

REVIEW

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Physical exercise among patients with systemic autoimmune myopathies

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Abstract

Systemic autoimmune myopathies (SAMs) are a heterogeneous group of rare systemic autoimmune diseases that primarily affect skeletal muscles. Patients with SAMs show progressive skeletal muscle weakness and consequent functional disabilities, low health quality, and sedentary lifestyles. In this context, exercise training emerges as a non-pharmacological therapy to improve muscle strength and function as well as the clinical aspects of these diseases. Because many have feared that physical exercise exacerbates inflammation and consequently worsens the clinical manifestations of SAMs, it is necessary to evaluate the possible benefits and safety of exercise training among these patients. The present study systematically reviews the evidence associated with physical training among patients with SAMs.

Keywords: Dermatomyositis, Physical exercise, Myositis, Polymyositis

Background

Systemic autoimmune myopathies (SAMs) are a heterogeneous group of rare autoimmune systemic diseases that primarily affect skeletal muscles [1, 2]. Depending on demographic, clinical, laboratory, histopathological, and evolutionary data, SAMs can be subdivided into dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), and others [3].

Patients with SAMs share a common clinical presentation characterized by skeletal muscle weakness, which ultimately leads to functional disability and increased morbidity and mortality [4].

Until the 1960s, absolute rest was recommended for patients with autoimmune rheumatic diseases to help treat the disease [5]. However, this recommendation has changed because sedentary behavior is now known to be associated with increases in triglyceride levels, blood pressure, insulin resistance, and cardiovascular risk [6, 7]. In this context, exercise training emerged as a non-pharmacological therapy for patients with SAMs, thereby contributing to the restoration of the muscle strength and functional capacity of these individuals and improving their clinical condition. Because exercise training among

these patients was prohibited for many years, it is necessary to understand the mechanisms through which physical exercise acts to improve these parameters, as well as the safety of recommending exercise training to treat these diseases. Thus, the purpose of this review was to describe the safety of exercise training among patients, particularly those with SAMs.

Methods

For the present study, a bibliographic search was performed using the electronic databases Medline and PubMed.

The descriptors were selected in January 2017 and were defined based on the following keywords (in English): dermatomyositis, inclusion body myositis, polymyositis, idiopathic inflammatory myopathies, aerobic capacity, muscle strength, functional capacity, physical activity, exercise training, resistance training, vascular occlusion training, and resistance training with vascular occlusion. These keywords were combined using the Boolean operators “AND” and “OR” and adapted to each database as needed. In addition, the reference lists of all retrieved articles were manually reviewed.

The following inclusion criteria were adopted: no time limit; published in English; original articles, case reports, case series, controlled clinical trials, or longitudinal experimental studies (with experimental and control groups); exercise/physical training interventions were conducted for

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individuals with SAMs; details of the intervention, such as duration, frequency, types of exercise and intensity, were listed; and muscle strength and/or functionality were evaluated and presented as primary or secondary outcomes through physical performance tests.

Abstracts of congresses, monographs, theses and dissertations, articles about other myopathies (e.g., muscular dystrophy, metabolic myopathy, and neuromuscular disease), and letters to the editor that were purely commentary were excluded from this review.

The search identified 26 articles. The concepts used in this study are explained in Table 1.

Literature review

The first studies that evaluated the effect of physical exercise on patients with SAMs were performed in the 1990s by Hicks et al. [8] (Table 2) and Escalante et al. [9] (Table 3). Hicks et al. [8] demonstrated that a 4-week quadriceps and biceps isometric strengthening program for patients with PM effectively increased isometric strength without increasing muscle enzyme serum levels. Escalante et al. [9] were the first to suggest that patients with active SAMs can participate in rehabilitation programs involving strength training. Furthermore, these programs were associated with a clinical improvement in strength without increasing muscle enzyme serum levels.

