

Exercise in Inflammatory Myopathies, Including Inclusion Body Myositis

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Abstract Exercise is an important part of treatment in patients with idiopathic inflammatory myopathies. Improved functioning, ability to perform activities of daily living, and health-related quality of life have been reported in adult polymyositis, dermatomyositis, and also recently inclusion body myositis following different exercise regimens, with no signs of increased muscle inflammation. Intensive resistance training could reduce clinical disease activity and reduce expression of genes regulating inflammation and fibrosis in chronic polymyositis and dermatomyositis. Today, exercise research in adult myositis is focused on understanding mechanisms for muscle impairment and improved muscle function in relation to exercise and verifying results from small, open studies in larger settings. There are no studies evaluating the effects of exercise over weeks or months in juvenile dermatomyositis, other than a case report; however, there is to our knowledge an ongoing effort to evaluate the safety and effects of exercise in patients with juvenile dermatomyositis.

Keywords Polymyositis · Dermatomyositis · Exercise · Inclusion body myositis · Juvenile dermatomyositis · Resistance training · Aerobic exercise · Inflammatory myopathy · Muscle impairment · Muscle function · Muscle weakness

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Introduction

The idiopathic inflammatory myopathies are rare conditions divided into adult polymyositis, dermatomyositis, and inclusion body myositis as well as juvenile dermatomyositis, with common symptoms such as reduced muscle function and longstanding fatigue [1]. Patients with adult polymyositis and dermatomyositis have proximal muscle weakness with most limitations in hip flexors [2], but these patients also have reduced grip strength [3] and limitations in distal lower limb muscles [4]. Lung fibrosis is a common symptom [5], and reduced aerobic capacity compared with healthy controls has also been reported [6]. Adult polymyositis and dermatomyositis patients usually respond to medical treatment with reduced inflammatory infiltrates in muscle tissue and normalized muscle enzyme levels in serum. However, the majority of patients suffer from sustained disability [7]. The reason for this is not totally clear, but there are data suggesting factors other than inflammation per se could contribute to muscle impairment. For example, major histocompatibility complex class I is upregulated on muscle fibers both before and after corticosteroid treatment, and interleukin-1 α is expressed in capillaries [8, 9], and there seems to be a reduced capillary blood supply in muscle tissue [10]. Furthermore, reduced levels of adenosine triphosphate and phosphocreatine during rest and during exercise in muscle tissue have been found [11]. These findings could support a hypothesis of an acquired metabolic disturbance contributing to sustained muscle impairment in polymyositis and dermatomyositis.

Patients with inclusion body myositis often have very slowly progressing muscle weakness, especially in finger flexors, quadriceps, and distal muscle groups of the lower limbs, together with a severe muscle atrophy [12]. These patients do not respond well to pharmacologic treatment;

however, one recent study suggests that patients receiving immunosuppressive treatment experience a slower mean progression of muscle weakness of -0.76% over several years compared with patients without medical treatment, with a mean of -1.03% [13]. These patients also have lower quality of life in domains of physical functioning, role-physical, general health, and social functioning compared with population-based reference values [14].

Juvenile dermatomyositis affects children of all ages, with its main symptoms of proximal muscle weakness and characteristic skin rash. A systemic disease with fever and weight loss is also very common, but the disease can also affect vessels, joints, the lungs, and the heart [15]. Medical treatment consists of high-dose glucocorticoids with additional immunosuppressive treatment, and many patients respond favorably. However, a group of patients need long-term treatment over years while still developing sustained functional limitation [16]. These patients also have reduced maximal oxygen uptake compared with healthy children [17, 18]. Poor sleep and fatigue are prevalent and affect quality of life [19].

Today, we believe that the accumulated evidence for safety and efficacy of exercise in adult polymyositis and dermatomyositis is fairly established, although most available studies have limitations. A recent systematic review of exercise studies in inflammatory myopathies (Table 1) showed foremost limitations in selection and allocation bias, as well as blinding, while the studies were given rather high scores for data collection methods and compliance [20], indicating a need for randomized controlled, single-blind studies in this area. There are a limited number of exercise studies in inflammatory myopathies, especially inclusion body myositis and juvenile dermatomyositis. During recent years, one study and several case reports have reported encouraging data with regard to improved muscle strength also in the most affected muscle groups (eg, the quadriceps) by different resistance training regimens. There are also recent data suggesting that intensive exercise is not only safe but might also reduce muscle inflammation and clinical disease activity in chronic polymyositis and dermatomyositis. This review mainly focuses on recent advances in inclusion body myositis.

