Published in final edited form as:

Curr Rheumatol Rep. 2014 July ; 16(7): 429. doi:10.1007/s11926-014-0429-4.

New Insights into the Benefits of Exercise for Muscle Health in Patients with Idiopathic Inflammatory Myositis

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Abstract

With recommended treatment, a majority with idiopathic inflammatory myopathy (IIM) develop muscle impairment and poor health. Beneficial effects of exercise have been reported on muscle performance, aerobic capacity and health in chronic polymyositis and dermatomyositis and to some extent in active disease and inclusion body myositis (IBM). Importantly, randomized controlled trials (RCTs) indicate that improved health and decreased clinical disease activity could be mediated through increased aerobic capacity. Recently, reports seeking mechanisms underlying effects of exercise in skeletal muscle indicate increased aerobic capacity (i.e. increased mitochondrial capacity and capillary density, reduced lactate levels), activation of genes in aerobic phenotype and muscle growth programs, and down regulation in genes related to inflammation. Altogether, exercise contributes to both systemic and within-muscle adaptations demonstrating that exercise is fundamental to improve muscle performance and health in IIM. There is a need for RCTs to study effects of exercise in active disease and IBM.

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Conflict of Interest Li Alemo Munters, Helene Alexanderson, and Ingrid E. Lundberg declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Compliance with Ethics Guidelines

Leslie J. Crofford wishes to acknowledge that her contribution to this paper is supported in part by NIH AR R01AR06083.

Keywords

Idiopathic inflammatory myopathies; Polymyositis; Dermatomyositis; Inclusion body myositis; Aerobic capacity; Aerobic metabolism; Exercise adaptations

Introduction

Muscle inflammation, muscle weakness and low muscle endurance are predominant features in patients with idiopathic inflammatory myopathy (IIM) [1, 2]. Adult IIM consist of polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM). In PM and DM especially, the proximal muscles are affected and interstitial lung disease (ILD) is common [3]. In the early phase of PM/DM before treatment, disease activity is generally high as measured by markedly elevated levels of creatine phosphokinase (CK) and typical inflammatory cell infiltrates in skeletal muscle. After the introduction of high-dose oral glucocorticoids and other immunosuppressive agents, most patients respond with less inflammatory manifestations from skeletal muscle and improved muscle performance. However, few regain their previous muscle function [4, 5]. Furthermore, a majority of patients also develop poorer health compared to the general population [6–10]. Patients with IBM have predominantly distal muscle weakness and are refractory to known pharmacological treatment, thus presenting with a progression of muscle weakness and disability and a majority of patients have lost independent walking ability after seven years of disease duration [11–13]. The lack of treatment effects and pathologic findings indicate that IBM may be a degenerative disorder rather than only an inflammatory disease [11, 14]. These patients also perceive poorer health than the general population [15].

Mechanisms causing impaired muscle performance in IIM

In the acute phase, systemic and local inflammation in skeletal muscle is a probable mechanism leading to impaired muscle performance in patients with PM/DM. However, the mechanisms causing the sustained muscle impairment in patients with established disease without obvious inflammation or muscle fiber atrophy are more uncertain. Secondary damage by the earlier inflammatory milieu, side effects of pharmacological treatment, and/or physical inactivity are hypothesized as contributing factors [4, 16–19]. Impaired skeletal muscle performance is not directly correlated to the immunological findings, which suggests the presence of non-immune mechanisms, such as endoplasmic reticulum (ER) stress, hypoxia, and autophagy [20, 21, 4]. Furthermore, muscle fiber degeneration, skeletal muscle atrophy, and failed muscle regeneration in patients with PM/DM may also explain the sustained muscle weakness [22].