Wiesinger et al. [10] was the first to conduct a prospective, controlled, and randomized study evaluating the effects of physical training on patients with SAMs. In that study, 14 patients with DM/PM (seven undergoing physical training and seven controls) were prospectively evaluated over a 6-week period. Patients undergoing physical training demonstrated significant improvements in aerobic capacity, isometric muscle strength, activities of

daily living, and quality of life compared with the control group. In addition, patients undergoing physical training showed an elevation in the inflammatory markers of the disease, suggesting that physical training is safe for these patients. Several additional studies have built on those preliminary studies to better understand the effects of physical training among patients with SAMs.

Physical exercise among patients with DM/PM

Patients with DM/PM have decreased aerobic capacity, with a lower peak oxygen consumption (VO_2 peak) [11, 12]. In addition, this decrease in aerobic capacity is positively correlated with a decrease in isometric strength, suggesting that the decrease in muscle strength among these patients impairs aerobic capacity [11].

The impairment in the aerobic capacity of these patients might also be related to elevated levels of blood lactate and the low proportion of type 1 muscle fibers, suggesting that patients with DM/PM show an impaired skeletal muscle oxidative capacity [13, 14]. Because one of the causes of mortality among patients with SAMs is cardio-pulmonary diseases [15, 16] and decreases in aerobic capacity are associated with an increased risk of these diseases [17, 18], it is essential to employ strategies that can improve these parameters among these patients.

Based on this assumption, Wiesinger et al. [19] studied eight patients with DM/PM in remission who engaged in a physical training program. These authors observed a 28% improvement in aerobic capacity after 6 months of training, which was considered clinically significant. The same authors [10] demonstrated a significant improvement in aerobic capacity after 6 weeks of physical training among 14 patients with DM/PM (7 in the training group and 7 controls) in a randomized study. Munters

Table 1 Concepts used in physical training

Term	Concept
Aerobic capacity	Maximum capacity of the individual to capture oxygen from the environment, transport it through the bloodstream, and use it in cellular respiration. It can be estimated using peak oxygen consumption (peak VO_2) via ergospirometry
Aerobic training	Training characterized by low and moderate intensity efforts with a prolonged duration (over 150 s). This training predominantly uses oxygen (O_2)-dependent bioenergetic pathways to meet the energy demand required by the activity
1RM	Test used to determine the maximum muscle strength of the individual, determined as the maximum amount of weight lifted in only one repetition during a standardized exercise
MVC	Test used to determine the maximum number of repetitions/contractions that the participant can perform with a preset load
Strength training	Training that uses exercises requiring a level of strength above that used in everyday tasks to increase muscle function. When prescribing this training, the 1RM and/or MVC test is necessary, and the training is based on the percentage of each participant's 1RM (usually between 50 and 80% of 1RM/MVC)
Isometric exercise	During this exercise, the production of muscle tension equals the external load imposed on the muscle. Moreover, this exercise is characterized by the absence of joint movement during its execution
Dynamic exercise	This exercise involves the displacement of the body in time and space, and it is characterized by alternations between eccentric and concentric contractions

1RM 1-repetition maximum test, MVC maximum voluntary contraction test

Table 2 Physical exercise in patients with chronic stable dermatomyositis, polymyositis, or both

