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High-intensity strength training in patients with idiopathic inflammatory myopathies: a randomised controlled trial protocol

Kasper Yde Jensen, Per Aagaard, Henrik Daa Schröder, Charlotte Suettas, Jakob Lindberg Nielsen, Eleanor Boyle, Louise Pyndt Diederichsen

ABSTRACT

Introduction Idiopathic inflammatory myopathies (IIMs) are rare diseases characterised by non-suppurative inflammation of skeletal muscles and muscle weakness. Additionally, IIM is associated with a reduced quality of life. Strength training is known to promote muscle hypertrophy and increase muscle strength and physical performance in healthy young and old adults. In contrast, only a few studies have examined the effects of high intensity strength training in patients with IIM and none using a randomised controlled trial (RCT) set-up. Thus, the purpose of this study is to investigate the effects of high-intensity strength training in patients affected by the IIM subsets polymyositis (PM), dermatomyositis (DM) and immune-mediated necrotising myopathy (IMNM) using an RCT study design.

Methods and analysis 60 patients with PM, DM or IMNM will be included and randomised into (1) high-intensity strength training or (2) Care-as-Usual. The intervention period is 16 weeks comprising two whole-body strength exercise sessions per week. The primary outcome parameter will be the changes from pre training to post training in the Physical Component Summary measure in the Short Form-36 health questionnaire. Secondary outcome measures will include maximal lower limb muscle strength, skeletal muscle mass, functional capacity, disease status (International Myositis Assessment and Clinical Studies Group core set measures) and questionnaires assessing physical activity levels and cardiovascular comorbidities. Furthermore, blood samples and muscle biopsies will be collected for subsequent analyses.

Ethics and dissemination The study complies with the Helsinki Declaration II and is approved by The Danish Data Protection Agency (P-2020–553). The study is approved by The Danish National Committee on Health Research Ethics (H-20030409). The findings of this trial will be submitted to relevant peer-reviewed journals. Abstracts will be submitted to international conferences.

Trial registration number NCT04486261.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs), collectively termed myositis, is a heterogeneous group of rare diseases that share features as non-suppurative inflammation of skeletal muscles and muscle weakness.¹ ² The main subsets of IIMs consists of polymyositis (PM), dermatomyositis (DM), sporadic inclusions body myositis (sIBM) and immune-mediated necrotising myopathy (IMNM).³ ⁴ ⁷

Patients with myositis generally respond well to prednisolone and other anti-inflammatory drugs,⁸ ⁹ with sIBM as an exception.¹⁰ ¹¹ Even though anti-inflammatory drugs in general reduce disease activity in IIM, patients typically do not fully regain their pre-disease muscle function.¹² ¹³ In addition, patients with IIM have reduced quality of life. Patients with a disease duration of roughly 7 years scored ~50% lower within the physical domain of the Short Form 36 (quality of life) questionnaire compared with healthy age-matched adults.¹⁵ ¹⁶ In a recent OMERACT (Outcome Measures in Rheumatology) survey on patient-reported outcome measures, patients with myositis listed ‘muscle symptoms’,
‘fatigue’ and ‘levels of physical activity’ as key challenging aspects of daily living. Therefore, it is paramount to address these aspects and improve physical function to increase quality of life for patients with myositis.

The effect of physical exercise has been investigated in patients with PM and DM in a few smaller non-randomised studies and in general, physical exercise was shown to be a safe and effective therapeutic tool to improve physical function and activities of daily living.

Two randomised controlled trials (RCT) concerning endurance training have been conducted in patients with PM and DM and aerobic exercise in combination with resistive endurance training led to improvements in general health, exercise performance and aerobic capacity, respectively, in patients with PM, DM and IMNM. The effect of high intensity strength training has only been investigated in limited number of patients with myositis (excluding sIBM) with promising results in terms of increased muscle strength, reduced disease activity and reduced signs of physical impairment, along with no signs of increased inflammation within the trained muscles. However, none of these studies included assessments of quality of life and despite the promising results, a strict RCT study design is currently lacking.

