


# The Role of Exercise to Improve Physiological, Physical and Psychological Health Outcome in Idiopathic Inflammatory Myopathies (IIM)

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**Abstract:** Idiopathic inflammatory myopathies (IIM) impact all aspects of health, physiological, physical, and psychological. Hallmark symptoms of IIM are muscle weakness, reduced muscle endurance and aerobic capacity. Recently, pain and fatigue as well as anxiety and depression have emerged as common and debilitating symptoms in patients with IIM. The aim of this scoping review is to, in a holistic way, describe how IIM impact patients' physiological, physical, and psychological health and how exercise has a role to treat as well as potentially counteract the effects of the disease. Inflammation induces non-immune response and organ damage. These changes with additional impact of physical inactivity lead to muscle impairment and reduced aerobic capacity. Pain, fatigue and low psychological well-being and overall quality of life are also common health aspects of IIM. Medical treatment can reduce inflammation but has in turn serious side effects such as muscle atrophy, type-II diabetes, and hypertension, which exercise has the potential to treat, and perhaps also counteract. In addition, exercise improves muscle function, aerobic capacity and might also reduce fatigue and pain. New evidence shows that reducing systemic inflammation may also improve patient-reported subjective health, quality of life and psychological well-being. Exercise in combination with medical treatment is becoming an important part of the treatment for patients with IIM as exercise has the potential to promote health aspects of various dimensions in patients with IIM.

**Keywords:** exercise, idiopathic inflammatory myopathies, treatment

## Introduction

The idiopathic inflammatory myopathies (IIM), or myositis, is an autoimmune, chronic disorder affecting skeletal muscle with clinical manifestations of muscle weakness and low muscle endurance. Myositis mainly affects proximal muscles in arms and legs as well as neck flexors leading to physiological, physical and psychological impairment negatively affecting quality of life and health.<sup>1-4</sup> Other organs are frequently involved such as joints, skin, lung, gastrointestinal tract and the heart, further negatively affecting outcome for patients with IIM. Treatment is based on high doses of glucocorticoids in combination with immunosuppressive drugs over a long period of time, often lasting for several years, and with disappointing results with persisting irreversible chronic manifestations such as muscle atrophy.<sup>5</sup> Side effects of the immunosuppressive treatment are common including osteoporosis with fractures, hypertension, diabetes and infections, further negatively affecting outcome and quality of life for patients with IIM.

The IIM is a heterogeneous group of diseases and was in adult individuals previously subgrouped, based on clinical and histopathological differences, into dermatomyositis, polymyositis, and inclusion body myositis. More recently due to the advances in the discovery of several myositis specific autoantibodies several new subgroups have been identified: antisynthetase syndrome, immune mediated necrotizing myopathy, and amyopathic dermatomyositis. In addition, there is

another subgroup called overlap myositis with features of myositis in combination with features of another defined autoimmune disorder, such as systemic sclerosis.<sup>6</sup> These subgroups vary in clinical presentation, treatment response and prognosis thus the recently identified subgroup, antisynthetase syndrome, has a high risk of a combination of myositis with arthritis and interstitial lung disease.<sup>7</sup> As the outcome varies between the IIM subgroups it is important to subclassify patients according to the combination of clinical manifestations, histopathology and serology. However, most published studies on outcome of IIM so far have been conducted in the “old” subgroups, polymyositis, dermatomyositis and inclusion body myositis which are likely to contain the new subgroups. A shared feature for most individuals with IIM is problems related to skeletal muscle involvement with structural and metabolic changes that affect muscle function, as well as leading to pain and fatigue. The aim of this scoping review was to, in a holistic way, describe how IIM may impact patients’ physiological, physical, and psychological health and how exercise has a role in the treatment to potentially minimize permanent damage and optimize health.

