

## **Långvarig fysisk aktivitet vid reumatoid artrit - självskattad hälsa, funktionshinder, sjukdomsaktivitet och bakomliggande mekanismer till muskelsvaghet och inflammation.**

### ***Populärvetenskaplig beskrivning***

Reumatoid artrit (RA) karaktäriseras av inflammation, generellt såväl som lokalt i leder och muskler. Smärta och trötthet är de viktigaste symptomen och muskelsvaghet och nedsatt kondition är vanlig. Patienter med RA löper också en ökad risk att dö i förtid, framför allt beroende på ökad förekomst av hjärt-/kärlsjuklighet. Riktlinjer för Hälsosam Fysisk Aktivitet (HFA) anger att varje vuxen person bör antingen konditionsträna tre gånger per vecka eller vara fysiskt aktiv på måttligt ansträngande nivå fem gånger i veckan samt därutöver styrketräna två gånger per vecka för att minska risken för sjuklighet och död i förtid. Med tanke på de problem reumatiker har, är HFA extra viktigt vid RA trots att sjukdomssymptomen i sig kan utgöra hinder för fysisk aktivitet. Det finns ytterst få vetenskapliga långtidsstudier av HFA vid RA och det behövs mer kunskap om mekanismer för hur HFA påverkar muskelsvaghet och inflammation vid RA.

Det övergripande syftet med hela det projekt, i vilket det sökta doktorandprojektet ingår, är att undersöka effekter hos patienter med RA av ett tvåårigt program för HFA beträffande självskattad hälsa, funktionshinder, sjukdomsaktivitet och händelser som tyder på hjärt-/kärlsjuklighet samt bakomliggande mekanismer till smärta, muskelsvaghet och inflammation i relation till HFA.

De specifika målen med det sökta doktorandprojektet är:

- Att jämföra karaktäristika mellan de patienter med RA som väljer att delta i ett program för implementering av HFA jämfört med dem som avstår deltagande.
- Att kartlägga allmän hälsoupplevelse, fysisk aktivitet, tilltro till förmåga att utöva fysisk aktivitet, aktivitetsbegränsning, smärta, trötthet, muskelfunktion, kondition och sjukdomsaktivitet samt deras inbördes relationer hos patienter med RA som väljer att delta i ett program för implementering av HFA.
- Att analysera ettårsresultaten av det tvååriga implementeringsprogrammet för HFA med avseende på allmän hälsoupplevelse, fysisk aktivitet, tilltro till förmåga att utöva fysisk aktivitet, aktivitetsbegränsning, smärta, trötthet, muskelfunktion, kondition och sjukdomsaktivitet.
- Att undersöka inverkan av HFA på lokal och systemisk inflammation.

450 patienter rekryteras via det svenska RA-registret från 6-8 anslutna reumatologkliniker och bedöms med tillförlitliga blodprover, kliniska tester, funktionstester, frågeformulär och skattningsskalor. Lika många ålders- och könsmatchade kontroller från andra än de ingående klinikerna kommer att slumpas ut via RA-registret för att utgöra en jämförelsegrupp till dem som deltar i HFA. De kommer att följas med sedvanliga läkarkontroller och vara fria att utöva fysisk aktivitet men inte erbjudas något särskilt program för detta. Extra blodprover samt muskelprover tas från ett mindre antal (n=20) deltagare och kommer att analyseras beträffande underliggande molekylära mekanismer. Samtliga deltagare i HFA kommer under ett år att delta i minst två 45-minuters träningspass per vecka för kondition och styrka på allmänna gym under ledning av sjukgymnast samt därutöver vara fysiskt aktiva på en måttligt ansträngande nivå minst fem gånger per vecka. De kommer då också att delta i stödgrupper för att öka sin kunskap om och tilltron till sin förmåga att bli och förbli fysiskt aktiva. Under påföljande år kommer deltagarna att få ett ökat individuellt ansvar för sin HFA, men fortfarande ha tillgång till gym och stöd av sjukgymnast. Under detta andra år kommer deltagande i stödgrupperna att vara frivilligt och organiseras av deltagarna själva. HFA-dagböcker kommer under hela projekttiden att föras av deltagarna själva. Sjukgymnaster kommer att utbildas i att planera och övervaka träning på ett standardiserat sätt, att coacha den fysiska aktiviteten i vardagen och att leda stödgrupper enligt särskilt koncept.