Two training studies performed comprehensive immunohistochemistry analysis, with a focus on inflammation and none of the studies observed signs of increased inflammation following the training interventions. Nonetheless, the effect of high-intensity strength training at the myocellular level has never been investigated in patients with PM, DM and IMNM.

The aims of the present study, therefore, are to use a RCT study design to investigate the effects of high-intensity strength training on (1) quality of life, (2) muscle strength, muscle mass, physical function and disease activity in patients with IIM compared with patients with control (IIM) receiving Care-as-Usual and (3) additionally, explorative outcomes as the underlying myocellular adaptations will be examined by repeated muscle biopsy sampling.

METHODS AND ANALYSIS

The current RCT is registered at ClinicalTrials.gov and any changes to the protocol will be implemented here.

Study design

The study is a two-armed RCT. Sixty patients diagnosed with IIM (PM, DM and IMNM) will be included in a 16-week training intervention study (figure 1). Patients will be allocated randomly in the two subject groups in a 1:1 ratio, with stratification of IIM subgroups to ensure even distribution between intervention arms (training vs no training). The randomisation code will be generated by a biomedical laboratory technician with no further relation to the study, using an online tool (Research Randomizer, www.randomizer.org). The study has conformed to the Standard Protocol Items: Recommendations for Interventional Trials guidelines for constructing a clinical trial.

Outside the scope of the RCT, we intend to perform a 1-year follow-up measurement, which would include the same outcome variables as pre-intervention and post-intervention, with the exception of muscle biopsies.

Blinding

The two physiotherapists who will be conducting the pre and post testing of physical function, maximal lower limb muscle power and dual-energy X-ray absorptiometry (DEXA) scans will be blinded to participants’ group allocation. The physician assessing IIM-specific disease measures (disease damage and activity, etc), as well as the statistician performing all statistical analysis will also be group allocation blinded. The patients and the lead investigator in charge of the supervised training cannot be blinded for group allocation.

Patients

Only patients with an affiliation to Copenhagen University Hospital, Rigshospitalet, will be assessed for eligibility in the study. Eligible patients will be identified through the electronic patient record system at Rigshospitalet by an extraction on diagnosis codes (M33.1—‘Other dermatomyositis’, M33.2—‘Polymyositis’, M33.3—‘Progressive systemic sclerosis (sclerosis of skin, muscle and internal organs) with myositis’, M33.4—‘Other specified systemic sclerosis with myositis’, M33.5—‘Unspecified systemic sclerosis with myositis’, M33.6—‘Systemic sclerosis without myositis’, M33.7—‘Other specified dermatomyositis’, M33.9—‘Unspecified dermatomyositis’).

Image
The weight will be progressively adjusted across successive training sessions at an intensity of 15 RM. At week three each session will consist of three sets of each exercise using a training load corresponding to 10 RM to failure, which will be kept for the remaining part of the training intervention. The weight will be progressively adjusted across successive exercise sessions when participants are able to complete two extra repetitions (ie, 12 repetitions) in the last set of the respective exercise. The training protocol will be a whole-body training protocol and consist of five exercises using machines: horizontal bench press, horizontal leg press, seated rows, weighted knee extension and seated biceps curls.

The respective muscles will be working for approximately 45s per set, with intermittent pauses of 90s.27 28 Borg scale (6–20) will be used for assessing perceived exertion during and following the exercise sessions (aim following session: 16–18). All training loads for each training session will be recorded in an individual training diary for each patient (eg, exercise adherence, training load and adverse events).

Care-as-Usual
Care-as-Usual is defined as maintaining the level of physical activity at the same level as prior to initiation of the study. Furthermore, the usual medical treatment related to the myositis disease will be maintained throughout the timeline of the study for both groups.

