PHYSICAL EXERCISE AS A TARGETED THERAPY IN IDIOPATHIC INFLAMMATORY MYOPATHIES

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To Hedvig, Erik, mamma och pappa
ABSTRACT

Idiopathic inflammatory myopathies are comprised of polymyositis (PM) and dermatomyositis (DM) with muscle impairment being the primary clinical feature. With the currently recommended treatment regimen, a majority of patients develop sustained impaired muscle performance and poor health for undetermined reasons. The overall aim was to test the hypothesis that sustained muscle impairment and poor health in patients with established PM/DM are consequences of low aerobic capacity and that the use of endurance exercise, as the targeted intervention, will contribute to beneficial systemic and muscle adaptations and to clinical improvement. A further aim was to evaluate the individual priorities (e.g., patient preferences) of patients with established PM/DM.

The effect of a 12-week endurance exercise intervention was evaluated in a multicenter, randomized control trial in patients with established PM/DM (Papers II-IV). Exercise performance, aerobic capacity (maximal oxygen uptake (VO\textsubscript{2} max)), and lactate levels in skeletal muscle were compared between patients (n = 23) and healthy controls (HC) (n = 12). Patients (n = 21) were randomized into an endurance exercise program or a nonexercise control group. Clinical assessments were performed at 0 and 12 weeks and consisted of: VO\textsubscript{2} max, health (SF-36), muscle performance and disease activity (International Myositis Assessment and Clinical Studies Group criteria). Disability assessments were repeated at 52 weeks in an open extension. Associations between changes in clinical outcome measures and muscle properties were studied in vastus lateralis muscles by measuring extracellular lactate levels with microdialysis and by analyzing muscle biopsies for: mitochondrial enzyme activities (citrate synthase and β-hydroxyacyl-CoA dehydrogenase); mRNA expression profile; target protein validation by western blot analysis and by immuno-histochemistry (capillary density and inflammatory markers). In Paper I, we describe the patient preference in patients with PM/DM (n = 28) using the MacMaster Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR).

Exercise performance and VO\textsubscript{2} max were lower in the patients than in the HCs, whereas their lactate levels at exhaustion were similar. 12 weeks of endurance exercise added to the recommended pharmacological treatment in patients with established PM/DM increased capillary density and mitochondrial capacity in skeletal muscle, which could have contributed to the markedly improved muscle performance through increased aerobic capacity. Lactate levels at exhaustion decreased. The improved health and decreased clinical disease activity could potentially be mediated through the demonstrated improved VO\textsubscript{2} max from the endurance exercise. 12 weeks of endurance exercise only had a long-term beneficial effect on muscle strength. Changes in gene expression following the endurance exercise program indicate activation of the aerobic phenotype and muscle growth pathways, which overwrites the muscle atrophy process and simultaneously suppresses the inflammatory response. However, other mechanisms, such as muscle weakness, also seem to contribute to impaired muscle performance in patients. The MACTAR revealed disease consequences important to individual patients that were not assessed in the recommended PM/DM outcome measures. Altogether the results of this thesis indicate that endurance exercise is essential to improve aerobic capacity, muscle performance, and health in these patients.


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LIST OF ABBREVIATIONS

PM  Polymyositis
DM  Dermatomyositis
MMT-8  Manual Muscle Test in 8 Muscle Groups
FI-2  Functional Index-2
MAP  Myositis Activities Profile
HAQ  Health Assessment Questionnaire
IMACS  International Myositis Assessment Clinical Studies Group
VO₂ max  Maximal oxygen uptake
MITAX  Myositis Intention To Treat Activity Index
IBM  Inclusion body myositis
HLA  Human leukocyte antigen
MHC  Major histocompatibility complex
TNF  Tumor necrosis factor
UV  Ultraviolet
CPK  Phosphocreatine kinase
AST  Aspartate aminotransferase
ALT  Alanine aminotransferase
LDH  Lactate dehydrogenase
ILD  Interstitial lung disease
ADL  Activities of daily living
IL  Interleukin
ER  Endoplasmatic reticulum
ATP  Adenosine-triphosphate
VEGF  Vascular endothelial growth factor
SF-36  Short Form–36
VAS  Visual Analogue Scale
MDI  Myositis Damage Index
DMARD  Disease-modifying antirheumatic drugs
GC  Glucocorticoids
AZA  Azathioprine
MTX  Methotrexate
CsA  Cyclosporine A
MMF  Mycophenolate mofetil
RCT  Randomized controlled trial
MACTAR  MacMaster Toronto Arthritis Patient Preference Disability Questionnaire
EG  Exercise group
CG  Control group
HC  Healthy control
WB  Western blot
IHC  Immunohistochemistry
Patient Global  Patient Global Assessment of Disease Impact
IQR  Interquartile range
VRM  Voluntary repetition maximum
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<th>Abbreviation</th>
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<tr>
<td>MYOACT global</td>
<td>Physician’s Assessment of Global Disease Activity</td>
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<td>MYOACTA extra</td>
<td>Global Extra-Skeletal Muscle Activity</td>
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<tr>
<td>RQ</td>
<td>Respiratory exchange ratio</td>
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<tr>
<td>Borg RPE scale</td>
<td>Borg Self-Reported Peripheral Exertion Scale</td>
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<td>Borg CR-10 scale</td>
<td>Borg Category Scale</td>
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<tr>
<td>CS</td>
<td>Citrate synthase</td>
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<tr>
<td>β-HAD</td>
<td>β-hydroxyacyl-CoA dehydrogenase</td>
</tr>
<tr>
<td>FLT3L</td>
<td>Fms-related tyrosine kinase 3 ligand</td>
</tr>
<tr>
<td>Kw</td>
<td>Weighted kappa coefficient</td>
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<tr>
<td>ICC</td>
<td>Intraclass correlation</td>
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<tr>
<td>IGF1R</td>
<td>Insulin-like growth factor receptor</td>
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1 BACKGROUND

1.1 IDIOPATHIC INFLAMMATORY MYOPATHIES

Idiopathic inflammatory myopathies are a heterogeneous group of disorders. Their primary clinical features are muscle weakness and low muscle endurance (Dalakas, 1995), (Hengstman et al., 2009). Typical cases are characterized by inflammatory cell infiltrates in muscle tissue (Dalakas, 1995). Based on specific clinical and histopathological differences, adult idiopathic inflammatory myopathies can be classified into three subgroups: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) (Dalakas, 1991). This study focuses only on adult patients with PM and DM; thus, IBM will not be discussed.

1.1.1 Epidemiology

PM and DM are relatively rare diseases with a yearly incidence rate of approximately 2 to 7 cases per 1 million inhabitants over the age of 16 years. Epidemiological data are scarce and somewhat unreliable due to the small patient cohorts that have been used for studies in the past (Dorph and Lundberg, 2002). Both PM and DM are more frequent in women than men (a ratio of 2.2 to 1) (Oddis et al., 1990). The peak of incidence in adults is between 50 to 60 years of age, although individuals in other age groups may be affected (Benbassat et al., 1980), (Tan et al., 2013). Although PM and DM are present worldwide, the ratio between them varies in different parts of the world, and a latitude gradient has been observed with DM being more common closer to the equator and PM being more frequent in countries at a northern latitude (Hengstman et al., 2000), (Okada et al., 2003).

1.1.2 Aetiology and pathogenesis

PM and DM are autoimmune diseases characterized by presence of T-lymphocytes in inflammatory infiltrates in muscle tissue and by autoantibodies, which are found in up to 80% of patients (Arahata and Engel, 1984), (Brouwer et al., 2001). Their aetiology is not known, but there are data to support that both genetic and environmental factors are risk factors for disease susceptibility and for the development of clinical features characterizing different subsets of myositis (Shamim et al., 2000), (Shamim and Miller, 2000). There is a clear association with certain human leukocyte antigen (HLA) class II alleles (Arnett et al., 1996). An even stronger association has been observed among certain subsets of myositis characterized by autoantibody profiles (Hengstman et al., 2006), (Chinoy et al., 2006). The most common autoantibodies in PM and DM are antinuclear autoantibodies (ANA), which are found in up to 80% of these patients (Brouwer et al., 2001). Of these autoantibodies, the anti-histidyl tRNA synthetase autoantibody, also called the anti-Jo-1 antibody, is the most frequent myositis-specific autoantibody and is found in 20% to 30% of patients with PM or DM. The association of PM/DM with certain HLA class II genotypes supports a role of a T-cell–driven immune response, as the only known function of major histocompatibility complex
(MHC) class II molecules is to present antigens to antigen-specific T-cell receptors (Arnett et al., 1996), (Shamim et al., 2000). There are also associations to non-MHC regions, such as a certain tumor necrosis factor (TNF) polymorphism, suggesting that multiple genetic factors are likely to contribute as risk factors for susceptibility to PM/DM or for severity of the diseases (Chinoy et al., 2006). Furthermore, some of the autoantibodies, like anti-Jo-1, may play a role in the development of different clinical phenotypes of PM/DM.

The most strongly linked environmental risk factor for DM is ultraviolet (UV) light, as illustrated by the above-mentioned association between DM and latitude and UV light exposure (Okada et al., 2003). Other environmental risk factors are infections and smoking (Andersson et al., 2003), (Christopher-Stine and Plotz, 2004), (Chinoy et al., 2012). There is a clear association between DM and malignancies (Zahr and Baer, 2011), (Airio et al., 1995). However, in the majority of patients, there is no proof of co-occurring or preceding infections, including detectable antigens in muscle tissue or the presence of anti-infectious antibodies (Ytterberg, 1994), (Tezak et al., 2000). Thus, it is likely that several different environmental factors could contribute to disease susceptibility in individuals with certain genetic contexts.

1.1.3 Diagnosis

Diagnoses of PM and DM are based on the presence of clinical and laboratory features that indicate muscle inflammation. The most often used diagnosis criteria were established by Bohan and Peter (1975a, 1975b) (Table 1). These are based on the presence of objective, symmetrical, and proximal muscle weakness; elevated serum levels of muscle enzymes (i.e., phosphocreatine kinase (CPK)); pathological electromyography and pathological muscle biopsy with signs of myopathy (regenerative and/or degenerative skeletal muscle fibers); inflammatory cell infiltrates with mononuclear inflammatory cells; and the exclusion of noninflammatory myopathy.
### Table 1. Bohan and Peter’s (1975a, 1975b) Diagnostic Criteria for Polymyositis and Dermatomyositis

1) Symmetric proximal muscle weakness

2) Elevation of serum muscle enzymes such as CPK, AST, ALT, aldolase, and LDH

3) Abnormal electromyographic findings, such as
   - short, small polyphasic motor units
   - fibrillations, positive sharp waves
   - insertional irritability
   - bizarre high-frequency repetitive discharges

4) Abnormal muscle biopsy findings, such as
   - mononuclear infiltration
   - regeneration and degeneration
   - necrosis

5) Skin rashes, such as
   - heliotrope rash
   - gottron sign
   - gottron papules

**Definite polymyositis: Criteria 1–4**
**Probable polymyositis: 3 of criteria 1–4**
**Possible polymyositis: 2 of criteria 1–4**

**Definite dermatomyositis: Criterion 5 and 3 of criteria 1–4**
**Probable dermatomyositis: Criterion 5 and 2 of criteria 1–4**
**Possible dermatomyositis: Criterion 5 and 1 of criteria 1–4**

The application of these criteria assumes that known infectious, toxic, metabolic, dystrophic, or endocrine myopathies have been excluded by appropriate evaluations. Symmetry is intended to denote bilateral, but not necessary equal, involvement.

CPK = Creatine phosphokinase; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; LDH = Lactate dehydrogenase

### 1.1.4 Clinical features

The severity of PM/DM is assessed as the disease activity and damage in the different organ systems as a result of the inflammatory process. Muscle inflammation and weakness and the development of premature muscle fatigue, especially in the proximal muscles, are cardinal features in patients with PM and DM (Hengstman et al., 2009), (Harris-Love et al., 2009).
Both PM and DM are inflammatory systemic connective tissue diseases, with muscle being the primary organ involved in most patients. However, other organs are frequently affected, and in some patients, another organ may be the most affected. Such extraskeletal muscle manifestations include the joints (arthritis), skin (rash), respiratory tract, gastrointestinal tract, and heart. Involvement of the respiratory tract is common; it may be present in up to 80% of patients and is associated with a high degree of morbidity and mortality (Marie, 2012), (Fathi et al., 2004), (Fathi et al., 2007). There are several ways that the respiratory tract system can be involved in myositis, including respiratory muscle weakness, aspiration pneumonia, dysphagia, and interstitial lung disease (ILD) (Hepper et al., 1964), (Oh et al., 2007), (Fathi and Lundberg, 2005). Inflammation of the skin is typical of DM, and several types of skin rash may be present (Albrecht et al., 2006). Arthritis often involves small joints with a symmetric distribution and is usually nonerosive. Patients may develop cardiac dysfunction, but in most cases, this is limited to subclinical arrhythmias (Lundberg, 2006). Ischemic heart disease is one of the major causes of death in PM/DM (Airio et al., 2006), (Lundberg and Forbes, 2008), (Marie, 2012).

In the early phase of the disease before treatment or at relapse, disease activity is generally high with typical inflammatory cell infiltrates in skeletal muscle. After a period of pharmacological treatment, most patients display a stable and low disease activity with less inflammatory manifestations from the skeletal muscle and other organ systems, but they are still impaired.

1.1.4.1 Skeletal muscle

The muscle symptoms in most patients with PM/DM have an insidious onset over weeks to months and mainly affect the proximal muscles with a symmetric distribution (Bohan and Peter, 1975a), (Bohan and Peter, 1975b). The primary muscle symptoms are muscle weakness and low muscle endurance, although some patients also experience muscle pain. Common clinical symptoms at onset are difficulties with walking up stairs or up hills, squatting, working with the arms above the head, and premature fatigue (Alexanderson et al., 2012). Later on during the course of the disease, if untreated or treatment resistant, most muscle groups may become involved, including the respiratory muscles. Occasionally, patients have a more rapid onset with the simultaneous involvement of many muscles groups. In the most severe cases, the patients may become confined to a wheelchair and/or need assisted ventilation. With the currently recommended treatment regimen, most patients improve their muscle performance, but few regain their previous muscle function—the reason for this is not fully understood (Zong and Lundberg, 2011), (Miller, 2012).

1.1.4.2 Whole body aerobic capacity, health, and activities of daily living

Despite recommended pharmacological treatment, a majority of PM/DM patients develop sustained limitations in activities of daily living (ADL) and poorer health compared to the general population (Marie et al., 2001), (Sultan et al., 2002), (Ponyi et
al., 2005), (Bronner et al., 2006), (Regardt et al., 2011) for not fully understood reasons (Zong and Lundberg, 2011). In the general population, the whole body aerobic capacity (assessed by maximal oxygen uptake, VO$_2$ max, m) is an independent indicator of health (Lakka et al., 1994). Furthermore, low whole-body aerobic capacity is a risk factor for other chronic diseases (Warburton et al., 2006) and is also a strong predictor of mortality (Myers et al., 2002). Based on this, a low VO$_2$ max, together with reduced muscle performance, contributes to the poor health and sustained disability found in patients with established PM/DM (Wiesinger et al., 2000).

1.1.5 Mechanism causing impaired muscle performance

In the acute phase, the mechanism leading to impaired muscle performance in patients with PM/DM is thought to be due to systemic and local inflammation in skeletal muscle. However, the sustained impaired muscle performance without obvious inflammation or muscle atrophy that is displayed in patients in the established phase of the disease is more uncertain but is thought to be due to secondary damage by the earlier inflammatory milieu, side effects of pharmacological treatment, and/or physical inactivity (Lundberg, 2001), (Nader and Lundberg, 2009), (Zong and Lundberg, 2011), (Hanaoka et al., 2012a), (Rayavarapu et al., 2012).