Trots förbättrad läkemedelsbehandling löper patienter med RA stor risk att drabbas av funktionshinder och förtida död. HFA kan vara ett sätt att minska dessa risker. Stigande sjukvårdskostnader gör att nya rehabiliteringsformer i miljöer utanför sjukvårdens ram måste prövas och det är viktigt att veta vad som karaktäriserar dem som kan och vill delta i nya typer av program. Det planerade projektet kommer att utvärdera ett försök i den andan. Den innehåller också delar som kommer att hjälpa oss att bättre förstå hur HFA bör läggas upp för att på bästa sätt påverka inflammation och muskelfunktion beroende på hur de underliggande faktorerna ser ut.

## **LONG-TERM PHYSICAL ACTIVITY IN RHEUMATOID ARTHRITIS**

### **- perceived health, disability, disease activity and underlying mechanisms related to muscle weakness and inflammation**

#### **Scientific aim**

The overall aim of this project, in which the doctoral thesis plan applied for is included, is to investigate the implementation of a two-year Health-Enhancing Physical Activity programme, including strength training (HEPA), among patients with rheumatoid arthritis (RA) and its outcome as regards general health perception, physical activity, exercise self-efficacy, pain, fatigue, muscle function and cardiovascular events as well as relations between HEPA and mechanisms underlying pain, low muscle function, reduced muscle mass, systemic and local inflammation.

#### **Specific goals of the present doctoral thesis**

- To compare characteristics (demographics, perceived health, pain, fatigue, activity limitation, disease activity) among patients with RA volunteering to participate in a HEPA implementation programme and patients declining participation.
- To survey perceived health, physical activity, exercise self-efficacy, activity limitation, pain, fatigue, muscle function, aerobic capacity, and disease activity as well as their relationships among patients with RA, who volunteer to participate in a HEPA implementation programme.
- To investigate the one-year outcome of a two-year HEPA implementation programme on perceived health, physical activity, exercise self-efficacy, activity limitation, pain, fatigue, muscle function, aerobic capacity, and disease activity.
- To investigate the influence of HEPA on local and systemic inflammation.

#### **Learning outcomes**

- Perform a multicenter study including the use of outcome measures to assess health perception, disability, disease activity and cardiovascular events.
- Retrieve data from the Swedish RA registry and match it with data collected by local collaborators.
- Understand molecular mechanisms that can be involved in systemic inflammation and local muscle inflammation.
- Analyse data, including multivariate and longitudinal statistics.
- Present data orally and in writing.
- Understand and apply principles of research ethics.

#### **Literature survey**

Systemic and local inflammation characterizes RA and the main symptoms are pain and fatigue. Pain is mainly of nociceptive origin and is generally localized to joints and muscles, but may also be generalized as secondary fibromyalgia. Fatigue is a perception arising from the complex interplay of biologic processes, psychosocial phenomena, and behavioural manifestations (Aaronson et al 1999). To some, fatigue is the subjective state of weariness related to reduced motivation, prolonged mental activity, or boredom. To others, fatigue may be related to excessive energy consumption, decreased oxygen carrying capacity (i.e. anemia), depleted hormones or neurotransmitters, or the diminished ability of muscle cells to contract (Poteliakhoff 1981).

Reduced body functions, particularly aerobic work capacity and muscle function is reportedly common in RA (Eurenius et al 2005). Involvement of skeletal muscle may be present both as myalgia, muscle weakness and loss of muscle mass, which could all affect performance in daily activities and quality of life (Sokka et al. 2008). Early treatment with DMARDs and the introduction of biologic agents have dramatically improved inflammation control during the past decade. However, far from all patients with RA benefit from them (Alonzo-Ruiz et al 2008). We have found that a majority of patients with early RA display poor muscle function (Eurenius et al 2005), which, together with pain, were important predictors of future health perception (Eurenius et al 2007). Whether this is still the case one decade after the introduction of the biologic agents is not known. Muscle strength training is affecting, not only muscle function, but also seems to reduce signs of inflammation and pain in

