of the acute exercise bout and training intervention. The increase in muscle strength observed in the training study was modest and borderline significant (8.8%; $p = 0.055$) and therefore it may be argued that the training intervention was insufficient to cause any effects within the wrist joint. Similarly, the intensity of the acute bout of handgrip exercise may also have been insufficient to affect synovial inflammation. However, in support of the positive effect of grip strength training, the study found a decrease in CF of 35% and therefore it could be reasonable to conclude that the training programme did not affect the perfusion of the synovial tissue in the RA patients in a negative way. Indeed, in patients with moderate disease activity, the decrease in CF might indicate that grip strength training has a positive effect on the perfusion of the synovial tissue in the wrist joint. Thirdly, handgrip exercise is non-aerobic and non-weight-bearing and hence knowledge is limited to the effects of this mode of isometric exercise (Ellegaard et al. 2012)..

Despite these limitations, the above studies were the first to investigate the direct influence of strength-based exercise *per se* and continued strength training on synovial inflammation in RA (Ellegaard et al. 2009a; Ellegaard et al. 2012). The results of these two studies appear to indicate that both acute and long-term handgrip exercise does not negatively affect synovial inflammation. However, information is limited to the effects of exercise on the wrist joint and the effects of aerobic, weight-bearing exercise is unknown. Therefore, further research is required to determine the effects of high-intensity resistance and aerobic weight-bearing exercise on synovial inflammation, and specifically in relation to large joints that have provoked concern in relation to joint damage.

Chapter 2: Thesis outline, aims and research questions

2.1 Overall aims and perspective

The benefits of exercise for the RA population are now clear but this patient group still remain insufficiently active. Therefore it is imperative to establish the current views of RA patients in relation to exercise and highlight any concerns that may exist. In addition to this, it is evident there are gaps in the current knowledge relating to the physiological effects of exercise on the large joints of people with RA and therefore these questions also form important areas for exploration.

Novel and specific measures such as serum COMP to directly assess cartilage breakdown, and colour Doppler ultrasound to assess synovial inflammation provide efficacious means of describing the direct effects of exercise on the large joints of people with RA. Assessing the acute effects of aerobic and resistance exercise on these markers will enable determination of the effects of exercise *per se*. Furthermore, determining the effects of continued exercise training on cartilage breakdown and inflammation will enhance the information available to health professionals when advocating exercise to patients with RA.

It is anticipated that further knowledge relating to these important issues will assist health professionals when talking to patients about exercise in two ways. Firstly, an awareness of the potential perceptions of RA patients will allow them to approach the topic of exercise and joint health with additional understanding and foresight. Secondly, elucidating the direct, physiological effects of exercise on the health of the joint will also provide health professionals with further information relevant to the questions and concerns that patients may pose. Brought together, it may be that enhancing exercise prescription for RA patients fosters an improvement in exercise uptake and adherence, with the subsequent increase in physical fitness levels and psychosocial well-being helping to negate the inactivity and co morbidities associated with the disease.

The specific aims of this thesis are as follows:

a) To qualitatively explore the perceptions of RA patients in relation to exercise and joint health and develop a measure to quantitatively assess these perceptions on a large scale.

b) To utilise novel, specific markers of cartilage breakdown and synovial inflammation to assess the acute and separate effects of aerobic and resistance exercise on joint health in the RA population and healthy controls.

c) To determine the effects of continued intensive exercise training on specific markers of joint health in RA.

The schematic displayed in Figure 2.1 (over page) describes the research questions, study methods and subsequent chapters included in this thesis.

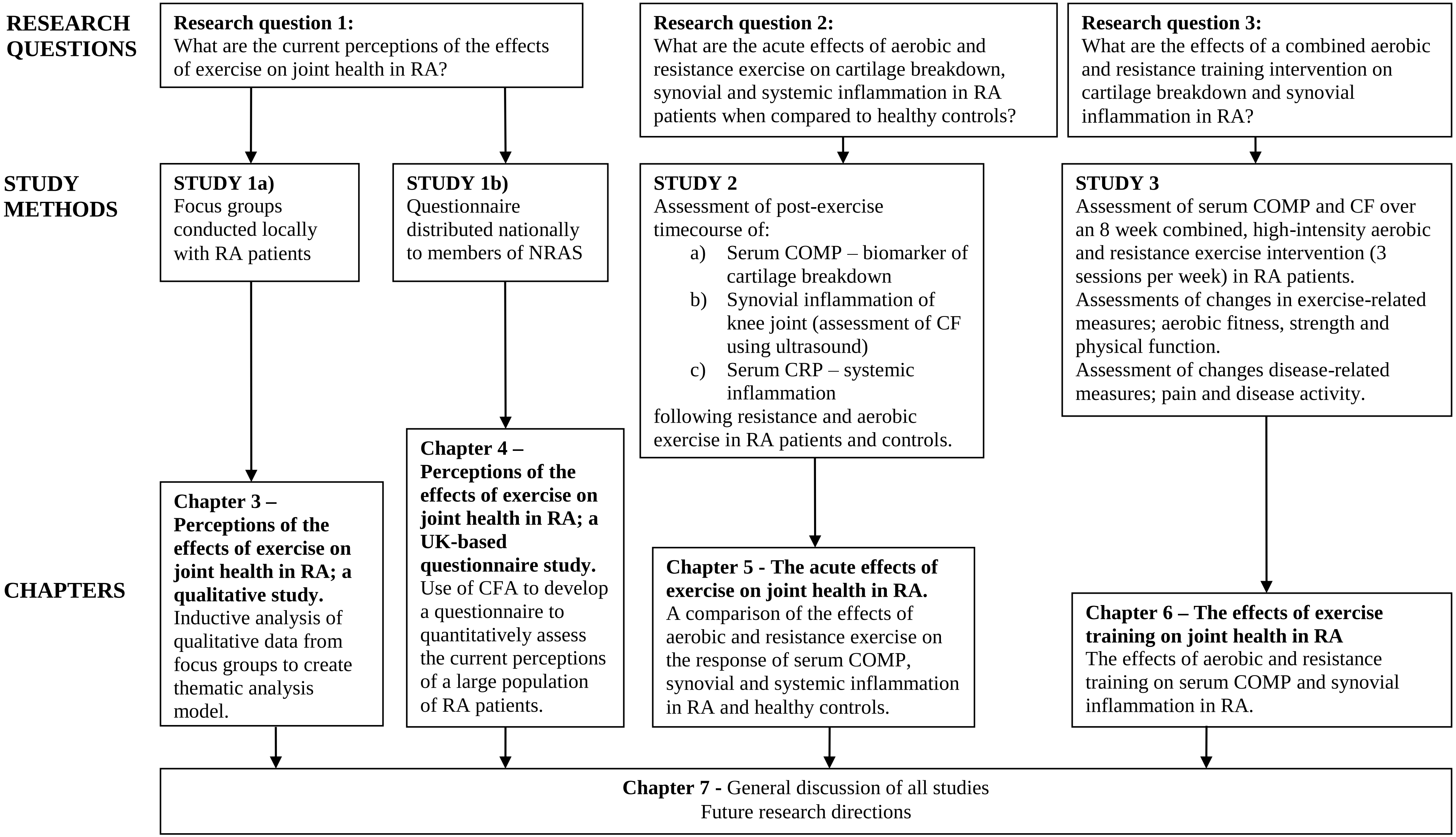

Figure 2.1 Overview of research questions, methodologies and chapters (NRAS: National Rheumatoid Arthritis Society; CFA: Confirmatory factor analysis; COMP: Cartilage Oligomeric Matrix Protein).

Chapter 3: Perceptions of the effects of exercise on joint health in rheumatoid arthritis patients; a qualitative study

This study has been published as an Original Article in *Rheumatology*:

Law, R.-J., Breslin, A., Oliver, E., Mawn, L., Markland, D., Maddison, P. J. and Thom, J. (2010). 'Perceptions of the effects of exercise on joint health in rheumatoid arthritis patients.' Rheumatology **49**(12): 2444-2451.

3.1 Abstract

Objectives

Exercise is important in rheumatoid arthritis (RA) management. However, RA patients are less active than the general population. This qualitative study explores the perceptions of patients regarding the effects of exercise on joint health.

Methods

A purposive sample of 12 female and 6 male RA outpatients (Age: 23 - 76 years; disease duration: 2.5 months – 33 years; HAQ score: 1.03 ± 0.71) participated in 4 moderated focus groups. The main questions addressed were; a) how do you feel exercise affects your joints; and b) what affects your exercise behaviour? Transcriptions were independently analysed with 455 meaning units identified. An inductive, thematic analysis was conducted using established techniques. Discussion with a third analyst contributed to consensus validation.

Results

16 constructs emerged, clustering into 5 themes, reflecting the issues relating to exercise and joint health in RA patients. Emergent themes were; 'Health professionals showing a lack of exercise knowledge', 'Not knowing what exercise should be done', 'Worry about causing harm to joints', 'Not wanting to exercise as joints hurt' and 'Having to exercise because it is helpful'.

Conclusions

RA patients demonstrated awareness of the advantages of exercise for their joints, both experientially and through education. However, they perceived that health professionals lacked certainty and clarity regarding specific exercise recommendations and the occurrence of joint damage. Thus, to enhance patient-centred exercise prescription in the RA population, uncertainties surrounding joint health, pain symptoms and exercise specificity need to be addressed, alongside continual emphasis of exercise benefits.

3.2 Background

As previously discussed, one of the key roles of the rheumatology healthcare professional is to promote exercise and the maintenance of an active lifestyle, thus maximising quality of life and functional ability. Understanding the perceptions of RA patients regarding exercise is a salient aspect of this role and has thus received previous research attention. For example, the importance of patient perceptions have been highlighted, alongside the suggestion that a positive mindset regarding exercise may be necessary to challenge the longstanding opinion that exercise exacerbates disease (Gecht et al. 1996). Previous research has also revealed that whilst patients with arthritis believe exercise to be an important factor in treatment, uncertainty about which exercises to do, and how to do them without causing harm, prevented many patients from exercising at all (Lambert et al. 2000). As discussed in Chapter 1, previous studies have also highlighted numerous other perceived barriers and facilitators to exercise in people with arthritis (Schutzer et al. 2004; Wilcox et al. 2006; Neuberger et al. 2007; Gyurcsik et al. 2009; Hutton et al. 2009). Furthermore, the outcome expectations of patients, rheumatologists and physiotherapists for high intensity exercise have been found to be significantly less positive than those for a conventional exercise programme (de Jong et al. 2004a). Additionally, in a qualitative study of OA patients', beliefs about exercise following the onset of disease revealed a group of patients who had previously exercised but had stopped because of their symptoms and because they believed exercise was damaging their joints (Hendry et al. 2006).

Limitations within the existing literature and previously documented concerns relating to the physiological effects of exercise on the joint (de Jong et al. 2003), may partially explain these perceptions. Hence, developing a better understanding of RA patient perceptions is important. As discussed in Chapter 1, the perceptions of RA patients, specifically regarding exercise and joint health are yet to be fully explored. Further exploration of this key area could help to identify the underlying concerns which may be limiting the likelihood of the positive effects of exercise becoming apparent in this population.

Therefore, the aim of the current study was to generate qualitative data using a focus group methodology in order to explore and describe the perceptions of the effects of exercise on joint health among RA patients. This type of approach provides an unconstrained and flexible means of exploring issues from the perspective of the participant and facilitates the emergence of aspects of their experience that may not have been considered previously. Furthermore, the interactive nature of focus groups presents an environment within which participants are influencing and being influenced by others, challenging personal perspectives and consequently fostering rich and plentiful data (Kitzinger 1995; Ong et al. 2006). The overall objective of this study was to enhance the information available to health professionals, allowing for a targeted, patient-centred approach to exercise prescription.

3.3 Methodology

Participant sampling

Following ethical approval, potential participants were identified from the outpatients Department of Rheumatology, Betsi Cadwaladr University Health Board. Patients were initially informed about the study by a Nurse Specialist or approached by the researcher during an exercise class (REPS; Rheumatology Exercise Programme[4]) held at the hospital. A participant information sheet provided further details and a formal invitation was sent to patients by post. A purposive sampling framework was created drawing upon the broad expertise of the research team, whereby participants were selected to reflect a range of the disease population (Kitzinger 1995; Patton 2002). Thus, focus groups of RA patients were created including both genders and varying in terms of age and disease duration, thus incorporating a broad range of experiences. Due to an under-representation of younger (< 40 years of age) females with shorter disease duration (< 2 years) and younger males with longer disease duration (> 2 years), the fourth and final focus group consisted of patients recruited to address this disparity. Figure 3.1 shows the recruitment of participants; thirty-four patients received the information sheet and a total of eighteen patients attended a focus group discussion. All participants gave written, informed consent.

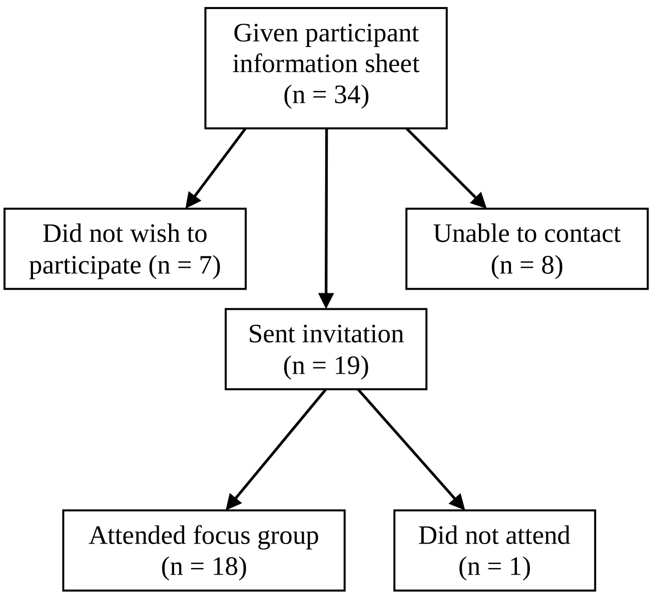

Figure 3.1 Recruitment flow diagram of focus group participants.

[4] REPS consisted of an 8-week circuit-based exercise programme of 8-12 stations incorporating high repetition, low resistance exercises, range of motion stretches and cardiovascular exercises of 2 to 2.5 minutes duration.

Focus group methods

Moderated focus group interviews of four to six RA patients were conducted at Bangor University, lasting approximately two hours each. The moderator and assistant moderator were both researchers, specialising in the areas of joint health in RA and motivational qualitative research, respectively.

Patient feedback was incorporated during the development of the interview guide (see Appendix 1), which was designed primarily to ascertain the perceived effects of exercise on joint health. In addition, factors affecting exercise behaviour were explored. Thus, following a section of introductory questions, participants were guided and encouraged by the moderator to discuss their experiences, opinions and concerns relating to two main questions:

1) How do you feel exercise affects your joints?
2) What affects your exercise behaviour?

The interview guide included prompts to further explore patient perceptions in relation to exercise type and the opportunity to discuss the effects of diagnosis on exercise behaviour. Finally, patients' thoughts regarding the statement 'Many people are afraid to exercise because they believe that it will cause further damage to their joints' (Arthritis Research Campaign 2005) were also invited. The role of the assistant moderator was to provide a closing summary, invite additional points and clarify any misinterpretations with the participants. The sessions were digitally audio-recorded and discussions relating to exercise and joint health were transcribed verbatim.

Data analysis

An inductive approach to the qualitative analysis was employed, applying methods described by Krueger and Casey (2000). Following each focus group, and prior to transcription, a written summary was made independently by the assistant moderator. As advocated by Pope and colleagues (2000), systematic content analysis of the data from the focus group transcripts occurred concurrently with data collection in order to improve moderation techniques and maximise the information gained. Principles from Heidegger's hermeneutic circle were adopted for data analysis, whereby the moderator read and re-read the discussion transcript in detail, identifying and coding key concepts and ideas by highlighting discrete words, sentences and series of sentences relevant to the issue of exercise and joint health (Heidegger 1962; Crist et al. 2003). These quotes formed the basic meaning units for analysis which were categorised through a process of comparing and contrasting. Preliminary themes were then identified to organise and understand the data (Scanlan et al. 1989).

To enhance scientific rigour, an additional researcher independently analysed the transcripts from each focus group, using a method of reading and re-reading the transcripts to confirm the emerging concepts, ideas and themes (Carr et al. 2003). Finally, a further discussion, involving the two initial analysts and an additional researcher took place during which data from the four focus groups were integrated, discussed and clarified. Factors including frequency, specificity, emotional expression and extensiveness of the comments were also considered during the process (Krueger et al. 2000; Patton 2002). Through ongoing interrogation of the data, maps and diagrams were developed in order to accurately depict the perspectives of people with RA in relation to exercise and their joint health. Divergences in opinion were considered with further discussion until consensus was formed on the constructs and themes to be included in the analytical model.

3.4 Results

Eighteen patients participated in four focus groups. The characteristics of these patients are detailed in Table 3.1. All patients fulfilled the American Rheumatism Association (1987) revised criteria for the classification of RA (Arnett et al. 1988) and had access to multidisciplinary rheumatology team care. Six patients had been regular attendees of the specialised exercise class (REPS).

Participant	Focus Group	Gender	Age	Disease duration (years)	MHAQ	REPS class
1	1	F	76	1.5	0.75	N
2	1	M	69	0.42	0	Y
3	1	F	65	6	1.5	Y
4	1	F	56	33	1.375	Y
5	1	M	74	0.5	1.25	Y
6	1	F	57	29	0.25	Y
7	2	F	40	9	1.375	N
8	2	F	58	9	0.75	N
9	2	F	57	1.25	0.5	N
10	2	F	66	16	2.125	N
11	3	M	73	21	2	N
12	3	M	66	0.75	1.25	N
13	3	F	44	16	1	N
14	3	F	65	15	2.125	N
15	4	M	62	4	0	Y
16	4	M	67	12	0	N
17	4	F	23	22	0.625	N
18	4	F	46	1.5	1.625	N

Table 3.1 Characteristics of the focus group participants (n = 18; M: male; F: female; MHAQ: Modified Health Assessment Questionnaire score; REPS: Rheumatology Exercise Programme; Y: Yes; N: No).

The meaning units consisted of a total of 455 quotes that were relevant to the issue of exercise and joint health. These varied in length from one word, to a sentence, to a paragraph. Identified concepts and ideas were represented in both of the main questions, thus the findings were integrated for analysis. Analysis of the data from the fourth focus group did not reveal any concepts or ideas additional to the original analysis, suggesting theoretical saturation had been reached. However, this data allowed further development of the model through clarification of the existing constructs. Sixteen constructs were established, clustering into 5 themes, reflecting participants' perceptions regarding exercise and joint health (Figure 3.2). The following themes emerged from the analysis; 'Health professionals showing a lack of exercise knowledge', 'Not knowing what exercise should be done, 'Not wanting to exercise as joints hurt ', 'Worry about causing harm to joints' and 'Having to exercise because it is helpful'. Quotes illustrating these themes and constructs are described in the following section.

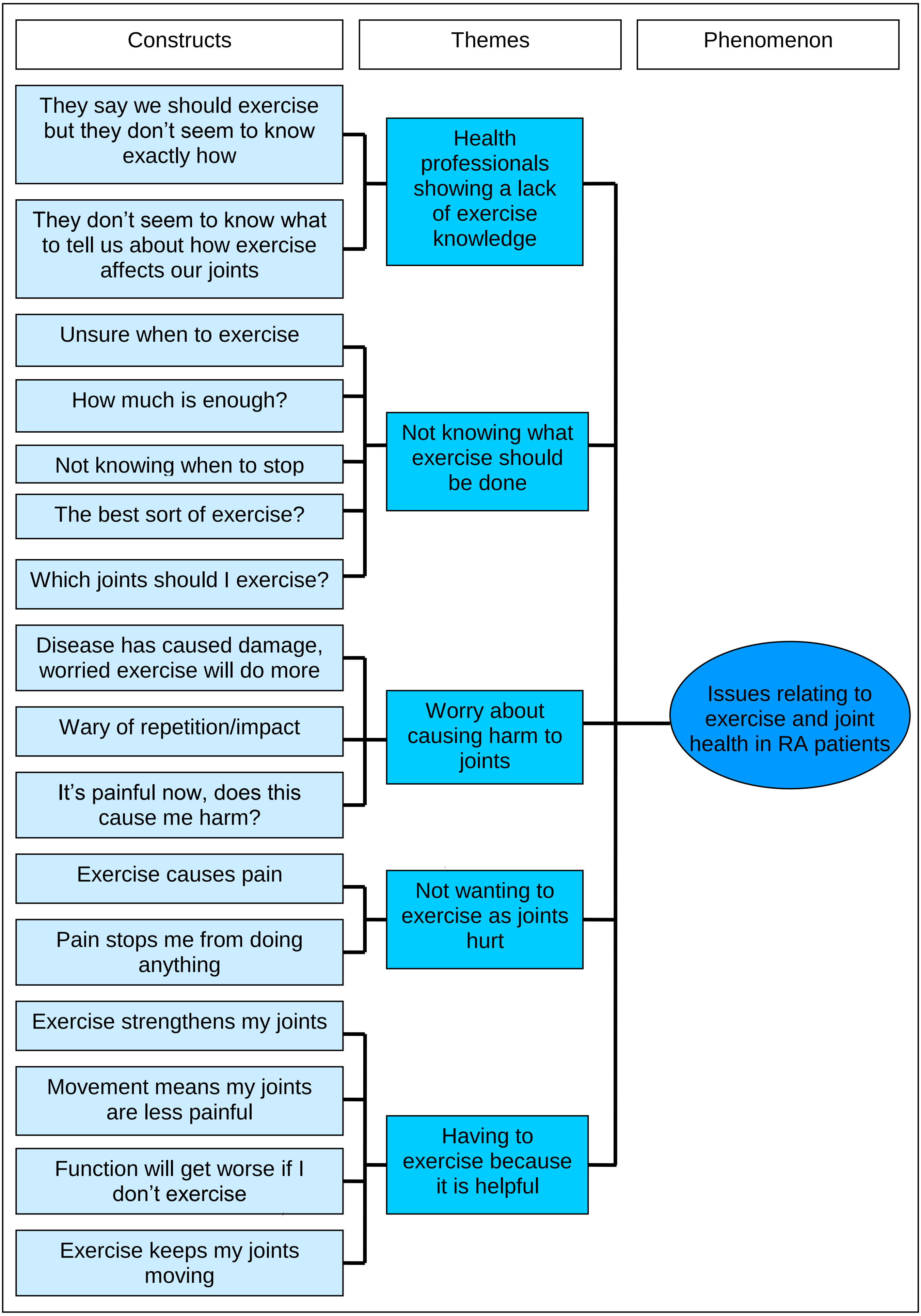

Figure 3.2 Analytical model of the issues relating to exercise and joint health in RA patients.

Health professionals showing a lack of exercise knowledge

This theme reflects patient perceptions that, whilst health professionals advocated exercise, they appeared to be uncertain regarding the specifics of exercise prescription and concerns about exercise and joint health. This is illustrated by the following extract:

FG 3, P 12: '….If I do that sort of thing and I get pain, I can go on doing it, now my next question [to a health professional] is am I doing myself harm if I get pain?'
P 11: 'mmmm'
P 13: 'Yeah'
P12: '[The health professional] can't tell me, right'
P14: 'No, that's what worries me'
P12: 'Nobody knows'

Not knowing what exercise should be done

This theme reflects patients' concerns about not knowing enough about exercise with respect to their disease, including doubts about the best forms of exercise to undertake, knowing when it is best to exercise, how much they should do, and when they should stop.

FG 3, P 12: 'I would really like to know what they call exercise and whether or not it conforms to what I think is exercise.'
FG 4, P 16: 'Yeah, it's, what is the exercise about. How do I do it, will it affect my worse little bits. You've got to go through the bit about it, you've got to read what the exercise is, you've got to look at what the exercise is, will I be alright with it...'

Patients were unsure if their current disease activity affected whether or not exercise would be beneficial;

FG 1, P 3: 'The only thing I can say is that there is no absolute this or that for me, sometimes it helps sometimes it doesn't. If I have a week when I don't do any exercise I can feel great, I can have a week when I do exercise and I feel great. There's no rhyme or reason to it for me.'

Furthermore, patients were unclear how much exercise they should do:

FG 2, P 9: 'It's difficult to know where to draw the line between 'oh for goodness sake, give it a bit of effort'…or 'you know this is harmful, it's time to stop.'

Not wanting to exercise as joints hurt

This theme reflects the negative influence of pain on patients' exercise behaviour. This was discussed in terms of disease-related pain prior to exercise:

FG 2, P 10: 'There's only one word that affects my exercise behaviour and that's pain.'

FG 2, P 9: 'I mean you can't exercise if you are in pain can you. You can't really do anything.'

FG 4, P 18: '…if it hurts you don't want to move.'

Exercise-related pain experienced during and following an exercise bout was also discussed;

FG 2, P 7: 'Immediately it would ache for a bit, then ease off and then the day after, it would still be, I know that was what aggravated it.'

Worry about causing harm to joints

As illustrated in the discussion excerpt below, this theme reflects the apprehension expressed by patients regarding joint damage as a potential consequence of exercise:

FG 3, P 12: 'The worry is whether you are damaging yourself really.'
P 13: 'Yeah.'
P 11: 'Am I going to be worse as a result of it?'
P 12: 'That's a significant anxiety for me.'

Previous damage, repetitive or impact-based exercise and pain additionally reinforced this concern:

FG 4, P16: 'You can do all the exercises out, it won't affect what's at the back of your head saying, if I do that, will I do any damage to what's already been damaged?'

FG 2, P 10: '…if you do something and it's that painful, it must be doing your joints some damage.'

FG 1, P 6: 'I've had two painful knees and I do think that after exercise its worse and I wonder if there's any damage caused.'

FG 2, P 8: '….got to be careful of a repetitive move.'

FG 2, P 10: 'I think impact is really disastrous …'

FG 4, P 15: '….I don't think weight impact, I don't think that would be very helpful.'

I have to exercise because it is helpful

This theme reflects the notion that patients felt they needed to exercise in order for strength, mobility and pain relief benefits to occur:

FG 1, P 1: 'I feel exercise is necessary, essential and helpful for joint health.'

FG 1, P 3: 'I only do it because I know it benefits me. I don't do it because I enjoy it.'

FG 3, P 14: 'Just that it helps to keep them lubricated doesn't it. It helps keep you moving, exercise. If you don't they seize up completely.'

FG 4, P 18: '…you are not so creaky for the rest of the day'… 'You have to do it otherwise you go all crunchy.'

FG 1, P 5: 'If you're strong where the muscles are, it helps to take the weight off the joint.'

FG 4, P 15: '…best way to relieve pain is to do something and it seems to soothe it and it goes away.'

Participants also highlighted the importance of functional advantages, often through a fear of becoming less able:

FG 3, P 14: 'It might have done me good in strengthening me, it must have done because I got from my wheelchair onto sticks.'

FG 2, P 10: 'I'm frightened that if I don't get up every morning, if I stay in bed it will become progressive.'

FG 4, P 18: 'We've all seen the arthritis people sat in the corner in a wheelchair, nobody wants that.'

Further quotes relevant to the themes above are available in Appendix 2.

Disconfirming elements

Whilst the model aims to encapsulate overall patient perceptions and represents the majority of views, it is important to highlight disconfirming elements that became evident during model development. For example, in relation to the theme ‘having to exercise because it is helpful’, some patients felt that exercise was not ‘helpful’ because it caused pain. For example, ‘I actually find if you push yourself it makes it worse (Participant 4, FG 1)’. Secondly, in relation to the theme ‘not wanting to exercise as joints hurt’, patients (especially those REPS class attendees), suggested that they would continue exercising even if it was painful and also that they felt it was ‘worth the risk’. As mentioned previously, in relation to the themes ‘not knowing what exercise should be done’, and ‘health professionals showing a lack of exercise knowledge’, REPS class attendees demonstrated greater knowledge of the types of suitable exercise they could do. An example is provided in a quote from Participant 3, FG 1: ‘There are lots of exercises that you can do at home…I’ll go to the stairs and spend 10 minutes as fast as I can up one step down, up down. Just that little exercise that we did.’

Additional concepts and ideas

Although not specific to joint health and thus beyond the scope of this research paper, additional concepts and ideas were revealed as barriers to exercise. These included fatigue, muscle pain and a lack of enjoyment, motivation and confidence. Concepts and ideas also emerged as factors which encouraged patients to exercise: social interaction, low cost, easy access, weight reduction and assistance from instructors. Lifestyle time constraints, medications and physical capabilities were also highlighted as factors affecting patients’ exercise behaviour.

3.5 Discussion

Using focus groups as an exploratory method, this study adopts an inductive approach to describe the perceptions of RA patients regarding exercise and joint health. The analytical model summarises the qualitative content of the focus groups, using words derived from the patient discussions and thus particularly pertinent to the RA population.

Consistent with the findings of previous research, it was evident that RA patients in the present study were aware of the benefits of exercise for their joints (Lambert et al. 2000), but were unsure of the specific exercise recommendations (der Ananian et al. 2006). The additional concepts and ideas (e.g., barriers, benefits and encouraging factors) emerging from the qualitative data of the present study are also similar to findings from previous studies of patients with arthritis (der Ananian et al. 2006; Neuberger et al. 2007; Gyurcsik et al. 2009; Hutton et al. 2009).

The current analysis highlights the challenges faced by patients when attempting to begin and maintain appropriate exercise, with difficulties arising as a result of incomplete information provided by health professionals (i.e., advising exercise but lacking a definitive explanation of how to do so). Further to this, the model presents the questions as indicated by patients regarding the recommended approach to exercise. These correspond with suggestions by the ACSM, who express exercise prescription using the FITT principle (Millar 2010). This incorporates the following: how often per week the patient should exercise (Frequency), how energetically or vigorously the patient should exercise (Intensity), how long the patient should exercise to obtain benefits (Time) and what type of exercises should be prescribed to the patient (Type) (Tancred et al. 1996). In addition, whilst it was clear that current disease state (i.e., pain and fatigue levels) often determined participation, patients were also unsure whether or not this pain or fatigue was a factor affecting the overall benefit of exercise. These queries suggest that patients require knowledge of the specifics of exercise prescription in order to include exercise as part of their RA treatment.

Joint pain was a definitive barrier in all groups and was perceived as a prominent factor in determining the patients' exercise behaviour, a finding similar to that of previous research (der Ananian et al. 2006). However, new findings were also revealed, including the notion that patients perceived uncertainties within the health profession regarding pain, joint health and exercise. In particular, this was in relation to whether the sensation of pain equated to the occurrence of damage and the effects of different types of exercise on the health of their joints. As previously identified in patients with OA (Hendry et al. 2006), worry that exercise may have detrimental effects on joint health was also exemplified in the present study. Additionally however, it emerged that patients in the current study were apprehensive when considering the effects of impact and repetitive exercises. Although the area requires further investigation, this concern corresponded with the current empirical evidence at the time recommending that those patients with extensive damage to the large joints should avoid high-intensity, weight-bearing exercise (Munneke et al. 2005). Coupled with a perception that health professionals are irresolute regarding the effects of different types of exercise on joint health, these concerns pose further challenges to RA patients when considering exercise.