## The Metabolic and Bioenergetic Disturbances in Skeletal Muscle in Patients with Idiopathic Inflammatory Myopathies

Inflammatory cell infiltrates have traditionally been considered as a main factor of muscle injury during acute phases in patients with IIM. Inflammatory infiltrates are thought to result in muscle fiber atrophy, myonecrosis, capillary loss, and hypoxia.<sup>8</sup> However, once immunosuppressive treatment has reduced the inflammatory burden, patients may still suffer from persisting muscle weakness. Previous studies have in fact suggested that muscle weakness may appear even before the infiltration of inflammatory cells,<sup>9</sup> suggesting that other mechanisms different from the inflammatory pathways may induce muscle dysfunction as supported by a mouse model for myositis (MHC class I model).<sup>10</sup> Some of these mechanisms of non-immune modulated injury are endoplasmic reticulum (ER) stress pathway activation, autophagy, and mitochondrial dysfunction based on investigations of muscle biopsies from patients with IIM as well as from the MHC class I mouse model.<sup>11</sup> Another non-inflammatory mechanism of muscle dysfunction is an altered metabolism of skeletal muscle due to chronic inflammation that will lead to a “vicious cycle” of chronic inflammation and muscle decondition.<sup>12</sup> According to this hypothesis, several factors such as fatigue, anemia, and muscle wasting occur due to the chronic inflammatory state. This state of muscle wasting can result in decreased cardiovascular performance and low physical activity that may increase the accumulation of visceral fat and sarcopenia promoting metabolic disorders, such as diabetes and atherosclerosis. In this context, tailored exercise programs could target these bioenergetic disturbances in skeletal muscle of patients with IIM.

## Myokines – the Muscle as an Anti-Inflammatory Mediator

Like immune cells, skeletal muscle cells can produce cytokines, also known as myokines, enabling a crosstalk between cells and other organs.<sup>13</sup> Among these myokines, tumor necrosis factor (TNF) and interleukin 6 (IL-6) are the two most studied. IL-6 is the first detectable myokine after contracting skeletal muscle and induces the synthesis of acute-phase proteins such as C-reactive protein.<sup>12,14</sup> Moreover, IL-6 is an important regulator of skeletal muscle metabolism: it mediates endogenous glucose production and participates in fat oxidation.<sup>15</sup> TNF is a key initiator and perpetuator of the systemic inflammatory response that follows a myriad of aggressors such as bacterial infections or chronic rheumatic conditions. In contrast to the cytokine response that follows infection or chronic inflammation, the myokine response following exercise is not preceded by an increase of TNF. The activation of IL-6 in muscle fibers is independent of the presence of TNF or NF- $\kappa$ B. Moreover, IL-6 induced by exercise has negative feedback on TNF. This suggests that IL-6 induced by exercise has a metabolic rather than pro-inflammatory effect.<sup>12</sup> Indeed, so far, research indicates that exercise is safe, not leading to increased inflammation in muscle tissue but in contrast may induce down-regulation of inflammatory genes.<sup>16,17</sup> Accordingly, exercise could be beneficial in patients with IIM due to its anti-inflammatory profile.

*Myostatin*, also known as growth differentiation factor 8, is a protein mainly involved in negative regulation of muscle growth and muscle mass.<sup>13</sup> In patients with a muscle wasting disease profile such as inclusion body myositis (IBM), myostatin has been targeted as a possible therapeutic pathway.<sup>18</sup> Indeed, Santos et al showed that training

attenuated myostatin gene expression and increased expression of myostatin inhibitors in muscle tissue from a patient with IBM. In this context, resistance training using vascular occlusion, that is, restricting muscle blood flow using tourniquet cuffs, has been implemented as a safe non-pharmacological intervention in patients with IBM.<sup>19–21</sup> In a study in patients with non-IBM myositis, Vernerová et al demonstrated that circulating levels of serum myostatin correlated positively with muscle strength and were negatively associated with disease activity as measured by physician global assessment.<sup>22</sup> Similar findings were reported by Mahoudeau et al suggesting that serum levels of myostatin could be used as a marker of disease activity in all patients with myositis.<sup>23</sup>

*Decorin* is a myokine released by contracting human myotubes (muscle cell precursors) and its serum levels are positively associated with levels of resistance exercise.<sup>13</sup> This myokine has an antagonistic effect on myostatin and, therefore, enhances proliferation and differentiation of muscle cell precursors by suppressing the inhibitory effect of myostatin.<sup>24</sup> Also, decorin inhibits the function of transforming growth factor-beta (TGF- $\beta$ ) and thus negatively influences fibrotic tissue formation.<sup>24</sup> Therefore, this is a potential therapeutic target for patients with myositis that should be considered for the future.

