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Development and evaluation of an exercise intervention programme to improve cardiovascular fitness and vascular responses in patients with rheumatoid arthritis

Submission date
18/12/2008

Recruitment status
No longer recruiting

Registration date
16/01/2009

Overall study status
Completed

Last Edited
30/04/2014

Condition category
Musculoskeletal Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims:
Heart disease is very common among patients with Rheumatoid Arthritis (RA). Also, RA influences the amount of muscle these patients have and several of them lose part of their muscle mass as the disease progresses. Despite the significant improvement in the medication and overall management of RA patients, both heart disease and muscle loss are still very common in these patients. In the general population we know that exercise is a very good way of reducing the risk for heart disease and also the best way to maintain healthy and well functioning muscles. For this reason we want to study the effects of a 6-month exercise training programme on heart disease risk and muscle mass in patients with RA.

Who can participate?
The study is open to patients with diagnosed RA that do not exercise regularly (no more than once a week for the last six months). However, patients who have had joint surgery recently (during the last 6 months), have been amputated, are receiving steroids by injection (during the last 3 months), have been diagnosed with any metabolic conditions (such as type II diabetes), or other wasting diseases (such as cancer, COPD, kidney failure etc.), or heart disease are not suitable for the present study. In total we will recruit 40 patients and divide them in two groups, one that will be exercising and one that will serve as a control (no exercise).

What does the study involve?
All patients in both groups will be assessed for a number of parameters at the beginning of the study, as well as 3 months and 6 months later. Specifically, we will measure their aerobic capacity (how much exercise can they do and how fast they can go), the activity and severity of their RA (how good or bad their disease is at the moment of the assessment), their risk for the development of heart disease (blood cholesterol, blood pressure, blood sugar), and the way their blood vessels work.
Patients in the exercise group will have to exercise three times a week. They will be following a specific programme that we will make for them, based on their individual needs (as measured

during the various tests). Each exercise session will last about 60 minutes and during this time they will perform several aerobic exercises (4-5 minutes long at relatively low speeds or resistance) and from three months onwards, we will add some resistance exercises (weights) to help them improve their muscle mass and function.
Patients in the control group will receive verbal information on the benefits of exercise, but we will not give them a specific exercise programme to follow. They will have to decide for themselves whether they want to exercise or not and what sort of exercise they want to be doing.

What are the possible benefits and risks of participating?
Possible personal benefits: Patients in the exercise group are likely to benefit directly from the study. Their fitness is very likely to improve; higher fitness levels are associated with better health overall and most significantly with low risk for heart disease. Patients in the control group are highly likely to be motivated towards a more active lifestyle, which could result in improved fitness with beneficial effects for their heart and overall health. Also, patients will be screened for risk factors for heart disease (such as your cholesterol) and if any are present, they will receive appropriate treatment.
General benefits: The information we will gather from all the people taking part will help us to understand much better some of the mechanisms that may be responsible for causing the heart and blood vessel problems of people with RA. Even more importantly, it may help us to identify ways of reducing these problems. In the future we hope we will be able to apply this knowledge to many more people with RA.
Possible risks: However helpful it may be, exercising may also carry some risks. Cases of falls, injuries, heart complications (such as heart attacks), even death, have been reported while exercising on less than 1 in 10,000 occasions - this is about 6 times less likely than having a serious road traffic accident in everyday life. During testing in the hospital laboratories (which usually test people at much higher risk for heart problems) all necessary precautions for this are routinely taken to minimise them.

Where is the study run from?
The study is run from the Clinical Research Unit of Russells Hall Hospital, Dudley Hospitals NHS Foundation Trust, in Dudley, UK and Action Heart Cardiac Rehabilitation Centre, in Dudley Hospitals NHS Foundation Trust, in Dudley, UK

When is the study starting and how long is it expected to run for?
The study started in September 2008 and finished in September 2011

Who is funding the study?
Dudley Hospitals NHS Foundation Trust R&D Directorate

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
0618

Study information

Scientific Title
Development and evaluation of an exercise intervention programme to improve cardiovascular fitness and vascular responses in patients with rheumatoid arthritis: an interventional single-blinded randomised-controlled study