In addition, secondary aerobic metabolic dysfunction in skeletal muscle induced by the pro-inflammatory environment causing hypoxia in skeletal muscle has been suggested to impair muscle function in chronic PM and DM [4, 23, 17]. Metabolic dysfunction that results in a compromised aerobic metabolism adversely affects intrinsic muscle functions and results in premature muscle fatigue [24]. Both mitochondrial and capillary functionality are a prerequisite for aerobic metabolic capacity within skeletal muscle and are directly related to endurance exercise performance [25–28]. Several signs of metabolic dysfunctions have been

recorded in patients with established PM and DM, including low levels of stored phosphocreatine and ATP in muscle tissue with decreased fatigue resistance and with fewer aerobic slow-twitch type I muscle fibers [29–32]. Abnormalities in the aerobic energy metabolism found in patients with PM/DM include mitochondrial and capillary pathology [33–37]. In two recent studies, lactate was measured after physical exercise. In one study, lactate concentrations in skeletal muscle were measured after a cycling test consisting of cycling to exhaustion at a power requiring 65 % of their individual $\text{VO}_{2\text{ max}}$ in patients with chronic PM/DM compared to healthy controls (HC) [38••]. The lactate concentration was used as a marker of anaerobic metabolism required and was similar in patients and HC, despite the fact that HC cycled for doubled the time and at 35 % higher absolute power outputs [38••]. In the other study, a fixed incremental submaximal aerobic treadmill test was used and blood lactate was assessed in PM/DM patients in both active and chronic disease phase compared to HC [39•]. Patients demonstrated higher blood lactate levels compared to HC despite that they exercised for a shorter time [39•]. Altogether, this indicates that altered aerobic metabolism capacity in skeletal muscle could contribute to the sustained muscle impairment, early onset fatigability, and to the low aerobic capacity found in patients with PM/DM [40, 38••, 39•]. Furthermore, Someya et al. evaluated exercise performance in patients with DM and ILD without clinical muscle weakness, suggesting that exercise performance is not limited by impaired lung function but rather by a muscle impairment even if it is asymptomatic [41].

In IBM, the pathophysiology is more uncertain, but both autoimmune and degenerative pathways seem to contribute to muscle damage [11, 14]. Cytotoxic-restricted T cells surround and destroy non-necrotic muscle fibers in IBM. Rimmed vacuoles are regularly present and are thought to contribute to myonuclear breakdown. Also, findings of several toxic aggregated proteins in skeletal muscle have been reported and are likely involved in IBM pathophysiology suggesting a protein homeostasis disorder. Recently, identification of autoantibodies against skeletal muscle IBM antigens has been reported. These autoantibodies may suggest a link between autoimmunity and degenerative features of IBM and also abnormal nucleic acid metabolism, contributing to muscle fiber damage in these patients. Magnetic resonance imaging (MRI) studies display abnormalities with fatty replacement of muscle tissue in IBM [12]. Several mechanisms are probably involved contributing to the impaired muscle performance found in patients with IBM.

Physical exercise in IIM

A physically active lifestyle is fundamental to maintain health. Nevertheless, patients with PM, DM, or IBM were previously discouraged from participating in physical exercise due to a fear that exercise would aggravate muscle inflammation and, thereby, muscle weakness. Several studies have suggested safety and benefits of supervised exercise for patients with adult IIM in an established and stable disease phase [42, 43] and to some extent in an acute disease phase [44–46] and in IBM [42, 11]. Physical exercise can also potentially prevent muscle atrophy caused by muscle inflammation, physical inactivity, and systemic glucocorticoid treatment [17]. However, a need for randomized controlled trial (RCT) designed studies has been suggested to validate the effects of exercise in IIM [43, 42],

especially in active PM/DM and in IBM. Furthermore, there is a need to more specifically evaluate the mechanisms underlying the beneficial effects of exercise in IIM [47].

Systemic and within-skeletal muscle adaptations to repetitive bouts of muscle contractions depend on its frequency, intensity, and duration. Aerobic exercise in healthy individuals improves aerobic capacity both systemically (whole-body aerobic capacity, $\text{VO}_2 \text{ max}$) and locally in the skeletal muscle mainly by improved capillarity and mitochondrial function. Resistance exercise, on the other hand, leads to muscle hypertrophy and increased muscle strength. Furthermore, physical exercise is suggested to have a down-regulating effect on systemic and local inflammation in muscle tissue in patients with PM and DM [17]. This review is focused on the recent advances in evaluating the effects of exercise and more specifically to evaluate the mechanisms underlying the beneficial effects on health by exercise, and the potential disease modifying effects suggested in adult IIM [48].