Heat shock protein 90, or *HSP90*, is another myokine with a crucial role in the adaptation of skeletal muscle to stress and activation of inflammatory cells. Two studies investigated the potential of this myokine as a biomarker for disease activity and damage but also as a predictor of response to treatment in patients with IIM. In one of these studies, Svec et al<sup>25</sup> evaluated the effect of an exercise protocol in addition to standard medical therapy on patients with IIM (n=27) in comparison with a control group (CG) with conventional treatment but no exercise protocol (n=23). Moreover, a healthy control group (n=18) followed a strenuous training protocol to mimic an exercise-induced non-inflammatory muscle damage. Plasma levels of HSP 90 and other cytokines (e.g., TNF and IL-6) were measured. The authors demonstrated that HSP90 levels were associated with traditional markers of muscle damage and inflammation; this was also observed in the healthy control group but not in the patient CG. Interestingly, the change in plasma levels predicted muscle endurance. In another study, Štorkánová et al<sup>26</sup> found that an exercise group kept stable levels of HSP90, but not the control group. These findings suggest that HSP90 may function as a myoprotective factor.

These studies indicate that by producing different myokines skeletal muscle is an active mediator of the inflammatory response and crucial regulator of non-inflammatory pathways. In this way, exercise may potentially reverse muscle damage occurring in patients with IIM.

## Metabolic Muscle Abnormalities in Patients with IIM

Patients with IIM may develop abnormal muscle bioenergetics such as low levels of phosphocreatine and nucleotide triphosphates measured by <sup>31</sup>P magnetic resonance spectroscopy (<sup>31</sup>P MRS) and high levels of urinary creatine.<sup>27</sup> A double-blind, randomized, placebo-controlled study in 24 patients with IIM found that a protocol of endurance exercise together with oral creatine supplementation improved the levels of phosphocreatine and nucleotide triphosphates measured by <sup>31</sup>P magnetic resonance spectroscopy.<sup>28</sup> This improvement was associated with better muscle performance as measured by functional tests indicating that oral creatine supplements combined with exercise may be a useful therapy in improving muscle physiology and thus muscle function.

## Exercise and Pancreatic $\beta$ Cell Function

Metabolic syndrome is highly prevalent in patients with myositis.<sup>29,30</sup> Insulin resistance (IR) interferes with the lipid metabolism and glucose homeostasis in insulin-sensitive tissue such as adipocytes and muscle cells. Weight, body mass index, and waist circumference are associated with insulin resistance in patients with myositis. However, other factors such as chronic inflammation and glucocorticoid treatment may be contributing factors to IR in patients with myositis.<sup>29</sup> De Oliveira et al<sup>31</sup> demonstrated that in addition to improved aerobic capacity and muscle strength, an exercise intervention in 9 patients with myositis resulted in improved  $\beta$ -cell function and insulin sensitivity which is one of the cluster cardiovascular risk factors included in metabolic syndrome (MetS).<sup>32</sup> This observation suggests that besides the direct effect on muscle physiology, exercise interventions may attenuate the cardiovascular risk in patients with myositis by improving insulin resistance.

## Body Composition

Body composition is the distribution and relationship between lean tissue mass (LTM), fat mass and mineral bone content. Normal ageing is related to low muscle quantity and quality as well as increased fatty infiltration of muscle. Individuals with altered body composition may suffer from functional decline as well as morbidity and mortality.<sup>33</sup> A study on Chinese patients showed that patients with newly diagnosed IIM had decreased LTM of the upper limbs and appendicular region.<sup>34</sup> Moreover, LTM measurements correlated with muscle strength, and muscle damage. Potential explanatory factors for accelerated decline in LTM may be, but are not restricted to, the inflammatory burden and dysregulation of myokines such as myostatin.<sup>35,36</sup> Further studies are required to fully assess the diagnostic and prognostic value of body composition in patients with IIM.