Study objectives
1. After 6 months, there will be significant improvements in the intervention group compared to the advice only group in the following cardiovascular and rheumatoid arthritis (RA)-related parameters:
1.1. Cardiovascular:
1.1.1. Cardiorespiratory fitness (primary objective)
1.1.2. Cardiovascular disease (CVD) risk factors and 10 year CVD event probability
1.1.3. Endothelial function
1.2. RA-related:
1.2.1. Disease activity
1.2.2. Physical function
1.2.3. Psychological well-being
2. Following a single exercise session, endothelial function will worsen and inflammation will be increased acutely. The magnitude of these adverse acute reactions will be reduced as fitness levels improve.
3. Following the completion of the intervention, patients who participated in the exercise group will be more likely to continue exercising than those in the advice only group. At 12 months, patients in the exercise group will be more likely to have adopted a more active lifestyle.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Dudley Local Research Ethics Committee gave approval on the 19th October 2006 (ref: 06/Q2702/66)

Study design
Interventional single-blinded randomised controlled study; single-centre

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Rheumatoid arthritis

Interventions
Individualised structured exercise training. Participants will be randomly assigned to either an exercise (intervention) or a non-exercise (control) group.

Intervention:
Based on the results of an exercise stress test, an individualised exercise programme will be prescribed for each participant. All available equipment (treadmills, cycle ergometers, hand ergometers, row ergometers, etc.) will be considered for utilisation. The decision about the exact equipment that will be used will depends on the patients' preferences, and the exercise physiologist's assessment on their ability of achieving the training targets stated below. Volunteers will be asked to maintain increased intensity (indicated by heart rate corresponding to 70% maximal oxygen uptake [VO2max]) for a duration greater than 30 minutes during each exercise session. Three exercise sessions per week will be prescribed. Two sessions will be conducted in a supervised environment and one in a non-supervised setting. During the former, heart rate and rate of perceived exertion will be monitored, whereas for the latter session, heart rate monitors (Polar S610i, Polar Electro Oy, Kempele, Finland) will be handed to patients. Heart rate monitoring will be used during each session to ascertain exercising at the prescribed intensity (i.e., for measuring adherence). In the case of absence, patients will be asked to replace the missed session(s).

Sessions will last about 55 minutes; 10 minutes warm-up, 30 - 40 minutes main session, and 5 - 10 minutes cooling down. Mode, intensity, duration and frequency of exercise will be reconsidered every month, in line with the principles of exercise periodisation. Supervision for the first three sessions will be on a one-to-one basis. In the case that a volunteer requires more assistance, full supervision will continue until they are properly familiarised with the equipment and feel

confident to exercise alone. Thereafter, patients will be exercising in a semi-supervised setting. Researchers will be available to assist if patients desire so, or in case of emergency. For the purposes of this research study, the duration of the exercise training for each patient will be 6 months. After that period participants in both groups will be offered the opportunity to continue on an exercise programme.

Control:
At the time of their baseline assessment, participants in the control group will receive advice (orally and in the form of widely available leaflets by the British Heart Foundation and the Arthritis Research Campaign) on the benefits of exercise; however, no other help or support, as far as exercise is concerned, will be provided.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Cardiorespiratory fitness (CRF) has been selected as the primary end-point because of its importance as a surrogate predictor of cardiovascular events and because it is the only relevant parameter that has been previously assessed pre- and post-exercise interventions in RA patients. In studies with RA patients, or healthy participants exhibiting similar baseline CRF values to RA patients, CRF increased by approximately 20% (standard deviation [SD] = 6.0) following exercise interventions similar to the one we are proposing. We, therefore, included in our power calculation (nQuery Advisor v 6.0, Statistical Solutions, MA, USA) 20% as the expected change (i.e., from 25 ml/kg/min to 30 ml/kg/min) with SD = 6.0. The desirable number of participants for our study to produce significant results ($p = 0.05$) with a power of greater than 0.80, is 19 in each group. To allow for participant attrition, estimated at 25% for the six-month exercise intervention, we will recruit 25 RA patients in each of the groups. Data from participants with less than 75% compliance will be excluded from the analyses.