Author	Patients (n)	Protocol (Exercises)	Time (week)	Evaluated Components	Inflammatory markers	Results
Hicks et al. [8]	1	Isometric strength	4	Isometric strength 3 MVC	↔ CPK	↑ Isometric strength
Wiesinger et al. [10]	14	Aerobic	6	VO ₂ peak Isometric strength Activities of daily living	↔ CPK	↑ VO ₂ peak ↑ Isometric strength ↑ Activities of daily living
Wiesinger et al. [19]	13	Aerobic	24	VO ₂ peak Isometric strength Activities of daily living	↔ CPK	↑ VO ₂ peak ↑ Isometric strength ↑ Activities of daily living
Alexanderson et al. [23]	10	Strength Dynamic	12	Muscle function Walking distance Quality of life	↔ CPK ↔ Immune / inflammatory markers	↑ Muscle function ↑ Walking distance ↑ Quality of life
^a Heikkilä et al. [44]	22	Strength Dynamic	3	Functional capacity Pain	↔ CPK	↑ Muscle function ↔ Pain
^b Varvu et al. [45]	19	Strength Dynamic	3	Respiratory function (Spirometry) Muscle strength	↔ CPK	↑ Respiratory function ↑ Muscle function
Harris-Love et al. [46]	1	Strength Eccentric	12	Isometric strength	↔ Muscle enzymes	↑ Isometric strength ↑ Concentric strength
Alexanderson et al. [23]	8	Strength Dynamic	7	10–15 MVC Functional capacity	↔ CPK	↑ 10–15 MVC ↔ Disease activity ↔ Functional capacity
Dastmalchi et al. [14]	9	Aerobic Strength	12	Type of muscle fiber Quality of life Functional capacity	Not reported	↑ Type I Fiber ↑ Functional Capacity ↑ Quality of Life
Chung et al. [47]	37	Strength Dynamic Creatine supplementation	20	Functional capacity Muscle strength Quality of life Pain and fatigue Anxiety and depression	↔ CPK	↑ Functional capacity ↑ Muscle strength ↔ Quality of life ↔ Anxiety and depression ↔ Pain and fatigue
Nader et al. [21]	8	Strength Dynamic	7	Genes related to inflammation and fibrosis	↓ CPK	↓ Genes related to inflammation and fibrosis ↓ Tissue fibrosis
Munters et al. [12]	9	Aerobic	12	Aerobic capacity Activity of mitochondrial enzymes	↔ CPK	↑ Aerobic capacity ↑ Activity of mitochondrial enzymes
Munters et al. [20]	11	Aerobic	12	Aerobic capacity Disability Disease activity Quality of life 5 MVC	↔ CPK	↓ Disease activity ↑ Muscle strength ↑ Quality of life ↑ Aerobic capacity ↑ Quality of life
Mattar et al. [25]	13	Strength Dynamic Vascular occlusion	12	Muscle strength Functional capacity Quality of life	↔ CPK ↔ Aldolase	↑ Muscle strength ↑ Functional capacity ↑ Quality of life
Munters et al. [22]	15	Aerobic	12	Aerobic capacity Proteomic analysis Molecular profile	↔ CPK	↑ Aerobic capacity ↑ Genes related to capillary growth, mitochondrial biogenesis, protein synthesis, cytoskeletal remodeling and muscular hypertrophy ↑ Genes related to the immune and inflammatory response and sarcoplasmic reticulum stress

CPK creatine phosphokinase, DM dermatomyositis, PM polymyositis, MVC maximum voluntary contraction, VO₂ peak oxygen consumption, ↑: increase, ↔: no change, ↓: decrease

^a included patients with inclusion body myositis

^b included patients with active disease

Table 3 Physical exercise among patients with dermatomyositis, newly diagnosed polymyositis, clinically active disease, or some combination therein

Author	Patients (n)	Disease activity	Protocol (Exercises)	Time (week)	Evaluated components	Inflammatory markers	Results
Escalante et al. [9]	5	Active	Strength Dynamic	8	Isometric strength	↔ CPK	↑ Isometric strength
Alexanderson et al. [24]	11	Active	Strength Dynamic	12	Muscle function Quality of life	↔ CPK	↑ Muscle function ↑ Quality of life
^a Varvu et al. [45]	19	Chronic/Active	Strength Dynamic	3	Respiratory function (Spirometry) Muscle strength	↔ CPK	↑ Respiratory function ↑ Muscle function
Mattar et al. [29]	3	Active	Strength Aerobic	12	Muscle strength Functional capacity Quality of life	↔ CPK↔ Aldolase	↑ Muscle strength ↑ Functional capacity ↑ Quality of life

CPK creatine phosphokinase, DM dermatomyositis, PM polymyositis, ↑: increase, ↔: no change

^a Active disease but with chronic evolution

et al. [12] corroborated these findings by demonstrating that aerobic training over a 12-week period effectively improved the aerobic capacity of patients with DM/PM and increased the activity of the mitochondrial enzymes in their skeletal muscles. Aerobic training also led to a change in muscle fiber type (increased type I fibers) in these patients as well as an increase in the cross-sectional area of the muscle, which contributed to improvements in aerobic capacity and decreases in muscle fatigue [14]. In addition, Munters et al. [20] demonstrated that aerobic training improves the overall health of patients with DM/PM in a multicenter study; furthermore, improved aerobic capacity through training was associated with reduced disease activity.

