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Exercise and outcome measures in patients with polymyositis and dermatomyositis

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To all individuals living
with myositis

PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals:

Paper I. Alexanderson H, Stenström CH, Lundberg I. Safety of a home exercise programme in patients with polymyositis and dermatomyositis: a pilot study. Rheumatology 1999;38:608-11.

Paper II. Alexanderson H, Stenström CH, Jenner G, Lundberg I. The safety of a resistive home exercise program in patients with recent onset active polymyositis or dermatomyositis. Scand J Rheumatol 2000;29:295-301.

Paper III. Alexanderson H, Lundberg IE, Stenström CH. Development of the Myositis Activities Profile – validity and reliability of a self-administrated questionnaire to assess activity limitations in patients with polymyositis/dermatomyositis. J Rheumatol 2002;29:2386-92.

Paper IV. Alexanderson H, Broman L, Tollbäck A, Josefson A, Lundberg IE, Stenström CH. The Functional Index-2, FI-2, a valid and reliable measure of impairment in patients with polymyositis and dermatomyositis. Submitted.

Paper V. Alexanderson H, Dastmalchi M, Esbjörnsson Liljedahl M, Stenström CH, Lundberg IE. Benefits of intensive resistive exercise in patients with stable and inactive polymyositis or dermatomyositis. Manuscript.

ABSTRACT

Polymyositis (PM) and dermatomyositis (DM) are chronic idiopathic inflammatory myopathies (IIM) which are clinically characterized by symmetrical proximal muscle weakness, fatigue, myalgia and extra-muscular involvement. Muscle impairment is the most significant feature of PM and DM with characteristic infiltrates of mononuclear inflammatory cells in muscle biopsies, elevated inflammatory parameters in serum and characteristic EMG changes, which separate these disorders from neurological disorders and also fibromyalgia. First-line pharmaceutical treatment is oral corticosteroids together with other immunosuppressive agents. Despite an initial favorable response to treatment most patients develop sustained disability. Historically, these patients have been discouraged from active exercise due to a fear of exacerbated disease activity and little is known of the potential effects of exercise. The lack of valid and reliable outcome measures for patients with PM and DM for assessment of impairment, activity limitation and participation restriction limit the ability to evaluate different types of interventions in these patients.

The aim of this thesis was to develop and evaluate exercise regimens regarding both safety and benefits for patients with chronic as well as active, recent onset PM and DM. Another objective was to develop disease-specific outcome measures and to evaluate their measurement properties.

An easy to moderate home exercise program was performed by patients with both inactive, chronic and active recent onset PM or DM five days a week for 12 weeks. An intensive resistive exercise program with a load of 10 voluntary repetition maximum (VRM) in five muscle groups was also performed by patients with chronic PM or DM three days a week for seven weeks. Assessments of disease activity and disability were conducted. A disease-specific, self-administered questionnaire to assess activity limitation, the Myositis Activities Profile (MAP) was developed based on activities presented in the ICIDH-2 beta-2 draft. The Functional Index 2 (FI-2) was developed based on the original FI to assess impairment. These two outcome measures were evaluated for different aspects of validity and reliability.

The home exercise program could be safely employed in patients with both chronic and active disease, as no signs of increased muscle inflammation could be detected either by analyses of muscle biopsies, Magnetic resonance imaging (MRI) or CPK-levels. The patient groups improved with significantly reduced disability. The intensive resistive 7-week exercise program resulted in significantly reduced impairment without any signs of increased disease activity as assessed by muscle biopsies and CPK-levels. Both the MAP and the FI-2 had satisfactory content validity, construct validity and reliability.

In summary, patients with chronic as well as active, recent onset PM or DM can perform individualized active exercise without increased muscle inflammation and with positive effects on muscle impairment, activity limitation and participation restriction. Active exercise should be included in the rehabilitation as an addition to pharmacological treatment. More research needs to be conducted to further minimize the patients' persisting impairment and activity limitation. The MAP and the FI-2 are valid, reliable and feasible instruments for assessing activity limitation and impairment and are also sensitive to change in these patients.

Keywords: Inflammatory myopathies, exercise, outcome measures, disability

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ABBREVIATIONS

AIMS2	Arthritis Impact Measurement Scale 2
ALAT	Alanine aminotransferase
AS	Ankylosing spondylitis
ASAT	Aspartate aminotransferase
ATP	Adenotriphosphate
CD3	Marker for T-cells
CD4	Marker for T-helper cells and macrophages
CD8	Marker for cytotoxic T-cells
CPK	Creatine Phosphokinase
CRP	C-reactive protein
CSA	Cross-sectional area
DM	Dermatomyositis
ESR	Erythrocyte sedimentation rate
FI	Functional Index
FI-2	Functional Index 2
HAQ	Stanford Health Assessment Questionnaire
Hb	Hemoglobin
HLA	Human leukocyte antigen
IBM	Inclusion body myositis
ICIDH	The International Classification of Impairment, Disability and Handicap
ICIDH-2	The ICIDH-2 beta- 2 draft
ICF	The International Classification of Functioning, Disability and Health
IIM	Idiopathic inflammatory myopathies
IL-1α	Interleukin 1α
ILD	Interstitial lung disease
Kin-Com	Kinetic computer
LD	Lactate dehydrogenase
MAP	Myositis Activities Profile
MCTD	Mixed connective tissue disease
MHC	Major histocompatability complex
MMT	Manual muscle test
MRC	Medical Research Counceil
MRI	Magnetic Resonance Imaging
NHP	Nottingham Health Profile
OA	Osteoarthritis
PCr	Phosphocreatine
PM	Polymyositis
RA	Rheumatoid arthritis
RPE	Rating of perceived exertion
SF-36	The MOS 36-item Short-Form Health Survey
SGDI	Subjective global disease impact
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis

DEFINITIONS

International classification of functioning, disability and health (ICF)

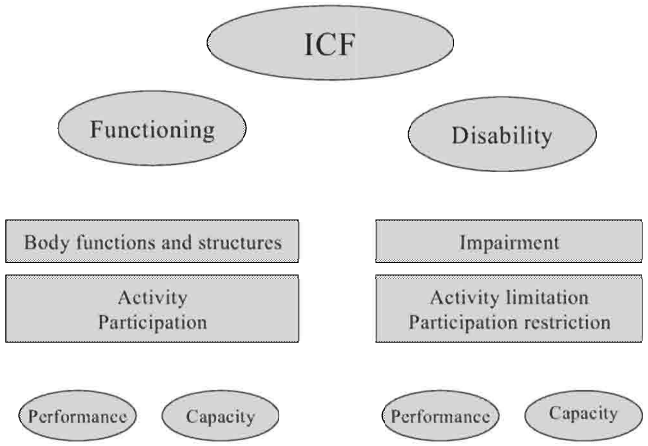
The World Health Organization (WHO) published the International Classification of Impairment, Disability and Handicap (ICIDH) in 1980 (WHO 1980). During the 1990s this classification was revised in several steps. In 1999, the ICIDH-2 beta-2 draft (WHO 1999) was published. The final International Classification of Functioning, Disability and Health (ICF) was press-released in 2001 (WHO 2001). The overall aim of the ICF is to provide a unified and standardized language and framework for the description of health and health-related status. The structure of the ICF offers the possibility to measure health status at several levels; impairment, activity limitation and participation restriction and also provides a model for how they interact. This structure enhances the possibility to grasp the total implications of a disease in an individual.

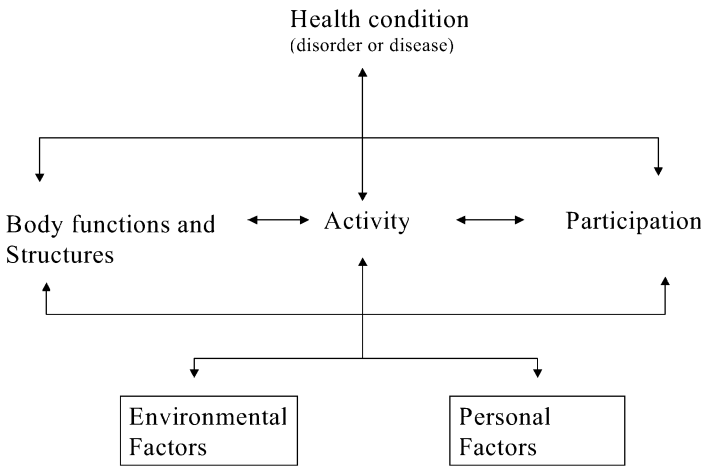
Functioning: An umbrella term encompassing all body functions and structures, the activities we do in daily life (activity), and how we participate in society (participation).

Disability: The umbrella term for the impacts of a health-related condition on different levels as impaired body functions and structures (impairment), limitations of our ability to perform activities of daily life (activity limitation), and restrictions in our ability to participate in society (participation restriction).

Performance: What we do perform in daily life in our environment.

Capacity: What we can perform under ideal circumstances.


ICF
Functioning
Disability
Body functions and structures
Activity
Participation
Impairment
Activity limitation
Participation restriction
Performance
Capacity
Performance
Capacity


Health condition
(disorder or disease)
Body functions and
Structures
Activity
Participation
Environmental
Factors
Personal
Factors

Aspects of validity and reliability

There are several properties of an outcome measure that are important to consider in clinical practice and in research. A useful measure must provide room on the scale to demonstrate improvement and deterioration, and should thus not contain floor or ceiling effects. Studies of test-retest reliability or intra-rater reliability are based on data obtained from questionnaires filled out on two occasions or assessments performed by one rater on different occasions, respectively, with the objective to provide information about the stability of test results with time. Inter-rater reliability studies are based on parallel assessments performed by two or several raters and are particularly important when more than one rater are part of the measurement process. Internal consistency reflects the homogeneity of items or tasks of an outcome measure (Finch *et al* 2002).

A measure is valid to the extent that it assesses what it was intended to measure and validity cannot be considered to be an all-or-none property but rather a matter of degree. There are several aspects of validity of an outcome measure to consider. Face validity reflects to what degree a measure appears to assess what it was intended to measure, and content validity to what degree the measure grasps all aspects of the domain it was intended to measure. Criterion validity can be divided into concurrent validity, the measure's results compared to the results of the golden standard obtained at approximately the same point in time, and the predictive validity, which illustrates if the measure has ability to predict some subsequent criterion event. In absence of a golden standard, a construct validity process can be applied, involving forming theories about the measure of interest and then assessing to what extent the measure provides results that are consistent with the theories. A more recent interpretation of construct validity is that it includes all aspects of validity (Finch *et al* 2002).

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INTRODUCTION

Polymyositis (PM) and dermatomyositis (DM) are chronic muscle disorders that could have implications for all levels of the life situation for those affected. They require long-standing medical treatment and follow-up and are most often cared for at a rheumatology or a neurology unit. The role of physical therapy in the care of these patients has been unclear for many years. The ambition of this thesis was to further develop and evaluate physical therapy assessment and treatment to improve rehabilitation for patients with PM and DM.

Historical background

PM and DM, together with inclusion body myositis (IBM), comprise a heterogeneous group of disorders categorized as the idiopathic inflammatory myopathies (IIM), characterized by inflammatory infiltrates in skeletal muscles with muscle weakness as major clinical findings (Dalakas 1991). The inflammatory myopathies have been known for many years as Wagner *et al* first described PM in 1863 and DM was first mentioned in 1887. Inclusion body myositis was first described in 1967 and juvenile inflammatory myopathies in 1912. (Maddison *et al* 1998).

This thesis concerns only adult patients with PM and DM, thus IBM and juvenile DM or PM will not be further discussed.

Clinical features

Both PM and DM are conditions primarily presenting with muscle impairment, e.g. decreased muscular strength and endurance, together with general fatigue, myalgia and also skin rashes in DM (Dalakas 1991, Mastaglia and Phillips 2002). Onset of PM and DM is most commonly slow with muscle weakness progressing over weeks to months (Oddis *et al* 1990). Skeletal muscle impairment will be further discussed later on in this introduction.

The dermatological manifestations of DM are often very characteristic with presence of Gottron´s papules over the extensor surfaces of the metacarpophalangeal and interphalangeal joints. Rashes can also appear on the upper eyelids together with edema over the scalp, neck, and trunk and over the upper and lower limbs (Plotz *et al* 1989, Spiera and Kagen 1998) and can often accompany or precede muscle weakness when the disease is exacerbated (Dalakas 1991).

Systemic manifestations can be divided into five categories: general systemic, cardiac, pulmonary, gastrointestinal and endocrine (Plotz *et al* 1989). Most patients complain of fatigue even when the acute phase of active muscle inflammation has subsided. Fever in PM and DM is usually mild. A weight loss could occur due to muscle atrophy, dysphagia and in some cases depression (Plotz *et al* 1989). Clinical manifest cardiac disease is rare as only six percent of 25 patients with PM and DM have cardiac symptoms, while 50% are asymptomatic

mainly with disturbances of the electrogram (Gonzales-Lopez *et al* 1996). Symptomatic cardiac disease, when present, can contribute to death in one out of five patients affected (Hochberg *et al* 1986). Clinically manifest interstitial lung disease (ILD) is much more frequent than cardiac disease and was estimated to be present in 5 - 46% of PM/DM patients (Hirakata and Nagai 2000) and can manifest as a non-productive cough and dyspnea (Plotz *et al* 1989, Marie *et al* 2002). Esophageal, gastric, and intestinal problems are often complaints of patients with PM and DM, for example dysphagia, esophageal reflux, dyspepsia and constipation (Horowitz *et al* 1986). Thyroid abnormalities can occur in patients with PM or DM, possibly in association with ILD (Plotz *et al* 1989).