Exercise in Inclusion Body Myositis

All together, four open studies and two case reports have evaluated safety and the effects of exercise in patients with sporadic inclusion body myositis. One study reported significantly improved strength assessed by handheld myometer before and after exercise in less affected muscle groups, but very small or no improvements in more affected muscle groups by resistance training 3 d/wk for 12 weeks,

with unchanged creatine phosphokinase (CPK) levels [21]. Arnardottir et al. [22] confirmed the safety of exercise by evaluating a 12-week home exercise program performed 5 d/wk for 12 weeks in combination with stationary biking or walks, without signs of increased inflammation by analysis of CPK levels and muscle biopsies. However, the study was not able to show improved muscle function in isokinetic knee extension or flexion assessed in a dynamic dynamometer (KIN-COM), manual muscle test, or by using the Functional Index assessing repetitive muscle function. One case report told the story of a man with polymyositis with low response to medical treatment and exercise that led the author to question if this patient in fact had inclusion body myositis [23]. After 1 year of physical therapist-supervised exercise and home exercise, the patient had reached a plateau of still-reduced quadriceps strength. Following a 12-week, 3-days-per-week eccentric quadriceps training of the right leg in a Biodex, with the left leg serving as a control, the patient improved 40% to 50% in the trained leg compared with the untrained leg. Levels of CPK, muscle pain, and muscle stiffness remained unchanged throughout the study. Another case report presented a man with established inclusion body myositis with steady progression of muscle weakness despite regular exercise during the past year [24•]. A protocol with submaximal leg press on the load of 15 voluntary repetition maximum (VRM) during vascular occlusion of the thighs twice per week for 52 weeks was well-tolerated with unchanged inflammation markers. The patient did not report excessive exertion, pain, joint injury, or muscle soreness at any time during the study, and there were no signs of increased inflammation in muscle biopsies. This patient improved about 16% in one VRM leg press knee extension, 60% in the functional test Timed-Up and Go, and thigh cross-sectional area of the quadriceps improved by 4.7% [24•].

Johnson et al. [25] were able to show improved function following a 16-week home exercise program in an open study including seven patients with inclusion body myositis with disease duration between 4 and 17 years (mean age, 68 years). Three of the participants were not dependent on walking aids, while two used a cane and two used a motorized buggy, revealing a variation of disease progression. Study participants performed the home exercise program twice per day, doing whole-body sit-to-stand exercises, biceps curl, shoulder press, heel lifts, isometric vastus medialis exercises, and ankle dorsal flexion. Exercise compliance was monitored by exercise diaries in which participants filled in daily exercise performance and perceived fatigue, muscle soreness, and dyspnea. Muscle strength was assessed by handheld myometer in 10 muscle groups. The group improved statistically significantly in all muscle groups, with the most prominent improvement in hip flexion (171%), elbow extension (~75%), and knee flexion and grip

Table 1 Published exercise studies in adult inflammatory myopathies

Study (design)	Patients, <i>n</i>	Disease activity	Exercise duration, wk	Type of exercise	Load/intended% of maximum	Outcome benefits	Results/benefits	Outcome safety	Results safety
Inclusion body myositis									
Spector et al. [21] (open study)	5	Chronic	12	Dynamic resistance	50–70	Isometric PT	0	CPK	0
Amaralotir et al. [22] (open study)	7	Chronic	12	Dynamic resistance, HE	NR	3 VRM Isometric PT	+	Biopsy	0
Johnson et al. [25] (open study)	7	Chronic	16	Dynamic resistance, HE	NR	Muscle endurance	0	CPK	0
Johnson et al. [26•] (open study)	7	Chronic	12	Aerobic/resistance, HE	80	Muscle strength Functional capacity	+	Biopsy	0
Gualano et al. [24•] (case report)	1	Chronic	52	Dynamic resistance/VO	60–70	Functional capacity VO _{2max} Muscle strength	+	Soreness CPK	0
Harris-Love [23] (case report, controlled)	1 (PM/IBM?)	Chronic	12	Dynamic eccentric	70	Balance Quality of life Thigh cross-sectional area	+	Biopsy	0
Polymyositis/dermatomyositis									
Wiesinger et al. [30] (RCT)	14	Chronic	6	Aerobic	60	Isometric PT	+	CPK	0
Wiesinger et al. [31] (controlled study)	13	Chronic	24	Aerobic	60	VO _{2-peak} Activity limitations	+	Pain ROM	0
Escalante et al. [29] (open study)	5	Active	8	Dynamic resistance, ROM	NR	VO _{2-peak} Isometric PT	+	CPK	0
Alexanderson et al. [35] (open study)	10	Chronic	12	Dynamic resistance, HE	NR	Activity limitations	+	CPK	0
Alexanderson et al. [36] (open study)	11	Active	12	Dynamic resistance, HE	NR	Isometric PT	+	CPK	0
Heikkilä et al. [32] (open study)	22	Chronic	3	Dynamic resistance, HE	NR	Muscle endurance Quality of life	+	CPK Biopsy	0
Värjü et al. [33] (open study)	19	Chronic/active	3	Dynamic resistance, ROM	NR	Muscle endurance Quality of life	+	MRI	0
						Muscle endurance Quality of life	+	CPK Biopsy	0
						Muscle endurance Activity limitations	+	MRI	0
						Isometric PT FVC	0	CPK	0
						Activity limitations	+	CPK	0

