Master's thesis

NTNU
Norwegian University of Science and Technology

Callan Wesley

An inconvenient truth:The association between maximal strength training, rate of force development, one repetition maximum, work economy and quality of life amongst persons with inflammatory rheumatic disease.

Master's thesis in Exercise Physiology
Supervisor: Professor Jan Helgerud
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Abbreviations

1RM	One Repetition Maximum
AS	Ankylosing Spondylolisthesis
BMI	Body Mass Index
COVID	Corona Virus Disease
C	Work Economy
CVD	Cardiovascular Disease
IRD	Inflammatory Rheumatic Disease
Kg	Kilograms
Mb	Body Mass
MST	Maximal Strength Training
RA	Rheumatoid Arthritis
SLE	Systemic Lupus Erythematosus
IL6	Interleukin 6
IL7	Interleukin 7
IGF1	Insulin-Like Growth Factor
IRD	Inflammatory Rheumatic Disease
VAS	Visual Analog Scale

Abstract

Background Rheumatisms is classified as chronic, systemic and autoimmune diseases. Symptoms include synovial inflammation, swollen joints, deformation of cartilage and bone structures. Systemic features such as cardiovascular, skeletal and pulmonary disorders are hallmark characteristics in rheumatic patients. Scientific evidence has shown that maximal strength training within the general population is effective for increasing their muscular strength, work economy, rate of force development along with reducing inflammatory cytokines. Inflammatory rheumatic disease (IRD) patients have reduced muscle strength and functional ability compared to the general population. **Objective** The aim of this study was to examine the efficacy of maximal strength training (MST) on rate of force development (RFD), one repetition maximum (1RM) and work economy (C). As well as investigate its role for effective pain and fatigue management within IRD patients. **Methods** The intervention group comprised of seven patients, all which were women aged 40 ± 11.6 yrs with IRDs were recruited from physicians and therapists in the Trøndelag area. These patients underwent a twenty-four session, eight week, three time per week, MST training period. The patients performed four sets of four repetitions dynamic leg press with emphasis on maximal mobilization of force in the concentric action with an intensity corresponding to ~85 % of the individuals 1RM. Comparisons were made to a control group, comprised of six IRD patients being exposed to standard pharmaceutical treatment for an eight week period. **Results** As a consequence of the twenty-four session MST period, leg press 1RM significantly increased (p = 0.018) by 29.3 ± 13.1Kg (22.5 %) more than the control group. Dynamic RFD, measured on a MuscleLab force plate installed on the horizontal leg press apparatus, also increased significantly compared to the control group (p = 0.002) by 29.0 ± 246.6N/s (66.5 %). The strength improvements in the MST group lead to an average improvement in work economy by -2.54 mL· min^{-1}·$kg^{-0.76}$ (p = 0.003) measured on a submaximal treadmill test. The MST group significantly improved quality of life with reference to the VAS pain (-10.6 mm, p = 0.001) and the VAS fatigue scores (-9.3 mm, p = 0.03). **Conclusion** An eight week, twenty-four session MST intervention in IRD patients was well tolerated with no adverse events recorded, the outcomes provided were statistically significant and clinically relevant for the treatment of IRD patients. MST can be recommended as a safe treatment for persons with IRD.

Keywords: inflammatory rheumatic disease, maximal strength training, rate of force development, work economy, pain, fatigue

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1. Introduction

1.1 Inflammatory Rheumatic Disease

The term inflammatory rheumatic disease (IRD) is classified accordingly as a chronic, systemic and autoimmune disease, with the main focus upon rheumatoid arthritis (RA)(D. L. Scott, F. Wolfe, & T. W. Huizinga, 2010), ankylosing spondylitis (AS)(Szabo et al., 2011), and systemic lupus erythematosus (SLE) (Stockton, Kandiah, Paratz, & Bennell, 2012). These medical conditions are characterized by a permanently defected active immune system, resulting in uncontrolled local and systemic inflammation (Wahren-Herlenius & Dorner, 2013). IRD patients experience a wide range of symptoms namely: fatigue, joint pain, rheumatoid cachexia, muscle atrophy, and increased risk for developing cardiovascular disease (Nurmohamed, Heslinga, & Kitas, 2015). Patients with IRD have a shorter life expectancy coupled with higher cardiovascular disease (CVD) related death compared to the general population (Pincus, Sokka, & Wolfe, 2001). Higher prevalence rates of atherosclerosis are exhibited within the IRD population, a traditional risk factor for CVD (Manzi et al., 1997). The roles of inflammation in atherosclerosis provides a crucial link between the elevated risk for developing cardiovascular events and IRD (Mason & Libby, 2015). IRD patients are at a higher risk for experiencing cardiovascular events compared to the general population (Agca, Heslinga, van Halm, & Nurmohamed, 2016). Increased CVD risk has been reported within the IRD population globally, with 1 in 12 women and 1 in 20 men being at risk for developing IRD (Crowson et al., 2011).

The overall global lifetime risk of developing IRDs is reported to be 5.1 % for men and 8.4 % for women (Crowson et al., 2011). Mainly as a consequence of a chronic proinflammatory status, a genetic component and traditional risk factors (Crowson et al., 2011). Chronic systemic inflammation is seen as the major contributing factor for the associated cardiovascular risk within the IRD population. The persistent chronic inflammation in patients with IRDs is coupled by increased muscle atrophy and deconditioning of the skeletal muscles (Benatti & Pedersen, 2015). Traditional risk factors such as diabetes, smoking, hypertension, and dyslipidaemia are independently associated with subclinical atherosclerosis and increased mortality rates in patients with IRDs (Crowson et al., 2013).

1.1.1 Rheumatoid Arthritis (RA)

RA primarily targets the small joints of the hands and feet by acting on their synovial tissues however, larger joints may still also be affected (Burrage, Mix, & Brinckerhoff, 2006). RA affects 0.5 % of the adult population worldwide (Carmona, Cross, Williams, Lassere, & March, 2010). The disease prevalence rates are three times more frequent in women than men when compared globally (D. L. Scott et al., 2010).

Overall total mortality and risk for developing CVD compared to the general population, is 1.5 times greater in RA patients, (Dhawan & Quyyumi, 2008) even among individuals without a history of smoking, diabetes, hypertension, or hypercholesterolemia (Rachel H. Mackey et al., 2015). Common characteristics include joint damage, disability, decreased quality of life and cardiovascular comorbidities (D. L. Scott, F. Wolfe, & T. W. J. Huizinga, 2010). Patients with RA also experience a loss of lean mass attributed to inflammation induced increased resting energy expenditure and protein catabolism. Body weight remains relatively unaffected as skeletal muscle wasting is replaced with adipose tissue (Benatti & Pedersen, 2015).

1.1.2 Ankylosing Spondylitis (AS)

AS targets the axial skeleton making it the most common form of inflammatory arthritis found in this area, affecting 0.1 % - 0.4 % of the global population with a male to female prevalence ratio of 2:1 (Braun & Sieper, 2007). The AS population are at 1.9 times higher prevalence risk across all age groups for developing CVD compared to age and sex matched controls (Agca et al., 2016), along with a 31 % increased risk of being administered into hospitals for these CVD (Szabo et al., 2011). The most common characteristics of AS are pain, stiffness, reduced mobility, increased disability and lowered quality of life (Nurmohamed et al., 2015).

1.1.3 Systemic Lupus Erythematosus (SLE)

SLE is categorized as a chronic autoimmune disease affecting a vast array of organs through its production of autoantibodies and deposition of immune complexes (Tsokos, Lo, Costa Reis, & Sullivan, 2016). SLE is believed to be multifactorial encompassing environmental factors, genetic factors and hormonal factors contributing to the development of the disease (Tsokos et al., 2016). General symptoms include fever, fatigue, musculoskeletal weakness and weight loss (Maidhof & Hilas, 2012).The SLE population are at a 1.27 times higher prevalence risk of experiencing CVD compared to the general

population (Bengtsson, Ohman, Nived, & Rantapää Dahlqvist, 2012).