PM and DM can occur in association with other rheumatic autoimmune disorders, such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc) Sjögren´s syndrome, mixed connective tissue disease (MCTD) and rheumatoid arthritis (RA) (Oddis *et al* 1990, Mastaglia and Phillips 2002).

Diagnosis and classification of the inflammatory myopathy

Bohan and Peter developed and presented the first proposed diagnostic criteria defining PM and DM and also presented criteria distinguishing these conditions from each other (Bohan-1975 part 1 and 2). Until that time no diagnostic criteria had been available, leading to difficulties in interpreting the results of earlier studies.
Classification according to Bohan and Peter (Bohan and Peter 1975a, 1975b):

1. Symmetrical weakness of the limb-girdle muscles and anterior neck flexors, progressing over weeks to months, with or without dysphagia or respiratory muscle involvement.
2. Muscle biopsy evidence of necrosis of Type I and II fibers, phagocytosis, regeneration with basophilia, large vesicular sarcolemmal nuclei and prominent nucleoli, atrophy in perifascicular distribution, variation in fiber size and inflammatory exudate.
3. Elevation in serum of skeletal muscle enzymes, particularly creatine phosphokinase (CPK) and often aldolase, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and lactate dehydrogenase (LD).
4. Electromyographic triad of short, small polyphasic motor units, fibrillations, positive sharp waves and insertional irritability, and bizarre high-frequency repetitive discharges.
5. Dermatological features including a heliotrope rash with periorbital edema, erythematous dermatitis over metacarpophalangeal and proximal interphalangeal joints (Gottron´s papules) and involvement of knees, elbows, medial malleolis, face, neck and upper torso.

Definite DM requires three or four criteria (plus the rash) and definite PM requires four criteria (without the rash). Probable disease comprises two criteria (plus the rash) for DM and three criteria (without the rash) for PM. Possible disease requires one criterion (plus the rash) for DM and two criteria (without the rash) for PM.

An approach to divide these classifications into five groups was also suggested:

Group I:	Primary, idiopathic polymyositis
Group II:	Primary idiopathic dermatomyositis
Group III:	Dermatomyositis (or polymyositis) associated with neoplasia
Group IV:	Childhood dermatomyositis (or polymyositis) associated with vasculitis
Group V:	Polymyositis or dermatomyositis with associated collagen-vascular disease

Several attempts have since been made to further develop these criteria or to present new classification criteria for PM and DM. Dalakas added criteria describing IBM as an entity of its own as being therapy resistant (Dalakas 1991). Love *et al* presented a new approach of categorizing myositis patients based upon presence or non-presence of myositis-specific autoantibodies (Love *et al* 1991). A definition of PM and DM was also proposed based solely on characteristics of muscle biopsy findings (Arahata and Engel 1984). However, recent studies have mostly used the classification criteria described by Bohan and Peter.

Medical treatment

High-dose corticosteroids during the first months with or without complementary immunosuppressive agents is the generally recommended medical treatment for patients with PM and DM (Oddis *et al* 1990, Mastaglia and Phillips 2002). However, as no randomized placebo-controlled trials have been conducted concerning corticosteroid treatment, the most optimal initial dose is not known. Thus current treatment recommendations are mainly based upon clinical experience and results of open trials. High-dose prednisone, 40-60 mg/day, has had beneficial effects in retrospective studies (Mulder *et al* 1963, Bunch 1981, Henriksson and Sandstedt 1982), although it seems that at least three months of treatment is necessary to obtain maximal improvement (Mulder *et al* 1963). One recent study suggests that a lower initial dose of 7.5 to 30 mg/day leads to the same functional outcome as do higher doses, only with less adverse affects such as vertebral fractures (Nzeusseu *et al* 1999). However, as this study was also retrospective, including only 25 patients and without standardized protocols, these results should be interpreted with caution.

A few randomized controlled studies evaluating the effects of other agents in combination with corticosteroid treatment have been published. There was no difference between treatments with azathioprine in combination with prednisone than with prednisone treatment alone during the first three months of treatment (Bunch *et al* 1980). However, a three-year follow up could report a significantly favorable effect of the combination therapy (Bunch 1981). One study reported that both cyclosporine A and methotrexate added to corticosteroid treatment are associated with clinical and laboratory improvements (Vencovsky *et al* 2000). A combination of methotrexate and azathioprine could also be beneficial in refractory patients with PM and DM even though no positive effects had been obtained by receiving these agents one at the time (Villalba *et al* 1998). Eight patients with DM who received high-dose intravenous immunoglobulin infusion

in addition to corticosteroids improved significantly compared to seven patients receiving prednisone and other immunosuppressive agents (Dalakas *et al* 1993). Several open studies confirm the notion of benefits of different combination therapies rather than treatment with prednisone as the only agent (Metzger *et al* 1974, Joffe *et al* 1993, Maeda *et al* 1997, Cherin *et al* 2002, Danieli *et al* 2002).

Despite initial favorable effect of pharmaceutical treatment, most patients develop longstanding muscle impairment and activity limitation (Marie *et al* 2001). There is thus an urgent need to improve therapies for patients with PM and DM. The lack of valid and reliable outcome measures for patients with myositis also limits the development of treatment for these patients.

Side-effects of medication / osteoporosis

Another problem with the currently used treatment is the frequently developed side-effects. One of the most threatening side-effects of long-term oral corticosteroid treatment in these patients is osteoporosis, which can lead to severe disability in patients with myositis (Clarke *et al* 1995). Vertebral fracture was the most common fracture among patients treated with corticosteroids for different conditions and there is a strong relationship between corticosteroid dose and fracture risk (van Staa *et al* 2002). As PM and DM mainly affect women in their middle ages, who already have an increased risk of developing osteoporosis, much effort should be taken to minimize the use of corticosteroid treatment. For this purpose the additional immunosuppressive agents play an important role in the treatment of these patients. Moreover, pro-inflammatory cytokines are believed to play a role in the pathophysiology of bone loss due to chronic inflammation (Daci *et al* 2002). As patients with PM and DM have increased expression of the pro-inflammatory cytokines interleukin-1α (IL-1α) and to some extent also tumor necrosis factor-α (TNF-α), this treatment mechanism might also be important for this group of patients.

There is evidence that exercise can diminish the risk of osteoporotic fractures in elderly and postmenopausal women through several mechanisms such as improved strength (Horber *et al* 1987) and balance leading to decreased fall risk (Swezey 1996, Kronhed and Moller 1998, Carter *et al* 2002). There are also studies suggesting that exercise can improve bone density in postmenopausal women (Aisenbrey 1986, Chien *et al* 2000, Wallace and Cumming 2000, Kemmler *et al* 2002). Steroid myopathy, atrophy of muscle fibers, hypertension, thrombosis and type II diabetes are other severe side-effects of corticosteroids (Schacke *et al* 2002). Patients with PM and DM should be carefully monitored for these side-effects and prevention and treatment interventions for osteoporosis are important factors of the rehabilitation of these patients. There is evidence that many of these side-effects could possibly be reduced by regular physical exercise. An improved knowledge of safety and possible benefits of exercise in patients with PM and DM is therefore critical, not only to improve outcome of muscle performance, but also to decrease the risk of side-effects of corticosteroid treatment.

Prognosis

Prognosis for patients with PM and DM has improved dramatically since the introduction of corticosteroid treatment during the 1950s. Long-term survival data from five studies conducted over one or two decades report a five-year survival ratio of 65 – 95 % and a 10 -15-year survival ratio of 53 – 85 % (Medsger *et al* 1971, Hochberg *et al* 1986, Maugars *et al* 1996, Uthman *et al* 1996, Marie *et al* 2001, Sultan *et al* 2002). There seems to be no obvious difference in survival rates between studies conducted during the last 20-30 years. Causes of death have thus been reported to be primarily from cancer but also from pulmonary or cardiac involvement and infections (Maugars *et al* 1996, Marie et al. 2002, Sultan *et al* 2002). It was also suggested that patients with dysphagia at first admission had a lower survival rate than those without dysphagia and that dysphagia also correlated to severeness of proximal muscle impairment (Medsger *et al* 1971). Patients with PM with a more pronounced muscle weakness had a slightly poorer outcome than had those with moderately reduced muscle function (Medsger *et al* 1971). It was also suggested that non-white men and women with PM and DM had higher mortality rates, respectively, than whites (Hochberg *et al* 1986).
Remission rates vary between different studies. Marie *et al* reported remission of PM and DM in 40 % of 77 patients in France (Marie *et al* 2001). Those who achieved remission were younger and had a tendency toward a shorter period of time between onset of symptoms and diagnosis compared to patients who experienced relapse of disease. Another recent study reported full remission in only 15% (Sultan *et al* 2002). No study has clearly defined the criteria for disease remission, thus these variations between studies might be ascribed to different definitions. No clinical manifestations or CPK-levels could predict a remission of disease. At age over 50 years, myositis associated with cancer or lung involvement (e.g. aspiration pneumonia) were predictors for a poorer prognosis (Marie *et al* 2001). However, it has been reported that early treatment is associated with a better outcome (Fafalak *et al* 1994).

There is a need for further studies to improve our understanding of the reasons for increased mortality and morbidity in these patients compared to the normal population. Even though the prognosis of patients with PM and DM has improved since the introduction of corticosteroid treatment many patients develop sustained disability and also experience severe side-effects due to the medications. It is therefore of outmost interest to conduct further investigations to optimize pharmaceutical interventions and also to explore the safety and benefits of other less conventional treatments such as exercise. Availability of a core set of valid and reliable outcome measures for these patients would make it more feasible to perform these investigations.

Epidemiology

There are a limited number of clinical trials conducted in patients with myositis. As PM and DM are rare diseases the number of patients included in these studies is often also limited. According to available studies, the incidence rate of PM and DM varies between 1 to 9 cases per million per year. An incidence of 7.6 cases per million per year was reported in the Swedish county of Gävleborg (Weitoft

1997), while a similar rate of 7.4 cases / million / year was observed in an Australian population (Patrick *et al* 1999). Studies have revealed a prevalence variation from 2.4 to 10.7 per 100 000, with the highest prevalence being reached in a county-based study from Sweden (Cronin and Plotz 1990, Ahlstrom *et al* 1993). The overall female to male ratio was 2.2:1 among residents in Pittsburgh, USA, while the ratio increased to 5:1 during childbearing years (15-44) (Oddis *et al* 1990). A few studies report increased incidence during the last decades, especially among African-American females (Medsger *et al* 1970, Oddis *et al* 1990). This trend may reflect improved diagnostic techniques and increased awareness of these conditions (Mastaglia and Phillips 2002). Polymyositis and dermatomyositis occur in all parts of the world. Some interesting data report increased relative prevalence of DM with decreasing latitude gradient from Reykjavik, latitude 64, to Athens, latitude 38 (Hengstman *et al* 2000). The rarity of these diseases necessitate international collaborations to conduct large enough clinical trials evaluating a sufficient number of patients.

Disease cause

The mechanisms causing PM and DM are largely unknown, as is the case with many other rheumatic conditions. Genetic and environmental factors are believed to be involved as in many other autoimmune diseases (Shamim and Miller 2000). Certain major histocompatability complex (MHC) class II, or human leukocyte antigen (HLA) class II molecules have been associated with PM and DM (Mastaglia and Phillips 2002). As for other environmental factors, little is known. Infectious agents have been suggested to be factors contributing to myositis onset (Nagaraja *et al* 1992, Ytterberg 1994b). A higher frequency of regular heavy physical exertion and emotional stress prior to PM/DM onset compared to controls of healthy siblings was also reported in one study (Lyon *et al* 1989).

Possible mechanisms causing impairment in myositis

There is a need for increased knowledge of disease mechanisms to improve treatment and outcome for myositis patients. PM and DM are characterized by inflammatory infiltrates in muscle biopsies (Bohan and Peter 1975, Arahata and Engel 1984). Other typical muscle biopsy findings are myofiber necrosis and regeneration. The role of inflammatory infiltrates in causing the clinical symptoms is not clear. Despite the differences in biopsy findings between PM and DM regarding inflammatory infiltrates, due to their similar clinical picture these disorders are managed in the same way. Moreover, most patients develop sustained impairment even though the inflammatory infiltrates have diminished after successful pharmaceutical treatment. The reason for this is not fully understood. It has been suggested that muscle weakness develops due to the inflammatory infiltrates in the muscle tissue, although the relationship between the muscle biopsy findings and clinical symptoms are not quite clear. There is a disassociation between biopsy pathology and muscle impairment. Other potential mechanisms could be muscle atrophy due to the disease itself, long-term corticosteroid treatment, fat replacement, or inactivity (Lundberg 2001). However,

most patients with PM and DM do not tend to develop severe muscle atrophy (Nyberg *et al* 2000).

Recently, expression of the pro-inflammatory cytokine interleukin 1α (IL-1α) in the capillaries and MHC class I antigen on muscle fibers was suggested to be related to muscle impairment. Up-regulation of these molecules along with muscle impairment was reported not only in patients with active recent onset PM and DM but also in patients with a chronic disease and in patients in an early phase of disease before diagnosis and corticosteroid treatment (Nyberg *et al* 2000, Englund *et al* 2002). Abnormalities such as thickening of capillaries (Gonzàlez-Angulo 1968) and also reduced capillary blood supply (Cea *et al* 2002), possibly leading to hypoxia in muscle tissue, are other potential mechanisms for muscle weakness. Patients with DM have been reported to have significantly lower levels of adenotriphosphate (ATP) and phosphocreatine (PCr) in affected muscles than healthy controls, and an inefficient utilization and regeneration of ATP and PCr during exercise and recovery (Park *et al* 1995). It has also been suggested that metabolic abnormalities such as low levels of magnesium occur in patients with DM and are related to muscle weakness and fatigue (Niermann *et al* 2002).

