Research protocol

High-intensity exercise based on self-management with digital coaching in patients with spondyloarthritis: a randomized controlled trial

NCT ID not yet assigned

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Project summary

Background: For people diagnosed with a spondyloarthritis (SpA) e.g. ankylosing spondylitis or undifferentiated spondyloarthritis, physical activity and exercise are important components in the self-management. Exercise, in addition to physical and mental symptoms related to the disease can easily feel overwhelming to exercise, and low adherence may result. By studying the effects of high-intensity interval training (HIIT) in comparison with training as usual on physiological, inflammatory, and self-reported disease parameters in patients with SpA, we intend to further investigate the short-term and longitudinal training effects, and refine the knowledge to tailor, coach, and stimulate to self-performed HIIT.

Objective: The purpose of this study is to investigate the short- (12 weeks) and long-term (12 months) effects of high- intensity interval training (HIIT) on physiological, inflammatory, and self-reported health parameters in patients with SpA. The aim is also to study the adherence to physical activity and exercise recommendations.

Design: A randomized controlled trial (RCT) design.

Participants: One hundred adults with a confirmed axial SpA from rheumatology clinics in southern Sweden will be recruited and randomized into two groups, the intervention group and the control group.

Intervention: Three high-intensity training sessions per week for three months, of which two interval sessions, with coaching both from a clinical physiotherapist and digital devices (watch and app) followed by nine months with sporadic coaching. The control group will go on with exercise as usual.

Primary outcome: Self-reported disease activity, inflammatory biomarkers (acute phase proteins).

Secondary outcomes: Physical fitness (aerobic capacity (VO_2max), blood pressure, grep strength), body composition and self-reported physical function, health status, well-being, pain, fatigue, adherence to physical activity and exercise recommendations, and confidence in one's own ability to manage pain, symptoms and high-intensity exercise, and additional serum biomarkers (listed in the Methodology section).

Project description:

Rationale

An increasing number of scientific reports are stating a role for exercise as medicine in different diseases, e.g., inflammatory musculoskeletal disorders. The importance of physical activity, exercise and rehabilitation as part of disease- and self-management have also been emphasized by both WHO and by the public health authority in Sweden (1, 2).

SpA is an umbrella term for a group of inflammatory diseases with a prevalence that varies between 0.2% - 1.6% globally (3). SpA can be divided into two forms; axial SpA characterized by inflammation in the spine and pelvic joints, and in peripheral SpA characterized by inflammation in peripheral joints, entesites and dactylites (4-6). The group axial SpA includes both patients with X-ray changes in the sacroiliac joints or spine (radiographic axial SpA) but also patients where these X-ray-verified changes have not yet been detected (non-radiographic axial SpA) (6). Recommended treatment consists of a combination of pharmacological and non-pharmacological interventions (7, 8). The non-pharmacological treatment includes physiotherapy with disease counselling and specific training (7, 9-11). There is an increased risk of comorbidity such as cardiovascular disease, obesity, depression and osteoporosis in patients with axSpA compared to the healthy population (12). The risk of several of the comorbidities that occur is considered to be reduced through an increased degree of physical activity (13-15). The increased cardiovascular risk is considered multifactorial but is partly explained by the chronic systemic inflammation and a low level of physical activity in the individuals living with the disease (11, 16).

The effects of HIIT with respect to inflammatory biomarkers are poorly studied in individuals with rheumatic diseases such as rheumatoid arthritis and SpA. Also, proteins secreted by muscle cells during physical activity, myokines, and their suggested effect to counteract the inflammatory process, need to be further studied (17-19). HIIT is believed to be able to affect both the disease outcome and the increased risk of cardiovascular morbidity (15), but more studies are needed to obtain sufficient evidence along with new biomarkers recently found to affect inflammation that can be implemented in a general maintenance of the individuals' systemic inflammatory status (20).

In the general population, the greatest positive effect is seen on cardiovascular disease and its risk factors during cardio training at a higher intensity (21-23). Studies show that individuals with SpA can exercise at a higher intensity level without exacerbating disease activity and that HIIT can reduce inflammation and reduce the cardiovascular risk factors for individuals with SpA (13, 15, 19, 24).