## Physical Impact of IIM

Muscle impairment including reduced muscle strength and muscle endurance is present in various degrees and can be related to certain autoantibodies. Patients with anti Mi-2-, and NXP-2 autoantibodies associated dermatomyositis and patients with anti SRP and HMGCR-associated immune mediated necrotizing myopathies often initially present with severe muscle weakness.<sup>37</sup> Antisynthetase autoantibodies seem to be less associated with muscle impairment, but rather to interstitial lung disease, arthritis, and Raynaud's phenomenon. However, patients with anti-EJ and anti-PL7 autoantibodies may have more muscle involvement compared with patients with other antisynthetase autoantibodies. Hip flexor muscles are most affected in patients diagnosed with non-IBM IIM.<sup>38</sup> Muscle endurance is also affected in patients with IIM, with impairment also in distal muscle groups of upper and lower extremities.<sup>39,40</sup> A cohort of 72 patients with recent onset non-IBM IIM were significantly more limited in dynamic muscle endurance compared with isometric muscle strength, with similar values at 1-year follow-up.<sup>41</sup> These results indicate that patients are more affected in dynamic muscle endurance compared with isometric muscle strength and that assessment of muscle endurance is essential to fully detect muscle impairments. Patients with non-IBM IIM have lower aerobic capacity compared with healthy controls matched for age and sex.<sup>42</sup> Patients with antisynthetase syndrome have worse aerobic capacity compared with patients with DM<sup>43</sup> as patients with antisynthetase syndrome often present with interstitial lung disease. Patients with interstitial lung disease also experience dyspnea and cough in various degrees. Impaired function in the diaphragm and other breathing muscles can also contribute to a low aerobic capacity. Pain is a very common symptom in patients with non-IBM IIM.<sup>44</sup> Patients self-report significantly more pain than patients with rheumatoid arthritis assessed by the SF-36 Bodily Pain domain.<sup>45</sup> Both pain and fatigue were by patients with non-IBM IIM deemed as two of the most important symptoms to assess.<sup>46</sup> Patients with inclusion body myositis develop severe muscle atrophy and muscle weakness over time, foremost in quadriceps, the finger flexors and dorsi- and plantar flexors of the ankle.<sup>38</sup> Cardiovascular involvement in IIM could possibly also add to fatigue and low physical capacity. The physical impact of IIM has a significant impact on quality of life and psychological health.

## Psychological Outcome Measures and Inflammation

Systemic inflammation itself, regardless of underlying diagnosis, has been associated to several symptoms associated with impaired psychological health.<sup>47–50</sup> These symptoms are also closely connected to the symptoms displayed in an inflammatory sickness response. The sickness response refers to a series of coordinated physiological and behavioural changes that occur in response to systemic inflammation aimed to promote recovery.<sup>51–53</sup> Classic inflammatory sickness behavior includes symptoms such as depression, anxiety, fatigue, increased pain sensitivity and malaise,<sup>54</sup> which all are common symptoms in patients with IIM. Furthermore, they are all important determinants of subjective health perception including general health and quality of life.

A link between subjective health and the immune system is well established in several conditions. For instance, a reduction of inflammation was associated with a higher quality of life in a randomized controlled trial (RCT) with patients with prostate cancer.<sup>55</sup> In IIM, the link between inflammation and subjective health perception is sparsely studied. However, a longitudinal association between reduced systemic inflammatory markers and improved patient global assessment was recently reported from a cohort of 1200 patients from the Myonet registry.<sup>56</sup> Furthermore, positive

affect and feeling of wellbeing contribute to reduced risk of disease development and progression in other chronic conditions such as cardiovascular and neurological diseases,<sup>57</sup> and is likely the case in myositis as well as suggested by a recent review.<sup>58</sup> The authors even suggest that improving psychological outcome measures such as health-related quality of life should be considered another therapeutic option in treatment of inflammatory myopathies.

There is a well-known discordance between patient and physician reported health in many conditions such as systemic lupus erythematosus,<sup>59</sup> inflammatory bowel disease<sup>60</sup> and rheumatoid arthritis.<sup>61</sup> This discordance was also shown between patient global assessment of disease activity and physician reported disease activity in patients with IIM where physical function and fatigue were found to contribute to the patient's global assessment, while muscle disease activity was the most important contributor to the physician reported disease activity.<sup>62</sup> These studies illustrate why it is of utmost importance to not only incorporate the physician's assessment, but also to routinely incorporate patient reported outcome measures (PROMs) when we aim for improving physical, physiological, and psychological outcomes.

Until now, only a few interventions have aimed to reduce inflammation to improve psychological outcomes. However, an evidence-based protocol combining resistance and aerobic exercises has been proposed to improve muscle function and reduce inflammation.<sup>63</sup> Reducing inflammation to improve psychological outcome measurements such as increased patient global assessment and increased health related quality of life could be a valuable complement to already existing treatment options that needs to be explored further in the future.