Table 1 (continued)

Study (design)	Patients, <i>n</i>	Disease activity	Exercise duration, wk	Type of exercise	Load/intended% of maximum	Outcome benefits	Results/benefits	Outcome safety	Results safety
Chung et al. [38] (RCT, double-blind)	37	Chronic	20	Dynamic resistance, HE, creatine/placebo	NR	FC Muscle endurance Muscle strength Quality of life Anxiety/depression PCr in muscle	+	CPK Pain	0 0
Alexanderson et al. [39] (open study, repeated measure)	8	Chronic	7	Dynamic resistance	70	5 VRM Muscle endurance Activity limitations	+	CPK Biopsy 6-item core set	0 0 +
Hicks et al. [28] (case report, controlled)	1	Chronic	6	Isometric resistance	60	Isometric PT	+	CPK	0

CPK creatine phosphokinase; DM dermatomyositis; FC functional capacity; FVC forced vital capacity; HE home exercise; IBM inclusion body myositis; NR not registered; NR not registered; PCr phosphocreatine; PM polymyositis; PT peak torque; RCT randomized controlled trial; ROM range of motion; VO vascular occlusion; VO_{2-peak} peak/maximal oxygen uptake; VROM voluntary repetition maximum; + = improvement, 0 = no change, - = worsening

strength (~70%). Interestingly, the group also improved about 40% in knee extension. Physical capacity assessed by timed required to climb one flight of stairs and to walk 30 m also improved by about 21% and 17%, respectively. Four participants also increased the numbers of sit-to-stands, while two remained unchanged and one showed a slight deterioration. Serum CPK levels remained unchanged, and only two patients reported short-term increases in muscle soreness, thus supporting the safety of this program. No follow-up muscle biopsies were performed, which is a limitation, as this could have provided insights on what effects this exercise program had on muscle characteristics [25].

In 2009, the same group published another open-label study evaluating an aerobic exercise component in addition to the aforementioned home exercise program [26•]. This study involved seven patients with inclusion body myositis with a mean age of 68 years and a history of declining muscle function during between 5 and 9 years. They exercised for 12 weeks, performing aerobic exercise on a stationary bike on 80% of maximal heart rate 3 d/wk. Another 3 d/wk, they performed six exercises from the previously described home exercise program in two sets, with a couple of minutes of rest in between. Aerobic capacity was assessed by a submaximal stationary bike test (not described in detail) but was referenced to a submaximal test on 65% of maximal oxygen uptake that needs to be established through a maximal oxygen uptake test [27]. The group improved their aerobic capacity by about 33% after the 12 weeks of exercise. Health-related quality of life was assessed by the Medical Outcomes Survey Short Form 36 (SF-36) questionnaire, which was able to capture significant improvement in all eight domains on a group level. Again muscle strength was measured by using the handheld myometer, with statistically significant improvements of between 11% and 40% in shoulder abduction, hip flexion, and abduction and knee flexion, while no changes were noted in other muscle groups (eg, knee extension and grip strength). This exercise program was not followed by significant changes in stair time or walk 30 m [26•]. A limitation of this latter study was the lack of information about the functional ability of the participants. Also, both studies were small, open-label studies lacking information on presence or absence of medical treatment. The difference in response rate in the most affected muscle groups between the twice-daily home exercise program and the combined aerobic/resistance home exercise program could be attributed to differences in exercise programs but also to differences in degree of disability or disease progression between the participating individuals of the two open studies. However, the results are encouraging for patients with inclusion body myositis, and it will be of great interest to replicate these studies in larger, multicenter-based randomized controlled trials, which could be enhanced by international collaboration. As immunosuppressive treatment might slow down the decline of muscle