Despite the overwhelming evidence that exercise will help in the disease management, individuals with the disease still find it difficult to make exercise a sustainable routine in their lives. Previous studies have shown that when a coach-led intervention ends, it is common with a large drop-out rate and that compliance decreases (19, 22). Our habits are deeply rooted, and a determined effort is needed to succeed with a behavior change, such as getting started with regular training or changing the type of a previously accustomed training routine (e.g., regarding intensity). Changing a behavior should therefore take place gradually and over a long period of time to have the best conditions to become permanent. With the help of repetition of the current training approach, partly under the guidance of a coach, partly through self-performed training sessions, the foundation is laid for the new training behavior to be maintained over time (25, 26). A person-centered approach with the opportunity to choose activity, and be able to vary activity and training sessions have proven to be important factors that increase compliance with HIIT (27). High-intensity training in self-selected activity performed as self-performed training outside the health care has been shown to work well for patients with cardiovascular disease (28, 29). At follow-up one year after the end of the training intervention, there was no significant difference in compliance between those who participated in coach-led high-intensity training and those who self-performed the training (30). Active coaching, registration of heart rate level during training and estimation of perceived effort have all been shown to be important to achieve the right training intensity (21, 22). Telehealth, in which health coaching is provided via telecommunications and other virtual communication devises outside traditional health care, is considered an important part of modern care, among other things, to encourage an increased degree of physical activity, exercise and behavior change. However, the effects of this type of intervention are still incompletely studied (31, 32). HIIT is thought to affect both the disease activity and factors associated with the risk of cardiovascular disease that exists in individuals with SpA, but the research is still insufficient.

The effects of HIIT on physical, inflammatory, and self-reported health parameters needs

to be further studied. The knowledge is also scarce on how to tailor the high-intensity training as a part of the self-management for individuals with SpA, with the aim to maintain regular exercise routines and sustainable health over time.

Objectives

The purpose of this study is to investigate the short- (12 weeks) and long-term (12 months) effects of self-performed high-intensity interval training (HIIT) on physiological, inflammatory, and self-reported health parameters in patients with SpA. The aim is also to study the adherence to the physical activity and exercise recommendations.

The primary hypothesis in this study is that there will be significant differences between the intervention group and the control group concerning self-reported disease activity, in some of the inflammatory biomarkers (acute phase proteins and pro-inflammatory cytokines), and in adherence to vigorous intensity performed physical activity and exercise both in the short and long term.

The secondary hypothesis is that there will be significant differences between patients in the intervention group and the control group regarding physiological health (aerobic capacity, blood pressure, grip strength, body composition), and self-reported health (physical function, health status, well-being, pain, fatigue, inactivity), and in the confidence in one's own ability to manage pain, symptoms, and high-intensity training, after both three- and twelve-months follow-ups.

Methodology

Study design and procedure

This study will be performed as a randomized controlled trial (RCT) study and will be adhering to the CONSORT statement (33). The results of a three-months intervention with high-intensity training, followed by nine months with customized coaching where the intervention group will be motivated and strengthened in their own confidence to continue training regularly at high-intensity levels, will be compared to the control group for primary- and secondary outcomes. The control group will continue with exercise as usual based on the treatment recommendations for patients with SpA (7, 10, 11).

Participants will be randomly assigned into intervention- and control groups. Simple randomization will be used for equal group allocation at three different rheumatology clinics in southern Sweden. The patients will choose a sealed note in which one of the words "intervention" or "control" is written, when the baseline assessment is completed at the first measurement occasion. The patients in the intervention group will then perform an estimation of her/his maximal heart rate (MHR) on a stationary bicycle and effort on the ratings of perceived exertion (RPE)-scale (34) to be confident at recognizing the level of effort at the appropriate heart rate (HR) to reach an intensity of at least 17 on RPE during the following HIIT sessions. After this initial assessment, the clinical coach will set up individual training zones (for intervals and active rest) and the focus thereafter is for the patients to continue the intervention in self-selected activities based on a standardized training setup. After 1, 2 and then again at 7 weeks, the patients will be offered follow-ups with coach-led HIIT and the individual HR zones will be readjusted if needed.

The patients in the control group will not receive any standardized exercise intervention but will be wearing a heart rate monitor watch during the year. The baseline tests include both patients in the experimental and control groups. Baseline tests will include physiological tests, body composition, blood tests, self-reported questionnaire including different health variables, collected during one visit. After 12 weeks of intervention, and after one year the same assessment will be made.

Participants

The patients will be recruited from rheumatological clinics in southern Sweden, through invitation via personal contact by the physiotherapist at the clinic.