Several of these observations suggest that not only the muscle inflammation, but also other factors, could contribute to muscle impairment. Patients with PM and DM seem to have disturbed metabolic and capillary function, suggesting that treatments other than immunosuppression could be of use. One such therapy could be physical exercise.

Impairment

Muscle impairment is the major clinical feature in patients with PM and DM (Henriksson and Sandstedt 1982, Tymms and Webb 1985, Maugars *et al* 1996). Descriptions of distribution of muscular involvement in the literature are somewhat contradictory. One study describes the distribution of muscle impairment to be diffuse, meaning that both proximal and distal muscle groups in both the upper and lower limbs are affected (Henriksson and Lindvall 1990). This was also demonstrated in another study reporting involvement of both proximal and distal muscle groups in 48 patients with PM/DM (Josefson *et al* 1996). It has also been suggested that distal muscle groups might be involved in a later stage of the disease, leading to difficulties in performing fine-motor movements (Dalakas 1991). The majority of studies report predominantly muscle impairment in proximal muscle groups e.g. muscle of the shoulder- and the hip girdle, neck flexors and thighs (Plotz *et al* 1989, Dalakas 1994, Maugars *et al* 1996, Uthman *et al* 1996, Sultan *et al* 2002). Both muscle strength and muscle endurance are affected (Lundberg and Chung 2000). Some patients also have muscle atrophy and loss of muscle mass. The problem of myalgia in PM and DM has not been extensively addressed in the literature. However, in a cohort of 107 patients with PM and DM, 58% experienced muscle pain at rest and 42% had exercise induced pain, indicating that myalgia is a serious problem for these patients. Muscle tenderness has been reported to be a sign of a disease flare (Henriksson and Lindvall 1990). One published study has explored the status of cardiovascular

fitness in patients with PM and DM and reported that these patients have lower maximal oxygen uptake compared to healthy controls (Wiesinger *et al* 2000).

Activity limitation

Patients with PM and DM have difficulties in performing activities of daily life such as rising from a chair, climbing stairs or washing hair and other activities requiring working with the arms above the horizontal line (Dalakas 1991). One study followed 257 patients over time and reported gradually increased activity limitation in patients with PM and DM regardless of age and disease course. However, older patients and patients with avascular necrosis and osteoporosis hade a five-fold increase in activity limitation assessed by the Stanford Health Assessment Questionnaire (HAQ) compared to younger patients without avascular necrosis (Clark *et al* 1995). An association between increased corticosteroid doses and increased HAQ score, and also the reverse were reported. Clarke *et al* were first to describe activity limitation in patients with PM and DM, although concentrating on reporting how side-effects of medical treatment affect activity limitation in these patients (Clark *et al* 1995).

As muscle weakness is the main feature of PM and DM, it is likely that impaired muscles are a major factor causing activity limitation. Despite this, very little is known about the impact of myalgia, fatigue and cardiovascular fitness. Information as to what extent sustained activity limitation experienced by these patients causes further impairment is also very limited. Difficulties to distinguish between limitations caused by muscle weakness *per se* and limitations caused by disease damage or medical side-effects limit our knowledge in this field. No study is available to describe to what extent these patients have activity limitation compared to patients with other rheumatic disorders or normal populations or whether various interventions affect the degree of activity limitation.

Participation restriction and health perception

A few studies have examined the consequences of PM and DM regarding health perception. One study described the health in 28 patients with PM and DM to be fairly good to very good, except for ratings of physical activity which was rated poor to very poor (Drouet *et al* 1996). However, as this study was available only as an abstract the outcome measure for health perception was not described in detail. Another study compared ratings of the Nottingham Health Profile (NHP) between patients with PM/DM and patients with rheumatoid arthritis (RA), osteoporosis (OP) and osteoarhtritis (OA) and also to healthy individuals (Chung *et al* 2001). All patient groups scored significantly poorer health in all domains; Energy, Pain, Emotion, Sleep, Social and Physical, than did healthy individuals. Patients with PM and DM scored significantly poorer than the other patient groups regarding domains Energy, Social and Physical, but lower than RA and OA patients in the domain Pain. There was no difference in scores of patients diagnosed with PM compared to those with DM (Chung *et al* 2001). Another study reported significantly poorer health for patients with PM or DM in all domains of the SF-36 than in the normal population (Sultan *et al* 2002). These

data indicate that PM and DM are conditions with impact on many aspects of life. Whether pharmacological treatment and exercise have effects on health perception and participation restriction have not yet been investigated in these patients. Little is also known how PM and DM affect the ability to keep up a gainful employment.

Physical activity

Physical activity can be defined as any kind of bodily movement (Macera *et al* 2003). Being physically active in one's spare time has become more and more important to staying healthy. A physically active life-style has predominated throughout most of the 45 000 year-long human history. As hunters, nomads, and later on as farmers, humans were physically active during a larger part of the day (Eaton and Konner 1985). With industrialization and advances in science and technology, our life-style has developed to be more and more sedentary (Booth *et al* 2000). Nowadays the majority of the populations in the western world are not physically active enough, which together with other risk factors contributes to major health-related problems such as cardiovascular disease. To reverse this trend much interest has been focused on implying physical activity in the general population during the last 10 years (Minor 2003) and several studies support that a higher level of physical activity can reduce disability and mortality due to for example cardiovascular disease, hypertension and diabetes mellitus (Macera *et al* 2003). Recommendations of physical activity for professionals and the general public have been stated (Sniezek *et al* 2003):

- General public should accumulate 30 minutes of moderate-intensity activity on most days of the week through daily activities.
- Sedentary adults should increase activity gradually to recommended levels
- Any physical activity is better than none

A chronic disease such as arthritis, resulting in a different kind of physical impairment than myositis, has been reported to be a barrier to physical activity (Seefeldt *et al* 2002) and much effort is now put into improving physical activity levels in persons with arthritis (CDC 2001). These goals might also be applicable to patients with PM and DM.

Muscular training in healthy individuals

In comparison to physical activity, exercise can be defined as activities with the goal to improve muscular strength, endurance or cardiovascular fitness (Macera *et al* 2003). The mechanisms behind improved muscle function after exercise are manyfold. Neuromuscular adaptation leads to early reaction of improvement (Leong *et al* 1999) while increased muscle fiber cross-sectional area, CSA, (McCall *et al* 1996), changes in muscle architecture (Kraemer *et al* 2002) and metabolic changes (Rooney *et al* 1994, Smith and Rutherford 1995, Shinohara *et al* 1998) are important mechanisms later on in the process. Different kinds of exercise confer different kinds of results. Several definitions of protocols for different type of exercises have been suggested; (i) low repetition/high intensity

exercises varying between 3-6 and between 6-8 repetitions, (ii) medium repetition/medium intensity varying between 9-11, 15-20, and 30-40 repetitions, and (iii) high repetition/low intensity varying between 20-28, 30-40, and 100-150 repetitions (Anderson and Kearney 1982, Stone and Coulter 1994, Campos *et al* 2002). It has been stated that healthy sedentary individuals can benefit from all kinds of exercise regimens and loads (Hakkinen 1985). More trained individuals need to conduct more specialized and more intensive exercises in order to improve (Sale *et al* 1990, Weiss *et al* 1999). Untrained individuals can benefit from both single-set and multiple-set exercise (Feigenbaum and Pollock 1999). Exercise conducted two to three days a week is necessary to increase muscular strength (Braith *et al* 1989).

Energy supply to skeletal muscles during exercise

A certain comprehension of the mechanisms of energy supply in healthy skeletal muscles is necessary to understand the possible mechanisms of muscle impairment in patients with myositis. Skeletal muscle is dependent on energy supply to perform any kind of work or exercise. Exercise of short duration and high intensity such as a 100-meter sprint requires immediate energy supply provided almost exclusively from the intra-muscular high-energy phosphates synthesized by the ATPase (McArdle *et al* 2001). Sufficient storage of ATP + PCr exists to walk briskly for one minute, to run at a marathon pace for 20-30 seconds or a 5-8 second sprint. To be able to continue exercising and recover from such a short-term prior all-out effort, additional energy sources such as carbohydrate and later on fat and protein are required for resynthesis of ATP. Aerobic metabolism rises during the first minutes of exercise and then becomes the major provider of energy transfer when work exceeds several minutes (McArdle *et al* 2001).

The energy to phosphorylate ATP during high-intensity exercise mainly derives from glycogen stored in the muscle through anaerobic glycolysis, resulting in lactate formation. During exercise performed with energy generated from oxygen uptake any lactate formed in the muscle will rapidly be oxidized by muscle fibers with high oxidative capacity. When lactate oxidation equals its production, lactate levels remain stable. One explanation for a blood lactate accumulation during this kind of exercise could be that there is a state of hypoxia in the muscle tissue (McArdle *et al* 2001).

Patients with myositis seem to have both disturbed circulation and metabolic environment in muscle tissue. As exercise can alternate these variables in healthy individuals, this might also be the case in patients with PM and DM.

Exercise in patients with other rheumatic diseases

Patients with RA have reduced muscle strength (Danneskiold and Grimby 1986) and aerobic capacity (Ekblom *et al* 1974, Ekdahl and Broman 1992). Some 30 years ago patients with rheumatoid arthritis (RA) were discouraged from active exercise and physical activity due to a fear of exacerbation of disease activity. Range of motion and isometric exercise was often applied (Semble *et al* 1990,

Sutej and Hadler 1991). Today, there is scientific evidence supporting different kinds of exercise regimens as both safe and beneficial (van den Ende *et al* 1998, Stenström and Minor 2003, van den Ende *et al* 2003). Most of the exercise studies conducted in patients with RA concern patients in a chronic and stable phase of the disease. Dynamic training proved to be more effective than isometric training (Ekdahl *et al* 1990, van den Ende *et al* 1996). Resistive exercises with different load (Rall *et al* 1996, van den Ende *et al* 1996, Hakkinen *et al* 1997, Komatireddy *et al* 1997), resistive home exercise (Stenstrom 1994) and intensive aquatic training (Stenstrom *et al* 1991) have been evaluated in these patients. A few studies have also evaluated intensive resistive exercise in patients with active RA with beneficial effects on muscle strength and physical function and without detrimental effects on disease activity (van den Ende et al. 2000, Hakkinen *et al* 2001). Patients with osteoarthritis (OA) and ankylosing spondylitis (AS) also suffer from reduced muscle strength and functional limitations (Fisher and Pendergast 1997, Ytterberg *et al* 1994a, Hopkins *et al* 1983). There is scientific evidence supporting benefits of exercise in patients with OA (Minor 1999), although the evidence for efficacy of exercise in patients with AS is more uncertain. One review stated that there is a tendency toward a short-term positive effect of exercise in patients with AS (Dagfinrud and Hagen 2001). There are several other studies reporting both short-term and long-term effects on patient global assessment of disease activity, function and pain (van Tubergen and Hidding 2002)

Very little is known about safety and benefits of exercise in other systemic rheumatic diseases such as systemic lupus erythomatosus (SLE) and systemic sclerosis (SSc). However, in both these patient groups, pulmonary dysfunction or low aerobic capacity could be limiting factors for exercise (Sakauchi *et al* 1995, Forte et al. 1999, Sudduth *et al* 1993).

Exercise in patients with muscular dystrophies

Muscular dystrophies include another heterogeneous group of patients suffering from muscle impairment. Duchenne muscular dystrophy (DMD), the milder form of Becker's muscular dystrophy (BMD), Limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, myotonic dystrophy and distal myopathy are conditions included in this group. The safety and efficacy of active exercise in these patients have been debated. A recent review reports some evidence for positive effects of low intensive or aerobic exercise in an early stage of DMD/BMD, while more intensive exercise should be avoided due to risk of muscle injury or death of myofibers (Ansved 2003). Patients with myotonic dystrophies may have beneficial effect on muscle strength after high-resistance exercise without proof of muscle damage. Little is known about effects of exercise in the other muscular dystrophies.

Physical therapy treatment and exercise in PM and DM

As mentioned before, the role of rehabilitation and physical therapy in patients with PM and DM has been unclear for many years. These patients have also been

discouraged from physical activity and exercise due to fear of exacerbation of disease activity as a result. Textbooks still recommend bed rest during active severe PM and DM with range of motion exercise as the only recommended intervention to prevent joint contractures. Active exercise might be cautiously introduced beginning with isometric exercise and then slowly continued with dynamic exercises when the patient is in a less active stage of disease. (Engel and Franzini-Armstrong 1994, Klippel and Dieppe 1994, Maddison *et al* 1998).

The hypothesis that exercise would increase muscle inflammation was grounded on data reporting increased CPK levels and muscle inflammation as a result of strenuous exercise in healthy individuals (Warhol *et al* 1984, Brown *et al* 1994, Tidball 1995, Jones *et al* 1986). Before the beginning of the 1990s no studies evaluating any physical therapy treatment in patients with PM and DM had been published. As these patients have persisting muscle impairment, exercise came to be the main non-medical therapy of interest to investigate.

As late as 1993 the first two case studies evaluating exercise in patients with PM/DM were published. One of them evaluated isometric exercise in the quadriceps muscles in one patient with chronic, stable PM without increased CPK levels and with positive results on muscle strength (Hicks *et al* 1993). The other case study included five patients with active, recent onset PM or DM. They also performed an exercise program without increased CPK levels as a result (Escalante *et al* 1993). As these studies altogether only included six patients the knowledge of the impact of exercise both in the chronic and the acute, active phase of the disease was very limited. Another limitation of these studies is that they only analyzed CPK levels to assess the safety of exercise. Bearing in mind the lack of correlation between CPK levels and degree of muscle inflammation and impairment (Kroll *et al* 1986), further studies investigating the safety and benefits of different exercise programs in all phases of the disease were needed.