strength over years, it will be of interest to determine if exercise could enhance this effect or have the same effect in patients without use of immunosuppressives. By adding data on physical activity and exercise level in the international myositis register, we might be able to study decline in function in patients with and without immunosuppressive treatment and with or without regular exercise treatment.

Exercise in Adult Polymyositis and Dermatomyositis

The first two case reports supporting the safety of resistance exercise in both chronic and active polymyositis and dermatomyositis were published in 1993 [28, 29]. The first randomized controlled study including a total of 14 patients with chronic disease revealed improved maximal oxygen uptake and isometric peak torque of the quadriceps in the exercise group compared with the sedentary control group following 6 weeks of aerobic exercise [30]. The efficacy of such a program was also reported in a longer perspective of 6 months in a controlled, nonrandomized study [31]. Analysis of CPK levels is the most common marker for muscle inflammation in exercise studies in myositis. A few open-label studies further supported the safety of resistance training in both chronic and active disease, reporting unchanged CPK levels and improved muscle function after short-term exercise periods [32, 33]. However, as CPK levels do not always correspond to muscle function or disease activity [34], our group chose to also analyze muscle tissue and MRI scans in addition to CPK levels following a resistance home exercise program performed 5 d/wk for 12 weeks in both established and active polymyositis and dermatomyositis [35, 36]. In an open-label study design, we were able to report on significantly improved repetitive muscle function assessed by the myositis-specific Functional Index and improved physical functioning domain of the SF-36 instrument in patients with established, stable, inactive disease activity without any signs of increased muscle inflammation in analysis of muscle biopsies, MRI, or serum inflammation markers [35]. Analysis of muscle biopsies in the patient group before they started the 12-week home exercise revealed a relatively lower proportion of type I oxygen-dependent muscle fibers and a relatively higher proportion of type IIC muscle fibers compared with age-matched controls [37]. Interestingly, the fiber type composition had shifted after the 12 weeks of exercise, as the relative proportion of type I fibers had increased significantly by 10%, while the proportion of type IIC fibers had decreased significantly by 2% [37].

The effect of creatine supplements in combination with exercise was evaluated in a 6-month, randomized controlled, double-blind study [38]. Thirty-seven patients were randomly assigned to a creatine group receiving a loading dose of 8 g/d creatine powder and a maintenance dose of 3 g/d for 5 months, while the placebo group was given the same amount of placebo

powder. All patients exercised with the aforementioned 5-days-per-week home exercise program for 5 months. Levels of creatine phosphate assessed by MRI increased after 3 and 5 months of exercise compared with the control group. The creatine group also improved significantly compared with the placebo group regarding physical capacity as measured by the Functional Aggregate Performance Score, and improved in repetitive muscle function as measured by the Functional Index and on the manual muscle test. There were no creatine-related adverse events, and the study concluded that creatine supplementation in addition to exercise is safe and effective in patients with chronic polymyositis and dermatomyositis. A 7-week intensive resistance training program improved 10 to 15 VRM muscle strength by 21% to 900% and muscle endurance as measured by the Functional Index 2 in 8 patients with established polymyositis and dermatomyositis [39]. This repeated measure study, including a baseline period without intervention, was the first to show not only unchanged inflammatory infiltrates and CPK levels by exercise, but also significantly reduced disease activity as assessed by the Myositis Intension to Treat score, and two patients were responders with decreased disease activity according to the International Myositis Assessment Clinical Study group responder criteria [40]. This study also resulted in downregulation in gene complexes controlling inflammation and fibrosis compared with before exercise as analyzed by Micro Array [41••]. These results suggest that exercise might reduce inflammation and disease activity in established polymyositis and dermatomyositis; however, this hypothesis needs to be tested in further studies.

Patients with active, recent-onset disease also improved significantly, as assessed by the Functional Index and in the SF-36 domains of physical functioning, bodily pain, and vitality without signs of aggravated disease in biopsies, MRI, or CPK levels, further supporting the safety of resistance exercise in patients with active muscle inflammation.