A clinical physiotherapist at each centre will identify eligible patients form their unit and, after checking the inclusion criteria in the medical record, contact the patients to further screen for cardiovascular or other comorbidities contraindicated for high-intensity training. After showing interest in participating, they will receive oral and written information (appendix 1). An informed consent will be signed by all included patients before the data collection will start.

Inclusion Criteria:

Aged 18-65. Axial SpA (ICD10 diagnosis of M45, M46.0, M46.1, M46.8 and M46.9). The patients should meet the general recommendations for physical activity, at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or doing at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate - and vigorous-intensity activity (35).

Exclusion Criteria:

Changed TNF and anti-inflammatory medication the previous three months, established, or symptoms of, cardiovascular disease or other comorbidities that make high-intensity training inappropriate. Lastly, those who already perform sufficient high-intensity interval training on a regular basis will be excluded from this study. At the initial visit the physiotherapist will start by measuring the chest thumb electrocardiography (ECG). In the event of two repeated deviating results regarding the ECG, the patients will be referred to the health centre for further investigation before any inclusion.

Outcome Measures

Primary outcome measures: (1) Self-reported disease activity, and (2) inflammatory biomarkers (acute phase proteins).

(1) Self-reported disease activity

The disease-specific Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (36) and Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP) (8) will be used to assess self-reported disease activity. BASDAI consists of six questions on fatigue, pain, tenderness, and morning stiffness. numeric questions (range 0-10). The final score is estimated by calculating the mean. ASDAS-CRP consists of four questions on pain in neck, back, and hip, morning stiffness, well-being, and pain/stiffness in other joints in addition to blood test of CRP. The final score is estimated using a formula (37) .

(2) Inflammatory biomarkers (acute phase proteins)

A total of approximately 4 ml blood will be drawn at baseline, after 12 weeks and after one year. To study C-reactive protein (CRP), Pentraxin-related protein (PTX3), and serum amyloid A1 (in μg/ml) the enzyme-linked immunosorbent assay (ELISA) will be used.

Secondary outcomes: *Physical fitness* (aerobic capacity VO_2max, blood pressure, grip strength), *body composition* and *self-reported variables* such as physical function, health status, well-being, pain, fatigue, adherence to physical activity and exercise recommendations and confidence in one's own ability to manage pain, symptoms, and high-intensity exercise. Venous blood samples will be drawn to study *lipoproteins, cytokines, myokines, and markers for bone remodulation*.

Physical fitness

Aerobic capacity (VO_2max) will be measured according to Åstrand with a submaximal cycle ergometer test on an indoor stationary bicycle (Monark 828E, Monark Exercise AB, Vansbro, Sweden) (38). Aerobic capacity will be presented relative to body weight and expressed as the total amount of oxygen metabolized per minute per kilogram of body weight (mL/kg/min) (39). Blood pressure will be measured. with an automatic blood pressure monitor (Omron M3, Omron Healthcare Co, Mukō, Japan), and a hand dynamometer (KERN Sohn GmbH, Balingen, Germany) will measure the maximum hand grip strength (kg) as another indicator of general body strength (40).

Body composition

The hight and weight of the participants will be measured, and BMI calculated. Proportion of fat and visceral fat area (VFA) will be assessed by bioelectrical impedance analysis (Inbody 770®, Seoul, Korea) (41).

Self-reported variables

Physical function will be measured with the Bath Ankylosing Spondylitis Indices for function (BASFI) (42). The BASFI consists of ten questions on body function, activity and participation and environmental factors. The final score will be estimated by calculating the mean.

Health status will be measured with the generic questionnaire EuroQol-5 domain (EQ-5D) consisting of five questions covering mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The total score range from 0-1 (no health to full health) (43).

Well-being will be measured with the Assessment of SpondyloArthritis International Society Health Index /ASAS-HI), consisting of 17 statements (yes/no) on pain, emotional functions, sleep, sexual functions, mobility, self-care and participation (44). The total score ranges from 0-17.

Pain will be measured with a pain mannequin, with 18 predefined regions (pain regions) where participants mark their painful areas on the pain figure if they have any They will also respond to questions about pain intensity (numeric rating scale, NRS 0-10, best to worst), duration and diurnal variation of pain. (45).

Fatigue will be measured with the Fatigue Severity Scale (FSS) (46) and on a numerical rating scale from 0-10 (no fatigue-worst possible fatigue) (47). FSS consists of nine statements of the consequences of fatigue. The total score range from 9-63 (best-worst).