All together eight articles have recently been published evaluating the effects of physical exercise in patients with adult IIM (presented in Tables 1, 2, 3). Three of them include PM/DM patients in an active disease phase, four have RCT or controlled study designs and two have evaluated long-term effects. The exercise programs consisted of supervised endurance/aerobic exercise in seven cases where two also included strengthening exercise, while only one study consisted of resistive home exercise. However, there is to our knowledge no newly published studies evaluating the effects of exercise in IBM (a review by Alexanderson and Lundberg report the effects of exercise in IBM) [42].

Effects of physical exercise on muscle performance and health

Five studies including patients in a chronic disease phase of PM or DM demonstrated improved muscle performance by endurance or aerobic exercise (Table 1). In the two multicenter RCTs, and in the controlled designed study, both muscle strength [assessed by five voluntary repetition maximum (5VRM) in knee extensor muscles] and cycling time to exhaustion on a power of 65 % of maximal oxygen uptake ($\text{VO}_{2 \text{ max}}$) were significantly improved in the exercise groups (EG), while the non-exercising control group was unchanged [49••, 38••, 50•]. The patients in the exercise groups in these three studies participated in the same supervised endurance exercise 3 times per week for 12 weeks. The training consisted of a 1-h exercise program of cycling at 70 % of $\text{VO}_{2 \text{ max}}$ for 30 min. This was followed by 20 min of endurance exercise of knee extensor muscle at about 30–40 % of 1 VRM. The non-exercised control group was kept on unchanged physical activity level during the 12 weeks. This endurance exercise program also resulted in systemic effects such as significantly increased $\text{VO}_{2 \text{ max}}$ and increased cycling power at $\text{VO}_{2 \text{ max}}$ in the exercise group compared to the control group [49••, 38••, 50•] (Table 2). In a case report by Dalise et al., five weeks of supervised aerobic exercise was performed 5 times/week, including 20 min walking on a treadmill on a velocity equivalent of 65–80 % of max predicted heart rate (HR) and 15 min of arm cycloergometer with 35–40 rpm velocity with very low load, resulted in increased muscle strength in 3 out of 4 assessed muscle groups (using one voluntary contraction, 1MVC) and in a 10-m walking test (10MWT) [51]. In an open study by Bertolucci et al., including 4 patients participating in 6 weeks of supervised aerobic exercise 3 times per week including 11 steps of incremental sub-maximal walking on a

treadmill (each step lasted for 2 min with increased inclination degree by 2.5 % per step where the exercise program was stopped if the patient exceeded 75 % of predicted HR) showed improvement in 10MWT in all four patients [39•]. Furthermore, three out of the four patients improved in a 6-min walking test (6MWT), while no change in 6MWT was revealed after 5 weeks of aerobic exercise in the case study [51, 39•] (Table 2).

Two studies evaluated the effect of endurance exercise or aerobic exercise on health in patients with chronic PM/DM (Table 2). In the case study, the patient was improved in the physical domain of the SF-36 [51]. Accordingly, in the multicenter RCT patients in the exercise group, but not in the non-exercised control group, improved in both the SF-36 Physical and Vitality domains after 12 weeks of endurance exercise [49••]. Furthermore, health was closely related to the VO_{2max} indicating that improved health could potentially be mediated through the demonstrated improved VO_{2max} [49••]. The RCT study evaluated long term effects by the 12- week endurance exercise program in a 1-year open extension [49••]. Patients in the exercise group kept their improved muscle performance at the 1-year follow-up, while the control group was unchanged compared to baseline; on the contrary, other disabilities were back to baseline values. These results support the importance of a physically active lifestyle, including endurance exercise, to maintain health in patients with chronic PM/DM.