As evident from past research, including findings from randomised controlled trials (Ekblom et al. 1975; Ekdahl et al. 1990; van den Ende et al. 1996; van den Ende et al. 2000; Häkkinen et al. 2001; de Jong et al. 2003; de Jong et al. 2005; Marcora et al. 2005; Lemmey et al. 2009), exercise is considered to be fundamentally beneficial for RA patients. As discussed in Chapter 1, exercise has been shown to increase the strength of tendons and ligaments, thus increasing joint function and stability. Joint lubrication, range of movement and flexibility is also increased (Cooney et al. 2011b). Furthermore, there is also an essential role of high-intensity, weight- and impact-bearing exercises in improving bone mineral density (de Jong et al. 2004b). Despite the aforementioned reservations, patients demonstrated an awareness of these advantages in terms of improving strength, mobility, and function and reducing pain. Subsequently, it is suggested that if the perception of exercise as a positive feature of RA treatment is to supersede the apparent negative connotations, continual emphasis of these benefits is of great importance (Gecht et al. 1996; de Jong et al. 2004a; Neuberger et al. 2007).

Of further relevance to an awareness of the benefits of exercise, the first focus group demonstrated more experiential and education-derived knowledge. This may be expected of attendees of a specialised exercise class. In contrast, the knowledge of non-attendees appeared to be mainly speculative. Whilst exercise class attendees did not highlight disadvantages to the same extent, queries relating to pain and its link with harm were expressed nonetheless, especially regarding exercises of a higher intensity. Upon analysis of the focus groups involving the non-exercise class attendees, a lack of clarity regarding exercise prescription became markedly evident. Although these patients were aware that it would be advantageous for them to partake in exercise, they appeared to have numerous unanswered questions.

Whilst offering a comprehensive account of the current perceptions of RA patients regarding exercise and joint health, and also drawing upon the valuable, interactive elements of focus group methodology, the present study has a number of limitations. Firstly, self-selected participants may be different in terms of disease severity, attitudes about health and exercise and sociodemographics, when compared to the disease population as a whole. Similarly, local communities vary widely in the availability of resources and programmes for individuals with arthritis (der Ananian et al. 2006). Therefore, the findings may not be as applicable in geographical areas with a different level of emphasis on exercise prescription for RA patients. A second limitation is that we used a relatively small sample of patients. However, the purpose to achieve sample saturation (i.e., recruiting patients with a range of characteristics and experiences) was fulfilled and the fourth focus group did not reveal any additional concepts or ideas to those already identified. Furthermore, the analysis was strengthened through the use of investigator and data source triangulation (i.e., two different analysts employed different methods of analysis and different methods were included within the interview guide to stimulate discussion). This enhanced the reliability, comprehensiveness and hence the overall validity of the study findings (Patton 2002).

3.6 Applications and conclusions

In addition to the pivotal role of the rheumatologist in influencing exercise prescription (Iversen et al. 1999; Iversen et al. 2004b), the following implications of the present study are also relevant to other health professionals involved in the treatment of RA patients (i.e. nurse specialists, physiotherapists, occupational therapists). Primarily, in order to enhance exercise prescription for RA patients, it is evident that the benefits of exercise need continual emphasis. In addition, concerns regarding joint health and pain symptoms need to be addressed, alongside the specificity of exercise recommendations.

This in-depth exploration of the perceptions of stable RA patients in North Wales relating to exercise and joint health also concludes that these patients are aware of the likely benefits of exercise but require clarification of specific exercise recommendations. Furthermore, this population have concerns about exercise and joint pain, the effects of exercise on joint health, alongside a perception that health professionals show uncertainty when imparting exercise knowledge.

These conclusions entail that further research is necessary to establish ways of addressing the fact that RA patients are currently faced with ambiguous and incomplete information regarding exercise and the health of their joints. Furthermore, it is important to further investigate and substantiate these findings by determining the perceptions of a larger population of RA patients. The results of this follow-up questionnaire study are described in Chapter 4.

Chapter 4: Perceptions of issues relating to exercise and joint health in rheumatoid arthritis; a UK-based questionnaire study

This manuscript is under first revision for publication in *Musculoskeletal Care:*

Law, R.-J., Markland, D. A., Maddison, P. J. and Thom, J. M. (2011). 'Perceptions of issues relating to exercise and joint health in rheumatoid arthritis: a UK-based questionnaire study.'

4.1 Abstract

Objectives

This questionnaire study investigates the perceptions of RA patients across the UK in relation to exercise and joint health. The validity of the measure is also assessed.

Methods

Members of the National Rheumatoid Arthritis Society (NRAS) with self-reported RA completed the questionnaire online. Items related to 5 factors that emerged from previous qualitative research. Participants responded using a 5-point Likert-style scale (strongly disagree - strongly agree). The International Physical Activity Questionnaire (IPAQ) assessed physical activity. The model was tested using confirmatory factor analysis (LISREL 8.8); statistical analyses were conducted using SPSS.

Results

247 responses were collected over 47 days (88% females; age: 18-77 years; disease duration: < 1-51 years). Acceptable factorial validity was revealed (S-B χ^2 = 774.47, df = 454, $p < 0.001$, RMSEA = 0.05, 90% CI RMSEA = 0.05 – 0.06, CFI = 0.94, SRMR = 0.09), with the following factor endorsements; ‘Health professionals show exercise knowledge’ (19%), ‘Knowing what exercise should be done’ (43%), ‘Having to exercise because it is helpful’ (72%), ‘Worry about causing harm to joints’ (44%), ‘Not wanting to exercise as joints hurt’ (52%). Patient concerns about joint pain, joint harm and how to exercise were significantly associated with lower physical activity ($p < 0.05$).

Conclusions

These results confirm that patients perceive exercise as beneficial. However, concerns about how to exercise, joint pain, causing harm to joints and a perceived lack of exercise knowledge amongst health professionals remain. Addressing these concerns may have implications for increasing physical activity within the RA population.

4.2 Background

The topic of joint health and exercise has been previously explored in Chapter 3 using qualitative analysis of small focus group discussions. It was found that although patients were aware of the benefits of exercise, they had concerns about joint pain, causing harm to their joints and exactly what exercises to do. Furthermore, concerns were expressed about the knowledge of health professionals regarding exercise prescription. In order to determine if these findings are applicable on a larger scale, the quantitative follow-up study described in this chapter sets out to develop and utilise a questionnaire designed to assess patient perceptions of the aforementioned issues. With advantages of enhanced anonymity, low cost, increased efficiency and the potential for wider geographical catchment (Joinson 1999; Gosling et al. 2004) an online questionnaire system was used. These systems have been used successfully to investigate the perceptions of RA patients (Gyurcsik et al. 2009).

Further investigation of this important area will inform health professionals about patients perceptions, particularly in relation to exercise and joint health. In fact, it has recently been highlighted that there is a need to develop a valid and reliable instrument to assess worries, fears and concerns specific to RA and physical activity (Ehrlich-Jones et al. 2011). If health professionals are encouraged to consider these views and beliefs and are able to adjust their approach and attitude accordingly, this may well improve patient perceptions and the overall success of their exercise recommendations.

4.3 Methodology

Participants

Following full ethical approval, a first draft of the questionnaire was piloted with outpatients with RA from the Department of Rheumatology, Betsi Cadwaladr University Health Board. Following final adjustments, a request to complete the final questionnaire was then distributed by email to members of the National Rheumatoid Arthritis Society (NRAS) and was also made available by e-newsletter and via the NRAS website.

Procedures

As part of the questionnaire development process, items were created to reflect the five-factor model from our previous qualitative research: 'health professionals showing a lack of knowledge', 'not knowing what exercise should be done', 'having to exercise because it is helpful', 'worry about causing harm' and 'not wanting to exercise as joints hurt' (Chapter 3). Item wording was founded primarily upon the thematic analysis of the previous study, which also assisted in the design of items that were likely to be easily understood by respondents (Barbour 2005). All content was systematically sampled to ensure similar numbers of items represented each of the factors in the model (Clark et al. 1995).

Items were then subject to assessment of content validity, which involved the use of a 5-point Likert-style scale to assess the representativeness of each item to the appropriate theme and the clarity of the individual item. This assessment was completed by four researchers with expertise in clinical research and questionnaire design, one of whom was involved in the analysis phase of the initial focus group study. A group of six health professionals with expertise in musculoskeletal disease also completed the assessment. Only those items assigned to the correct theme and with mean representativeness and clarity scores of above 4 were considered for retention. Finally, in order to use straightforward and unambiguous language, appropriate adjustments were to item wording were made based on comments from patients and health professionals. Responses to these items were then scaled using a 5 point Likert-style scale with anchors 1 = strongly disagree and 5 = strongly agree. To assess concurrent validity, the Self-Efficacy for Exercise Scale (SEE) (Resnick et al. 2000) was also included. Demographic information (age, gender and disease duration) was sought from participants, alongside a measure of their current physical activity levels (International Physical Activity Questionnaire; IPAQ). The IPAQ short form assesses moderate, vigorous physical activities and walking in the last 7 days (Craig et al. 2003). Calculation of energy expenditure in metabolic equivalent minutes per week (MET-minutes) using the relevant scoring protocol (including the removal of outliers) allowed participants to be categorised into low, moderate or high physical activity groups (available at: http://www.ipaq.ki.se/). The final questionnaire is available in Appendix 3.

The Bristol Online Survey system was used to present the questionnaire which participants then completed online. A tick-box incorporated into the questionnaire design enabled all participants to give informed consent before completion. The questionnaire was accessible from late August to mid-October 2010 and for 47 days in total. After approximately one month further attempts for data capture were made in the form of a reminder email, changing the wording of the invitation to increase importance (i.e. from 'can you' to 'please') and moving the research to a more prominent position on the website.

Statistical analysis

Statistical techniques were used to assess the validity and reliability of the structural model and subsequent items. To determine whether the data collected conformed to the *a priori*-specified model (Schmacker et al. 2004), the model was tested using confirmatory factor analysis (CFA) in LISREL (version 8.8). Whilst considering substantive meaningfulness, redundant and ambiguous items were removed based on high modification indices (indicating cross-loading items) and low factor loadings (cut-off < 0.4). To correct for departure from multivariate normality, the Satorra-Bentler scaled χ^2 (Satorra et al. 2001) was used to assess fit, alongside the root mean squared error of approximation (RMSEA; acceptable fit ≤ 0.06) and its 90% confidence interval, the comparative fit index (CFI; acceptable fit ≥ 0.95), and the standardised root mean square residual (SRMR; acceptable fit < 0.08) (Hu et al. 1999). Following calculation of subscale means, Pearson's correlation and between-group analyses (ANOVA) were carried out using the Statistical Package for the Social Sciences (SPSS).

4.4 Results

At the time of distribution, 1842 NRAS members were patients with self-reported RA. The final sample included 247 participants (217 females, 30 males) and represented a wide range of ages, years of disease duration, physical activity levels and self-efficacy. There were significant, positive correlations between participant age and disease duration and also between physical activity levels and self-efficacy for exercise (Table 4.1). 58% of respondents stated they had another medical condition other than RA; mainly hypertension (n = 39), high cholesterol (n = 30) and osteoarthritis (n = 30).

Questionnaire factorial validity and reliability

Initially, 64 items were created to reflect the five-factor model. Following assessment of content validity and the piloting process, 39 items remained for inclusion in the primary CFA. Following data interrogation, 7 poorly performing items were removed and the final 32-item model represented an acceptable fit (S-B χ^2 = 774.47, df = 454, $p < 0.001$, RMSEA = 0.05, 90% CI RMSEA = 0.05 – 0.06, CFI = 0.94, SRMR = 0.09). Table 4.1 displays subscale means and inter-factor correlations. Composite reliabilities indicated acceptable internal consistency of the factors (> 0.8) and correlations between the factors and SEE provided evidence for the concurrent validity of the scale. Item factor loadings and individual item response means are shown in Table 4.2.

		Mean ± SD	Age (years)	Disease duration (years)	Physical Activity (MET-minutes)	Self-efficacy for exercise (SEE)	Factors 1	2	3	4	5
	Age (years)	52 ± 11	-	-	-	-	-	-	-	-	-
	Disease duration (years)	9 ± 9	.18**	-	-	-	-	-	-	-	-
	#Physical Activity (MET-minutes)	3103 ± 2891	.01	-.01	-	-	-	-	-	-	-
	Self-efficacy for exercise (SEE)	4.81 ± 2.47	-.00	.03	.26**	-	-	-	-	-	-
1	Health professionals showing a lack of exercise knowledge	3.42 ± 0.88	-.14*	-.09	-.04	.01	-	-	-	-	-
2	Not knowing what exercise should be done	2.90 ± 0.88	-.13	.04	-.19*	-.35**	.53**	-	-	-	-
3	Worry about causing harm to joints	3.15 ± 0.91	.00	.06	-.23*	-.50**	.27**	.68**	-	-	-
4	Not wanting to exercise as joints hurt	3.28 ± 0.82	-.02	.07	-.28*	-.25**	.14**	.55**	.53**	-	-
5	Having to exercise because it is helpful	3.88 ± 0.70	-.09	.00	.08	-.22**	.10**	-.23**	-.07**	-.25**	-

Table 4.1 Characteristics (age, disease duration and physical activity) and subscale scores (1 – 5; strongly disagree-strongly agree) of the questionnaire respondents. Data is displayed as mean ± standard deviation (SD). Factors 1 - 5 relate to the subscales in column 1. Correlations among factors and correlations between factors and participant characteristics: * = significant correlation; $p < 0.05$; ** = significant correlation; $p < 0.01$. (n = 247; # = following deletion of outliers; n = 241)

	Item	Item response (Mean ± SD)	Health professionals showing a lack of exercise knowledge	Not knowing what exercise should be done	Worry about causing harm to joints	Not wanting to exercise as joints hurt	Having to exercise because it is helpful
30	I don't think health professionals know what exercises to recommend	3.40 ± 1.07	.97				
33	Health professionals have not been able to answer my questions about exercise	3.10 ± 1.04	.78				
4	Health professionals are not specific about exactly how to exercise	3.78 ± 1.10	.61				
31	I don't think health professionals know what to tell me about how exercise affects my joints	3.37 ± 1.07	.98				
23	Health professionals seem to know what to tell me about exercise	3.46 ± 1.10	.81				
35	I wonder if I should exercise at all	2.02 ± 1.14		.59			
25	I am unsure when to exercise	2.96 ± 1.21		.79			
32	I don't know what the best sort of exercise is	3.08 ± 1.21		.89			
29	I am unsure how much exercise I should do	3.29 ± 1.17		.85			
11	I don't know which joints I should exercise	2.94 ± 1.28		.97			
34	I am unsure if it is a good idea to exercise when my joints are 'bad'	3.14 ± 1.13		.75			
13	I am concerned that exercise will add to damage that has already been caused by my disease	3.00 ± 1.11			.88		
7	I wonder if I am causing damage if it hurts when I exercise	3.48 ± 1.13			.88		
20	I worry that exercise will cause more damage to my joints	2.90 ± 1.13			.94		
9	I worry about exercise causing harm to my joints	3.15 ± 1.17			.95		
17	Joint damage is in the back of my mind when I exercise	3.22 ± 1.14			.63		
38	Pain doesn't affect whether I exercise or not	3.52 ± 1.15				.68	
8	Pain affects if I want to exercise or not	3.80 ± 1.00				.67	
27	Pain affects whether I exercise or not	3.51 ± 1.13				.70	
15	Pain doesn't affect whether I want to exercise or not	3.45 ± 1.15				.65	

1	I would not consider exercising if my joints are hurting	3.06 ± 1.29	.86	
19	I don’t want to exercise because my joints are painful immediately afterwards	2.62 ± 1.13	.60	
16	I don't want to exercise when I'm in pain	3.57 ± 1.17	.97	
10	If my joints hurt I don't want to exercise	3.46 ± 1.17	.99	
5	I don’t want to exercise because I know my joints will hurt the day afterwards	2.55 ± 1.26	.73	
28	I worry that I will end up disabled if I don't exercise	3.78 ± 1.04		.45
14	I feel exercise is helpful for my joint health	4.09 ± 0.98		.72
37	I feel exercise makes my joints stronger	3.78 ± 1.04		.61
16	I worry that my joint function will get worse if I don't exercise	4.03 ± 0.95		.66
18	Exercise helps to keep my joints moving	4.12 ± 0.89		.67
22	I find that if I keep mobile through exercising, I have less pain in my joints	3.36 ± 1.06		.59
21	I feel my joints need exercise	4.07 ± 0.89		.71

Table 4.2 Standardised parameter estimates for exercise and joint health questionnaire items. *Note:* all estimates $p < 0.01$. Reverse-keyed items: 15, 23, 38.

Patient perceptions

To further describe the results the five subscales are split into two categories; those relating to perceptions of the effects of exercise and those relating to exercise prescription. Patient agreement or endorsement refers to a response of 'agree' or 'strongly agree' (4 or 5 on Likert-style scale). The percentage of participants who endorsed each item was calculated and the mean for each subscale is reported.

Perceptions of the effects of exercise

Analysis revealed that 72% of patients endorsed the factor 'Having to exercise because it is helpful' (agreed or strongly agreed with items relating to this subscale), 44% agreed with the factor 'worry about causing harm to joints' and 52% agreed with the factor 'not wanting to exercise as joints hurt' (Figure 4.1).

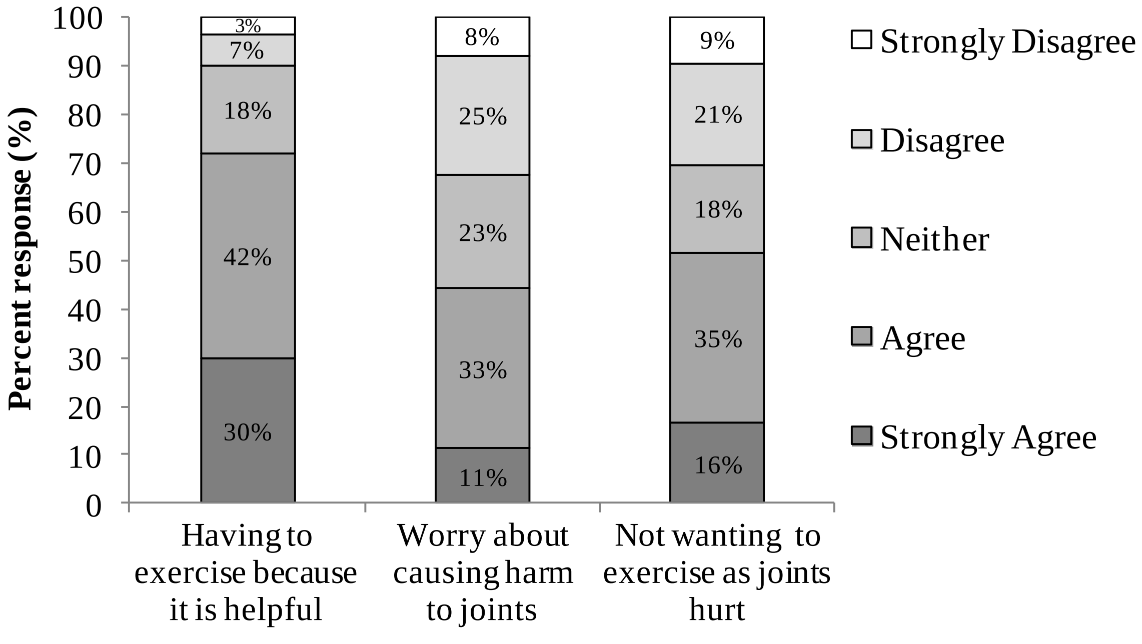

Figure 4.1 Percentage agreement and disagreement of RA patients with items relating to 'exercise perception' factors (n = 247).

Exercise prescription

For ease of interpretation, the labels for these subscales have been reversed to maintain consistency with the subscales relating to perceptions of the effects of exercise. Specifically, 'I don't know what I should be doing' is modified to '*knowing* what exercise should be done' and 'health professionals show a lack of exercise knowledge' is modified to 'health professionals *show* exercise knowledge'. 43% of participants endorsed the subscale 'knowing what exercise should be done' and 19% endorsed the subscale 'health professionals show exercise knowledge' (Figure 4.2).

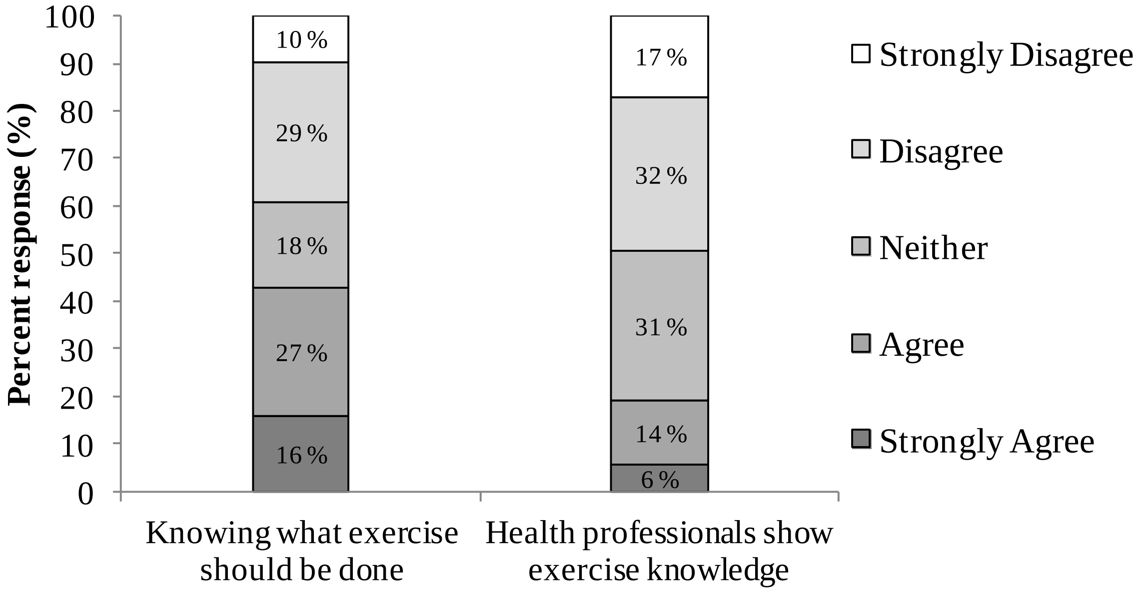

Figure 4.2 Percentage agreement and disagreement of RA patients with items relating to 'exercise prescription' factors (n = 247).

There was a small but significant negative correlation between age and the subscale 'Health professionals show a lack of exercise knowledge' ($p = 0.03$). However, there were no significant correlations between any of the other subscales and age or disease duration. There were significant negative correlations between IPAQ score (MET-minutes) and the factors 'not knowing what exercise should be done', 'worry about causing harm to joints' and 'not wanting to exercise as joints hurt' (all $p < 0.001$), with greater agreement with these themes observed in those with lower physical activity levels (Table 4.1).

Further analysis of the IPAQ data revealed that 24.5% of patients were categorised as participating in low levels of physical activity, 36.9% were categorized as participating in moderate levels of physical activity and 38.6% were categorized as participating in high levels of physical activity. Participants in the low physical activity category showed significantly greater mean scores for items relating to the subscale 'Not wanting to exercise as joints hurt'. Mean responses were 9% and 20% higher in the low physical activity category when compared to those patients in the moderate and high physical activity categories, respectively. For this analysis, the assumption of homogeneity of variance was violated and therefore the Brown-Forsythe *F*-ratio (Field 2009) is reported ($F_{(2, 216.59)} = 236.83$, $p < 0.001$; Figure 4.3). There were no significant differences between males and females in their agreement with the five subscales.

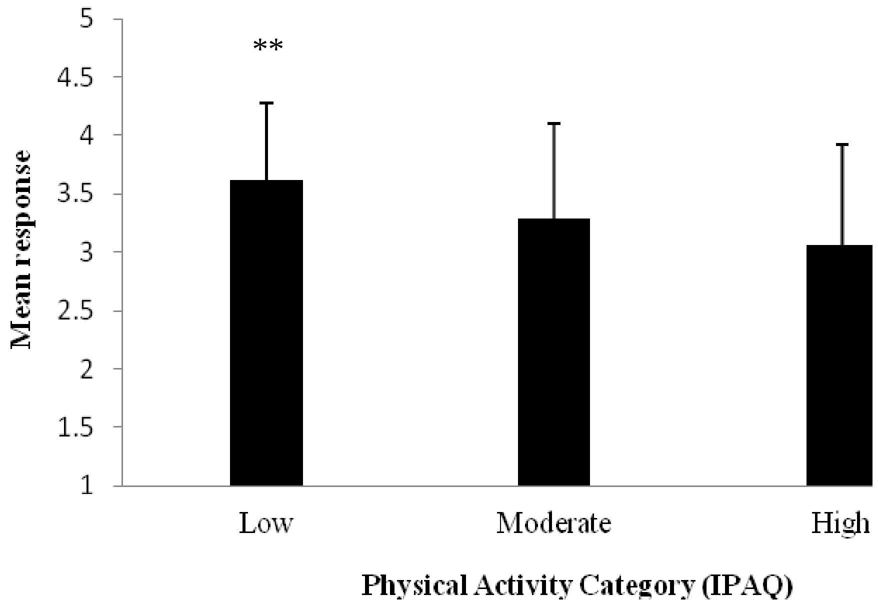

Figure 4.3 Mean response to items relating to the subscale 'Not wanting to exercise as joints hurt'. (** = p < 0.01 when compared to Moderate and High) (n = 241).

4.5 Discussion

To our knowledge, this is the first report to describe the perceptions of RA patients in relation to exercise, and specifically joint health, in a quantitative way. The study highlights that positive views about exercise are prevalent within the RA population, with the large majority agreeing with the subscale ‘having to exercise because it is helpful’. However, patients remain worried about joint pain, the effects of exercise on joint health, how they should exercise and the knowledge of health professionals. In addition, whilst further work is needed to confirm the appropriateness of the scoring method applied (i.e. using Item Response Theory or Rasch Analysis), the final version of this questionnaire shows acceptable factorial validity and therefore addresses the need for the development a useful tool for examining perceptions of issues relating to exercise and joint health in people with RA (Ehrlich-Jones et al. 2011).

This study also confirms our previous small-scale qualitative study which described patients’ perceptions of the effects of exercise (Chapter 3). Furthermore, research by Hendry et al. (2006) identified a group of patients with osteoarthritis who stopped exercising due to a fear it was damaging their joints. Our research provides evidence that this perception also exists in the RA population. Similarly, our findings that RA patients perceive exercise as a helpful part of their treatment but that joint pain often forms a major barrier, confirm previous findings in the general arthritis population (der Ananian et al. 2006; Wilcox et al. 2006; Gyurcsik et al. 2009; Hutton et al. 2009).

In relation to exercise prescription, just over half the patients in the current sample felt that they did not know what exercise they should be doing, substantiating earlier findings by Lambert et al. (2000). Indeed, only 19% of RA patients in this study agreed that health professionals showed exercise knowledge, with only around 5% showing ‘strong’ agreement and with half of the participants in *disagreement* with this theme. Interestingly however, many patients indicated that they neither agreed nor disagreed with this theme. While the reason for this neutrality was not stated, it may have been that patients were unable to recall a conversation or indeed that they had never had a conversation with a health professional about exercise.

On the other hand, it is important to note that a large proportion (43%) of patients expressed that they did know what exercise they should do. Since only a relatively small percentage of patients felt that health professionals showed exercise knowledge (19%), we hypothesise that these patients, as members of an information and support-providing charity such as NRAS, had accessed alternative sources of information, independent of health professional advice. This would correspond with research suggesting that health professionals do not introduce exercise-based intervention because of a lack of time, inadequate training, perceived ineffectiveness as a behavioural counsellor and a view that patients lack interest (Calfas et al. 1996; Iversen et al. 1999). Furthermore, Iversen et al. (2004b) found that only 51% of rheumatologists felt they knew when exercise was appropriate for patients with RA and only 22% felt confident to instruct patients as to how they should exercise. Despite this, a conversation about exercise is four times more likely to occur during a consultation if initiated by the rheumatologist (Iversen et al. 2004a).

Recent research by Ehrlich-Jones et al. (2011) found that increased physical activity in RA patients was significantly associated with beliefs about the beneficial effects of exercise, a relationship that was not observed in this study. However, the current study focussed specifically on joint health and the relationship between the subscale responses and physical activity suggest that those patients who indicated more concern about harming their joints, joint pain and about how to exercise, were less physically active. This corresponds with research findings that physical inactivity in RA is associated with higher levels of pain and disease activity (Sokka et al. 2009). It is important to note however that this subscale data does not allow differentiation between those patients who were less physically active because they felt exercise *caused* pain and those patients who avoided exercise because of *current* RA-related pain. The reader is referred to Table 4.2 for mean responses to individual items.

The NRAS members who completed the questionnaire represented a wide range of ages and disease duration, and the gender distribution was also typical of the RA population. Additionally, whilst data relevant to the geographical location of participants is limited, 96% of the total NRAS memberships were known to be from England or Scotland, hence the current study cohort captured the potential for differing perceptions from the initial focus group study based in Wales. Apart from a weak trend towards older individuals showing less agreement with the factor 'Health professionals showing a lack of exercise knowledge', there appeared to be no significant relationships between theme agreement and age. There also appeared to be no relationship between theme agreement and disease duration, suggesting that these factors may not have a strong influence on patient perceptions. Hence, health professionals can be encouraged to apply the findings of this study across a range of ages and disease durations.

With further reference to this particular sample, it is important to consider the following points while interpreting the results. Firstly, many participants in this sample stated that they had additional co-morbidities, the effects of which may have influenced perceptions relating to exercise. However, this observation is generalisable to the broad RA population, with the established RA patient typically having one or more comorbid condition (Briggs et al. 2009). Furthermore, the questionnaire was also designed and distributed to be specific to RA and so this characteristic is not considered to detract from overall conclusions.

Secondly, it is very encouraging to note that 40% of the sample fell into the high physical activity category. However, it has been found that RA patients typically perform no regular, weekly exercise (Sokka et al. 2008) and therefore these physical activity levels are uncharacteristic of this patient group. Hence it may be suggested that the NRAS members who chose to complete the questionnaire, formed a subgroup of patients who were pro-active in their RA management, explaining the high physical activity levels. Furthermore, it is possible that responses may have been biased by overestimation of physical activity or social desirability (Eurenius et al. 2005). Thirdly, the relatively low response (16%) to the questionnaire is also a limitation and it may indeed be that that those who responded to the questionnaire were those who were especially keen on exercise (Semanik et al. 2004; Eurenius et al. 2005).

As may be expected, a positive relationship between self-efficacy for exercise and physical activity was also observed in the current sample (Gecht et al. 1996). Nevertheless, it is also important to stress that if this sample did represent a more physically active section of the RA population, another more sedentary sample who do not benefit from the information and support provided by NRAS, might have expressed heightened uncertainties and less self-efficacy regarding exercise than did this cohort. Finally, it is also important to consider the limitations of internet-based research. This sampling method has been criticised for lacking demographic diversity as internet users are often of a higher socio-economic status and a younger age (Krantz et al. 2000). Therefore, as evidenced by the mean age of the current sample, this method did not capture the views of older individuals with RA or those with limited or no internet access. Importantly however, this method allowed the questionnaire to be designed in a way that enabled prevention of human error (i.e. participants missing questions) and enabled wider advertisement of the questionnaire by means of a webpage post and e-newsletter.

4.6 Applications and conclusions

This UK-wide study concludes that the majority of NRAS members with self-reported RA hold positive perceptions about exercise. However, this population, who reported higher levels of physical activity than the general RA population, still have concerns about how to exercise, exercise and joint pain and the effects of exercise on joint health. Furthermore, many of these patients perceive that health professionals are uncertain when imparting exercise knowledge. In terms of the tool used, the final version of the questionnaire shows acceptable factorial validity and may well be useful for further research into this area.