Assessment of CRF:
Exercise tolerance testing (ETT) will be adopted. Depending on each patient's functional limitations, a treadmill, a cycle ergometer or an arm ergometer will be utilised. CRF will be determined using a calibrated breath-by-breath system (Metalyzer 3B, CORTEX Biophysik GmbH, Leipzig, Germany) allowing continuous measurement of oxygen uptake (VO2), and lung ventilation. During ETT, blood pressure, heart rate and cardiac function using a 12 lead electrocardiogram (ECG), will also be monitored. Relevant data will be automatically stored every 30 seconds. Heart rate corresponding to 70% VO2max will be used to determine optimum exercise intensity.

Treadmills and cycles are the most commonly used devices for clinical exercise testing. The treadmill provides a more common form of exercise (i.e., walking) and patients are more likely to attain a higher oxygen consumption compared to cycling. However, cycling is a non weight-bearing activity, and, as such, might be more comfortable for patients with RA. Arm ergometer is an alternative method for exercise testing for patients that can not perform leg exercise, however, because lesser muscle groups are used, oxygen consumption is 20 - 30% lower compared to treadmill exercise. For non physically-active individuals, protocols with smaller increments between stages, such as ramp protocols, are more suitable. For treadmill testing, our protocol will start at a speed of 2.0 mph for 1 minute. Speed will increase thereafter by 0.5 mph

every 1 minute until 4.0 mph. Thereafter, inclination of the treadmill will increase every 30 seconds by 1%. Testing is terminated when the participant reaches voluntary exhaustion. Cycle protocol will start with the patient cycling at 60 - 80 revolutions per minute with initial resistance of 25 Watts (W), as in the modified Astrand-Rhyming protocol. The resistance will be increased by 15 W every minute, until patient reaches voluntary exhaustion. Similarly, in arm ergometry, a constant cranking rate of 50 - 60 revolutions per minute will be kept. Initial resistance of 10 W will be increased by 5 W every minute.

Timepoints of assessments: CRF will be assessed at three different timepoints:
1. Baseline; before the participants are allocated to a group (intervention versus control)
2. Three months after the intervention (or control condition) has began
3. Six months after the intervention (or control condition) has began

Secondary outcome measures

Cardiovascular outcomes:
1. Individual risk factors for the development of cardiovascular disease (CVD) and 10-year CVD event probability: individual CVD risk factors (i.e. hypertension, hyperlipidaemia, hyperinsulinaemia) will be assessed. On the basis of these, the 10-year CVD event probability will be calculated using the latest version of the Joint British Societies' risk calculator.
2. In vivo endothelial function: endothelial function in the macrovasculature will be assessed using flow mediated dilation when the patient is in a fasted state. The brachial artery will be monitored by Doppler Ultrasound (ACUSON Antares ultrasound system with a VF 10-5 Transducer and SieClear, BW SieScape Imaging software, Siemens PLC, Munich, Germany) before, during, and after flow mediated dilation as well as administration of a single dose of nitro-glycerine (Glyceryl Trinitrate oral spray).
3. Endothelial function in the microvasculature will be assessed using Laser Doppler dual wavelength imaging (Moor LDI-2 SIM, Moor Instruments Ltd, Devon, UK). Acetylcholine, an endothelium-dependent vasodilator, and sodium nitroprusside, and endothelium-independent vasodilator, will be separately administered by iontophoresis. Blood flow will be assessed continuously 1 minute before iontophoresis and 2 minutes after iontophoresis using laser Doppler imaging.