Outcome measures

There were few valid and reliable outcome measures for patients with PM and DM. Outcome measures used in patients with PM and DM in daily practice and research when I started working on my thesis are listed below.

Measurement of serum levels of CPK has been the major outcome measure for disease activity in PM and DM. However, CPK levels do not always correlate well with either degree of inflammatory infiltrates or muscle impairment or activity limitation (Tymms and Webb 1985, Kroll *et al* 1986, Nzeusseu *et al* 1999, Vencovsky *et al* 2000). However, in some patients CPK levels can be useful markers to assess disease activity (0ddis and Medsger 1988). During the last decade Magnetic Resonance Imaging (MRI) has proven to be a valid assessment tool to localize inflammation and also to evaluate effects of treatment in PM and DM (Park *et al* 1995). The use of MRI is costly and not available everywhere and can thus not be used as a general outcome measure in clinical practice. Muscle biopsies of affected muscle groups, such as mainly the vastus lateralis, the tibialis anterior or deltoideus, are useful for diagnosing PM and DM (Haddad *et al* 1994). The ‘semi-open’ percutaneous conchotome technique allows repeated biopsies to

some extent as a method to verify a flare of disease or to evaluate the effects and safety of treatment (Dorph *et al* 2001). As the inflammatory infiltrates focally localize in the muscle tissue there is always a risk of false negative results. Furthermore, the invasiveness of the method and the problem with potential sampling error limits the use of muscle biopsies as an outcome measure in clinical practice.

Manual Muscle tests (MMT) have been used previously in a majority of studies as impairment measures (Rider 2002). The MMT can be performed in several different versions, the most often used is the Medical Research Counceil (MRC) scale scored either of 0 - 5 or 0 – 10 (Kendall *et al* 1993). However, the reliability of the MMT in patients with limited muscular impairment has been questioned (Frese *et al* 1987). A Cybex- or a Kin-Com devise has been used in a few studies to measure isometric muscular performance in PM and DM (Escalante *et al* 1993, Hicks *et al* 1993, Wiesinger *et al* 1998a, 1998b). These techniques are valid and reliable for strength measurements in healthy individuals (Snow and Blacklin 1992), but have not yet been validated and investigated for reliability for patients with impaired muscle function as in PM and DM. These techniques are also costly and require trained personnel. The Functional Index in myositis (FI), the first impairment outcome measure developed for patients with PM and DM was published in 1996 (Josefson *et al* 1996). The FI was determined to have excellent intra- and inter-rater reliability but validity assessment was limited. As the FI had not been used in any outcome studies its sensitivity to change was unknown.

To assess activity limitation, the Disability Index of the Stanford Health Assessment Questionnaire (HAQ) has been used in one study (Clarke et al. 1995). The HAQ was developed and evaluated for patients with RA, but has not yet been evaluated for myositis patients. No disease-specific instrument was available to measure activity limitation in myositis patients. Two generic instruments to measure activity limitation and health perception have been used for PM/DM patients, the SF-36 (Ware and Sherbourne 1992) and the Nottingham Health Profile (NHP) (Hunt et al. 1981), the latter being investigated for sensitivity to change in patients with PM and DM (Chung *et al* 2001). Both these questionnaires have been translated to Swedish and are validated for the Swedish population (Sullivan *et al* 1995, Wiklund and Dimenas 1990). Clearly, patients with PM and DM have participation restriction, although it is not known what effect different interventions could obtain.

In respect to onset age, degree of muscle inflammation and muscle weakness, patients with PM and DM form a very heterogeneous group. As a result there is a great variation of impairment, activity limitation and participation restriction/ health perception experienced by each and every patient.

Rationale for this thesis

This summary described evidence indicating disturbed circulation, expression of pro-inflammatory cytokines in capillaries and MHC class I antigen expression on muscle fibers, disturbed metabolic function possibly leading to chronic muscle impairment but probably also to activity limitation and participation restriction in

patients with PM and DM. Current available pharmaceutical treatment often leads to diminished degree of inflammatory infiltrates in muscle tissue, but in most cases does not satisfactorally affect disability. There is a lack of scientific evidence for optimal initial and long-term treatment doses of immunosuppressives and side-effects are common. However, as there is increasingly stronger evidence for safety and benefits of exercise in other rheumatic diseases and also data suggesting that resistive exercise can reduce the side-effects of corticosteroid treatment, positive effects of exercise and physical activity might be expected in patients with myositis but have yet to be investigated. The limited availability of valid and reliable outcome measures for these patients calls for a broader spectrum of disease-specific outcome measures to improve our possibilities to better evaluate different kinds of interventions.

AIM OF THESIS

The aim of this thesis was twofold:
The first aim was to investigate the safety and benefits of resistive exercise in patients with PM and DM with chronic disease as well as with active recent onset disease. A second aim was to develop disease-specific outcome measures to assess impairment and activity limitation in these patients.

Specific aims

I To evaluate the safety of a resistive 12-week home exercise program employed in patients with chronic, inactive PM or DM regarding disease activity, impairment (muscle function and pain), activity limitation (walking distance) and perceived health.

II To investigate whether the 12-week home exercise program could be safely employed in patients with recent onset, active PM or DM regarding disease activity, impairment (muscle function) and perceived health.

III To develop a disease-specific, self-administered questionnaire, the Myositis Activities Profile (MAP), for the assessment of activity limitation / participation restriction in patients with PM and DM, and further to investigate its content validity, construct validity and test-retest reliability.

IV To revise the content of the Functional Index in myositis (FI) and to evaluate content validity, construct validity and inter- and intra-rater reliability of a revised version, the Functional Index-2.

V To evaluate the safety and benefits of a seven week, intensive, resistive exercise program in patients with stable, chronic PM or DM, regarding disease activity, impairment, activity limitation and participation restriction.

METHODS

Patients

Most patients included in this thesis were recruited from the Department of Rheumatology at Karolinska Hospital, Stockholm. As this is a nonselective referral center for the Stockholm area and nearby counties, patients with various degree of disease activity and impairment are admitted. Patients were all diagnosed with definite, probable or possible PM or DM according to the criteria of Bohan and Peter (Bohan and Peter 1975a, 1975b). A few of the patients in cohort two in paper III were also recruited from the Department of Rheumatology at Huddinge University Hospital, Stockholm and most patients in cohorts four and five (IV) were recruited from Sahlgrenska University Hospital in Göteborg. Diagnosis of these patients were verified as PM or DM from medical charts. Some patients participated in several cohorts and studies.

A total of 89 patients participated in this thesis work. A majority of these patients were ambulant without assistance and managed activities of daily living without community assistance. A few patients used aid devices for walking and one patient was in permanent need of a wheelchair. Demographic data and the accumulative number of patients are presented in Table 1.

Outcome measures

Physicians' global assessment of disease activity assessed by using the Visual Analogue Scale (VAS) 0-100, was used to identify patients for inclusion (I-V) and also used as an outcome measure (V).

Repeated muscle biopsies from vastus lateralis were included to assess disease activity (I, II, V). Three to four specimens of 10 – 80 mg each were taken from different angles in the muscle tissue. The same neuropathologist evaluated all muscle biopsies performing a routine histopathology evaluation (I, II, V). A further evaluation of inflammation was performed using immunohistochemistry to assess degree of inflammation as the number of $CD3^{+}$ T-cells per tissue section area (I, II).

To assess disease activity MRI scans of the thighs were carried out (I, II) (Park et al. 1995, Fraser et al. 1991).

Analyses of CPK levels and C-reactive protein (CRP) were carried out from blood samples (I-V).

In Study IV maximal voluntary right shoulder flexor and knee extensor isokinetic muscle strength and endurance were evaluated using an isokinetic dynamometer. Maximal voluntary isokinetic muscle strength and endurance were measured in the range of motion (ROM) from 20° to 120° of shoulder flexion and from 90° to 30° of knee extension, respectively (Figure 2).

Table 1
Demographic data of all patient cohorts included in this thesis.

Paper	Patients included n	Patients accu-mulative n	Female/ Male n	Age years md (range)	Diagnosis PM/DM	Diagnosis duration, years md (range)
I	10	(10)	8/2	53 (27-60)	5/5	4.0 (2.0-10.0)
II	11	(21)	8/3	47 (23-80)	7/4	0.2 (0.1-0.2)
III						
Total	42	(49)	31/11	57 (23-81)	27/15	4.0 (0.2-20.0)
C 1	10		8/2	52 (31-66)	6/4	3.0 (1.0-7.0)
C 2	24		17/7	60 (26-79)	17/7	4.0 (2.0-10.0)
C 3	31		23/8	56 (24-79)	18/12	5.0 (0.2-20.0)
C 4	17		11/6	58 (26-70)	8/9	5.0 (1.0-20.0)
IV						
Total	78	(89)	52/26	-	-	-
C 1	53		38/15	na	32/21	3.0 (0.0-21.0)
C 2	4		2/2	54 (53-56)	3/1	4.0 (2.4-5.0)
C 3	25		16/9	55 (28-73)	16/9	5.0 (1.5-29.0)
C 4	13		8/5	53 (27-69)	7/6	3.3 (0.2-18.0)
C 5	13		5/8	54 (27-76)	7/3	4.2 (2.0-18.1)
V	8	(89)	4/4	53 (44-61)	2/6	5.0 (3.0-29.0)

PM = Polymyositis, DM = dermatomyositis, C = Cohort

Ten to 15 voluntary repetition maximum (VRM) (approximately 70% of 1 VRM) was used to assess muscle strength (V). Five muscle groups were evaluated; the deltoideus and the quadriceps muscles on right and left side separately using free weights, the latissimus dorsii / biceps, the gastrocnemius, and the abdominal muscles using training apparatus (Figure 3). Ten to 15 VRM equalizes the weights with which an individual can perform only 10-15 repetitions, but not more.

To measure distal muscle impairment the Grippit was used (I-V). The Grippit is an electronic force instrument measuring both maximum grip force and grip force over a 10-second period of time in Newton (Nordenskiold and Grimby 1992).

The Borg CR-10 scale was used for assessments of pain (V). It is a category scale with ratio properties where numbers are anchored to verbal expressions ranging from 0-10 (Borg 1982). The Borg CR-10 scale was also used to assess muscular exertion after each task of the FI-2 (IV, V). The Borg RPE scale ranging from 6 (very, very light) to 20 (very, very hard) was used for assessment of perceived central exertion during performance of a seven-minute walking test on a treadmill (I).

The Functional Index in myositis (FI) was used for functional assessments (I-IV) (Josefson *et al* 1996). Grip strength was measured with the Grippit instrument, which was considered more reliable than the sphygmomanometer originally included in the FI. A new six-grade scale was developed according to the normal values of the Grippit for men and women for right and left hand, respectively.

The Functional Index-2, FI-2, was developed in Study IV in this thesis and also used as an outcome measure (V). Every task is scored individually as the number of correctly performed repetitions. Maximal number of repetitions is 60 for all but the two latter tasks, for which maximal number of repetitions is 120. After completion of each task, the patient's subjective muscular exertion is rated on the Borg CR-10 scale.

To measure walking ability a 7-minute walking test at a self-selected walking speed on a treadmill (Cardionics Sweden 2115) was used (I). After completion, the walking distance in meters and the rating of perceived exertion assessed by the Borg RPE scale 6-20 were registered.

The disability index Stanford Health Assessment Questionnaire (HAQ) (Fries *et al* 1980, Ekdahl *et al* 1988) and the Arthritis Impact Measurement Scale 2 (AIMS2) (Meenan *et al* 1992, Archenholtz and Bjelle 1997) were used as activity limitation contructs in Study III. The HAQ was also used as an outcome measure in Study V.

The Myositis Activities Profile (MAP) was developed as a disease-specific tool to assess activity limitation in Study III in this thesis and was also used as an activity limitation construct (IV) and as an outcome measure (V).

The SF-36, a generic instrument to measure health perception was used as outcome measure (I, II) (Ware and Sherbourne 1992, Sullivan et al. 1995).

Subjective global disease impact (SGDI) was used as a participation restriction construct in Study III (Josefson *et al* 1996). The VAS was also used to measure disease impact on well-being as a participation construct (IV) as well as an outcome measure to assess patients' global assessment of overall impact of disease on well-being.

Table 2
Outcome measures used in the Studies I-V this thesis.