1.1.5.1 Inflammation

The expression of cytokines, such as interleukin (IL)-1 alpha and the alarmin high-mobility group box protein 1, is upregulated in skeletal muscle tissue and can contribute to a pro-inflammatory environment and muscle impairment in patients with PM and DM (Nyberg et al., 2000), (Lundberg, 2000), (Grundtman et al., 2010), (Zong et al., 2013a). Major histocompatibility complex (MHC) class I molecules are frequently expressed in muscle fibers in patients in the early disease phase and also in established PM/DM, even without inflammatory infiltrates (Englund et al., 2002). Transgenic mice overexpressing MHC class I have been shown to have decreased force production in skeletal muscle (Salomonsson et al., 2009). However, the role of inflammatory infiltrates and the inflammatory milieu in skeletal muscle causing impaired muscle performance is not clear.

1.1.5.2 Impaired aerobic capacity in skeletal muscle

The impaired skeletal muscle performance is not directly correlated to the immunological findings, which suggests the presence of nonimmune mechanisms, such as endoplasmic reticulum (ER) stress, hypoxia, and autophagy (Rayavarapu et al., 2011), (Henriques-Pons and Nagaraju, 2009), (Zong and Lundberg, 2011). Furthermore, muscle fiber degeneration, skeletal muscle atrophy, and failed muscle regeneration in patients with established PM/DM may also explain their muscle weakness (Loell and Lundberg, 2011).

In addition, a secondary aerobic metabolic dysfunction induced by the pro-inflammatory environment that causes hypoxia in skeletal muscle has been suggested to impair muscle function in established PM and DM (Zong and Lundberg, 2011), (Nader
et al., 2010), (Nader and Lundberg, 2009). The energy metabolic system in muscle cells is designed to supply the energy needed for prolonged low-intensity, as well as acute high-intensity, muscle activities. During prolonged low-intensity activities, the energy demand is low and energy is mainly provided by the oxygen-dependent aerobic metabolism. The energy substrates used in the aerobic pathways are mainly carbohydrates and fatty acids, which feed into the citric acid cycle located in the mitochondria. Citrate synthase (CS) is an essential enzyme of the citric acid cycle, and \(\beta\)-hydroxyacyl-CoA dehydrogenase (\(\beta\)-HAD) is an important enzyme in \(\beta\)-oxidation, which is the process by which fatty acids are broken down to enter the citric acid cycle. During acute high-intensity muscle activities, the energy demand is high and muscle cells also have to use the oxygen-independent anaerobic metabolism. The rapid energy production via the anaerobic pathways results in the accumulation of lactate and hydrogen ions and the breakdown of phosphocreatine to creatine and phosphate ions. Muscle activities that rely on a large component of anaerobic metabolism result in skeletal muscle fatigue with decreased contractile function and impaired performance. Metabolic dysfunction that results in a compromised aerobic metabolism adversely affects intrinsic muscle functions and results in premature muscle fatigue (Westerblad et al., 2010). Mitochondrial functionality is essential in the aerobic metabolism and in endurance muscle performance. When mitochondrial respiration is inhibited, muscle fatigue will occur rapidly in skeletal muscle (Westerblad et al., 2010). Both mitochondrial and capillary functionality are a prerequisite for aerobic metabolic capacity within skeletal muscle and are directly related to endurance exercise performance (Booth and Thomason, 1991), (Hepple et al., 1997), (Hood, 2001), (KA, 2012).

Several signs of metabolic dysfunctions found in established PM and DM are low levels of stored phosphocreatine and ATP in muscle tissue with decreased fatigue resistance and fewer aerobic slow-twitch type I muscle fibers (Park and Olsen, 2001), (Chung et al., 2003), (Dastmalchi et al., 2007). Abnormalities in the aerobic energy metabolism found in patients with PM/DM include mitochondrial and capillary pathology (Grundtman et al., 2008), (Blume et al., 1997), (Temiz et al., 2009), (Varadhachary et al., 2010). In arthritis, mutations in mitochondrial DNA are strongly associated with the local inflammatory environment, showing a link to pro-inflammatory pathways and mitochondrial dysfunction (Harty et al., 2012). Mitochondrial dysfunctions have been reported in patients with PM and DM, and these have been associated with impaired muscle function despite the use of recommended pharmacological treatment (Blume et al., 1997), (Temiz et al., 2009), (Varadhachary et al., 2010). In addition, micro-vessel circulation that is changed by thickened endothelial cells in muscle tissue, a reduced capillary blood supply, and a low total number of capillaries in the acute and chronic disease phases may impair oxygen transportation to the muscle tissue (Cea et al., 2002), (Grundtman et al., 2008). Furthermore, expression of total vascular endothelial growth factor (VEGF), which is a hypoxia marker, has been found to be upregulated in skeletal muscle in patients with established PM and DM (Grundtman et al., 2008). Experiments with induced hypoxia in skeletal muscle, by inhibition of mitochondrial respiration, demonstrated that premature muscle fatigue is a
consequence of hypoxia (Zhang et al., 2006). The mechanisms that lead to impaired muscle performance in established PM/DM have not been identified. However, altered aerobic metabolism capacity in skeletal muscle is a likely cause of the muscle impairment and the low whole-body aerobic capacity found in established PM/DM (Wiesinger et al., 2000).

1.2 RECOMMENDED OUTCOME MEASURES IN MYOSITIS

The International Mysositis Assessments Clinical Study (IMACS) Group has validated outcome measures for disease activity and disease damage and recommends using the Short Form–36 (SF-36) to assess health-related quality of life (Rider et al., 2011).

Disease activity assesses the manifestations of myositis, which are thought to be reversible and are direct results of the inflammatory process. The Myositis Disease Activity Assessment Tool includes physicians’ assessment of disease activity in different organ systems, including constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiovascular, others, and muscle. It also includes an overall assessment of global extraskeletal muscle (including all organ systems except the muscle) and global disease activity. For the evaluation of treatment effects, the IMACS Group recommends the use of IMACS core measures, including outcomes for disease activity, such as patient’s and physician’s global disease activity on the Visual Analogue Scale (VAS); the Manual Muscle Test in eight muscle groups (MMT-8); the Health Assessment Questionnaire (HAQ); and a laboratory assessment of CPK and an assessment of extraskeletal muscle disease activity in six organ systems (using the Myositis Intention to Treat Activity Index (MITAX) or the Global Extraskeletal Muscle Disease Activity) (Rider et al., 2011).

Disease damage includes persistent (> 6 months) and irreversible changes in pathology or function that result from the inflammatory process in PM/DM and/or the side effects of pharmacological therapy. Disease damage assesses the manifestations of myositis that are thought to be irreversible and that result directly from the disease process. This assessment includes the Myositis Disease Damage Index (MDI), which evaluates damage in 11 organ systems including muscle, skeletal, cutaneous, gastrointestinal, pulmonary, cardiovascular, peripheral vascular, endocrine, ocular, infection, malignancy, and physician’s global damage (Isenberg et al., 2004), (Rider et al., 2009), (Sultan et al., 2011), (Rider et al., 2011).

In addition, two myositis-specific outcome measures have been developed to assess muscle endurance, the Functional Index-2 (FI-2) (Alexanderson et al., 2006) and ADL, the Myositis Activities Profile (MAP) (Alexanderson et al., 2002), (Alexanderson et al., 2012).

However, none of the assessments recommended by the IMACS Group or the myositis-specific outcomes reflect patient preference. A patient preference outcome serves to identify individual disease-related disabilities that are most important for improving the condition of the individual patient. Fixed-item assessments may include disabilities not
relevant for all patients and may omit disabilities important to other individuals (Verhoeven et al., 2000a), (de Jong et al., 2003), (Wright and Young, 1997), (Jolles et al., 2005). International collaborations, such as the European League Against Rheumatism and Outcome Measures in Rheumatology, have identified outcomes for assessing patients’ preferences as a highly important research focus (Kirwan et al., 2005), (Sanderson and Kirwan, 2009).

1.3 TREATMENT
Recommended treatment for PM/DM consists of pharmacological treatments in combination with physical exercise interventions, as well as support from a rheumatology team including a nurse, occupational therapist, physical therapist, rheumatologist, and social worker. Physical exercise supervised by a physical therapist is used to rebuild muscle performance and improve ADL. There is limited research of the effectiveness of both pharmacological and physical exercise interventions in PM/DM (Miller, 2012), (Alexanderson and Lundberg, 2012). At present, there is no cure for PM/DM; in addition, according to clinical data, only a few patients will reach a stage of remission.

1.3.1 Pharmacological treatment
The pharmacological treatments for PM/DM include corticosteroids and other immunosuppressive agents for reducing the inflammation that contributes to the disease activity.

The cornerstone of the pharmacological treatment is a glucocorticoid (GC) given in high starting doses (0.75 to 1.00 mg/kg/day) administered for 2 to 4 weeks. Randomized placebo-controlled pharmacological trials in PM/DM are largely lacking; therefore, treatment recommendations are mainly based on small open studies and case reports. With high doses of GC, there is a substantial risk of GC-related side effects, such as osteoporosis, diabetes mellitus, and steroid myopathy; thus, a combination of GC and another immunosuppressive drug is usually recommended (Clarke et al., 1995), (Carpinteri et al., 2010), (Schakman et al., 2008). Other disease-modifying antirheumatic drugs (DMARDs) can be used to taper off the use of GC. The most common DMARDs for PM/DM are azathioprine or methotrexate (Bunch et al., 1980), (Bunch, 1981), (Gordon et al., 2012). If this treatment is ineffective or not tolerated, other DMARDs that have been beneficial in case reports or case series are cyclophosphamide and cyclosporine A, tacrolimus, or mycophenolate mofetil (Gordon et al., 2012). Two biologic agents, rituximab and anakinra, have been tested in refractory PM/DM with some promising results (Oddis et al., 2013), (Zong et al., 2013b).

Although many patients improve at least partially from pharmacological treatment, a majority have persisting muscle impairment, disability, and reduced health (Zong and Lundberg, 2011), (Regardt et al., 2011), (Bronner et al., 2006), (Ponyi et al., 2005). These findings indicate that some patients with PM/DM in an established disease phase
that are kept on stable pharmacological treatment generally do not improve in muscle performance and health.

1.3.2 Physical exercise

A physically active lifestyle is fundamental to maintaining health. Nevertheless, patients with PM and DM used to be discouraged from participating in physical exercise. For many years, patients with inflammatory myopathies were told to avoid physical exercise due to a fear that exercise would aggravate muscle inflammation and, thereby, muscle weakness. During the last decade, the data accumulated from several small studies have revealed the benefits and safety of exercise interventions for established PM and DM (Alexanderson and Lundberg, 2012), (Habers and Takken, 2011). Physical exercise also has a potential to prevent muscle atrophy due to muscle inflammation, physical inactivity, and systemic GC treatment (Nader and Lundberg, 2009). Thus, there is a need for physical exercise intervention studies with a randomized controlled trial (RCT) design and a need to increase the understanding of mechanisms that contribute to both muscle impairment and the mechanisms behind improved muscle function after exercise to enable the implementation of an optimal physical exercise regime (Alexanderson and Lundberg, 2012), (Habers and Takken, 2011), (Nader and Lundberg, 2009).

Systemic and within-skeletal muscle adaptations to repetitive bouts of muscle contractions depend on its frequency, intensity, and duration. Endurance exercise in healthy individuals improves aerobic capacity both systemically (whole-body aerobic capacity, VO\textsubscript{2} max) and locally in the skeletal muscle mainly by improved capillarity and mitochondrial function. Resistance exercise, on the other hand, leads to muscle hypertrophy and increased muscle strength. Only one RCT study was identified that evaluated an endurance exercise intervention in PM/DM patients with established disease. The 6-week exercise program revealed improved whole-body aerobic capacity and improved muscle strength with no change in plasma levels of CPK as a marker of muscle inflammation (Wiesinger et al., 1998a). Eight patients from this study continued the endurance exercise regimen for 6 months, resulting in a 28% improvement in whole-body aerobic capacity without an increase in inflammatory activity (Wiesinger et al., 1998b). Furthermore, physical exercise is suggested to have a downregulating effect on systemic inflammation and local inflammation in muscle tissue in patients with PM and DM (Nader and Lundberg, 2009). In addition, an exercise intervention in patients with established PM and DM resulted in upregulation in genes related to aerobic metabolism and downregulation in genes related to inflammation and fibrosis in skeletal muscle (Nader et al., 2010).

Taken together, these studies indicate that an endurance exercise intervention could potentially increase the aerobic capacity and muscle performance in PM/DM patients in an established disease phase. However, this needs further investigation and is therefore the topic of this thesis.
2 AIM
The overall aim of this study was to test the hypothesis that sustained muscle impairment and low health in established PM and DM are consequences of low aerobic capacity and that endurance exercise as a targeted intervention contributes to beneficial systemic and muscle adaptations and to clinical improvement. A further aim was to evaluate the preferences of patients with established PM/DM and to assess the measurement properties of a patient preference tool.

Paper I
The aim of this study was to evaluate each patient’s individual priorities (i.e., preferences) regarding which disabilities related to PM/DM should receive the most attention using the MacMaster Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR). The MACTAR was correlated to myositis outcomes and evaluated to determine its test-retest reliability.

Paper II
The objective of this randomized, controlled, multicenter study was to determine whether a 12-week endurance exercise program could improve health, patient preferences, ADL, muscle performance, and VO$_2$ max and reduce disease activity, as well as to evaluate correlations between VO$_2$ max and health, in patients with established PM/DM. Furthermore, we evaluated muscle performance, patient preference, ADL, and health in a 1-year open extension study.

Paper III
The major objective of this randomized, controlled, multicenter study was to determine whether patients with established PM/DM display impaired aerobic capacity in skeletal muscle compared to healthy controls (HCs) and to determine if endurance exercise can improve skeletal muscle performance and aerobic capacity in patients with established PM/DM.

Paper IV
The aim of this randomized controlled pilot study was to determine the potential mechanisms underlying the beneficial adaptations in skeletal muscle of endurance exercise in patients with established PM/DM.
3 METHODS

3.1 STUDY DESIGN

An overview of the study design for Papers I, II, III, and IV is presented in Table 2. In Papers II to IV, the effect of a 12-week endurance exercise intervention was evaluated in a multi-center RCT in patients with established PM/DM.

**Paper I**
Over a 1-year period, patients with PM/DM were evaluated at their annual visits to their Rheumatology Unit at the Karolinska University Hospital in Sweden. They took part in a semi-structured interview (MACTAR) two times, with a 1-week interval between the test sessions.

**Paper II**
The controlled part of paper II was a multicenter RCT that evaluated the effects of a supervised 12-week endurance exercise program compared to a nonintervention control group (CG) with a 1-year open extension followup. Patients were recruited at three centers; the Karolinska University Hospital, the Sahlgrenska University Hospital, and the Uppsala University Hospital in Sweden.

**Paper III**
In the first part of Paper III, patients with PM/DM were compared to age- and gender-matched HCs. In the second part, the patients were randomized to perform a 12-week endurance training program (exercise group) or to a nonexercising CG. The RCT was based on three hypotheses: (i) Patients display impaired endurance due to reduced aerobic capacity and muscle weakness, (ii) endurance training improves their exercise performance by increasing the aerobic capacity, and (iii) endurance training has general beneficial effects.

**Paper IV**
This pilot study was a hypothesis-driven exploratory step of a large RCT evaluating molecular effects in the skeletal muscle of a supervised 12-week endurance exercise program compared to a nonintervention CG. Patients with available paired muscle biopsies, from baseline and after 12 weeks, were included. Due to the limited amount of muscle tissue, the muscle biopsies were selected to be used for either microarray gene expression analysis or protein target validation by Western blot or for immunohistochemistry (IHC) analysis for the quantification of capillaries and inflammatory markers.
Table 2. Study Design Overview for Papers I, II, III, and IV.