Table 1 Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tr>
<td>Patients, age ≥18 years old, fulfilling the criteria for IIMs by EULAR/ACR,42 43</td>
<td>Patients with sporadic inclusion body myositis and overlap myositis (myositis combined with another autoimmune rheumatic diseases), except Sjögren Syndrome.</td>
</tr>
<tr>
<td>Prednisolone ≤5mg/day and stable dosage of immunosuppressive treatment for at least 1 month prior to inclusion in the study.</td>
<td>Comorbidity preventing resistance training (eg, severe heart/lung disease, uncontrolled hypertension (systolic &gt;160 mm Hg and/or diastolic &gt;100 mm Hg), severe knee/hip arthritis).</td>
</tr>
<tr>
<td>IIM diagnosis established at least 6 months prior to inclusion in the study.</td>
<td>Alcohol and/or drug abuse. Defined by the guidelines issued by The Danish Health Authority.</td>
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</tbody>
</table>

EULAR/ACR, European League Against Rheumatism/American College of Rheumatology; IIMs, idiopathic inflammatory myopathies.

Outcome variables
All study outcome measures are presented in table 2. All outcome measures will be measured at baseline and following the 16-week intervention period. Demographical information (age, gender, disease duration and time from first symptoms) will be drawn from clinical records from the electronic patient record system at Rigshospitalet.

Primary outcome
The primary outcome variable will be the change in the Physical Component Summary (PCS) measure from baseline to 16 weeks assessed by the Short Form-36 health questionnaire (SF-36), with scores ranging from 0 (worst) to 100 (best).32 The SF-36 is proposed by The International Myositis Outcome Assessment Collaborative Study Group (IMACS) as the preferred quality of life assessment tool.32

Secondary outcomes
Assessment of physical function and maximal muscle strength
Physical function will be tested using Functional Index 3,35 30s chair rise,34 timed up-and-go35 and 2-min walk testing.36 Leg power will be measured by power rig.37 Handgrip strength will be measured38 and lastly a test for static balance with three feet positions (feet together, semi tandem and full tandem) will be performed.39

Body composition
Body composition as well as whole-body, appendicular (arms and legs) and lower-limb lean mass will be evaluated by DEXA. Bioimpedance measures will also be collected.

Disease activity and damage
Several outcome measures proposed by the IMACS to evaluate disease activity and disease damage in patients with IIM will be obtained.2 Patient and Physician Global
Assessment of Disease Activity and Extramuscular Global Assessment will be evaluated using a Visual Analogue Scale (VAS, 100 mm). The Manual Muscle Test will be used to determine muscle strength in eight predefined muscles. Muscle strength is graded from 0 (zero; no contraction felt in the muscle) to 10 (normal; holds test position against strong pressure).

Perceived physical function is reported by the patients, using the Health Assessment Questionnaire. Plasma creatine kinase (CK) will be measured by blood sampling. Patient and Physician Global Assessment of Disease Damage will be evaluated using a VAS (100 mm).

Questionnaires

The International Physical Activity Questionnaire - long (IPAQ-long) concerning the level of self-reported physical activity and a questionnaire concerning medical conditions, current medication, heart symptoms and so on, will be filled out by all study participants. The Mental Health Component Summary measure from the SF-36 will also be recorded.

Cardiovascular co-morbidities

Traditional cardiovascular risk factor will be measures, including body mass index, systolic and diastolic blood pressure, plasma lipid profile (low-density lipoprotein, high-density lipoprotein, triglycerides and total cholesterol) and glycated haemoglobin (HbA1c). In addition, troponins, N-terminal pro b-type Natriuretic Peptide (NT-proBNP) and ECG will be measured.

Explorative outcomes

Muscle biopsy

Biopsy samples will be acquired ad modum conchotome vastus lateralis (~100 mg). Immunohistochemistry will be used to analyse myofiber cross-sectional area, fibre type composition, B-lymphocytes and T-lymphocytes, macrophages, satellite cells and myonuclei.