Outcome measures	I	II	III	IV	V
VAS, physicians' global assessment	X	X	X	X	X
Muscle biopsy	X	X			X
MRI	X	X			
Laboratory assessments	X	X	X	X	X
Isokinetic measures				X	
10-15 VRM					X
Grippit	X	X	X	X	X
Borg CR-10, pain					X
Borg CR-10, exertion				X	X
Borg RPE	X				
FI	X	X	X	X	
FI-2				X	X
Walking distance	X				
HAQ			X		X
AIMS2			X		
MAP			X	X	X
SF-36	X	X			
SGDI	X	X	X		
VAS, disease impact on well-being				X	
VAS, patients' overall impact on well-being					X

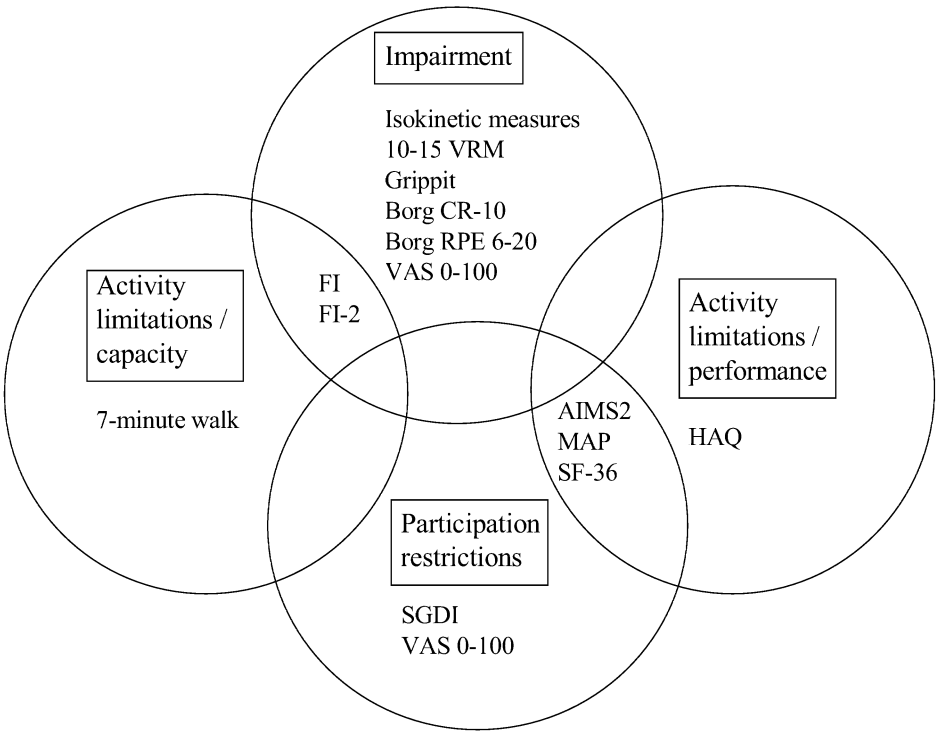

Figure 1
Outcome measures used in this thesis listed according to the ICF.
VRM = voluntary repetition maximum, VAS = Visual analogue scale,
HAQ = Stanford Health Assessment Questionnaire, AIMS2 = Arthritis Impact Measurement Scale 2, MAP = Myositis Activities Profile, SF-36 = The MOS 36-item Short-Form Health Survey, SGDI = subjective global disease impact.

Figure 2A

Figure 2B

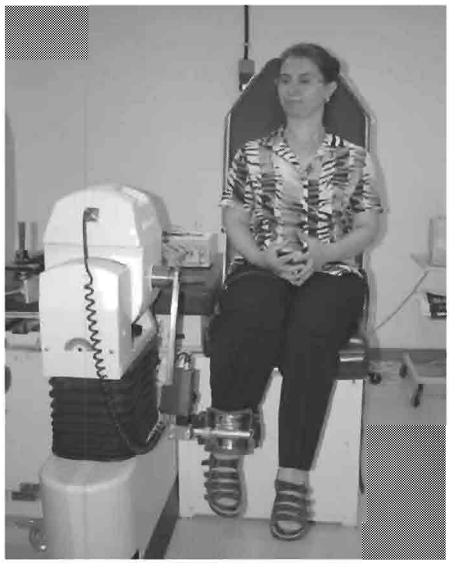

Figure 2C

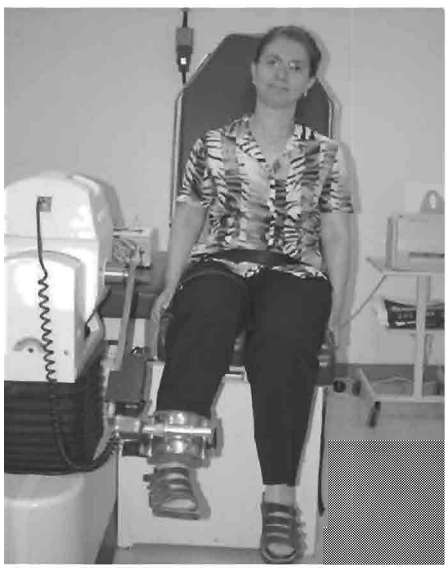

Figure 2D

Figure 2
Isokinetic measurements. Start angle of shoulder flexion 20° (2A), stop angle of 120° (2B). Start angle of knee extension 90° (2C), stop angle of and 30° (2D).

Exercise programs

When developing the home exercise program used in the first exercise studies (I, II), no previous well-described exercise regimens developed for patients with PM or DM was available. The program was designed to target affected muscle groups and also to be adjustable to different levels of muscle impairment. The 15-minute home exercise program contained resistive exercises against gravity or added weights. The program contained step-up exercises for warm-up and exercises for shoulder abduction and shoulder flexion using a pulley apparatus. Squeezing of the soft handles of the pulley apparatus was conducted for grip strength exercises. Resistive muscle exercises were included for shoulder, quadriceps, pelvic/hip, abdominal and neck flexor muscles. The program ended with stretching exercises for trapezius muscles, the quadratus lumborum muscles, teres major and minor, hamstrings, quadriceps and the gastrocnemius muscles (Appendix 1).

The home exercise program was divided into an easy version for patients with an FI score of < 38, and a moderate one for patients with a higher FI score. The easy program did not include any resistive exercises for shoulder muscles and the straight leg rising in a supine position was modified to hip flexion in a sitting position. The moderate program could be used without any additional weights or with weight cuffs of 0.25 to 2 kg depending on level of impairment according to the FI. The patients exercised for approximately 30 minutes performing the home exercise program and also a 15-minute self-paced walk, five days a week for 12 weeks. They were instructed to fill out an exercise diary and they had telephone contact with a physical therapist once a week during this period.

The more intensive exercise program (V) included resistive exercises with a well-defined load. The one-hour program started with a 10-minute warm-up either on a treadmill or an ergometer cycle at approximately 50% of the individual estimated maximal heart rate. Then exercises of shoulder flexor, the quadriceps, the latissimus dorsi / biceps, the gastrocnemius and the abdominal muscles were performed with a load of 10 voluntary maximal repetition (VRM). The program ended with stretching of the trapezius muscles, the quadriceps muscles, the pectoralis muscles and the gastrocnemius muscles. The patients exercised three days a week for seven weeks at the physical therapy department at Karolinska Hospital (V) (Figure 3).

Assessment procedures (I, II, V)

In papers I and II all assessments (muscle biopsies, blood samples, the FI, the walking test (I) and the SF-36 were conducted before and after the 12-week exercise period.
In paper V the assessments of 10-15 VRM, FI-2, the MAP, the Grippit and the Borg scale were carried out by an independent observer on three occasions, four weeks prior to study start, at study start and after seven weeks of exercise. Muscle biopsies and blood samples were taken and assessments of patient's and physicians' global assessment of disease activity and the HAQ were carried out twice, before and after the exercise period.

Figure 3A

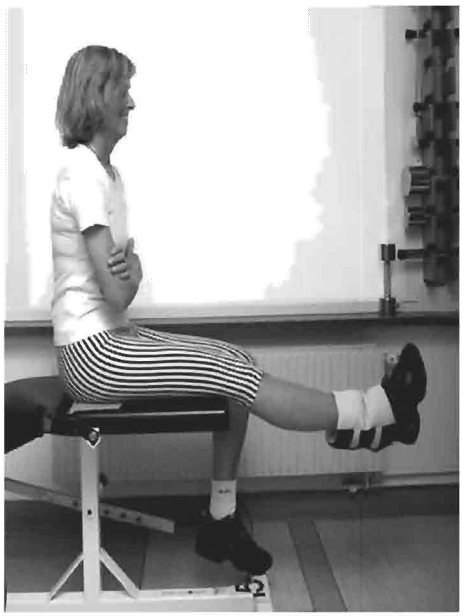

Figure 3B

Figure 3C

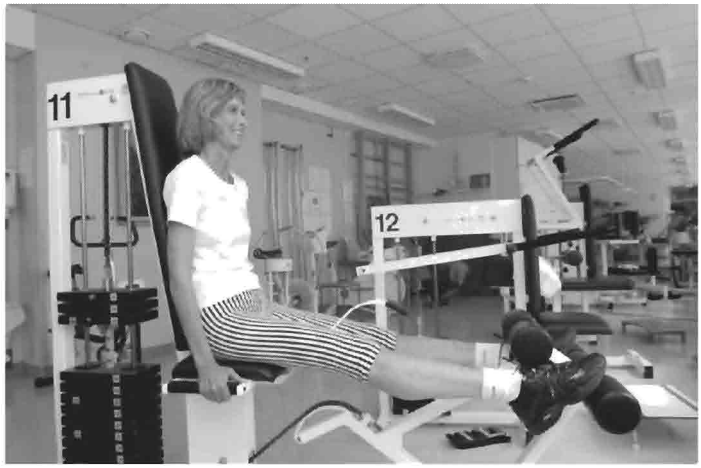

Figure 3D

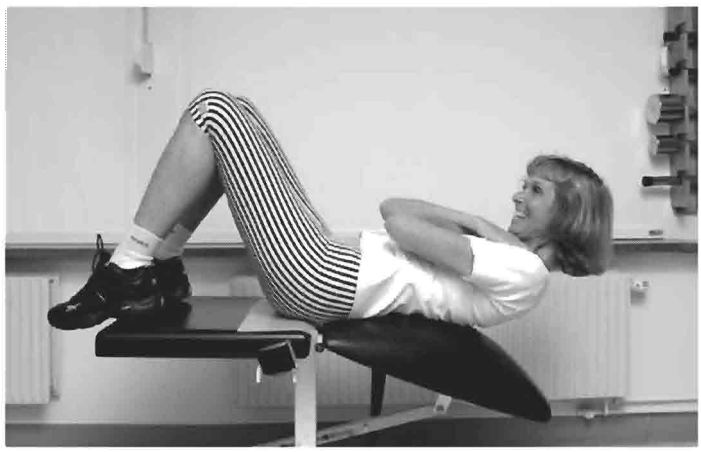

Figure 3E

Figure 3

Test positions of dynamic 10-15 VRM and exercise positions on a 10 VRM load in five muscle groups used in paper V. Deltoideus (3A), quadriceps (3B), latissimus dorsii/biceps (3C), gastrocnemius (3D) and abdominal muscles (3E).

Developing the Myositis Activities Profile (III)

While working with the two first exercise studies (I, II) my awareness of the need for disease-specific and improved outcome measures increased. Study III therefore aimed at developing a disease-specific activity limitation questionnaire. All together four cohorts of patients were included for different parts of this study (Table 1).

To ensure content validity of the MAP, patients in cohort one rated both difficulty to perform and importance of being able to perform each of 81 activities on a 10-grade scale from 1 (no difficulty / not at all important) to 10 (impossible to do / very important). These activities of the first draft of the MAP were taken from a total of 385 activities included in the ICIDH-2 beta-2 draft. The median value of difficulty to perform and the importance of being able to perform the selected activities were pooled together and those scored $\geq$ 6.0 were taken to the second draft of the MAP where the wording of the question for each activity was modified to include both difficulty and importance (How much trouble does … cause you daily life?). Each question was rated using a seven-grade scale from 1 (no trouble at all) to 7 (impossible to do) and the questions were listed in sub-scales congruent with the categories of the ICIDH-2 beta-2 draft.

Patients in cohort two filled out the second draft of the MAP and analyses of internal redundancy and internal consistency were made. To test our hypotheses of construct validity patients in cohort three performed the FI, filled out the third and final draft of the MAP, the AIMS2, the HAQ and rated their subjective global disease impact (SGDI). These assessments were performed on the same day. Blood samples for analyses of CPK-levels were also taken. For test-retest reliability patients in cohort four filled out the final draft of the MAP twice with a one-week interval.

Developing the Functional Index-2 (IV)

To further improve impairment assessments Study IV was also a methodological study. In this study all together five cohorts were included for the different parts of the study (Table 1).

Floor and ceiling effects of the original FI were scrutinized by analyzes of the 287 FI performed in previous studies or clinical practice from 1996 to 2001 by patients in cohort one. To secure content validity a group of health professionals and patients in cohort two were then invited to comment on relevance and importance of each task of the FI. A revised FI was developed and evaluated for construct validity as patients in cohort three performed the revised FI, isokinetic measurements of both muscular strength and endurance of shoulder flexor and knee extensor muscles, filled out the MAP, rated subjective disease impact on well-being on a VAS and had blood samples taken for analyses of CPK-levels. In this part of the study the patients visited the clinic three times. The first visit was for learning the isokinetic procedures. On the second visit the patients performed the revised FI, filled out the MAP and rated disease impact on well-being. On the third visit the isokinetic measurements of strength and endurance were performed.

Patients in cohorts four and five were then included for investigations of inter- and intra-rater reliability of the final draft, the Functional Index-2 (FI-2).

Statistical analyses

Because of small samples and the use of many methods producing ordinal data, non-parametric statistics have mainly been used in this thesis. Normally distributed data were analyzed with parametric statistics. Consequently descriptive data are presented as median values and ranges or means and standard deviations, respectively.

To evaluate the differences between status at baseline and after 12 weeks of exercise the Wilcoxon Sign Rank test was used in Studies I, II.

For analysis of correlation, the Spearman Correlation coefficient (r_s) was used in Studies III and IV.

Test-retest reliability was analyzed by the Weighted Kappa coefficients and the Sign test in Study III. Inter- and intra-rater reliability were analyzed by Intra Class Correlation coefficients (ICC) in Study IV.

The repeated measures ANOVA was used to compare ratio data on a group level on the three evaluation occasions and the Friedman ANOVA was used for ordinal data (V).

Results were also analyzed individually for each patient and improvement criteria according to Paulus were applied (Paulus et al. 1990).

Level of significance was set to $p < 0.05$ in Studies I, II and V.

Table 3
Statistical analyses used in the studies I-V in this thesis.

Analyses	I	II	III	IV	V
Wilcoxon Sign Rank test	X	X			
Spearman Correlation coefficient (rs)			X	X	
Weighted Kappa coefficients			X		
Signed test			X		
Intra Class Correlation (ICC)				X	
Repeated measures ANOVA					X
Friedman ANOVA					X

Ethics

All studies included in this thesis were approved by the local ethic committee at the Karolinska Hospital (I, II, III, and V) or the ethic committees of the Karolinska Institutet and Sahlgrenska Hospital in Göteborg (IV).