The current study also has important implications for health professionals when recommending exercise. The legacy of previous treatment recommendations (Partridge et al. 1963) and research provoking concern about exercise for RA patients (Munneke et al. 2005), may have contributed to the formation of negative perceptions about the effects of exercise on joint health. Nevertheless, the advances in pharmacological treatment for RA now enable many individuals to live a full and active lifestyle and therefore it is necessary for health professionals to make concentrated efforts to promote the vital benefits of exercise for people with RA. Moreover, the alleviation of patient concerns about joint pain and damage, alongside clear and specific exercise recommendations are especially important.

Health professionals working with RA patients can play a vital role in achieving these objectives. Therefore, addressing health professionals' negative perceptions and uncertainty about exercise for this population is imperative in order to increase exercise participation and the health of people with RA. Hence, exploring the perceptions of rheumatologists, physiotherapists, occupational therapists and nurse specialists in relation to these issues is paramount and has since been the focus of a follow-up study detailed in Appendix 4 and 5 (Halls et al. 2012a; Halls et al. 2012b).

4.7 Summary and perspective

The research described in this Chapter reports the perceptions of a large cohort of RA patients in relation to exercise, and specifically joint health. In confirmation of the findings from the previous small-scale qualitative study described in Chapter 3, it was found that the majority of participants held positive views about exercise but that many patients remained worried about joint pain, the effects of exercise on joint health, how they should exercise and the knowledge of health professionals. Additionally, findings from the study described in this chapter revealed that patients who indicated more concern about harming their joints, joint pain and about how to exercise, were also less physically active.

Overall, the research described in the previous two chapters (Chapters 3 and 4) explores the perceptions of patients with RA in relation to exercise and joint health. Encouragingly, this research demonstrates that patients know exercise is beneficial and forms an important part of their treatment. However, it is clear that patient concerns regarding exercise and joint health need addressing to improve physical activity levels in RA.

As previously discussed, one of the key roles of the rheumatology health professional is to promote exercise. However, the research discussed in Chapters 3 and 4 has also highlighted that patients perceive a lack of knowledge amongst health professionals. Analogous to this, it is evident from comprehensive review of the literature that there are gaps in the current knowledge surrounding the effects of exercise on joint health. Thus, it may be that the unanswered questions regarding exercise and joint health, which are evidently important to RA patients, are limiting the ability of health professionals to recommend exercise.

Therefore, the research described in the following Chapters aims to address some of the gaps in the current literature by investigating the effects of acute and continued, intensive aerobic and resistance exercise on cartilage breakdown and synovial inflammation.

Chapter 5: The acute effects of exercise on joint damage and inflammation in RA

5.1 Abstract

Objectives

The potential detrimental effects for large weight-bearing joints have previously been highlighted and the effects of exercise *per se* are unknown. Research also suggests that patients have concerns about the effects of exercise on joint health. Therefore, our aim was to investigate the acute effect of high-intensity aerobic and resistance exercise on cartilage turnover, synovial and systemic inflammation.

Methods

8 stable RA patients (age: 60 ± 12 years; disease duration: 19 ± 12 years; mean ± SD) with a history of knee symptoms and 8 matched, healthy control participants performed two types of exercise. Aerobic exercise involved ~30 minutes of interval walking training (50-70% MHR). Resistance exercise involved 3 sets of 8 repetitions at 80% of 1 repetition-maximum of leg press, leg extension, leg curl exercises. Serum COMP, CF, and serum CRP were assessed prior to, immediately following and 30 minutes, 1, 2, 6 and 24 hours post-exercise. Mixed model ANOVA with repeated measures was used for statistical analysis.

Results

Serum COMP and CRP were significantly higher in the RA group (RA; CRP: 16.2 ± 17.3 mg/L; COMP: 1359 ± 381.9 ng/ml, CTL; CRP: 1.3 ± 1.2 mg/L; COMP: 1179 ± 446.3 ng/ml; p = .046 and p > 0.00, respectively). However, there were no changes between the time points after either the resistance or aerobic exercise session. No clinically significant levels of synovial inflammation were observed prior to or following exercise.

Conclusions

This preliminary further confirms that intensive exercise is not detrimental to joint health in patients with inactive RA. These findings will help facilitate the transfer of positive information relating to exercise and joint health. Further research will determine if continued high-intensity training affects the acute response to exercise.

5.1 Background

One of the key roles of the rheumatology health professional is to promote exercise and the maintenance of an active lifestyle. However, as discussed in Chapters 3 and 4, it is evident that patients still harbour concerns relating to the potentially detrimental effects of exercise on the health of their joints. Furthermore, it has also been revealed that RA patients perceive an uncertainty within the health profession relating to exercise and joint health. These perceptions may not be surprising considering that the underlying pathophysiological mechanism concerning joint health following exercise is yet to be fully elucidated (Anandarajah et al. 2004). As detailed previously (Chapter 1), research findings relating to the effects of exercise training on joint health are encouraging (de Jong et al. 2009). Despite this however, these previous studies are limited in their ability to determine whether or not exercise *per se* aggravates joint damage or inflammation, as they have conducted cross-sectional or chronic training programmes and not studied the acute effects of exercise. Furthermore, it has been acknowledged that additional information is required relating to the optimal mode of exercise for people with RA (Combe et al. 2007; National Collaborating Centre for Chronic Conditions 2009). Therefore, it is important to determine the potentially differential effects of aerobic and resistance exercise on joint health. The next chapter of this thesis focuses on the acute physiological effects of aerobic and resistance exercise on cartilage breakdown (serum COMP), synovial inflammation (CF) and systemic inflammation (serum CRP) in RA.

The effect of exercise mode on joint health

Aerobic walking and progressive resistance training are two exercise modes that have been successfully adopted by people with RA (Hurkmans et al. 2009). In general, aerobic and resistance exercise both involve movement repetitions against a resistance. However, these two modes of exercise may have divergent effects locally as a result of the differential stressors placed upon the joints. Whilst aerobic exercise is characterised by low resistance and 200 or more repetitions, resistance exercise is often associated with multiple sets of between 1 and 10 repetitions and a higher resistance (Knuttgen 2007). However, research directly comparing the acute effects of aerobic and resistance exercise on loading of the human joint is limited.

An early study investigated quadriceps muscle force and patello-femoral joint reaction force (PFJR) in three young men during level walking, climbing and descending stairs, knee bending and quadriceps exercises against resistance. With specific relevance to the current study, it was concluded that PFJR was higher during knee extension exercise (nearly 1.5 times body weight) when compared to level walking (0.5 of body weight). When stair walking was performed, the PFJR attained an even higher level of 3.3 times body weight. Of further interest, a higher joint reaction force was observed with an increase in quadriceps muscle force and an increase in the angle of knee flexion. For example, when the knee is flexed to larger angles, such as during deep knee bends, PFJR was 7.6 times body weight This also explains the reduced forces observed with level walking when joint angles and muscle forces remain small (Reilly et al. 1972).

With further reference to walking exercise, researchers have investigated the effects of walking speed and gradient on joint loading. Specifically, research has demonstrated that faster walking speeds increases the dynamic loading on musculoskeletal system (heel-strike initiated shock waves) (Voloshin 2000). Similarly, Spyropoulos et al. (2008) investigated the effect of different walking conditions on impact loading in healthy and osteoarthritic women. Using accelerometry, this study also confirmed that slow walking (1.5 miles per hour) resulted in significantly lower tibial deceleration than fast walking (2.5 miles per hour). Furthermore, significantly lower tibial deceleration was observed during level walking when compared to uphill (+ 6 degrees) and downhill (- 6 degrees) walking, with a trend towards higher tibial deceleration when uphill walking was performed. Both the healthy control group and the group of participants with OA showed similar values.

Considering the above differences between aerobic and resistance exercise in terms of joint loading, the direct effects of different modes of exercise on serum COMP, synovial and systemic inflammation are important to establish in RA. As described in Chapter 1 however, few studies have assessed the acute effects of exercise and even fewer have compared the acute effects of different modes.

To the author's knowledge, there are no studies investigating the acute response of serum COMP to different modes of exercise in the RA population. In healthy individuals, the acute effects of different mechanical loading protocols on serum COMP was recently investigated by Niehoff and colleagues (2010). Running was found to significantly increase serum COMP concentration by approximately 39%, while slow knee-bends did not induce any changes. In conclusion, the authors suggested that serum COMP elevation may depend on the frequency of the applied loads. On the other hand, a study by the same authors including a healthy sample of seven males and seven females found no difference in the magnitude of the change in serum COMP or the duration of elevation when comparing the response to drop-jumping and running exercise, both of 30 minutes duration (Niehoff et al. 2011). Therefore, it appears that the effect of different modes of exercise on serum COMP is yet to be established.

In terms of the inflammatory aspects of RA, synovial inflammation has only been assessed in response to low-intensity handgrip exercise, with no significant changes in CF observed in the wrist joint (Ellegaard et al. 2009a). In healthy individuals, Collier et al. (2010) concluded that resistance exercise (three sets of ten repetitions of eight upper and lower body exercises at 65% 1RM) caused a greater increase in blood flow to the active muscles when compared to aerobic exercise (30 minutes cycling at 65% VO_2 peak[5]). Of potential relevance to joint health, one may speculate that this increase in systemic blood flow may also cause an increase in localised blood flow to the joint.

In terms of systemic inflammation, the acute response to exercise of various modes and intensity of exercise was recently investigated in a sample of twelve sedentary but otherwise healthy males. In a randomised cross-over design, participants completed four exercise protocols of forty minutes each; aerobic cycling exercise at 50% and 30% of maximal aerobic workload, and resistance exercise at 60% and 80% of 1RM. It was found that serum CRP was significantly elevated at twenty-four hours post-exercise in the higher intensity resistance exercise condition. Overall, the results suggested that serum CRP increases at 24 hours post-exercise were greater with high-intensity resistance exercise when compared to when serum CRP was measured following a low-intensity exercise protocol (Mendham et al. 2011). Overall however, it appears there are no research studies to date comparing the effects of different modes of exercise on synovial or systemic inflammation in RA.

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[5] Maximal oxygen uptake (VO_2 max) as limited by symptoms such as fatigue is known as VO_2 peak Moore, GE, Marsh, AP, Durstine, JL (2009). Approach to exercise and disease management. ACSM's Exercise management for persons with chronic diseases and disabilities. J. L. Durstine, G. E. Moore, P. L. Painter and S. O. Roberts. Champaign, IL, Human Kinetics**:** 12-13..

Summary and specific objectives

In summary, previous study designs have not described the direct effects of exercise on the rheumatoid joint or compared the effects of different modes of exercise on cartilage breakdown and synovial inflammation. Hence the aim of the current research is to address these limitations by examining the acute effects of aerobic walking and lower-body resistance exercise on serum COMP, synovial and systemic and inflammation. Furthermore, to elucidate any changes that may be specific to RA, this study compares the effects observed in this patient group with the effects in a healthy control group.

If exercise of both modes proves to have no detrimental effect upon joint health and inflammation in RA, health professionals are in a strong position to advocate the advantages of both forms of exercise. Moreover, it may be that RA patients will be more likely to exercise if they can do so without fear of exacerbating their disease. With a greater understanding, it may also be possible to enhance the specificity of exercise recommendations for RA patients. Overall, it is proposed that the findings from this research will enhance the understanding of rheumatology health professionals when recommending exercise to RA patients. In addition, this research will provide further information in relation to the biological and clinical relevance of the chosen outcome measures.

Specific objectives of this chapter include determining and comparing the acute effects of aerobic walking and lower-body resistance exercise in a group of RA patients and a healthy control group. The following main outcome variables will be assessed; a) cartilage breakdown (serum COMP); b) synovial inflammation (CF) of the knee joint. Secondary outcome variables include; c) systemic inflammation (serum CRP); and d) knee joint pain.

5.2 Methodology

This study gained full ethical approval from the North West Wales Research Ethics Committee. Pilot testing allowed researchers to perfect techniques and make necessary amendments before the final protocol was used. The investigation formed a randomised crossover design with repeated measures; a group of RA patients and a group of age-matched, healthy control participants were assessed prior to and at six time points in the twenty-four hours following two types of exercise, performed at least one week apart.

Participant sampling and selection

Patients with RA were recruited from the outpatient clinic of the Department of Rheumatology, Betsi Cadwaladr University Health Board. Inclusion criteria were a diagnosis of RA, fulfilling the American Rheumatism Association (1987) revised criteria (Arnett et al. 1988) and having presented with knee symptoms in the past year. 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). See Appendix 6 for patient recruitment and inclusion flow diagram. Healthy age and gender-matched controls were also recruited from the local area. Fully informed, written consent was obtained from all participants. Participants were given £30 as a contribution towards travel expenses.

As there were no existing data comparing the increases in serum COMP between healthy controls and RA patients following exercise, an *a priori* sample size calculation was based on data from previous studies with healthy participants. These indicated that levels of serum COMP rise to approximately 9 ± 3 U/L within thirty minutes of exercise and then return to baseline levels. A COMP level of > 15 U/L is indicative of severe cartilage degradation (Specialty Laboratories, 2004). Using this difference of 6 U/L in a formal sample size calculation, a sample size of four participants in each group was identified as the minimal number necessary to determine significance (DSS Research 2009). This method may overestimate effect size, hence sample size was increased accordingly. Therefore the aim was to recruit twenty participants in total, comprising of ten healthy controls and ten patients with RA.

Study protocol

Participants visited the departmental laboratory on five occasions in total; one familiarisation session, two exercise sessions and two brief assessment sessions twenty-four hours post-exercise. The first familiarisation session enabled fully informed consent to be given, participants were familiarised with the equipment and testing procedures and the intensity of the exercise sessions was determined.

Questionnaires

All participants completed the standardised School of Sport Health and Exercise Sciences departmental health questionnaire, designed to collect self-disclosed information regarding previous medical conditions, current physical health and physical activity data. The International Physical Activity Questionnaire (IPAQ) was also administered to assess current physical activity levels (Craig et al. 2003) (available at: http://www.ipaq.ki.se/). Calculation of energy expenditure (MET-minutes) using the relevant scoring protocol allowed participants to be grouped into a low, moderate or high physical activity categories. A knee involvement self-report questionnaire was developed for patients to give details relating to their previous knee symptoms (see Appendix 7). This formed part of the inclusion criteria and allowed the recording of pain, warmth or tenderness experienced in relation to the knee joint and also provided space for the patient to qualitatively describe their knee symptoms. In order to assess disease activity, the 4 item Rheumatoid Arthritis Disease Activity Index (RADAI) was also administered to all participants. This self-report questionnaire combines 4 items (current and global disease activity, pain and morning joint stiffness). The internal consistency and convergent validity of this measure has been confirmed in RA (Stucki et al, 1995). The MHAQ was also administered in order to assess ability to perform activities of daily living and psychological status (Pincus et al. 1983; Pincus et al. 1999).

Exercise familiarisation and testing

The familiarisation visit also allowed researchers to determine individual exercise intensities for the two exercise sessions. The aerobic exercise familiarisation involved a sub maximal treadmill walking test (Ebbeling et al. 1991) . The first four minutes of this test formed the warm-up, with the participant choosing their own walking speed, adjusting the pace to be brisk but comfortable (recommended between 2 and 4.5 mph). If heart rate was not within 50

- 70% HRmax within 1 minute, speed was adjusted accordingly. After 4 minutes, the gradient was increased to 5% and the participant continued walking at the same speed for another 4 minutes. HR was monitored throughout and rating of perceived exertion (RPE; central and peripheral; see page 96 for further detail) was recorded at end of both stages (Borg 1998). This test provided information to set the required speed and gradient of the treadmill in order to elucidate the required intensities for the walking exercise session.

To enable the intensity of the resistance exercise session to be determined, ACSM guidelines for clinical populations were followed to establish an 8 repetition maximum (8RM) (Whaley 2006). This was defined as the maximum weight the participant could lift eight times whilst maintaining good form (Howley 2001) and was determined for the following lower-body exercises; leg curl, leg extension and leg press. Using the Brzycki formula, 8RM was then converted to 1RM (Brzycki 1993) and 80% of this was calculated to determine the load for the exercise session described on the following pages.

Exercise assessment sessions

The order of exercise session completion (aerobic or resistance) was randomised by means of a computerised randomisation programme (www.randomisation.com) and assessment sessions for the two different modes of exercise took place at least one week apart. Following recommendations by Andersson et al. (2006b), baseline blood samples and ultrasound assessments were taken following 30 minutes of rest on both occasions. Figure 5.1 shows a schematic of the familiarisation and exercise sessions including baseline and post-exercise assessments of the outcome variables. The aerobic and resistance exercise sessions are described on the following pages.

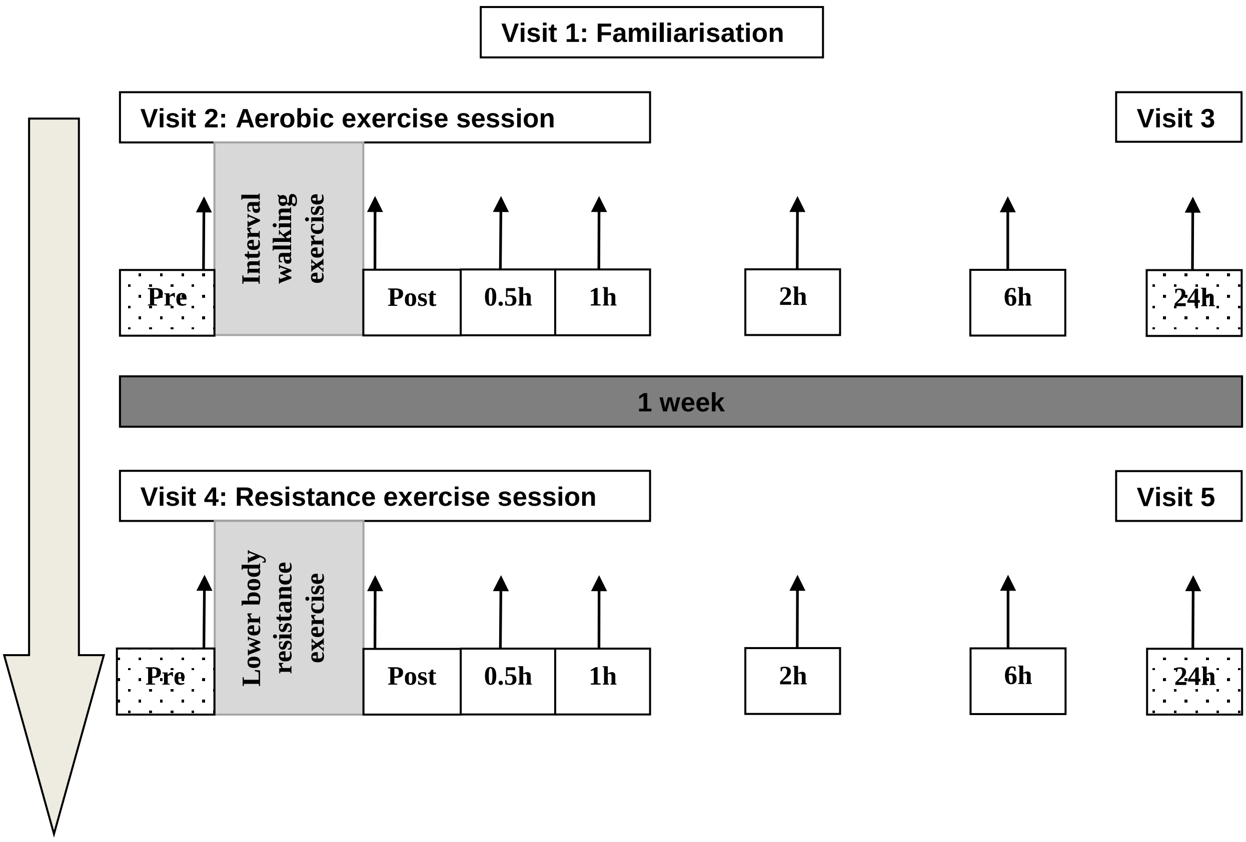


Figure 5.1 A schematic overview of the study protocol determining the acute effects of exercise. Visits 2 - 3 and 4 - 5 (aerobic and resistance exercise sessions) were completed in a random order, one week apart. Arrows indicate time points at which blood samples and US assessments were made.

Aerobic exercise session

Following ACSM guidelines for exercise prescription in this population (Millar 2010) and corresponding with the intensity of the RAPIT programme (de Jong et al. 2003), the aerobic exercise session involved a warm-up of 5 minutes walking at 40 - 50% HRmax, followed by a 20 minute interval walking exercise session. This consisted of 4 intervals of 3 minutes walking at a high-intensity (target heart rate: 70 - 90% HRmax) and 2 minutes walking at low-intensity (target heart rate: 40 - 50% HRmax). The session concluded with a warm-down of 5 minutes walking a low-intensity. Walking exercise was performed in the departmental laboratory on a treadmill (HPcosmos Mercury 4 Med, Nussdorf-Traunstein, Germany) and HR was determined using telemetry (Polar RS800, Finland).

Resistance exercise session

Following an identical warm-up of five minutes treadmill walking at 40 - 50% HRmax, ACSM guidelines for strength training exercise were followed, with leg curl, leg extension and leg press exercises performed during the session (Millar 2010). One set of fifteen repetitions with half-load was completed before each exercise after which participants performed three sets of eight repetitions at 80% of calculated 1RM. A one minute rest occurred between sets and exercises. Exercises were performed with dynamic muscle action, at a moderate repetition velocity (1 – 2 sec concentric, 1 – 2 sec eccentric), with the whole session totalling approximately 30 minutes. Exercises were performed in the departmental laboratory using commercially available weights machines (seated leg extension/curl; Powersport International Limited, 1986) and a bespoke leg press machine which utilised resistance bands to adjust load. The equipment used is shown in the Figure 5.2 below.

a)

b)

Figure 5.2 Images to show resistance exercise equipment. a) Leg extension/leg curl machine b) Leg press machine

Assessment of outcome variables

Following both of the thirty minute exercise sessions, participants remained resting in the laboratory. Blood samples, followed by ultrasound measurements, were taken immediately post and at 0.5, 1, 2 and 6 hours post-exercise. During this rest period, refreshments and audiovisual entertainment were made available for participant comfort and participants were refrained from any unnecessary walking or movements. Participants then returned home and reported to the laboratory the following day for a final assessment of the outcome variables at 24 hours post-exercise. Participants were asked to refrain from physical exercise and a rest period of 30 minutes was implemented prior to the 24 hours post-exercise sample.

Cartilage breakdown (Cartilage oligomeric matrix protein)

Venepuncture was performed by a researcher trained in phlebotomy. Samples were allowed to clot for at least one hour and then centrifuged (4°C, 3000 rpm). Serum was frozen to -80°C and stored until analysis. Serum COMP was measured by a commercially available double monoclonal sandwich enzyme-linked immunosorbent assay (Human COMP ELISA kit KA0021, Abnova Corporation, Taiwan). Differences due to inter-assay variation were eliminated by comparing concentrations within participants and by testing all samples of each participant on the same plate. Procedures were performed according to the manufacturer's specifications and standard curves were generated for each plate. The detection limit of the assay was < 0.4 ng/ml. Intra-assay and inter-assay coefficients of variation (CV) were 4.9% and 6.6%, respectively and R^2 curve fit for all curves were > 0.97. The average CV when comparing aerobic and resistance serum COMP at baseline was 8.4%.

Systemic inflammation (C-Reactive Protein)

Blood samples for this measure were collected and stored using the methods described above. These were then analysed using the standard clinical procedures for high-sensitivity CRP analysis at the local hospital laboratory of the Betsi Cadwaladr University Health Board.

Synovial inflammation (Colour Fraction)

Synovial inflammation was determined using an US machine (MyLab 50 X Vision, Biosound Esaote, Genoa, Italy), equipped with vascular software for two-dimensional real-time imaging and colour Doppler. With the participant in supine position, a clinical goniometer was placed at the midpoint of the tibia to establish the correct joint angle and a pillow was used to support the limb at the required angle. The synovium of both knees were examined longitudinally and transversally at the suprapatellar recess of the knee, in 20° flexion (Kasukawa et al. 2007). Marking of the skin ensured the same area was assessed at each time point (Figure 5.3).

A B C D

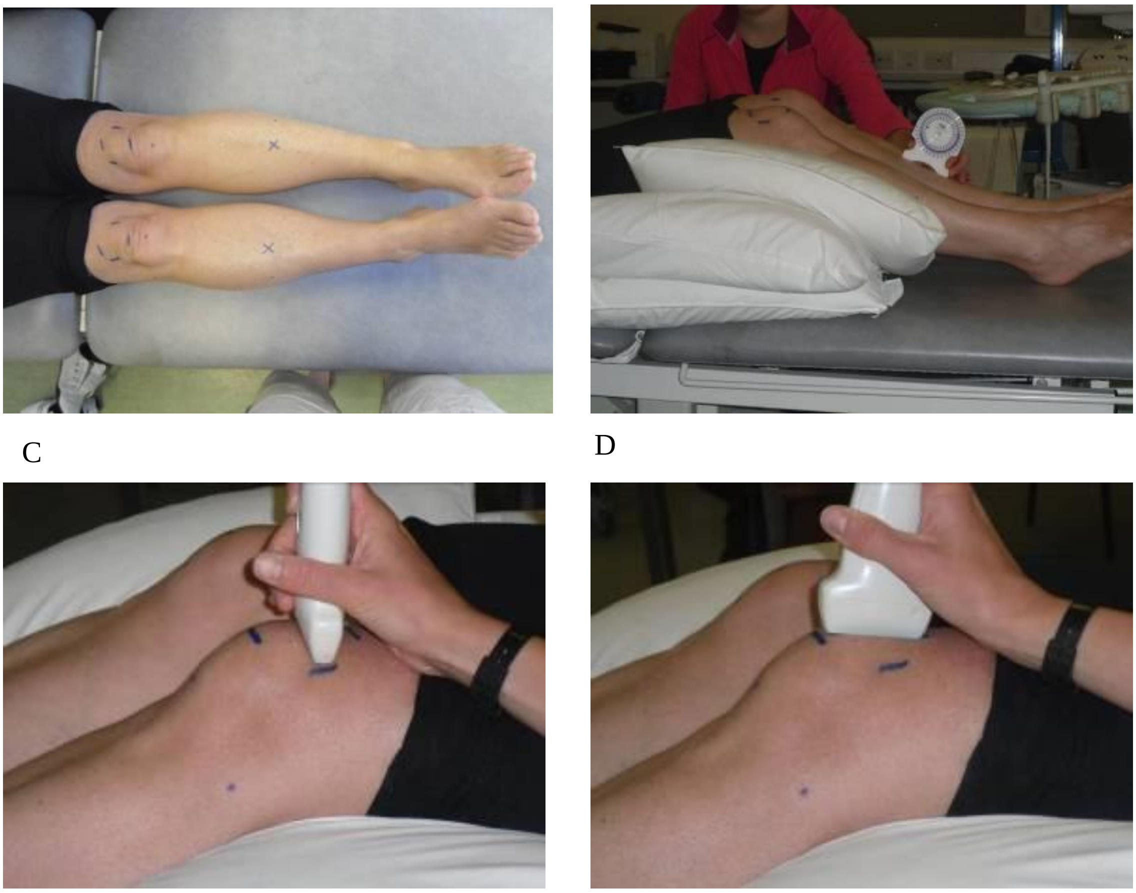
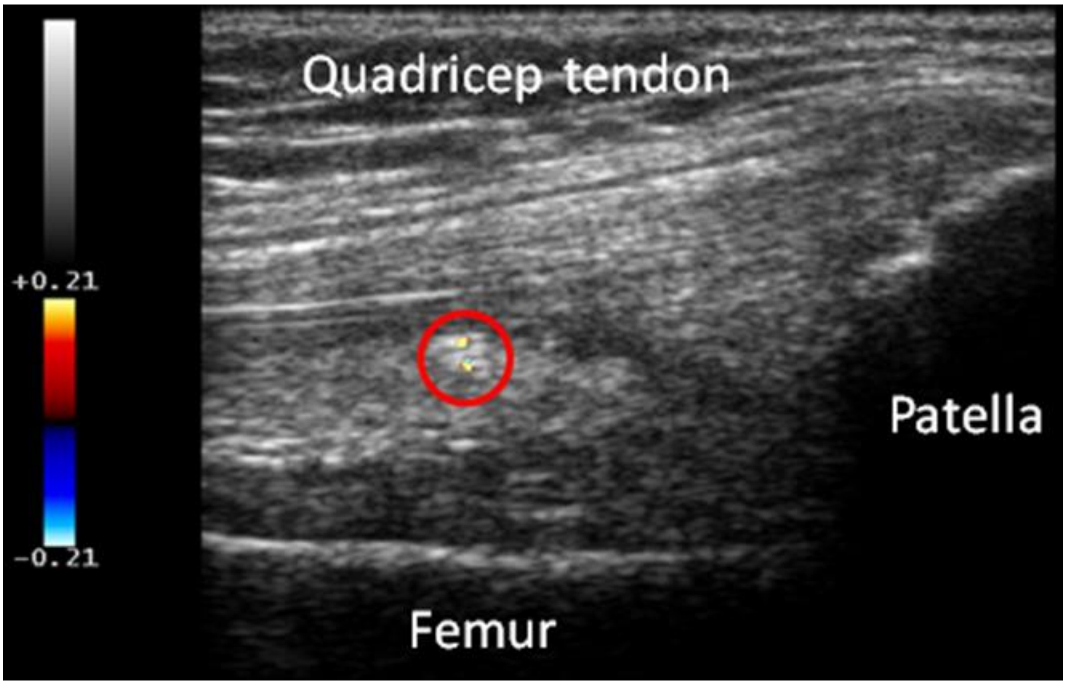


Figure 5.3 Images to show ultrasound assessment methodology. A) Anatomical marking to ensure correct placement of goniometer and US probe; B) Use of the clinical goniometer to ensure consistent angle for image capture; C) Transverse scanning probe placement; D) Longitudinal scanning probe placement.

Grey-scale US was utilised to identify the region of interest (ROI). This was defined as the area encompassed by the quadriceps tendon, patellar and femur, with 0.5 cm of patellar visible on the screen image (see Figure 5.4). Colour Doppler was then applied to enable the visualisation of blood flow. Colour Doppler settings (i.e. depth, frequency and gain) were standardised for all participants, with minimal adjustments to gain made as necessary to reduce artefact. To enable analysis of intra-rater reliability, three separate images were attained for each of the four separate scans at each time point.



Scale: 5mm intervals

Figure 5.4 Colour Doppler US image showing the anatomical structures of ROI within which the box was placed. The red circle highlights an example area of synovial inflammation as detected by the US scan.

Before analysis, all images were cropped to remove identifiable information (Windows Paint version 6.0). Therefore, all images were evaluated with the condition, time, group and name of the participant 'blinded'. Following advice from a consultant radiologist with expertise in musculoskeletal sonography, colour pixels that were identifiable as blood vessels as opposed to inflammatory hyperaemia were replaced with a black square. CF was then determined quantitatively using the colour Doppler image obtained with the maximum colour pixels. After transferring to a processing programme (MatLab), a standardised box was used to encompass the ROI and was placed to contain as many of the vascular flow pixels as possible (Fukae et al. 2010). The calibrated box size for analysis of the longitudinal scans was 35 x 17 mm and for the transverse scans, the box size was 33 x 23 mm (horizontal length x vertical length; see Figure 5.10 in results section). These two box sizes were determined based on the average synovium size from previously captured images. The number of colour pixels in relation to the number of grey scale pixels was expressed in order to determine CF (Terslev et al. 2003). To assess the inter-rater reliability of image analysis, all images from 5 RA patients and 5 control participants were analysed by another researcher using the same methodology.