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Prospective, explorative, cross-sectional</td>
<td>Prospective multicenter RCT, 1-year open extension</td>
</tr>
<tr>
<td><strong>Participants/</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>settings</strong></td>
<td>28 PM/DM patients recruited from the annual</td>
<td>23 PM/DM patients recruited at 3 rheumatology university units in Sweden;</td>
</tr>
<tr>
<td></td>
<td>team visits at the Rheumatology Unit at</td>
<td>patients participated in an endurance exercise intervention, and 16 of</td>
</tr>
<tr>
<td></td>
<td>Karolinska University Hospital, Stockholm,</td>
<td>the patients were evaluated for long-term effects</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td></td>
</tr>
<tr>
<td>**Methods/</td>
<td>Semi-structured interview and clinical</td>
<td>Clinical evaluation of an endurance exercise intervention and its long-</td>
</tr>
<tr>
<td><strong>data sources</strong></td>
<td>assessment</td>
<td>term effects</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>Descriptive, test of validity (Spearman’s</td>
<td>Analysis of between-group interactions (group x time) (mixed model);</td>
</tr>
<tr>
<td></td>
<td>correlation), and test-retest reliability</td>
<td>correlation between variables (Pearson’s correlation); descriptive and</td>
</tr>
<tr>
<td></td>
<td>(weighted kappa, intraclass correlation)</td>
<td>statistical analysis of responders (Fisher’s exact test)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Prospective, explorative, cross-sectional,</td>
<td>Pilot, hypothesis-driven, explorative RCT</td>
</tr>
<tr>
<td></td>
<td>prospective multicenter RCT</td>
<td></td>
</tr>
<tr>
<td><strong>Participants,</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>settings</strong></td>
<td>23 PM/DM patients recruited at 3 rheumatology</td>
<td>15 PM/DM patients were recruited at the Karolinska University Hospital;</td>
</tr>
<tr>
<td></td>
<td>university units in Sweden and 12 matched</td>
<td>patients with paired muscle biopsies as part of a larger RCT evaluating</td>
</tr>
<tr>
<td></td>
<td>HCs were analyzed at baseline; 16 of the</td>
<td>the effects of endurance exercise were included</td>
</tr>
<tr>
<td></td>
<td>patients participated in an RCT evaluating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>an endurance exercise intervention</td>
<td></td>
</tr>
<tr>
<td>**Methods/</td>
<td>Clinical and molecular expression in skeletal</td>
<td>Clinical molecular expression and microarray in skeletal muscle; evaluation</td>
</tr>
<tr>
<td><strong>data sources</strong></td>
<td>muscle comparing patients and controls</td>
<td>of an endurance exercise intervention</td>
</tr>
<tr>
<td></td>
<td>and the effects of an endurance exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td>intervention in the patients</td>
<td></td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>Analysis between controls and patients at</td>
<td>Analysis within the group of skeletal muscle; gene expression (fold change,</td>
</tr>
<tr>
<td></td>
<td>baseline (student t-test) and within the</td>
<td>right-tailed Fisher’s exact test) and molecular expressions (paired t-test);</td>
</tr>
<tr>
<td></td>
<td>group after the intervention (student paired</td>
<td>descriptive and statistical analysis of responders (Fisher’s exact test)</td>
</tr>
<tr>
<td></td>
<td>t-test); descriptive analysis of responders</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

12
3.2 PARTICIPANTS

All patients were diagnosed with definite or probable PM/DM according to Bohan and Peter’s criteria (Table 1). Patients fulfilling the inclusion criteria for Paper I and for Papers II to IV were included. The inclusion criteria for Paper I were a PM/DM diagnosis duration of more than 6 months and speaking and understanding the Swedish language. The inclusion criteria for Papers II to IV were over the age of 18, a PM/DM diagnosis duration of more than 6 months, exercising zero to one time a week, and stable medication for at least 1 month. Exclusion criteria were severe heart or lung conditions, severe osteoporosis, and not being able to exercise.

The HCs included in Paper III were matched for age, gender, and physical activity and exercise level (exercising zero or one time a week) and were selected from each patient’s nongenetic, related family members and friends and healthcare professionals.

Patients included in the analysis for Papers II to IV are presented in Table 3. In Paper I, only 3 of the 28 patients were included in Papers II to IV (see Table 3).
Table 3. Overview of Patients Included in the Analysis for Papers II to IV.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>A</td>
<td>EG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^1</td>
</tr>
<tr>
<td>B</td>
<td>EG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^1</td>
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<tr>
<td>C</td>
<td>EG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^1</td>
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<td>X</td>
<td></td>
<td></td>
<td>X^1</td>
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<tr>
<td>F</td>
<td>EG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^2</td>
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<tr>
<td>G</td>
<td>EG</td>
<td>X</td>
<td>X</td>
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<td>H</td>
<td>EG</td>
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<tr>
<td>I</td>
<td>EG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>EG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^2</td>
</tr>
<tr>
<td>K</td>
<td>EG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^2</td>
</tr>
<tr>
<td>L</td>
<td>(EG)*</td>
<td>X</td>
<td></td>
<td></td>
<td>X^1*</td>
</tr>
<tr>
<td>M</td>
<td>CG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^1</td>
</tr>
<tr>
<td>N</td>
<td>CG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>O</td>
<td>CG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^1</td>
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<tr>
<td>P</td>
<td>CG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^1</td>
</tr>
<tr>
<td>Q</td>
<td>CG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^1</td>
</tr>
<tr>
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<td>CG</td>
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<td>X</td>
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<td>X^2</td>
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<td>X</td>
<td>X</td>
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<td>T</td>
<td>CG</td>
<td>X</td>
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<tr>
<td>U</td>
<td>CG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X^2</td>
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<tr>
<td>V</td>
<td>CG</td>
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<td>X</td>
<td>X</td>
<td>X^2</td>
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<td>X</td>
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<tr>
<td>Y</td>
<td>OB</td>
<td>X</td>
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<tr>
<td>Z</td>
<td>OB</td>
<td>X</td>
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<td></td>
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<tr>
<td>Å</td>
<td>OB</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PM/DM = Polymyositis/dermatomyositis; EG = Exercise Group; CG = Control Group; HC= Healthy controls; OB= Only baseline assessment; * = only included in microarray analysis in paper IV; ^1 = Included in microarray analysis; ^2 = Included in immunohistochemistry (IHC) and Western blot (WB) analysis in paper IV.

3.2.1 Paper I

Twenty-nine patients seen at their annual visits to the Rheumatology Unit at the Karolinska University Hospital in Sweden during a 1-year period fulfilled the inclusion criteria and were thereby invited to participate in Paper I. Twenty-eight patients agreed...
to participate, while one patient declined for unknown reasons. The patients’ baseline characteristics are presented in Table 4.

**Table 4.** Characteristics of Patients in Paper I

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>Median (quartiles)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, (range)</td>
<td>57 (28–74)</td>
</tr>
<tr>
<td>Sex, female/male, n</td>
<td>15/13</td>
</tr>
<tr>
<td>Diagnosis, PM/DM, n</td>
<td>11/17</td>
</tr>
<tr>
<td>Disease duration, years (range)</td>
<td>9 (1–32)</td>
</tr>
<tr>
<td>MMT-8, 0–80</td>
<td>77 (72–80)²</td>
</tr>
<tr>
<td>HAQ, 0–3.00</td>
<td>0.50 (0.13–1.00)²</td>
</tr>
<tr>
<td>Patient Global, VAS, 0–100</td>
<td>44 (26–59)⁴</td>
</tr>
<tr>
<td>CPK, μcat/l</td>
<td>1.8 (1.3–2.6)²</td>
</tr>
<tr>
<td>Physician’s global disease activity, VAS, 0–100</td>
<td>1 (0–5)³</td>
</tr>
<tr>
<td>Global extra disease activity, VAS, 0–100</td>
<td>0 (0–6)³</td>
</tr>
<tr>
<td>Global disease damage VAS, 0–100</td>
<td>18 (8–23)³</td>
</tr>
</tbody>
</table>

*Values are in median (quartiles) unless otherwise indicated.

1 = one missing case, ² = two missing cases, ³ = three missing cases, ⁴ = one case excluded; MMT = Manual Muscle Test of 8 Muscle Groups; HAQ = Health Assessment Questionnaire; Patient Global = Patient Global Assessment of Disease Impact on Well-Being; CPK = Serum creatine phosphokinase (normal values < 2.5 μcat/liter in women, < 3.0 μcat/liter in men); VAS = Visual Analogue Scale

**3.2.2 Paper II**

Twenty-eight patients were assed for eligibility and evaluated for fulfilling the inclusion criteria by the treating physician at three rheumatology units (Karolinska University Hospital, Sahlgrenska University Hospital, and Uppsala University Hospital). Of them, five were excluded (three did not meet inclusion criteria, one declined, and another was excluded due to personal reasons). Therefore, 23 patients were randomized into an exercise group (EG) or a control group (CG). Twenty-one of these patients (EG, n = 11; CG, n = 10) were included in the analysis of the clinical effects of a 12-week endurance exercise program. Sixteen patients (EG, n = 9; CG, n = 7) were analyzed for long-term effects. Baseline characteristics are presented in Table 5 and a flow chart in Figure 1.
### Table 5. Characteristics of Patients in Paper II

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>Exercise group† (n = 11)</th>
<th>Control group† (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female/male), n</td>
<td>10/1</td>
<td>6/4</td>
</tr>
<tr>
<td>Diagnosis (PM/DM), n</td>
<td>5/6</td>
<td>4/6</td>
</tr>
<tr>
<td>Age, years</td>
<td>62 (16)</td>
<td>60 (15)</td>
</tr>
<tr>
<td>Duration since diagnosis, years</td>
<td>8 (8)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>DMARD treatment (GC/MTX/AZA/RITUX/MMF/CsA), n</td>
<td>6/3/4/0/1/0</td>
<td>6/2/2/0/1</td>
</tr>
<tr>
<td>Daily GC dose, mg</td>
<td>1.25 (5)</td>
<td>2.50 (5)</td>
</tr>
<tr>
<td>MMT-8, 0–80</td>
<td>75 (9)</td>
<td>75 (11)</td>
</tr>
<tr>
<td>HAQ, 0.00–3.00</td>
<td>0.50 (0.37) (^1)</td>
<td>0.44 (0.25)</td>
</tr>
<tr>
<td>CPK, µcat/l</td>
<td>1.7 (2.9) (^1)</td>
<td>1.7 (1.5) (^2)</td>
</tr>
<tr>
<td>Physician’s global disease activity VAS, 0–100</td>
<td>4 (10) (^1)</td>
<td>1 (10) (^1)</td>
</tr>
<tr>
<td>MITAX, 0.00–1.00</td>
<td>0.11 (0.11)</td>
<td>0.13 (0.08) (^1)</td>
</tr>
<tr>
<td>Global damage VAS, 0–100</td>
<td>28 (47) (^1)</td>
<td>18 (30) (^1)</td>
</tr>
</tbody>
</table>

*Data in median (interquartile range = IQR) if not stated otherwise. PM/DM = Polymyositis/dermatomyositis; DMARD = disease-modifying antirheumatic drugs; MMT-8 = Manual Muscle Test of 8 Muscle Groups; HAQ = Health Assessment Questionnaire; CPK = serum creatine phosphokinase (normal values < 2.5 µcat/liter in women and < 3.0 µcat/liter in men); VAS = Visual Analogue Scale; MITAX = Myositis Intention To Treat Activity Index; GC = Glucocorticoids; MTX = Methotrexate; AZA = Azathioprine; CsA = Cyclosporine A; MMF = Mycophenolate mofetil; RITUX = Rituximab. \(^1\) = One missing data. † = No statistical differences between EG and CG in any of the variables using Mann-Whitney U-test, p < 0.05.
Figure 1. Flow chart for Paper II for patients through the randomized control trial and the 1-year open extension followup. $^1$ = One patient in the EG was excluded because he/she did not exercise; $^2$ = One patient was excluded because he/she started to exercise despite being in the CG; $^3$ = Two patients in the EG were lost to follow-up; $^4$ = In the CG, one patient was lost to followup and two were excluded because they started to exercise.

3.2.3 Paper III

After being assessed for eligibility, 23 patients were included in Paper III in a multicenter setting at three rheumatology units (Karolinska University Hospital, Sahlgrenska University Hospital, and Uppsala University Hospital). These 23 patients were compared to 12 HCs that matched the patients’ characteristics according to the inclusion criteria. All HCs were recruited in Stockholm, Sweden. In the controlled part of the study, 16 patients were randomized into the EG (n = 9) or the CG (n = 7). Four patients were excluded due to missing reliable metabolic data, one declined to participate, and two patients were excluded for personal reasons. The patient characteristics and flow chart are shown in Table 6 and Figure 2.
Table 6. Characteristics of Patients in Paper III

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>Patients*</th>
<th>Healthy controls*</th>
<th>Exercise group*</th>
<th>Control group*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 23</strong></td>
<td><strong>n = 12</strong></td>
<td><strong>n = 9</strong></td>
<td><strong>n = 7</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td><strong>Median (range)</strong></td>
<td><strong>Median (range)</strong></td>
<td><strong>Median (range)</strong></td>
<td></td>
</tr>
<tr>
<td>Sex (female/male), n</td>
<td>17/6</td>
<td>9/3</td>
<td>8/1</td>
<td>6/1</td>
</tr>
<tr>
<td>Diagnosis (PM/DM), n</td>
<td>11/12</td>
<td>NA</td>
<td>4/5</td>
<td>¾</td>
</tr>
<tr>
<td>Age, years</td>
<td>58 (37–77)</td>
<td>51 (31–71)</td>
<td>60 (48–72)</td>
<td>58 (42–77)</td>
</tr>
<tr>
<td>Duration since diagnosis, years</td>
<td>7 (1–33)</td>
<td>NA</td>
<td>8 (1–13)</td>
<td>7 (2–33)</td>
</tr>
<tr>
<td>DMARD treatment (GC/MTX/AZA/RITUX/MMF/ CsA), n</td>
<td>13/9/5/2/1/1</td>
<td>NA</td>
<td>5/3/3/0/1/0</td>
<td>5/2/2/1/0/1</td>
</tr>
<tr>
<td>Daily GC dose, mg</td>
<td>5 (1–10)</td>
<td>NA</td>
<td>5 (1–8)</td>
<td>2 (2–5)</td>
</tr>
<tr>
<td>MMT-8, 0–80</td>
<td>75 (42–80)</td>
<td>NA</td>
<td>76 (42–79)</td>
<td>73 (57–77)</td>
</tr>
<tr>
<td>HAQ, 0.0–3.0</td>
<td>0.5 (0.0–1.8)</td>
<td>NA</td>
<td>0.5 (0.0–1.4)</td>
<td>0.5 (0.4–1.8)</td>
</tr>
<tr>
<td>CPK, µcat/l</td>
<td>2 (1–62)³</td>
<td>NA</td>
<td>2 (1–62)³</td>
<td>2 (1–4)³</td>
</tr>
<tr>
<td>Physician global disease activity VAS, 0–100</td>
<td>4 (8–16)²</td>
<td>NA</td>
<td>4 (0–14)³</td>
<td>2 (0–10)³</td>
</tr>
<tr>
<td>MITAX, 0–1.0</td>
<td>0.1 (0.0–0.2)²</td>
<td>NA</td>
<td>0.1 (0.0–0.2)</td>
<td>0.1 (0.1–0.2)³</td>
</tr>
<tr>
<td>Physician global damage VAS, 0–100</td>
<td>18 (0–62)²</td>
<td>NA</td>
<td>22 (7–62)³</td>
<td>22 (10–49)³</td>
</tr>
</tbody>
</table>

*Data in median (range) if not stated otherwise. PM/DM = Polymyositis/dermatomyositis; ¹ = Patients with reliable lactate levels at baseline were randomly assigned to an exercise group or a control group. NA = Not assessed; DMARD = Disease-modifying antirheumatic drugs; MMT = Manual muscle test; HAQ = Health assessment questionnaire; CPK = Creatine phosphokinase (normal values < 2.5 µcat/liter in women, < 3.0 µcat/liter in men); VAS = Visual analogue scale; MITAX = Myositis Intention To Treat Activity Index, GC = Glucocorticoids; MTX = Methotrexate; AZA= Azathioprine; CsA = Cyclosporine A; MMF = Mycophenolate mofetil; RITUX = Rituximab; 1 = One missing data; 2 = Two missing data; 3 = Three missing data; * = No statistical difference in any of the variables between groups; patients versus healthy controls and the exercise groups versus the control group assessed by Mann-Whitney U-test (p < 0.05).
Figure 2. Flow chart for patients in Paper III; \(^1\) = One patient randomized into the CG was excluded due to starting exercise despite being in the CG.