RESULTS

Safety of exercise in patients with PM and DM

The patients in the first study were selected for persisting muscle impairment and a stable chronic disease (I). At study start one patient had a perivascular infiltrate in the first biopsy and another patient had increased CPK-levels, although no patient had signs of inflammation as assessed by MRI scans. After 12 weeks no signs of increased muscle inflammation could be detected in any of these three measures (Figure 4).

In the second study (II) the patients were selected to have active, recent onset PM or DM. Ten of the 11 patients had inflammatory infiltrates in their initial muscle biopsies before starting with corticosteroid treatment. One biopsy was normal in a patient with DM. Three patients had MRI scans indicating an ongoing inflammation while five scans appeared normal. Serum levels of CPK were above normal in eight of the eleven patients prior to exercise. No signs of increased inflammation were detected by either muscle biopsy, MRI or CPK-levels after the exercise program (Figure 4, II: Table 5). On the contrary, all three variables were reduced during the 12-week exercise period.

The patients in the third exercise study (V) were selected for having a chronic, clinically stable disease. A few patients had small inflammatory infiltrates in the initial muscle biopsy before starting the exercise program (V). The repeated biopsy performed after the seven-week exercise period showed no additional inflammatory infiltrates (V: Table 3) or increased CPK levels as compared to before exercising (Figure 4). No patient rated increased pain as assessed by the Borg CR-10 scale after the exercise period. This more intensive exercise program was also well tolerated by the patients, as eight out of nine patients completed the exercise program. One of the patients experienced increased swelling and tenderness of the metacarpophalangeal joints in both hands but was able to complete the study.

The effect of exercise on disability

The patients in Study I improved as they reached significant impairment reductions assessed by the FI (Figure 5), activity limitation assessed by the 7-minute walking test, as well as significantly improved health perception assessed

by the SF-36 physical functioning domain (Table 4). The patients in Study II also improved with reduced impairment assessed by the FI (Figure 5) and improved health perception assessed by the SF-36 domains, Physical functioning, Bodily pain and Vitality (Table 4). This further supports the safety of these exercise regimens. In Study V no significant differences occurred in the group during the four weeks prior to baseline. After the seven weeks of exercise the group improved with significantly reduced impairment compared to baseline as assessed by 10-15 VRM in four muscle groups and also by the FI-2 shoulder flexion tasks bilaterally (V: Table 1). All patients were responders to the 20% criteria of clinically minimal change of the 10-15 VRM (V: Figure 1 A-G) and the FI-2. One patient responded in grip strength. No patient deteriorated in any muscle group of the 10-15 VRM and five patients deteriorated in scattered tasks of the FI-2 at the 7-week follow-up compared to baseline. No patient deteriorated in grip strength.

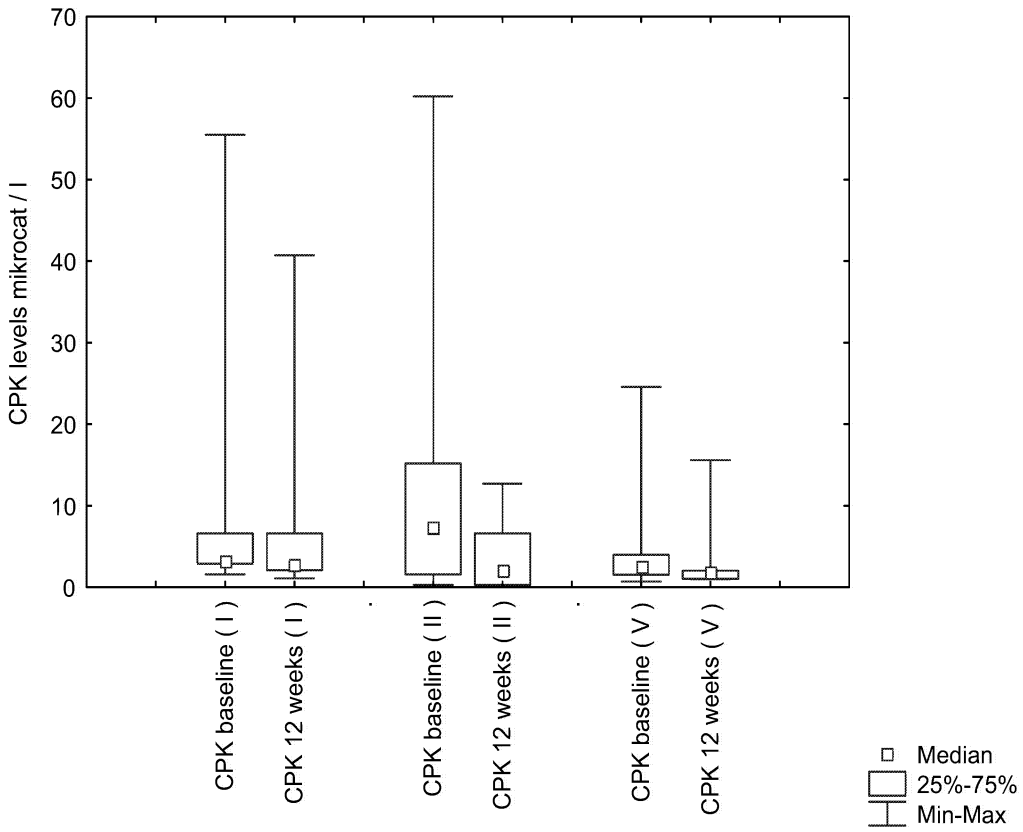

Figure 4
Median CPK-levels (μcat/l) before and after exercise in three exercise studies in 10 patients (I), 11 patients (II), and seven patients (V) respectively, normal values < 2.5 (μcat/l) for women and < 3 (μcat/l) for men.

The group as a whole did not improve significantly in activity limitation or participation restriction measures. Two patients were responders according to our criteria for reduced activity limitation assessed by the MAP. They responded in MAP sub-scales Movement and Activities of moving around and the single item Social activities. One patient deteriorated in the MAP single item Leisure activities. No changes were evident for the HAQ or overall disease impact on well-being in any patient (V).

Table 4
Perceived health assessed by SF-36 and walking distance in patients before and after 12 weeks of exercise (I, II).

	I		II	
	Baseline n = 10 md (range)	12 weeks n = 10 md (range)	Baseline n = 11 md (range)	12 weeks n = 11 md (range)
Physical Functioning	57.5 (20-80)	75 (20-83)*	45 (0-95)	65 (10-95)*
Role-Physical	12.5 (0-100)	75 (0-100)	0 (0-100)	0 (0-100)
Bodily pain	87.5 (24.5-100)	51 (31-100)	41 (0-84)	72 (22-100)*
General Health	52 (15-87)	55 (25-92)	60 (15-97)	60 (25-100)
Vitality	77.5 (20-100)	70 (10-100)	25 (0-85)	45 (5-90)*
Social Functioning	87.5 (25-100)	100 (25-100)	50 (12.5-100)	100 (25-100)
Role-Emotional	100 (0-100)	100 (0-100)	0 (0-100)	100 (0-100)
Mental Health	90 (40-100)	92 (24-100)	62 (8-96)	82 (60-100)
Walking distance, m	312 (81-422)	404 (124-549)*	na	na

* = $p < 0.05$, na = not assessed

Validity and reliability of the MAP

The first draft of the MAP consisted of eighty-one activities from categories three to eight; 3) Movement activities, Activities of moving around, Self-care activities, Domestic activities, Interpersonal activities and Performing tasks and major life activities, of the ICIDH-2 beta-2 draft (III). Activities from category one and two, Learning and applying knowledge and Communication activities were excluded. The 37 highest rated activities with a median value ≥ 6.0 or above were taken to the second draft of the MAP. Due to internal redundancy and poor internal consistency six activities were excluded, thus the final draft of the MAP included 31 items divided into four sub-scales and four single items (III: Table 2).

The total median of the MAP correlated moderately with the HAQ score and less with the FI, SGDI, and CPK levels. The MAP sub-scales Movement activities, Activities of moving around, Self-care activities, Domestic activities, and single items Social activities and Avoid over exertion correlated to corresponding sub-scales of the AIMS2 (III, p 2388).

Weighted Kappa coefficients ranged from 0.56 to 0.76 for the four sub-scales and from 0.56 to 0.77 for the four single items and no systematic differences were obtained between test- and retest occasions (III: Table 4).

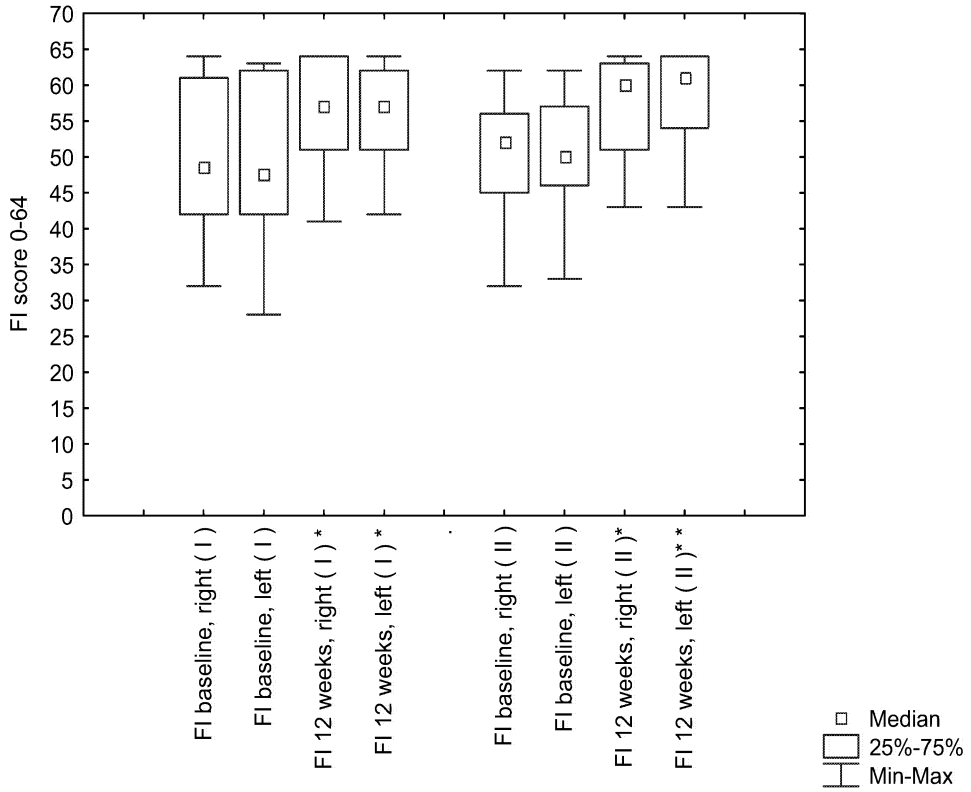

Figure 5

Median values of Functional Index (FI) on the right and left sides before and after a 12-week home exercise program in patients with chronic, stable PM and DM (I) and in patients with active, recent onset PM and DM (II). Max score of the FI is 64. * = $p < 0.05$, ** = $p < 0.01$.

Validity and reliability of the FI-2

In Study IV the scrutiny of the 287 original FI revealed ceiling effects of several tasks of the original FI, the elbow flexion, the hip abduction tasks, the transfer from side to side, up to sitting and PEF (IV: Figure 1). No tasks were redundant, but several had had poor internal consistency. According to the opinion of the health professionals and the patients in cohort two, all above-mentioned tasks except the elbow flexion task should be excluded. A revised version of the FI was developed containing nine functional tasks; elbow flexion, shoulder flexion, shoulder abduction, head lift, sit-ups, hip flexion, step test, heel lift and toe lift. The maximal number of repetitions was increased from 20 to 60 for all tasks but the latter two, which had 120 repetitions as maximum. A pace of 40 nods per minute, given by a metronome, resulting in 20 repetitions per minute, was added to standardize the movement velocity for all tasks but the latter two, which were given a pace of 80 nods per minute, giving 40 repetitions per minute. The Grippit test was considered important to measure, but was not included in the FI score as it is not a functional test.

The correlation between the revised FI shoulder flexion task and the isokinetic shoulder flexor test was moderate and correlations between the FI step test and the isokinetic knee extensor test were lower, as were the correlations between the FI and the other constructs (IV: Table 2). The elbow flexion task also had ceiling effects in the revised FI and was therefore excluded, leading to the final version FI-2 containing eight functional tests (IV: Figure 2). The ICC coefficients of the inter-rater reliability of the tests of the FI-2 ranged from 0.86 to 0.99, indicating no systematic differences. For intra-rater reliability, the ICC coefficients ranged from 0.56 to 0.99. Systematic differences were revealed in the shoulder flexion task, right and left sides, as well as in the right shoulder abduction task $p < 0.05$. The error of measurement of the different tasks of the FI-2 varied between three and 16 repetitions (IV: Table 3).

GENERAL DISCUSSION

The results of this thesis mainly contribute to broaden knowledge of the aspects of safety and benefits of exercise in patients with PM and DM and also introduces two outcome measures specifically developed to assess impairments and activity limitation / participation restriction in this group of patients. The exercise regimens used did not result in increased inflammatory infiltrates in muscle biopsies and no signs of increased muscle inflammation was detected by analysis of CPK levels (I, II, V) or MRI of the thigh muscles (I, II). The patient groups improved significantly with reduced impairment, activity limitation and participation restriction. FI-2 and the MAP proved to be valid and reliable outcome measures to assess impairment and activity limitation respectively.