Joint pain and Rating of Perceived Exertion (RPE)

Joint pain was assessed using an adapted version of the Pain Intensity Scale (Cook et al. 1997) before, during and after exercise sessions. This involved the patient indicating their pain level on a 10 point scale, with descriptors ranging from 'no pain at all' (0) to 'extremely intense pain (almost unbearable; 10)'. RPE was also assessed during exercise using the Borg CR10 scale (Borg 1998). 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 standardised set of instructions were presented to each participant prior to each experimental condition.

Statistical analysis

Data were analysed using SPSS. For all main outcome variables, data was assessed for normality using the Shapiro-Wilk test and mixed model factorial analysis of variance (ANOVA) with repeated measures was used to identify the following interactions; group by condition, group by time, condition by time, group by condition by time. Main effects for group, time and condition were also tested. Due to the small dataset and because missing data values for absolute serum COMP and CRP were assumed as missing completely at random, no data imputation was performed (West 2009). One-way ANOVA's were conducted to establish between group (RA and control) differences in exercise intensity when performing aerobic and resistance exercise. Significance was accepted at $p < 0.05$. Data are mean ± SD unless otherwise stated.

Intra-class coefficient (ICC) analysis was used to assess intra-rater reliability when performing each scan and also to assess inter-rater reliability in image analysis. Values > 0.70 (Crohnbach's - α) were considered acceptable (Vincent 1999).

5.3 Results

Participant characteristics

Eight participants with RA and eight healthy age and gender-matched controls completed the protocol (Figure 5.5). Participant characteristics are shown in Table 5.1.

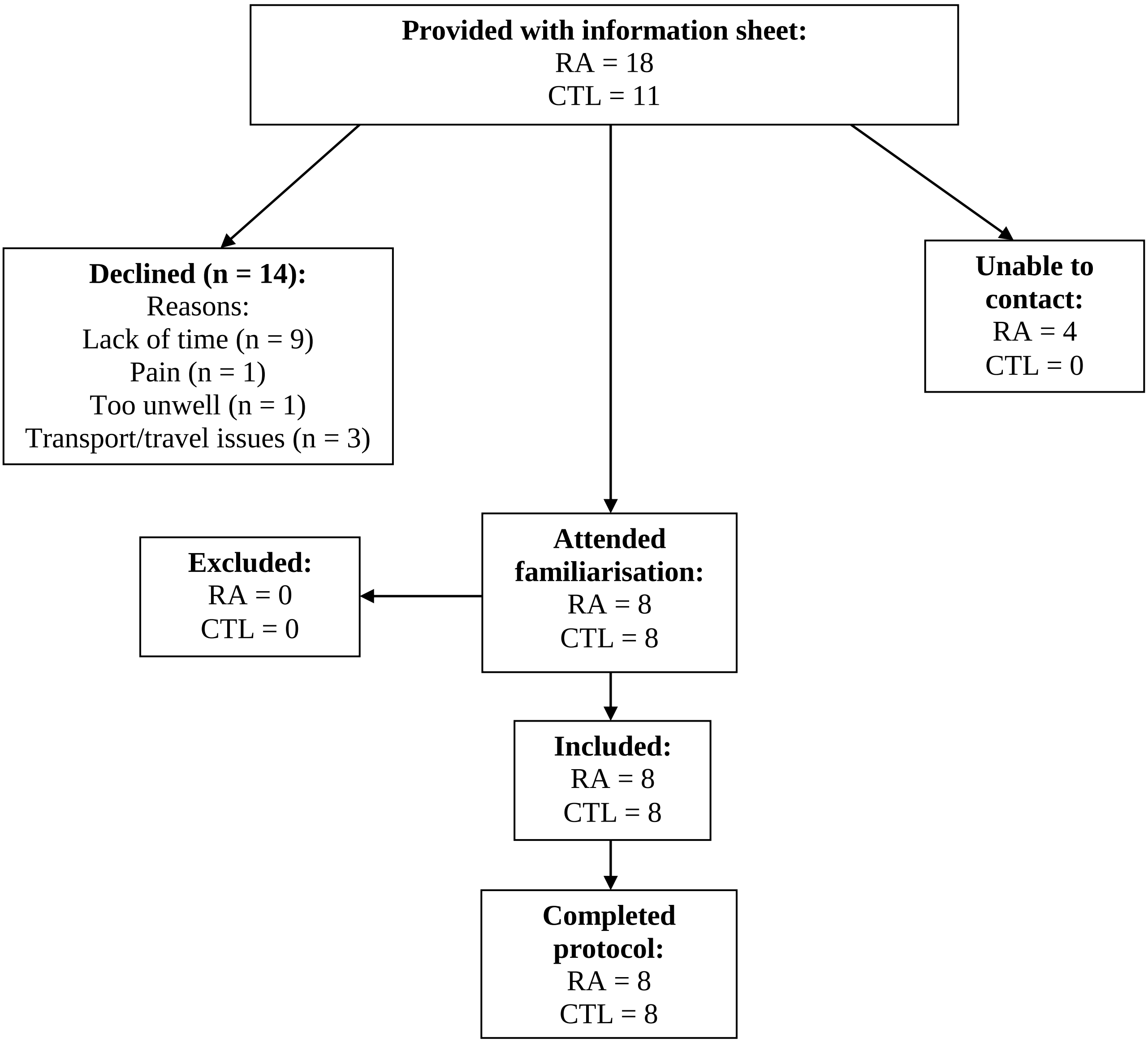


Figure 5.5 Recruitment flow diagram of participants for investigation of acute effects of exercise, detailing participant recruitment, familiarisation and protocol completion. (CTL = healthy controls, RA = rheumatoid arthritis patients).

Characteristic		RA	CTL
Age (years)		60 ± 12	60 ± 14
Gender		6 F, 2 M	6 F, 2 M
BMI		24.8 ± 4.1	27.4 ± 3.8
IPAQ category (number of patients):			
	Low	1	1
	Moderate	5	5
	High	2	2
RA disease-related characteristics			
Disease duration (years)		9 ± 11 (range = 5 – 36)	-
RADAI		3.1 ± 2.2	-
MHAQ		1.6 ± 0.4	1.1 ± 0.2
Medications (number of patients):			
Methotrexate only (17.5mg per week)		2	
Corticosteroid (2.5 mg per day)		2	
20mg Methotrexate + 50mg etanercept/week		1	
25mg Methotrexate + 5mg prednisolone per week		1	
No medication		1	
2mg/day T-cell inhibitor		1	

Table 5.1 Participant characteristics for RA (n = 8) and CTL (n = 8) group in the investigation of the acute effects of exercise. Data are mean ± SD unless otherwise stated. M = male, F = female, BMI = Body Mass Index, IPAQ = International Physical Activity Questionnaire, RADAI = Rheumatoid Arthritis Disease Activity Score, MHAQ = Modified Health Assessment Questionnaire.

Intensity of aerobic and resistance exercise sessions

There were no significant differences in % HRmax observed between the RA and control group ($t = 0.886$, $p = 0.392$). Furthermore, the RA and control group worked at similar speeds ($t = -1.245$, $p = 0.234$) and similar gradients during the high-intensity intervals ($t = -.554$, $p = 0.588$). Central RPE was similar across both groups and exercise condition ($F = .290$, $p = 0.599$). Peripheral RPE values were significantly higher during the resistance exercise when compared to aerobic exercise ($F = 27.2$, $p < 0.0001$), a pattern that was observed in both the RA and CTL group ($F = 0.00$, $p = 0.996$).

Leg press and leg curl 8RM was slightly lower in the control group compared to the RA group, whereas the RA group demonstrated a slightly higher 8RM for the leg extension exercise compared to the control group. However, overall, these differences were not significant (leg press: t = -.1.252, p = 0.237; leg extension: t = 0.391, p = .702; leg curl: t = -.980, p = 0.394; Figure 5.6). There were no significant differences in training workload (weight x number of repetitions) between the RA and control group for either of the three exercises (leg press: t = -1.454, p = 0.168 0.05; leg extension: t = 0.411, p = 0.687; leg curl: t = -0.784, p = 0.446; Table 5.3).

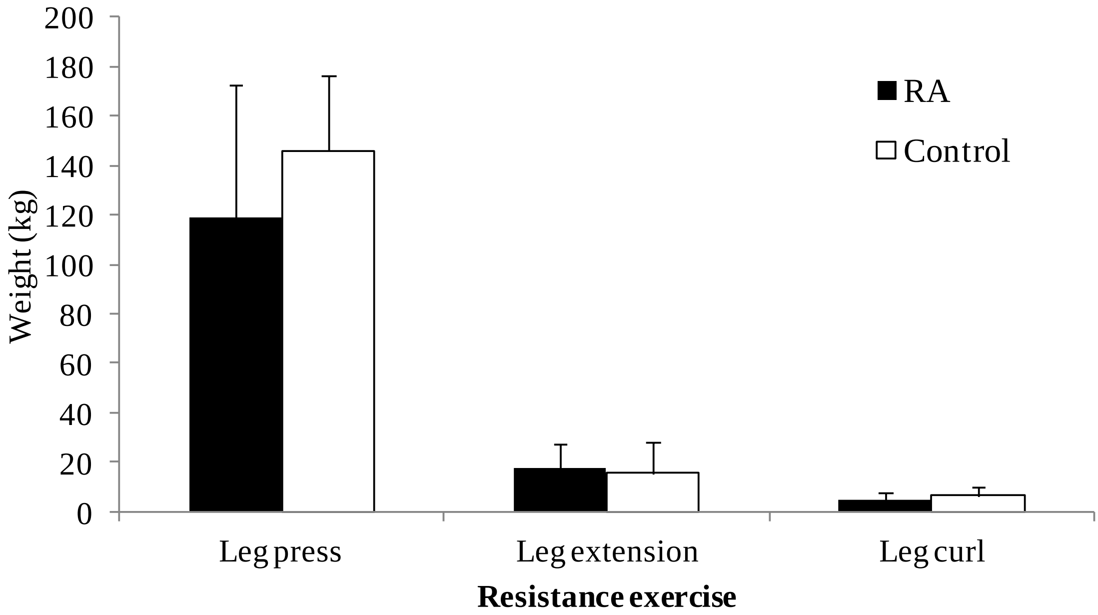


Figure 5.6 Comparison of leg press, leg extension and leg curl 8RM between the RA and CTL group. Data are mean ± SD.

	Average speed (km/h)		Average gradient (%)		% HRmax		pRPE		cRPE		Pain	
	HI	LI	HI	LI	HI	LI	HI	LI	HI	LI	HI	LI
RA	4.77 ± 0.86	2.38 ± 0.83	1.6 ± 2.3	0 ± 0	68 ± 8	63 ± 9	11.4 ± 1.5	10.7 ± 1.4	12.6 ± 0.9	11.1 ± 0.8	0.5 ± 0.7	0.5 ± 0.6
CTL	5.11 ± 0.83	3.0 ± 0.71	2.4 ± 2.9	0 ± 0	65 ± 5	59 ± 7	11.9 ± 1.7	10.2 ± 1.3	13.0 ± 1.3	10.5 ± 1.6	0 ± 0	0 ± 0

Table 5.2 Characteristics of the aerobic interval walking exercise session in the RA and CTL group. Data are Mean ± SD. HRmax = age-predicted maximum HR; pRPE = peripheral RPE; cRPE = central RPE; HI = high-intensity interval; LI = low-intensity interval. NB: n = 7 in CTL group for % HRmax data due to heart rate monitor malfunction.

	Workload			pRPE			cRPE			Pain		
	LP	LE	LC	LP	LE	LC	LP	LE	LC	LP	LE	LC
RA	3873.8 ± 1874.2	568.4 ± 303.0	165.2 ± 86.6	13.6 ± 2.5	13.1 ± 2.2	13.8 ± 1.2	12.4 ± 2.3	11.3 ± 1.3	11.5 ± 4.0	2.1 ± 3.2	2.1 ± 2.7	2.3 ± 3.2
CTL	5536.7 ± 2637.3	496.5 ± 390.7	206.7 ± 122.2	12.6 ± 2.8	13.8 ± 2.5	14.3 ± 2.5	11.7 ± 2.2	12.8 ± 2.6	12.9 ± 2.6	0 ± 0	0 ± 0	0 ± 0

Table 5.3 Characteristics of the resistance exercise session in the RA and CTL group. Data are Mean ± SD. Workload = weight (kg) x repetitions; LP = leg press; LE = leg extension, LC = leg curl; pRPE = peripheral RPE; cRPE = central RPE.

Main outcome variables

Cartilage Oligomeric Matrix Protein

Statistical analysis revealed no significant interactions. However, a significant main effect for group was revealed when considering absolute serum COMP levels. Serum COMP was shown to be 12% higher overall in participants with RA when compared to the healthy control participants (RA: 1347 ± 149 ng/ml, CTL: 1190 ± 150 ng/ml, F = 4.077; p = 0.046). In terms of the change in serum COMP over time following exercise, there were no significant differences observed between the time points (F = 0.389; p = 0.881) after either the resistance or aerobic exercise session (F = 0.443; p = 0.507). Figure 5.7 shows the post-exercise timecourse of absolute serum COMP in the RA and control group following both exercise conditions.

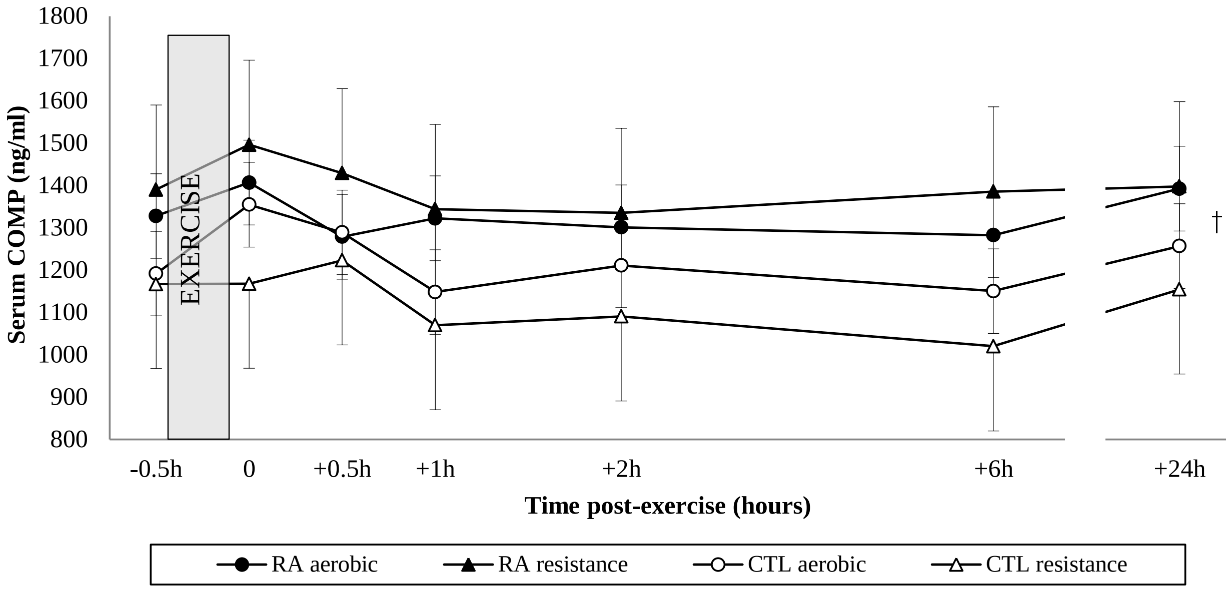


Figure 5.7 The post-exercise time course of absolute serum COMP over time and exercise condition in the RA and healthy control group. † = significant main effect for group ($p < 0.05$). Missing values were replaced with individual mean for graphical representation. Data are means ± standard error.

When combining the mean absolute serum COMP data from the aerobic and resistance exercise sessions, the mean change from baseline to immediately post-exercise an effect size of 0.25 was calculated (Cohen 1992).

When considering percentage change from baseline, it can be observed that the mean percentage change from baseline was higher immediately post-exercise (+9.7%) when compared to the percentage change at 1 hour post-exercise (-6%), 2 hours (-5.5%) and 6 hours (-7.8%) post-exercise. Similarly, the mean percentage change from baseline at 30 minutes post-exercise (+2.5%) was also higher than the percentage change at 2 hours and 6 hours post-exercise. Finally, the percentage change from baseline was lower at 6 hours post-exercise (-7.8%) when compared with change from baseline at 24 hours post-exercise (+2.1%). These trends were observed in both conditions across both groups (Figure 5.8).

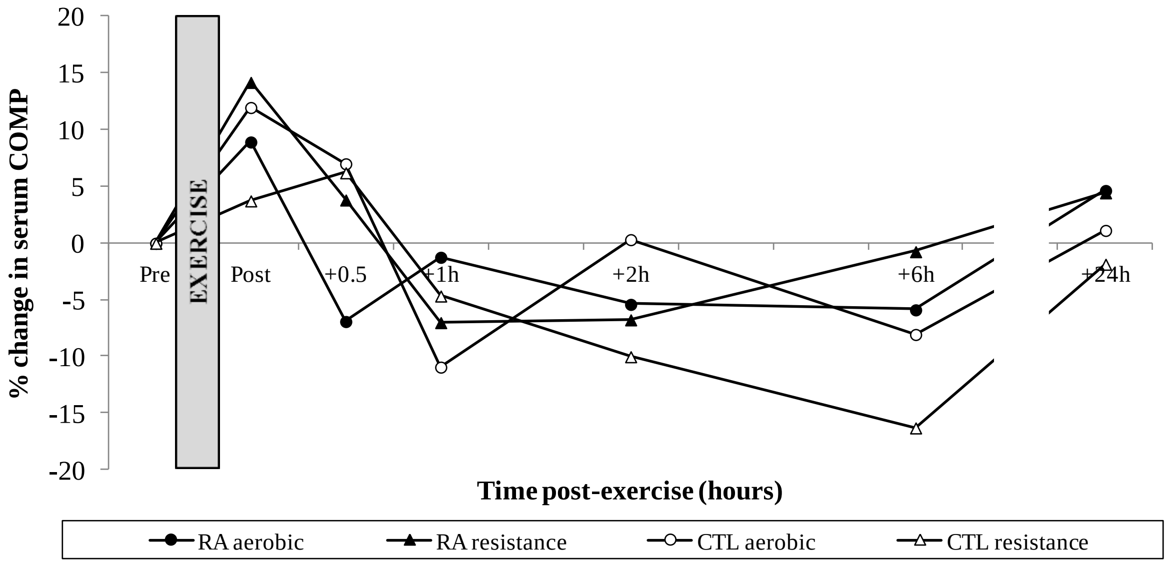
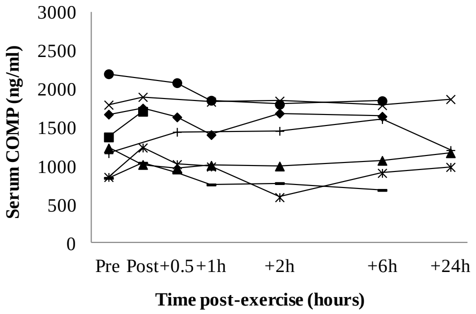
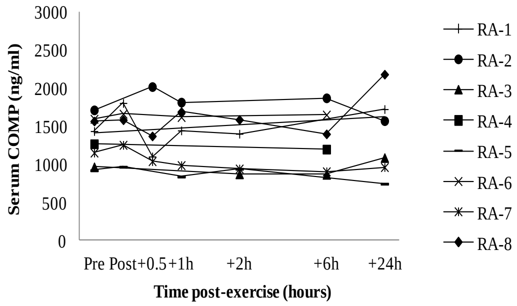


Figure 5.8 Mean change (%) from baseline in serum COMP over time and exercise condition in the RA and CTL group. Missing values were not replaced with individual means.

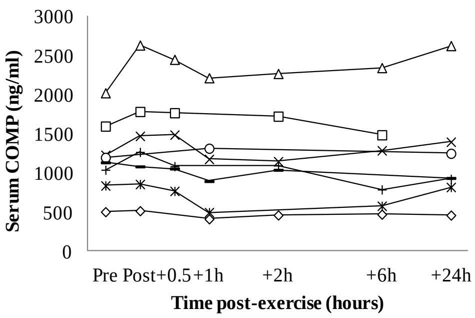
Figure 5.9 (a – d) shows the individual changes in absolute serum COMP for the 8 RA patients and 8 healthy controls, when assessed prior to and following aerobic and resistance exercise. When considering these individual changes over time, it is evident that within participant variability over time and condition was low.



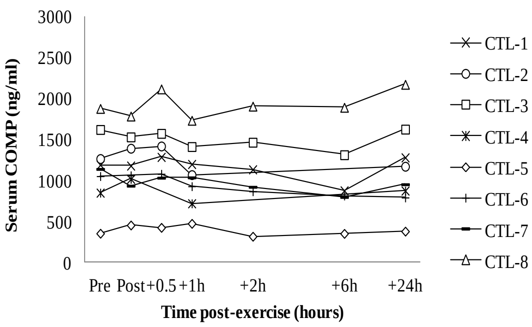
a) Response of serum COMP in the RA group following aerobic exercise



b) Response of serum COMP in the RA group following resistance exercise



c) Response of serum COMP in the CTL group following aerobic exercise



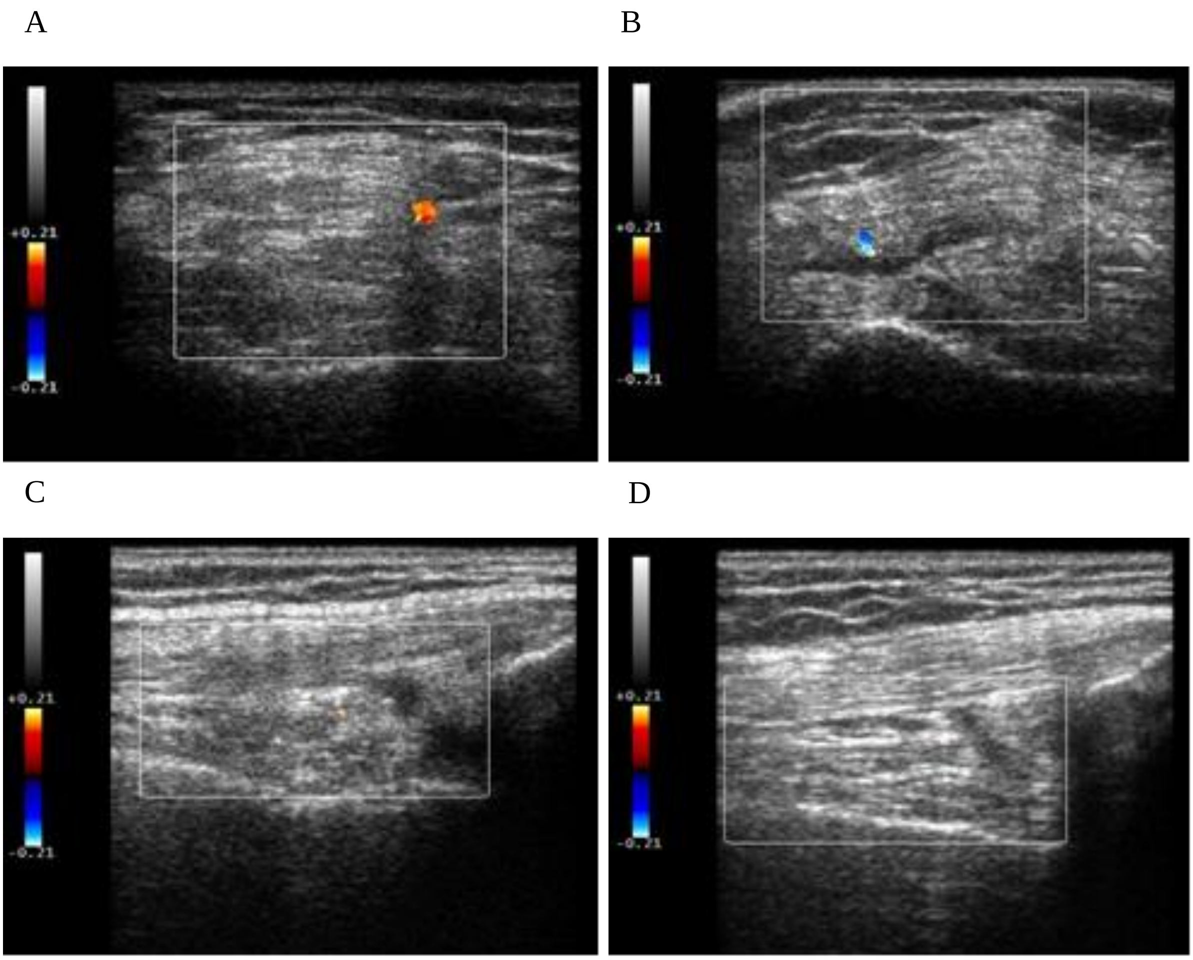
d) Response of serum COMP in the CTL group following resistance exercise

Figure 5.9 Individual response of absolute serum COMP over time and exercise condition in the RA and CTL group. Each line represents an individual participant.

Synovial inflammation

To assess the inter-rater reliability of the ultrasound image analysis, two independent researchers analysed the images. Data from a total of 574 images were included in the ICC analysis, revealing an acceptable ICC (Crohnbach's α = 0.803). Data from 226 images (reliability across 3 repeat images per scan, per time point, per participant) and 383 data points (reliability across 2 images per scan, per time point, per participant) were included when assessing intra-rater reliability. This was also acceptable (α = 0.798 and 0.824, respectively).

The findings from quantitative assessment of synovial inflammation (CF) are described in the next section. However, in addition to the quantitative, computerised analysis of the US images, any image displaying inflammation (both at baseline and post-exercise) was discussed clinically with a consultant musculoskeletal radiologist with a high level of expertise in musculoskeletal ultrasound. All inflammatory blood flow observed at all time points was rated as extremely mild and, in the view of the musculoskeletal ultrasonographer, unlikely to be associated with any detrimental effect to the health of the synovial joint. The images below display the maximum CF observed in the RA group, indicating the condition (resistance or aerobic exercise) and time point. The white box identifies the ROI (Figure 5.10).



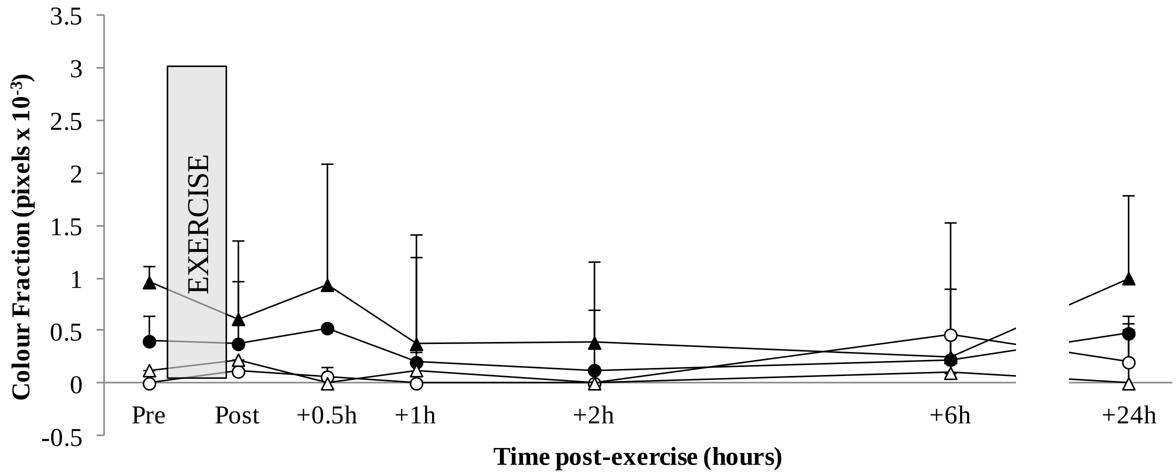
Scale: 5mm intervals

Figure 5.10 Examples of knee joint ultrasound scans of those RA patients presenting with the maximum CF. A) Transverse, 6h post aerobic exercise, CF x 10^{-3} = 8.6; B) Transverse, 1h post aerobic exercise, CF = 7.1; C) Longitudinal, 30 minutes post resistance exercise, CF = 3.5; D) Longitudinal, pre resistance exercise, CF = 3.

To quantitatively assess synovial inflammation, the overall CF (left and right knee combined) obtained from longitudinal and transverse scans at each time point for each condition (resistance or aerobic exercise) were analysed. The mean CF over time prior to and following both aerobic and resistance exercise in the RA and healthy control group is shown in Figure 5.11 (a: longitudinal scans, b: transverse scans). The RA group showed significantly higher levels of synovial inflammation overall when considering both longitudinal (Mean ± SE; RA: 0.489 ± 0.22 x 10^{-3}, CTL: 0.101 ± 0.22 x 10^{-3}, F = 12.323; $p = 0.001$) and transverse scans (RA: 0.938 ± 0.41 x 10^{-3}, CTL: 0.199 ± 0.41 x 10^{-3}, F = 13.000; $p < 0.001$). However, no significant interactions or main effects of condition (aerobic or resistance exercise) were revealed when the knees were scanned both longitudinally and transversely. When assessed longitudinally, there were no significant changes in CF over time (Figure 5.11a). When assessed transversely however, a significant main effect of time was observed ($F = 2.600$; $p = 0.032$). Specifically, when considering the overall mean change in CF from baseline ($0.159 \pm 0.28 \times 10^{-3}$), an increase was observed at 1 hour ($0.928 \pm 1.46 \times 10^{-3}$; $p = 0.046$) and 24 hours post-exercise ($0.950 \pm 1.03 \times 10^{-3}$; $p = 0.007$).

Additional analysis of the data, specifically at 1 hour post-exercise and 24 hours post-exercise, revealed no significant interaction between group (RA or CTL) and exercise condition (aerobic or resistance) ($F = 0.031$, $p = 0.863$). However, at 1 hour post-exercise the CF in the RA group was higher than that of the CTL group (RA: $1.756 \pm 0.442 \times 10^{-3}$, CTL: $0.100 \pm 0.442 \times 10^{-3}$, $F = 0.7025$, $p = 0.02$), but no main effect for exercise condition was observed. At 24 hours post-exercise, the resistance exercise sessions showed greater CF than that of the aerobic sessions (resistance: $1.537 \pm 0.471 \times 10^{-3}$; aerobic: $CF = 0.363 \pm 0.205 \times 10^{-3}$, $F = 5.446$, $p = 0.035$). However, there was no significant main effect for group at 24 hours. The data are displayed graphically in Figure 5.11b.

a)



b)

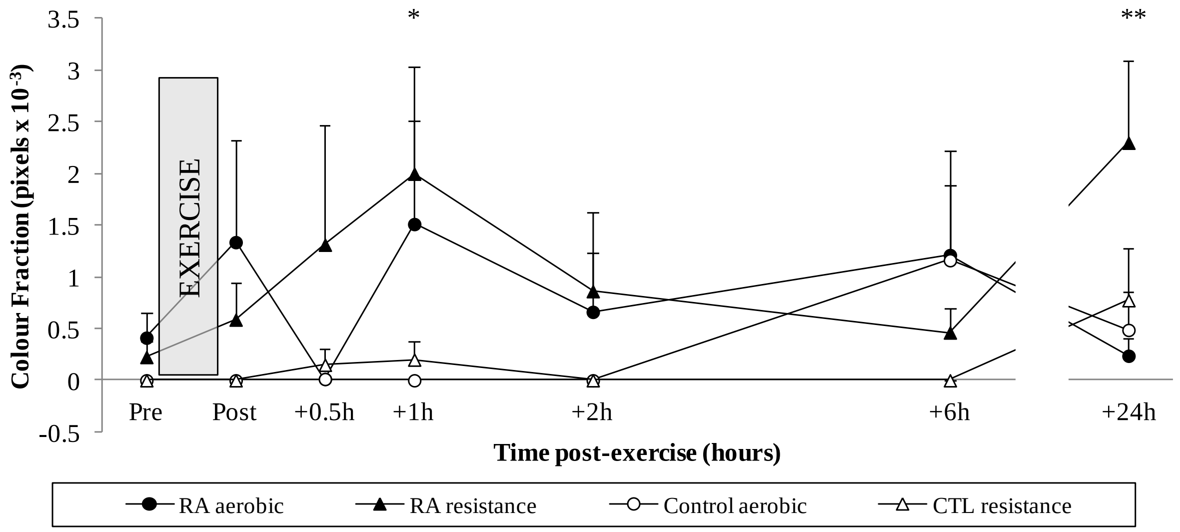


Figure 5.11. CF response over time and exercise condition in the RA and CTL group. a) Longitudinal scans b) Transverse scans. Data are mean CF (x 10^{-3}) of the left and right knee combined, error bars indicate standard error. * = significant difference overall from baseline ($p < 0.05$), ** = significant difference overall from baseline ($p < 0.01$).