Adherence to physical activity and exercise recommendations will be objectively measured through the heart rate monitor watch in average minutes of moderate/vigorous level of physical activity per week. Self-reported adherence to physical activity and exercise recommendations will be collected through three validated questions including information on intensity, frequency, and duration (1).

Confidence in one's own ability to manage pain, symptoms, and high-intensity exercise will be measured with the Arthritis Self-Efficacy Scale (ASES) for pain and symptoms (48), and the Swedish Exercise Self-Efficacy Scale (S-ESES) (49). The ASES subscale for pain has five items and the subscale for symptoms has six items. The total scores range from 10-100 (low to high self-efficacy). The S-ESES consists of 10 statements where each question has four response options, from not at all safe to completely confident. The total score ranges from 10-40

Lipoproteins, cytokines, myokines, and markers for bone remodulation
Pro-inflammatory cytokines and chemokines (TNF-α, IL-6, IL17a, IL-18, IL-21, IL-23, CXCL10, in pg/ml); additional inflammation-related proteins (VEGF-A, IL-1Ra, IL-8, MIP-1a, MIP-1β in pg/ml, serum calprotectin (in µg/ml), albumin for CRP/albumin ratio in mg/ml; myokines (irisin, BDNF in ng/ml); bone and cartilage proteins (DKK-1 in pg/ml, osteocalcin, sclerostin, osteopontin in ng/ml, FGF-23 in pg/ml, BMP- 7, MMP-3 in ng/ml); liver-derived protein (FGF-21) in ng/ml); and plasma lipoproteins (ApoB and ApoA1) in g/L will be analyzed. Protein biomarkers will be measured on a Luminex MAGPIX® system (Luminex Corporation, Austin, TX) or with ELISA (Microplate reader, Molecular Devices), while

plasma samples will be sent to the hospital chemistry lab for analysis according to the current laboratory standards (lipoproteins). The samples to be analyzed with ELISA and Luminex will be stored at -80°C in a biobank at FoU Spenshult, Halmstad (R&D-Spenshult) and the analyzes will be performed in the Rydberg Laboratory at Halmstad University.

Intervention

High-intensity interval training

The patients in the intervention group will be instructed to perform two HIIT/week and one further training session at moderate or high-intensity of their own choice every week mostly on their own for 12 weeks. Structured coaching will be given by a physiotherapist with support of text messages and a HR feedback from a fitness watch (Polar Ignite, Polar Electro Oy, Kempele, Finland) that the patient will use. The approach is based on a person-centred care approach with self-selected activity that engages large muscle groups, such as cycling, Nordic walking, running, swimming, rowing, cross-training. During the first 12 weeks, coach-led sessions are offered on at least three occasions, during week 1, 2 and 7 with the aim of guiding the patients to the right intensity of training during the HIIT sessions. The intensity will be individually based on the patient's MHR and physical capacity. If necessary, additional coach-led sessions will be offered during the first 12 weeks. After the 12 initial weeks, the intervention continues for another nine months with customized coaching where the patients will be motivated and strengthen in their own confidence to continue with HIIT sessions. During this time, the participants will go on and register the training sessions with the fitness watch, and they will be contacted once a month by their coach for guidance on regular training.

The intervention begins with a coach-led interval session during week 1 consisting of 4x4 min intervals with 3 minutes active rest (at 50-70% of MHR) between each interval. The first session will be performed on a stationary bicycle. The session will start with a warm-up to a heart rate of 60-70% of MHR, afterwards the load will be increased to 85% of MHR in the interval with the intention to reach 90% at some point during each interval. Perceived exertion will be assessed with the RPE scale and the goal is to reach at least RPE 17 during the intervals (50). The session will end with a cool down at <60% MHR. The patient will be able to choose between different interval sessions, but the total time for the intervals in each session should be 15 minutes. In addition to the two HIIT session, the patient will be

instructed to perform one further high-intensity training each week at a HR of at least 75% of MHR or at RPE 14. At least one rest day should be planned in between each session.

The continuous monitoring of HR and individual coaching will be based on data available through the fitness watch. The different sessions of high-intensity training will be registered by the patients using their fitness watch and a web-based coaching platform. The coaching physiotherapist will log in as a coach and be able to follow the training sessions digitally every week. During the first four weeks, the patients will be contacted once a week by e.g., phone by coaches at the clinic. After week 4, the follow-up of each patient will be based on their own wishes, but at least once/month. Three text messages/week will be sent to the patients in the intervention group during the initial 12 weeks with a reminder to stay active.

