Exercise as a therapeutic modality in patients with idiopathic inflammatory myopathies

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Purpose of review
To present scientific evidence on clinical and molecular effects of exercise in adult and juvenile idiopathic inflammatory myopathies focusing on recent studies.

Recent findings
In patients with inclusion body myositis (IBM), one small, open study recently for the first time reported on improved muscle strength and functional capacity after a twice-a-day home exercise programme, whereas earlier studies have not been able to show any or only small improvements, mainly in less-affected muscle groups. For patients with polymyositis and dermatomyositis a few studies have reported reduced clinical disease activity after resistance training in patients with chronic phase of disease. These observations are supported by downregulation of genes regulating inflammation and fibrosis in muscle tissue following this type of training. These results may indicate that resistance exercise might reduce muscle inflammation in adult polymyositis and dermatomyositis. A first case report has described safety and benefits of an exercise programme in a child with dermatomyositis, and a few studies support the safety of single exercise bouts or exercise tolerance tests in juvenile dermatomyositis.

Summary
Accumulated evidence supports safety and efficacy of exercise in polymyositis and dermatomyositis, although data are more inconclusive for efficacy in patients with IBM. There is a need for larger studies to further ensure efficacy in IBM and juvenile dermatomyositis.

Keywords
aerobic exercise, dermatomyositis, inflammatory response, polymyositis, resistance training

INTRODUCTION

The adult idiopathic inflammatory myopathies are divided into polymyositis, dermatomyositis and sporadic inclusion body myositis (IBM). Polymyositis and dermatomyositis are rare conditions with reduced muscle function, general fatigue and interstitial lung disease [1]. Muscle weakness is most prominent in proximal muscles in patients with polymyositis or dermatomyositis [2]. However, a recent study reported approximately 50% of grip strength compared with reference values [3], and impairment of distal lower limb muscles was evident when using the muscle endurance measure Functional Index 2 [4] in patients with polymyositis or dermatomyositis suggesting involvement also in distal muscle groups in these conditions. Aerobic capacity is low in these patients compared with healthy individuals [5]. Patients with chronic polymyositis and dermatomyositis identified sexual activity, walking and bicycling, sleep and social activities as limited and most important to improve [6]. In addition, degree of activity limitation seemed to be associated to disease duration and higher glucocorticoid doses [7], and reduced quality of life (QoL) is reported from patients with polymyositis and dermatomyositis [8]. Thus, there is a clear need for improved treatment, and the role of exercise as treatment will be further discussed below.

Sporadic IBM is also a rare condition, but the most common acquired muscle disease in adults affecting individuals over 50 years of age [9] with progressing muscle weakness and muscle atrophy

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KEY POINTS

- Moderate-to-intensive resistance and aerobic exercise is well tolerated, reducing disability in adult chronic, low-active myositis.
- Easy-to-moderate resistive exercise is well tolerated in patients with active, recent-onset disease.
- Encouraging results of improvement by resistance and aerobic exercise in inclusion body myositis need to be confirmed in larger studies.
- Data suggesting that intensive exercise can reduce inflammation in polymyositis and dermatomyositis need confirmation in larger studies.
- Today, there is limited experience of exercise in juvenile dermatomyositis.

mainly in the quadriceps and in distal muscle groups of upper and lower extremities. These patients respond poorly to medical treatment and develop severe muscle weakness over decades; however, degree of progression seems to vary between individuals [10]. Patients with IBM also have low QoL compared with population-based reference values regarding physical functioning, role physical, general health and social functioning [11].

Juvenile dermatomyositis affects 2–3 million children per year. The most prominent symptoms are characteristic skin rash and proximal muscle weakness. Systemic disease with fever and weight loss is very common, and involvement of vessels, joints, lungs and heart may also occur [12]. 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 still developing sustained functional limitation [13]. These patients also have reduced maximal oxygen uptake (VO_{2max}) compared with healthy children [14,15] and with children with juvenile dermatomyositis in remission [16].