Although aerobic training has important benefits for patients with DM/PM, the molecular effects of physical exercise on the skeletal muscles of these patients are unknown. Physical exercise might positively modulate the genetic profile of patients with DM/PM. Nader et al. [21] evaluated the genes related to inflammation and fibrosis in eight patients with DM/PM undergoing strength training. After 7 weeks of training, the expression levels of genes related to skeletal muscle inflammation and fibrosis were reduced, and these changes were accompanied by a reduction in tissue fibrosis among these patients. Similarly, Munters et al. [22] evaluated the effect of a 12-week aerobic training program on the molecular profile of the skeletal muscles of seven patients with DM/PM compared with eight controls. After 12 weeks, the patients undergoing training showed increased expression levels of genes related to capillary growth, mitochondrial biogenesis, protein synthesis, cytoskeletal remodeling, and muscle hypertrophy as well as decreased expression of genes related to inflammation, immune response, and endoplasmic reticulum stress [22]. These data suggest that the training activates an aerobic phenotype and promotes muscle growth as

well as suppresses the inflammatory response in the muscles of these patients.

As with aerobic capacity, patients with DM/PM show a significant decrease in muscle strength, primarily in the proximal muscles, which in turn leads to functional impairment [1, 2]. Several studies have demonstrated that physical training plays an important role in reversing the losses in muscle strength and function in patients with DM/PM [19, 23–25]. Escalante et al. [9] was the first to demonstrate an increase in muscle strength among three patients with DM/PM who engaged in physical training for 2 weeks. Based on these preliminary data, Wiesinger et al. [25] studied eight patients with DM/PM who participated in a physical training program for 6 months and observed increases in isometric strength, which led to improvements in activities of daily living (e.g., sitting down, standing up, and walking) in these patients. Alexanderson et al. [23] corroborated these data when they demonstrated that an intensive 7-week physical training program led to increases in muscle strength, helping to improve the impairments and limitations in daily activities without increasing inflammatory markers.

Strength training with intensities ranging from 70 to 80% of one-repetition maximum (1RM) has been recommended to increase muscle strength and mass [26]. As an alternative to this type of exercise, the practice of low-intensity strength training (20 to 30% of 1RM) combined with partial blood flow restriction likely induces similar improvements in muscle strength and hypertrophy in both healthy individuals and patients with chronic diseases [25–27]. Because patients with SAMs are generally unable to exercise at high intensities, this type of training is an alternative to conventional strength training. Mattar et al. [25] were the first to demonstrate that low-intensity strength training combined with partial blood flow restriction was a safe and effective method of increasing muscle strength, function, and

mass and that it could lead to significant improvements in the quality of life of patients with DM/PM. These results suggest that this type of training act as a new non-pharmacological therapy to reverse the clinical manifestations associated with these diseases.

Physical exercise among patients with DM/PM during clinical disease activity

The data presented above lead us to believe that physical exercise is a powerful aid in improving the impaired physical abilities of patients with DM/PM. In addition, because inflammatory markers were not exacerbated in the studies presented, exercise training might be safe for these patients.

However, newly diagnosed patients and those with clinical disease activity are often fearful regarding the use of exercise training. Because patients present with a high degree of inflammation, fear remains about exercising during these periods.