Control group

The patients in the control group continues with their regular physical activity and exercise routines as before, i.e., they should keep following the general recommendations for physical activity and exercise (51). The control group will be instructed to use the fitness watch and log their training on the web-based coaching platform in the same way as the intervention group, during their physical activity and exercise, to enable comparisons at the end of the intervention.

Data management and analysis

Data analysis will be performed using Microsoft Excel and IBM SPSS (IBM SPSS Statistics for Windows, Version 24.0. IBM, Armonk, New York, USA). The level of significance is set to $p<0.05$. Demographic data will be summarised using descriptive statistics. Depending on if the data is normally distributed or not, appropriate statistical method will be used based on which data (categorical, ordinal, interval) that will be analyzed. If normally distributed, the main outcomes will be analyzed with two-way ANOVA. To find a minimum difference between the groups according to self-reported disease activity (15), a sample size calculation of 50 patients for two subgroups, approximately 100 participants, will be needed to obtain a power of 80% at a significance level of 5%.

Ethical and social considerations

The study will be accomplished in the terms of the Declaration of Helsinki (52). The Swedish Ethical Review Authority approved the study (2019-04155, 2022-03114-02).

The included patients will receive oral and written information of the physical tests, the

blood samples, the questionnaires, and the intervention before the start of data sampling. All patients will give the permission to participate by signing an informed consent before any data is collected. A screening will be performed before inclusion, through questions about comorbidities (lung disease, cardiovascular disease or other disease other than SpA). An ECG will be taken at the initial baseline visit to rule out atrial fibrillation and the blood pressure will be measured to check for high blood pressure. If no exclusion criteria will be detected in these assessments the anthropometric and physiological tests (body composition, grip strength, submaximal cycling test) will be performed by trained test leaders. During these tests, the prevailing guidelines, and regulations for testing, handling of data, including the personal data will be followed. Blood samples will be drawn by trained healthcare professionals who follow the regulations and requirements for reporting and registration that exist regarding blood sampling and analysis. The amount of blood (20 ml per occasion) is not considered to pose an increased risk to the patients. The participants will be informed that the high-intensity training included in the intervention does not comprise greater risks than if they train high-intensity in other settings. They will be informed that HIIT can cause temporary dizziness and high blood pressure and that due to glycogen deficiency in the body, in very rare cases, it can cause temporary unconsciousness. They will also be informed about the safety that has been established, where the test leaders will be well acquainted with emergency care during the baseline MHR test. Furthermore, defibrillators are available in connection with the premises that will be used in case of an incident. The patients will be instructed to avoid food and drink two hours before the baseline visit, prior to measurement of the body composition and taking the blood tests. When a MHR test will be done (patients assigned to intervention group), we will offer a sweet beverage before this test. Furthermore, patients are instructed to abstain from tobacco 30 minutes before the tests and not to exercise on high-intensity level the evening before the tests. The participants will be well informed about their volunteering, and that they can choose to end their participation at any time, without it affecting future contact with the coach, test leader or care unit.

All collected study-specific data (questionnaires, physical assessments, blood analysis) will be managed confidential and the patients' personal data will be replaced by codes, meaning no data can be linked to any identifiable individual. The researcher involved in the data collection will be the only one who has access to the code key. All data will be entered manually into Excel by responsible researchers. The results from the routine

blood samples will be entered into the medical record in accordance guidelines and the Patient Data Act and data will then retrieved from there to the Excel files. During the project, data will be stored in such a way that no unauthorized individuals will have access to it. Only researchers in the project will have access to the coded data for the analysis and the results will be presented at group levels. The freezers, in which saved blood samples will be stored, are locked, and located in alarmed rooms at the biobank and at the university.

After the analyses are finished the collected data will be stored on a security-protected server at Halmstad University, and the blood samples will be stored in a biobank at FoU Spenshult. After finished the sampling, the key code will be stored in a safe at Halmstad University and only the project manager will have access.

Gender issues

Research is lacking regarding effects of high-intensity interval training. Thus, in this project we will study both women and men together, for the intention to provide insights on the effect of high-intensity exercise on physiological, inflammatory, and self-reported health parameters in patients with SpA. Due to the limited number of participants, there will be no opportunity to study gender specific issues.

Trial registration number: ClinicalTrials.gov xxx

Timetable

2022– identification/inclusion of patients and start of the intervention. One center at a time will include patients
2023-2025 – ending the one-year intervention
2023-2024 – starting analyses of short-term effects
2025-2026 – analyses of long-term effects and reporting the results

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