SLE prevalence is six times more frequently in women compared to men for every age and ethnic group (Frances Rees et al., 2016). Persons of black ethnicity had the highest incidence and prevalence rates, whereas those with white ethnicity had the lowest incidence and prevalence rates (Black ethnicity 31.46/100 000 person-years, White ethnicity 6.73/100 000 person years) (F. Rees, Doherty, Grainge, Lanyon, & Zhang, 2017).

1.2 Cardiovascular Disease Associated with IRD

CVD is classified accordingly as diseases involving the heart or blood vessels including coronary heart disease, peripheral artery disease and congenital heart defects. IRD patients are at significantly higher risk for developing CVD than the general population (Crowson et al., 2011) (RA:1.5 times (Dhawan & Quyyumi, 2008), AS:1.9 times (Agca et al., 2016),SLE:1.27 times (Bengtsson et al., 2012)). Lower levels of physical activity in IRD patients are being directly linked to a substantially increased risk of developing CVD (Benatti & Pedersen, 2015). Reducing disease activity and inflammation is imperative for reducing the comorbidities of CVD (R. H. Mackey, Kuller, & Moreland, 2017). Medication has been seen to effectively target inflammation associated with IRD, but in many cases results in undesirable side effects namely hypertension and dyslipidaemia which contributes negatively back to the vicious cycle predisposing IRD patients to heightened CVD risk (Nurmohamed et al., 2015).

1.2.1 Exercise as Medicine

IRD patients are commonly linked to impaired muscle functions and muscle atrophy. The loss of muscle functions in autoimmune disorders can consequently result in decreased functional performance and quality of life, increasing disability and the need for care (Lundberg & Nader, 2008). Symptoms manifest as structural joint damage, bone density loss, muscle weakness, fatigue, stiffness and pain (Lee & Weinblatt, 2001). Resulting in functional limitations and reduced ranges of motion, which significantly compromises their ability to partake in physical activity giving rise to insufficient fitness levels, forcing decreased engagement in physical activity and negatively affecting their quality of life (Ekdahl & Broman, 1992).

The reduced range of joint motion is linked to thickened joint capsules, increased joint fluid, and destruction of cartilage and bone (Klareskog, Catrina, & Paget, 2009). The reduced muscle function in RA is a result of decreased muscle strength and muscle atrophy.

Resulting from joint instability, muscular inflammation, and increasing tendon and ligament length (Klareskog et al., 2009). Maximal strength training (MST) is no longer associated with increased inflammation in IRD but seen as a form of medicine to advocate anti-inflammatory responses in IRD patients (Benatti & Pedersen, 2015). Implementing a form of heavy resistance training has been seen to disrupt the vicious cycle of chronic inflammation (Benatti & Pedersen, 2015) by direct (after each bout of exercise) and indirect (improving body composition, physical capacity, comorbidities and cardiovascular risk factors) effects leading to increased muscle mass and decreasing whole-body fat mass (Halvorsen & Christie, 2010). Myokines are released by the skeletal muscles in response to physical activity, therefore acting directly on anti-inflammatory responses and indirectly having anti-inflammatory effects by their nature (A. M. Petersen & B. K. Pedersen, 2005). These myokines include Interleukin-6 (IL-6), Interleukin-7 (IL-7), and Insulin-like growth factor 1 (IGF-1) and have been reported to induce anti-inflammatory effects in response to training stimuli (Benatti & Pedersen, 2015). Thus, IRD patients could potentially benefit from anti-inflammatory responses derived from skeletal muscles by engaging in regular MST.

1.3 The Vicious Cycle

Benatti and Pedersen (2015) proposed a vicious cycle phenomenon recognized in patients with IRDs. As a result of excessive disease related production of cytokines predisposing patients with IRDs to atherosclerosis, sarcopenia, metabolic disorders, dyslipidaemia and insulin resistance. The proinflammatory nature of cytokines can heighten further disability and force further disengagement in physical activity. Promoting the accumulation of visceral fat, a known activator of the inflammatory pathways linked to atherosclerosis (Sarzi-Puttini et al., 2010). Accompanying physical inactivity is fatigue and muscle atrophy, causing deconditioning and exacerbated chronic inflammation, forming a loop that negatively effects cardiovascular health and physical activity (Benatti & Pedersen, 2015).

1.4 Maximal Strength Training

Strength is defined as the result of numerous force-producing muscles, performing maximally, either isometrically or dynamically during a single voluntary effort of a defined task (Hoff & Helgerud, 2004). MST has been reported to increase both the percentage and the size of Type II muscle fibers, supporting the potential role as a countermeasure to maintain both physical function along with fall prevention in this population (Wang et al., 2017).

Within a patient population MST has been documented to induce significant improvements in overall strength and RFD (Hoff et al., 2007).

Maximal strength is defined with a 1RM in a standard movement task i.e.-leg press (McArdle, Katch, & Katch, 2015, p. 502). Greatest strength gains are experienced in low repetition high load, MST sessions incorporating 85-95 % of 1RM, working to augment maximal voluntary contractions targeting improvements in the rate of force development (D. G. J. J. o. S. Behm & Research, 1995). This is of great importance for IRD patients as muscle volumes and strength declines with increasing disease activity (Felipe Martinelli Lourenzi et al., 2017). High loads evoke greater strength improvements over low loads (19.6 and 8.8 % respectively). It has been postulated that higher loads are needed to accomplish complete motor unit activation associated with gains in strength (Schoenfeld, Peterson, Ogborn, Contreras, & Sonmez, 2015). Where as evidence suggests complete recruitment is incomplete in low loads leading to a superior impact on local muscle endurance rather than muscular strength (Schoenfeld et al., 2015).

1.4.1 MST vs CONV

Heggelund, Fimland, Helgerud, and Hoff (2013) reported work economy was improved 30 and 17 % after MST and conventional (CONV) training programs respectively. The MST group reported statistically significant improvements in maximal strength over the CONV group (Heggelund et al., 2013). Campos et al 2002 also reported training with 3-5RM for four sets and three minute rest periods was more effective than 9-11RM for three sets and two minute rest periods. RFD was improved 155 and 83 % in MST and CONV respectively. Behm and Research (1995) suggest that intentional velocity is more important than actual velocity during a movement sequence. The intended high velocity movements are speculated to be more beneficial as they stimulate maximal motor neuron firing frequency coupled with enhanced muscle fibre recruitment (D. G. Behm & Sale, 1993). MST is more effective than CONV for untrained and moderately trained subjects, work economy (13 %), maximal strength (15 %) and RFD (72 %) improved significantly more when compared to CONV (Heggelund et al., 2013).

1.4.2 MST, Inflammation and CVD

Inflammation is implicated in the pathogenesis of IRD and contributes to all the stages of atherosclerosis and CVD, through plaque formation and eventual plaque ruptures (Libby, 2008). Inflammatory cytokines levels are reported to be inversely proportional to

muscular strength levels (A. M. W. Petersen & B. K. Pedersen, 2005). Steensberg et al. (2002) reported cytokines and myokines are secreted from skeletal muscles as a response to muscular contractions from MST. The skeletal muscle operating as an endocrine organ, exerts anti-inflammatory effects, acting locally or systemically on adipose tissues and organs (Steensberg et al., 2002). MST can be used to counteract this association by increasing muscular strength and subsequently reducing inflammatory cytokines within the IRD patient population, reducing rates of premature mortality from cardiovascular events (Volaklis et al., 2015).

1.4.3 MST and Work Economy

Work Economy (C) is measured as the steady rate of oxygen consumption whilst exercising at a specified submaximal intensity below the lactate threshold (Morgan, Martin, & Krahenbuhl, 1989). Therefore C refers to the ratio between work output and energy costs (Hoff, Gran, & Helgerud, 2002).