Exercise in Juvenile Dermatomyositis

Today, there is no study evaluating the safety and effects of exercise in a group of patients with juvenile dermatomyositis over weeks and months. However, children are physically active by nature, and thus far, no reports have been published recommending a cautious approach to exercise in these patients. A case report told the story of two twin girls, aged 7, one of whom had chronic, inactive juvenile dermatomyositis, and the other healthy. Both children performed a 1-h aerobic and resistance exercise program twice weekly for 16 weeks. The exercise program was well-tolerated, with improved muscle function and aerobic capacity [42•]. A single resistance exercise bout on about 60% of maximum did not yield increased CPK levels or acute reduction in muscle function in a group of children with chronic, inactive disease

Table 2 Publications on exercise and exercise tolerance in patients with juvenile dermatomyositis

Study (design)	Patients/healthy subjects	Disease activity	Exercise type	Outcomes	Results
Omori et al. [42•] (case report)	1/1	Chronic	Resistance training	VO _{2max} MMT	+
Maillard et al. [43] (controlled study)	20/20	Chronic/active	Single-bout resistance training	CPK Handheld dynamometer PAG disease activity MRI	0 0 0 0
Hicks et al. [18] (controlled study)	14/14	Chronic/low–moderate	–	CPK, LDH VO _{2peak} W _{peak}	0 Patients have reduced VO _{2peak} and W _{peak} compared with healthy individuals
Drinkard et al. [17]	12/14	Chronic	–	Peak heart rate VO _{2peak} AT, RER _{peak} ΔVO ₂ /ΔW	Patients have lower peak heart rate, VO _{2peak} , AT, and ΔVO ₂ /ΔW than healthy individuals
Takken et al. [44] (controlled study)	13	Active/remission	–	VO _{2peak} W _{peak}	Patients with active disease have reduced VO _{2peak} and W _{peak} compared with patients in remission.
Takken et al. [45]	15	Active/remission	–	VO _{2peak} Relative VO _{2peak} Exercise time (treadmill)	Children with dermatomyositis had significantly reduced VO _{2peak} , relative VO _{2peak} , and exercise time compared with reference values from healthy individuals
Takken et al. [46]	16	Chronic	–	WAnT VO _{2peak} W _{peak} (stationary bike)	Acceptable reliability for the WAnT and very good reliability for the aerobic exercise test

ΔVO₂/ΔW slope of oxygen uptake/power relationship; AT anaerobic threshold; CPK creatine phosphokinase; LDH lactate dehydrogenase; MMT manual muscle test; PAG physician's global assessment; RER_{peak} peak respiratory exchange ratio; VO_{2max}/VO_{2peak} maximal/peak oxygen uptake; WAnT Wingate anaerobic exercise test; W_{peak} peak watt; + = improvement, 0 = no change, – = worsening

[43]. Takken et al. [44] have published studies aiming to evaluate the validity and feasibility of maximal exercise tolerance tests in juvenile dermatomyositis. A maximal stationary bike test was well-tolerated by children with inflammatory inactive as well as active disease [44]. Furthermore, a maximal aerobic test on a treadmill and an all-out anaerobic stationary cycle test were also found to be safe and feasible for juvenile dermatomyositis patients [45, 46]. Children with juvenile idiopathic arthritis have been found to be less physically active than their peers, which also might be the case with children with juvenile dermatomyositis. Considering that children with arthritis respond well to adapted resistance training and aerobic exercise [47], and the available case reports and exercise tolerance studies in dermatomyositis show encouraging results (Table 2), a great need exists for well-designed studies in patients with various disease activity to improve our knowledge on how to prescribe individualized exercise therapy for juvenile dermatomyositis patients.

Conclusions

Recent studies support the safety and efficacy of resistance training and aerobic exercise in patients with adult polymyositis and dermatomyositis. There are encouraging data to support the idea that resistance exercise could improve muscle strength even in the most affected muscle groups in patients with inclusion body myositis and also reduce disease activity in chronic polymyositis and dermatomyositis patients. Most of these studies are small and open label, and large, randomized controlled trials through international collaboration are needed to confirm these results. Also, for patients with juvenile dermatomyositis, a need exists for collaborative studies to evaluate the safety and efficacy of resistance exercise. In conclusion, there are data to support the idea that adaptive exercise could be recommended in combination with medical treatment for patients with adult polymyositis and dermatomyositis.

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