RESISTANCE TRAINING

Up to the recent decades, patients with inflammatory myopathies were refrained from active exercise because of fear of increased muscle inflammation. The first case studies [17,18] reporting safety of exercise were published in 1993. A few years later, we reported beneficial effects of a 5-days-a-week for 12-week resistance home exercise programme [19]. Patients with chronic, stable polymyositis and dermatomyositis improved significantly by 17% in repetitive muscle performance with improved perceived health without signs of increased inflammation in serum, muscle biopsies or magnetic resonance imaging [19]. Eleven patients with recent-onset, active polymyositis and dermatomyositis performed the same resistance home exercise programme, and improved repetitive muscle function significantly by 18% and improved perceived health, without signs of increased inflammation [20]. A 3-week exercise and spa regimen was also well tolerated with unchanged serum creatine phosphokinase (CPK) levels and with improved isometric strength by 17–37% and 34–46% by 10 patients with active disease and 11 patients with chronic disease, respectively [21]. Significant improvements by 11% were achieved in another 3-week muscle and range of motion exercise study [22]. The so far largest randomized controlled exercise trial in myositis concluded that the 5-days-a-week resistance home exercise programme in combination with creatine supplements was well tolerated and more effective to improve physical capacity and muscle function than exercise alone [23]. All patients exercised for 5 months and the creatine group ingested a loading dose of 8 g/day and a maintenance dose of 3 g/day, whereas the control group received placebo. The creatine group had higher levels of phosphocreatine in thigh muscles assessed by magnetic resonance spectroscopy at the end of the study. In a repeated measure design study [24] including eight patients with chronic, inactive polymyositis and dermatomyositis, the participants performed an intensive resistance training programme 3 days a week for 7 weeks on a load of 10 voluntary repetition maximum (VRM). The group improved by 20–900% in 10 VRM in four out of five muscle groups and also by 29–49% in muscle endurance in shoulder flexion. The group also improved significantly in the disease activity score Myositis Intention to Treat Index, and two patients were responders with reduced disease activity according the International Myositis Assessment and Clinical Studies response criteria [25]. All exercise studies for adults are summarized in Table 1 [17–24,26–28,29▪,30–32,33▪].

Until recently, there were only two open studies investigating the safety and effects of exercise in patients with IBM. One of these studies [26] reported improvements in mainly less-affected muscle groups by resistance training 3 days a week for 12 weeks with unchanged serum CPK levels. The other study [27] was not able to detect any improvements in muscle function following above-mentioned 5-days-a-week resistance home exercise programme but supported the safety of exercise with unchanged serum CPK levels and no signs of increased inflammation in repeated muscle biopsies [27]. Since then, a few case studies and open studies

Table 1. Published exercise studies in adult patients with inflammatory myopathies