The improved C observed in their study (-0.10 ± 0.08 $L \cdot min^{-1}$) could be seen as a reduction in whole body pulmonary oxygen consumption at a standard submaximal work load owed to the improvements made in 1RM (28 %), as a result of improved RFD (23 %) (Barrett-O'Keefe, Helgerud, Wagner, & Richardson, 2012) and peak force (28 %) (Heggelund et al., 2013). Resulting in standard submaximal workloads being relatively smaller (Hoff et al., 2002).

MST has been linked to improvements in lactate kinetics along with improved neural recruitment. This can be seen by increased time to exhaustion ($p = 0.014$) with respect to improved C with no subsequent increases in $VO2_{max}$. (Farrell, Lantis, Ade, Cantrell, & Larson, 2018)

1.4.4 Allometric Scaling

For comparative purposes, normalization of strength measures to body size using allometric scaling is recommended. Allometric scaling in strength is used to establish a relationship between different body sizes and variables (McArdle et al., 2015). Inter-subject variability in weight and height is inherent across any population and sexes (Helgerud, 1994), thus it is important to take this into consideration in any population you are testing. Body size variables include body mass (Mb), height and fat free mass. Absolute force and torque measurements normalized for body mass are significantly influenced by height. It has thus

been suggested to use body mass raised to the power of 0.66 ($Mb^{0.66}$) to be independent of height when measuring force (Folland, Mc Cauley, & Williams, 2008). It was concluded that when assessing individuals or groups with different body masses, age, and sex, scaling must be used to assess maximal strength to avoid bias with body mass.

1.5 Neural Adaptations

Neural adaptations are a term used to encompass a selection of specific factors. The benefits of neural adaptations from MST training have been of major interest within the disease populations, with respect to these specific factors namely: enhanced efferent neural drive, increased co-contraction of antagonist, selective activation of motor units, increased rate coding, increased motor neuron recruitments and enhanced synchronization (D. G. J. J. o. S. Behm & Research, 1995).

RFD relies upon the speed of the muscles contractile elements to develop force (Aagaard, Simonsen, Andersen, Magnusson, & Dyhre-Poulsen, 2002), dependent upon the motor unit firing frequency and the motor unit recruitment (Dahl, Rodahl, Stromme, & Åstrand, 2003). Increased motor unit recruitment and enhanced motor neuron firing frequencies are reported after MST (53 %, $p<0.05$) within multiple sclerosis patients (Fimland, Helgerud, Gruber, Leivseth, & Hoff, 2010), this could be positively translated over to IRD patients, for improved RFD along with improved muscular strength.

RFD has been documented to deteriorate at a more pronounced rate than maximal strength (64 and 44 % respectively) within aging and patient populations (Izquierdo, Aguado, Gonzalez, Lopez, & Hakkinen, 1999). Fast movements and balance adjustments are imperative for fall prevention. The relatively long period needed to reach maximal strength (≥300 ms) may not be available and of significant use, thus making RFD (100-200 ms) of vital importance for fall prevention. (Aagaard et al., 2002)

1.6 Current Management

The main goal of current treatment strategies are to lower the disease activity and achieve remission by targeting systemic inflammation (Smolen et al., 2014). However, the current management to alleviate systemic inflammation within the IRD population is through the use of pharmacological treatment (Ford et al., 2007). Despite advances in pharmacological treatment, disability is still a main hallmark feature in IRDs. Disability not only has an effect reducing the quality of life on a personal level. This disability leads to vast social and economic burdens (Verstappen et al., 2004). It should be mention that the majority of treatment costs

originate from the associated comorbidities of IRD and not the disease itself therefore, the need for improved cost effective treatment strategies is of ever growing interest within the IRD patient population worldwide (Ridker, 2009).

1.7 The Aim Of The Study

The prescription of exercise as a potential anti-inflammatory tool is still a relatively new concept within the IRD patient population. The World Health Organisation and American College of Sports Medicine along with various other national health authorities (Lemmey et al., 2009) have advocated progressive resistance training as an additional therapy for IRD patients. However, resistance training especially MST is rarely prescribed or undertaken.

In this study:

- The primary aim of this study was to investigate if twenty-four sessions of maximal strength training influenced the rate of force development, one repetition maximum and work economy in patients with inflammatory rheumatic disease, along with investigating whether maximal strength training is considered a safe an effective intervention for patients with inflammatory rheumatic diseases.
- The secondary aim of this study is to investigate how maximal strength training affects inflammatory rheumatic disease patients quality of life with regards to pain and fatigue.

Hypothesis:

Twenty-four sessions of maximal strength training will be safe and well tolerated by patients with inflammatory rheumatic diseases, significant improvements in rate of force development, one repetition maximum, work economy and quality of life will be observed.

2. Methods

2.1 Study design

The current study was a blocked randomized, controlled clinical trial with a blinded assessor which meant randomly assigning patients equally into each treatment block. Block randomization offers a simple means of achieving balance within a study whilst reducing the opportunity for bias (Efird, 2011). All tests and exercise sessions were conducted between January-March 2020. This study was performed in accordance with the World Medical Association under the rules and regulation of the Helsinki Declaration and was approved by the regional research ethics committee. All patients read, agreed and signed the informed consent literature prior to testing. Patients were randomly allocated into the intervention or control group once they met our inclusion criteria *(see Table 2)*. The randomisation process was carried out by the leader of the Clinical Research unit at Trenher Klinikken. The randomizer was not part of the testing or training of the patients during this intervention. All physiological testing in connection to this study were carried out on the same day for all the individual patients at baseline and post-treatment. A total of four tests per patient were conducted. The intervention group consisted of twenty-four sessions of MST, whilst the control group consisted of an eight week control period where normal pharmaceutical treatment was administered. All control group test measurements were conducted only at baseline. Failure to complete the post-treatment assessments after the eight week control period was due to the COVID-19 outbreak and forced closure of the clinic by the Norwegian National Health Authorities, a total of two tests per person were conducted within the control group. The IRD patients diagnosis prior to participation in our study are present in *Table 1*.

Table 1 IRD patients diagnosis prior to participation

Diagnosis	**Intervention Group (n=7)**	**Control Group (n=6)**
Polyarthritis	1	1
Spondylarthritis	3	1
Psoriatic Arthritis	2	3
Other	1	1

2.2 Patients

Thirteen patients in total were recruited for this study. Seven patients, all which were women, aged 40 ± 11.6 years made up the intervention group. The control group comprised of six patient, two women and four men, aged 50.5 ± 11.8 years. Patients were referred from physicians and therapists in the Trøndelag area to the TrenHer Klinikken, recruitment for this study then followed.

Before inclusion to our study therapists ensured that all subjects were qualified to partake in our current study, with stable health and correct disease diagnosis. Patients were considered eligible if they met our inclusion and exclusion criteria as implemented in *Table 2*. Patients with other identified comorbidities present were not excluded from the study. Admission to this study was done by free will. All recruited patients were informed that participation would not influence the quality or type of treatment they would be receiving and were allowed to withdraw from this study at any time. Informed consent forms (in Norwegian) were signed prior to the commencement of the study. The baseline-testing, post-treatment testing and MST sessions of all the patients along with the data collection were conducted at the TrenHer Klinikken in Trondheim, Norway over the time period of January to April 2020. The force plate utilized was the MuscleLab Force Plate by ErgoTest measuring at 1000 Hz. The leg press utilized was the Gymleco Active Line 343 horizontal leg press with 180 kg fixed weight stack attached. A Dell Laptop configured to windows ran MuscleLab 19 recording programme, with all recorded data being exported and backed up to excel after completion of each testing day.