## **The Effects of Exercise on Molecular Pathways of Muscle Metabolism. Improving Physiological Health Outcome**

Abnormal energy metabolism and mitochondrial disturbances have been observed in a small group of 10 patients with established IIM. For example, a lower proportion of type I muscle fibers compared with healthy individuals and impaired oxygen transport to the mitochondria in skeletal muscle have been observed in patients with established disease.<sup>64–66</sup> Endurance training has shown to regulate molecular pathways that mediate aerobic capacity and capillary growth as well as mitochondrial enzyme activity. In a controlled trial with a 12-week endurance exercise intervention, the exercise induced a significant change in gene expression, proteome, and capillary density in patients with IIM.<sup>16</sup> Specifically, an up-regulation of genes involved in capillary growth and proteins related with protein (muscle) synthesis was found. Simultaneously, a down-regulation of genes involved in protein degradation and genes related to immune response and ER stress was observed. In another randomized controlled trial, increased activity of two skeletal muscle mitochondrial enzymes (i.e., citrate kinase and  $\beta$ -hydroxyacyl-CoA dehydrogenase) was observed in patients exposed to an intensive endurance exercise program; but not in the control group.<sup>67</sup> Moreover, the increased mitochondrial activity was associated with an improved aerobic capacity. In a follow up study using skeletal muscle from the patients who underwent a randomized, controlled trial evaluating the effect of endurance exercise, Boehler et al found that exercise-induced microRNAs seemed to support downregulation of transcripts involved in immune response, glycolytic metabolism, and muscle atrophy.<sup>68</sup> Moreover, endurance exercise seems to reduce the activation of NF $\kappa$ B pathway suggesting that muscle tissue from patients with IIM may respond to exercise comparable to healthy muscle tissue. Further, this endurance exercise program reduced expression of the protein Harakiri which has detrimental effects on mitochondrial function, along with reduced expression of Toll-Like Receptor 7 (TLR7).<sup>69</sup> These findings indicate that exercise may be helpful as a glucocorticoid-sparing agent intervention. Detailed information on exercise programs and effects on physiological health outcomes are presented in [Tables 1 and 2](#).

## **The Effects of Exercise on Muscle Function and Aerobic Capacity. Improving Physical Health Outcome**

Exercise is emerging as an effective treatment to improve physical aspects of IIM, e.g., muscle function, aerobic capacity, pain, and fatigue. Since the end of the 1990s up to now almost 40 publications all show that exercise is safe, without risk of increased inflammation or disease activity.<sup>2,72,91</sup> A systematic review using the GRADE system assessing the risk of bias (+ insufficient, ++ limited, +++ moderate-strong, and ++++ strong evidence), based on all 5 published randomized controlled trials (RCT) published up to 2019 showed that a combination of aerobic exercise and resistance training can

**Table I** Exercise Effects on Physiological, Physical and Psychological Health Outcomes in Adult Non-IBM IIM

Study/design	Diagnosis/ Patients, n/ Disease Activity/ HCs, n	Exercise Duration, Intensity, Frequency	Physiological (Disease activity, Inflammation,	Physical	Psychological
RESISTANCE TRAINING Escalante et al 1993 <sup>70</sup> Open study	PM, DM Active n = 5	Dynamic and ROM 8 weeks NR	CK: 0	<b>Muscle strength: +</b>	NA
Alexanderson et al 1999 <sup>71</sup> Open study	PM, DM Established n = 10	Dynamic, home- based 12 weeks NR 5 d/week	CK: 0 MRI: 0 Biopsy: 0	<b>Muscle endurance: +</b>	<b>QoL, SF-36: PF: + RP: +</b>
Dastmalchi et al 2007 <sup>66</sup> Open study (same exercise protocol as Alexanderson <sup>71</sup> )	PM, DM n = 9 Established HC n = 11	Resistance, home exercise 12 weeks 5 d/week	<u>Fibre type</u> Pre-exercise: <b>Pts fewer type I fibres vs HCs (P &lt; 0.05)</b> Post-exercise: <b>Pts more type I fibres vs baseline (P &lt; 0.05)</b> <u>CSA</u> Pts-HC: 0 Post-exercise: <b>Type I increased Type 2 increased (P &lt; 0.05)</b>	NA	
Alexanderson et al 2000 <sup>72</sup> Open study	PM, DM Active n = 11	Dynamic, home based 12 weeks NR 5 d/week	CK: 0 MRI: 0 CD3+ T-cell: 0	<b>Muscle endurance +</b>	<b>QoL: PF + BP + V + ADL: 0</b>
Heikkilä et al 2001 <sup>73</sup> Open study	PM, DM, IBM Established n = 22	Dynamic 3 weeks NR	CK: 0	<b>Muscle endurance +</b> Grip strength 0 Pain 0	
Varju et al 2003 <sup>74</sup> Open study	PM, DM Established, active n = 19	Dynamic 3 weeks NR 5 d/week	CK: 0	<b>Muscle strength: +</b> <b>FVC: +</b> <b>Fatigue: +</b> Pain 0	NA
Alexanderson et al 2007 <sup>75</sup> Open, repeated measures	PM, DM Established n = 8	Dynamic 7 weeks 10 VRM (70% of max) 3 d/week	<u>6-item core set</u> <b>Resp: n = 2</b> <b>MITAX: +</b> CD3+ T-cell: 0	<b>Muscle strength: +<sup>a,b,c</sup></b> <b>Muscle endurance: +<sup>a,d</sup></b>	ADL: 0