Study/design	Patients (*n*)	Diagnosis	Disease activity	Exercise/ duration	Load/intensity % of max	Outcome benefits	Results benefits	Outcome safety	Results safety
Resistance training,									
Hicks *et al.* [18], (case report, controlled)	1	Polymyositis	Chronic	Isometric, 6 weeks	60	Isometric PT	+	CPK	0
Escalante *et al.* [17] (open study)	5	Polymyositis/ dermatomyositis	Active	Dynamic, ROM/8 weeks	Not registered	Isometric PT	+	CPK	0
Spector *et al.* [26] (open study)	5	IBM	Chronic	Dynamic/ 12 weeks	50–70	Isometric PT 3 VRM	0 +	CPK Biopsy	0 0
Alexanderson *et al.* [19] (open study)	10	Polymyositis/ dermatomyositis	Chronic	Dynamic/ 12 weeks	Not registered	M. endurance QoL	+ +	CPK Biopsy MRI	0 0 0
Alexanderson *et al.* [20] (open study)	11	Polymyositis/ dermatomyositis	Active	Dynamic/ 12 weeks	Not registered	M. endurance QoL	+ +	CPK Biopsy MRI	0 0 0
Heikkilä *et al.* [22] (open study)	22	Polymyositis/ dermatomyositis/ IBM	Chronic	Dynamic/ 3 weeks	Not registered	M. endurance Activity limit.	+ 0	CPK	0
Arnardottir *et al.* [27] (open study)	7	IBM	Chronic	Dynamic/ 12 weeks	Not registered	Isometric PT M. endurance	0 0	CPK Biopsy	0 0
Varjú *et al.* [21] (open study)	19	Polymyositis/ dermatomyositis	Chronic/active	Dynamic/ 3 weeks	Not registered	Isometric PT FVC Activity limit.	+ + +	CPK	0
Harris-Love [28] (case report, controlled)	1	Polymyositis/IBM?	Chronic	Eccentric/ 12 weeks	70	Isometric PT	+	CPK Pain ROM	0 0 0
Alexanderson *et al.* [24] (open study, repeated measure)	8	Polymyositis/ dermatomyositis	Chronic	Dynamic/ 7 weeks	70	5 VRM M. endurance Activity limit	+ + 0 (+/–)[a]	CPK Biopsy 6-item Core set	0 0 +
Chung *et al.* [23] (RCT, double-blinded)	37	Polymyositis/ dermatomyositis	Chronic	Dynamic/ 20 weeks	Not registered	Funct. capac. M. endurance M strength QoL Anxiety/depression	+ + + 0 0	CPK MRS Pain	0 + 0
Johnson *et al.* [30] (open study)	7	IBM	Chronic	Dynamic/ 16 weeks	Not registered	M. strength Funct.capac.	+ +	CPK Soreness	0 0
Gualano *et al.* [29▪] (case report)	1	IBM	Chronic	Dynamic/ vascular occlusion	60–70	M. strength Balance QoL Thigh cross-sectional area	+ + + +	Biopsy	0
Aerobic exercise									
Wiesinger *et al.* [31] (RCT)	14	Polymyositis/ dermatomyositis	Chronic	6 weeks	60	VO_{2peak} Isometric PT Activity lim.	+ + +	CPK	0
Wiesinger *et al.* [32] (controlled study)	13	Polymyositis/ dermatomyositis	Chronic	24 weeks	60	VO_{2peak} Isometric PT Activity lim.	+ + +	CPK	0
Johnson *et al.* [33▪] (open study)	7	IBM	Chronic	12 weeks	80	VO_{2max} Funct.capac.	+ 0	CPK	0

CPK, creatine phosphokinase; Funct. capac, functional capacity; IBM, inclusion body myositis; M., muscle; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PT, peak torque; QoL, quality of life; RCT, randomized controlled trial; ROM, range of motion; VO_{2max}, maximal oxygen uptake; VO_{2peak}, peak oxygen uptake; VRM, voluntary repetition maximum.

have reported encouraging results with improved muscle function also in more affected muscle groups. One of these case studies [28] presented the story of an idividual with unsure diagnosis. According to muscle biopsies, the patient had polymyositis, but considering the lack of treatment response, it could not be ruled out that the patient had IBM. This patient had reached a plateau of muscle function with regular strength training and home exercise but improved 40–50% in isometric quadriceps strength with 12 weeks of submaximal eccentric training in a Biodex (Biodex Medical Systems, Shirley, NY) of the right leg compared with the untrained left leg, without elevated serum CPK levels, increased muscle stiffness or pain. Another case report [29▪] described a human with IBM with slowly deteriorating muscle strength despite regular training for at least a year. Never-elevated serum CPK levels, the absence of myalgia or muscle tenderness with reoccurring falls confirmed the diagnosis of IBM. After 12 weeks of submaximal resistance training on the load of 15 VRM $\times$ 3 in leg press knee extension and squat exercises during vascular occlusion of the thighs, the patient improved by about 16% in one VRM leg press knee extension. The Timed-up and Go test improved by 60% and the thigh cross-sectional area improved by 4.7% [29▪]. Markers of inflammation such as erythrocyte sedimentation rate, C-reactive protein (CRP) and serum CPK levels remained unchanged during the exercise period, and the patient never reported excessive exhaustion, pain, joint injury or muscle soreness. Muscle biopsies taken from the right vastus lateralis before and after exercise were without signs of increased inflammation. A 16-week, twice-a-day home exercise programme was evaluated in an open study [30] reporting improved muscle strength and physical capacity in seven patients with definite IBM. They had between 4 and 17-year disease duration, and all patients experienced a steady decline in muscle strength and functional ability prior to starting the exercise programme. The home exercises contained sit-to-stand exercises, biceps curls, shoulder press and finger and wrist flexors with free weights, seated rowing with Theraband (Theraband, System of Pregressive Exercise, The Hygenic Corp, OH) for the upper extremities and calf raises, isometric vastus medialis exercises and ankle dorsi flexion for the lower extremities. All patients filled out an exercise diary including exercise performance and rating-perceived degree of fatigue, soreness and breathlessness. The group improved in isometric muscle strength between 23–171% in all tested muscle groups assessed by handheld myometer. Hip flexors improved the most followed by elbow extensors and knee flexors. Interestingly, also the most-affected muscle groups such as knee extensors and finger flexors improved statistically significant by about 28 and 48%, respectively. The group also improved by about 17% in the mean time required to walk 30 m and reduced the time required to climb one flight of stairs by about 21%, which were statistically significant changes. Furthermore, three patients improved slightly in sit-to-stand ability, whereas two patients remained unchanged and one experienced a slight decline. The exercise programme was well tolerated with an adherence of 90–95%, and only two patients reported short-term muscle soreness without increased serum CPK levels. There is a need for larger randomized controlled trials (RCTs) to confirm the efficacy of these new training protocols that have reported positive effects in IBM: twice-a-day home exercise, eccentric exercise and submaximal exercise during vascular occlusion. Such studies could be conducted in a multicenter design through international collaboration.