The figures on the following page show the CF of the individual participants over time following aerobic and resistance exercise. Figure 5.12 (a – d) shows the individual CF response when knees were scanned longitudinally and Figure 5.13 (a – d) shows the individual CF response when knees were scanned transversely. It is evident from these figures that although the CF in general was minimal, the CF was highly variable within participants and over condition and time.

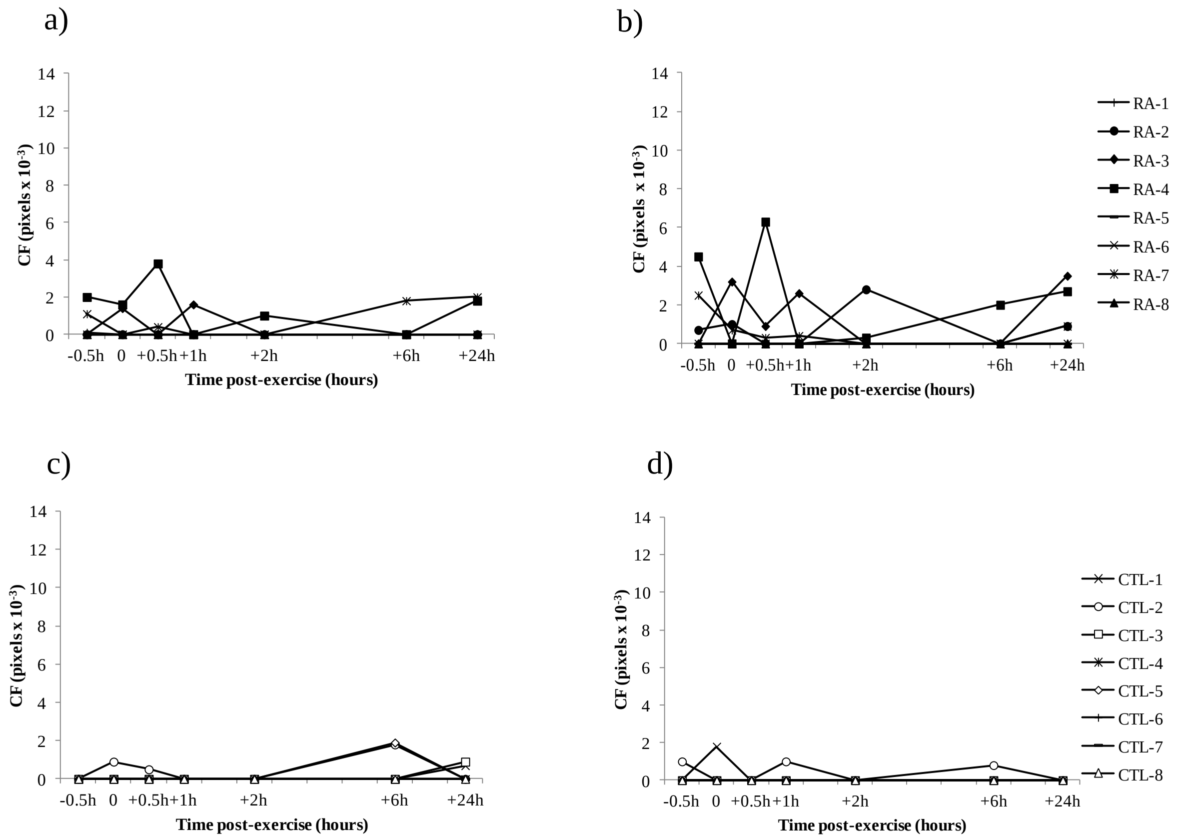


Figure 5.12 Individual longitudinal CF response over time and exercise condition in the RA and CTL group. a) RA aerobic; b) RA resistance; c) CTL aerobic; d) CTL resistance. Data are means of the left and right knee combined.

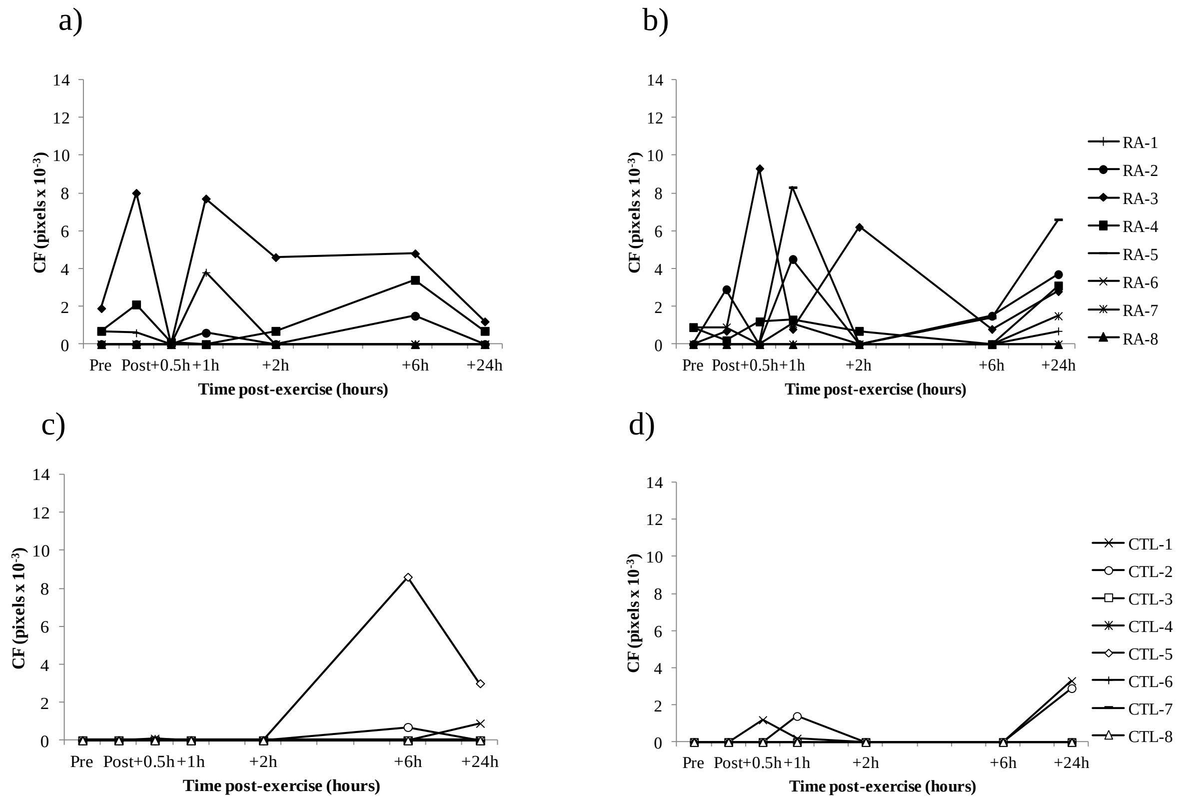


Figure 5.13. Individual transverse CF response over time and exercise condition in the RA and CTL group. a) RA aerobic; b) RA resistance; c) CTL aerobic; d) CTL resistance. Data are means of the left and right knee combined.

Systemic inflammation: C - reactive protein

Serum CRP levels were shown to be higher overall in participants with RA when compared to the healthy control participants (RA: 14.3 ± 2.1 mg/L, CTL: 1.3 ± 1.9 mg/L, $F = 67.7$; $p < 0.001$). In terms of the change in serum CRP over time, there were minimal changes between the time points, in either the resistance or aerobic exercise session ($F = 0.282$, $p = 0.598$). The post-exercise changes in serum CRP of the two groups over the two exercise conditions are shown in Figure 5.14.

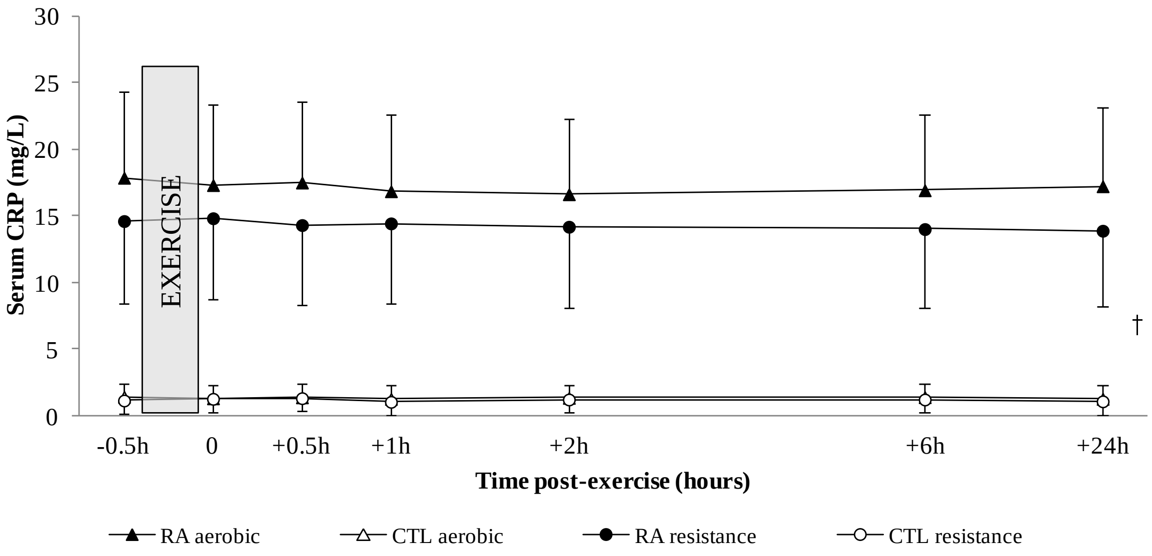


Figure 5.14 The post-exercise time course of serum CRP over time and exercise condition for the RA and CTL group. † = significant main effect for group between RA and CTL ($p < 0.01$). Missing values were replaced with individual mean for graphical representation. Values are means, error bars show standard error.

Pain

No pain during either forms of exercise was observed in the control group, however the RA group showed a non-significant trend towards greater knee joint pain during the resistance exercise (aerobic: 0.5 ± 0.7; resistance: 2.2 ± 3.0; on a 1 – 10 scale, $t = -2.084$, $p = 0.076$). These mean numerical ratings are equivalent to the descriptors '0.5 = very faint pain, just noticeable', 1 = 'weak pain' and 2 = 'moderate pain'. No patients showed any pain greater than 4 on the pain intensity scale, equivalent to 'somewhat strong pain' (Table 5.3).

5.4 Discussion

This is the first study to compare the acute effects of different modes of exercise on serum COMP, synovial and systemic inflammation, in RA patients and healthy controls. The main findings demonstrate that, in both groups, there were no significant changes in absolute serum COMP or CRP following both the aerobic and resistance exercise at the measured time points. Furthermore, despite some significant post-exercise changes in CF, the synovial inflammation observed at baseline and at all time points post-exercise was extremely mild. Similarly, minimal levels of joint pain were reported throughout both exercise protocols.

The current results are able to confirm findings identified in previous research. Christensen et al. (2011) also found that serum COMP was significantly higher in RA patients when compared to healthy controls. Furthermore, although not significant, absolute serum COMP tended to increase as expected post-exercise and returned to around baseline levels between 30 minutes and one hour post-exercise, as observed in OA and healthy populations (Mündermann et al. 2005; Andersson et al. 2006b; Mündermann et al. 2009). Additionally, as shown by other researchers, serum COMP of both the RA and control participants showed further decreases as a result of rest (Andersson et al. 2006b; Mündermann et al. 2009; Helmark et al. 2010). However, the second increase in serum COMP at five and a half hours observed by Mündermann et al (2005), was not confirmed in the current study. These patterns are also evident when considering the percentage change in serum COMP from baseline in the current study. The higher percentage change from baseline observed at 24 hours post-exercise is probably indicative of a general increase in activity levels prior to this blood sample (i.e. when participants were at home), when compared to the extended seated rest when participants remained in the laboratory post-exercise. Overall however, as no interactions were observed, it is evident that neither aerobic or resistance exercise or whether or not a participant had RA had any differential effect on the change in serum COMP from baseline over time.

Interestingly, on examination of individual data, the highest serum COMP levels over time were observed in a control participant (1783 – 2632 ng/ml). Corresponding with previous research (Neidhart et al. 2000), this particular individual was involved in hill running. Few patients exhibited 'high' serum COMP levels (> 1790 ng/ml) (de Jong et al. 2008) at any time point during either of the exercise protocols. Only one RA patient (RA-2) exhibited a higher range of COMP levels in both aerobic (1572 ng/ml – 2019 ng/ml) and the resistance exercise session (1798 ng/ml – 2195 ng/ml). Interestingly, this 67 year old female patient had the lowest level of physical activity and a relatively high body mass index (BMI; 31.2). Corresponding with previous findings, a high BMI has previously been found to be associated with raised levels of serum COMP (Jordan et al. 2003). This patient also had the highest MHAQ score, with obvious damage to her hands having been diagnosed with RA for 36 years. However, the serum COMP levels observed in this individual are in contrast with previous research suggesting that serum COMP is highest in early RA (Lindqvist et al. 2005; Fujikawa et al. 2009).

When considering synovial inflammation, it is important to remember that the appearances of synovial inflammation were evaluated clinically by an experienced musculoskeletal ultrasonographer and it was concluded that the colour Doppler signals observed were extremely minor. Furthermore, they were not associated with clinical features such as pain or swelling. Therefore it can be postulated that these changes were indicative of fluctuations in normal blood flow (Ellegaard et al. 2009a) rather than pathological changes.

When assessed quantitatively, synovial inflammation was significantly higher in the RA group compared to the control group (0.388×10^{-3} and 0.739×10^{-3} higher overall CF for longitudinal and transverse scans, respectively). The elevations in CF observed at one hour post-exercise in the current study when knees were scanned transversely correspond somewhat with the findings of Ellegaard et al. (2009a). The potential changes at the other post-exercise time points have not previously been assessed by other researchers. However, statistical analysis of the transverse CF data from the current study revealed that overall CF across both groups and conditions was significantly elevated from baseline at 1 hour and 24 hours post-exercise. There were no significant changes in CF when the longitudinal scans were analysed. This may be expected as the area captured whilst scanning transversely contains a proportionally larger area of the synovium and hence the transverse scanning orientation may well have detected inflammation not picked up when scanned longitudinally.

Post-hoc analyses of the mean changes revealed significant increases in transverse CF at 1 and 24 hours post-exercise. However, when considering the individual CF responses, it was evident that only two RA patients displayed a higher CF at one hour post-exercise and that these were two different patients in the resistance and aerobic conditions. This is an example of the large within-participant variability observed when using this method of analysis. A significant increase in overall CF also occurred at 24 hours post-exercise. However, at this time point, the higher CF was demonstrated following resistance exercise in comparison aerobic exercise, with no differences observed between the groups. When considering the individual CF responses, a reduced CF was observed at 24 hours following aerobic exercise, coupled with a somewhat consistent increase in CF observed at 24 hours following resistance exercise (mainly in the RA group). However, again, it is clear that the majority of the post-exercise responses in both groups were highly variable within individuals and over time. With reference to the individual patient mentioned previously (RA-2), this individual presented with slight elevations in CF at 1 hour and 2 hours post-exercise. However, as with the other RA patients, her ultrasound scans showed very low grade synovial inflammation, despite having experienced pain in her right knee for the past five years. Overall, her RA appeared to be relatively well-controlled with her serum CRP remaining below 5 mg/L throughout the study protocol.

In terms of systemic inflammation, the heightened serum CRP levels characteristic of the RA population (Kindmark 1972; Amos et al. 1977) were evident in the current study. However, there were no significant changes in serum CRP in the time period following either mode of exercise, even at 24 hours post-exercise as previously observed (Drenth et al. 1998; Neidhart et al. 2000; Kasapis et al. 2005). It may have been that the intensity and duration of the exercise in the current study was not sufficient to cause elevations in serum CRP.

This novel study incorporates a strong research design, including full randomisation, a healthy control group and within-subjects comparison between the two exercise types. The RA patients were in a stable phase of their treatment (Terslev et al. 2003; Skoumal et al. 2006) and confounding variables including age (Wisłowska et al. 2005; Fujikawa et al. 2009), male gender (Villim et al. 2001; Jordan et al. 2003) and physical activity were controlled by matching control and RA patients for these variables. It is important to note however that the higher % HRmax observed in the RA group, at comparably lower speeds, indicated lower physical fitness in the RA group. Bias was minimised as researchers were blinded to individual, group, condition and time for both ultrasound and blood sampling analysis. Additionally, standardised laboratory methods reduced intra- and inter-assay variation, as demonstrated by excellent coefficients of variation and R^2 curve fit. To control for potential error inherent to US methodology, all scans were performed using the same machine, by the same operator and with the angle of the knee maintained in a position of 20° flexion. Furthermore, probe placement was guided by previous measurements and images were captured with a standardised view of specific anatomical landmarks. Frequent contact with a consultant musculoskeletal radiologist enabled regular monitoring of technique and further interpretation of any atypical images (e.g., artefact or blood vessels). Moreover, good intra-rater and inter-rater reliabilities of the US analysis were demonstrated. A further strength of the study includes the higher exercise intensity undertaken by the participants compared to that of previous studies in other similar groups. Importantly, these exercise protocols were also well-tolerated by participants, including those who had not previously trained using gym equipment.

The current study also addresses a number of the limitations of previous studies. Firstly, whilst a long-term follow-up study refuted earlier suspicions relating to the increased deterioration of the large joints, it included only a small proportion of the original RAPIT participants (de Jong et al. 2009). Furthermore, previous studies have been limited in terms of elucidating the pathological mechanisms pertaining to the effects of exercise on joint health (Anandarajah et al. 2004). Therefore, this study provides additional information relating to the direct effects exercise on joint health in RA and adds further support to the notion that both aerobic and resistance exercise, albeit acutely, are not detrimental to the large joints of the knee. Secondly, it is important to note that many of the previous studies did not assess serum COMP at a predefined time in relation to exercise (de Jong et al. 2008). This compromised validity as serum COMP may have been influenced by prior exercise (Neidhart et al. 2000; Mündermann et al. 2005; Andersson et al. 2006b; Kim et al. 2007; Mündermann et al. 2009; Niehoff et al. 2010), or rest (Mündermann et al. 2005; Andersson et al. 2006a; Andersson et al. 2006b; Mündermann et al. 2009; Helmark et al. 2012) of an unknown quantity. However, the current study provides data describing the time course of serum COMP following standardised exercise protocols and rest periods prior to blood sampling, hence enhancing the reliability and validity of the findings. Thirdly, this study protocol also addresses limitations in the literature relating to the effects of intensive exercise on synovial inflammation. Specifically, the only previous study to investigate the acute effects of exercise in RA involved low-intensity handgrip contractions as the exercise stimulus (Ellegaard et al. 2009a)whereas the current study furthers previous investigations by investigating the acute response to high-intensity aerobic and resistance exercise of the large weight-bearing joints of the lower body. The present study is also the first to analyse colour Doppler signals quantitatively (using the CF method) in any of the large joints. Finally, to the authors knowledge, no previous studies have investigated the acute effects of exercise on systemic inflammation (i.e. serum CRP) in people with RA.

Limitations

While overall findings of the present study suggest that the chosen markers of joint health were similar across both modes of exercise and indicated no detrimental response, there are some limitations of the current study that should be considered. Firstly, the study was limited in terms of power due to small participant numbers and therefore larger randomised controlled trials are required to fully confirm the current findings. However, with regards to serum COMP, it is important to note that when considering the mean change in absolute serum COMP from baseline to immediately post-exercise, the effect size calculated was indicative of a small influence of the exercise protocols (Cohen 1992).

Secondly, the lack of significant increase in absolute serum COMP post-exercise was unexpected and contrasts with previous research (Mündermann et al. 2005). In addition, in contrast to the findings from Niehoff and colleagues (2010), no significant differences were revealed according to the mode of exercise, with both forms of exercise showing similar, minimal changes from baseline. It may well have been that the two forms of exercise included in the current study were not as diverse or intense enough in terms of musculoskeletal load and repetitive impact (Thompson et al. 2001). Indeed, due to the untrained, sedentary characteristics of the participants there were also some limitations relating to the intensity of the exercise sessions. Some of the participants had not previously exercised using gym equipment and were not capable of the exertion required to work at an intensity of 70 - 90% HRmax as specified in the protocol. However, approximately 60 - 70% HRmax was achieved in the high-intensity intervals, which meets current ACSM guidelines (Millar 2010) and 50 - 60% HRmax was achieved during the low-intensity intervals, which was higher than the 40-50% HRmax specified in the protocol. Furthermore, the exercise protocols in the current study also included increases in gradient and speed, shown by researchers to increase the dynamic loading on the musculoskeletal system (Voloshin 2000; Spyropoulos et al. 2008).

Thirdly, the current study was limited as despite previous knee involvement, objective evidence of synovial inflammation was minimal. However, while colour Doppler signals have previously been observed in the knees of people with RA (Kasukawa et al. 2004; Kasukawa et al. 2007), the majority of previous researchers have investigated synovial inflammation of the wrist joint. These joints are commonly affected in RA (Fleming et al. 1976) and were selected by previous authors based on their high representativeness of RA disease activity (Ellegaard et al. 2009a). Hence, in order to assess the acute response to exercise in the knee joint, future research will need to establish overt synovial inflammation as an inclusion criterion. Notwithstanding this limitation, this investigation forms the first study to use CF as an analysis method when assessing the knee joint and provides valuable methodological information for future researchers.

Serum COMP and knee joint synovial inflammation as markers of joint health

In terms of the use of serum COMP as a marker of cartilage breakdown, interesting questions have also been raised as to whether increased serum COMP indicates increased synthesis, increased breakdown or modifications in clearance. Furthermore, as COMP is also produced and released from other tissues, including the synovium, ligament and meniscus and tendon (Di Cesare et al. 1994; Di Cesare et al. 2000), the exact origin of the COMP detected in the serum is unknown. Despite its increasing use as a marker of cartilage breakdown and a surrogate marker of joint damage, it is acknowledged that further research is required to address the limitations in the current understanding of the specificity of COMP, alongside its metabolism and clearance. However, it is also important to note the low CV for serum COMP (calculated from the repeat baseline measurements), which indicated that within participant day-to-day biological variability in serum COMP was low. This, coupled with a lack of diurnal variation in serum COMP (Andersson et al. 2006a), supports serum COMP as a stable biomarker and therefore strengthens the study conclusions relating to the effect of exercise.

Regarding the use of US to assess synovial inflammation of the knee joint, well-controlled methods for US image attainment and analysis were maintained. However, the effect of machine, operator and patient-related factors cannot be ruled out as factors potentially affecting US image acquisition (Zayat et al. 2012). Based on previous research (Kasukawa et al. 2007), we used an angle of 20° flexion, but recent findings suggest that an angle of 30° flexion may be advantageous in terms of capturing an image with the maximum colour Doppler (Zayat et al. 2012). More specifically, the study by Zayat and colleagues (2012) demonstrated that, in comparison to 0° and 90°, scanning of the knees in a 30° position were associated with the highest grey-scale and colour Doppler scores. In explanation of their results, the authors discuss the theory that some joint positions and the presence of effusion cause higher intra-capsular pressures to develop (Wingstrand et al. 1987; Wingstrand et al. 1997). They suggest that these changes in intra-capsular pressure, resulting from changes in joint position, may in turn lead to change in the dynamics of synovial fluid and synovial membrane. This may further act to compress the small neo-vasculature within the synovium leading to reduction or even no colour Doppler signal.

Despite these limitations, this study is the first to show the post-exercise time course of serum COMP, CF and serum CRP in RA patients and healthy controls. It is an important finding that there were no significant increases post-exercise in serum COMP and that any trends towards an increase observed returned to baseline. Furthermore, exercise did not appear to exacerbate low level synovial and systemic inflammation. This study also provides enhanced knowledge regarding the use of serum COMP as a biomarker and the use of novel US analysis methodology to assess synovial inflammation of the large joints. Additionally, this study provides enhanced information about the effects of two forms of exercise that are relevant to the RA population.

5.5 Applications and conclusions

The results of current research can be used to inform health professionals regarding the effects of two types of high-intensity exercise that are well-tolerated by stable RA patients with established disease (> 5 years), and low systemic disease activity. Although also limited to patients without overt synovial inflammation of the knee joint, these findings suggest that there is no acute detrimental effect of high-intensity aerobic or resistance exercise on cartilage breakdown, synovial or systemic inflammation. If larger-scale randomised controlled trials are able to confirm these findings on a long-term basis, walking and resistance exercise can continue to be recommended for this population, without a fear of detrimental effects for the large, weight-bearing joints.

This study also informs the development of the research described in Chapter 6. Considering the well-known benefits of exercise training for the cardiovascular system, muscle strength, physical function and psychosocial well-being in RA, the following chapter aims to determine the effects of a continued high-intensity exercise training programme on these specific markers of joint health in RA.

Chapter 6: The effects of exercise training on joint health in RA

6.1 Abstract

Objectives

Intensive aerobic and resistance exercise has shown no acute detrimental effect on cartilage breakdown, synovial inflammation of the knee and systemic inflammation in RA. However, the effect of continued exercise training on these markers of joint health are unknown. Therefore, the aim of this study was to investigate the effect of an intensive, progressive aerobic and resistance exercise training intervention on joint health in RA.

Methods

9 stable RA patients (age: 57 ± 14 years; disease duration: 13 ± 10 years; mean ± SD) completed an 8-week combined and progressive exercise programme designed to improve aerobic fitness and lower-body strength. Partipants were assessed at baseline and 1 hour post-exercise at weeks 0, 4 and 8. The main outcome variables were serum COMP, synovial inflammation of the knee joint (colour fraction; CF) and systemic inflammation (serum CRP). ANOVA with repeated measures was used for statistical analysis using SPSS.

Results

No changes in post-exercise serum COMP, synovial inflammation or serum CRP were observed over the 8-week intervention. There were also no clinically significant levels of synovial inflammation prior to exercise and no change in CF for either group over the 8-week training period. Furthermore, the exercise intervention was well-tolerated and significant improvements in aerobic fitness, lower body strength and physical function were observed.

Conclusions

This research offers further confirmation that, in patients with inactive RA, continued intensive exercise training is not detrimental to joint health. Moreover, it appears that the acute response to exercise is not affected by continued exercise training. The intervention also offered important benefits and therefore it is anticipated that these findings will assist health professionals when prescribing exercise to people with RA.

6.2 Background

The improvements in aerobic capacity, muscle strength, functional ability, and psychological well-being that are inherent to continued exercise training in this population are now well-known (e.g., de Jong and Vlieland, 2005; Marcora et al., 2005), and as previously discussed, regular exercise is now considered an important component in the management of RA. Findings from Chapter 3 highlighted that patients are aware of these benefits but are also concerned about the potentially detrimental effects of exercise on the health of their joints. Furthermore, patients perceive that health professionals are uncertain about the issues relating to exercise and joint health. These patient perceptions offer potential reasoning for the insufficient levels of physical activity observed in this population (Lee et al. 2012).

In order to provide health professionals with sufficient information to clearly advocate exercise and address the issues associated with joint health for this population, it is important that research continues to address the gaps in the knowledge surrounding exercise and joint health. Given previous concerns, this enhanced information is especially important in relation to the large joints. Findings from Chapter 5 indicated that both high-intensity aerobic and resistance exercise *per se* do not cause acute increases in cartilage breakdown or exacerbate low level synovial or systemic inflammation. However, the effects of continued exercise training on these specific markers of joint health are unknown and form the focus of the research described in this chapter.

Exercise training, joint damage and inflammation

High-intensity exercise is now considered to offer the greatest benefit for RA patients, with studies providing evidence that this form of training does not cause further deterioration of joint damage when assessed using X-rays (de Jong et al. 2003; de Jong et al. 2004a). The biomarker serum COMP has recently been used by previous researchers, and in Chapter 5, as a sensitive marker of cartilage breakdown. Following three months of exercise training, de Jong and colleagues (2008) demonstrated that the RAPIT programme participants did not show significant increases in serum COMP. However, the authors also acknowledged that a limiting aspect of their study was that serum COMP was not measured at a particular time in relation to completing the exercise (de Jong et al. 2008). Furthermore, it is unknown if the acute response to exercise changes with continued exercise training.

Synovial and systemic inflammation is characteristic of RA and the acute response to aerobic and resistance exercise was also investigated in Chapter 5. A novel ultrasound image analysis method (CF) was used to quantitatively assess knee joint synovial inflammation (Terslev et al. 2003; Ellegaard et al. 2009a). To our knowledge, there has only been one previous study to investigate the effects of exercise training on CF in RA (Ellegaard et al. 2012). This study involved an 8-week low-intensity handgrip exercise intervention and assessed synovial inflammation and CF in the wrist joint. There were no significant differences in CF between the exercise group and control group when assessed pre and post intervention. Furthermore, although not significant, a 35% decrease in CF was observed in the exercise group. However, the effects of a high-intensity exercise programme on synovial inflammation of the large joints have not yet been investigated in RA.

Results from the study described in Chapter 5 also indicated no acute detrimental effects of either aerobic or resistance exercise on systemic inflammation, indicated by levels of serum CRP. Similarly however, it is unknown if the acute response to exercise changes with progressive high-intensity exercise, therefore this study also aims to address this question.

Exercise training modes in RA

The main randomised controlled trials discussed previously (e.g., the RAPIT study by de Jong et al. 2003) and most other exercise studies in RA (Lyngberg et al. 1994; van den Ende et al. 1996; Häkkinen et al. 1999; McMeeken et al. 1999; van den Ende et al. 2000; Häkkinen et al. 2001; de Jong et al. 2003) have utilised interventions involving a combination of high-intensity aerobic and resistance exercises for RA. However, the effects of different exercise training modes have been investigated by Ettinger et al. (1997) in OA patients. In a comparison of the effects of a twelve week aerobic, resistance or health education programme, it was found that both types of exercise intervention were associated with significant improvements in disability, physical performance and pain with no significant differences in radiographic disease progression. Furthermore and with specific reference to joint health, the study described in Chapter 5 compared the acute effects of high-intensity aerobic walking and resistance training exercise and demonstrated no differences in the effects of either mode of exercise on markers of joint health. Therefore, due to the important benefits associated with both resistance and aerobic exercise, a combined exercise programme is generally favourable and also recommended in the current guidelines for the management of RA (American College of Rheumatology Subcommittee on Rheumatoid Arthritis 2002; Luqmani et al. 2006; Combe et al. 2007;

Luqmani et al. 2009; National Collaborating Centre for Chronic Conditions 2009; American College of Sports Medicine 2010).