### 3.2.4 Paper IV

Fifteen patients (EG = 7 and CG = 8) from the larger RCT with the available paired baseline and 12-week followup muscle biopsies were included in Paper IV. Due to the limited amount of muscle tissue, the muscle biopsies were selected for either the microarray gene expression analysis \((n = 8)\) or the protein target validation using Western blot or using IHC analysis for quantification of capillaries and inflammatory markers \((n = 7)\). One patient from the EG and one patient from the CG were excluded in all clinical, IHC, and Western blot analyses and the corresponding statistical analysis. However, one patient in the EG could not be excluded in the microarray analysis, which was performed on a group level before it became clear that this participant’s adherence to the exercise program was not satisfactory. Patient characteristics and flow chart are shown in Table 7 and Figure 3.
Table 7. Characteristics of Patients in Paper IV

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>Microarray</th>
<th>IHC/WB</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EG† (n = 4)</td>
<td>CG† (n = 4)</td>
<td>EG† (n = 3)</td>
</tr>
<tr>
<td></td>
<td>Md (IQR)*</td>
<td>Md (IQR)*</td>
<td>Md (IQR)*</td>
</tr>
<tr>
<td>Sex (female/male), n</td>
<td>3/1</td>
<td>3/1</td>
<td>3/0</td>
</tr>
<tr>
<td>Diagnosis (PM/DM), n</td>
<td>1/3</td>
<td>1/3</td>
<td>2/1</td>
</tr>
<tr>
<td>Age, years</td>
<td>66 (19)</td>
<td>63 (16)</td>
<td>69 (24)</td>
</tr>
<tr>
<td>Duration since diagnosis, years</td>
<td>10 (3)</td>
<td>8 (24)</td>
<td>1(2)</td>
</tr>
<tr>
<td>DMARD treatment (GC/MTX/AZA/RITUX), n</td>
<td>2/1/2/0</td>
<td>3/1/0/0</td>
<td>3/2/1/0</td>
</tr>
<tr>
<td>Daily GC dose, mg</td>
<td>2.5 (5.0)</td>
<td>2.5 (3.5)</td>
<td>5.0 (6.2)</td>
</tr>
<tr>
<td>MMT-8, 0–80</td>
<td>73 (8)</td>
<td>75 (11)</td>
<td>76 (1)</td>
</tr>
<tr>
<td>HAQ, 0.0–3.0</td>
<td>0.62 (0.88)</td>
<td>0.38 (0.25)</td>
<td>0.50 (1.00)</td>
</tr>
<tr>
<td>CPK, µcat/l</td>
<td>1.6 (1.3)</td>
<td>1.4 (0.5)</td>
<td>1.3 (3.2)</td>
</tr>
<tr>
<td>Physician global disease activity VAS, 0–100</td>
<td>1 (4)</td>
<td>0 (1)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>MITAX, 0–1.0</td>
<td>0.22 (0.19)</td>
<td>0.11 (0.13)</td>
<td>0.10 (0.05)</td>
</tr>
<tr>
<td>Physician global damage VAS, 0–100</td>
<td>49 (51)</td>
<td>18 (30)</td>
<td>9 (30)</td>
</tr>
</tbody>
</table>

* Data in median (md) and interquartile range (IQR) if not stated otherwise. IHC = Immunohistochemistry; WB = Western blot; PM/DM = Polymyositis/dermatomyositis; DMARD = Disease-modifying anti-rheumatic drugs; MMT = Manual Muscle Test; HAQ = Health Assessment Questionnaire, CPK = Serum creatine phosphokinase (normal values < 2.5 µcat/liter in women and < 3.0 µcat/liter in men); VAS = Visual Analogue Scale; MITAX = Myositis Intention To Treat Activity Index, GC = Glucocorticoids; MTX = Methotrexate; AZA = Azathioprine; RITUX = Rituximab; † = No statistical differences between EG and CG in any of the variables in the microarray group or in the IHC/WB group, p < 0.05 (Mann-Whitney U-test).
3.3 ENDURANCE EXERCISE INTERVENTION

For the endurance exercise program, the EG performed 1 hour of exercise three times a week for 12 weeks. They cycled at 70% of their VO$_2$ max, with a time goal of cycling for 30 minutes. This was followed by 20 minutes of muscular endurance exercise, namely, knee extensors at about 30% to 40% of one voluntary repetition maximum (VRM). In addition, shoulder flexors and flexors and extensors of the trunk were exercised at the same intensity but were not evaluated. During the first two weeks, the exercise intensity was gradually increased from 50% to 70% of each patient’s individual VO$_2$ max. The EG exercised twice a week at the physical therapy departments at each of the three centers and once a week with the same program at home using an exercise bike and weight cuffs provided by the project. The CG was instructed to not change the exercise or the physical activity level. All patients kept exercise diaries, and the EG was supervised by a single physical therapist at each center. The exercise diaries were collected and all exercise equipment were returned at 12 weeks, and no further supervision or instructions regarding physical exercise were given to either the EG or the CG.

3.4 ASSESSMENTS

In all four papers, assessments recommended by the IMACS Group and specific measures were used to evaluate the patient preference and measurement properties of
the MACTAR (Paper I) and the effect of endurance exercise on clinical and laboratory assessments (Papers II to IV). The included assessments are shown in Table 8.

<table>
<thead>
<tr>
<th></th>
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</thead>
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<td><strong>Clinical assessments</strong></td>
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<td>Disease activity</td>
<td>IMACS 6-item core, global disease activity VAS</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Disease damage</td>
<td>Myositis damage tool</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Patient preference</td>
<td>MACTAR</td>
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<td>X</td>
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</tr>
<tr>
<td>Aerobic Capacity</td>
<td>VO$_2$ max</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Health</td>
<td>SF-36</td>
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<td>X</td>
<td></td>
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</tr>
<tr>
<td>ADL</td>
<td>MAP</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle performance</td>
<td>Cycling time, at 65% of VO$_2$ max</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Muscle performance</td>
<td>5VRM</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Muscle performance</td>
<td>FI-2</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory assessments in skeletal muscle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate concentration</td>
<td>Microdialysis</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial enzyme activity</td>
<td>CS, β-HAD</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>mRNA expression profiling</td>
<td>Microarray</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Expression inflammatory cells</td>
<td>IHC (CD3, CD68, CD163)</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Expression capillaries</td>
<td>IHC (CD31, CD34)</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Protein expression</td>
<td>Western blot (FLT3 ligand)</td>
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<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

### 3.4.1 Paper I

The Dutch-modified MACTAR is a semi-structured interview consisting of a baseline and an followup interview (Appendix) (Verhoeven et al., 2000a). We translated and
adapted the Dutch MACTAR according to the process described by Guillemin (Guillemin, 1995). One part of the MACTAR concerns the disabilities prioritized by the patients and the other part concerns how different aspects of health are affected by rheumatic disease, namely global health, physical function, social function, and emotional function. In the latter part of the interview, the patient was asked to identify all disabilities related to his or her rheumatic disease. The disabilities identified were then ranked by the patient according to importance of improvement. The five highest ranked disabilities were recorded. The MACTAR score varied from 19 to 39, with 39 indicating no disability.

Measures of disease activity and disease damage included the physician’s assessment of global disease activity on VAS (MYOACT global, VAS 0-100); global extraskeletal muscle disease activity (MYOACT extra, VAS 0-100), including the assessment of six organ systems (Miller et al., 2001), (Isenberg et al., 2004), (Sultan et al., 2008); and the serum levels of CPK. The MDI global include assessments of 11 organ systems (Isenberg et al., 2004).

Assessments of muscle function, activity limitation, and participation restriction and health were included. The MMT measures isometric strength in eight muscle groups, each scored from 0 to 10, with a score varying from 0 to 80 (with 80 indicating full strength). The HAQ is comprised of 20 questions divided into 8 categories. The HAQ score is from 0 to 3 (with 3 indicating an inability to perform) (Ekdahl et al., 1988), (Fries et al., 1980). We used patients’ global assessment of disease impact on their well-being on a VAS (0–100, with 100 being severe impact). We used the SF-36 to assess health. It is comprised of eight dimensions (physical function, role physical, bodily pain, general health, vitality, social function, role emotional and mental health) scored from 0 to 100, with 100 being optimal health (Sullivan et al., 1995).

Two PM/DM-specific measures for assessing muscle impairment and activity limitation were included: The FI-2 and MAP. The FI-2 is a valid disease-specific outcome measuring muscle endurance in patients with PM/DM (Alexanderson et al., 2006). The numbers of repetitions in seven muscle groups are scored from 0 to 60 and in two muscle groups from 0 to 120 (60/120 indicates no muscle impairment). MAP measures ADL and consists of 31 items divided into 8 subscales scored from 1 to 7, with 1 indicating no difficulty (Alexanderson et al., 2002).

3.4.2 Assessments in Papers II, III, and IV

The effects of the endurance exercise were evaluated using clinical assessments and laboratory assessments in Papers II to IV.

3.4.2.1 Whole-body aerobic capacity, health, patient preference, ADL, and muscle performance

In papers II, III, and IV, a VO₂ max test was performed on an ergometer bicycle. The patients started cycling at 30 to 40 W, and the required power output was increased by
10 W every minute. The VO$_2$ max was determined by incremental cycling to exhaustion. Pulmonary minute ventilation and gas exchange (O$_2$ uptake and CO$_2$ output) were measured breath by breath (Sensor Medics, V max 229TM, Yorba Linda, CA, USA). The system was calibrated for airflow and gas exchange before each test. The VO$_2$ max was defined as the highest O$_2$ uptake rate measured during the test and was expressed as l min$^{-1}$; in addition, the power performed (in W) at the time of VO$_2$ max was recorded. To ensure that the cycling was performed to exhaustion and hence reliable VO$_2$ max measurements were obtained, we also measured the respiratory exchange ratio (RQ), which is defined as the ratio between the exhaled CO$_2$ and the inhaled O$_2$. At the end of the test, the patients self-reported peripheral exertion and central exertion using the Borg Self-Reported Peripheral Exertion (RPE) Scale (6–20) (Borg, 1974).

Paper II included assessments of health, patient preference, limitation in ADL, and muscle performance. For the assessment of health, we used the SF-36 (Sullivan et al., 1995). The MACTAR, with reliable measurement properties, was used to assess patient preferences (Alemo Munters et al., 2011). The MAP was used to assess limitations in ADL (Alexanderson et al., 2002). We also used the 5VRM, which measures muscle strength (i.e., the maximum load the patient can lift in a full range of motion in five repetitions). Knee extensors were assessed in a standardized sitting position from 90 degrees of knee flexion to full knee extension in the left and right leg. After completing each test, the patients rated perceived muscle exertion according to the Borg Category Scale (CR-10; 0–10, with 10 being maximal exertion) (Borg, 1974).

In Papers III and IV, cycling endurance tests were performed by the patients and HC at baseline and by patients after the 12-week period. Cycling was performed at a power requiring 65% of the VO$_2$ max obtained in the baseline VO$_2$ max test and was continued until exhaustion. At exhaustion, self-reported peripheral and central exertions were recorded on the Borg RPE scale (6–20) (Borg, 1974), and heart rate was also measured.

### 3.4.2.2 Clinical disease activity and disease damage

In Papers II, III, and IV, assessment of disease activity was performed using the IMACS Core Set Measures (Isenberg et al., 2004), (Miller, 2012), including the patient’s and physician’s global disease activity on a VAS (0-100), MMT-8 (0–80), HAQ (ADL, 0–3), a laboratory assessment of CPK (µkat/L reference values: < 2.5 µkat/l in women and < 3.0 µcat/l in men), and the assessment of extraskeletal muscle disease activity in six organ systems using MITAX and global extraskeletal muscle activity (on VAS, 0-100). We assessed disease damage at baseline using the physician’s global damage tool (Isenberg et al., 2004), (Sultan et al., 2011).

In Paper II, we also used erythrocyte sedimentation rate (ESR) (reference value: < 20 mm), C-reactive protein (CRP) (reference value: < 3 mg/l), and CPK for the assessment of disease activity and to elucidate a flare in the open extension part of the study.
3.4.2.3 Lactate expression in skeletal muscle in vivo

In Papers III and IV, the extracellular concentration of lactate was measured in vivo using microdialysis (Figure 4). Two thin catheters with a 3-cm-long membrane and a diameter of 0.5 mm (CMA 63) were inserted in the vastus lateralis 2 cm apart under local anesthesia (Lundberg et al., 2002). A reference catheter was inserted in the subcutaneous abdominal fat tissue. The microdialysis experiments were performed in patients and HC at baseline and in patients after the 12-week intervention (training or control) by the same two physicians, a nurse, and a physical therapist throughout the study. The microdialysis probes were perfused with a physiological solution at a flow rate of 1 µl min⁻¹. Water-soluble substances in the interstitial fluid diffused across the semipermeable dialysis membrane and entered the perfusate, which was collected in small vials. The cycling endurance test (see above) started after an 80-minute equilibration at rest, during which one vial of perfusate per catheter was collected every 20 minutes. After the endurance test, subjects rested for 60 minutes while the vials with perfusate were collected every 20 minutes. An analysis of the lactate concentration was made directly using a Clinical Microdialysis Analyzer (ICSUS, CMA, Solna, Sweden). Vials collected from the vastus lateralis muscle during the 20 minutes directly after cycling to exhaustion showed the highest lactate concentrations, and the mean lactate concentration in vials obtained from the two catheters at this time interval was used in subsequent assessments.
3.4.2.4 Molecular expression in skeletal muscle in vitro

In Papers III and VI, muscle biopsies were taken from the vastus lateralis muscle under local anesthesia using a semi-open technique (Dorph et al., 2001).

In Paper III, we measured the activities of two mitochondrial enzymes in skeletal muscle, CS and β-HAD, which reflect the mitochondrial volume–to–cell volume ratio and the capacity for fatty acid β-oxidation, respectively (Holloszy and Coyle, 1984), (Reisch and Elpeleg, 2007). Muscle biopsies were freeze-dried, dissected free of nonmuscle constituents, and weighed. Tissue was then homogenized with ground glass homogenizers in an ice-cold buffer (HxB) consisting of 50 mM KH$_2$PO$_4$ and 1 mM EDTA, 0.05% (vol/vol) Triton X-100, pH 7.5. The homogenate was centrifuged at 1,400 x g for one minute (4° C). Aliquots of the supernatant were analyzed for CS and β-HAD with standard spectrophotometric techniques (Alp et al., 1976), (Bass et al.,
1969). Enzyme activities were assayed at room temperature (approximately 22°C) under conditions that yielded linearity with respect to extract volume and time. Protein content was measured in the supernatant with the Bradford assay (Bio-Rad Laboratories AB, Sundbyberg, Sweden), and the activities were adjusted for protein content.

In Paper IV, mRNA expression profiling of the collected skeletal muscle biopsies was performed using Affymetrix Human Genome U133 Plus 2.0 microarrays. Standard procedures were done as described in the manufacturer’s protocol and as previously published (Chen et al., 2000). To investigate the molecular networks and pathways associated with gene lists in Paper IV, ingenuity pathway analysis (Ingenuity Systems®, www.ingenuity.com) was used to identify gene interactions and to prioritize molecular pathways differentially affected in different groups. The complete list of genes generated was used for the analysis of the molecular functions and interacting networks.

In Paper IV, validation of the gene expression was performed on a selected protein (Fms-related tyrosine kinase 3 ligand, FLT3L) using Western blot. Proteins were extracted from muscle tissue using a tissue protein extraction reagent supplied with a complete protease inhibitor cocktail. Gel electrophoresis was carried out on the NuPAGE® Novex® Bis-Tris gel system (Invitrogen AB, Sweden), and proteins were transferred on a polyvinylidene difluoride membrane using a Trans-Blot SD semi-dry transfer cell (Bio-Rad Laboratories AB, Sweden). The membranes were incubated with FLT3 ligands (Novus Biologicals, Cambridge, UK). The bands were detected by enhanced chemiluminescence, and band intensities were measured using the Gel Doc XR system from Bio-Rad.