<p>Nader et al 2010<sup>17</sup> Open study (same protocol as Alexanderson<sup>76</sup>)</p>	<p>PM, DM Established n = 8</p>	<p>Same as () Dynamic 7 weeks 10 VRM (70% of max) 3 d/week</p>	<p><u>Biopsy, mRNA expression</u> <b>34 pro-inflammatory genes downregulated</b> (-1.5 to -3.5 fold) (p&lt;0.04–0.003) <u>Biopsy, mRNA expression</u> <b>3 pro-oxidative metabolism genes upregulated</b> (+1.6 to +1.8 fold) (p&lt;0.04–0.005) <b>4 pro-lipid synthesis genes downregulated</b> (-1.5 to -2.6 fold) (p&lt;0.02–0.008) <b>22 pro-fibrotic genes downregulated</b> (-1.5 to -3.7 fold) (p&lt;0.4–0.004) <b>3 anti-fibrotic genes upregulated</b> (+1.5 to +2.7 fold) (p&lt;0.04–0.02)</p>	<p>NA</p>	
<p>Chung et al 2007<sup>28</sup> RCT, double-blind</p>	<p>PM, DM Established n = 37 CrG n = 19 PlacG n = 18</p>	<p>Dynamic, home based 20 weeks NR 5 d/week</p>	<p><b>CK: 0% change in PCr/β-NTP ratio EG-CG: +</b></p>	<p><b>Physical capacity EG-CG + Muscle strength EG-CG + Muscle endurance EG-CG + Pain 0 Muscle strength + Phys cap +</b></p>	<p>QoL: Depression: 0</p>
<p>Mattar et al 2014<sup>77</sup> Open study</p>	<p>PM, DM Established n = 13</p>	<p>Dynamic, vascular occlusion 12 weeks 30% of max 2 d/week</p>	<p><b>Phys Global VAS: + Pat Global VAS: +</b> CK, Ald: 0 CSA +4.5%</p>		
<p>Regardt et al 2014<sup>78</sup> Open study</p>	<p>PM, DM Established n = 11</p>	<p>Dynamic, home-based hand exercise 12 weeks 3 d/week</p>	<p>CK: 0</p>	<p><b>Pinch grip strength: + Grip strength: 0</b></p>	<p><b>QoL: All SF-36 domains +</b> (including MH) ADL: + ADL: 0</p>

(Continued)

Table I (Continued).

Study/design	Diagnosis/ Patients, n/ Disease Activity/ HCs, n	Exercise Duration, Intensity, Frequency	Physiological (Disease activity, Inflammation,	Physical	Psychological
Spiritovic M, et al 2021 <sup>79</sup> RCT	PM, DM established disease n=53 EG n=30 CG n=23	EG: 24 weeks, supervised. Once a week: 40 min of daily activity training, Once a week, 30 min resistance and stability training CG: No intervention	<b>EG: TNF+</b> Trend IL1 $\beta$ - Trend MCP-1 - <b>CG: TNF+</b> <b>IL1<math>\beta</math>: -</b> EG and CG: CK, LD 0 EG: <b>Local mRNA</b> <b>TNF+</b> IL1 $\beta$ , IL-6, IL-8, MCP-1: 0	<b>Muscle strength and endurance</b> <b>EG-CG: +</b> <b>EG-CG: Force vector area +</b> <b>ECM/BCM +</b>	<b>Depression</b> <b>EG-CG+</b> EG and CG: QoL 0 EG and CG: Fatigue 0 <b>ADL EG-CG+</b>
Svec X et al 2022 <sup>25</sup> (Same exercise protocol as Spriritovic <sup>79</sup> )	PM, DM Established disease n=70 EG n=27 CG n=25 HC n=18	EG: 24 weeks, supervised. Once a week: 40 min of daily activity training, Once a week, 30 min resistance and stability training CG: No exercise HC-strenuous exercise	<b>Plasma Hsp90</b> <b>EG-CG: +</b> EG: 0 (stabilizing) CG: 0	NA	NA
<b>AEROBIC EXERCISE ALONE OR IN COMBINATION WITH RESISTANCE TRAINING</b> Wiesinger et al 1998 <sup>80</sup> RCT	PM, DM Established n = 14 EG n = 7 CG n = 7	Aerobic, stationary cycling + step-up class 6 weeks 60% VO <sub>2max</sub> 2–3 d/week	CK: 0	<b>Aerobic capacity</b> <b>EG-CG: +</b> <b>Muscle strength</b> <b>EG-CG: +</b>	<b>ADL</b> <b>EG-CG: +</b>
Wiesinger et al 1998 <sup>81</sup> CT	PM, DM Established n = 13 EG n = 7 CG n = 6	Aerobic, stationary cycling + step-up class 24 weeks 60% of VO <sub>2max</sub> 1–2 d/week	CK: 0	Aerobic capacity <b>EG + / CG 0</b> Muscle strength <b>EG + / CG 0</b>	<b>ADL</b> <b>EG: +</b> CG: 0