Alexanderson et al. [28] evaluated the effect of intensive physical training performed at home five times per week over a 12-week period on the clinical disease activity of patients with DM/PM. After 12 weeks, significant increases were observed in muscle strength and function, which in turn led to an improvement in the quality of life of these patients. These authors suggested that this physical exercise program was safe because the inflammatory markers did not increase; therefore, exercise training was recommended for the rehabilitation of these patients. Similarly, Mattar et al. [29] conducted a case series study of three patients with clinical DM/PM activity and assessed the safety and effect of aerobic training combined with supervised strength training over a 12-week period. After this period, physical training was well tolerated and safe (i.e., increases in creatine phosphokinase (CPK) and aldolase levels were not found). In addition, specific parameters of aerobic capacity, muscle function, and quality of life improved, suggesting that supervised physical training positively affects these parameters during clinical disease activity.

Alexanderson et al. [24] were the first to demonstrate that physical exercise is safe during this period for patients newly diagnosed with DM/PM. A total of 19 patients newly diagnosed with DM/PM receiving high doses of prednisone were selected. The patients were randomized into a training group ($n = 10$) and a control group ($n = 9$). The patients in the training group were instructed to perform an intensive physical training program (five times per week for 12 weeks); the patients were then evaluated at the 24th, 52nd, 78th and 104th weeks. No significant differences were found between the training and control groups with regard to the parameters evaluated; however, intensive physical training was found to be safe for these patients because it did not exacerbate inflammation

during the evaluated period, suggesting that exercise training is safe even for newly diagnosed patients.

Physical exercise in patients with IBM

Although the effects of physical training on patients with DM/PM have been well described in the literature, few studies have evaluated the effect of physical training on patients with IBM.

Studies comparing the aerobic capacity of these patients with healthy controls are scarce. Because patients with IBM also present with significant impairments in their mitochondrial oxidative capacity [30, 31], studies are necessary to determine whether these patients have impaired aerobic capacity. To date, only one study has evaluated the effect of 12 weeks of stationary bicycle training combined with strength training on the aerobic capacity of seven patients with IBM (Table 4). After 12 weeks of physical training, a 38% increase in aerobic capacity was observed among these patients [32].

Like those with DM/PM, patients with IBM present with an important impairment in muscle strength as a characteristic of the disease [33, 34]. Spector et al. [35] examined five patients with IBM who completed a 12-week progressive strength-training program. These authors did not observe an increase in the cross-sectional area of the muscle; however, a significant increase in muscle strength was shown without the exacerbation of inflammatory markers. Low-intensity strength training combined with partial blood flow restriction is also an important aid when reversing the losses in strength and muscular function as well as stimulating the increase of muscle mass in these patients. Gualano et al. [36] were the first authors to demonstrate that strength training combined with partial blood flow restriction for 12 weeks effectively and safely increased muscle strength (through the 1RM test), balance, and function as well as lead to 15.9, 60, and 4.7% increases in the cross-sectional area of muscle in a case study of a patient with IBM resistant to all types of treatment. In addition, there was an improvement in quality of life, varying from 18 to 600%. In addition to these effects, the same research group [37] demonstrated that strength training combined with the partial restriction of blood flow for 12 weeks decreased the expression of the myostatin gene and increased the expression of endogenous myostatin inhibitors. These data might partially explain the increase in muscle mass observed in the aforementioned case study [36]. Corroborating the previous findings, Jorgensen et al. [38] examined a 74-year-old man with who participated in strength training combined with partial blood flow restriction over a 12-week period. These authors observed substantial increases in mechanical muscle strength and gait speed, suggesting that this type of training reverses the losses in strength and functional capacity associated with these patients.