Rheumatoid arthritis outcomes:
1. Disease activity: using the disease activity score 28 (DAS28). This is a composite assessment consisting of the patient's self-assessment of overall health during the last week on a visual analogue scale, a 28-joint count and the current erythrocyte segmentation rate (ESR). Serological assessments of disease activity are described below.
2. Physical function: using the Anglicised version of the 40-item Stanford Health Assessment Questionnaire (HAQ). Participants will rate their ability (over the past week) to carry out 20 activities within eight aspects of daily living (dressing/grooming, rising, eating, walking, hygiene, reach grip and errands/tasks) on a four-point scale from 'without any difficulty' to 'unable to do'. For each aspect patients also respond whether they receive assistance from people or use specific devices. The HAQ is internally consistent (a = 0.89) and has excellent pre- to post-physician visit temporal stability (r = 0.99). Physiotherapists' ratings have excellent agreement with RA patients' ratings.
3. Psychological well-being: anxiety and depression will be assessed using the Hospital Anxiety and Depression Scale (HADS). The HADS consists of 14 items (7 each for anxiety and depression) rated on various four-point scoring systems. Comparisons with psychiatric ratings have shown both subscales to be discriminantly valid. The subscales are also internally consistent (a = 0.85 and 0.78, respectively) and convergently valid among RA patients. Quality of Life will be assessed using the EuroQol (EQ-05). The EQ-05 questions self-assessed problems across five items on mobility, self-care, usual activities, pain, discomfort and depression/anxiety. Each item

has three levels of severity: 'no problems', 'some problems' and 'severe problems'.
4. Serological assessments of risk factors, inflammatory mediators and endothelial function: full blood count, serum biochemistry, ESR, high sensitivity C-reactive protein [hsCRP], blood glucose, lipids, von Willebrand Factor (vWF) and thrombotic variables will be assessed using routine laboratory procedures in our laboratory. Internal quality controls on all analysers are carried out daily, and external quality controls fortnightly, utilising the Welsh External Quality Assurance Screen (WEQAS). Insulin will be measured using a solid phase two-site chemiluminescence immunometric assay using an Immunolite 2000 Analyser (Diagnostic Products Corporation, Los Angeles, CA, USA). Insulin sensitivity will be assessed by calculating the Homeostasis Model Assessment - Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI). Relevant cytokines and adhesion molecules (vascular panel, including: interleukin 1a [IL1a], interleukin 1b [IL1b], IL2, IL4, IL6, IL8, IL10, tumour necrotising factor alpha [TNFa], interferon-gamma, vascular endothelial growth factor, endothelial growth factor, macrophage chemo-attractant protein-1, inter-cellular adhesion molecule-1, vascular cell adhesion molecule-1, E-Selectin, P-Selectin, L-Selectin) will be measured using a fully automated RANDOX biochip array system (Randox Laboratories Ltd, Co. Antrim, UK) in our research laboratory. This performs simultaneous quantitative detection of multiple analyses from a single sample.

Timepoints of assessments:
1. Baseline; before the participants are allocated to a group (intervention versus control)
2. Three months after the intervention (or control condition) has began
3. Six months after the intervention (or control condition) has began

Overall study start date
01/09/2008

Completion date
31/12/2009

Eligibility

Key inclusion criteria
1. Patients with rheumatoid arthritis (both genders, aged greater than 18 years of age)
2. Informed consent
3. Sedentary lifestyle (no participation in structured exercise for the preceding 6 months)
4. Stable disease (no changes in disease-modifying anti-rheumatic drugs [DMARDs] - including biologics - or oral steroids and no parenteral steroid administration in the last 3 months)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants

Key exclusion criteria
1. Recent joint surgery (in the preceding 6 months)
2. Amputation
3. Recent DMARD or oral steroid changes (in the preceding 3 months)
4. Parenteral steroid administration (in the preceding 3 months)
5. Co-morbidity incompatible with exercise as per American College of Sports Medicine guidelines

Date of first enrolment
01/09/2008

Date of final enrolment
31/12/2009

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Russells Hall Hospital
Dudley
United Kingdom
DY12HQ

Sponsor information

Organisation
Dudley Group of Hospitals NHS Foundation Trust (UK)

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Sponsor type
Hospital/treatment centre

Website
http://www.dgoh.nhs.uk/_public/_servportals/rheumatology/default.asp

ROR
https://ror.org/014hmqv77

Funder(s)

Funder type
Government

Funder Name
Dudley Group of Hospitals NHS Foundation Trust (UK):

Funder Name
R&D Directorate Cardiovascular Programme Grant

Funder Name
Department of Rheumatology - Arthritis Research Campaign have provided an infrastructure support grant (ref: 17682)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/11/2013		Yes	No

Results article	results	01/04/2014	Yes	No