Table 2 Inclusion and Exclusion Criteria

Inclusion Criteria
• One or more prior rheumatic disease diagnosis • Patients of both sexes were deemed eligible • Patients had to be 18 years of age or older • Able to perform our specific tests
Exclusion Criteria
• Pregnancy or planned surgical intervention during the study period • Rheumatic diagnosis not involving systemic inflammation • Under the age of 18 years old • Failure to meet the minimum required session number • Failure to be present on testing days

2.3 Interventions

After baseline assessment the intervention group then participated in a twenty-four session (80 % minimum completion rate) MST programme under the completed supervision of physiotherapists, nurses and physiologists. The overall exercise group consisted of twenty patients per session. Exercises involving the use of the back pull down (low row was used if shoulder mobility was restricted or if overhead movement caused pain), seated chest press and horizontal leg press were utilized. Emphasis was placed on the horizontal leg press to always be utilized first. A total of four repetitions and four sets per exercise were conducted. Maximal mobilization of the forces in the concentric muscle action were emphasized. Rest periods were set at two to three minutes between each set. Resistance was subjectively based for each patient on 85 % of their 1RM weight obtained at baseline testing. The ability to perform five repetitions on the specified weight during the MST session lead to the weight being increased by five kilograms (kg) for the subsequent session. MST sessions ran weekly and patients were required to join all three exercise sessions per week. Each MST exercise session was expected to last between 60-90 minutes. Informative personalized exercise sheets were handed out to each patient prior to every MST session incorporating the list of exercises to be performed, the weight to be lifted, correct seat height, along with repetitions and set numbers. Normal rheumatology treatment and medication was unchanged throughout the MST intervention period. Important to be aware of, these patients were concurrently involved in a 4x4 high intensity interval training study. These intervals took place prior to the engagement in the MST exercise sessions and may have negatively impacted the amount of weight being lifted per session (Sveaas et al., 2014).

2.4 Outcomes

Assessment for both primary and secondary outcome measures were conducted at baseline and immediately following the intervention or control period between January and March 2020. For each assessment, subjects performed specific physiologist guided exercise tests as well as two separate VAS questionnaires for pain and fatigue. The exercise tests incorporated in this study were the 1RM horizontal leg press test immediately followed by a maximal RFD test, having refrained from strenuous exercise for twenty-four hours prior to testing. Foot placement was not standardized but recorded for each patient for comparative purposes in the post-treatment tests. Data displayed as baseline characteristics were obtained either directly from the patients themselves or indirectly by use of medical records with their

approval.

Importantly, due to the corona virus disease-19 pandemic (WHO 2020), it was not possible to conduct post-testing for the control group. As evident in previous studies, no improvements were forecasted in any of the outcome measures within the control group (Lemmey et al., 2009; Felipe Martinelli Lourenzi et al., 2017; Sveaas et al., 2014). For this reason, baseline values were used and then reported as viable post-treatment values for the control group.

2.4.1 Maximal Strength Training

Maximal strength was determined by the maximal weight lifted for one repetition, measured in kg's. The 1RM performed by the patients was assessed on the Gymleco active line 343 horizontal leg press, located at the TrenHer Klinikken in Trondheim, Norway. Patients started in the upright position with their legs fully extended. Physiologists assisted the patients on the initial upwards motion to bring them to a fully extended position prior to the start of each attempt. Initially the patients performed three sets of dynamic warm-up with 40, 70 and 80 % of estimated 1RM with five, three and one repetitions respectively. The patients were also given verbal feedback during the warm up and maximal strength tests to encourage good technique, concentration and maximal effort given in each attempt. For a repetition to be valid an angle of 90 degrees had to be created between the Femur of the upper thigh and the Fibula of the lower leg during the repetition (90 degree flexion in the knee joint). Seat position was adjusted (± 4 cm) as the subsequent weight increased, due to the increased compression forces applied from the body onto the backrest of the seat negatively affecting the true 90 degrees knee angle achieved during the eccentric muscle action. When a patient successfully executed the repetition maximum attempt, the weight was subsequently increased by 5-10 kg accordingly for the following attempt. Failure to complete a subsequent lift was used in all cases as an indication a true 1RM was achieved.

2.4.2 Rate of Force Development

The RFD test was assessed dynamically immediately following the 1RM test, with use of the MuscleLab force plate mounted onto the Gymleco horizontal leg press with steel brackets. The RFD was calculated with use of 10 and 90 % of the maximum and minimum values on the force (N)/time (ms) curve. The program used to record and analyse this data was MuscleLabs in house recording program (MuscleLab 19). The weight corresponding to

80 % of the 1RM value was utilized for the RFD test. The implementation of 80 % over the most commonly used 70 % of the 1RM value was proposed in our protocol as our population is patient based thus, leading to less shear forces being developed due to the patients not being separated from the force plate during the movement. Being an important factor for reducing the possible occurrence of injuries during testing. The data was measured in $N \cdot s^{-1}$ at 1000 Hz. Patients were required to started in the upright position with their legs fully extended. Physiologist assisted the patients on the initial upwards motion to bring them to a fully extended position prior to the start of each RFD attempt. Patients were given verbal encouragement and feedback to make sure each attempt was executed with maximal effort. For a repetition to be valid a short pause period at the bottom of the movement (90 degree knee angle), correlating over to a stable line on the RFD graph prior to the rise in concentric lift forces must be present. Maximal mobilization of force in the concentric phase must be emphasized to produce the highest force values possible over the three attempts. No validations were available for this apparatus.

2.4.3 Questionnaires

Measures of pain and fatigue were assessed using the Visual Analog Scale (VAS) questionnaire. Patients completed the VAS for pain and fatigue after all baseline and post-treatment measurements were conducted. The VAS is used in the social and behavioural sciences to measure a variety of subjective events. The VAS is a self-reported questionnaire containing two main questions in our study, one regarding pain and the other regarding fatigue both within the past week prior to filling out the questionnaire. A straight 100 mm horizontal line is used in the VAS whose end anchors indicate the extreme boundaries of either pain or fatigue. Patients respond to the VAS by placing a mark along the line at the position which best describes their current perceived pain levels (up to and including the week prior) for the one and their current perceived fatigue levels (up to and including the week prior) for the other. Evidence indicates that descriptors at intermediate points of the scale lead to clustering of the results around such. To avoid this, no descriptors except for the extremes (no pain/no fatigue and the worst imaginable pain/the most severe fatigue) will be used. (Scott & Huskisson, 1976)

For both VAS-pain and VAS-fatigue 0-100 mm scales were used, a change of ≥10.5 mm will be considered as the minimum clinically important difference based on data in rheumatoid arthritis (Wells, Li, Maxwell, MacLean, & Tugwell, 2007; Wolfe & Michaud, 2007) and psoriatic arthritis (Kwok & Pope, 2010) to measure total pain and fatigue. The

validity and reliability of both VAS-pain and VAS-fatigue were previously reviewed by Hawker, Mian, Kendzerska, and French (2011) and Hewlett, Dures, and Almeida (2011). VAS-pain: test-retest reliability is high among literate rheumatology outpatients (r = 0.94), validity is highly correlated to other measures of pain (range r = 0.62–0.91). With an excellent ability to detect change. VAS-fatigue: test-retest reliability is strong (r = 0.66-0.74), content validity: no standard format; construct validity: strong; criterion validity: variable, moderate to strong. With a good ability to detect change.

2.4.4 Work Economy

Work economy was assessed at baseline and post-treatment using a single stage, five-minute bout exercise test on a GymSport TX200 treadmill with zero inclination at a speed of 4 $km \cdot h^{-1}$. All patients were required to walk unassisted during this period without the use of the handrails. Their overall average oxygen uptake (VO_2) during the fourth minute was used to assess their work economy.

2.5 Sample Size

A strength calculation was performed based upon existing relevant literature and thus expected progress. Statistical strength was set at 0.8. Statistical significance level was set at 0.05. An increase of twenty percent is expected throughout the MST intervention (Serra-Rexach et al., 2011). Calculations yielded that sixteen patients would be needed for the current study. As this is a patient population with highly irregular and unpredicted periods of sickness, to account for dropouts twenty participants will be recruited for this study.