Three studies include PM/DM patients in an acute disease phase and demonstrated improved muscle performance by physical exercise [52, 53•, 54••] (Table 1). To our knowledge, only one RCT designed study evaluating the effects of exercise in active onset PM/DM has been published [54••]. This RCT evaluated a resistive home exercise program both in a short- and long-term perspective. At the time of diagnosis, patients were introduced to high-dose glucocorticoids together with other immunosuppressive treatment. After 4 weeks of treatment, the exercise group started the resistive home exercise program, exercising proximal muscles against gravity of extra weights allowing 10 repetitions and a 20-min walk on 50–70 % of predicted maximal HR. Patients followed this exercise schedule, also receiving weekly telephone support, 5 days a week for 12 weeks, followed by 12 weeks of non-supervised gym exercise twice a week. The control group performed a range of motion exercise program, without telephone support, 5 days a week for 24 weeks [54••]. Both groups improved significantly in muscle performance assessed by the Functional Index and aerobic capacity assessed by a submaximal treadmill test, while only minor changes were seen regarding health (assessed by the Nottingham Health Profile) at the 24-week follow-up. A 2-year follow-up revealed that a majority of patients in the exercise group maintained a physically active lifestyle with regular exercise, while only two patients in the control group were physically active. Improvements in muscle performance and aerobic capacity were maintained up to 1 year, while only the exercise group maintained within-group improvement up to 2 years. (Tables 1, 2). Effects of supervised aerobic exercise combined with strength training in patients with active PM were assessed in both a case report by Hejazi et al. and a case series study by Mattar et al. [52, 53•] (Tables 1, 2). In the case report, a patient with a disease flare of PM was introduced to pharmacological treatment (prednisolone 50 mg/day and methotrexate 7.5 mg/week) concurrently accompanied by 4 weeks of intensive exercise 5 days per week. The exercise program consisted of strengthening exercise for upper and lower extremities, walking and cycling (for 15–20 min)

and ADL training. The patient improved in muscle strength in 22 out of 36 muscle groups [52]. The case series included three patients with persistent active PM despite pharmacological treatment with glucocorticoids and/or other immunosuppressives. Prior to and during performance of the exercise program, patients were kept on a stable pharmacological treatment. A supervised both aerobic and strengthening exercise program was performed twice a week for 12 weeks and consisted of 40 min strength training [3 sets of 8–12 repetition maximum (RM)] and 40 min of aerobic treadmill walking on an intensity correspondent to the ventilator anaerobic threshold (VAT) to 10 % below the respiratory compensation point. All patients improved in walking time to VAT, one patient improved in one repetition maximum (RM) in all three tested muscle groups, and two patients improved in two out of three muscle groups. Furthermore, two out of three patients increased in $\text{VO}_{2\text{ peak}}$, while all patients improved in health assessed by the SF-36 by the exercise program [53]. Altogether, these results indicate that exercise can be safely used as an adjuvant treatment combined with pharmacological treatment in active PM/DM, suggesting increased beneficial effects on muscle performance and health. Furthermore, early introduced physical exercise seems to facilitate a physically active lifestyle in a long term perspective.

Effects of physical exercise on skeletal muscle

Four studies evaluated the within-muscle adaptations in skeletal muscle by endurance or aerobic exercise in patients with chronic PM/DM [51, 38•, 50•, 39•] (Table 1). All four studies indicate an improvement in aerobic capacity in skeletal muscle by exercise, and these were associated with the beneficial changes demonstrated in muscle performance, systemic adaptations, and health. In the multicenter RCT and controlled study, both by Alemo Munters et al., significantly increased aerobic capacity in the exercise groups after the 12 weeks of supervised endurance exercise was demonstrated, while the non-exercised control groups was unchanged. These changes were revealed by reduction in lactate levels in vastus lateralis muscle, assessed using a microdialysis technique, after cycling to exhaustion at 65 % of $\text{VO}_{2\text{ max}}$ and by increased mitochondrial enzyme activities [citric synthase (CS) and beta-hydroxyacyl-CoA dehydrogenase (β -HAD)] in muscle biopsies from the vastus lateralis muscle [50•, 38•]. Furthermore, in the exploratory controlled designed study, evaluating the same exercise program, resulted in increased capillary density and up-regulation in gene expressions related to capillary growth and mitochondrial biogenesis as well as up-regulation in genes related to muscle hypertrophy, protein syntheses and cytoskeletal remodeling in the exercise group, while the control group demonstrated a non-synchronized regulation of genes [50•]. At follow-up, both the open study and the case report demonstrated reduced blood lactate compared to baseline at recovery after a bout of physical exercise, also indicating increased aerobic capacity within skeletal muscle by aerobic exercise [51, 39•]. These findings indicate that endurance and aerobic exercise in patients with chronic PM/DM are beneficial by a shift to aerobic metabolism within skeletal muscle and by activating aerobic phenotype and muscle growth pathways, which overwrites the muscle atrophy process.