In Paper IV, to obtain information on the expression of inflammatory cells and the number of capillaries before and after the 12-week exercise program, IHC was applied on sectioned muscle biopsy specimens. The staining of muscle tissue was performed with mouse monoclonal antibodies directed against CD3 (a marker of T cells, BD Biosciences, San José, California, USA), anti-CD68 (a marker of monocyte/macrophage lineage, KP-1 clone, Dako Cytomation, Glostrup, Denmark), and anti-CD163 (a marker for resident macrophages, Ber-MAC3; DakoCytomation) according to a standard protocol (Frostegård et al., 1999). Staining with a mouse monoclonal anti-CD31 (a marker of endothelial cells, clone EN4, Novakemi, Sweden) antibody and an anti-CD34 (a marker of endothelial cells, Dako) antibody was performed as previously described (Ulfgren et al., 1995). Stained tissue sections were examined using a Polyvar II microscope (Reichert-Jung, Vienna, Austria) and photographed with a digital Leica camera 300F (Leica, Cambridge, UK). Expression of CD3, CD68, CD163, CD31, and CD34 was also assessed quantitatively using a computer-assisted image analysis of coded samples. The images were analyzed with a Quantimet 600 image analyzer (Leica). The CD3- and CD68-positive staining was expressed as the number of positive cells per area, and the CD163-positive staining was expressed as the percentage of total area of counterstained tissue. The number of
capillaries was expressed as the number of CD31 and CD34 stained capillaries per area. The number of fibers per area was evaluated in the same sections.

3.5 DATA COLLECTION AND PROCEDURE

In Paper I, data collection was performed within the regular healthcare process in a rheumatology unit, while in Papers II, III, and IV, data collection was performed in a multicenter RCT setting.

3.5.1 Paper I

All patients who came to the Rheumatology Unit at the Karolinska University Hospital for their annual checkup with the myositis team care between February 2005 and January 2006 and who met the inclusion criteria were invited to participate in Paper I. Recommended myositis outcomes were performed by the myositis team members. The MACTAR interview was added to the recommended outcomes, and all interviews were performed by the same physical therapist trained to perform the interview. The interviews were performed twice, with a 1-week break in between them.

3.5.2 Papers II, III, and IV

In Papers II, III, and IV, patients fulfilling the inclusion criteria were recruited from 2007 to 2011 at three centers, the Karolinska University Hospital, the Sahlgrenska University Hospital, and the Uppsala University Hospital in Sweden. Patients were randomized by an independent nurse using a randomization list into the EG or CG. The physical therapist responsible for exercise coaching at each center was then contacted and informed about group allocation by the nurse. The patients in the CG were instructed not to change their physical activity and exercise level during the 12-week period. All patients in Papers II, III, and IV recorded their physical activity and exercise level in diaries. According to the ethical permit, patients in the CG were invited to participate in the exercise program after the 12-week period, but only two accepted this invitation and were excluded in the 1-year analysis. In Paper II, assessments of health, patient preference, limitations in ADL, and 5VRM were performed by the same physical therapist at each center before and after the 12-week period and after 52 weeks. In Papers II, III, and IV, assessments of disease activity were performed at the start of the study and after 12 weeks by the same rheumatologist at each center. In addition, the VO2 max test was performed by one laboratory technician at each center.

In Paper III, twelve HCs matched for age, gender, and physical activity level were identified among each patient’s nongenetic, related family members and friends and healthcare professionals. All HCs were recruited in Stockholm, Sweden. In Papers III and IV, the cycling endurance tests performed at baseline and after the 12-week period were supervised by the same nurse and physical therapist. In Papers III and IV, the microdialysis experiments were performed in patients and HCs at baseline and in patients after the 12-week period by the same two physicians, nurse, and physical therapist. In Papers III and IV, biopsies were taken from the patients before and after the 12-week period. Due to technical reasons, biopsies were only taken from patients who were recruited at the Karolinska University Hospital and at the Uppsala University Hospital.
Hospital. In Paper IV, RNA expression profiling of the skeletal muscle biopsies were analyzed at the Research Center for Genetic Medicine, Children’s National Medical Center in Washington, DC, USA. The mitochondrial enzyme activities analysis, IHC, and Western blot analysis of the skeletal muscle biopsies were all performed at the Karolinska Institutet. All assessments in Papers II, III, and IV were performed in for all participants in the following order: The VO₂ max test, the microdialysis experiment, the clinical assessments, and the muscle biopsies. All assessors in Papers II, III, and IV were blinded to the type of intervention (i.e., exercise or control).

3.6 DATA ANALYSIS

An overview of the analysis included in Papers I, II, III, and IV is shown in Table 9. The level of significance was set to p < 0.05 in all papers.
### Table 9. Data Analysis and Statistical Methods Used in Papers I to IV.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Descriptive analysis</strong></td>
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<tr>
<td>Mean, 95% CI</td>
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<tr>
<td>Mean (± SD)</td>
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<td>X</td>
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<td>Mann-Whitney U-test</td>
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<td>Pearson’s correlation coefficient</td>
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<td>Specificity, sensitivity</td>
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<td>Right-tailed Fisher’s exact test</td>
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</tr>
</tbody>
</table>

### 3.6.1 Paper I

The prioritized disabilities of the MACTAR were presented and compared descriptively with the items in the HAQ and the MAP. Correlations between the MACTAR and the other constructs were performed. A correlation coefficient of $r_s > 0.90$ was considered very high, $r_s = 0.70–0.89$ was high, $r_s = 0.50–0.69$ was moderate, $r_s = 0.26–0.49$ was low, and $r_s = 0.00–0.25$ was very low or no correlation (Munro, 1997).

For analysis of random variations between the test and retest, a weighted kappa coefficient ($K_w$) and intraclass correlation (ICC) were used. Weighted kappa coefficients were interpreted as the following: $K_w = 0.81–1.0$ was very good, $K_w =$
0.61–0.80 was good, \( K_w = 0.41–0.60 \) was moderate, \( K_w = 0.21–0.40 \) was fairly poor, and \( K_w < 20 \) was very poor (Landis and Koch, 1977). An ICC correlation of < 0.75 was considered to indicate low to fair reliability, while a correlation > 0.75 indicated good to excellent reliability (Shrout PE, 1979).

### 3.6.2 Paper II

All data were analyzed with a mixed model. Changes in SF-36, MACTAR, MAP, 5VRM, MMT-8, \( VO_2 \) max, physician’s global disease activity, and global extraskeletal muscle activity during different intervals of time were analyzed using a mixed linear model with Time (0 and 12 weeks or 0, 12, and 52 weeks) as the within-subjects variable and Group (exercise and control) as the between-subjects variable and the Group*Time interaction. For the analysis of correlation between health (SF-36 for physical function) and \( VO_2 \) max (l/min, watt) we used Pearson’s correlation coefficient and interpreted the correlation coefficient as in Paper I (Munro, 1997).

A responder in muscle performance and \( VO_2 \) max was defined as improving \( \geq 20\% \) in 5VRM or by \( \geq 10\% \) in \( VO_2 \) max compared to baseline (Paulus et al., 1990). To define reduced disease activity, the proposed definition by IMACS was used (Rider et al., 2004). To be a responder, a patient should improve \( \geq 20\% \) in 3 out of 6 IMACS core measures with no more than two being worse by \( \geq 25\% \), which could not include MMT, as muscle weakness is the main symptom in PM/DM. Fisher’s exact test was used to investigate difference between the EG and the CG regarding the frequency of responders and nonresponders in disease activity, \( VO_2 \) max, and 5VRM. Data were analyzed for sensitivity, specificity, positive and negative likelihood ratio in relation to response in \( VO_2 \) max versus in disease activity.

An interim power analysis showed 86% power in the Group*Time interaction and a significant difference in \( VO_2 \) max. It also indicated a sample size of 9 patients in each group, giving an 80% power to detect a significant difference in the primary outcome of \( VO_2 \) max. Patient recruitment was then stopped.

### 3.6.3 Paper III

A student’s unpaired t-test was used to detect differences between the patients and HCs. For evaluation of the effects of endurance training, measurements performed before and after the intervention period were compared using a student’s paired sample t-test. A power test was performed assuming changes in physiological measurements after endurance training being 30% ± 20% of the control value. With a power of 0.80 and an alpha of 0.05, this gave a sample size of six. Based on this, we aimed for 9 patients in the EG, but some analyses were performed with \( n = 7 \) (\( VO_2 \) max measurements) or \( n = 3 \) (mitochondrial enzyme activities).

We used the proposed definition by IMACS to define improvement in disease activity during the intervention period, as in Paper II (Rider et al., 2004). A responder was
defined as improving by $\geq 20\%$ in the MMT and/or cycling time at the 12-week followup compared to baseline (Paulus et al., 1990).

### 3.6.4 Paper IV

We used the proposed definition by IMACS to define improvement in disease activity during the intervention period, as in Paper II (Rider et al., 2004). Improved muscle performance (cycling time) compared to baseline by $\geq 20\%$ or in VO$_2$ max by $\geq 10\%$ was defined as a responder (Paulus et al., 1990). Fisher’s exact test was used to investigate difference between the EG and the CG regarding the frequency of responders and nonresponders according to the IMACS disease activity measures, cycling endurance test, and VO$_2$ max. A paired student t-test was used to investigate within-group difference for EG and CG, and a student t-test was used to investigate between-group difference. Pearson’s correlation test was used to investigate the association between the number of capillaries and VO$_2$ max at the 12-week followup. The microarray analysis association between the molecules in the given function/pathway was calculated using the right-tailed Fisher’s exact test. The canonical pathways were additionally analyzed using the ratio of the number of molecules from our dataset belonging to the particular pathway divided by the total number of molecules in that pathway.

### 3.7 ETHICAL CONSIDERATIONS

All participants in Papers I to IV were given written and oral information about the specific study design. They were ensured confidentiality and informed that their contribution were voluntary and could be terminated at any time and that it would not interfere with their future care. Signed informed consent was received from all participants. The collection of muscle biopsies in Papers III and IV was optional. In Paper III, the HCs were identified among the patients’ nongenetic related family members and friends since they could benefit from it more than others. The healthcare professionals that were invited to participate as HCs were able to decline and terminate their participation at any time and were assured that it would not interfere with their professional life. According to the ethics approval, patients in Paper II randomized to the CG were invited to participate in the endurance exercise program after the 12-week period. The study designs for Papers I to IV were approved by the local ethic review boards at the Karolinska University Hospital in Stockholm, Sweden. The study designs for Papers II and III were approved by the local ethic review boards at Sahlgrenska University Hospital in Gothenburg and the Uppsala University Hospital in Uppsal, both Sweden. The study design for Paper IV was approved by the Children’s National Medical Center Institutional Review Board, Washington, DC, USA. The study designs for Papers II to IV were registered at ClincalTrials.gov, Identifier NCT01184625.
4 RESULTS AND DISCUSSION

4.1 PAPER I

4.1.1 Patient preference

The patient preference assessment included disabilities not covered by the recommended patient-reported outcomes in patients with established PM/DM. A total of 43 different disabilities were identified using the MACTAR in these patients. The most frequently reported disabilities were limitations in sexual activity, walking, social activities, sleep, and cycling. Of these activities, only walking was covered by the IMACS recommended HAQ, and only walking and social activities were included in the myositis-specific MAP. Eleven of 28 patients identified sexual activity among the five disabilities that were most important to improve and this was not covered by any of the other outcome measure. More specifically, only 28% of the identified disabilities were covered by items of the HAQ, while the MAP covered 67%. Others have also reported discrepancy between self-selected disabilities and fixed-item outcomes. In Dutch rheumatoid arthritis (RA) patients, HAQ was found to only cover 48% of the MACTAR self-selected disabilities (Verhoeven et al., 2000a). In Swedish RA patients, 53% of the selected disabilities were represented in the HAQ (Alemo Munters et al., 2013, Disability and Rehabilitation, submitted). A diversity of disabilities identified by the MACTAR have been reported in patients with different health and external conditions (Sanchez et al., 2009), (Verhoeven et al., 2000a), (Alemo Munters et al., 2011), (Nguyen et al., 2010), (Mouthon et al., 2008), (Alemo Munters et al., 2013, Disability and Rehabilitation, submitted). These results indicate that with MACTAR, it is possible to identify disabilities adapted to the different personal, social, and environmental contexts of the individual patients and, furthermore, enables them to select the most important disabilities to evaluate.

A good to excellent test-retest reliability was revealed for the MACTAR score in patients with established PM/DM. The test-retest reliability of the MACTAR assessed in myositis is in concordance MACTAR properties in RA (Alemo Munters et al., 2013, Disability and Rehabilitation, submitted). Furthermore, the MACTAR has been suggested to be more responsive and sensitive to change than other outcomes and was highly responsive to pharmacological treatment in active and physical exercise treatments for RA (Verhoeven et al., 2000b), (Verhoeven et al., 2000a), (de Jong et al., 2003). It has also been reported that MACTAR is sensitive to change in patients with low back pain and systemic sclerosis (Sanchez et al., 2011), (Nguyen et al., 2010). Altogether, our study indicates that disease consequences that are most important to improve for individual patients are not completely revealed by IMACS-recommended or myositis-specific outcomes. The MACTAR has promising measurement properties in established PM/DM and only assesses changes in disabilities that are important to the individual patient. We suggest adding MACTAR to the recommended outcomes for the evaluation of treatment effects that matter to the patients with established PM/DM.
4.2 PAPER II

4.2.1 Effects of endurance exercise on health and whole body aerobic capacity

We determined that 12 weeks of endurance exercise improves health in patients with established PM/DM. All patients tolerated the exercise program well without any adverse events, except one patient that was not able to perform the exercise program for unknown reasons. The EG improved compared to the CG in the SF-36 domain of physical function and vitality. Consistently, the EG improved in the domains of physical function, general health, vitality, and mental health, while the CG remained unchanged. The improved health was clinically relevant (Bjorner et al., 2007). The EG also improved compared to the CG in VO$_2$ max. Ten out of 11 of the patients exposed to the endurance exercise were responders in VO$_2$ max compared to 1 participant in the nonexercise CG. It is worth noting that patients with global damage, muscle damage, and a long disease duration also improved in VO$_2$ max after completing the endurance exercise. Despite treatment with GC and immunosuppressive agents, a majority of PM/DM patients develop poor health compared to the general population (Regardt et al., 2011), (Bronner et al., 2006), (Ponyi et al., 2005). Open-label studies have shown that physical exercise in patients with both chronic and active PM/DM may lead to improved health (Alexanderson et al., 1999), (Alexanderson et al., 2000). Furthermore, lower VO$_2$ max was found in PM/DM patients compared to HCs (Wiesinger et al., 2000). This indicates that low VO$_2$ max in established PM/DM contributes to the sustained poor health observed in these patients, similar to the general population (Lakka et al., 1994), (Myers et al., 2002). Accordingly, we determined that improved health was strongly related to the improved VO$_2$ max. In other populations, increased VO$_2$ max has been found to contribute to improved health (Sokka and Hakkinen, 2008), (Warburton et al., 2006). Endurance exercises for 12 weeks improve health in patients with established PM/DM. These results also indicate that improved health could potentially be mediated through improved VO$_2$ max in these patients.

4.2.2 Effects of endurance exercise on disease activity

We found that endurance exercise decreased disease activity in patients with established PM/DM. We demonstrated lower disease activity after the endurance exercise program compared to before. More patients (7 out of 11) in the EG were responders with reduced disease activity compared to none in the CG. Also, patients with various disease damage, comorbidities, gender, and disease duration responded with reduced disease activity after the endurance exercises (Table 10). Although the changes in disease activity were small and the 20% change proposed by the IMACS Group (Rider et al., 2004) might be within the error of measurement, it is worth noting that no CG patient was a responder.