patients with RA (Stenström and Minor 2003). The underlying molecular mechanisms for muscle loss and muscle weakness in RA remain undefined, but a number of hypotheses related to effect of systemic inflammation on muscle contractility, protein turnover and metabolism may offer possible explanations (Lundberg & Nader 2008). Furthermore, in a long term perspective patients with RA have an increased risk of premature death due to cardiovascular disease compared to the general population. This risk seems to be related to the burden of inflammation and possibly also to the physical inactivity associated with it. Many of these clinical problems or co-morbidities can be prevented or attenuated by HEPA in healthy individuals (Fischer et al 2007). Public health guidelines on HEPA include twice-weekly muscle strength training in addition to either daily moderate-intensity physical activity or aerobic exercise three times a week (Nelson et al 2007).

Considering the above, there seems to be a case for HEPA among patients with RA in order to maintain functioning and long-term health. We have previously found that a majority of patients with RA do not accumulate enough HEPA in order to maintain good physical and mental health and thus reduce their risk of co morbidity (Eurenius et al 2005). Further, the outcome of HEPA guideline implementation among patients with RA has only been studied in two randomized controlled studies with somewhat contradictory results (van den Berg et al 2006, Brodin et al 2008). An internet-based physical activity intervention among patients with RA including individually tailored supervision, exercise equipment, and group contacts was more effective with respect to the proportion of patients who reported HEPA that meet the demands of public health recommendations than an internet-based program without these additional elements. However, subsequent health-related improvements were not found (van den Berg et al 2006). We found that a one-year coaching programme for HEPA improved perceived health and muscle function among patients with RA beyond the health benefits already obtained by medication (Brodin et al 2008). However, the effects were rather small, the mechanisms behind the findings were unclear as we were not able to measure a change of HEPA behaviour, and the benefits were not retained over a one-year follow-up period (unpublished data). Furthermore, guidelines on HEPA have recently been updated (Nelson et al 2007) to include strength training, which calls for other settings and strategies than the previous guidelines (Pate et al 1995) that were implemented in our previous study (Brodin et al 2008). Thus, HEPA can no longer be managed entirely in an everyday environment, but requires access to gym facilities. Better methods to measure physical activity and better developed behaviour medicine strategies to implement, not only the adoption of HEPA behaviour, but also its maintenance over time will probably also result in better long-term outcome (Swärdh et al 2008). No studies have yet evaluated the effect of physical activity interventions on cardiovascular events among patients with RA and altogether more studies, particularly with long-term perspectives, are needed in this area. Our hypothesis is that a two-year programme to implement HEPA will improve perceived health, increase physical activity, improve exercise self-efficacy, reduce pain and fatigue, increase muscle strength and aerobic capacity, and have beneficial long-term effects on cardiovascular events. Another important issue is to investigate the generalizability of results obtained in studies applying HEPA programmes by comparing characteristics of participants to those of non-participants. This has been investigated in detail only in one previous study, which was carried out in the Netherlands (deJong et al 2004).

Joint inflammation is the main characteristic of RA and systemic inflammation with increased serum levels of CRP present in most cases. Muscle involvement, in particular loss of muscle mass, is reported in up to 2/3 of patients with RA and may be profound, so called rheumatoid cachexia (Roubenoff et al 1992). This reflects a catabolic state of muscle with protein degradation and may be induced by the systemic inflammation mediated by pro-inflammatory cytokines, e.g. TNF- $\alpha$  and interleukin-1. Another possible explanation for involvement of muscles in patients with RA could be systemic activation of micro-vessels including those in the muscles. This is supported by a previous study, in which we found that a subset of patients with RA and a more severe disease, i.e. extra-articular RA, had signs of endothelial cell activation in micro-vessels in muscle tissue with e.g. expression of the proinflammatory cytokine interleukin-1 $\beta$  (Turesson et al 2001). It is also possible that pro-inflammatory molecules, e.g. cytokines, may exhibit a direct effect on muscle fibres and their contractile abilities, as supported by results from *in vitro* studies, in which TNF had a direct effect on Ca<sup>2+</sup> release in muscle fibres, making the muscles more easily fatigued (Reid et al 2002). Further,