To our knowledge, within-muscle adaptations to physical exercise have not been evaluated in patients with PM/DM in an active disease phase.

Effects of physical exercise on disease activity

Three studies evaluated the effects of the same program of supervised endurance exercise, in patients with chronic PM/DM, on clinical disease activity using the recommended International Myositis Association Clinical Studies group (IMACS) 6-item core set, including the patient's and physician's global disease activity rated on a visual analogue scale (VAS), manual muscle test in eight muscle groups (MMT-8), Health Assessment Questionnaire (HAQ), a laboratory assessment of CPK, and the assessment of extra-skeletal muscle disease activity on VAS [55, 5] (Table 3). Two RCTs and one controlled designed study by Alemo Munters et al. reported a reduction in clinical disease activity by exercise according to the IMACS responder criteria as a majority of patients in the exercise group were responders with reduced disease activity, while none or only one patient in the control groups were responders (Table 3) [38•, 49•, 50•]. All patients in the RCT that responded with reduced disease activity by the exercise were also improved in $\text{VO}_{2\text{ max}}$ (with a sensitivity of 70 % and specificity of 100 %) [49•]. Furthermore, a down-regulation of gene expressions associated with inflammation/immune response and ER-stress were reported after 12 weeks of endurance exercise in the exercise group [50•]. Since the patients were in a chronic disease phase, only a few or scattered inflammatory cells were observed in muscle tissue sections at baseline and also after the 12 weeks of endurance exercise. Accordingly, there was no change in the number of CD3+ T cells and CD68+ macrophages after the 12 weeks of endurance exercise in either the exercise group or the control group [50•]. Four studies evaluated the effect of supervised endurance or aerobic exercise on serum creatine phosphokinase levels (CPK) in chronic PM/DM [51, 50•, 49•, 38•]. In three studies, a majority of the patients in the exercise groups had lower CPK levels after compared to before the exercise intervention, which was not the case in the non-exercised control groups and similar results were also seen in a case report [50•, 49•, 38•, 51]. Altogether, these results indicate that supervised endurance exercise decreases clinical disease activity, may reduce CPK, and suppresses genes in the inflammatory response in skeletal muscle. The reduced clinical disease activity may potentially be mediated by increased $\text{VO}_{2\text{ max}}$.

Three studies evaluated the effect on muscle enzymes in serum by supervised combined aerobic and strength exercise in PM/DM patients in an acute disease phase and the effect of resistive home exercise in recent onset acute PM/DM [52, 53•, 54•] (Table 3). In the RCT study in patients with recent onset active PM/DM, effects of exercise was evaluated on disease activity by analysis of serum CPK levels and findings of inflammatory infiltrates in muscle biopsies [54•]. At the time of diagnosis, patients had markedly elevated CPK levels which were to the more part normalized at the time of exercise start. Thereafter, the CPK levels remained low throughout the study for both the exercise group and the control group. Analysis of muscle biopsies revealed less inflammatory infiltrates after 24 weeks compared to baseline in both groups [54•]. In the case series by Mattar et al., two out of three patients had reduced CPK and aldolase levels in serum after the exercise program, while, in the case study, reductions in levels of CPK, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were reported after the exercise intervention [53•, 52]. These results confirm that adding controlled exercise in combination with pharmacological treatment is safe in patients with PM/DM in an acute disease phase.