It is not clear how exercise may reduce disease activity; however, exercise has an anti-inflammatory effect via increased circulating anti-inflammatory cytokines, including the IL-1 receptor antagonist, IL-10 (Walsh et al., 2011), a decrease in pro-inflammatory...
cytokines (e.g., TNF) (Sloan et al., 2007), and an increase in IL-6, which is thought to stimulate anti-inflammatory cytokines (Petersen and Pedersen, 2005). Furthermore, exercise-modulated anti-inflammatory cytokine changes have been directly detected in muscle tissue (Gielen et al., 2003), (Greiwe et al., 2001). Endurance exercise might be more effective than resistance training to achieve anti-inflammatory effects and, hence, to reduce disease activity (Walsh et al., 2011). Our study shows that a majority of the participants responded with reduced disease activity, whereas we previously reported that 2 out of 8 patients responded following resistance training according to IMACS criteria (Alexanderson et al., 2007). One suggested mechanism is that endurance exercise resulting in improved VO\(_2\) max may activate the vagus nerve and give rise to anti-inflammatory activity, hence suppressing cytokine production (Sloan et al., 2007), (Tracey, 2009). Consistent with this, all EG responders with reduced disease activity were also responders with improved VO\(_2\) max. The sensitivity that a responder in VO\(_2\) max also was a responder in disease activity was 70%, and the specificity was 100%. Endurance exercise reduced clinical disease activity in patients with established PM/DM. These results indicate that the reduction in disease activity stemmed from improved whole-body aerobic capacity in these patients. These results also indicate that endurance exercise may potentially be disease modifying in combination with conventional pharmacological treatment in patients with established PM/DM.
**Table 10. Characteristics and Assessment of the Disease Damage of Patients in Paper II and Results of Responders with Reduced Disease Activity**

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>EG/CG</th>
<th>Gender</th>
<th>Global damage VAS, 0-100</th>
<th>Diagnosis duration, Years</th>
<th>Comorbidities*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A†</td>
<td>EG</td>
<td>Female</td>
<td>20</td>
<td>7</td>
<td>Dysphagia, hyperlipidemia, hypertension</td>
</tr>
<tr>
<td>B†</td>
<td>EG</td>
<td>Female</td>
<td>11</td>
<td>9</td>
<td>Dysphagia, previous throat malignancy</td>
</tr>
<tr>
<td>C†</td>
<td>EG</td>
<td>Male</td>
<td>62</td>
<td>11</td>
<td>Osteoporosis, pulmonary fibrosis, previous myocardial infarction</td>
</tr>
<tr>
<td>D</td>
<td>EG</td>
<td>Female</td>
<td>60</td>
<td>26</td>
<td>Osteoporosis, pulmonary fibrosis, previous myocardial infarction</td>
</tr>
<tr>
<td>E†</td>
<td>EG</td>
<td>Female</td>
<td>58</td>
<td>8</td>
<td>Dysphagia, osteoporosis, angina pectoris, previous myocardial infarction</td>
</tr>
<tr>
<td>F†</td>
<td>EG</td>
<td>Female</td>
<td>9</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>G</td>
<td>EG</td>
<td>Female</td>
<td>NA</td>
<td>13</td>
<td>None</td>
</tr>
<tr>
<td>H†</td>
<td>EG</td>
<td>Female</td>
<td>32</td>
<td>8</td>
<td>Amenorrhea, lung fibrosis</td>
</tr>
<tr>
<td>I</td>
<td>EG</td>
<td>Female</td>
<td>24</td>
<td>10</td>
<td>Osteoporosis, pulmonary fibrosis, hypertension, upper tract infection</td>
</tr>
<tr>
<td>J</td>
<td>EG</td>
<td>Female</td>
<td>7</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>K†</td>
<td>EG</td>
<td>Female</td>
<td>37</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>L</td>
<td>CG</td>
<td>Female</td>
<td>10</td>
<td>4</td>
<td>Hypertension</td>
</tr>
<tr>
<td>M</td>
<td>CG</td>
<td>Male</td>
<td>0</td>
<td>8</td>
<td>None</td>
</tr>
<tr>
<td>N</td>
<td>CG</td>
<td>Female</td>
<td>18</td>
<td>8</td>
<td>Osteoporosis, hyperlipidemia, diminished lung function</td>
</tr>
<tr>
<td>O</td>
<td>CG</td>
<td>Male</td>
<td>40</td>
<td>28</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>P</td>
<td>CG</td>
<td>Female</td>
<td>18</td>
<td>7</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Q</td>
<td>CG</td>
<td>Male</td>
<td>49</td>
<td>2</td>
<td>Osteoporosis, pulmonary fibrosis, pneumocystis carinii infection, hyperlipidemia</td>
</tr>
<tr>
<td>R</td>
<td>CG</td>
<td>Male</td>
<td>NA</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>S</td>
<td>CG</td>
<td>Female</td>
<td>4</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>T</td>
<td>CG</td>
<td>Female</td>
<td>25</td>
<td>33</td>
<td>Osteoporosis, dysphonia, dysphagia, previous malignancy</td>
</tr>
<tr>
<td>U</td>
<td>CG</td>
<td>Female</td>
<td>41</td>
<td>10</td>
<td>Only global and muscle damage assessed</td>
</tr>
</tbody>
</table>

EG = Exercise group; CG = Control group; NA = Not assessed; † = Clinical improvement in disease activity for patients with polymyositis and dermatomyositis (Rider et al., 2004); * = Individual comorbidities assessed using the Myositis Disease Damage Tool (Isenberg et al., 2004), (Sultan et al., 2011)
4.2.3 Effects of endurance exercise on muscle performance

We found that endurance exercise improves muscle function in patients with established PM/DM. The EG improved compared to the CG in 5VRM. Eight out of 11 patients in the EG were responders with improved knee extensor 5VRM. These patients were also responders in VO\textsubscript{2} max. Conversely, only two patients in the CG were responders in 5VRM and one in VO\textsubscript{2} max. Resistance exercise promotes muscle growth and increase muscle strength (Rivas and Fielding, 2013), (Fry, 2004); it has also been found to increase strength in patients with chronic PM/DM (Alexanderson et al., 2007). Skeletal muscle adaptations are a direct consequence of intensity, frequency, volume, and type of exercise, and more specific endurance exercise improves aerobic capacity (i.e., mitochondrial biogenesis), whereas resistance exercise leads to the hypertrophy of contractile muscle proteins (myosin and actin) (Hawley, 2002), (Hawley, 2009), (Coffey and Hawley, 2007). All responders in 5VRM also improved in VO\textsubscript{2} max, indicating that the effects of endurance exercise included both cardiovascular and skeletal muscle adaptations. These results indicate that endurance exercise improves muscle function and also has a potential to increase muscle strength in patients with established PM/DM.

4.2.4 Effects of endurance exercise on patient preference and ADL

Endurance exercise was found to improve patient preference as well as ADL in patients with established PM/DM. The EG displayed a within-group improvement in patient preference that exceeded the error of measurement, which was not seen in the CG (Alemo Munters et al., 2011). Patient preference assessment (MACTAR) was highly responsive to interventions with patients with RA (de Jong et al., 2003), (Verhoeven et al., 2000a), (Verhoeven et al., 2000b); however, our study could only detect improvement within the EG. Nevertheless, the mean change score in the EG at 12 weeks was higher than recorded in an exercise study in RA (de Jong et al., 2003). Furthermore, a minor improvement in ADL was displayed in the EG compared to the CG, indicating that endurance exercise seems to improve ADL more than resistance training (Alexanderson et al., 2007). However, the clinical relevance of the minor changes in ADL is uncertain. These results indicate that endurance exercise improves ADL to some extent and may improve patient preference.

4.2.5 Long-term effects of endurance exercise

Twelve weeks of endurance exercise had long-term beneficial effects on muscle performance, patient preference, ADL, and health in patients with established PM/DM. Patients in both the EG and CG remained in a stable disease phase without flares and with only minor changes in pharmacological treatment. After 1 year, the EG was still improved (by 5.7 kg) in knee extensor muscle strength performance (5VRM) compared to the baseline, while the CG was unchanged compared to baseline. Furthermore, there was a between-group difference in favor of the EG in the left leg. However, all other parameters were back to baseline values or even lower, suggesting that the patients in the EG did not maintain the high exercise levels after the 12-week intervention. In line
with this, improved exercise performance requires continued exercise training to maintain elevated aerobic capacity; i.e., increased mitochondrial function in the skeletal muscle (Zierath and Hawley, 2004), (Egan and Zierath, 2013), (Coffey and Hawley, 2007). To maintain health, a physically active lifestyle, including regular endurance exercise, is mandatory (Sokka and Hakkinen, 2008), (Warburton et al., 2006). Others have suggested that professional support for behavioral lifestyle changes seems to be essential in chronic diseases (Avery et al., 2012). Twelve weeks of endurance exercise had a 1-year beneficial effect on muscle strength in patients with established PM/DM. These results also indicate that to maintain improved health professional support to sustain a physically active lifestyle, including endurance exercise, is essential in these patients.

4.3 PAPER III

4.3.1 Aerobic capacity in the patients and HCs

We found that patients with established PM/DM displayed impaired endurance exercise performance due to reduced aerobic capacity but not due to muscle weakness compared to the HCs. Their exercise performance, assessed as cycling time to exhaustion, and VO2 max were lower than the HCs, whereas their lactate levels in the vastus lateralis muscle at exhaustion were similar to the HCs. No difference was displayed between the patients and HCs in lactate levels, RQ values, experienced exertion level, or percentage of maximum heart rate in the fatigued state; all these four measures would be lower if the exercise ended prematurely due to improper muscle activation (McComas et al., 1995). Thus, in the present study, patients with PM/DM showed decreased performance during the cycling endurance exercise, which can be explained by reduced aerobic capacity, which is in agreement with a previous study (Wiesinger et al., 2000). This indicates that low aerobic capacity rather than an inability to adequately activate skeletal muscle limits exercise performance in patients with established PM/DM.

4.3.2 Effects of endurance exercise on aerobic capacity in skeletal muscle and exercise performance

We found that endurance exercise improves exercise performance in patients with PM/DM in an established disease phase by increasing the aerobic capacity. The patients in the EG increased their cycling time, VO2 max, and CS and β-HAD activities in the vastus lateralis muscle, whereas lactate levels at exhaustion were decreased after 12 weeks of endurance exercise. Endurance exercise triggers mitochondrial biogenesis in trained muscles (Hood, 2001), (Adhihetty et al., 2003), (Wu et al., 2002). Also, mitochondrial function, as CS activity, correlates closely to both whole-body aerobic capacity (VO2 max) and aerobic capacity within the muscle (Tonkonogi and Sahlin, 1997), (Rasmussen and Rasmussen, 2000), (Irricher et al., 2003). These findings of increased mitochondrial capacity by endurance training are in accordance with previous studies showing improved aerobic capacity and the upregulated transcription of genes for proteins involved in aerobic metabolism in PM/DM patients exposed to a period of physical exercise (Wiesinger et al., 1998b), (Nader and Lundberg, 2009), (Wiesinger et
al., 1998a). Increased aerobic capacity in skeletal muscle leads to an aerobic metabolism shift and thereby less lactate production during exercise of a given intensity (Holloszy and Coyle, 1984). In line with these results, a case study demonstrated a lower lactate concentration at the end of an endurance test after 5 weeks of endurance training compared to baseline values in a patient with chronic PM (Dalise et al., 2012). It is worth noting that all patients exposed to the training program improved their endurance exercise performance; i.e., including the patients with initially severely decreased whole-body aerobic capacity. These results indicate that 12 weeks of endurance exercise in patients with established PM/DM adapt their aerobic properties in the skeletal muscle, including increase in mitochondrial enzyme activities, and thereby improve their endurance exercise performance.

4.3.3 Natural course of muscle performance over time

We found that patients with PM/DM in an established disease phase who maintain a stable physical exercise level but only exercise once a week or less for 12 weeks will not see changes in their exercise performance and whole body and skeletal muscle aerobic capacity. This was displayed by no consistent changes in cycling time to exhaustion, VO$_2$ max, mitochondrial enzyme activities, or lactate levels in the vastus lateralis muscle during the 12-week study in the nonexercise CG. It is worth noting that the patients in the present study, as well as in previous studies, were given GC and conventional immunosuppressive treatment for at least 6 months, which consequently is not sufficient to regain full muscle performance (Alexanderson and Lundberg, 2012), (Miller, 2012). Others have observed that the local inflammatory environment is associated with mitochondrial dysfunctions (Harty et al., 2012). In addition, long-term GC treatment may cause mitochondrial dysfunction (Mitsui et al., 2002) and a muscle wasting condition ( cachexia), leading to atrophy in the skeletal muscle (Hasselgren, 1999), (Hanaoka et al., 2012a), (Walsmith and Roubenoff, 2002), (Rall and Roubenoff, 2004); in addition, these deleterious effects may be aggravated when combined with low levels of physical activity (Fitts et al., 2007). These factors could explain the persisting impaired muscle performance in PM/DM patients after conventional pharmacological treatment (Hanaoka et al., 2012a), (Hanaoka et al., 2012b), (Lundberg, 2001). Also, disuse of the skeletal muscle alone negatively impacts muscle function by activating atrophy pathways in the skeletal muscle, including the downregulation of mitochondrial function and protein synthesis (Chen et al., 2007). Physical exercise is suggested to override GC treatments’ atrophic action on skeletal muscle (Schakman et al., 2009), (Hanaoka et al., 2012a), (Hanaoka et al., 2012b). All together, this indicates that an important mechanism contributing to sustained reduced aerobic capacity and impaired muscle performance in patients with established PM/DM is low mitochondrial capacity in the skeletal muscle. We suggest adding endurance exercise to the GC and conventional immunosuppressive treatment to improve or even lead to regained endurance performance, as well as skeletal muscle and whole-body aerobic capacity in patients with established PM/DM.
4.3.4 Other mechanisms causing impaired muscle performance

Patients with established PM/DM also display impaired muscle performance due to mechanisms other than reduced aerobic capacity. Although the EG recorded increased VO\textsubscript{2} max after the 12 weeks of endurance exercise, they did not reach the VO\textsubscript{2} max that the HCs recorded at their baseline assessment (Mean [± SD] of VO\textsubscript{2} max [l/min]: 1.91 ± 0.30 versus 2.28 ± 0.55, p < 0.05). This was shown despite the fact that both the HCs and the PM/DM patients at inclusion had similar exercise habits (only exercising once or less per week). The cycling test performed by the PM/DM patients required relatively low muscle power output compared to HCs, and exercises requiring a larger muscle force may have been limited by the muscle weakness in PM/DM patients. For instance, exercises such as “walking up one flight of stairs” and “getting up from the ground/floor” have been reported as difficult to perform by patients with established PM/DM (Alemo Munters et al., 2011), (Alexanderson et al., 2012), (Alexanderson et al., 2002). In the present study, a lactate concentration in the skeletal muscle was determined after subjects cycled until exhaustion at their individual power requiring 65% of their VO\textsubscript{2} max at baseline. The lactate concentration, and hence the extent of anaerobic metabolism required, was similar in the PM/DM patients and HCs at exhaustion despite the fact that the HCs cycled at higher power outputs. A different result would have emerged if the patients and HCs would had performed a fixed endurance test; i.e., cycling with the same absolute power output in both groups. The power output tolerated by the PM/DM patients would be lower than for the HCs, and markedly higher lactate levels would be expected in the PM/DM patients at the end of a fixed cycle test. In line with these assumptions, a recent case study showed markedly higher lactate levels in a PM patient compared to an HC after a fixed endurance test (Dalise et al., 2012). This indicates that not only low aerobic capacity contributes to low exercise performance in establishing PM/DM, but also that other mechanisms, such as muscle weakness, contribute to impaired muscle function in patients with established PM/DM.