2.6 Randomization

Block randomization with an allocation ratio of 1:1 was implemented in the current study. Before recruitment, it was decided upon that the first block would be allocated to the intervention group, whereas the second block would be allocated to the control group. The group leader at TrenHer was responsible for the randomization process as he was not involved in the training or testing of the patients.

2.7 Statistical Analysis

Statistical analyses were performed using the software program SPSS, version 24 (SPSS Inc). Means and standard deviations (SD) for all variables were computed using descriptive statistics. All values are expressed as mean ± SD. Significant level was set at $p<0.05$. Figures were made using GraphPad (GraphPad Prisma 8, LaJolla, CA, USA). To test for normality of the data, the Smirnov Kolmogorov test was used. All the data was seen to be normally distributed. The baseline values were compared against the post-treatment values to calculate significant intergroup and intragroup changes in all the variables over the study period. Baseline to post-treatment changes were assessed by use of the Paired T-test for intragroup changes whereas intergroup changes were assessed by use of the Unpaired T-test (both two-tailed). A trend towards significance was accepted at $p<0.1$.

3. Results

Thirteen patients with IRD completed our study at the TrenHer Klinikken located in Trondheim, Norway. Patients were selected accordingly to the inclusion and exclusion criteria set aside for this study *(see table 2)*. Seven patients were allocated to the MST intervention group and six patients were allocated to the control group. Patients in the intervention group attended all the necessary exercise session and assessment visits. Control group patients were only able to attend baseline-test visits due to the COVID-19 outbreak.

3.1 Characteristics and Strength Profile of the Participants

Results of all physiological variable measure during MST testing at baseline and post-treatment are summarized in *Table 3* and *Table 4*.

Table 3 Inflammatory Rheumatic Patients Characteristics Pre and Post Intervention and Control period.

	Intervention Group (n=7)		**Control Group (n=6)**			
Outcome	**Baseline**	**Post-Treatment**	**Baseline**	**Post-Treatment**	**95% CI**	***p*-value**
Subjects	7	7	6	6		
Female/Male	7/0	7/0	2/4	2/4		
Age (years)	40 ± 11.6	40 ± 11.6	50.5 ± 11.8	50.5 ± 11.8	-3.8 ± 24.8	0.855
Height (cm)	167.9 ± 6.9	167.9 ± 6.9	175.7 ± 6.7	175.7 ± 6.7	-0.5 ± 16.1	0.953
Body Weight (Kg)	87.6 ± 28.8	87.5 ± 27.7	105.4 ± 21.2	105.4 ± 21.2	-1.2 ± 1.3	0.055
BMI (Kg/m^2)	30.7 ± 7.9	30.7 ± 7.7	34.0 ± 5.4	34.0 ± 5.40	-0.4 ± 0.4	0.050

Note: Values for age, height, body weight and BMI are presented as mean ± SD. *p<0.05, **p<0.01
BMI: Body Mass Index, CI: Confidence Interval
p-value for difference in Δ between groups.

3.1.1 Rate of Force Development

The rate of force development evaluation along with peak force, showed a statistically significant intergroup difference between the MST intervention group and the control group with amplified results favouring those in the MST intervention group (RFD: p = 0.002, PF: p = 0.005) *(see Table 4).* The intragroup differences within the MST intervention group showed a statistically significant difference in post-treatment values compared to those obtained at baseline for RFD (p = 0.021) as illustrated in *figure 1*, and PF (p = 0.06) *(see table 4).*

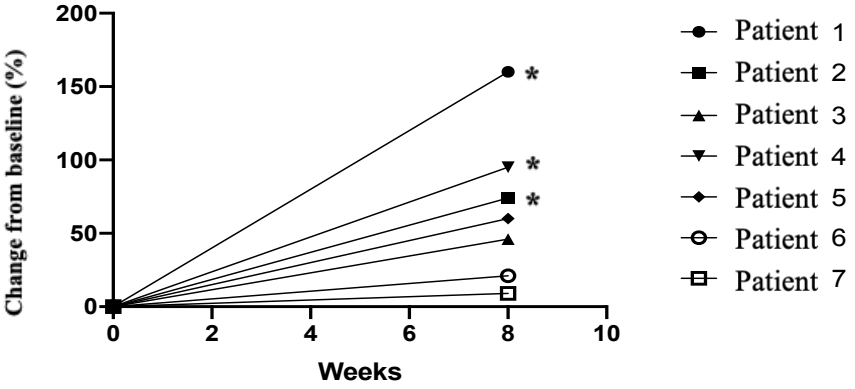

Figure 1. Percentage change in absolute RFD ($N \cdot s^{-1}$) from baseline to post-treatment within the MST intervention group. Data is presented as individual percentage change per patient. * significant difference within patients from baseline to post-treatment ($p < 0.05$)

3.1.2 Maximal Strength

The muscular strength evaluation using the 1RM weight being lifted, showed a statistically significant intergroup differences between the MST intervention group when compared to the control group with amplified results favouring those in the MST intervention group in both absolute ($p = 0.018$) and relative ($p = 0.018$) terms *(see Table 4)*. The 1RM intragroup difference within the MST intervention group reported a statistically significant difference in post-treatment values compared to those obtained at baseline as illustrated in *figure 2*, for both absolute ($p = 0.001$) and scaled 1RM ($p = 0.003$). The 1RM was reported to be improved by 22.2 % within the MST intervention group after twenty-four sessions.

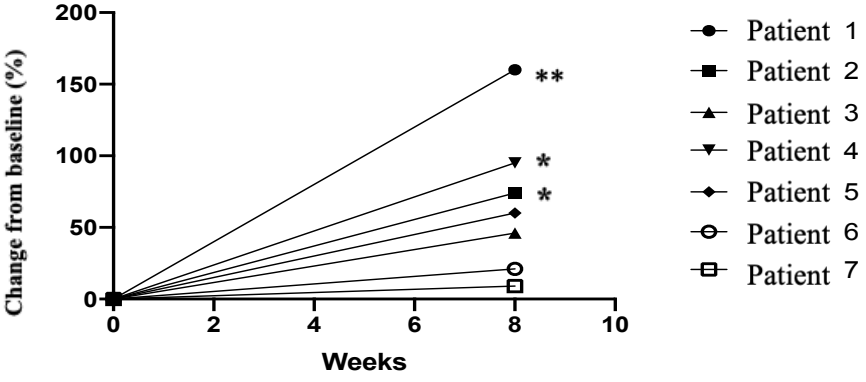

Figure 2. Percentage change in scaled 1RM ($Kg^{0.66}$) from baseline to post-treatment within the MST intervention group. Data is presented as individual percentage change per patient. * significant difference within patients from baseline to post-treatment ($p < 0.05$) ** significant difference between groups from baseline to post-treatment ($p < 0.01$).

3.1.3 Work Economy

This study advocates that MST in IRD patients using heavy loads (85 % 1RM) , few repetitions (four repetitions) and maximal intentional velocity for potential improvements in C. The evaluation of C using a single stage five minute bout of exercise at a submaximal speed of 4 $km \cdot h^{-1}$ and no inclination, showed statistically significant intergroup differences between the MST intervention group when comparisons to the control group were made. Amplified results favoured those in the MST intervention group ($p = 0.003$) *(see Table 4)*. Following the intervention period the MST intervention group had an improved intragroup C reflected by a reduced oxygen cost of walking (-2.5 $ml \cdot min^{-1} \cdot kg^{0.76}$) at the given submaximal speed, however these intragroup result were not statistically significant ($p>0.05$).

3.2 Disease Activity (VAS pain and fatigue)

According to the questionnaire, the intervention groups self-reported overall health VAS score for pain decreased by 10.6 mm ($p = 0.236$)*(see Table 4)* during MST along with a decrease of 9.3 mm for fatigue ($p = 0.257$)*(see Table 4)*. Patients reported to have felt less pain and reduced levels of fatigue even though the results did not indicate a significant intragroup change from baseline to post-treatment ($p>0.05$) as illustrated in *figure 3*. The VAS pain scores indicated a clinically important difference present accompanied with a trend towards a clinically important difference present for the VAS fatigue scores within the MST intervention group. When comparisons to the control group were administered, both the VAS pain ($p = 0.001$) and VAS fatigue ($p = 0.03$) scores where seen to have statistically significant differences after twenty-four sessions of MST.