Developing the exercise programs

The knowledge about safety and effects of exercise was very limited when the home exercise program was developed in 1995. The exercise program was developed with caution not to risk a flare of disease, and yet with the intention of being effective. The program was also designed as a home exercise program to be easy to include in the patients' daily activities. The easy and the moderate programs were developed to be feasible for use by patients with various degree of muscle impairment. Another similar home exercise program had earlier been developed and evaluated in patients with RA with ensured safety and effects of increased functional capacity, joint mobility and also led to decreased number of tender and swollen joints and activity-induced pain (Stenstrom 1994). On the basis of results from the home exercise programs (I and II) the more intensive exercise program (V) was developed to investigate if further impairment and activity limitation reductions could be reached. The exercised muscle groups were chosen to represent described impairment in PM and DM and also to include distal muscle groups.

Safety and benefits of exercise

While working with this thesis three studies were published concerning safety and benefits of exercise in patients with PM and DM. One study evaluated a six-week exercise program for a total of 60 minutes of ergometer cycling and step-up exercises of 60% of their estimated maximal heart rate in patients with chronic PM or DM. Seven patients were randomized to the exercise group and another seven to a non-intervention control group. The exercise group improved significantly with reduced impairment (e.g. maximal oxygen uptake and isometric strength) compared to the control group and no increased CPK-levels could be detected (Wiesinger *et al* 1998a). A similar exercise program was also evaluated for the same group of patients during a six-month-period with similar results (Wiesinger *et al* 1998b). Most recently, a study was published evaluating an exercise program of approximately 70% of 1 repetition maximum (RM) in 10 patients with active as well as 11 patients with chronic PM and DM, and reported reduced impairment without increases of CPK-levels (Varjú *et al* 2003). One major limit of these studies and earlier performed exercise studies is that CPK-levels were used as the only outcome measure for safety evaluation and CPK-levels do not always correlate well to the degree of muscle inflammation and impairment (Kroll *et al* 1986). In our studies we also analyzed muscle biopsies and MRI scans and were therefore able to further ensure the safety of exercise in PM and DM patients. Our studies are concord with the two exercise studies conducted in patients with IBM in which unchanged CPK-levels (Spector *et al* 1997) and no signs of increased inflammatory infiltrates in muscle biopsies (Arnardottir *et al* 2003) after exercise were reported. Data suggesting that strenuous exercise causes muscle inflammation was recently contradicted by a study in which young, healthy, well-trained individuals performed extreme eccentric cycling exercises without inflammatory infiltrates as a result. This study also suggested that multiple muscle biopsies *per se* and not exercise caused the inflammatory infiltrates reported in previous studies of healthy well-trained athletes (Malm *et al* 2000).

The safety of exercise was further supported by the fact that the home exercise program (I, II) was well tolerated and had excellent compliance, which was also the case with the intensive exercise program (V). Most patients in all exercise studies subjectively reported reduced impairment and improved overall well-being and that it was satisfying to be able to perform resistive exercise. This supports that the significantly reduced disability reached in our studies reflected a clinically relevant improvement. An increased sense of well-being was also experienced after a long-term aquatic exercise program in patients with RA (Stenstrom *et al* 1991), and also by patients with IBM performing strength training at a level of five RM (Spector *et al* 1997) and also the same home exercise program used in this thesis (Arnardottir *et al* 2003). Self-efficacy is an important factor for maintenance of exercise in patients with other rheumatic diseases and there are studies reporting positive effects on several health behaviors such as self-efficacy, depression and coping after a patient education program (Lorish and Boutaugh 1997) or a self-management program (Lorig et al. 1999, Barlow et al. 2000, Lorig et al. 2001). Another study reported that exercise treatment alone could have a positive effect on self-efficacy in patients with OA (Rejeski et al. 1998). For further information of what myositis patients consider to be clinically relevant improvements and their subjective opinions of what interventions are the most important for optimal health studies with a qualitative approach are needed.

No patient rated their pain as increased after any of the exercise programs, which agrees with results from other studies (Wiesinger *et al* 1998a, Varjú *et al* 2003). However, as the patients in paper V and also those reported by Varjú *et al* rated their pain as low to moderate at study start, indicating that pain was not a major complaint, it is not yet known whether this intensive exercise program would be tolerated by patients with more severe pain. However, the two patients with arthralgias and arthritis did not tolerate parts of the intensive resistive exercise program as well as did the other patients without joint pain, indicating that loads should be slightly reduced for myositis patients with joint problems. All studies evaluating exercise in patients with PM and DM have come to the same conclusion of the safety aspect supporting that moderate to intensive exercise is not harmful for patients, irrespective of disease activity.

Studies I and II were open studies and therefore mainly aimed to evaluate the safety aspects of exercise. The use of a control group or another study design including a baseline period would have been preferable to ensure the efficacy of the home exercise program. However, we could conclude that the patients in both groups (I, II) improved significantly with reduced impairment and improved health perception. This was not the case in patients with IBM in whom no significant impairment reductions could be detected after a six-week strength training program on the intensity of 5 RM (Spector *et al* 1997) or the same 12-week home exercise program used in Studies I and II (Arnardottir *et al* 2003). As the patients in Study I had a stable, chronic disease and had basically unchanged medication during the whole exercise period, it is likely that the improvements achieved were an effect of the home exercise program.

Interestingly, the clinical improvements in the patients with chronic PM and DM (I) were accompanied by a significant change in fiber type composition after 12 weeks (our unpublished data). At study start the patients had a disturbed type I

and type II fiber composition with a mean of 30% type I slow-twitch fibers and 70% type II fast-twitch fibers in vastus lateralis compared to normal values of approximately 50% of each fiber type. After 12 weeks of exercise the fiber type composition was normalized to a mean of 40% type I, and 60% type II fibers in the vastus lateralis muscle. The increases of slow-twitch type I fibers seen after exercise could explain the impairment reductions assessed by the FI and further supports a clinically significant beneficial effect of the home exercise program. Whether the disturbed fiber type composition in chronic PM and DM is a result of the disease, the pharmaceutical treatment or physical inactivity is not known. In comparison, patients with long-standing RA with muscle impairment were reported to have normal fiber type distribution in the vastus lateralis (Nordemar *et al* 1976).

The patients in Study II were in an active phase of disease and did not have stable medication during the exercise period, thus we could not draw any certain conclusions of the benefits of the exercise. The patients in Studies I and II were also followed-up every three months for one year. Significantly reduced muscle impairment was still recorded after 52 weeks compared to study start in the patient group with chronic disease in Study I (our unpublished data). Similar improvements were detected up to 24 weeks from study start in the patients with active, recent onset disease in Study II (our unpublished data). An interesting finding is that there seemed to be no difference in degree of impairment between patients in a chronic phase (I) and patients with active, recent onset (II) PM or DM (Figure 5). Degree of impairment was also very similar between patients in cohort I, Study IV, with chronic disease (duration > six months) and active disease (duration < six months) (IV: Figure 1). Another study concording with these results has recently been presented (Varjú *et al* 2003). This supports the notion that mechanisms other than muscle inflammation *per se* play a significant role in the development of impairment. One could speculate what the pharmaceutical treatments of today could contribute to reduce impairment. The new biological agents attacking specific parts of the immune system, such as IL-1α, might be able to improve outcome for these patients.

The myositis home exercise program was performed with 10 repetitions per exercise. No measurement of heart rate or perceived exertion during the exercise program was made, which could have enhanced the ability to establish the intensity of the program. It might be speculated that the 10 repetitions of each exercise in the program became more strength training oriented for those patients with low FI score who performed the easy program or the moderate program without additional weights, requiring a large percent of their maximal muscular capacity, while patients with higher FI-score might have used less of their maximal capacity performing the 10 repetitions even with additional weight cuffs. No intensity as to percent of maximal heart rate was established for the 15-minute walk as the patients were instructed to walk with at a self-selected pace. The program presented by Wiesinger *et al* was performed with a submaximal heart rate of 60% of max. However, as this intensity was kept up for 60 minutes and bearing in mind the endurance deficiency in these patients the program was probably experienced as rather muscular exerting for some of the patients.

Study V did not include a control group due to the limited number of patients meeting our inclusion criteria that were available at the rheumatology clinic. Instead, a baseline period of four weeks before exercise start was used. The stable baseline status followed by significant improvements at seven weeks compared to baseline supports the efficacy of the exercise program.

The marked improvement in 10-15 VRM was expected as the exercise program was performed with the load of 10 VRM. However, the expected overlap effects to also include improvements in muscle endurance assessed by the FI-2 were not achieved to the same extent. One explanation for this might be that the 10-15 VRM measures and the exercise program were performed in exactly the same muscle groups, in the same range of motion and the same velocity, while the endurance measures evaluated the same muscle groups as well as additional muscle groups, although, not in the same initial positions and velocity. Other explanations for the lack of overlap effects on muscle endurance could be either a lack of motivation in the patients to perform their maximal number of repetitions after having performed the 10-15 VRM evaluations, or that this exercise program was too strength training oriented, even though the exercises were performed in three sets to improve muscular endurance. The gains in 10-15 VRM might even have been at the expense of muscular endurance. Therefore it might be speculated that a more varying exercise program containing both high intensive/low repetition and low intensive/high repetition exercises might be more efficient to optimize improvement.

A more marked increase in grip strength was also expected as some of the exercises required use of grip strength and as a correlation between hand function and activity limitation has been reported in patients with RA (Dellhag and Buckhardt 1995, Vliet Vlieland *et al* 1996). As only one patient was responder in maximal and mean Grippit, the exercise program might not have included enough grip strength properties or was too short-term. The Grippit was concluded to be reliable in these patients (IV) with a small error of measurement, which supports the instruments ability to reflect changes in grip strength.

As the exercise program lasted for only seven weeks, the reduced muscle impairment was probably mainly due to neural adaptations. A process leading to increased muscle fiber area, increased number of capillaries and metabolic changes might also have contributed. Investigations of the muscle biopsies taken before and after exercise might be able to explain some of our results with regards to both improvements and deteriorations. Our intensive program (V) was well defined with the intensity of 10 VRM, which was similar to the intensity of the most recent published exercise program in patients with PM and DM (Varjú et al 2003). As treatment with warm mud and massage was also employed, the ability to establish the actual effect of the training program is limited.

The relative short period of exercise could explain why few differences in activity limitation were obtained. A longer exercise period would most likely result in less activity limitation. The two patients who did respond with reduced activity limitation as assessed by the MAP did so in the sub-scales Movement, Activities of moving around and Social activities, which could be connected to the reduced muscle impairment obtained by the exercise program. The patient who

deteriorated in MAP score did so in the sub-scale Leisure activities. This might be ascribed to that the time and effort the patients put into participating in this exercise program was to consuming, leaving insufficient energy and time for family life and other interests.

The number of patients included in each of the three exercise studies was limited due to the rareness of PM and DM, limiting our ability to apply the results to a general population. However, these studies included patients of both genders, of various ages and disease activity and degree of impairment. To be able to compare efficacy of different kinds of exercise regimens multi-center studies need to be conducted to reach sufficient power.

It is encouraging that the results of available exercise studies confirm eachother with regards safety and benefits of active exercise in these patients (Hicks *et al* 1993, Escalante *et al* 1993, Wiesinger *et al* 1998a, 1998b, I, II, V, Varjú *et al* 2003). Following these studies the published review papers on this topic suggest that active exercise can also be cautiously employed in patients with active PM and DM, although it is still recommended to start with isometric exercise and range-of-motion exercises (Hicks 1998, Mahowald 2001). One review published last year gave well-defined recommendations of passive ROM exercises in bedridden patients with severe disease activity or in patients with muscle strength of $< 2/5$. With increased strength of 3/5 a combination of active isometric and isotonic exercises with elastic straps and when the muscle strength has increased to $\geq 4/5$ a more aggressive approach can be employed, included exercises with free weights or resistive machines (Oddis 2002).

Outcome measures in Studies I, II, V

The original FI was modified as the Grippit instrument was used for measures of grip strength instead of the sphygmomanometer originally used in the index. The modified grip strength scale was calculated from normal values of maximal strength on the right and left sides for men and women separately. The seven-minute walking test used in Study I was not validated or evaluated for reliability for patients with PM and DM prior to study start. Later on this measure was tested for intra-rater reliability. Unpublished data suggest that this treadmill test is reliable after one learning occasion with an error of measurement of 70 meters. The patient group improved to a median of 92 meters after 12 weeks compared to baseline, indicating that the patients did improve in walking distance above the error of measurement.

The 10-15 VRM measures were well tolerated by the patients. In most cases one or two trials were necessary to establish the weight with which the patients could perform 10-15 repetitions and not more. If a second or third trial was necessary, this was performed after approximately five minutes of rest while testing another muscle group. These measures took around 30 minutes altogether to complete. The 10-15 VRM was measured rather than 1 VRM, mainly for safety reasons. Such maximal exercises are hard to perform correctly, which could increase the risk for injuries as these patients were not accustomed to exercising with this intensity and because some of them were being treated with corticosteroids. It

would have been preferable to measure exactly 10 VRM and not 10-15 VRM to minimize the error of measurement. However, 10-15 VRM was used to minimize the number of trials before reaching the correct load as these measures were followed by the rather energy-requiring FI-2 and also grip strength measures. It would also have been possible to measure only two muscle groups using the exact 10 VRM. Nonetheless, the number of repetitions did not differ > 2 repetitions in most patients in most measures of most muscle groups.

Developing the outcome measures

The ICIDH (WHO 1999) was constructed to be applied world-wide, resulting in inclusion of daily activities that might not be relevant to individuals living in the western world. Activities that were considered by the research group as non-relevant for patients with PM or DM living in the western world were excluded, resulting in an 81-item first draft of the MAP. It might be possible that some activity was wrongly excluded due to the research group's predetermined opinions of activity limitations in these patients. However, much effort was made to include as many activities as possible without presenting a too extensive first draft that would be impossible to fill out in an acceptable range of time.