4.4 PAPER IV

We found that 12 weeks of endurance exercise had a general beneficial effect on the clinical status of patients with established PM/DM. Patients in the EG improved compared to the CG regarding cycling time and VO\textsubscript{2} max; furthermore, lactate levels in the vastus lateralis muscle at exhaustion were decreased in the EG (Figure 5). Five out of 6 patients in the EG were responders with reduced disease activity compared to the CG. Patients in the CG did not show any consistent changes during the 12-week study (Figure 5). These beneficial clinical changes in the EG indicate molecular adaptations in the skeletal muscle due to the 12-week endurance exercise.
Figure 5. Cycling time and aerobic capacity increased in PM/DM patients after 12 weeks of endurance exercise. (A) Individual data of the concentration of lactate in muscle dialysate after cycling versus cycling time (at the same absolute work load for each subject) obtained in 6 patients before (open circles) and after (filled circles) endurance exercise; mean data (± SD) before (open triangle) and after (filled triangle) training are also shown. (B) The same as A, but for 6 patients in the nonexercise CG; mean data (± SD) of VO₂ max. (C) Before (white bars) and after (black bars) the 12-weeks intervention period in the EG (n = 6) and the CG (n = 6). (D) Display mean data (± SD) of the change in VO₂ max after versus before the intervention period in individual subjects.

4.4.1 Effects of endurance exercise on gene expression in skeletal muscle

We found that clinical improvements from endurance exercise in patients with established PM/DM are associated with beneficial regulations of the genes in the skeletal muscle. In the EG, the upregulation of genes related to capillary growth, cytoskeletal remodeling, muscle hypertrophy, mitochondria biogenesis, and protein synthesis was noted. Also, there was an upregulation in genes that promote angiogenesis; VEGF-mediated angiogenesis, such as IGFR1 (Bid et al., 2012); and the proliferation of endothelial cells, as well as the downregulation in a few genes related to angiogenesis. VEGF is the central growth factor in angiogenesis (Prior et al., 2003), (Gustafsson, 2011); however, it is not a prerequisite for angiogenesis (Hoier et al., 2012). Capillary growth can be mediated by other factors, such as FLT3L (Solanilla et al., 2000), (Dooley et al., 1997). Downregulation in genes related to capillary growth
may be important for a controlled angiogenic process (Hoier et al., 2012). Endurance exercise is also associated with the upregulation in genes related to mitochondrial biogenesis (Irrcher et al., 2003), (Coffey and Hawley, 2007). In contrast, resistance exercise stimulates the protein synthesis of the skeletal muscle’s contractile properties inducing muscle hypertrophy and increases muscle strength (Rennie et al., 2004), (Hakkinen, 1989), (Coffey and Hawley, 2007). The recorded changes in gene expressions in patients with established PM/DM following the endurance exercise program indicate beneficial molecular adaptations in skeletal muscle promoting an enhanced aerobic phenotype and activating the muscle growth program, which overwrites the muscle atrophy process. They also support the reported clinical improvements in these patients.

4.4.2 Effects of endurance exercise on capillary density in skeletal muscle

We found that upregulation in genes related to capillary growth was associated with increased capillary density in skeletal muscle in established PM/DM after 12 weeks of endurance exercise (Figure 6).

![Figure 6. Immunohistochemical staining of CD34+ endothelial cells of capillaries (arrow) in skeletal muscle biopsy from a representative patient (A) at baseline, and (B) after a 12-week endurance exercise program (original magnification x40). Courtesy of Joan Raouf and Eva Lindroos.](image)

At baseline, the total number of CD34-positive capillaries per area (mm²) did not differ between the EG and the CG. A pairwise comparison within the EG and the CG showed that the number of CD34-positive capillaries per mm² was higher after the endurance exercise (mean ± SD, 35 ± 22 versus 53 ± 18 capillaries/mm²) but was unchanged in the CG (Figure 7). Furthermore, the mean change in capillary density after compared to before the intervention period was increased in the EG but unchanged in the CG (Figure 7). Endurance exercise is a powerful stimulus leading to remodeling within the exercised skeletal muscle, and with repeated bouts of exercise, an increase in capillary density develops (Prior et al., 2003), (Gustafsson, 2011). Increased capillarity in muscle, among other factors such as mitochondrial biogenesis, directly increases aerobic capacity within skeletal muscle, thereby contributing to an improvement in
endurance exercise performance (Booth and Thomason, 1991), (Hepple et al., 1997), (Hood, 2001), (KA, 2012). Increased capillary density after 12 weeks of endurance exercise may contribute to an increase in aerobic capacity in skeletal muscle in patients with established PM/DM.

**Figure 7.** Capillary density, CD34-positive capillaries per area (mm²), in the *vastus lateralis* muscle is increased in PM/DM patients after 12 weeks of endurance exercise. (A) Individual data of capillary density obtained in three patients before (filled symbols) and after (open symbols) 12 weeks of endurance training. (B) Mean data (± SD) of the change in capillary density after versus before the intervention period in individual subjects in the exercise group (trained) and in the control group (control).

### 4.4.3 Effects of endurance exercise on inflammatory expression in skeletal muscle

We found that endurance exercise decreases disease activity in patients with established PM/DM. A reduction in clinical disease activity was recorded in a majority of the EG patients. Furthermore, a downregulation in genes related to inflammation/immunity and ER stress was recorded in the EG. The CG displayed nonsynchronized regulation of the genes, although upregulation in the genes related to type 1 interferon and apoptosis was observed. As opposed to the EG, the genes in CG did not exhibit any distinct common pathways. The lack of consistent changes in the genes of the CG does not reflect the initial levels of expression in these genes; however, the inconsistency does confirm the characteristics of the control function of the group. In most patients, only a few or scattered inflammatory cells were observed in muscle tissue sections at baseline and at the 12-week followup in both the EG and the CG. Accordingly, no difference was seen in the number of T cells and macrophages within the EG and CG or between the groups before or after the 12-week endurance exercise period. Anti-inflammatory changes in skeletal muscle, modulated by exercise, have been reported in patients with other chronic inflammatory diseases like chronic obstructive lung disease, lending further
support to an anti-inflammatory effect of exercise on muscle tissue (Gielen et al., 2003), (Grewe et al., 2001). Endurance exercise decreases clinical disease activity and suppresses genes in the inflammation response in the skeletal muscle; however, it lead to no change in the number of T cells and macrophages in the skeletal muscle.

4.5 METHODOLOGICAL CONSIDERATIONS AND DISCUSSIONS

4.5.1 Evaluation of endurance exercise intervention

In Paper II, we were able to demonstrate improvements in health and aerobic capacity, as well as reduced disease activity, by an endurance exercise intervention in an RCT study. The improved health assessed with the SF-36 was clinically relevant (Bjorner et al., 2007). Paper II had some clear limitations. The changes in disease activity reported in the EG were small, although they were in accordance with the IMACS improvement criteria. The proposed 20% change in disease activity might be within the error of measurement in some individuals depending on low baseline values; however, the changes were synchronized in the EG (Rider et al., 2004). It would have been of interest to quantify a potential relationship between reduced disease activity and increased VO$_2$ max and exercise performance through testing. Unfortunately, the six-item core set in the IMACS does not consist of one total score, and is therefore not suitable for quantifying relationships. However, we were able to demonstrate that all patients in the EG with reduced disease activity also improved in VO$_2$ max and exercise performance. It is worth noting that no patient in the CG exhibited a reduction in disease activity according to these criteria. For analysis of improvement in individual patients in 5 VRM, we used the responder criteria suggested by Paulus et al. (1990). We believe that the improvement in 5VRM in the EG is clinically relevant. The reported improvement in the ADL (measured with MAP) by the endurance exercise was minor and the clinical relevance of the change in ADL assessment by MAP is uncertain.

We did not detect any significant difference in the endurance exercise in the intended primary outcome measure FI-2. Initially, we performed a power analysis based on mean values of improvement and SEM from a previous open exercise study in PM/DM that indicated a sample size of 15 patients in each group, giving 80% power to detect a significant difference in the intended primary outcome FI-2. As we had delays in patient recruitment, we decided to perform interim analysis. The VO$_2$ max was determined to be more sensitive to change than FI-2 due to the type of exercise performed. Thus, the VO$_2$ max was instead selected as primary outcome and used for interim analysis. The interim power analysis showed 86% power in the (Group * Time) interaction and significant difference in VO$_2$ max; it indicated a sample size of nine patients in each group, giving 80% power to detect a significant difference in the primary outcome of VO$_2$ max. This finding may indicate that the FI-2 is not a sensitive outcome measure to evaluate cycling endurance exercises.
We may only generalize our results to the physical therapist–supervised exercises performed with the same intensity, frequency, duration, and type of exercise in patients with established PM/DM. Due to the relative paucity of males in the EG, the external validity regarding exercise effects in men is limited. However, patients responded to the endurance training despite various amounts disease damage and disease duration. Thus, endurance training is effective in PM/DM patients even when they are in a chronic stable disease phase with severe muscle dysfunction. Another limitation is that patients did not keep exercise diaries during the open extension part of the study. Despite these limitations, we suggest that a physically active lifestyle including regular endurance exercise is mandatory in established PM/DM to maintain health, just as in the general population and for other diseases (Sokka and Hakkinen, 2008), (Warburton et al., 2006).

In Paper III, one limitation was that the median age of the HC group was 7 years younger than that of the patients, which might cause the differences between the groups to be exaggerated. However, it should be noted that there was no statistical difference in age between the two groups and they maintained a similar level of physical exercise at inclusion. Another clear limitation is the relatively low number of patients in the EG and the CG. A power analysis showed that for physiological assessments, we needed measurements from at least six subjects before and after the endurance exercise period. Nine patients were included in the EG, but it was not possible to obtain all measurements for all individuals at both baseline and the 12-week follow-up. Measurements of mitochondrial enzyme activities were clearly underpowered, with only three patients in the EG. However, all three subjects showed clear increases in mitochondrial enzyme activities after the 12 weeks of endurance exercise, which fits with the concurrent increases in VO$_2$max and endurance performance from a physiological perspective. Furthermore, no consistent changes during the 12 weeks were expected in the CG, and thus our results were consistent with this expectation. However, we believe that our data clearly demonstrated improved aerobic capacity in the whole body and skeletal muscle by 12 weeks of endurance exercise in patients with established PM/DM.

Our results may also indicate that exercise ended due to muscle weakness in patients with established PM/DM. The patients’ cycling exercise required relatively low muscle power output compared to HC and exercise requiring a larger fraction of muscle force may be limited by muscle weakness. Furthermore, lactate levels—and hence the extent of anaerobic metabolism required—were similar in PM/DM patients and healthy controls at exhaustion, although healthy controls cycled for longer times and at higher power outputs. We believe that a markedlly different picture would emerge if we had instead used a fixed endurance test, that is, with the same absolute power output and duration in both patients and HC. Finally, a fixed endurance test would have enabled us to determine whether muscle weakness contributes to impaired muscle performance in PM/DM patients in an established disease phase. We believe that direct measurement of lactate levels in vivo in skeletal muscle by the microdialysis technique is a novel methodological approach to assess mechanisms contributing to muscle impairment in...
patients with PM/DM. The microdialysis technique was feasible and could also be used for analysis of other potential factors contributing to muscle impairment in these patients. Furthermore, the measure of mitochondrial enzyme activities in skeletal muscle was used for the evaluation of treatment effects, which we believe is also a novel approach in these patients.

Paper IV was a pilot study with clear limitations, including the small sample size, especially in terms of the muscle biopsy analysis. This can be explained by the invasiveness of this part of the protocol. However, all analyses included evaluation of both an exercise and a nonexercise control group. In addition, another clear limitation was that the WB and IHC analyses were performed on muscle biopsies from one subgroup of patients and the microarray analyses on a different subgroup of patients because of limitations related to the muscle samples. However, there were no clinical differences between the two subgroups in the baseline assessments. Protein analyses both by western blot and by immunohistochemistry are less sensitive to changes than gene expression on the mRNA level. Therefore, small changes in protein level may have been missed in our analyses. Furthermore, one patient randomized to the EG did not exercise according to the exercise program and was thereby considered a non-responder in the clinical assessments. Thus, this patient was excluded in all analyses but could not be excluded in the microarray analysis, which was performed at the group level before it became clear that the adherence to the exercise program was not satisfactory in this case. This patient’s data might have diminished the measured beneficial effects of endurance exercise on gene expressions.

Although the gene expression changes were significant and clearly synchronized in the EG, and not demonstrated in the nonexercising CG, the fold-changes detected were small. This is in contrast to the observed larger changes of mRNA expression in skeletal muscle as a result of one acute single exercise bout. Accordingly, smaller fold changes have been observed after each exercise bout (Perry et al., 2010), (Prior et al., 2003), indicating that high fold changes are not to be expected in a long-term perspective such as over 12 weeks. The muscle biopsies were collected at baseline and at the 12-week follow-up one week after the last exercise session. This might explain the small mRNA fold changes detected in our study, since we evaluated the effects of a 12-week endurance exercise program, and may be considered to evaluate the chronic effects of endurance exercise (Hawley, 2002). Furthermore, others have determined that increased transcription occurs immediately post-exercise, while morphological changes in skeletal muscle such as capillary growth and hypertrophy are slow processes and may take weeks to months (Egan et al., 2013). Protein synthesis must exceed protein breakdown for an extended period through repeated bouts of endurance exercise to enhance exercise performance (Hawley, 2009), (Coffey and Hawley, 2007). Time-course studies using the western blotting technique have demonstrated that a significant increase in protein content was only detectable within days following exercise stimuli (Morton et al., 2009). The FLT3L gene exhibited the highest fold change (4.3-fold change) in our microarray analysis, and was thus selected for protein target validation.
The low fold change in the FLT3L gene may explain why change in the FLT3L protein was not demonstrated with the WB analysis in the EG.

Capillary growth in skeletal muscle formed by sprouting and/or splitting of endothelial cells by endurance exercise stimuli was well established with the IHC technique in the EG after 12 weeks. Despite the methodological limitations, the clear clinical improvements were recorded for the exercise group, indicating physiological adaptations in skeletal muscle due to the endurance exercise.

4.5.2 Patient perspective

All patients included in Paper I were in an established disease phase with low disease activity. Despite the small sample size, both female and male patients of various ages, disease durations, disabilities, and education levels were included; thus, the external validity seems reasonable for patients with established PM/DM. MACTAR was translated and cross-culturally adapted according to the process proposed by Guillemin (1995). The validity testing only included a descriptive comparison of MACTAR for the recommended fixed item myositis assessments and testing of construct validity. MACTAR seems to be responsive to endurance exercise in patients with established PM/DM. We could only detect an improvement in patient preference by MACTAR in the EG, while there was no difference compared to CG. On the other hand, the improvement in MACTAR by endurance exercise was higher than reported in another exercise study in RA patients (de Jong et al., 2003) and exceeded the error of measurement (Alemo Munters et al., 2011).

4.6 FUTURE PERSPECTIVE

Endurance exercise improves health in patients with established PM/DM. We suggest that this is mediated through improved aerobic capacity. However, the mechanisms by which improved aerobic capacity contributes to improved health need to be further assessed both systemically and locally in skeletal muscle in these patients. However, the improved health was not maintained at the 1-year follow-up, suggesting that a longer duration than 12 weeks of endurance exercise is important for improvements in health in these patients. Professional support for behavioral lifestyle changes seems to be essential in chronic diseases, and should be further investigated in PM/DM patients.

We evaluated the effect of endurance exercise on mitochondrial enzyme activities and capillary density in only a few patients. They displayed clear increases in mitochondrial function and capillarity. These changes were not detected in the nonexercise control group. These are novel analyses in PM/DM patients and may be performed again with a larger sample size. Twelve weeks of endurance exercise improved muscle strength both at 12 weeks and in the long term. We believe that adaptations in skeletal muscle included muscle hypertrophy, which would support the increased muscle strength. Genes related to muscle growth support improved muscle strength, although assessments of muscle volume, fiber sizes, and the cross-sectional area of skeletal muscle should also be performed. In an ongoing study, protein content assessed by
proteomics from three patients in EG support our clinical and gene expression results, indicating an increase in proteins involved in mitochondrial function, muscle remodeling, calcium signaling, and cytoskeleton signaling pathways (un-published data). These data will be analyzed more extensively in future.