In older adults, walking training has been shown to protect against age-associated increases in blood pressure, decreases in peak aerobic capacity and decreases in thigh strength. High-intensity walking was also found to be more beneficial than moderate intensity continuous walking training (Nemoto et al. 2007). Randomised controlled trials in OA have revealed significant increases in aerobic capacity as a result of walking-based training interventions (50–70% heart rate reserve), lasting 12 weeks (Ettinger et al. 1997; Peloquin et al. 1999). Similar results were found in a study that included RA and OA patients, with an additional trend observed towards improved disease activity in the walking group compared to the control group (non-aerobic range of motion exercises). This improvement was also maintained when re-assessed at nine months (Minor et al. 1989). Taken together, these findings suggest that an exercise intervention incorporating high-intensity walking exercise is likely to offer several advantages for the RA population.

Progressive resistance training (PRT) has been consistently shown as a method of improving body composition, strength and physical function in RA (Lemmey 2011). Furthermore, high intensity PRT has been shown to be an effective adjunct treatment of cachexia in RA patients (Marcora et al. 2005). In a recent systematic review and meta-analysis, it was concluded that continued resistance exercise training acts to decrease disability, functional capacity impairment and swollen and tender joint count (Baillet et al. 2012). Importantly, as discussed by de Jong et al. (2004a), weight- and impact-bearing exercises, such as walking and resistance training, also have an essential role in improving bone mineral density of RA patients.

Summary and specific objectives

Previous investigations have been limited in their ability to address the research requirements highlighted in the NICE guidelines (National Collaborating Centre for Chronic Conditions 2009) as they have not investigated whether or not short-term exercise interventions (less than 3 months) are potentially harmful to the large joints of people with RA. This is due the use of relatively insensitive outcome measures such as radiographical evidence of joint damage progression. Therefore, the present study aims to further explore the pathophysiological mechanisms associated with continued exercise training and joint health by assessing post-exercise serum COMP and synovial inflammation over an 8 week exercise intervention.

The results from the study described in Chapter 5 demonstrated that any changes in serum COMP had returned to baseline (or below) by 1 hour post-exercise, a finding that corresponds with others (Mündermann et al. 2005; Andersson et al. 2006b; Mündermann et al. 2009). Therefore, assessment of serum COMP at this standardised time point (1 hour post-exercise) will enable determination of the effects of exercise training on cartilage breakdown. The quantitative assessment of synovial inflammation was variable but interpreted clinically as extremely minor at all assessment time points in the protocol. However, to determine if continued exercise training affects this specific measure of knee joint synovial inflammation, it is also important to assess this outcome at a standardised time point post-exercise. Furthermore, this study design allows investigation of whether or not continued exercise training affects the acute response to exercise.

Since the study described in Chapter 5 indicated minimal effects of both high-intensity aerobic and resistance exercise, the next step is to establish the effects of a combined exercise training programme on joint health. Overall, if the present exercise intervention proves to have no detrimental effect upon joint destruction and inflammation in RA, this will add support to the notion that health professionals are in a strong position to definitively advocate the advantages of exercise. Moreover, it may be that health professionals can make exercise recommendations with more certainty surrounding the positive effects and lack of detrimental effects of exercise on joint health. Consequently, patients may well feel more able and willing to exercise without fear of exacerbating their disease.

The specific objectives of the current study include determining the effect of an eight-week walking and lower-body resistance exercise training programme on the following main outcome variables; a) cartilage breakdown (serum COMP), b) synovial inflammation of the knee joint (CF). The following measures formed secondary outcome variables; c) systemic inflammation (serum CRP); d) knee joint pain; e) physical function and f) disease activity score (DAS). To determine the efficacy of the intervention, aerobic fitness (predicted VO_2max) and strength (8 RM of lower body exercises) were also assessed. Based on the data collected in Chapter 5, it was hypothesised that, over the eight week period, serum COMP, synovial and systemic inflammation would show levels similar to baseline when assessed at 1 hour post-exercise. In addition, it was hypothesised that patients would show improved aerobic fitness, lower-body strength and physical function as a result of the training intervention.

6.3 Methodology

The study gained full ethical approval from the North West Wales Research Ethics Committee. Pilot testing allowed researchers to perfect techniques and make necessary amendments before the final protocol was used. This investigation formed a single cohort observational design with repeated measures. The main outcome variables were assessed at four time points during an eight week resistance and walking exercise programme.

Participant sampling and selection

Patients with an RA diagnosis according to American Rheumatism Association (1987) criteria and capable of performing exercise were recruited from the outpatients' clinic of the Department of Rheumatology, Betsi Cadwaladr University Health Board. Patients who expressed interest following participation in the previous study were also contacted. Clearance for participation in this study 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 condition). See Appendix 6 for a flow diagram detailing the patient inclusion process.

The nature of the current research is such that a non-significant change in the main outcome variables over the eight-week training period is favourable. Therefore, the usual methods of sample size determination based on detecting significant *changes* over time were incompatible. Therefore, as the overall objective of the intervention was to produce improvement in aerobic and strength-based fitness, sample size calculations were based on this principle.

Data were used for sample size calculations from a previous study that investigated the effects of 36 sessions of a combined aerobic and resistance exercise intervention in RA patients (van den Ende et al. 1996). Using the means and standard deviations of the VO_2max data, an effect size of 0.65 was calculated. With an alpha error level of 5% and a Beta error level of 50%, a sample size of 6 for a single-group study was identified as the minimal number of participants required to detect a significant difference in VO_2max pre- and post-training intervention (http://www.dssresearch.com/toolkit/sscalc/size.asp). There was a lack of data available to perform a power analysis for strength-based exercise within the study by van den Ende et al.

(van den Ende et al. 1996). Based on a data from a 36-session intervention (Marcora et al. 2005), an effect size of 0.76 was calculated, with a sample size estimation of 5 participants. Due to a shorter intervention time (24 sessions) and because this method may overestimate effect size, sample size was increased accordingly, also allowing for the potential for participant drop-out. Therefore, the study aimed to recruit a sample size of 12 participants.

Study protocol

The schematic below summarises the study protocol (Figure 6.1), with further details provided in the following sections. In summary, following full explanation of the procedures, participants were asked to visit the laboratory for a familiarisation session and baseline assessment of the outcome variables. At least 2 days after this session, participants began the exercise programme, which extended over an eight-week period. These individually supervised sessions took place in the exercise laboratory and occurred three times per week, with at least 48 hours between each session. At week 4 (visit 13) and week 8 (visit 24), the exercise session was followed by assessment of the outcome variables at 1 hour post exercise. Participants also attended a final debrief session allowing the last assessments to be made and to receive a full explanation of their results.

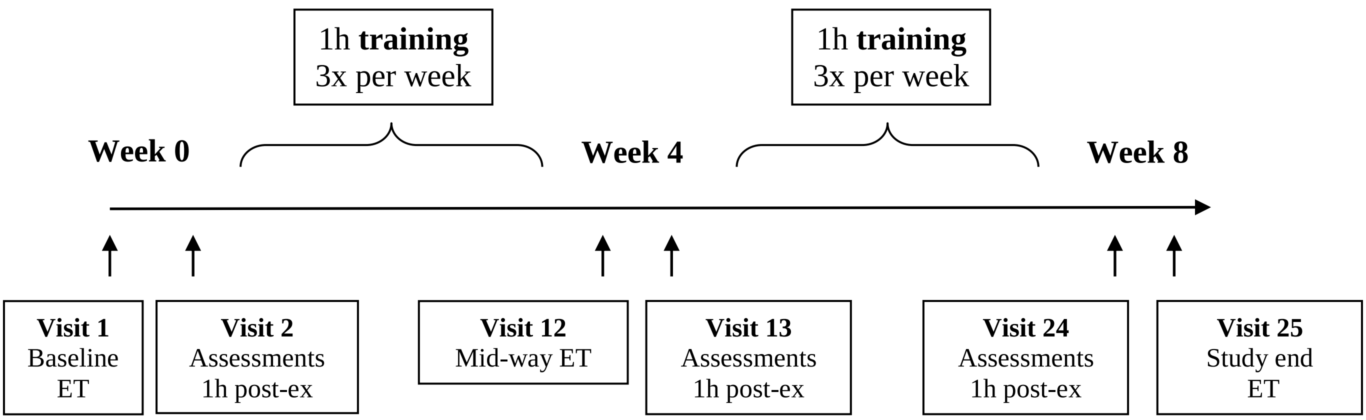


Figure 6.1 A schematic to show assessment time points for the main outcome variables, exercise tests and sessions over the 8-week training intervention (ET; submaximal aerobic fitness walking test, lower body maximal strength testing and physical function). Exercise training sessions took place three times per week. Serum COMP, US and serum CRP assessments were made at 1 hour post-exercise following training sessions at Visit 2, 13 and 24.

Familiarisation session

The aim of the familiarisation session was to acquire informed consent and familiarise patients with the equipment and testing procedures. The departmental health questionnaire, the modified health assessment questionnaire (MHAQ) and the International Physical Activity Questionnaire (IPAQ) were also completed (for details see Chapter 5). A DAS-28 was performed by an experienced consultant rheumatologist, including a 28 swollen and tender joint count and a general health score using a simple visual analogue scale. Serum CRP was included in the overall DAS calculation. Following a 30 minute rest period, blood samples and US assessments took place. Resting measurements of blood pressure were taken manually using a sphygmomanometer and stethoscope and heart rate was observed using telemetry (Polar RS800, Finland).

The submaximal treadmill walking test (Ebbeling et al., 1991) was then performed. This test allowed prediction of baseline VO_2max and provided the information required to set the speed and gradient of the treadmill to elucidate the appropriate intensities for the walking exercise part of the training. This test also formed the aerobic warm-up for the resistance exercise familiarisation. To enable the intensity of the resistance exercise component of the session to be determined, ACSM guidelines were followed to establish an 8RM for the following exercises; leg press, leg extension and leg curl (Whaley 2006). These methodologies are detailed in Chapter 5. A different leg press machine (HUR Main Line Leg Press 3540) was utilised for the duration of the training intervention (Figure 6.2). This machine used air pressure to adjust resistance. The same treadmill was also used throughout the training intervention (HPcosmos Mercury 4 Med, Nussdorf-Traunstein, Germany).

Figure 6.2 Leg press machine used for resistance training intervention.

During the familiarisation session, participants were also asked to perform two simple functional tests to determine baseline functional ability of the lower body (Rikli et al. 2001). These were conducted as follows:

a) Timed ‘8 foot up and go’: From a seated position on a chair and without using arms for assistance, participants were asked to walk around a cone positioned 8 feet away and return to the seated position as quickly as possible. The amount of time taken was recorded.
b) 30 second ‘sit to stand’: From a seated position on a chair, participants were asked to rise to the standing position and return to a seated position without using their arms to assist as quickly as possible. The number of times participants were able to do this in 30 seconds was recorded.

The aim of this familiarisation session was also to highlight any risk (cardiovascular or otherwise) that may have required the researcher to seek further guidance or exclude the participant.

Exercise intervention and assessment of outcome variables

The exercise intervention comprised of supervised exercise training sessions thrice weekly for eight weeks and followed exercise prescription guidelines for people with RA (Millar 2010). The sessions included approximately 1 hour of exercise in total. Participants performed a short warm-up and cool-down, including 5 minutes of low-intensity walking on the treadmill and flexibility exercises to stretch the hamstrings, quadriceps and calf muscles in each session.

The main part of the exercise session consisted of aerobic interval-based walking exercise, followed by lower body resistance training. As described in Chapter 5, the walking exercise involved a 20 minute interval training session on a treadmill including four intervals of 3 minutes walking at a high-intensity and 2 minutes walking at a low-intensity. Target heart rates were 70-90% HRmax for the high-intensity intervals and 40-50% HRmax for the low-intensity intervals. Resistance exercises included the following lower limb exercises; leg press, leg extension and hamstring curl. Participants performed one set of 15 repetitions with half the pre-determined load first, followed by three sets of eight repetitions at 80% of 1RM.

A one minute rest period was timed between sets and exercises. Exercises were performed with dynamic muscle action, at a moderate repetition velocity (1 – 2 sec concentric, 1 – 2 sec eccentric), with the whole resistance section totalling approximately 20 minutes (Marcora et al. 2005). Peripheral RPE, central RPE and HR were also monitored throughout (see Chapter 5).

To enable adjustment of the exercise load in proportion to changes in aerobic fitness and specific muscle strength, the intensity of the aerobic walking and resistance exercise was progressive over the intervention period. More specifically, if HR did not reach the target zone during the walking exercise, increases in speed (whilst maintaining a walking gait), followed by gradient, were used create the desired exercise intensity. A central RPE value of 13 or above (somewhat hard) was used as a guide that workload was of a sufficient intensity and a reduction in RPE at the same workload was considered an indicator that intensity could be increased. The treadmill walking protocol performed at familiarisation was used to re-assess predicted VO_2max at 4 weeks and was subsequently used as a further guide for exercise progression. In terms of the resistance exercises, peripheral RPE was used as an indicator for progression in the same way as above. Furthermore, if on the last set of 8 repetitions, the participant was able to perform further repetitions at the current workload for one to two repetitions over the 8 required, a 2.5–5% increase in load was attempted in the next session (Kraemer et al. 2004; Ratamess et al. 2009). Formal re-assessment of 8RM took place at 4 weeks and was also used to adjust the training weight. Minor adaptations to ensure participant comfort and to account for variations in disease state were made were made as necessary over the 8 week period.

Blood samples and ultrasound assessments in order to assess serum COMP, serum CRP and CF took place one hour post-exercise at the beginning of week 1 and at the end of weeks 4 and 8. Methodologies for assessment of these outcome variables were identical to those described in Chapter 5. Furthermore, re-assessment of functional ability, arthritis-specific pain, DAS and MHAQ also took place at weeks 0, 4 and 8. Joint pain and RPE were also monitored as previously described (Chapter 5).

Statistical analysis

Results were analysed using fully within-subjects repeated measures ANOVA in SPSS. Data were assessed for normality using the Shapiro-Wilk test. Sphericity was assessed using Mauchly's test of sphericity. If significant, the Greenhouse-Geisser correction was used if Epsilon < 0.75 and the Huynh-Feldt correction if Epsilon > 0.75. When a significant main effect for time was observed, follow-up pairwise comparisons, with Bonferroni adjustment, were used to identify the time points between which significant changes occurred. Data are mean ± SD unless otherwise stated. Significance was accepted at $p < 0.05$.

6.4 Results

Nine patients with RA were recruited and all participants completed the full protocol. Figure 6.3 displays the flowchart of participants through the recruitment process; thirty-five patients received the information sheet, eleven attended familiarisation and nine patients completed the full protocol.

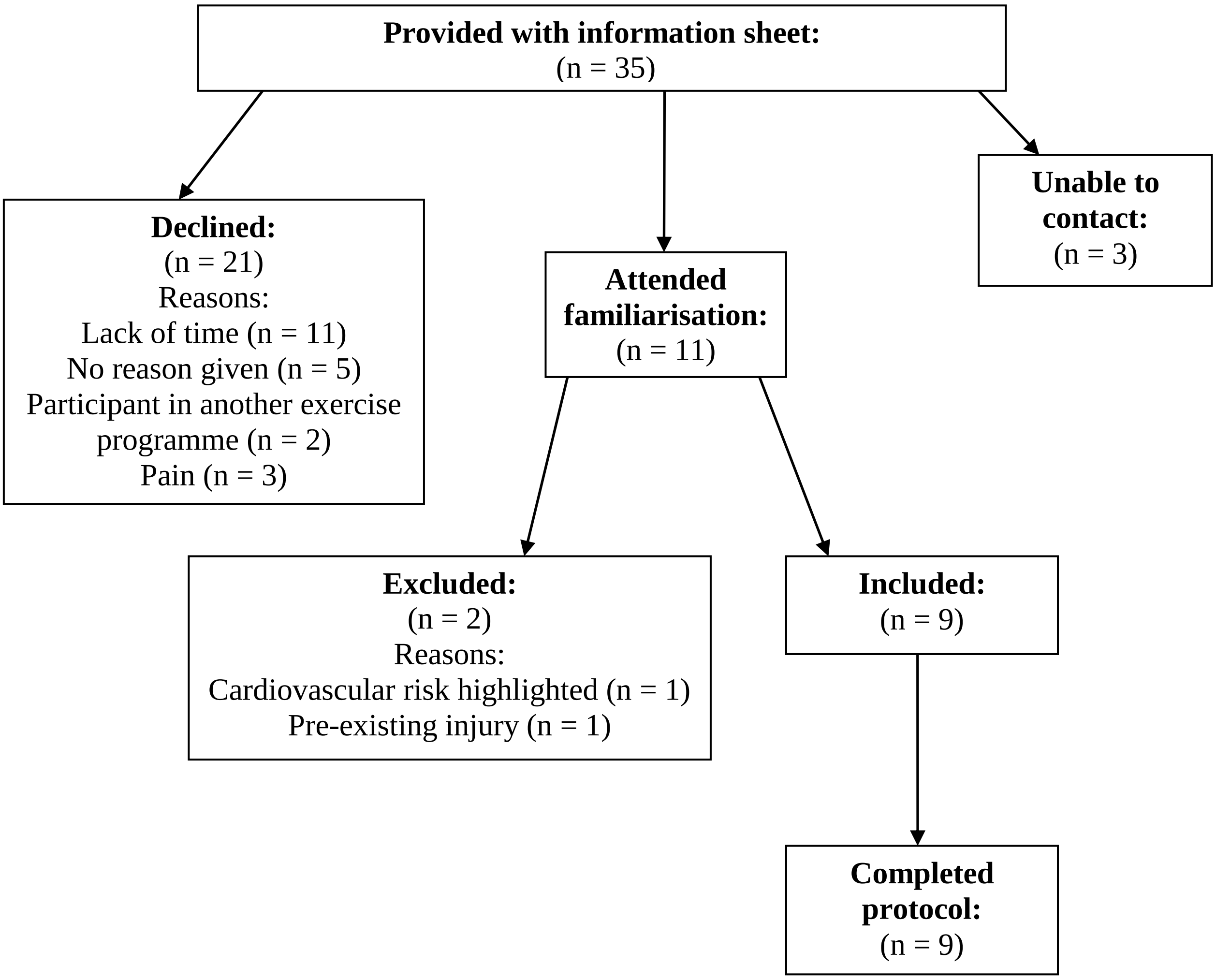


Figure 6.3 Recruitment flow diagram of RA patients for the 8-week exercise intervention.

The patient characteristics of the final cohort that undertook the exercise intervention are displayed in Table 6.1. Medical treatment was stable in all but two of the RA patients. One of these patients was prescribed biological therapy and received a Rituximab infusion at week 4. The other patient ceased medical RA treatment (methotrexate) during the first week of the start of the intervention study onset and was given a preliminary corticosteroid steroid injection (120mg depo-medrone) during week two. This patient did not require any further treatment during the course of the intervention period.

Characteristic		
Age (years)		57 ± 14
Gender		8 F, 1 M
BMI		26.4 ± 3.2
IPAQ category (number of patients)		
	Low	2
	Moderate	5
	High	2
Disease-related characteristics		
Disease duration (years)		13 ± 10
DAS-28		2.45 ± 1.02
MHAQ		0.53 ± 0.55
Medications		
Methotrexate only		4
Methotrexate + biologic		2
Combination DMARD		1
Other DMARD		1
NSAID[#]		2
No medication		1

Table 6.1 Participant characteristics of RA participants completing the 8-week exercise intervention. Values are mean ± SD. (M: male; F: female; BMI: Body Mass Index; IPAQ: International Physical Activity Questionnaire; DMARD: Disease Modifying Anti-Rheumatic Drugs; DAS-28: Disease Activity Score-28; MHAQ: modified Health Assessment Questionnaire. # = in addition to anti-rheumatic drugs.

Exercise progression, exercise performance and function ability

Out of a maximum of 24 exercise sessions, total attendance was 21.8 ± 3.0 sessions, with the majority of patients completing the full number of sessions. However, one patient attended only 2 exercise sessions during the final four weeks of the intervention due to a reaction to medical treatment (Rituximab infusion). Figure 6.4 displays the weekly attendance of patients over the exercise intervention period.

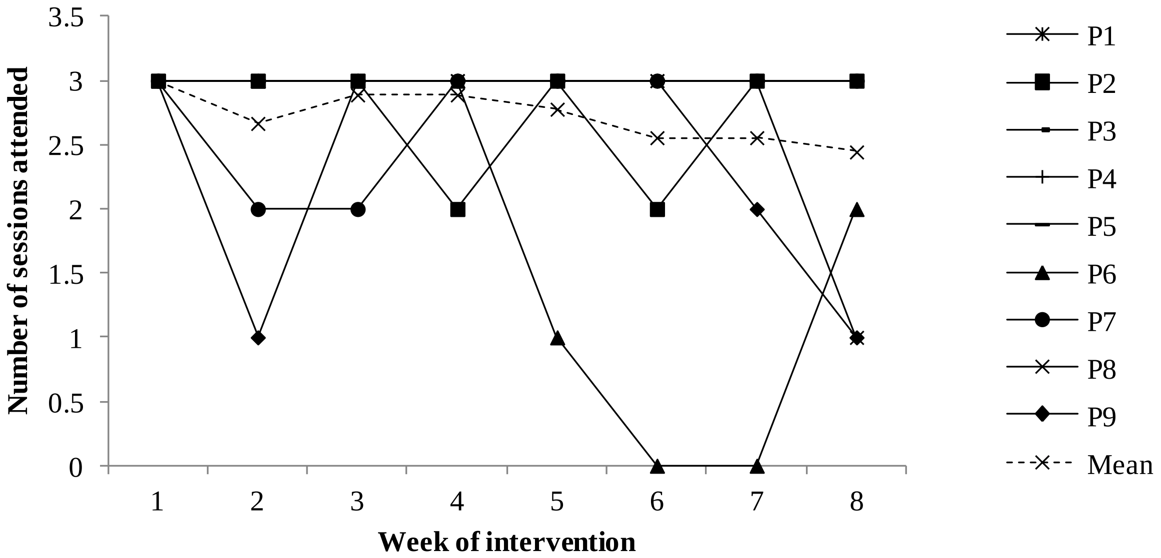


Figure 6.4 The number of sessions attended over the 8-week exercise training intervention. Data shows individual session attendance and overall mean.

The progression in walking exercise intensity over the 8 week period is displayed in Figure 6.5. A significant main effect of time was revealed with increases in average walking speed observed (week 1: 4.8 ± 1.1 km/h; week 4: 5.1 ± 0.7 km/h: week 8: 5.5 ± 0.6 km/h; F = 4.69; p = 0.049). Post-hoc tests revealed that significant increases occurred between weeks 4 and 8 (p = 0.046). A significant main effect of time was also shown for average gradient, which increased from 0.81 ± 0.9% in week 1 to 2.0 ± 1.3% in week 8 (F = 0.05; p = 0.002; Figure 6.5). Post-hoc tests revealed that significant increases occurred when comparing the average gradient between week 1 and week 8 (p = 0.029).

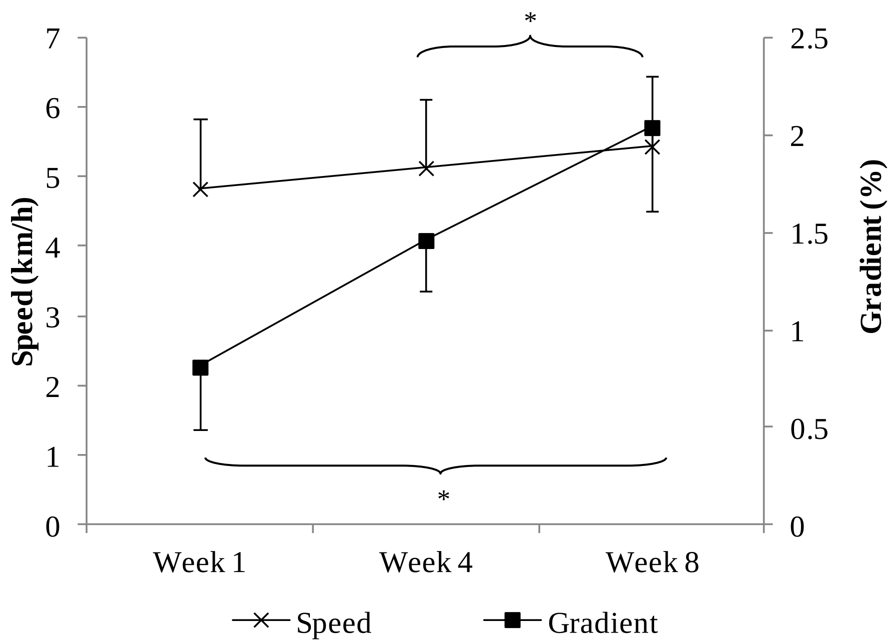


Figure 6.5 Progression of average high-intensity speed and gradient over the 8-week training intervention. Data are mean ± SE, * = p < 0.05.

In terms of the average weight lifted during the training programme, average increases between week 1 and week 8 were 14%, 36% and 47% for the leg press, leg extension and leg curl, respectively. Statistical analysis revealed a significant main effect for time for the weight lifted during leg press ($F = 4.09$, $p = 0.04$) and leg extension ($F = 4.18$, $p = 0.035$) exercises, with significant increases observed between week 1 and week 8 (Table 6.2).

	Week 1	**Week 4**	**Week 8**
Leg press (kg)	127.7 ± 29.3	132.59 ± 29	143.6 ± 31.4 *
Leg extension (kg)	15.0 ± 5.1	15.8 ± 4.5	20.5 ± 7.5 *
Leg curl (kg)	5.8 ± 3.6	6.8 ± 3.9	7.8 ± 3.3

Table 6.2 Progression of the weight lifted during the resistance exercise (leg press, leg extension, leg curl) section of 8-week training intervention. Data are mean ± SD, * = significant increase from week 1 ($p < 0.05$).

Aerobic fitness also showed a significant main effect of time (week 0: 29.8 ± 8.4 ml/kg/min; week 4: 30.7 ± 7.6 ml/kg/min; week 8: 32.5 ± 8.3; $F = 7.6$, $p = 0.005$). Specifically, significant increases were observed between week 0 and 8 ($p = 0.014$) and between weeks 4 and 8 ($p = 0.008$) (Figure 6.6).

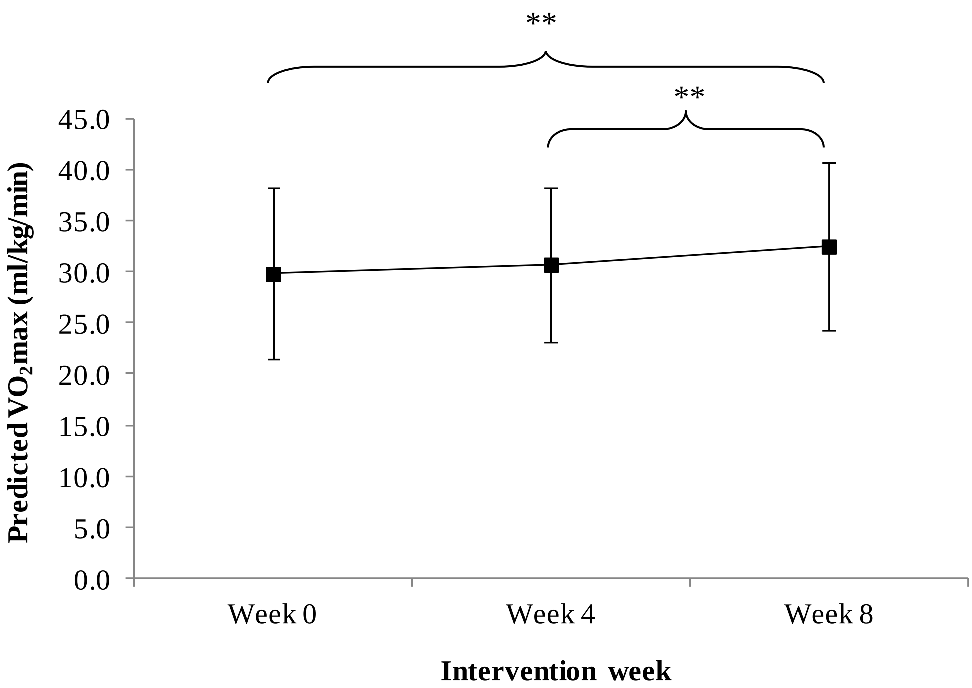


Figure 6.6 Change in predicted VO_{2max} over the 8-week training intervention. Data are mean ± SD. ** = significant ($p < 0.01$).

Significant increases in leg strength performance (predicted 1RM) were also observed over the 8 week exercise period (Figure 6.7). Analysis of the leg press revealed a significant main effect for time (Week 0: 166.2 ± 27.9 kg; Week 4: 184.7 ± 36.6 kg; Week 8: 196.9 ± 38.8 kg; $F = 15.762$, $p = 0.002$). Specifically, significant increases in leg press predicted 1RM were revealed between weeks 0 and 4 ($p = 0.009$), weeks 4 and 8 ($p = 0.007$) and between baseline and week 8 ($p = 0.003$). A significant main effect of time was also revealed for leg press predicted 1RM (Week 0: 8.1 ± 4.8 kg; Week 4: 11.5 ± 5.9 kg; Week 8: 12.8 ± 6.3 kg; $F = 12.787$, $p < 0.0001$). Post-hoc tests revealed significant increases in predicted 1RM were observed between week 0 and week 4 ($p = 0.009$) and also between baseline and week 8 overall ($p = 0.004$). The increases in leg extension predicted 1RM approached significance (Week 0: 21.3 ± 7.9 kg; Week 4: 33.6 ± 19.8 kg; Week 8: 32.4 ± 10.2 kg, $F = 3.332$, $p = 0.09$).

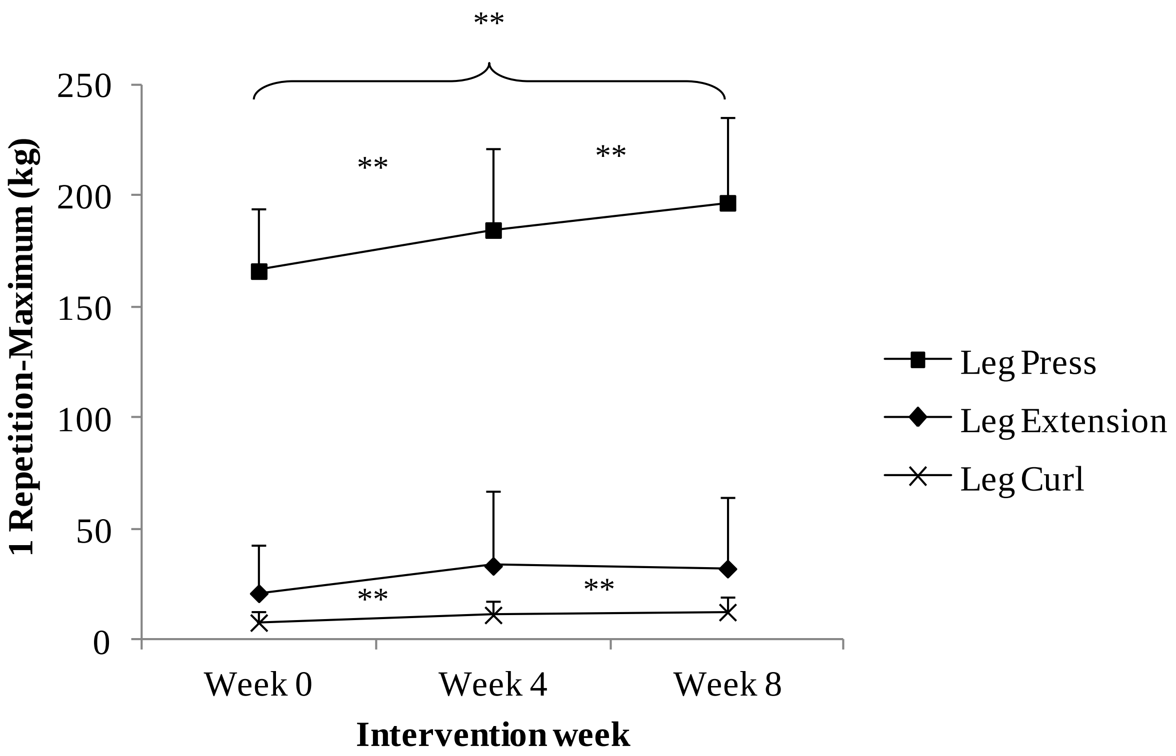


Figure 6.7 Change in 1RM over the 8-week training intervention for lower body resistance exercises; leg press, leg extension and leg curl. Data are mean ± SD. ** = significant ($p < 0.01$).