Statistical considerations

The calculation of the number of subjects is based on the PCS values from the SF-36 questionnaire in patients with PM and DM reported by Poulsen et al. Reported PCS values were 36.5 with a SD for 9.5. The current study is a superiority trial and intends to demonstrate a significant change with the training intervention protocol of at least 20% with a statistical significance level of 0.05 and a
statistical power of 80% while anticipating a dropout rate of 10%. Based on sample size calculations (www.scaledenvelope.com/power/continuos-superiority) based on the above-mentioned values and dropout rate, a total of 60 patients was estimated to be recruited.

**Statistical analysis**
The primary outcome variable is the change in PCS using the SF-36 questionnaire from baseline to post 16 weeks of intervention. The statistical analysis of the primary outcome will be conducted using an ‘intention-to-treat’ approach. For the primary outcome, an independent t-test will be conducted to determine the difference in change between the two groups. Likewise, independent t-tests will be conducted to determine all other outcomes measured throughout the study. In addition, a ‘per protocol’ approach also will be employed. The criteria for being included in the ‘per protocol’ analysis is having participated in at least two-third of all exercise sessions.

**ETHICAL ASPECTS AND DISSEMINATION**

**Ethical considerations**
The study will stay true to the Helsinki declaration II and is approved by The Danish National Committee on Health Research Ethics (H-20030409). Further, the study is approved by The Danish Data Protection Agency (P-2020–553) and all data accumulated will be handled confidentially and under secrecy in accordance with the guidelines and approval conditions of The Danish Data Protection Agency. Written and verbal informed consent will be collected from all patients prior to participation in the study, according to Danish law (see online supplemental file 1 for patient consent form). In publication, there will not be any information that could identify any of patients partaking in the project.

There is no commercial interest at stake within the project. Possible ‘conflict of interests’ will be uncovered before the start of the intervention.

**Dissemination policy**
The results of the current RCT will be published in peer-reviewed journals. Abstracts will be submitted for poster presentations at international conferences (eg, American College of Rheumatology). Authorship is granted to authors who provide essential contributions to the creation of the final publications. Both contributions via writing and/or assisting in conducting the clinical trial are accepted.

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**Contributors**
LPD is the principal investigator on the current trial. KYJ is the coordinator of the trial and has drafted the manuscript. PA, CS and HDS are co-coordinators of the trial and supply academical depth and experience. EB provided statistical expertise. JLN provided insight and expertise concerning clinical trials. All authors took part in the study design and assisted with the project funding. All authors have participated in the design of the trial and assisted with the draft of the manuscript and read and approved the final manuscript.

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**Competing interests**
None declared.

**Patient consent for publication**
Not required.

**Provenance and peer review**
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**Supplemental material**
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home exercise in patients with recent-onset polymyositis and dermatomyositis: a multicenter randomized controlled
endurance exercise in patients with established polymyositis.

National committee on health research ethics

(S4)

Informed consent for participations in health-related research project.

**Title of the research project:** High-intensity strength training in patients with idiopathic inflammatory myopathies: Changes in quality of life, muscle strength, function and myocellular parameters

**Declaration from the participant:**

I have received written and oral information and I know enough regarding aims, methods, advantages, and disadvantages to agree to participate.

I know that participation is voluntary and that I will always be able to withdraw my consent without losing my present and future rights to treatment.

I give my consent to participate in the current research project. Furthermore, I consent to my biological material being collected and kept in a biobank for future research. I have received a copy of this consent form, as well as a copy of the written information concerning the research project.

Participant’s name: __________________________________________________________

Date: __________ Signature: ____________________________

If any new and essential health-related information is discovered during the research project, you will be informed. If you would like _not to_ receive any new and essential health-related information concerning you, please mark this with an **X**: _______

Do you wish to be informed about the scientific results from the research project and any possible consequences concerning you? (Please mark with an **X**)

Yes: _______  No: _______

**Declaration from research informant:**

I declare that the participant has received both written and oral information concerning the research project.

Based on my professional judgment, the participant has been given adequate information to make an informed decision regarding the participation in the current research project.

Name of the research informant: _________________________

Project identification: (e.g., Committee project-ID, EudraCT nr., version no./date or similar):

___ H-20030409 ___