Endurance exercise reduced clinical disease activity in patients with established PM/DM. A down-regulation in genes related to the immune response and inflammation was determined. The effect of endurance exercise on markers known to be involved in the inflammatory response in PM/DM such as HMGB1 and IFNα-activity should also be assessed in patients’ skeletal muscle.

Sustained impairment of muscle performance in patients with established PM/DM, despite treatment with immunosuppressive drugs, has been well established in previous literature. We suggest that impaired aerobic capacity in skeletal muscle contributes to the impaired muscle performance in these patients. A sign of reduced aerobic capacity in skeletal muscle is reduced capillarity, which has been shown in these patients compared to HC (Grundtman et al., 2008). Another sign of impaired aerobic capacity is mitochondrial pathology in skeletal muscle, which has been found in patients with PM/DM (Blume et al., 1997), (Varadhachary et al., 2010), (Temiz et al., 2009). However, comparison of the mitochondrial function in skeletal muscle to healthy controls has not been performed in these patients. Potential mechanisms contributing to low aerobic capacity in skeletal muscle may include both disease- and treatment-related factors such as those secondary to the local inflammatory environment in skeletal muscle and side effects of long-term glucocorticoid treatment. The effect of these factors on skeletal muscle and muscle performance should be tested in laboratory and functional studies. Our data also suggest that mechanisms other than reduced aerobic capacity, such as muscle weakness, contribute to sustain impairment in muscle performance in established PM/DM. One way to test this is to let patients with established PM/DM and HC perform a fixed endurance test, such as cycling to exhaustion, with the same absolute power output in both groups and to compare lactate levels in vastus lateralis muscle and cycling time at exhaustion. Reduced calcium release from the sarcoplasmatic reticulum in skeletal muscle could also lead to muscle weakness and needs to be tested in PM/DM patients. The microdialysis technique provides the possibility to assess calcium release and metabolic dysfunctions directly in skeletal muscle, as well as enabling the search for other molecules involved in the disease process or thought to be involved in the development of muscle impairment. A more extensive analysis of gene expressions in the CG would clarify whether a more synchronized pattern will emerge to find factors contributing to sustained muscle impairment in patients with established PM/DM. An increased knowledge about factors contributing to impaired muscle performance would enable treatment to be tailored, and may even allow prevention of damage to skeletal muscle in these patients.

MACTAR reveals patients’ individual priorities and may aid in target setting in clinical settings; it might therefore allow better targeted rehabilitation and treatment in PM/DM patients. However, this needs to be evaluated.
4.7 CLINICAL IMPLICATIONS

We suggest introducing endurance exercise in patients with established PM/DM, since patients responded despite initial markedly reduced muscle performance, disease damage, and long-term disease duration. We recommend that endurance exercise should be individually adapted to clinical status. It should be introduced at a low level; thereafter the intensity should be increased gradually to 70% of max VO$_2$ max under supervision by a physical therapist. Furthermore, to enable the molecular and clinical adaptations demonstrated, a 12-week period of endurance exercise performed three times per week for 60 minutes seems to be required. We also believe that professional support for behavioral lifestyle changes, including an active lifestyle and endurance exercise, may contribute to maintaining improvements and may even increase the reported beneficial effects over the long term perspective in these patients. For safety reasons, a VO$_2$ max test with electrocardiography is suggested before starting an endurance exercise program. This is especially important in patients with heart conditions and ILD, and will assist to establish exercise intensity.

MACTAR might be considered as a patient preference outcome in clinical trials and in clinical care in patients with established PM/DM. It may also be used as a tool in goal setting for these patients’ treatment. We suggest adding MACTAR to the recommended outcomes for the evaluation of treatment effects that matter to the individual patient with PM/DM.

4.8 CONCLUSIONS

- Twelve weeks of endurance exercise in addition to immunosuppressive treatment improves muscle performance and health and reduces clinical disease activity in patients with established PM/DM. Endurance exercise increases capillary density and mitochondrial capacity in skeletal muscle, which could contribute to markedly improved muscle performance through increased aerobic capacity. Improved health and decreased clinical disease activity could potentially be mediated through improved VO$_2$ max. Endurance exercise lead to changes in gene expressions and activates aerobic phenotype and muscle growth pathways, which overwrites the muscle atrophy process and simultaneously suppresses the inflammatory response. A short term endurance exercise program only has a long-term beneficial effect on muscle strength. A maintained physically active lifestyle, including endurance exercise, seems mandatory to sustain health in these patients.

- Impaired muscle performance in patients with established PM/DM may be due to low aerobic capacity in skeletal muscle. Low mitochondrial capacity and low capillary density in skeletal muscle are possible mechanisms contributing to the sustained impairment of muscle performance. However, other mechanisms such as muscle weakness could also contribute to impaired muscle performance in these patients.
- The disease consequences that are most important for improvement in individual patients are not completely captured by the IMACS recommended or myositis-specific outcomes measures. MACTAR exhibits promising measurement properties in established PM/DM.
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APPENDIX

MACTAR-BASLINJE

Datum: ................................................
Namn: ................................................
Personnummer: ........................................


1a. Hur var ditt allmänna hälsotillstånd under den gångna veckan? Tyckte du att det var:

☐ 3p. Mycket bra
☐ 2p. Ganska bra
☐ 1p. Inte så bra

1e. Jämförande fråga med MACTAR-UPPFÖLJNING. Ger schablopoäng ☑ 4p.

Intervjuaren: Tycker du att din reumatiska sjukdom gör att du har svårt att uträtta saker eller utföra aktiviteter som du tidigare klarade utan svårighet?

Ej poängsatt ☐ Nej ☐ Ja

Intervjuaren: Kan du berätta för mig vilka aktiviteter det rör sig om? För att hjälpa dig ska jag ge dig några exempel:

Instruktion: För att listan över sysslor ska bli så fullständig som möjligt måste du läsa upp alla exemplen för din samtalspartner. Anteckna alla sysslor som patienten nämner. Se aktivitetslista nästa sida...
Fråga 2a till 2e.

Intervjuaren: Har du tillföljd av din reumatiska sjukdom svårt med...

1. aktiviteter inomhus, t.ex. matlagning eller annat hushållsarbete?

2. aktiviteter som har att göra med att klä på dig, t.ex. knäppa knappar, dra en tröja över huvudet etc.?

3. aktiviteter i arbetet, utomhus, köra bil eller andra transportmedel, t.ex. cykla?

4. aktiviteter i samband med fritids- och hobbyverksamhet, t.ex. sport som fotboll och simning eller annat som att sy eller snickra? Hur är det på semestern?

5. utföra sociala aktiviteter, t.ex. besöka någon, spela kort, delta i föreningsliv etc.?

6. avseende på ditt sexualliv?

7. att bibehålla dina matvanor?

8. att sova om nätterna?

9. att umgås med din familj?

Om du sammanbor med make/partner, har du då:

10. på grund av din reumatiska sjukdom svårigheter i relationen till din make/partner?

Om du (dessutom) har ett eller flera hemmavarande barn, har du då:

11. på grund av din reumatiska sjukdom svårigheter i relationerna till dem?

Intervjuaren: För att kunna rangordna aktiviteterna i listan efter deras betydelse måste du genomföra följande steg: Välj i den här listan över aktiviteter ut den som du helst skulle vilja kunna utföra igen utan besvär på grund av din reumatiska sjukdom

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Sammanlagd poäng fråga 2a till 2c:  
☐ 10p. (Ovägda poäng)  
☐ 30p. (Vägda poäng)
3a. I hur hög grad är du, nöjd med ditt liv och med din livskvalitet?  
Har du under den gångna veckan beträffande ditt liv varit:

☐ 3p. Helt nöjd

→ gå vidare till fråga 4 lägg till 1p för fråga 3b

☐ 2p. Ganska nöjd

☐ 1p. Inte så nöjd

3b. Är det din reumatiska sjukdom som gör att du inte är helt nöjd med din livskvalitet?

☐ 1p. Nej

☐ 0p. Ja

4a. Vad anser du om dina fysiska funktioner som helhet?  
Har du under den gångna veckan tyckt att du fungerat fysiskt:

☐ 5p. Bra

→ gå vidare till fråga 5 lägg till 1p för fråga 4b

☐ 4p. Ganska bra

☐ 3p. Varken bra eller dåligt

☐ 2p. Ganska dåligt

☐ 1p. Dåligt

4b. Är det din reumatiska sjukdom som gör att du fysiskt inte fungerar så bra som du skulle kunna göra?

☐ 1p. Nej

☐ 0p. Ja
5a. Hur skulle du, vilja karakterisera din sociala funktion under den gångna veckan? (Tänk exempelvis på dina kontakter på arbetet, med vänner och med familjemedlemmar)
Har du under den gångna veckan tyckt att du socialt har fungerat:

☐ 5p. Bra
→ gå vidare till fråga 6 lägg till 1p för fråga 5b
☐ 4p. Ganska bra
☐ 3p. Varken bra eller dåligt
☐ 2p. Ganska dåligt
☐ 1p. Dåligt

5b. Är det din reumatiska sjukdom som gör att du socialt inte fungerar så bra som du skulle kunna göra?

☐ 1p. Nej
☐ 0p. Ja

6a. Hur skulle du, vilja karakterisera ditt känsoliv under den gångna veckan? (Tänk exempelvis på om du i stort sett har känt dig lycklig eller inspirerad)
Har du under den gångna veckan tyckt att ditt känsoliv har varit:

☐ 5p. Bra
→ Avsluta genom att lägga till 1p för fråga 6b
☐ 4p. Ganska bra
☐ 3p. Varken bra eller dåligt
☐ 2p. Ganska dåligt
☐ 1p. Dåligt

6b. Är det din reumatiska sjukdom som gör att ditt känsoliv inte är så bra som det skulle kunna vara?

☐ 1p. Nej
☐ 0p. Ja

Total summa:..................
MACTAR-UPPFÖLJNING

Datum: ........................................

Namn: .......................................... 

Personnummer: ..................................

Instruktion: Läs först upp frågan och läs sedan upp alla svarskategorierna. 
Ge sedan patienten tillfälle att reagera spontant. Markera rutan för det givna svaret.

1a. Hur var ditt allmänna hälsotillstånd under den gångna veckan? 
   Tyckte du att det var:

   □ 3. Mycket bra 

   □ 2. Ganska bra 

   □ 1. Inte så bra

Instruktion: Fråga 1b till 1d är allmänna frågor som ej är poängsatta.

1b. Har du sedan vår första intervju märkt någon förändring beträffande din 
    reumatiska sjukdom?

   Ej poängsatt

   □ Nej → gå vidare till fråga 2

   □ Ja

1c. Har din reumatiska sjukdom blivit bättre eller sämre?

   Ej poängsatt

   □ Bättre

   □ Sämre

1d. Kan du säga vad det är som har förändrats med avseende på din reumatiska sjukdom?

   Ej poängsatt
1e. Om du tänker tillbaka på hur din reumatiska sjukdom var två veckor innan du började med den nya behandlingen, hur mycket bättre eller sämre har det allt som allt blivit med din reumatiska sjukdom?

☐ 7. Mycket bättre
☐ 6. Bättre
☐ 5. Något bättre
☐ 4. Samma
☐ 3. Något sämre
☐ 2. Sämre
☐ 1. Mycket sämre

Intervjuaren: Du minns kanske vår första intervju, där du fick berätta om vilka aktiviteter du hade svårigheter med.

2a. Har du sedan den första intervjun märkt någon förändring i den svårighet som du har med (aktivitet 1)? Har du:

☐ 3. Mindre svårighet
☐ 2. Samma svårighet
☐ 1. Mer svårighet

Är förändringen:  
 Ej poängsatt

☐ Avsevärda
☐ Obestämbar
☐ Obetydlig

2b. Har du sedan den första intervjun märkt någon förändring i den svårighet som du har med (aktivitet 2)? Har du:

☐ 3. Mindre svårighet
☐ 2. Samma svårighet
☐ 1. Mer svårighet

Är förändringen:  
 Ej poängsatt

☐ Avsevärda
☐ Obestämbar
☐ Obetydlig
2c. Har du sedan den första intervjun märkt någon förändring i den svårighet som du har med (aktivitet 3)? Har du:

☐ 3. Mindre svårighet
☐ 2. Samma svårighet
☐ 1. Mer svårighet

Är förändringen: 

Ej poängsatt
☐ Avsevärd
☐ Obestämbar
☐ Obetydlig

2d. Har du sedan den första intervjun märkt någon förändring i den svårighet som du har med (aktivitet 4)? Har du:

☐ 3. Mindre svårighet
☐ 2. Samma svårighet
☐ 1. Mer svårighet

Är förändringen: 

Ej poängsatt
☐ Avsevärd
☐ Obestämbar
☐ Obetydlig

2e. Har du sedan den första intervjun märkt någon förändring i den svårighet som du har med (aktivitet 5)? Har du:

☐ 3. Mindre svårighet
☐ 2. Samma svårighet
☐ 1. Mer svårighet

Är förändringen: 

Ej poängsatt
☐ Avsevärd
☐ Obestämbar
☐ Obetydlig
3a. I hur hög grad är du, nöjd med ditt liv och med din livskvalitet? Har du under den gångna veckan beträffande ditt liv varit:

☐ 3. Helt nöjd
   → gå vidare till fråga 4, lägg till 1p för fråga 3b

☐ 2. Ganska nöjd

☐ 1. Inte så nöjd

3b. Är det din reumatiska sjukdom som gör att du inte är helt nöjd med din livskvalitet?

☐ 1. Nej

☐ 0. Ja

3c. Hur nöjd har du varit med din livskvalitet sedan den första intervjun? Har den:

Ej poängsatt

☐ Blivit bättre

☐ Inte förändrats

☐ Blivit sämre

4a. Vad anser du om dina fysiska funktioner som helhet? Har du under den gångna veckan tyckt att du fungerat fysiskt:

☐ 5. Bra
   → gå vidare till fråga 5, lägg till 1p för fråga 4b

☐ 4. Ganska bra

☐ 3. Varken bra eller dåligt

☐ 2. Ganska dåligt

☐ 1. Dåligt
4b. Är det din reumatiska sjukdom som gör att du fysiskt inte fungerar så bra som du skulle kunna göra?

☐ 1. Nej
☐ 0. Ja

4c. Hur har du fungerat fysiskt sedan den första intervjun?

**Ej poängsatt**

☐ Blivit bättre
☐ Inte förändrats
☐ Blivit sämre

5a. Hur skulle du, vilja karakterisera din sociala funktion under den gångna veckan? (Tänk exempelvis på dina kontakter på arbetet, med vänner och med familjemedlemmar)
Har du under den gångna veckan tyckt att du socialt har fungerat:

☐ 5. Bra

→ gå vidare till fråga 6, lägg till 1p för fråga 5b

☐ 4. Ganska bra
☐ 3. Varken bra eller dåligt
☐ 2. Ganska dåligt
☐ 1. Dåligt

5b. Är det din reumatiska sjukdom som gör att du socialt inte fungerar så bra som du skulle kunna göra?

☐ 1. Nej
☐ 0. Ja
5c. Hur har du fungerat socialt sedan den första intervjun?

*Ej poängsatt*

- Blivit bättre
- Inte förändrats
- Blivit sämre

6a. Hur skulle du, vilja karakterisera ditt känsloliv under den gångna veckan? (Tänk exempelvis på om du i stort sett har känt dig lycklig eller inspirerad)
Har du under den gångna veckan tyckt att ditt känsloliv har varit:

- 5. Bra

  → gå vidare till fråga 6c, lägg till 1p för fråga 6b

- 4. Ganska bra
- 3. Varken bra eller dåligt
- 2. Ganska dåligt
- 1. Dåligt

6b. Är det din reumatiska sjukdom som gör att ditt känsloliv inte är så bra som det skulle kunna vara?

- 1. Nej
- 0. Ja

6c. Hur har ditt känsloliv varit sedan den första intervjun?

*Ej poängsatt*

- Blivit bättre
- Inte förändrats
- Blivit sämre