Altogether, these results may indicate that physical exercise has a potential to reduce disease activity in established PM and DM. More evidence has, at this point, emerged indicating that endurance and aerobic exercise might be more effective to reduce disease activity than strength and resistance training in chronic PM/DM. These findings may implicate that physical exercise potentially could reduce disease activity also in active disease. Overall, we suggest that adapted supervised exercise should be used as a complement to medical treatment in all phases of the disease to maximize muscle performance, aerobic capacity, and health, as well as to minimize the risk of side effects by the glucocorticoid treatment. Furthermore, endurance exercise seems to contribute to improved muscle performance and health and reduced disease activity, potentially also mediated by increased aerobic capacity within skeletal muscle in patients with chronic PM/DM. We suggest that supervised exercise may be more beneficial than home exercise programs, but home exercise with telephone support introduced early in the disease course may be beneficial to facilitate a physically active lifestyle in a long-term perspective. There is still a need for larger RCTs to study the effects of exercise in active PM and DM as well as in IBM.

Conclusions

The recent published controlled and RCT studies verify especially beneficial effects of aerobic/endurance exercise such as improved muscle performance and health in chronic PM/DM. A short-term endurance exercise program has long-term beneficial effects on muscle strength, while the effects reduce over time if subjects stop exercising. Furthermore, physical exercise leads to within-muscle adaptations such as increased aerobic capacity which may be mediated through increased capillary density and mitochondrial capacity. Also, physical exercise seems to reduce clinically assessed disease activity in PM/DM. Accordingly, systemic effects such as increased maximal oxygen uptake seems closely related to reduced disease activity and health, indicating a possible disease modifying effect of physical exercise. A growing body of evidence is emerging regarding safety to exercise in pharmacologically treated active PM/DM. Furthermore, physical exercise seems to have potential beneficial effects such as improve muscle performance, aerobic capacity and health and possibly may decrease disease activity also in active PM/DM. A RCT evaluating effects of exercise in IBM is lacking.

Altogether, endurance and aerobic exercise contributes to both systemic and within-muscle adaptations in chronic PM/DM indicating that supervised physical exercise is fundamental to improve muscle performance and health in IIM. The novel analysis of within-muscle adaptations to endurance exercise adds important understanding of treatment effects and mechanisms involved in the improvement of sustained muscle impairment in pharmacological-treated patients with chronic PM/DM, but remains to be further determined as well as to define the optimal exercise program for both active and chronic IIM patients in future studies.

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•• of major importance

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Table 1

Recent published studies evaluating effects of exercise on muscle performance and with-in muscle adaptations in patients with chronic or active polymyositis (PM) or dermatomyositis (DM)

Study (design)	Disease phase (subjects included, n)	Exercise duration, weeks (times/week)	Type of exercise	Muscle performance	Results (p value)	Effects with-in muscle	Results (p-value)
Dalise (Case report) [51]	Chronic PM (1)	5 (5)	Supervised Aerobic	1MVC in 4 muscles, 10MWT	+3/4 + (NA)	Blood lactate	Reduced at recovery (NA)
Alemo Munters (Multicenter, RCT, long term) [49]	Chronic PM/DM (23) EG, n = 12 CG, n = 11	12 (3), 52 (Open extension)	Supervised, Endurance (EG) Non-interventional (CG)	5 VRM	<i>At 12 w</i> EG: + (<0.05) CG: 0 (NS) <i>At 52 w</i> EG: + (<0.001) CG: 0 (NS)	NA	NA
Alemo Munters (Multicenter, RCT) [38]	Chronic PM/DM (16) EG, n = 9 CG, n = 7	12 (3)	Supervised Endurance (EG) Non-interventional (CG)	Cycling to exhaustion on 65% of VO _{2 max}	EG: + (<0.01) CG: 0 (NS)	Lactate in muscle: CS; β-HAD	EG: Reduced (<0.01); + (<0.001); + (<0.05). CG: 0 in all variables (NS)
Alemo Munters (Controlled) [50]	Chronic PM/DM (15) EG, n = 7 CG, n = 8	12 (3)	Supervised Endurance (EG) Non-interventional (CG)	Cycling to exhaustion on 65% of VO _{2 max}	EG: + (<0.01) CG: 0 (NS)	mRNA gene expression Capillary density	EG: Up-regulation in capillary growth (<0.01); mitochondrial biogenesis (<0.01); muscle hypertrophy (<0.01); CG: Non-synchronized changes. EG: + (<0.05) CG: 0 (NS)
Bertolucci (Open) [39]	Chronic PM (4)	6 (3)	Supervised Aerobic	10MWT	+4/4 (NA)	Blood lactate	4/4 reduced at recovery (NA)
Hejazi (Case report) [52]	Active PM (1)	4 (5)	Supervised Aerobic, Strength	Strength in 36 muscles	+ 22/36 (NA)	NA	NA
Mattar (Case series) [53]	Active PM (3)	12 (2)	Supervised Aerobic, Strength	Time to VAT, Strength in 2 muscles/person	+ 3/3 +4/6 (NA)	NA	NA
Alexanderson (RCT, long term) [54]	Active PM/DM (19) EG, n = 10 CG, n = 9	12 (5) + 12 (2), 104 (Open extension)	Home exercise: Resistive (EG) ROM (CG)	Functional Index	<i>At 24 w</i> EG: + (<0.001) CG: + (<0.001) <i>At 104 w</i> EG: + (<0.05) CG: 0 (NS)	NA	NA