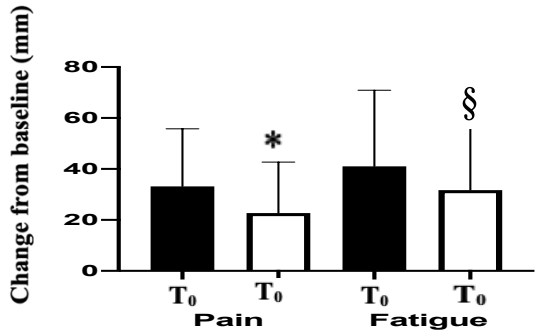

Figure 3: Overall change in absolute VAS score (mm) from baseline to post-treatment for pain and fatigue within the MST intervention group. Data is presented mean ± SE. * clinically important difference within patients from baseline to post-treatment ($mm \geq 10.5$). § trend towards a clinically important difference within groups from baseline to post-treatment ($p < 0.1$) T_0, baseline; T_1, post-treatment.

Table 4: Comparisons Between Groups For Primary and Secondary Outcomes.

	Intervention Group (n=7)		Control Group (n=6)			
Outcome	**Baseline**	**Post-Treatment**	**Baseline**	**Post-Treatment**	**95% CI**	***p*-value**
Subjects	7	7	6	6		
1RM (Kg)	134.3 ± 29.1	163.6 ± 34.5**	175.7 ± 6.7	175.7 ± 6.7	-41.1 ± -17.5	0.018
1RM Scaled ($Kg^{0.66}$)	7.2 ± 1.0	8.6 ± 0.9**	7.9 ± 1.5	7.9 ± 1.5	-2.1 ± -0.7	0.018
RFD ($N \cdot s^{-1}$)	1031.7 ± 679.4	1319.6 ± 535.9*	1335.4 ± 717.6	1335.4 ± 717.6	-671.5 ± -189.1	0.002
Peak Force (N)	1472.1 ± 279.4	1575.1 ± 279.8**	1942.3 ± 567.8	1942.3 ± 567.8	-677.0 ± -183.67	0.005
Work Economy ($ml \cdot min^{-1} \cdot kg^{0.76}$)	37.1 ± 2.7	34.5 ± 10.5	40.5 ± 5.04	40.5 ± 5.0	-0.9 ± 0.3	0.003
VAS Pain	33.1 ± 22.7	22.6 ± 19.7	37.0 ± 23.7	37.0 ± 23.7	-8.7 ± 29.8	0.001
VAS Fatigue	41.0 ± 29.9	31.7 ± 24.2	35.5 ± 28.6	35.5 ± 28.6	-8.5 ± 27.0	0.030

Note: Values for 1RM, RFD, PF and Work Economy are presented as mean ± SD. *p<0.05, **p<0.01
RFD: Rate Of Force Development, 1RM:One Repetition Maximum, VAS: Visual Analog Scale.
p-value for difference in Δ between groups.

4. Discussion

To our knowledge, this is the first population-based study which investigated the association between maximal strength training, rate of force development, one repetition maximum, work economy and quality of life amongst 18-65 year old patients with inflammatory rheumatic disease. The major novel findings of our study were that a MST intervention performed in a medical setting for twenty-four sessions was an effective strategy to improve 1RM as well as RFD and subsequently reduce the CVD risk within IRDs. Improvements in 1RM were closely accompanied by an increase in RFD reflecting greater newton values reached over smaller time periods. Secondly, MST lead to significant improvements in C along with quality of life and magnified these measures more than standard medical treatment. The twenty-four sessions of MST were well tolerated by the IRD patients and no adverse events were reported. The MST IRD patients experienced significant improvements in RFD (p = 0.002), PF (p = 0.005), 1RM (p = 0.018) and C (p = 0.003) when comparisons to the control group were made. In addition, twenty-four sessions of MST resulted in lower reported pain (-10.57 mm) and fatigue (-9.29 mm) levels within the IRD patients.

4.1 Characteristics and Strength Profile of the Patients

4.1.1 Maximal Strength

Patients with IRDs experience losses in muscle volumes along with declines in muscular strength with increasing disease activity (Felipe Martinelli Lourenzi et al., 2017). Greatest strength improvements are experienced in low repetition high load, MST sessions incorporating 85-95% 1RM, working to augment maximal voluntary contractions, targeting improvements in the rate of force development (D. G. J. J. o. S. Behm & Research, 1995). The improvements seen in muscular strength following a MST intervention are generally not accompanied by muscular hypertrophy (Aas et al., 2020). Therefore, the strength improvements after twenty-four sessions of MST are owed primarily to neural factors rather than muscular factors. The MST intervention group improved 1RM substantially and significantly more from baseline to post-treatment with reference to 1RM values in absolute ($p = 0.001$) and scaled ($p = 0.003$) terms. Statistical intergroup differences were also present between the MST intervention and control group ($p = 0.018$). The overall strength improvement were recorded 22.2 % higher in the post-treatment compared to those recorded at baseline for the MST intervention group. This is owed to standard workloads becoming relatively smaller (Hoff et al., 2002). Muscular strength improvements by use of an MST intervention can be done within IRD patients to combat against muscular atrophy and strength decrements whilst providing joint stability and preserving joint range of motion (F. M. Lourenzi et al., 2017). Thus, allowing IRD patients to experience better physical functioning to perform everyday activities related to daily living. The possibility of reducing CVD mortality within IRD patients by promoting regular MST, involving major muscle groups of the upper and lower body three times a week cannot go unnoticed. Therefore, MST should be used to compliment pharmacological treatment to reduce the CVD burden rather than as a replacement.

4.1.2 Rate of Force Development

The magnitude of the activation, and the force produced by the muscles are dependent upon the number of motor units recruited and the rates at which the motor neurons discharge their action potentials. The recruitment order of motor units during rapid contractions follows that of the size principle, as low threshold motor units are recruited before larger threshold motor units (Maffiuletti et al., 2016). The present study demonstrated significant intragroup

and intergroup RFD ($p = 0.021$, $p = 0.002$) and PF ($p = 0.006$, $p = 0.005$) improvements respectively after the twenty-four session MST period in IRD patients. The intervention can be seen to improve the muscle force-generating capacity within IRD patients. These changes in RFD and PF within the IRD patient population as stated prior are owed to neural adaptations specifically: increased motor unit recruitment, enhanced motor neuron firing frequencies and increased rate coding. The RFD relies upon the ability of the muscles contractile elements to develop force. The ability to produce higher force values more rapidly were predominantly due to enhanced muscle activation at the onset of the contraction (Andersen & Aagaard, 2006).

Improvements in neuromuscular function as seen by improved RFD and PF values may lower the risk of falls and fractures, this is of particular importance given the significant risk of fractures as seen within IRD patients (Baillet, Vaillant, Guinot, Juvin, & Gaudin, 2012). Improved RFD and PF as evident from the MST intervention group may lead to relatively smaller time periods spent in the less efficient force development phase, compared with the more efficient force maintenance phase during activities of daily living. The muscle mass involved and co-contractions from antagonists may be reduced and contribute to improved functional efficiency (Berg, Nyberg, Windedal, & Wang, 2018), having positive contributions towards everyday tasks for IRD patients.

4.1.3 Work Economy

The results of our current study on C are in line with those observed in previous research investigated on healthy subjects (Hoff 1999,2002). Similarly, MST was shown to positively affect C in our study. Barrett-O'Keefe et al. (2012) reported that the changes responsible for the improved C following a MST intervention period solely originate from the trained muscle bed. Therefore, suggesting a reduced blood flow to the active muscles being the main mechanism for the improved C rather than changes in the metabolic capacity (Barrett-O'Keefe et al., 2012).