mice with collagen induced arthritis (CIA), a common model for RA, developed decreased muscle force per cross sectional area in the soleus muscle, a postural muscle containing oxidative fibres (unpublished data). This was accompanied by changed levels of muscle fibre proteins indicating that arthritis caused oxidative stress in muscles and that this caused an impaired myofibrillar function leading to muscle weakness (unpublished data). One hypothesis to be tested in the present study is that joint inflammation has a negative effect on muscle function, expressed as both muscle loss and direct effects on muscle fibres, e.g. on contractility proteins, and that this could be reverted by physical activity. The effect on contractility proteins is supported by the experimental study mentioned above, but whether this is relevant in humans with RA needs to be tested. Thus, an additional hypothesis to be tested is that physical activity will decrease systemic inflammation and expression of inflammatory molecules in muscle tissue.

## **Materials and methods related to the doctoral study plan presently applied for**

### *Design*

This project will be performed within the context of the population-based Swedish RA registry, presently including 29 000 cases, which enhances data collection and provides excellent opportunities for long-term follow-up and identification of matched controls. The study includes multiple designs and consists of (i) a comparison of characteristics between patients accepting to participate in a HEPA implementation programme and those who decline, (ii) a cross sectional survey of health perception, disability, and disease activity and their inverse relationships among patients that volunteer to participate in the HEPA implementation programme, (iii) a prospective longitudinal cohort study with matched controls to investigate the clinical outcome of an upgraded version of a previously evaluated HEPA program (Brodin et al 2008). Each cohort participant will be compared to matched controls as described below and effect sizes on a group level will be compared to those from our previous study (Brodin et al 2008). We believe that a cohort study with matched controls from separate centres will give more valid answers to our questions than a randomized control design because long-term compliance will be better when a supportive environment is created in a participating centre and contamination effects between intervention and control groups as well as effects of repeated measurements of controls are avoided. Studies on underlying mechanisms to expected HEPA benefits on (iv) systemic inflammation and local muscle inflammation will include a subsample of the cohort.

### *Participants*

A random sample of 450 patients with RA according to the American College of Rheumatology (ACR) criteria (Arnett et al 1988) will be recruited from 6-8 rheumatology clinics via the Swedish RA registry. The participants need to be independent in daily living, speak and understand Swedish without problems, not initially obtain the levels required for HEPA, and should not have other major diseases that prevent them from HEPA. With perceived health rated on a visual analogue scale as the **primary endpoint** of the study, a power analysis indicated that 91 patients per group would confer conclusive results ( $\alpha=0.2$ ,  $\beta=0.05$ ). To allow for full-powered gender-based analyses and considering that only 20-25 % of patients with RA are men, we thus plan to include 450 participants in the cohort.

Controls (n=450) matched for age and gender, who fulfil the above inclusion criteria, will be recruited in a similar way and be compared in retrospect as to demographic data, general health perception, activity limitation, pain, fatigue, disease activity and medication retrieved from the RA registry.

A subsample of 20 cohort participants will be selected for the studies on mechanisms related to HEPA effects on inflammation and muscle weakness. Considering the small sample size and in order to get as homogenous a group as possible only females, which constitute 75-80% of the RA population, will be included in this subsample. Age and gender matched biopsies from healthy individuals will be available within the research group.

### *Intervention - HEPA programme*

The aim of the two-year programme is to implement the present guidelines on HEPA (Nelson et al 2007). During the first study year each participant will take part in at least two 45-minute exercise sessions, including strength training and aerobic exercise, and encouraged to perform additional

moderate-intensity physical activity at least 30 minutes on most of the other days of the week. A 45-minute exercise session in a public gym will consist of warm-up, circuit training and cool-down with stretching. The circuit will consist of 20 stations; of which ten provides muscle strength training of eight major muscle groups and ten provide aerobic exercises. Each station will take 30 s and 3x10 repetitions of each muscle strengthening task will be reached after three circuits. Participants will be trained and encouraged to put as much effort into the strength training that it corresponds to an estimated 50-80% of 1 RM and check after each circuit that their heart rate corresponds to 60-85% of their age predicted maximum. A physiotherapist will be present to instruct and assist in adjusting the programme to each participant's needs and preferences. During the second year, the participants' will take responsibility for their own HEPA, but still have optional access to training facilities and physiotherapy advice. Diaries will be kept by all participants to record HEPA.