A significant main effect for time in sit-to-stand (week 0: 14.4 ± 2.9 repetitions; week 4: 17.1 ± 3.6 repetitions; week 8: 18.8 ± 3.2 repetitions: $F = 13.579$, $p = 0.003$) and 8-foot up and go performance (week 0: 4.2 ± 1.0 seconds; week 4: 4.1 ± 1.1 seconds; week 8: 3.8 ± 0.7 seconds; $F = 4.522$, $p = 0.002$) was observed (see Figure 6.8). Specifically, a significant increase in sit to stand performance was observed between weeks 4 and 8 ($p = 0.031$) and also week 0 and 8 ($p = 0.002$).

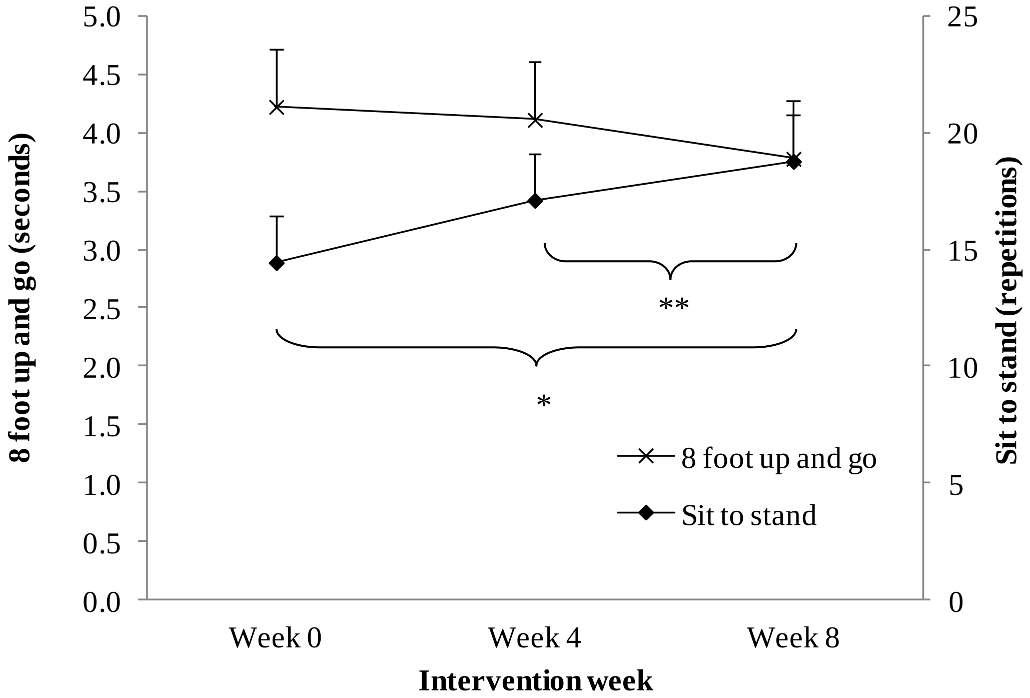


Figure 6.8 Change in functional test performance as assessed over the 8-week training intervention. Data are mean ± SD. ** = significant ($p < 0.01$), * = significant ($p < 0.05$).

Intra-assay coefficient of variation for serum COMP ELISA analysis was 2.37% and R^2 curve fit was 1.00. There was no significant change in absolute serum COMP from baseline (806.7 ± 258.1 ng/ml) to when measured 1 hour post-exercise at week 1 (822.5 ± 236.4 ng/ml), week 4 (748.6 ± 265.9 ng/ml) and week 8 (778.4 ± 283.4 ng/ml; $F = 1.05$, $p = 0.380$; Figure 6.10). An effect size of 0.10 was calculated when considering the change from baseline to week 8 in mean serum COMP levels.

No synovial inflammation was observed at baseline (CF = 0.00) and this was maintained throughout the exercise intervention. Systemic inflammation (serum CRP) also showed non-significant variations from baseline (CRP: 3.11 ± 1.83 mg/L) over the intervention period (Week 1: 3.22 ± 2.39 mg/L; Week 4: 5.04 ± 5.15 mg/L; Week 8: 3.11 ± 2.20 mg/L; $F = 1.18$, $p = 0.337$, Figure 6.9).

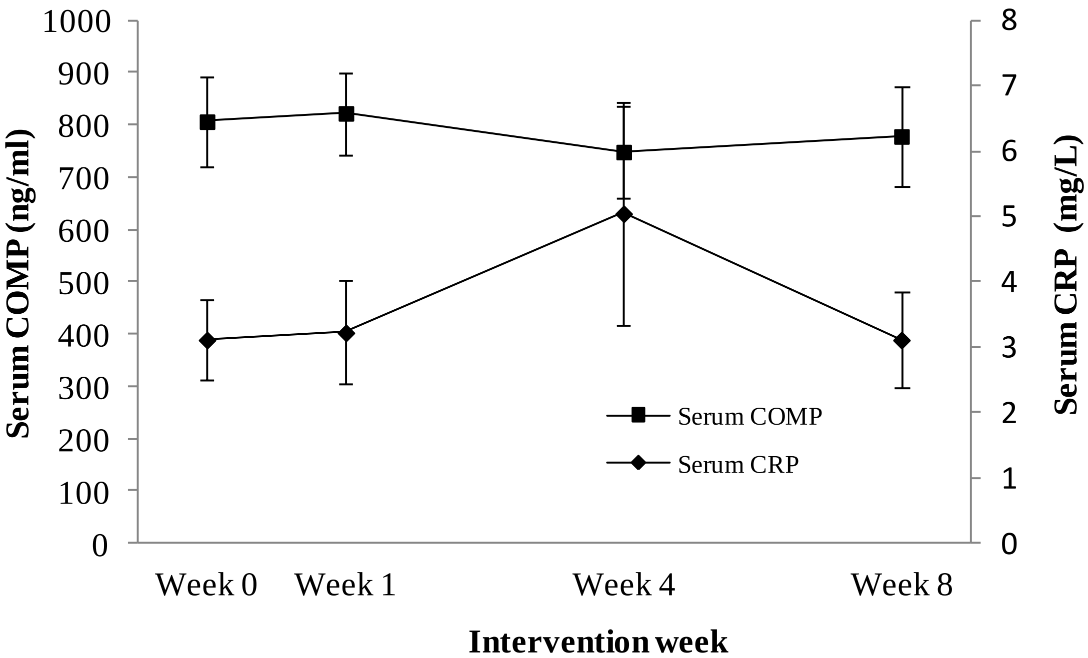


Figure 6.9 Absolute serum COMP and CRP over the 8-week training intervention. Blood samples were taken at week 0 (pre-exercise) and weeks 1, 4 and 8 (assessed post-exercise) of the training intervention. Data are mean ± SE.

Disease related findings

General arthritis pain, disease activity (DAS-28) and MHAQ remained low over the intervention period, with no significant changes observed (Table 6.3).

	Week 0	Week 4	Week 8	Significance
Pain (1-10)	1.44 ± 1.67	1.44 ± 1.88	1.33 ± 1.94	p = 0.928
DAS-28	2.45 ± 1.02	2.57 ± 1.11	2.50 ± 1.08	p = 0.873
MHAQ	0.53 ± 0.55	0.42 ± 0.60	0.41 ± 0.59	P = 0.651

Table 6.3 Change in RA-related pain, DAS-28 and MHAQ over the 8-week training intervention. Data are mean ± SD.

Protocol modifications

Patients were generally able to perform the high-intensity exercises safely and effectively. However, some adjustments were made to exercises to ensure participant comfort. For example, extra padding was used during the leg curl exercises for one patient and alternative stretches were incorporated with another. Concerns were highlighted in relation to one patient during the intervention who continued to present with an abnormally low heart rate during exercise, despite reporting high levels of central RPE. However, electrocardiogram results revealed that this patient had normal sinus rhythm and therefore the exercise intervention was continued, utilising RPE to guide exercise intensity. One other patient experienced hip pain during the exercise sessions and sometimes whilst at home. Exercise intensity was reduced for approximately one week and following consultation with a physiotherapist, this patient was recommended further appropriate stretching exercises and encouraged to continue exercising. The pain subsided and the patient completed the full protocol. There were no serious adverse events during the course of the intervention and the progressive exercise programme was very well-tolerated by all patients. Finally, due to travel and time constraints, three patients completed a small number of exercise sessions (maximum of six sessions) at a local gym. However, these sessions were fully supervised, the exercise equipment was similar to those used in the departmental laboratory and the exercise intensity was maintained.

6.5 Discussion

The present study assesses cartilage breakdown and synovial and systemic inflammation in RA patients over an 8 week period of intensive exercise training, offering a rigorous investigation of the effects training specific to joint health, and utilising novel analysis techniques. This study provides new evidence that serum COMP, synovial and systemic inflammation was similar at 1 hour post-exercise at weeks 1, 4 and 8 when compared to pre-exercise at week 0. Hence, these results demonstrate that any transient increases in serum COMP returned to pre-exercise levels within 1 hour, even when intensive exercise was performed regularly over an 8-week period. As shown by previous researchers, the main findings also show that the exercise programme successfully improved aerobic fitness, lower body strength and physical function (Ekdahl et al. 1990; Lyngberg et al. 1994; Noreau et al. 1995; Rall et al. 1996; van den Ende et al. 2000; Bilberg et al. 2005; Marcora et al. 2005; Lemmey et al. 2009), with no detrimental effects in terms of pain or disease activity (van den Ende et al. 2000). Interestingly, the findings from the current study indicate that four weeks of training was sufficient to significantly improve leg press and leg curl muscle strength. However, when considering aerobic capacity and physical function, the present results indicate that a minimum of four weeks training may be necessary for significant improvements to occur.

These group responses are encouraging. However, there were some individual patients that also warrant further comment. As previously noted, one patient received a Rituximab infusion mid-way through the study intervention. This caused her to feel unwell for approximately three weeks and consequently adherence was low during the last half of the intervention (two sessions in total). However, when re-assessed at week 8, this patient still demonstrated increases in strength and aerobic-based fitness when compared to week 0 and week 4. One patient also ceased medical treatment for her RA prior to the study and despite this, no adverse effects during the exercise intervention were observed.

One of the main strengths of the current study was the fact that blood samples were taken at a standardised time post-exercise. In contrast to previous studies investigating the effects of exercise training on serum COMP in RA (Chua et al. 2008; de Jong et al. 2008; Liphardt et al. 2009; Petersen et al. 2010), a rest period of thirty minutes was applied before baseline blood samples. Furthermore, all samples at week 1, 4 and 8 of the exercise intervention were taken at a standardised time of 1 hour post-exercise, during which the participants remained resting in the laboratory. As previously discussed in Chapters 1 and 5, this strengthens the validity and reliability of the data as the serum COMP values reported are reflective of cartilage breakdown without the potential confounding influence of unknown prior physical activity.

Another strength of the current study is that the 8-week exercise intervention involved a combination of progressive, high-intensity aerobic and resistance exercise in a format that has previously been recommended to this patient population. The design of the current programme also works to address the gap in the knowledge relating to the effectiveness of short-term (less than 3 months) training programmes (National Collaborating Centre for Chronic Conditions 2009). Furthermore, the focus of the intervention was on the lower body and therefore enhances the knowledge relating to the effects of exercise on the large, weight-bearing joints. This is important as this is an area that has previously provoked concern (de Jong et al. 2005).

Thirdly, the exercise programme was well-tolerated and well-adhered to by the RA patients in this study. Participants were required to visit the departmental laboratory on twenty-five occasions over an 8-week period, amounting to a total of approximately 42 hours. Hence, the time and travel commitment that was required of participants was considerable. However, apart from one patient who became unwell following a reaction to a Rituximab infusion at week four, adherence was excellent. Moreover, participants were provided with information regarding their aerobic and strength-based fitness, alongside potential future training intensities and were offered the opportunity to participate in a local exercise referral scheme following the intervention. All participants who had not been physically active prior to the intervention (and hence had no established exercise routine to continue post-intervention) took up this opportunity and commenced regular, partially-supervised exercise.

Limitations

The limitations associated with serum COMP, synovial inflammation of the knee joint and CF analysis are discussed in detail in Chapter 5. Similarly, the current study is also limited in terms of participant number. However, it is important to note the very small effect size

(Cohen 1992) when considering the change from baseline to week 8 in mean serum COMP levels.

The lack of CF observed is partially reflective of the inclusion criteria applied to the participants for the current study. Specifically, previous knee involvement was not an essential criterion for inclusion and none of the patients recruited presented with swollen or tender knees. However, it is a positive finding that continued intensive exercise did not appear to stimulate synovial inflammation, despite the increased exercise intensity incorporated in the present study when compared to others (Ellegaard et al. 2012).

When considering participant characteristics, it is important to consider the limitations associated with the participants who agree to take part in exercise training studies such as this. As discussed by Lemmey (2011), it is likely that these volunteer participants are less disabled than the general RA population. In fact, this is demonstrated by the low MHAQ scores in the current study cohort, alongside low disease activity and pain levels. Furthermore, such volunteers may well already be keen on exercise. Only 2 of the 9 participants in the current study were characterised as taking part in 'low' levels of physical activity and therefore the group would be expected to have higher levels of physical fitness. Correspondingly, aerobic fitness levels in this population were higher than previously observed in RA patients recruited in a general clinic setting (e.g., 19.9 ± 4.2 ml/kg/min) (Cooney et al. 2011a). In addition, serum COMP and serum CRP were also low at baseline and no synovial inflammation (CF) was observed at any time point in this group of patients. Taken together, these findings suggest that the application of the current study is limited to patients with low levels of disability, disease activity and pain, alongside those with low serum COMP, CRP and no synovial inflammation of the knee joint. As previously mentioned however, the symptoms associated with RA are now often very well-controlled for many patients (Scott et al. 2010) and hence, the results of the current study may well be applicable to a large proportion of people with RA.

Finally, it is important to acknowledge the limitations of not incorporating a non-exercising control group into the study design. Specifically, the effects of *not* exercising over an 8 week period on cartilage breakdown, synovial and systemic inflammation in RA remains unclear. Furthermore, the effects in a healthy control group are unknown. However, the fact that there was no change in any of the disease-related variables (i.e.

disease activity or medication use) over the course of the intervention indicates a strong likelihood that participation in the exercise intervention would form the main factor influencing the outcome variables associated with joint health. Encouragingly however, as there were no changes in these variables over the exercise intervention, it is reasonable to conclude that the exercise programme had no detrimental effect on these patients.

In summary, the eight week intensive exercise programme adopted by the RA patients in the current study successfully improved aerobic fitness, lower body strength and physical function. Cartilage breakdown, synovial and systemic inflammation showed no changes over the training period and disease activity and pain remained low. Furthermore, it appears that continued exercise training does not affect the acute response to exercise. These findings strengthen the evidence available to health professionals when recommending exercise to this patient group, affirming that exercise offers important benefits without detrimental consequences.

6.6 Applications and conclusions

The findings of this study provide further evidence of the safety and effectiveness of regular, intensive aerobic and resistance exercise training for RA patients with stable disease of over 3 years, low systemic disease activity and without overt synovial inflammation of the knee joint,. Therefore, health professionals are provided with further supporting information enabling them to recommend exercise with further credence and address patient concerns relating to joint health.

Further research is required to address the limitations associated with the range of patients to whom these results can be applied. Specifically, the effects of continued exercise on patients presenting with synovial inflammation of the knee joint is yet to be determined. Furthermore, the effect of continued, high-intensity exercise on serum COMP levels of patients with active disease and patients with ‘high’ serum COMP levels is also an area for additional investigation. Finally, it is necessary to reliably determine the effects of longer term exercise programmes (i.e. more than three months) on these outcome variables.

Notwithstanding these limitations, the current study assesses cartilage breakdown, synovial and systemic inflammation at a predetermined time post-exercise and therefore provides evidence that continued intensive exercise training does not detrimentally affect joint health, without the potentially confounding effects of unknown prior activity. Furthermore, to the authors knowledge, this is the first investigation to explore the effects of intensive exercise training on synovial inflammation of the large joints in RA. The current study also provides a basis from which larger-scale randomised controlled trials can be designed. Overall, with confirmation of these encouraging findings, it is anticipated that patient perceptions relating to exercise and joint health will improve, increasing the likelihood that RA patients will incorporate regular exercise into the management of their condition.

Chapter 7: General discussion

7.1 Background

The views associated with exercise and joint health in RA have changed considerably over the last decades. Due to fears that physical exercise was detrimental in terms of disease activity and progression, previous management of RA involved bed rest and splinting of the affected joints (Duthie 1951). However, it became clear that there were also worrying consequences of this treatment including joint contracture and muscle wasting (Nordemar et al. 1981). Hence, physical exercise has now become an important component in the management of this chronic condition, with numerous benefits for the patient, particularly when physical training is performed at a high-intensity (van den Ende et al. 1996).

Notwithstanding the established benefits, this patient population are insufficiently active (Lee et al. 2012) and since these patients are at greater risk of developing cardiovascular disease (Metsios et al. 2009), cachexia (Roubenoff et al. 1992) and osteoporosis (Franck et al. 2009), this physical inactivity is of marked concern. Thus, knowledge of the current perceptions of RA patients regarding exercise is important to determine in order to address the potential issues that may be influencing exercise behaviour.

Of additional relevance is the limited understanding of the pathophysiological mechanisms affecting joint health in RA as a result of exercise (Anandarajah et al. 2004). Whilst offering encouraging findings as to the safety of exercise for RA patients, research to date has mainly been cross-sectional in nature and has utilised relatively insensitive measures of joint health. Therefore, to fully substantiate the non-detrimental effect of intensive exercise on the joint health of people with RA, this thesis aimed to determine the effects of exercise *per se* using measures sensitive to the potentially subtle changes in joint health. Cartilage destruction and synovial inflammation are characteristics of the impaired joint health associated with RA, and novel markers of these phenomena have received previous research attention. Serum COMP has been utilised as a marker of cartilage breakdown in response to exercise in healthy controls (Mündermann et al. 2005) and individuals with OA (Andersson et al. 2006b). In addition, synovial inflammation has been measured quantitatively using ultrasonography techniques, mainly to assess the hyperaemia occurring in small joints of the wrist of people with RA (Ellegaard et al. 2009a). This thesis examines the acute response of these specific markers of joint health to intensive exercise, alongside the effects of continued intensive exercise training on this response, providing information to improve understanding in this area.

By combining the exploration of patient perceptions with enhanced knowledge surrounding the physiological effects of exercise on joint health, this thesis contributes novel and comprehensive findings to the area of exercise in RA, elucidating important information for health professionals, future researchers and RA patients.

7.2 Summary of findings

Following in-depth qualitative (Chapter 3) and quantitative (Chapter 4) exploration of patient perceptions, it is now evident that concerns about exercise and joint health exist within the RA population. Patients are unsure exactly how they should exercise and appear to be further discouraged from exercise due to worries about pain. Moreover, patients perceive that health professionals are uncertain about exercise recommendations and joint health. Despite this, findings suggest that patients are aware that exercise offers important benefits for their joints.

In terms of the physiological aspects of exercise and joint health, the study in Chapter 5 demonstrates that patients with inactive RA show elevated serum COMP when compared to a healthy control group, matched for age and gender. However, there appears to be no acute effect of intensive aerobic or resistance exercise on absolute serum COMP or CRP in both the RA and healthy control groups taking part in this study. Synovial inflammation also remained at a minor level over the post-exercise time period (Chapter 5). Similarly, it appears that this lack of detrimental effect holds over an 8 week period of intensive combined aerobic and resistance training (Chapter 6). Encouragingly, the exercise intervention was also well-tolerated by this group of RA patients, with significant improvements in aerobic and strength-based physical fitness, enhanced physical function and no changes in disease activity or pain.

7.3 Significance of findings

There are important implications of the findings from this thesis, both for health professionals involved in the care of people with RA and future researchers. Both Chapters 3 and 4 provide evidence that RA patients are concerned about joint damage, joint pain and how to exercise. The findings described in Chapter 4 specifically highlight that in the study population of

NRAS members, factors including joint pain, not knowing what exercise to do and a fear of causing joint damage may also be negatively influencing physical activity levels.

Importantly however, it may also be postulated that a typical sample of RA patients would have less access to exercise information and be less physically active than the groups described in these studies. Specifically, NRAS members' agreement with questionnaire items relating to 'knowing what exercise should be done' was relatively high compared to the knowledge these patients perceived amongst health professionals. This cohort also reported higher levels of physical activity than would be expected of this population in general. Hence, perceptions relating to their own lack of exercise knowledge, alongside worries about joint damage and pain may be more pronounced in a sample of RA patients who are not members of a support and information-providing organisation such as NRAS. Therefore, whilst it is vital that rheumatologists, physiotherapists, occupational therapists and nurse specialists involved in the care of people with RA consider and address these issues, these findings also highlight the importance of organisations such as NRAS in disseminating knowledge and advocating exercise.

Accordingly, the findings described in Chapters 5 and 6 give further credence to the recommendation of regular high-intensity aerobic walking and resistance exercise for stable RA patients with low systemic disease activity and synovial inflammation. Specifically, findings suggest that these two forms of exercise may be advocated to patients with these characteristics without a fear of detrimental effects in terms of cartilage breakdown, synovial or systemic inflammation. The study described in Chapter 5 demonstrates that while absolute serum COMP is higher in RA, the responses to aerobic and resistance exercise are similar in healthy control participants, suggesting that having RA does not significantly alter the response to exercise. Furthermore, in our target population of RA patients who had well-controlled disease, the findings in Chapter 6 demonstrate that serum COMP consistently shows levels similar to that of baseline at 1 hour post-exercise over an 8 week aerobic and resistance exercise intervention. These findings suggest that the short-term effect of exercise on serum COMP does not change as a result of continued training. Synovial inflammation was minor at baseline, an observation that was sustained over the 24 hours following an acute bout of both aerobic and resistance exercise. Furthermore, the findings from Chapter 6 demonstrate that synovial inflammation also remained inactive over the 8 week period of continued exercise training. Therefore, it appears that in RA patients without clinically evident synovitis of the knee joint, exercise such as that involved in the current study does not stimulate or further its development. Moreover, as the exercise intervention was well-tolerated, with significant improvements in physical fitness and function and with no detrimental effect on disease activity or pain, the benefits of this form of exercise training for RA patients are clear. Indeed, these patients demonstrated similar improvements in aerobic capacity (Kohrt et al. 1991), lower body strength and physical function (Latham et al. 2004) to those observed in healthy population of a similar age. The findings from Chapters 5 and 6 are limited in their application to patients with well-controlled disease. However, following the introduction of biologic agents, clinical remission is now a realistic goal when managing RA (Jayakumar et al. 2012) and therefore these results may well be applicable to a large proportion of the RA population. Another potential limitation in the application of these results is that only lower body exercises were included in the exercise protocol. However, it is important to note that these findings are of marked value given the previous concerns relating to exercise and the health of the large, weight-bearing joints (de Jong et al. 2003).

This thesis also provides additional information regarding the outcome measures and methodologies used that may be useful for future researchers. Serum COMP was utilised for the studies described in this thesis due to its standing as a specific and sensitive biomarker, used by previous researchers to indicate cartilage breakdown (Mündermann et al. 2005; Wisłowska et al. 2005; Andersson et al. 2006b; de Jong et al. 2008). However, there are limitations of serum COMP that are important to for future researchers to consider. Firstly, whilst it is believed that COMP may play a role in cell proliferation and apoptosis, as well as in the regulation of cell movement and attachment (Garnero et al. 2000), the consequences of the loss of this protein from tissue can only be speculated and limited information about the function of the protein is available. Secondly, as discussed below, there is also speculation surrounding the significance of elevated serum COMP and whether this is in fact indicative of detrimental effects for the synovial joint. Interestingly, COMP also has been found to be secreted by the synovial cells (Recklies et al. 1998) and therefore, one of the questions in RA is whether COMP reflects inflammation as well as structural deterioration of cartilage.

As discussed by Saxne and Heinegard (1992), COMP is readily detected in the serum of healthy individuals, suggesting that the turnover of COMP is a normal, on-going process. Hence, at any given time, there is on-going breakdown, new synthesis and repair. Therefore, overall, increased release should also reflect the replacement of lost molecules (Garnero et al. 2000). Consequently, there are two trains of thought when considering serum COMP as a biomarker of joint damage. In the first, it may be that elevated levels of serum COMP are merely indicative of increased metabolic activity (which includes the synthesis of ‘new’

COMP), and not permanent cartilage destruction. On the other hand, higher levels of serum COMP are found in patient populations characterised by erosive joint disease when compared to healthy controls (Christensen et al. 2011). Furthermore, cross-sectional studies have shown that elevated COMP levels are associated with decreased cartilage volume (Niehoff et al. 2010) and increased radiological joint damage (de Jong et al. 2008). Research also shows that serum COMP levels are higher in early RA when disease is most active, aggressive and less well-controlled (Fujikawa et al. 2009). These findings support the notion that high serum COMP may well be indicative of irreversible cartilage breakdown. Furthermore, in some cases, increased serum COMP has been shown to predict radiological joint damage (Petersson et al. 1998).

More recently however, and albeit in a healthy population, researchers have suggested that exercise interventions (i.e. thirty minutes of drop-jumps and running exercise in this case), may not in fact be strenuous enough to expect cartilage destruction to occur (Niehoff et al. 2011). Consequently, these researchers assume that post-exercise increases in serum COMP are not a result of cartilage destruction, but instead an indication of normal turnover and short-term adaptation (Niehoff et al. 2011).

As previously discussed, it was an unexpected finding that absolute serum COMP did not increase significantly post-exercise. Considering that significant increases in absolute serum COMP have been observed in healthy individuals following as little as 30 minutes walking on a level track (Mündermann et al. 2005), the reason for the results observed in the current study remains unclear. However, in comparison to the participants in our study, the healthy individuals included in the study by Mundermann et al. (2005) were of a younger age. Hence, with knowledge that increasing age is associated increased serum COMP (Jordan et al. 2003), a potential hypothesis is that an increased age is associated with a blunted serum COMP response to exercise. Furthermore, compared to the healthy cohort in the study by Mundermann et al. (2005), participants in the current study were generally sedentary individuals. Animal studies demonstrates that chronic loading of cartilage such as that occurring with exercise can lead to changes to the biochemical and mechanical properties of articular cartilage (Roemhildt et al. 2010). Consequently, researchers have speculated that the effect of varying physical activity levels on the properties of cartilage may also lead to similar adaptations in humans (Niehoff et al. 2011). Accordingly, this may explain the limited response to exercise observed in the current study when compared to others. In fact, the greatest response of serum COMP to exercise was observed in an individual who regularly participated in high-impact physical activity.

Another limitation of serum COMP as a biomarker is that it is currently not possible to identify the origin of its release (D'Souza et al. 2009). It is known that COMP is also released from the synovium, meniscus, ligament and tendons (Di Cesare et al. 1994; Di Cesare et al. 2000). Therefore, it is likely that changes in serum COMP may also reflect release from these other structures. In large joints such as the knee, changes in cartilage turnover involve a large cartilage mass and therefore the contribution to the circulation of fragments from these joints is greater and more easily detectable than if only smaller joints were involved in exercise (Fex et al. 1997). The fact that only lower body exercise was performed by participants in both of the current studies, worked to isolate the effects of exercising the large, weight-bearing joints but may also offer a reason for the lack of significant increases in serum COMP.

In terms of the lack of clinically significant synovial inflammation observed in the current studies, it is assumed this was due to the low levels of disease activity observed. Recent research also suggests that a greater knee joint angle for ultrasound scanning than that used in the current study may have allowed the capture of maximal levels of synovial inflammation (Zayat et al. 2012). However, this study is the first to quantitatively assess the effects of exercise on synovial inflammation of the knee in a group of patients with RA and provides useful methodological information for future researchers. Encouragingly, serum CRP and pain showed minimal changes both acutely and over a continued period of exercise training.

7.4 Applications, conclusions and future directions

In addition to enhancing the knowledge and understanding of the areas surrounding exercise and joint health in RA, the studies described in this thesis act as stimulus for further important investigations.

Firstly, given the important finding that patients perceive uncertainty within the health profession regarding exercise and joint health, an in-depth study of the perceptions of health professionals involved in the care of people with RA forms an essential follow-up investigation. This investigation has since been conducted and the findings are described in abstract format in the Appendix 4 and 5 (Halls et al. 2012a; Halls et al. 2012b). It may be that health professionals require further education about exercise for this population (including patient perceptions), in order to promote a firm and consistent message to patients. Furthermore, considering the availability of a factorially valid questionnaire to assess patient perceptions about exercise (Chapter 4), it may be important to explore these issues in a more typical cohort of RA patients (i.e. those who are not members of a support and information providing charity), in subgroups of patients with active or inactive RA and other ethnicities. Furthermore, exploring the best method of approaching, educating and encouraging the RA population in terms of maintaining a lifestyle that involves exercise is also essential. It may be that exercise needs to be ‘sold’ as having significance akin to medical treatment (i.e. a prescription for exercise).

Secondly, our studies examining the effects of acute exercise and continued exercise training offer preliminary evidence that absolute serum COMP in RA is not significantly affected by aerobic or resistance exercise. However, because the participants involved in these studies had low disease activity and, due to the fluctuating nature of RA, it would also be of value to determine the effects of exercise in patients with higher disease activity. Further research including patients with active disease is also required to examine the usefulness of ultrasonography in assessing synovitis of the knee joint in response to exercise. Additional studies could also explore the potentially differential responses in other joints and in patients with early and established RA.

Thirdly, this thesis provides further information for future researchers regarding the outcome measures used. With reference to serum COMP and its usefulness as a biomarker, it is evident that further investigation is required to confirm the precise role of COMP and whether elevated levels indicate increased breakdown, synthesis or modification in clearance.

Alternative cartilage biomarkers are now available, however knowledge about the effects of exercise on these markers are either unknown or appear be insensitive to any potential changes in cartilage metabolism as a result of exercise. One example is cross-linked C-telopeptide (CTX-II) which is a degradation product of type II collagen (the basis of articular cartilage). CTX-II has been suggested to predict joint damage progression in RA (Landewé et al. 2004). In the recent study by Helmark and colleagues (2012), the urinary CTX-II levels of eleven OA patients remained unchanged immediately following thirty minutes of one-legged knee-extension exercise. When investigating the effects of exercise training in OA, the study by Petersen et al. (2010) also showed no significant changes in urinary CTX-II levels following twelve weeks of leg strength training. This marker can only be assessed in the urine. However, an immunoassay has been developed for assessment of type II collagen degradation in the serum, named C2C. This marker is also elevated in RA (Poole et al. 2004). However, to the author’s knowledge, the effects of acute exercise and exercise training on these markers has not been investigated. Another possible marker is human cartilage glycoprotein-39 (YKL-40), which is secreted by chondrocytes and synovial fibroblasts and is also thought to reflect cartilage destruction (Syversen et al. 2009). Physical exercise for twenty-five minutes has shown to have no effect on serum YKL-40 in healthy individuals when measured at one and three hours post-exercise (Johansen et al. 2008). Of further relevance to joint health, the effect of exercise on the lubricin expression in RA is currently unknown (see Chapter 1 for more detail), and may offer an exciting direction for future research.