This is an important factor within any patient population, as the patients C can propose challenges that restrict their ability to partake in any form of physical activity and may even be associated with a decreased quality of life (Heggelund et al., 2013). The MST intervention group resulted in 3.6 % improvements in walking economy when compared to controls. These changes indicate that the MST intervention groups ability to perform more work or the same amount of work with a reduced effort. As evident from our study, the patients quality of life by measure of the VAS pain scores and the VAS fatigue scores were

improved with bettered C. This study indicates that a MST intervention of twenty-four sessions is an effective means of improving C within IRD patients. The recorded C of the IRD patients improved statistically more within the MST intervention group compared to those of the control group ($p = 0.003$). This was also evident with average intragroup improvements of -2.5 ml·min·kg$^{0.76}$ from baseline to post-treatment, after the twenty-four session MST intervention period. Both high intentional velocity along with heavy loads are seen to be the most important factors for improving C (Heggelund et al., 2013) thus, providing MST with the most potent stimuli for improving C (Wang et al., 2017). The increased 1RM strength values induced by MST correlates positively with RFD and the overall improved C.

The increased RFD as observed in our MST intervention group lead to longer atonic periods between muscular contractions as well as an enhanced perfusion of the active lower leg skeletal muscles. The increased 1RM values as seen between baseline to post-treatment as evident in our MST intervention group, lead to an overall reduction in the relative load being placed on the muscles (Osteras, Helgerud, & Hoff, 2002). Thus, as seen in our current study the force required during a standard submaximal workload is shifted lower down on the recruitment hierarchy after the MST intervention, utilizing a greater percentage of more efficient type I muscle fibers (Berg et al., 2018). The reduction in the relative load being placed on the muscles may even improve the patients stability when walking, subsequently reducing the oxygen costs needed (Wang et al., 2010). Although it was not measured, the MST incorporating the leg press apparatus may have influenced the distribution of type I and type II muscle fibers. Counteracting the loss of type II muscle fibers cross sectional area and positively impacting on the C (McGuigan et al., 2001).

4.2 Disease Activity and Quality of Life

Quality of life was used as a measure of treatment efficacy and assessed by the VAS score for pain and fatigue. As seen in *Figure 3,* after twenty-four sessions of MST the disease activity measured by the VAS score assessing pain and fatigue reported statistically significant intergroup improvements for VAS pain ($p = 0.001$) and VAS fatigue ($p = 0.03$) when compared to the control group. However, none of the parameters tested showed significant intragroup changes within the MST intervention group, meaning that the IRD patients pain and fatigue levels experienced were not exacerbated by participation in this current twenty-four session MST intervention. Although both intragroup VAS pain and VAS

fatigue scores for the MST intervention group showed promising improvements for overall quality of life in patients with IRDs. The VAS pain score showed to have clinically important improvements (-10.6 mm) from baseline to post-treatment in the MST intervention group. However, even though the improvements in the VAS fatigue score for the MST intervention group did not report to be clinically important (-9.3 mm), there was a trend ($p<0.1$) present towards achieving values of clinical importance. This indicates that even though the patients were exposed to heavy strenuous workloads, this did not exacerbate the feeling of pain or fatigue in IRD patients. As a consequence of the MST intervention, IRD patients are less limited during activities of daily living, having more energy whilst reporting lower levels of pain and fatigue. This is of increasingly importance to take note of for the application of MST amongst IRD patients with reference to quality of life as they are now able to perform activities of daily living whilst not being limited by pain and fatigue.

Responsible for the changes in the VAS score for pain and fatigue could be due to improved 1RM and RFD, as evident by strong correlations between the changes in these parameters and the subsequent bettered VAS scores. The increased walking performance as indicated by an improved C allows the IRD patients to perform more work or to perform the same amount of work with less physical strain. Being of utmost importance when referenced to activities of daily living where walking is the most commonly used form of movement leading to less fatigue and improved pain. This is also the first study using the VAS to investigate the effects of pain and fatigue after an MST intervention in patients with various IRDs. Thus, data regarding these parameters for comparative purposes are sparse.

Our results reveal a possible link between improved inflammatory marker profiles and strength improvements (1RM) as evident in our MST intervention group. Steensberg et al. (2002) reported cytokines and myokines are secreted from skeletal muscles as a response to muscular contractions following MST. The skeletal muscle operating as an endocrine organ, exerts anti-inflammatory effects, acting locally or systemically on adipose tissues and organs (Steensberg et al., 2002). Pain and fatigue scores measured by the VAS decreased following our MST intervention period compared to prior participation. Thus, explaining a possible rationale for these improvements. However, these parameters were not investigated in our study. This issue should be investigated in greater detail in future studies.

4.4 Inflammation and CVD

MST is associated with reduced levels of inflammatory markers and cytokines (Ogawa, Sanada, Machida, Okutsu, & Suzuki, 2010). This supports the idea that engaging IRD patients in a twenty-four session MST intervention will be an effective measure in reducing systemic low grade inflammation and subsequently reducing the burden of CVD within the IRD patient population. Poor muscular strength is reported to be strongly associated with high levels of inflammatory markers (Schaap, Pluijm, Deeg, & Visser, 2006). Therefore, inflammation can be seen to be associated with a loss of muscle mass and subsequently muscular strength. The loss of skeletal muscle mass and muscular strength is of ever growing importance as these are primary factors in IRDs that contribute to frailty, leading to a profound impairment on the patients quality of life (Ogawa et al., 2010).

Longitudinal evidence indicates that regular strength training induces the suppression of systemic low grade inflammation (A. M. Petersen & B. K. Pedersen, 2005). Therefore the reduction in pain and fatigue reported by the VAS questionnaire may be linked to the anti-inflammatory effect induced by our current twenty-four session MST study. The observed increase in 1RM from MST is therefore imperative to combat against low grade inflammation within the IRD population. The atherosclerotic process is characterized by constant low grade inflammation. Strength training can be seen to offer a protective mechanisms to counter atherosclerosis by protecting the cardiovascular system against vascular inflammation as well as reducing systemic low grade inflammation (Abramson & Vaccarino, 2002).

4.5 Safety of MST in IRD

The IRD patients expression for safety is the consistent result of no worsening disease activity related to strenuous exercise (Sveaas et al., 2014). For many years MST has been considered inappropriate for IRD patients to participate in. Concerns included heightened disease activity, joint damage, pain and fatigue (Lemmey et al., 2009) and inevitably were warned against participation in such activities. Consequently many practitioners still do not advocate any form of strenuous strength training to their patients (Metsios et al., 2008). The results from our current study show that MST within the IRD patient population is seen to be a safe intervention as pain and fatigue were not exacerbated during the twenty-four session training period, by reference to the VAS pain and fatigue scores. No incidences of inflamed joints or joint damage were reported. Thus, patients with IRD can take advantage of the vast beneficial health and wellbeing effects by part taking in regular MST.

4.6 Strengths and Limitations

The major strength of this study was the nature and setting in which it was conducted. The study was conducted in a real world setting supporting the real world nature of varying compliance between patients. This is the first study to investigate MST in IRD patients where comorbidities did not result in exclusion to our study, allowing for greater generalization of the patients results. Patients suffering from IRDs experience unstable and irregular disease activity. Daily and weekly variance in perceived health may vary considerably. With persons suffering from these diseases considering themselves healthy one day, while the next day they may experience joint pain and illness. It is thus difficult to have these conditions fixed and patients having to resort to the use of anti-inflammatory drugs to combat arising issues. These factors have to be taken into consideration when assessing and interpreting the results. High standard deviations are a possible result of this.