As the original FI was found to mainly include tasks reflecting the phenotype of PM and DM it was natural to further develop the FI and evaluate the revised version rather than developing a whole new functional measure. No evaluation of normal values for the maximal number of repetitions correctly performed was conducted. The maximal number for the different tasks in the FI-2 of 60 and 120, respectively, was obtained by testing a few patients with a previously known low grade of impairment. They were both men and women between the age of 31 to 50 and were all able to perform up to approximately 60 and 120 repetitions. One patient with long-standing severe impairment was also asked to perform the same tasks to evaluate possible minimal score of the revised FI. A study to investigate FI-2 in healthy individuals of different age-groups is planned for later on this year. The results from this study might result in adjustments of the maximal number of repetitions for the FI-2.

Outcome measures developed in this thesis

The MAP is the first developed disease-specific outcome measure for activity limitation / participation restriction for patients with PM and DM. The use of the internationally recognized theoretical framework, the ICIDH-2 beta-2 draft and also the input from professionals and patients during the development of the MAP has likely ensured its content validity. The first two categories of the ICIDH-2 beta-2 draft, Activities of learning and applying knowledge and Communication activities were excluded due to not previously being described as limited in patients with PM and DM. The setting of cutoff point at ≥ 6.0 was pragmatic as no defined values for cutoff exists and a predetermined preference of approximate number of items included. It was surprising that everyday activities such as rising from a chair or brushing of teeth were not rated high for difficulty and importance

while less frequent activities such as maintaining of cleaning domestic appliances were.

Altogether, six activities included in the second draft of the MAP were excluded due to redundancy or poor consistency. Two questions concerning sexual activities included in the second draft of the MAP were not answered by a third of the patients in cohort 2, and were thus excluded due to practical ethical reasons. These results agree with a previous study reporting that questions of this nature might be considered as too personal (Fries et al. 1980). The two latter sub-scales of the first draft of the MAP, Interpersonal activities and Performing tasks and major life activities, initially included rather few activities. This led to poor consistency in these sub-scales; however, as the remaining four questions in these sub-scales were rated to be important, they were retained as single items. One important aspect that might have influenced the patients' rating of difficulty and importance of the activities is that all patients in cohort one (III) live in a big city. Individuals living in smaller towns or in rural areas might have rated difficulty and importance of certain activities differently.

As no disease-specific activity limitation instrument was available, the AIMS2 containing similar sub-scales, and the HAQ were the instruments of choice for comparisons with the MAP for evaluation of construct validity. According to our hypothesis the MAP was most convergent with the HAQ, less with the FI and subjective global disease impact and divergent with CPK levels. It was also expected that the different sub-scales of the MAP would correlate moderately to good with corresponding sub-scales of the AIMS2. The fact that the MAP did not correlate excellently with the HAQ and the AIMS2 supports the need for a disease-specific questionnaire to assess activity limitation and participation restriction in patients with PM and DM.

The differences between the preliminary draft ICIDH-2 and the final ICF might have resulted in a somewhat changed organization of the MAP. If the MAP had been built on the ICF it might have included more questions on participation restriction as activity and participation are put together in the ICF, but were listed separately in the ICIDH-2 (Table 3). However, it is not likely that the content of the MAP would be different in other aspects due to also consulting the patients and health professionals as regards to what activities were not important to include in the MAP. The MAP was valid and reliable and also proved to be sensitive to change as demonstrated in Study V, indicating the value of using this instrument, and it seems that the MAP was more sensitive to change than the HAQ according to our criteria for improvement. This could be ascribed to that the HAQ is developed for patients with arthritis, thus not capturing the specific limitations of patients with myositis. Whether this instrument will be valid in other populations still needs to be tested. For this purpose translation to other languages and cultures need to be carried out (Guillemin 1995). One study presented another approach to measure activity limitation in patients with RA, using a continuous ambulatory activity monitor to quantify amount and intensity of daily activities (Munneke *et al* 2001). Using this technique patients can be monitored at home while performing subjectively relevant daily activities instead of rating perceived limitations while performing predetermined activities. However, such measurement might be technically demanding.

Table 5
Categories for Activity of the ICIDH-2 and activity / participation of the ICF.

ICIDH-2 beta-2	ICF
Activities of Learning and applying knowledge	Learning and applying knowledge
Communication activities	General tasks and demands Communication
Movement activities Activities of moving around	Mobility
Self-care activities	Self-care
Domestic activities	Domestic life
Interpersonal activities	Interpersonal interactions and relationships
Performing tasks and major life activities	Major life areas Community, social and civic life

The FI-2 is the first functional outcome measure for impairment evaluated both for content and construct validity as well as for reliability for patients with PM and DM. The original FI was useful in patients with high degree of impairment and had excellent inter- and intra-rater reliability. However, our clinical experience of floor- and ceiling effects of the FI from several years of use was supported by the results of the scrutiny of all the FIs performed at our clinic. As the patients and members of our research group did not suggest any additional tasks of the FI, and also rated a majority of the FI tasks as relevant and important to measure, the content validity of the FI-2 was secured. The elbow flexion task, measuring the biceps muscles, had a ceiling effect in both the original FI and the revised FI. These results and the fact that the biceps muscle has not been described as being affected in patients with PM and DM support the exclusion of this task from the FI-2. The retention of shoulder flexion, hip flexion, step test and head lift tasks in the FI-2 is in accordance with the disease phenotype of myositis (Plotz *et al* 1989), although this is not the case with the muscle groups used for the sit-up task.

Our results support the FI-2 as a measure of muscle impairment. For the upper limb the FI-2 measures endurance, in accordance with our hypothesis. From our results, it seems that the FI-2 lower limb tasks measure strength rather than endurance. The lack or correlation between the FI-2 step test task and the measures of isokinetic knee extensor endurance might be ascribed to the differences in initial position of the patients of these tests and that the latter is open-chained while the former is closed-chained. The overall low to moderate correlations between the FI-2 tasks and the isokinetic measurements could be due to that the patients in cohort three were heterogeneous and consisted of a rather small number of patients. The isokinetic measures might also not have been ideal to compare with the functional tasks of the FI-2, as they do not reflect the functional use of muscles. However, no golden standard for functional measurement of muscle impairment is available. As the FI-2 requires dynamic muscle work the isokinetic measurements were considered as more appropriate to use for comparisons than the isometric measurements that have been used in these

patients in previous studies (Escalante *et al* 1993, Hicks *et al* 1993, Wiesinger *et al* 1998a, 1998b).

Only the right side isokinetic shoulder flexors and knee extensors were measured in an effort to minimize the time required to perform the tests. One patient could not perform the shoulder flexor tasks of the FI-2 against gravity in the whole ROM required and could thus not perform the isokinetic shoulder flexor measures. This could indicate that isokinetic measurements might not be valid for patients with muscle strength > 3 of the Manual Muscle test scale 0-5. This patient was excluded from the correlation analysis for upper limb tests. The isokinetic measures were feasible in the remaining 22 patients.

Several studies presenting normal values of isokinetic strength measures have been published (Neder *et al* 1999, Baron 1995, Mayer *et al* 1994, Nicholas *et al* 1989, Ivery and Calhoun 1985). A direct comparison of isokinetic strength of patients with PM and DM with these normal values are hampered by the variance in subjects included, equipment used and also velocities and angles. Another problem is that all normal values are measured as peak torque and not mean torque, which was considered to be more reliable in patients with muscle impairment. We chose to measure isokinetic strength and endurance in the velocity of 90° / sec which was similar to the movement velocity of the FI-2 tasks.

All three physical therapists performing the reliability measurements of the FI-2 had long experience of performing the original FI and were therefore familiar with a majority of the tasks. This might be the reason for them managing with only written instructions without additional information and practice before study start. The intra-rater reliability of the FI-2 was mainly good to excellent, although surprisingly not to the same extent as for inter-rater reliability. This concerns mainly the sit-up task for which the inter-rater reliability was excellent and the intra-rater reliability was poor. This is hard to explain and could be ascribed to chance. This and that abdominal muscle groups are not described as affected in patients with PM or DM could support the exclusion of this task in an attempt to further shorten the FI-2. The systematic differences between test and retest were probably due to some patients performing more repetitions at retest. This might be explained by either day-to-day variations of health status in the patients or, perhaps more likely, by the patients being more cautious with the first test in order to avoid over-exertion. A learning occasion might reduce this fear and improve the reliability of the FI-2.

A total of three patients in cohorts three to five reported long-lasting delayed-onset muscle soreness after performing the revised FI or the FI-2. This pain subsided after a maximal of three weeks. Very little is known about the mechanisms causing this post-exercise muscle soreness in healthy individuals and even less in patients with myositis.

The number of patients included in Studies III and IV is limited due to the rareness of PM and DM. A larger number of patients would have resulted in more stable analyses for content and construct validity and also for reliability. Nonetheless, an advantage of our studies was that patients of both genders and in

various ages and phases of disease were included, not limiting the use of the outcome measures for certain groups of patients.

In 2001 a preliminary core set of measures for disease outcome assessment in both adult and juvenile PM and DM was presented by the International Myositis Outcome Assessment Collaborative Study Group (Miller et al. 2001). The six-parameter core set the group recommended to be included in all clinical trials as; physician and patient/parent global disease activity using a VAS or Likert scale, muscle strength by MMT, physical function by the HAQ, laboratory assessments of muscle enzymes, and assessment of extra-skeletal muscle involvement. The group also reported consensus of patient assessment of health-related quality of life by the SF-36. The FI was included as an extended measure in addition to the MMT. The same group recently presented minimal clinically important change in core set measures. The median change for patients' and physicians' global assessments and extra skeletal muscle activity was set to 20%, muscle strength and physical function to 15% and muscle enzymes to 30% (Rider *et al* 2003). This collaboration has resulted in a consensus for outcome measures to use in clinical trials, which will probably enhance the possibility to perform multi-center studies to improve the power and interpretation of results obtained in different studies. However, investigations must be conducted to further ensure validity and reliability of these measures. The criteria for improvement criteria used in Study V were stricter as regards measures for impairment and activity limitation, but were otherwise in accordance with the minimal clinically important change in core set measures presented by Rider *et al*.

The role of exercise in the rehabilitation of patients with PM and DM today

During the last decade while working on my thesis, recommendations of rehabilitation for patients with PM and DM have gradually changed from passive treatment including no active exercise or physical activity to a much more active treatment. Several studies evaluating different kinds of pharmaceutical treatments and also exercise have been conducted at our own clinic during recent years. A randomized controlled multi-center study aiming to investigate the effect of early employed active resistive exercise in patients with recent onset active PM and DM has been ongoing since 1998. In another multi-center randomized controlled study creatine substitution together with exercise has been evaluated. The results of these two studies will be analyzed in the near future. A study exploring the degree of impairment of grip strength and function and a study with the objective to evaluate the reliability of an assessment tool to measure dynamic balance in these patients have also been conducted.

The first two exercise studies were a part of a whole rehabilitation program for patients with PM and DM, also including patient education. This patient education program was designed according to programs used in RA patients and has been carried out once a year since 1996. During the years of my thesis work a unique myositis team has developed comprising two physicians, one nurse, one physical therapist, one occupational therapist and one social worker with special interest in patients with myositis. The team meets every third week discussing current

patients and planning visits for patients included in our studies. All patients meet the team at least once a year for standardized follow-up. When visiting the physical therapist all patients are given individualized advice on how to keep up a feasible level of exercise and a majority of the patients at our clinic are regularly physically active or participate in some kind of organized exercise at least once a week. The clinic can also offer aquatic training and strength training in groups for these patients.

This spring the team, together with the entire myositis research group, invited patients with PM, DM and IBM from different parts of Sweden and their relatives to the fifth annual information meeting at which we presented results from our studies, and also the studies planned for the future.

Today the safety of exercise has been fairly well established along with the notion that patients with PM and DM can reduce disability and improve health perception by exercising. However, very few patients experience a total regain of capacity, which implies the need for further investigations on how to optimize treatment and outcome. Further work on adequate outcome measures for this group of patients is also needed.

CONCLUSIONS

Moderate resistive exercise is safe to employ in patients with chronic, inactive PM and DM regarding disease activity, impairment, activity limitation and perceived health and might also reduce disability and improve perceived health in these patients.

Moderate resistive exercise can be safely employed in patients with active, recent onset PM and DM regarding disease activity, impairment and perceived health.

The Myositis Activities Profile (MAP) is valid and reliable for assessing activity limitation / participation restriction in patients in various phases of their disease. Further evaluation of sensitivity to change after long-term interventions still needs to be conducted along with cross-cultural adaptation for use in other countries.

The Functional Index-2 is a valid and reliable impairment / activity limitation outcome measure, considering one learning occasion, to assess muscle endurance in patients in various stages of PM and DM.

Intensive muscular training is safe and beneficial for patients with chronic PM and DM regarding disease activity, impairment, activity limitation and participation restriction.

Recommendations for rehabilitation for patients with PM and DM

- All patients should be carefully and regularly monitored with reliable and valid outcome measures as regards to impairment, activity limitation and participation restriction.

- All patients should be informed about the safety and benefits of regular active exercise and physical activity and should also be instructed in active resistive dynamic exercise regimens of choice, individually adjusted according to disease activity and muscle impairment.

- All patients should be offered continuous physical therapy contact in addition to team contact, to keep up the exercise level for longer periods.

- Active exercise and physical activity can be performed as long as the patient does not experience increased muscle impairment or pain. In such case the exercise intensity should be adjusted, although not discontinued.

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