AEROBIC EXERCISE

Intensive aerobic exercise in patients with polymyositis or dermatomyositis has been proven well tolerated and effective to improve aerobic capacity and muscle strength in a 6-week small randomized controlled study [31], and long-term effectiveness, 6-months, of this exercise programme was confirmed in a controlled study [32]. Aerobic capacity has been less investigated in patients with IBM, and today, there are no data on aerobic capacity in patients compared with healthy individuals; however, as these patients experience increasing disability with difficulties to perform aerobic activities, it is reasonable to hypothesize that these patients have a reduced aerobic capacity. A recent open study [33▪] was able to show improved aerobic capacity and muscle strength in patients with IBM from a 12-week training programme. This study included seven patients with disease duration of 5–9 years all experiencing long-term decline of muscle strength and functional performance. The exercise programme consisted of stationary cycle home exercise on 80% of initial maximal heart rate three times per week in combination with the home exercise programme previously described [30] performed in two sets 3 days per week, never-performing aerobic and muscle exercise on the same day. The group improved significantly in aerobic capacity (l/min) by 33%, and muscle strength assessed by handheld myometer improved in some of the tested muscle groups, shoulder abduction, hip flexion and abduction and knee flexion, whereas there was no improvement in ability to walk or to climb stairs.

Notably, this 12-week aerobic/resistance training programme performed once a day did not result in improved strength in knee extensors, finger flexors or functional capacity as opposed to the results from the 16-week twice-a-day resistance home exercise described above. The authors do not discuss this discrepancy, but it could be hypothesized that the differences in exercise period, exercise frequency or different levels of disability in the small groups of patients included could be contributing factors. Furthermore, it might be more important for these patients to primarily improve strength and the ability to walk or climb stairs, which could lead to increased physical activity with positive effects on aerobic capacity, which should be taken into consideration when designing future training programmes of these patients.

EXERCISE IN JUVENILE DERMATOMYOSITIS

Recently, a first case report was published describing the effects of an exercise programme in a patient with juvenile dermatomyositis. A 1-h exercise programme with aerobic exercise and resistance training on about 70% of maximal effort, performed twice a week for 16 weeks was well tolerated by a child with chronic, inactive juvenile dermatomyositis, and the child improved in both muscle function and aerobic capacity [34▪]. Another study [35] concluded that a single resistance exercise session on about 60% of maximum does not produce increased inflammation or reduced muscle function in patients with active as well as chronic, inactive juvenile dermatomyositis. Further, a maximal cycle test was well tolerated by children with both active and chronic disease [16], and both a maximal aerobic test on a treadmill [36] and an anaerobic all-out cycle test [37] were found well tolerated and feasible in patients with juvenile dermatomyositis. A summary of studies in juvenile dermatomyositis is summarized in Table 2 [15,16,34▪,35–37].