Table 4 Physical exercise in patients with chronic inclusion body myositis

Author	Patients (n)	Protocol (Exercises)	Time (week)	Evaluated Components	Inflammatory markers	Results
Spector et al. [35]	5	Strength Dynamic	12	Isometric strength 3 MVC	↔ CPK ↔ Immune / inflammatory markers	↑ Isometric strength ↑ 3 MVC ↔ Increased cross-sectional area
Arnardottir et al. [39]	7	Strength Dynamic	12	Isometric strength	↔ CPK ↔ Cytokines ↔ Adhesion molecules	↑ Isometric strength
Johnson et al. [32]	7	Aerobic	12	VO ₂ peak Functional Capacity	↔ CPK	↑ VO ₂ peak ↔ Functional capacity
	7	Strength Dynamic	16	Muscle strength Functional capacity	↔ CPK	↑ Muscle strength ↑ Functional capacity
Gualano et al. [36]	1	Strength Dynamic With vascular occlusion	12	Muscle strength Balance Quality of life Cross-sectional area	↔ CPK	↑ Muscle strength ↑ Balance ↑ Quality of life ↑ Cross-sectional area
Santos et al. [37]	1	Strength Dynamic With vascular occlusion	12	Myostatin gene Myostatin inhibitor genes	↔ CPK	↓ Myostatin gene ↑ Myostatin inhibitor genes
Jorgensen et al. [38]	1	Strength Dynamic With vascular occlusion	12	Isometric strength Functional capacity Gait speed	↔ CPK	↑ Isometric strength ↑ Functional capacity ↑ Gait speed

CPK creatine phosphokinase, MVC maximum voluntary contraction, VO₂ peak oxygen consumption, ↑: increase, ↔: no change

Physical exercise performed at home is also an important therapy for patients with IBM. Intensive home training (5 days per week for 12 weeks) was also found to be safe (no increase in creatine phosphokinase levels) and effective at increasing the muscle strength and function of these patients [39], suggesting that this practice effectively rehabilitates patients with IBM.

Future prospects and final considerations

SAMs are characterized by periods of clinical activity and remission. During clinical disease activity, patients present with a significant decrease in skeletal muscle strength, which remains lower throughout the lifespan. This decrease in strength leads to functional impairment and consequent decreases in daily activities, resulting in marked sedentary lifestyles among these patients.

The data presented in this review suggest that physical training is an important non-pharmacological tool for increasing muscle strength, improving functional impairment, and improving the quality of life of patients with SAMs. In addition, physical training likely improves the impaired aerobic capacity of patients with SAMs. This effect is likely associated with the ability of physical training to improve the molecular profile (thereby increasing the expression of the genes related to mitochondrial neangiogenesis and biogenesis) and leading to increases in the activities of mitochondrial enzymes and the type I fibers in the skeletal muscle [12, 21, 22].

Additional studies are needed to better understand how physical exercise acts in the pathogenesis of SAMs. The causes of these diseases are not yet known; however, immune and nonimmune mechanisms are most likely involved [40–43]. Studies that demonstrate how physical exercise affects these parameters might help to understand how exercise training acts toward the clinical improvement of these diseases.

Clinical, controlled, and randomized studies of patients with IBM are necessary to show the real effects of physical exercise among this population. Physical training likely stimulates increases in muscle strength and improves the aerobic capacities of these patients; however, without an increase in the cross-sectional area of the muscle [32, 35, 39]. Strength training with vascular occlusion appears to efficiently increase strength, function, balance, and the cross-sectional area of muscle in these patients [36, 37]. Thus, this type of training is an alternative to conventional training that is capable of stimulating increases in the muscle mass of patients with IBM. Because these patients are generally resistant to drug therapy, the use of strength training with vascular occlusion is an important aid to minimize the clinical manifestations of this disease.

Studies have yet to evaluate the effect of physical exercise among patients with immune-mediated necrotizing myopathy; therefore, future trials should explore this area.

Conclusions

The data presented in this review suggest that physical training is an important tool for increasing muscle strength, improving functional impairment, and improving the quality of life of patients with SAMs. In addition, physical training likely improves the impaired aerobic capacity of patients with SAMs.

Abbreviations

CPK: Creatine phosphokinase; DM: Dermatomyositis; IBM: Inclusion body myositis; PM: Polymyositis; RM: repetition maximum; SAMs: Systemic autoimmune myopathies; VO₂ peak: Peak oxygen consumption

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Authors' contributions

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