Alemo Munters et al 2013 <sup>42</sup> RCT, 1-year open extension	PM, DM Established n = 23 EG n = 12 CG n = 11 HCs n = 12	EG: Aerobic, stationary cycling + resistance, dynamic (home based and hospital) 12 weeks 70% of VO <sub>2max</sub> 30–40 VRM 3 d/week CG: non exercising	<u>6-item core set</u> <b>EG: Resp. n = 7</b> CG: Resp. n = 0 CD3+T cell: 0	<b>Aerobic cap:</b> <b>EG-CG: +</b> <b>Muscle strength:</b> <b>EG-CG: +</b>	<b>Patient preference</b> <b>EG: +</b> <b>ADL</b> <b>EG-CG: +</b> <b>QoL</b> <b>EG-CG: +</b>
Alemo Munters et al 2013 <sup>67</sup> RCT	PM, DM Established n = 21 EG n = 11 CG n = 10 HCs n = 12	(Same exercise protocol as Alemo Munters <sup>53</sup> )	<u>6-item core set</u> <b>EG: Resp. n = 6</b> CG: Resp. n = 0 Lactate levels <b>EG-CG: +</b>	<b>Biking endurance:</b> <b>EG-CG: +</b>	NA
Munters LA et al 2016, <sup>16</sup> RCT (same exercise protocol as Alemo Munters <sup>42</sup> )	PM, DM Established n = 15 EG n = 7 CG n = 8	NA	<u>Gene expression</u> <b>EG: 5 genes (ER-stress)</b> <b>down-reg: +</b> (- 1.3 to -2.6 fold) <b>12 genes (remodeling/ hypertrophy) up-reg: +</b> (1.1 to 4.3 fold) <b>11 genes (mitochondrial biogenesis/protein synthesis)</b> <b>Up-reg: +</b> (1.1 to 1.2 fold) <b>CG: 4 genes (apoptosis)</b> <b>up-reg: -</b> (1.1 to 1.6 fold) <b>6 genes (protein synthesis/ immune remodeling)</b> <b>down-reg: -</b> (-1.1 to -1.6 fold)	NA	NA

(Continued)

Table 1 (Continued).

Study/design	Diagnosis/ Patients, n/ Disease Activity/ HCs, n	Exercise Duration, Intensity, Frequency	Physiological (Disease activity, Inflammation,	Physical	Psychological
Alexanderson et al 2014 <sup>76</sup> RCT, 2-year open extension	PM, DM Active n = 19 EG n=10 CG n=9	Resistance, home-based + aerobic, outdoor walking 12 weeks, NR, 50–70% of predicted max HR, 5 d/week	<u>CPK</u> Pre-exercise: 0 24 w: 0 <b>52 w: EG-CG +</b> 104 w: 0 <u>CD-3+ T-cell</u> EG: 0 CG: 0	<b>Muscle endurance:</b> <b>EG: +, CG: +</b>  <b>Aerobic cap:</b> <b>EG: +, CG: +</b>	NHP EG-CG: 0 EG: + Energy CG: + Sleep
Boehler J et al 2017 <sup>68</sup> Subset from a RCT (Same exercise protocol as Alemo Munters <sup>42</sup> )	PM, DM Established n=6 EG n=3 Performed intensive aerobic and endurance-based resistance training, 3d/week, see ref 22 above. CG n=3 Non-exercising	EG: Aerobic, stationary cycling + resistance, dynamic (home based and hospital) 12 weeks 70% of VO <sub>2max</sub> , 30–40 VRM 3 d/week CG: non exercising	<b>Transcriptional regulation +</b> ↓PEDF signaling, ↓protein kinase signaling ↓glucocorticoid receptor signaling <b>Protein level +</b> ↓oxidative stress, ↑ mitochondrial biogenesis ↑muscle remodeling These together indicate: ↓immune response, ↑aerobic metabolism ↓muscle atrophy	NA	NA
Boehler J et al 2019 <sup>69</sup> Subset from a RCT (same exercise protocol as Alemo Munters <sup>42</sup> )	PM, DM Established n=3 (All from EG in ref 22)	Aerobic, stationary cycling + resistance, dynamic (home based and hospital) 12 weeks 70% of VO <sub>2max</sub> , 30–40 VRM 3 d/w	<b>Downregulation of mitochondrial damage protein Harakiri + and TLR7 +</b>	NA	NA
de Souza JM et al 2019 <sup>82</sup> Open study	IMNM Established n=8	Resistance training (supervised) 12 weeks 8–12 RM in 3 sets Aerobic exercise, moderate- intensity treadmill walking/ running. 30–50 minutes	6-item core set: 0 (PGA, patient VAS, MMT, HAQ, MYOACT, CPK)	<b>Muscle strength: +</b> Aerobic capacity: 0 (VO <sub>2max</sub> ) (time to anaerobic threshold, time to exhaustion and time to respiratory compensation point +)	NA