MOLECULAR EFFECTS OF EXERCISE

That exercise may have beneficial effects on inflammation stems from observations in healthy individuals. As one example, physically active individuals have lower levels of markers for systemic inflammation such as CRP and interleukin-6 than non-physically active individuals [38]. Furthermore, there was a dose-dependent relationship with lower levels in those that were more physically active [38]. Also, in patients with chronic inflammatory diseases such as rheumatoid arthritis and chronic obstructive lung disease, physical exercise or regular physical

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

Study/design	Patients/healthy individuals	Disease activity	Outcomes	Results
Omori *et al.* [34▪] (case report)	1/1	Chronic	VO_{2max} MMT CPK	+ + 0
Maillard *et al.* [35] (single exercise bout)	20/20	Chronic/active	Handheld dynamometer PAG disease activity (VAS) MRI CPK LDH	0 0 0 0 0
Hicks *et al.* [15] (controlled study)	14/14	Chronic, low-moderate	VO_{2peak} W_{peak}	Patients have reduced VO_{2peak} and W_{peak} compared with healthy individuals
Takken *et al.* [16] (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.* [36]	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.* [37]	16	Chronic	WAnT VO_{2peak} W_{peak} (stationary bike)	Acceptable reliability for the WAnT test and very good reliability for the aerobic exercise test

CPK, Creatine phosphokinase; LDH, lactate dehydrogenase; MMT, manual muscle test; MRI, magnetic resonance imaging; PAG, physician's global assessment; VO_{2max}, maximal oxygen uptake; VO_{2peak}, peak oxygen uptake; W_{peak}, peak Watt; WAnT, Wingate anaerobic exercise test.

activity may lower levels of systemic inflammation as summarized by Nader and Lundberg [39]. In another chronic condition such as chronic heart failure, in which subclinical inflammation may be present, exercise training reduced serum levels of tumor necrosis factor, and in men with type 2 diabetes, an exercise-dependent reduction in plasma levels of interleukin-6 was observed.

Information on molecular effects of exercise in patients with polymyositis and dermatomyositis has been gained from investigations of repeated muscle biopsies. From these investigations, it has been demonstrated that patients with chronic polymyositis or dermatomyositis with low degree of inflammation have a low proportion of oxygen-dependent type I fibers compared with healthy individuals, which may contribute to the low muscle endurance experienced by these patients [40]. The mechanism for this fiber-type skewing is not clear but could be a long-term consequence of a chronic inflammatory disease or of long-term glucocorticoid treatment or maybe from low degree of physical activity, as this aberrant fiber-type composition was not present in biopsies taken at the time of myositis diagnosis [41▪▪]. Thus, after the above-described clinically beneficial 5-days-a-week 12-week home exercise programme, a higher frequency of the oxygen-dependent type I fiber was observed. In the above-mentioned 7-week intensive resistance exercise programme in patients with polymyositis and dermatomyositis with low degree of inflammation, training resulted in marked reductions in gene expression reflecting proinflammatory and profibrotic gene networks. These changes were accompanied by a reduction in tissue fibrosis and in collagen I content [42▪▪]. In addition, consistent with the exercise-associated increase in VO_{2max}, a subset of transcripts was associated with a shift toward oxidative metabolism. Thus, resistance exercise training can induce a reduction in inflammation and fibrosis in skeletal muscle.

CONCLUSION

Based on accumulated evidence, we believe that adapted exercise is well tolerated and effective in adult chronic polymyositis and dermatomyositis, although we need to understand more on effects of exercise in active, recent-onset disease. Furthermore, we need to increase knowledge of mechanisms contributing to muscle weakness to be able to improve treatment. Most exercise studies have included patients that are responders to medical treatment, and our clinical experience indicates that response to exercise is lower, or even lacking altogether, in patients who do not respond or tolerate immunosuppressive treatments. The encouraging data on exercise response in IBM need to be confirmed in larger multicenter RCTs. Our own clinical experience of the twice-a-day 16-week home exercise programme in IBM suggests that patients find it challenging to sustain adherence despite interim follow-up and exercise diary. Exercise research in rheumatoid arthritis focuses on strategies to sustain regular physical activity and exercise. Future research needs to focus on obstacles for maintenance of physical activity and exercise, also in patients with inflammatory myopathies. There are ongoing efforts to evaluate effects of exercise in patients with juvenile dermatomyositis, which could improve the clinical care, also for these patients.

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REFERENCES AND RECOMMENDED READING

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- ▪ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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