PM Polymyositis; *DM* Dermatomyositis; *RCT* Randomized controlled trial; *EG* Exercise group; *CG* Control group; *NS* Non-significant; *10MWT* 10 Meters Walking Test; *5VBM* 5 Voluntary Repetition Maximum; + improved; 0 unchanged; – worsen; *NA*; not assessed; *VO₂ max* maximal oxygen up-take; mitochondrial enzymes *CS* citric synthase; β -HAD beta-hydroxyacyl-CoA dehydrogenase; *VAT* ventilator anaerobic threshold; *ROM* Range Of Motion

Recent published studies evaluating effects of exercise on whole body systemic effects and health in patients with polymyositis (PM) or dermatomyositis (DM)

Table 2

Study (design)	Disease phase (subjects included, n)	Exercise duration weeks (times/week)	Type of exercise	Systemic effects	Results (p value)	Health	Results (p value)
Dalise (Case report) [51]	Chronic PM (1)	5 (5)	Supervised Aerobic	6MWT	0 (NA)	SF-36	Physical +, Mental 0 (NA)
Alemo Munters (Multicenter, RCT, long term) [49]	Chronic PM/DM (23) EG, n = 12 CG, n = 11	12 (3), 52 (Open extension)	Supervised, Endurance (EG) Non-interventional (CG)	VO ₂ max At 52 w NA	EG: + (<0.01) CG: 0 (NS)	SF-36	At 12 w EG: Physical + (<0.001); General Health + (<0.01); Vitality + (<0.01); Mental Health + (<0.05) CG: 0 (NS) At 52 w EG: General Health + (<0.05) CG: Mental Health + (<0.05)
Alemo Munters (Multicenter, RCT) [38]	Chronic PM/DM (16) EG, n = 9 CG, n = 7	12 (3)	Supervised, Endurance (EG) Non-interventional (CG)	VO ₂ max Power at VO ₂ max	EG: + (<0.01) CG: - (p<0.05) EG: + (<0.001) CG: 0 (NS)	NA	NA
Alemo Munters (Controlled) [50]	Chronic PM/DM (15) EG, n = 7 CG, n = 8	12 (3)	Supervised, Endurance (EG) Non-interventional (CG)	VO ₂ max	EG: + (<0.05) CG: 0 (NS)	NA	NA
Bertolucci (Open) [39]	Chronic PM (4)	6 (3)	Supervised Aerobic	6MWT	+3/4 (NS)	NA	NA
Mattar (Case series) [53]	Active PM (3)	12 (2)	Supervised Aerobic, Strength	VO ₂ peak	+2/3 (NA)	SF-36	+3/3 (NA)
Alexanderson (RCT, long term) [54]	Active PM/DM (19) EG, n = 10 CG, n = 9	12 (5) + 12 (2), 104 (Open extension)	Home exercise: Resistive (EG) ROM (CG)	Aerobic capacity	At 24 w EG + (<0.001) CG + (<0.001) At 104 w EG: + (<0.05) CG: 0 (NS)	NHP	At 24 w EG: Energy + (<0.05) CG: Sleep + (<0.05) At 104 w EG: 0 (NS) CG: 0 (NS)