During the first year participants will also take part in regular support group meetings, which will be designed to increase their knowledge and strengthen their self-efficacy for adopting and maintaining HEPA. Their thoughts about their body function and their possibilities for HEPA will be discussed, goals for their HEPA formulated and documented in a structured manner based on the principles of graded activity training, perceived obstacles to successful implementation discussed and problem-solving strategies to help overcome present and future barriers discussed and documented. Oral and written feedback on progress and on homework assignments between group meetings will be given. Goals will be systematically evaluated and adjusted whenever required and variation as to types of HEPA will be encouraged. During the second year, group meetings will be optional and the participants will have to take charge of them.

Physical therapists at the participating centres will be trained to plan and supervise the organized training sessions, to be in charge of the support groups and to coach the participants' everyday HEPA according to study-specific manuals.

### ***Data collection***

All cohort participants will be assessed with valid and reliable methods developed for people with arthritis or for generic use as follows:

*For descriptive purposes (at baseline, after 12 and 24 months by independent assessors):*

- Demographic data on age, height, weight and Body Mass Index, body composition, length of education and marital status from the RA registry completed with interviews
- Data on medication from the RA registry

*To test clinical outcome (at baseline, after 12 and 24 months by independent assessors):*

- General health perception, pain and fatigue with VAS ratings and/or questionnaires depending on the results of ongoing studies on the measurement properties of various fatigue scales
- Physical activity with the International Physical Activity Questionnaire or the Stanford Brief Activity Survey depending on the results of ongoing studies on their measurement properties in an RA population
- Exercise self-efficacy with the Exercise Self-efficacy Scale
- Activity limitation with the Stanford Health Assessment Questionnaire, Disability Index from the RA registry
- Grip strength electronically with the Grippit
- Lower limb function with the Timed Stands Test
- Aerobic capacity with a submaximal bicycle ergometer test
- Disease activity with the disease activity score (DAS) 28 based on erythrocyte sedimentation rate, the number of swollen and tender joints and self-rated general health perception from the RA registry

*To test outcome on local and systemic inflammation at baseline and after 12 months subsample participants will be assessed as follows:*

- Muscle biopsies from m. vastus lateralis will be taken and analysed for:

- gene expression by micro-array analysis using Affymetrix and with real-time PCR (TaqMan analyse) focusing on genes involved in inflammation and in cellular metabolism
- protein expression by proteomics by immunohistochemistry (IH) or western blot for molecules that come up in the gene expression analysis and in addition: TNF, interleukin (IL)-1, activation markers of endothelial cells and reactive oxygen species/reactive nitrogen species. Quantification of IH will be performed by computerized image analysis
- Blood tests from the whole cohort will be investigated for:
  - C-reactive protein and erythrocyte sedimentation rate

### ***Data analyses***

Non-parametric statistics will mainly be used to analyze cohort data due to the ordinal data produced in most assessments. Logistic regression models will be used to analyze relationships between sets of data. Unpaired and paired tests as well as ANOVAs will be used to analyze within- and between-group differences and changes. Data will be analyzed both for those, who complete the study and for those originally included to the HEPA group or the matched comparison group (intention to treat). Effect sizes will be estimated to allow for comparisons between the results of our previous study (Brodin et al 2008) and the presently planned HEPA programme. In addition multiple regression models and/or cluster analysis will be performed to control that (i) many of the assessments chosen for the study may represent both confounders and outcome, (ii) patients from both groups may or may not adopt/maintain HEPA. Additional data analyses in the subsample are described above.

### ***Ethical considerations***

Ethics approval will be obtained from regional research ethics committees. All participants will be asked for participation by a letter containing information about the study. Those willing to participate will be given the opportunity for additional information during a subsequent telephone call where inclusion and exclusion criteria will also be checked. Written consent, including the permission to extract data from the Swedish RA registry, will be obtained. Muscle biopsies taken by the semi-open biopsy technique using a conchotome is the routine procedure for diagnostic biopsies. The technique is well established and has been used in patients with muscle diseases and in healthy individuals in the research units where patients for the subsample will be recruited. A specific written consent will be obtained from this subsample and we will adhere to bio bank law for handling of biopsies.