In terms of the use of US to quantitatively assess synovial inflammation of the knee joint in RA, this method had many advantages in terms of its specificity for localised inflammation and non-invasive nature. However, in order to fully examine the effects of acute exercise and exercise training on this measure, a future study would need to confirm the presence of knee synovitis prior to inclusion.

Finally, the current NICE guidelines for the management of RA in adults recommend that further research should take place with regards to the best methods of delivery, the optimal mode and level of activity, and methods of maximising long-term concordance (National Collaborating Centre for Chronic Conditions 2009). This study offers additional details of an exercise programme with exercise intensities that are both safe and beneficial for people with RA. However, further research to examine the specific frequency, intensity and type of exercise necessary to offset the increased risk of cardiovascular disease, cachexia and osteoporosis in RA would also be of great advantage for this patient population.

Clearly, this thesis promotes exercise as a beneficial adjunct to the medical treatment of RA. Taken together, the findings of this thesis offer further understanding of the issues faced by patients in relation to exercise and joint health, alongside providing enhanced information as to specific, positive physiological effects of exercise on joint health in RA. The overall conclusions provide further support for the promotion of exercise as a safe and beneficial form of treatment, whilst encouraging health professionals to acknowledge and address the potentially negative patient perceptions that may exist. In summary, it is anticipated that these findings will impact upon the overall advocacy of exercise for patients with RA, improving perceptions, physical activity levels, the success of treatment and ultimately, quality of life. Furthermore, this thesis provides additional information relevant for the development of further research in this important area.

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Appendix 1. Involvement in techniques and methods

Ethical approval for all studies was managed by **R-J Law**, with assistance from A. Breslin, J. Thom and P. Maddison.

Study 1a)

Participant identification, recruitment and consent (**R-J Law**, A. Breslin and M. Williams)

Focus group interview guide development (**R-J Law**, E. Oliver, D. Markland, A. Breslin, J. Thom, P. Maddison)

Focus group moderation (**R-J Law**, with assistant moderator E. Oliver)

Transcription of focus group discussions (R-J Law)

Qualitative analysis of data and development of thematic analysis model (**R-J Law**, L. Mawn, E. Oliver, J. Thom, with expert advice from J. Noyes)

Study 1b)

Questionnaire item development and design (**R-J Law**, D. Markland, L. Mawn, J. Thom, P. Maddison, members of the rheumatology multidisciplinary team and outpatients of the rheumatology department)

Questionnaire distribution (A. Bosworth and L. Love of the National Rheumatoid Arthritis Society)

Questionnaire data analysis (**R-J Law** and D. Markland)

Study 2 and 3

Study design (**R-J Law**, J. Thom and P. Maddison)

Participant identification, recruitment and consent (**R-J Law**, A. Breslin and Y. Ahmad)

Exercise and assessment sessions (**R-J Law**, with assistance from Z. Saynor/J. Gabbitas)

Venepuncture (**R-J Law** and Z. Saynor/J. Gabbitas)

COMP ELISA (**R-J Law** and M. Fortes); CRP analysis (pathology department at Ysbyty Gwynedd).

Ultrasound image capture (**R-J Law**, with expert advice from A. Kraus)

Design of software to assess CF (L. Kuncheva).

Ultrasound image analysis (**R-J Law** and Z. Saynor/J. Gabbitas)

Statistical analysis of data (**R-J Law**, with expert advice from the North Wales Organisation for Randomised Trials in Health (NWORTH).

Appendix 2. Focus group interview guide

Ysgol Gwyddorau Chwaraeon, Iechyd ac Ymarfer
Prifysgol Bangor

Adeilad y George
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Focus group interview guide

Good morning and welcome

Thank you for taking the time to join our discussion regarding how you perceive exercise to affect the health of your joints. My name is Becki Law and I am a PhD student here in the School of Sport, Health and Exercise Sciences, Bangor University. Assisting me is Emily Oliver, who is another PhD student here.

As you will have read in the information sheet I gave to you, the aim today is to discuss the current perceptions of people with rheumatoid arthritis regarding exercise. It is anticipated that the information from this and other groups will help us to develop a questionnaire which will then be distributed nationally. In the long-term, it is hoped that this information will enhance the standard of care provided by rheumatology health professionals, making it more patient-centred.

I am here today to guide a discussion about your views relating to exercise and your joints, so feel free to outline your questions and concerns. However I am not in a position to answer your questions about rheumatoid arthritis and exercise at this stage. If you do have any queries or worries after the session, Nurse Specialist Anne Breslin is available to have a chat with at Ysbty Gwynedd. Her contact details are on the information sheet I gave to you.

There are no right or wrong answers, we are interested in everybody’s views and it really is important that you are as honest as possible.

We are recording the session so we don’t miss any of your comments. No names will be included in any reports and your comments are confidential. I would also like to ask that people within this discussion also maintain this confidentiality. When we have all the information we need and have developed the questionnaire, I can send you this alongside the overall results of the study.

We have name tents front of us here this morning, this will help all of us to remember names. I am here to guide the discussion and I have a set of pre-prepared questions. However, please do not feel you have to respond to me all the time. Feel free to have a conversation with each other about the questions. If somebody is talking a lot, I may ask you to give someone else a chance. If you aren’t saying much, I may call on you to tell us some more.

I have put a few guidelines up on the flipchart:

- ✓ You should speak freely
- ✓ Your opinions are important

- ✓ There are no right or wrong answers, we are interested in both positive and negative comments
- ✓ Don't worry about building a consensus
- ✓ Don't worry about being on the right track
- ✓ Please don't talk at the same time, allow others to speak

Feel free to get up and get more refreshments whenever you like. Let's begin.
[5 minutes]
1. OPENING

Tell us your name and for how long you have been living with RA?
[5 minutes]

2. INTRODUCTORY/TRANSITION

When you hear the term 'exercise' and 'physical activity', what comes to mind?

Prompts: Any differences between the two terms?

Could you tell us a little bit about the exercise/physical activity you are involved in your general day-to-day life.

Prompts: On a good day, on a bad day?

[10 minutes]

3. KEY QUESTIONS

The process below will be used for the following 3 questions:

i. silent idea generation – blank sheet provided [5 minutes x 3 = 15 minutes]
ii. discussion to share ideas [10 minutes x 3 = 30 minutes]

a) How do you feel exercise affects your joints?
Prompts: What advantages/disadvantages do you feel exercise has for your joints?
Do you feel different types of exercise have different effects?

b) What affects your exercise behaviour?
Prompts: How do your thoughts about exercise affect your exercise behaviour?
How do your thoughts about your joints affect your exercise behaviour?
Significant others?

BREAK? [15 mins]

c) How has rheumatoid arthritis affected your exercise behaviour?
Prompts: How did you feel about exercise before you had RA?
How did you feel when you were first diagnosed?
How do you feel now?
How do you see the future in terms of exercise and your RA?

Additional sections:

Previous researchers (Hendry *et al.*, 2006) have found that the onset of symptoms related to arthritis can cause people to change their exercise behaviour.

- ❖ Can you place yourself into any of these categories?

[FLIPCHART]

Type	**Characteristic**
Long-term sedentary	Have never exercised.
Long-term active	Have continued to exercise.
Retired from exercise	Used to exercise but have stopped because of their symptoms.
Converted to exercise	Have recently started to exercise.

- ❖ Do you feel there should be any additional categories?

(10 minutes)

What do you think about the following quote? (10 minutes)
[FLIPCHART]
'Many people are afraid to exercise because they believe that it will cause further damage to their joints' (ARC Keep Moving leaflet).

4. ENDING QUESTIONS

Of everything we have discussed during the session, do you have any final thoughts on exercise and your joints?

Is there anything you would like to add/anything we have missed? (10 minutes)

5. ASSISTANT MODERATOR SUMMARY

Is this an adequate summary?
Has anything been missed/misinterpreted? (10 minutes)

TOTAL TIME: 1 hour 45 minutes

Closing

I would like to take this opportunity to once again thank you for your participation in the focus group today. Your help towards developing our questionnaire and furthering the knowledge regarding patient views is much appreciated. If you would like a copy of the questionnaire and results of the study, please ensure you have provided your contact details on the consent form.

Feel free to help yourself to more refreshments and continue to chat, I will be around for a little while longer.

Appendix 3. Additional extracts of patient perceptions

Health professionals showing a lack of exercise knowledge

FG3,P12: '...you start asking questions like 'why, what's in it for me, if I don't do it, is it going to do me harm, if I exercise and I get pain is that doing me harm? And I went round all the departments asking if I exercise and I get pain is it doing me harm and the answer is they don't know, and they don't actually say that but they don't know.'

When introduced to the quote 'Many people are afraid to exercise because they believe that it will cause further damage to their joints';

FG2,P8: '…I think it's a symptom of misinformation and no information. That's why people believe that. They are not educated on day one to believe that things are possible with the right help…'

Not knowing what exercise should be done

FG1,P3: 'Do you think you have to do different exercises for muscle to joints?'
P4: 'Do you know, I haven't got a clue. I don't know, I just find that doing exercise makes my muscles hurt and possibly more.'

FG1,P3: 'If you do it fast it does raise your heart rate. And how much do you need to raise your heart rate, you don't know how much. Do you raise your heart rate until you can't breathe?'
P2: '220 minus you age, that's your maximum then 80% of that, 4 fifths, you can work it out. So 220 minus your age and you shouldn't go anywhere near that, you should exercise at say three quarters of that, certainly not more than 80%.'
P2: 'A steady rate.'
P3: 'Would fast walking do that?'
P2: 'It would, you could feel it.'
P3: 'Would you have to run?'
P1: 'If you're breathless.'
P4: 'You're doing over.'
P1: 'If you're out of breath, you're doing it. You can tell.'
P4: 'I didn't actually realise there was a formula for it.'

FG3,P12: 'But I would love to have some measurement that shows me that its doing me some good.'
P13: 'The other thing I find that if I start hurting, is it best to stop, for it not to get any worse or if I do carry on even for 5, 10 minutes, the knock on effect in an hour is that I'm going to be so much worse and have to go and lie down. So I guess it's sometimes a case of possibly knowing when to stop and finding a balance.'

FG4,P17: 'I think again, it's just the type of exercise that you do. Obviously not something too strenuous, but sometimes you need reassurance as well before you do something. You think well, is that good for me or is that bad for me?'

FG4,P15: 'Only if you do too much I think.'
P18: 'Or if you do the wrong thing as well, I think you could easily do the wrong thing.'

Not wanting to exercise as joints hurt

FG1,P4: 'I agree. And sometimes it's more pain than gain.'

FG2,P9: 'When it hurts to move, you're not going to exercise are you because just a simple movement, I know you are not going to exercise in the middle of the night but if you cant turn over in bed and you cant lift a blanket, if you feel the equivalent of that in the day, you are not going to contemplate exercise are you.'
P8: 'No.'
P10: 'That's right.'

FG2,P7: 'I used to do aerobics which I couldn't do afterwards. As you said, repetitive movements. So I stopped that because it was too painful, the impact and different things. So I couldn't do that.'

FG3,P14: '...Two years in the gym of once a week as you say, which did no good but again, I don't know if it did do any good, it probably strengthened me, but it didn't help with the pain.'

FG4,P18: 'I've not just done the thing that hurts, I've done the other things. It's like a weird thing where you've got to do like press-ups against the wall. That used to leave everything burning, that was a horrible thing to have to do.'

Worry about causing harm to joints

FG1,P3: 'What is the point of exercising to the degree where you damage yourself?'
P6: 'I think it's a possibility.'
P3: 'I do think about that, I do wonder, I'm not totally convinced that it won't even though I'm told it won't.'
Moderator (BL): 'Is it something that you worry about?'
P3: 'Not worry, but I don't believe that it doesn't and it won't. It could, I don't have any proof that it isn't going to damage my joints.'

FG2,P8: 'I've also got disadvantage of impact, running hill walking, anything that's sudden, shaking the hands, just don't do because it causes inflammation and then pain. One follows on from the other.'

Following introduction to the quote 'Many people are afraid to exercise because they believe that it will cause further damage to their joints';

FG3,P11: 'That's a very important issue and that's what as you say you've been talking about. Yeah you are afraid to do certain things but anything extreme you draw back from because you think oh what's going to happen. Yeah that's how I see it anyway.'

I have to exercise because it is helpful

FG1,P5: 'Yes, yes it made a hell of a difference, otherwise I wouldn't be able to do anything, I couldn't have worked without exercise.'

FG1,P2: 'No I've got a very short thing I say, if you don't use it you'll loose it. If people sit around all day, they'll end up sitting around all day.

FG2,P10: ‘Keep what you’ve got.’
P8: ‘Keep it all going.’
P10: ‘Yeah.’

FG3,P12: ‘When you say that improved you, mean that improved the pain?’
P14: ‘It improved the pain and it improved the mobility.’
P12: ‘And then you could take more exercise.’
P14: ‘And then I could take more, and then I’m walking up the mountain.’

FG4,P17: ‘I find it does ease your joints doesn’t it as well, makes them feel a bit less stiff.’

FG4,P18: ‘Well you have to do it otherwise you go all crunchy.’

Appendix 4. Exercise and joint health questionnaire

Questionnaire: Issues relating to joint health and exercise in Rheumatoid Arthritis

You are being invited to take part in a research study. Before you decide whether or not to be involved, it is important for you to understand why the research is being done and what it will involve.

This questionnaire is part of our study 'Current perceptions of the effects of exercise on joint health in rheumatoid arthritis'. To investigate these perceptions we have developed a questionnaire using information from focus group discussions involving people with rheumatoid arthritis (RA). By administering this questionnaire, we are able to collect information from a large number of people, which will allow us to assess these perceptions on a wider scale. The overall objective of this research is to further the knowledge of health professionals so that they can provide an enhanced patient-centred approach to exercise prescription.

Your taking part in this study is entirely voluntary. It is up to you to decide whether or not to take part and you are free to withdraw at any time and without giving a reason. However, we ask that you only complete this questionnaire if you have been diagnosed with RA by your rheumatologist. If you decide to participate, it will involve completing the following online questionnaire which consists of 4 sections, including questions relating to:

1) you and your RA
2) your current physical activity levels
3) your perceptions relating to exercise and joint health
4) your confidence to perform exercise

It should take approximately 30 minutes of your time.

The results will then be analysed by researchers and written up as part of a PhD thesis. We also anticipate that the findings will be published in rheumatology journals and presented at prestigious international rheumatology conferences. In addition, we will encourage those involved with looking after RA patients to consider the implications of our results (i.e. to adopt a particular approach towards RA patients and exercise). This may well be of benefit to yourself and others in the future.

To confirm that you have read and understood the information above, have had the opportunity to ask questions and that you wish to participate, please click *'Continue'* at the bottom right of the screen.

Thank you for taking the time to read this, please feel free to contact Becki Law using the contact details below should you have any queries.

Becki Law
School of Sport, Health and Exercise Sciences
Bangor University, Telephone: (01248) 388286, Email: r.law@bangor.ac.uk

Data protection statement:
When you respond to a survey you will be asked to provide certain information which may identify you. When this is the case the researcher or research group responsible for the survey will also be able to access this information in order to process the survey data.

However, no identifiable information will be included in the actual research findings. Any identifiable information requested will be kept securely in accordance with the requirements of the Data Protection Act 1998 and Bangor University's Data Protection Policy. Where data is collected anonymously no personal data is asked for or retained and survey data will be held securely.

You and your RA

1. Have you been diagnosed with Rheumatoid Arthritis?
☐ YES ☐ NO

If you have answered 'NO', please do not complete any further questions and go to:

https://survey.psychology.bangor.ac.uk/no_ra_joint_health_exercise

If you have answered 'YES', please continue and answer the following questions.

2. I am…
☐ Male ☐ Female

3. Please indicate your age ☐

4. Please indicate your date of birth (e.g. DD-MM-YYYY) ☐

5. When were you diagnosed with RA? ☐
(if you are unsure of the exact date, please provide an approximation)

6. Do you have any other medical conditions?
☐ YES ☐ NO

Please indicate any other diagnosed medical conditions:
(select all that apply)

☐ Cardiovascular disease
☐ Osteoporosis
☐ Osteoarthritis
☐ Hypertension
☐ High cholesterol
☐ Diabetes

☐ Asthma or any other lung disease

☐ Anxiety/depression

☐ Other *(please specify)*

7. Is there anything else you wish to tell us about 'you and your RA?' *(Optional)*

Your physical activity levels

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The following questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your housework, to get from place to place, and in your spare time for recreation, exercise or sport.

8. Think about all the vigorous activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.

During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics or fast bicycling? ☐

If you answered 'No vigorous physical activities' please skip to Question 10.

9. For this question, please ensure you complete both columns to indicate the TOTAL amount of time you performed vigorous physical activity on one of those days.

	How many hours?	How many minutes?
a. How much time (in hours and minutes did you usually spend doing vigorous physical activities on one of those days.	☐	☐

Please leave blank if you don't know/not sure

10. Think about all the moderate activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis?

(Please do not include walking) ☐

If you answered 'No moderate physical activities', please skip to Question 12.

11. For this question, please ensure you complete both columns to indicate the TOTAL amount of time you performed moderate physical activity on one of those days.

	How many hours?	How many minutes?
a. How much time (in hours and minutes) did you usually spend doing moderate physical activities on one of those days?		

Please leave blank if you don't know/not sure

12. Think about the time you spent walking in the past 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

During the last 7 days, on how many days did you walk?

If you answered 'No walking', please skip to Question 14

13. For this question, please ensure you complete both columns to indicate the TOTAL amount of time you spent walking on one of those days.

	How many hours?	How many minutes?
a. How much time (in hours and minutes) did you usually spend walking on one of those days?		

Please leave blank if you don't know/not sure

14. This last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

For this question, please ensure you complete both columns to indicate the TOTAL amount of time you spent sitting.

	How many hours?	How many minutes?
a. How much time (in hours and minutes) did you usually spend sitting on a week day?		

Please leave blank if you don't know/not sure

15. Is there anything else you wish to tell us about 'your physical activities levels'? *(Optional)*

Your thoughts about exercise and your joint health

16. Please indicate (✓) your level of agreement in relation to each of the statements below:

	1 = Strongly disagree **2 = Disagree** **3 = Neither agree nor disagree** **4 = Agree** **5 = Strongly agree**				
	1	**2**	**3**	**4**	**5**
a. I would not consider exercising if my joints are hurting					
b. I believe that I need to use my joints to keep them working					
c. If my joints are painful, doing exercise is out of the question.					
d. Health professionals are not specific about exactly how to exercise					
e. I don't want to exercise because I know my joints will hurt the day afterwards					
f. I don't want to exercise when I am in pain					
g. I wonder if I am causing damage if it hurts when I exercise					
h. Pain affects if I want to exercise or not					
i. I worry about exercise causing harm to my joints					
j. If my joints hurt I don't want to exercise					
k. I don't know which joints I should exercise					
l. I feel people with RA should be careful of impact-based exercise (e.g. jogging)					
m. I am concerned that exercise will add to damage that has already been caused by my disease					
n. I feel exercise is helpful for my joint health					
o. Pain doesn't affect whether I exercise or not					
p. I worry that my joint function will get worse if I don't exercise					
q. Joint damage is in the back of my mind when I exercise					
r. Exercise helps to keep my joints moving					
s. I don't want to exercise because my joints hurt immediately afterwards					
t. I worry that exercise will cause more damage to my joints					
u. I feel my joints need exercise					
v. I find that if I keep mobile through exercising, I have less pain in my joints					

w. Health professionals seen to know what to tell me about exercise					
x. Health professionals don't seem to know what to tell me about exercise					
y. I am unsure when to exercise					
z. I feel people with RA should be careful of repetitive movements					
aa. Pain affects whether I exercise or not					
ab. I worry that I will end up disabled if I don't exercise					
ac. I am unsure how much exercise I should do					
ad. I don't think health professionals know what exercise to recommend					
ae. I don't think health professionals know what to tell me about how exercise affects my joints					
af. I don't know what the best sort of exercise is					
ag. Health professionals have not been able to answer my questions about exercise					
ah. I am unsure if it is a good idea to exercise when my joints are 'bad'					
ai. I wonder if I should exercise at all					
aj. I am unsure if it is OK to exercise when my joints are 'good'					
ak. I feel exercise makes my joints stronger					
al. Pain doesn't affect whether I want to exercise or not					
am. I feel exercise relieves joint pain					

17. Is there anything else you wish to tell us about 'your thoughts about exercise and your joint health? *(Optional)*

18. Please indicate how confident you are right now that you could exercise for 20 MINUTES, 3 TIMES PER WEEK in each of the situations below:

	0 = Not at all confident 10 = Very confident										
	0	1	2	3	4	5	6	7	8	9	10
a. If the weather was bothering you											
b. If you were bored by the programme or activity											
c. If you felt pain when exercising											
d. If you had to exercise alone											
e. If you did not enjoy it											
f. If you were to busy with other activities											
g. If you were tired											
h. If you felt stressed											
i. If you felt depressed											

19. Is there anything else you wish to tell us about ‘your confidence to perform exercise’? *(Optional)*

20. Please use the space below to make any comments as to how you feel this survey could be improved. *(Optional)*

21. If you wish to receive details of the findings of this study upon completion, please provide your email address below. *(Optional)*

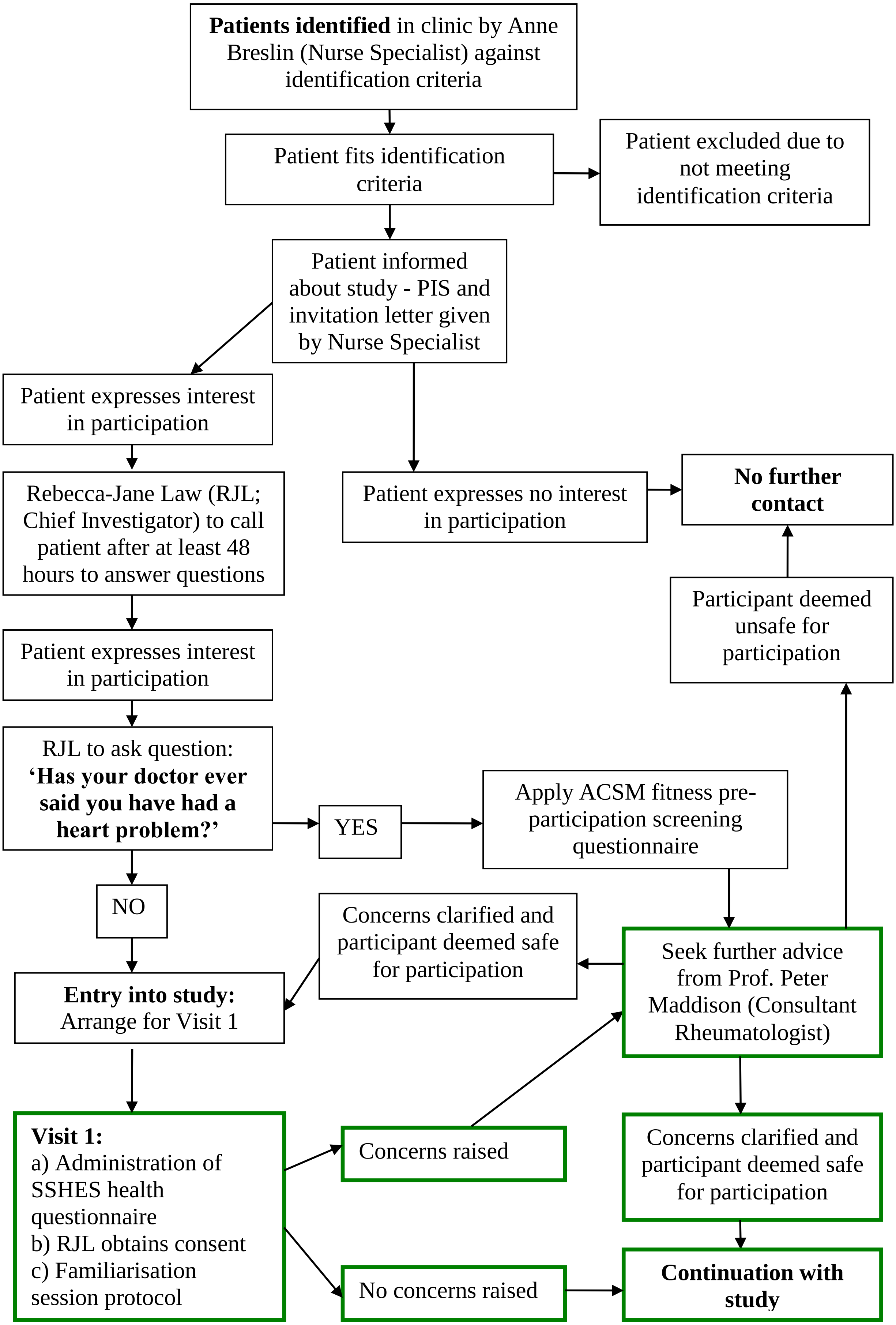
This survey is now complete…

We would like to take this opportunity to sincerely thank you for completing this survey, you participation is greatly appreciated.

If you have provided your email address, you will be sent information summarising the overall research findings.

Kind regards.

Appendix 5. Patient recruitment and inclusion flow diagram



Note: Boxes in bold indicate pathway following Visit 1.

Appendix 6. Knee involvement questionnaire

Name: …………………………………………………….

Question	LEFT		RIGHT	
	Yes	No	Yes	No
Have you ever experienced **pain** in your knee joint(s)?				
Are you currently experiencing **pain** in your knee joint(s)?				
Have you experienced **pain** in your knee joint(s) in the last week?				
Have you ever experienced **swelling** of your knee joint(s)?				
Are you currently experiencing **swelling** of your knee joint(s)?				
Have you experienced **swelling** of your knee joint(s) in the last week?				
Have you ever experienced your knee joint(s) **feeling warm**?				
Are you currently experiencing your knee joint(s) **feeling warm?**				
Have you experienced your knee joint(s) **feeling warm** in the last week?				
Have you ever experienced **tenderness** of your knee joint(s)?				
Are you currently experiencing **tenderness** of your knee joint(s)?				
Have you experienced **tenderness** of your knee joint(s) in the last week?				

When did you first begin experiencing symptoms relating to your knee joint (s)?

………………………………..

Please use the space below to describe any other symptoms you have experienced in your knee joints:

………………………………………………………………………………………

………………………………………………………………………………………

………………………………………………………………………………………

………………………………………………………………………………………

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Appendix 6. Health professionals' perceptions of the effects of exercise on joint health in rheumatoid arthritis (RA) patients I; a questionnaire study

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Background
Exercise is an important factor in the treatment and management of RA. Our previous research has indicated that RA patients perceive health professionals (HPs) lack certainty and clarity regarding exercise in RA management and its relationship to joint damage (Law et al., 2010). Therefore we set out to investigate perceptions of HPs regarding the effects of exercise on joint health in RA patients using a questionnaire.

Methods
The online questionnaire included a brief introduction followed by 3 questionnaire sections. Section 1 incorporated 8 questions about demographics. Section 2 included a measure of participant's current physical activity levels (IPAQ). Section 3 focused upon participants' thoughts about exercise and RA patient joint health and included 40 multiple choice questions each relating to 1 of 5 themes. Questionnaires were distributed via professional networks and websites, and sent to rheumatology HPs identified from the BSR handbook. Confirmatory factor analysis (CFA) was conducted and total percentage responses for each theme were calculated. One-way ANOVAs were conducted on each of the variables of practitioner category, IPAQ classification, age, gender and location of practice.

Results
137 rheumatology HPs (95 females, 42 males; 76 rheumatologists, 24 nurses, 18 physiotherapists, 10 occupational therapists, 9 other HPs; age: 27-65 years) completed the questionnaires. CFA removed 4 items with low factor loadings and the 2 themes relating to HPs exercise knowledge were combined resulting in the following 4 themes: 1. HPs showing a lack of exercise knowledge; 2. Worry about causing harm to joints; 3. Not wanting to recommend exercise as patients are in pain; 4. Having to recommend exercise because it is helpful. The final 36-item model showed acceptable fit (SB χ^2 =863.04, *df* =588, *p*<0.000, RMSEA =0.06, CFI =0.93, SRMR =0.94). Large percentages of respondents strongly disagreed or disagreed with Themes 1, 2 and 3 with responses of 78%, 86% and 90%, respectively. Only 63% of respondents strongly agreed or agreed with Theme 4. These responses varied depending on practitioner category only.

Conclusions
HPs believed they did not lack exercise knowledge, they mostly did not worry about exercise causing harm to joints and did not avoid recommending exercises to patients due to concerns about pain. This is in direct contrast to our findings about the perceptions of RA patients (Law et al., 2010). However, only two-thirds of HPs felt that exercise was helpful for RA patients. Further research in the form of focus groups is required to investigate the differences between RA HPs and patients and the underlying reasons for this in greater detail. Variation in the responses from the different practitioner categories also need to be investigated further so that education and resources can be provided where appropriate.

Appendix 7. Health professionals' perceptions of the effects of exercise on joint health in rheumatoid arthritis (RA) patients II; a follow-up focus group study

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Background

Exercise is important in the management of RA. Our research has indicated that RA patients perceive health professionals (HPs) lack certainty and clarity about exercise in RA management and its relationship to joint damage (Law et al., 2010). Furthermore, our questionnaire study of rheumatology HPs suggested that perceptions of HPs and patients are not concurrent (Halls et al., 2011). We therefore set out to explore HPs' perceptions regarding the effects of exercise on joint health in RA patients' further using focus groups.

Methods

Four moderated focus groups were conducted with multi-disciplinary teams (MDTs) of rheumatology HPs (n = 24; 19 females, 5 males; 5 rheumatologists, 8 nurses, 5 physiotherapists, 4 occupational therapists, 2 other HPs; age: 30 - 60 years; duration working with RA: 3 - 32 years) from across the North-West United Kingdom. The main questions addressed included: (i) What are your thoughts about exercise and joint health in your RA patients? (ii) What do you tell your RA patients about exercise? and (iii) Why do the perceptions of patients and HPs differ? Focus group recordings were transcribed verbatim and transcripts were analysed using framework analysis. Discussion with three associated researchers consolidated validation at different stages of analysis.

Results

Focus group analysis identified twenty one constructs and five themes as factors relating to HPs' perceptions of exercise and joint health in their RA patients. The five emergent themes were: 'Exercise is beneficial', 'Concerns about damage to joints', 'Patients have barriers to exercise', 'HP knowledge differs' and 'Patients may think service delivery is vague'.

Conclusions

HPs articulated acute awareness of the benefits and importance of exercise for RA patients. Concerns regarding exercise, particularly weight-bearing exercise were expressed explicitly, as well as indirectly, which could lead to confusion for RA patients. The perceived lack of a solid evidence base was highlighted as a reason for these concerns. Moreover, the complexity of RA treatment and management was felt to negatively impact the likelihood of exercise prescription. When managing RA, HPs provide individualised care and promote self-management. This may explain why patients perceive their MDTs lack certainty and clarity about exercise in RA management and its relationship to joint damage. Further research is warranted to address the uncertainties of HPs regarding exercise and joint health.