The unforeseen widespread of the COVID-19 virus lead to a lower number of subjects being able to be included in our study compared to that outlined in our sample size calculations. Forced closure of clinics and all public facilities by The Norwegian Health Authorities made it impossible to incorporate a larger number of IRD patients. Therefore, our sample size might be a possible limitation, a greater number of participants as referenced to by our initial power calculation may result in more comparable results across the IRD population. Several trends were evident across our specific tests and the inclusion of more patients at post-treatment would have enhanced the statistical power and could have produced results of statistical significance.

Due to our current study being a blocked randomized controlled clinical trial we did not have control over which patients were placed into which group. This lead to a miss match of genders between the groups and within the groups which may exaggerate results when comparing statistical analysis between the intervention and control group. Normalizing men and women equally across the intervention and control group could lead to more accurate representations across the IRD population. Two patient were required to train in the hack squat during the MST intervention period compared to baseline and post-treatment where the use of the horizontal leg press apparatus was administered. The implementation of the hack squat was due to specific past injury concerns and body dimension issues leading to discomfort. The different training equipment and subsequent altered mechanical loading of the muscles could lead to underestimated 1RM and RFD values at post-treatment.

The VAS pain and the VAS fatigue score measurements were only taken twice, once at baseline and once at post-treatment per patient. These results reflect the status of the patient at the exact time when these given test were being administered with reference up to a week prior. Therefore not being a true representation of what occurred during the whole intervention period i.e. per session changes. Making it unclear if the improvement in pain and fatigue were linear or if symptoms may have worsened initially before improving. The inclusion of a broad spectrum of individual diseases which are categorized under IRD into our current study, made it impossible to give individualized results and recommendations per disease. But rather generalized recommendation and results for the spectrum of diseases which fell under IRD. Inclusion of a greater number of patients for each disease sub category could be beneficial to identify trends and correlations per individual disease.

The current study was performed in the framework of a master's thesis, therefor a limitation was the time constraints as the intervention had to be completed between January and March 2020. Making a long term study impossible and not allowing for a follow up assessor to track the overall progress and long term benefits MST has on combating pain and fatigue within IRDs.

5. Conclusion and Practical Implications

In conclusion, eight weeks of MST was well tolerated by patients with IRD, accompanied with significantly improvements in RFD ($p = 0.002$), PF ($p = 0.005$), 1RM ($p = 0.018$), and C ($p = 0.003$) when compared to controls. Reductions in pain and fatigue were noted across all the MST patients. Intragroup results reported clinically important differences were present in the VAS pain scores and a trend towards clinically important present in the VAS fatigue scores within the MST intervention group. Intergroup analysis reported statistically significant differences in both the VAS pain ($p = 0.001$) and the VAS fatigue ($p = 0.03$) scores both in favour of the MST intervention group. Based on these findings, this study suggests MST can be safely recommended for patients with IRDs as pain and fatigue were not exacerbated from MST, accompanied with no incidences of inflamed joints or joint damage reported. MST is recommended for patients with IRD for improvements in 1RM, RFD, PF, C, VAS pain and fatigue scores whilst reducing CVD risk.

6. Future Directions

The present study examined the effect MST had on inflammatory rheumatic disease patients over a period of twenty-four sessions. Further investigations are needed to investigate the effect MST has on IRD patients with respect to specific blood biomarkers namely IL-6, IL-7 and CRP. Since it is still unclear on the cytokine response from MST within IRD patients. A future study should involve a longer trial period with a follow up assessor to evaluation how effective MST is in combating pain and fatigue in a long term context. Along with investigating the adherence patients have to an MST treatment program without constant supervision over a long term period.

7. Perspectives

The reduced muscular strength levels as evident in IRD patients, are linked to the vicious cycle of chronic inflammation and inactivity. The severity of the disease relates to the magnitude of the impairment proposed by Benatti and Pedersen (2015). Improved maximal strength and RFD are shown to improve IRD patients functional status and quality of life. MST does not effect VO_{2max} but contributes towards the improved aerobic endurance performance due to the enhanced C. Therefor MST should be used together with an aerobic endurance training intervention to complement each other encompassing a multitude of factors contributing to improving the anti-inflammatory patients profile and CVD risk.

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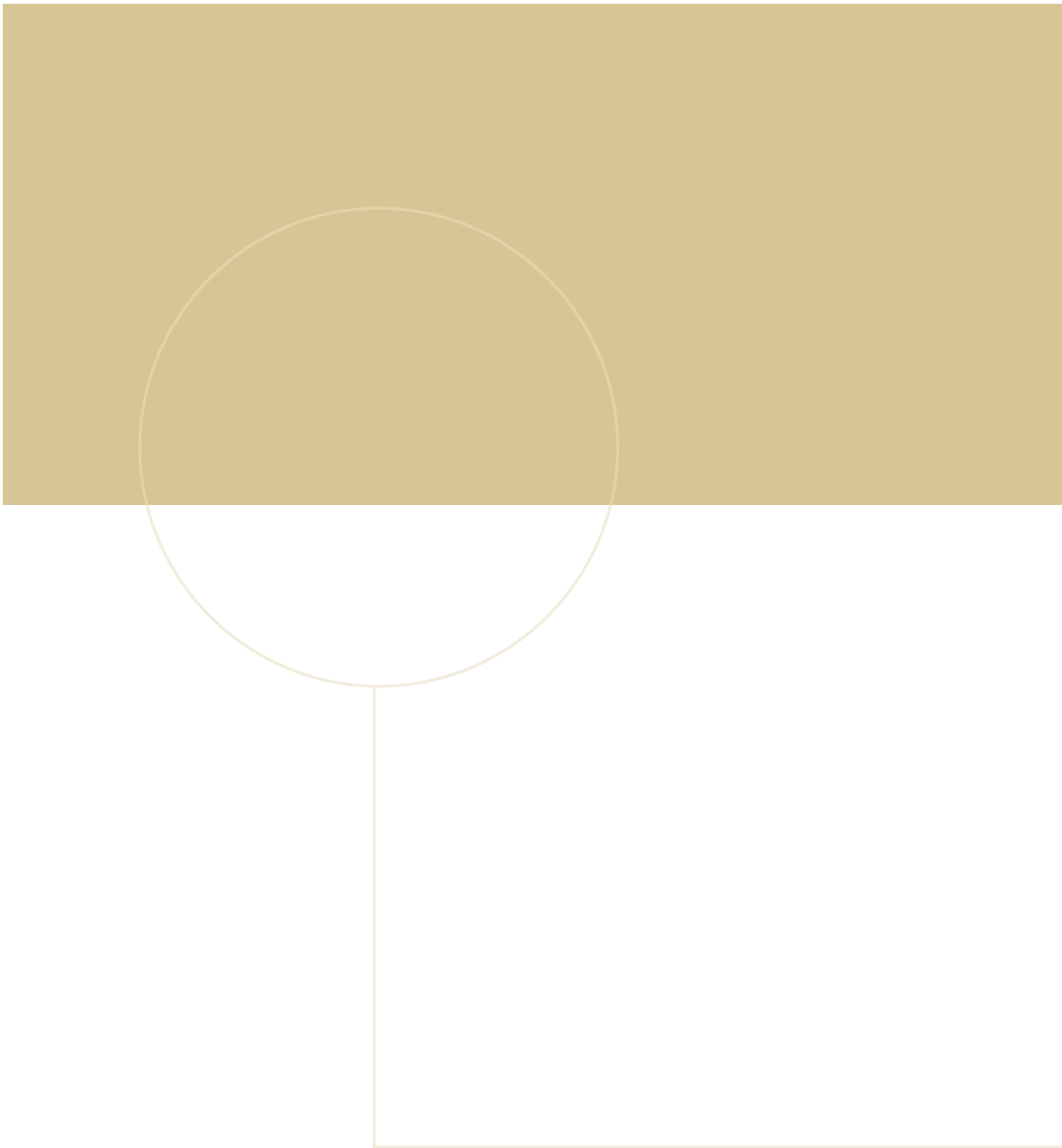

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