### **Studies/planned publications of the present doctoral project**

- I.** Differences in characteristics between patients with RA accepting to participate in a HEPA implementation programme and those who decline.
- II.** Health perception, disability, and disease activity and their relationships among patients with RA participating in a HEPA implementation programme.
- III.** One-year outcome of a two-year HEPA implementation programme on health perception, disability, disease activity, and cardiovascular events.
- IV.** To investigate the influence of HEPA on local and systemic inflammation.

### **Context of the doctoral training**

The doctoral project applied for is part of a larger project involving several senior scientists, post docs and fellow doctoral students with different professional backgrounds. Represented among senior scientists are a physiotherapist (Christina Opava), a rheumatologist (Ingrid Lundberg), a psychologist (professor Irene Jensen, KI), a pain physiologist (Eva Kosek, KI) and an exercise physiologist (Christer Malm, Umeå). With the learning outcomes specified at the first page of this application, we consider the planned doctoral project to be distinct from other planned sub projects and, together with courses and other activities within the National post graduate school of health care sciences, as an well suited part of doctoral training. The future doctoral student will further have excellent opportunities to collaborate with fellow students and post docs that take care of other sub projects related to pain mechanisms, cardiovascular risk, and more detailed mechanisms related to local muscle inflammation.

The supervisors all have previous experience of performing clinical physical activity studies among healthy females and/or those with rheumatic disease. Professors Opava and Lundberg both have research groups, in which the future PhD student will participate regularly to learn and benefit from the expertise of their co-workers. Dr. Fridén is a registered post-doc in professor Opava's group and professors Lundberg and Opava have collaborated for a long time, including common PhD student supervision. Both professors Lundberg and Opava have experience of supervision within the context of the National post graduate school of health care sciences and are familiar with the requirements as to participation of both doctoral student and supervisors in its scheduled activities. Main supervisor Christina Opava spends some 75% of her work time on research and will have time for another doctoral student in addition to the only one that is presently active. Despite other duties, the co-supervisors count on having enough time for their respective 20% and 10% supervision. Christina Opava has previously, with grants from the Scientific Council and the Swedish Rheumatism Association among others, performed a similar multi-centre study as the one presently applied for resulting in three PhD theses. Grants for the planned project are also presently/will be applied for from the same sources. Financial resources are also available for this project from Combine.

On a national level, the planned project is part of one work package within the Combine consortium, a national network that has received SEK 60 millions during five years to perform translational research on chronic inflammation ([www.combinesweden.se](http://www.combinesweden.se)). Further, the planned project is a multi-centre study with at least 6 participating clinics in different parts of Sweden and collaboration with the Swedish RA registry and a gym company with sites all over Sweden. Possibilities for international change are present within the European network Autocure, coordinated from the department of rheumatology, Karolinska university hospital.

There is a workplace in the 'doctoral student room' at the Division of physiotherapy, Department of NVS, where the student will have immediate access to supervisors Opava and Fridén. Facilities for molecular studies are available at the Centre of Molecular Medicine, where professor Lundberg provides support through her research group. Data collection will start during the fall of 2010 with analyzes starting one year later. This will leave plenty of room for extensive participation in courses within the National post graduate school of health care sciences during 2010-11. Data from studies I and II are planned to be analyzed during 2011 and 2012 while those from studies III and IV will be analyzed during 2013-2014.

### **Significance of the planned PhD project**

Patients with RA suffer increased risk of disability, co-morbidity and premature death. HEPA could be one important measure to reduce this risk. Perceived health was chosen as the main outcome of our study as there are good reasons to assume that HEPA will improve emotional and physical well-being among patients with RA. On a societal level, rising health care costs call for the development and evaluation of new forms of rehabilitation, including HEPA, in new settings. The planned study will evaluate such a measure in a real-life environment and also identify the characteristics of those willing and able to benefit from them. It also includes parts that will help us to better understand relations between HEPA and mechanisms underlying inflammation and poor muscle function and thus improve the right choice of target for HEPA and to tailor it to each individual.

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