PM Polymyositis; DM Dermatomyositis; RCT Randomized controlled trial; EG Exercise group; CG Control group; NS Non-significant; + improved; 0 unchanged; - worsen or reduced; NA: not assessed; VO₂ max maximal oxygen up-take; VO₂ peak peak value oxygen up-take; ROM Range Of Motion; 6MWT 6 Minutes Walking Test; SF-36; Short form 36 questions; NHP Nottingham Health Profile

Table 3

Recent published studies evaluating effects of exercise on clinical disease activity, disease activity/inflammatory characteristics within muscle in patients with chronic or active polymyositis (PM) or dermatomyositis (DM)

Study (design)	Disease phase (subjects included, n)	Exercise duration (weeks, times/week),	Type of exercise	Clinical disease activity	Results (p-value)	Muscle characteristics	Results (p value)
Dalise (Case report) [51]	Chronic PM (1)	5 (5)	Supervised Aerobic	NA	NA	CPK	Reduced (NA)
Alemo Munters (Multicenter, RCT, long term) [49]	Chronic PM/DM (23) EG, n = 12 CG, n = 11	12 (3), 52 (open extension)	Supervised, Endurance (EG) Non-interventional (CG)	IMACS core set At 52 w NA	At 12 w EG: 7/11 reduced (<0.01) CG: 0/10 reduce	CPK At 52 w NA	EG: 6/11 reduced (NA) CG: NA
Alemo Munters (Multicenter, RCT) [38]	Chronic PM/DM (16) EG, n = 9 CG, n = 7	12 (3)	Supervised, Endurance (EG) Non-interventional (CG)	IMACS core set	EG: 6/9 reduced (NA) CG: 1/6 reduced (NA)	CPK	EG: 5/8 reduced (NA) CG: 3/6 reduced (NA)
Alemo Munters (Controlled) [50]	Chronic PM/DM (15) EG, n = 7 CG, n = 8	12 (3)	Supervised, Endurance (EG) Non-interventional (CG)	IMACS core set	EG: 5/6 reduced (<0.05) CG: 1/7 reduced (NA)	mRNA gene expression Expression of inflammatory cells	EG: Down-regulation in immune response/inflammation ; ER-stress (<0.01) CG: Up-regulation in type 1 interferon, apoptosis EG and CG: 0 (NS)
Hejazi (Case report) [52]	Active PM (1)	4 (5)	Supervised Aerobic, Strength	NA	NA	CPK ESR CRP AST ALT	Reduced in all variables (NA)
Mattar (Case series) [53]	Active PM (3)	12 (2)	Supervised Aerobic, Strength	NA	NA	CPK Aldolase	2/3 reduced in both (NA)
Alexanderson (RCT, long term) [54]	Active PM/DM (19) EG, n = 10 CG, n = 9	12 (5) + 12 (2), 104 (Open extension)	Home exercise: Resistive (EG) ROM (CG)	NA	NA	CPK Inflammatory infiltrates At 104 w NA	At 24 w: EG: 0 (NS) CG: 0 (NS) At 104 w: EG: 0 (NS) CG: 0 (NS) At 24 w: EG: 0 (NA) CG: 0 (NA)

PM Polymyositis; DM Dermatomyositis; RCT Randomized controlled trial; EG, Exercise group; CG Control group; NS Non-significant; + improved; 0 unchanged; - worsen or reduced; NA, not assessed; IMACS International Myositis Association Clinical Studies Groups 6- item disease activity core set; ER-stress Endoplasmic reticulum stress; CPK Creatine phosphokinase; AST Aspartate aminotransferase; ALT Alanine aminotransferase; ROM Range Of Motion