de Oliveria et al 2019 <sup>31</sup> Open study	PM, DM, ASS Established n=9	Resistance training (supervised) 12 weeks 8–12 RM, Aerobic exercise, moderate- intensity treadmill walking/ running. 30–50 minutes	6-item core set: 0 (PGA, patient VAS, MMT, HAQ, MYOACT, CPK) ↓ <b>Muscle fat mass +</b> ↓ <b>Body fat mass +</b> Blood lipids 0 Glucose, mg/dL 0 ↓ <b>Insulin, UI/mL +</b> ↓ <b>C-peptide mg/dL +</b> <b>Muscle strength</b> <b>12 mo</b> MMT 0–5 Right side 0 <b>Left side +</b> Isokinetic torque 0 <b>Pain 12 mo +</b>	<b>Muscle strength +</b> <b>Aerobic capacity</b> <b>VO<sub>2max</sub> (+)</b> <b>Time to exhaustion +</b> <b>Time to RCP +</b>  CPK 0 CRP 0	<b>HAQ-DI</b> <b>ADL 12 mo</b> <b>EG-CG +</b> <b>QoL SF-36 at 12</b> <b>mo</b> <b>EG-CG</b> <b>RP +</b> <b>GH +</b> <b>At 1 mo</b> <b>EG-CG</b> <b>V +</b> <b>RE +</b> PF 0 BP 0 SF 0 MH 0
Tiffreau V et al 2017 <sup>83</sup> RCT	PM Established n=21 EG n=10 CG n=11	EG: 4-week in-hospital rehab: Resistance training (60% / 1RM) daily in 2 sets. Aerobic exercise, (60% of est. VO <sub>2max</sub> ) 3 d/week. Inspiratory/expiratory breathing exercise, 30-min walking, ROM exercise Home exercise with parts of above rehab program daily. CG: prescription of 30 min physical therapy 3 d/week.			

**Notes:** +, statistically significant within-group improvement; 0, no statistically significant change/no statistically significant difference between groups; -, statistically significant within-group worsening, (+ %); change in percentage without statistical analysis. <sup>a</sup>No significant changes between -4 weeks and baseline in any of the measures; <sup>b</sup>significant improvement in deltoids, quadriceps, gastrocnemius, abdominal muscle groups, but not in biceps/latissimus dorsi; <sup>c</sup>all eight participants improved >20% (defined as clinically relevant change); <sup>d</sup>improved significantly in shoulder flexion task, but not in other muscle groups.

**Abbreviations:** ADL, Activities of daily living; AFPS, aggregate functional performance score; CK, creatine phosphokinase; CSA, cross-sectional area; CT, controlled trial; d/week; days/week; DM, dermatomyositis; ECM/BCM, extracellular mass to body cell mass ratio; EG-CG +, statistically significant improvement in EG vs CG; FVC, forced vital capacity; HAQ, Health Assessment Questionnaire; HC, healthy control; HR, heart rate; IBM, inclusion body myositis; IL1 $\beta$ , interleukin 1-beta; LD, lactodehydrogenase; MCP-1, Monocyte chemoattractant protein 1; MITAX, Myositis Intention to treat activity index; MMT-8, MMT 8 muscle groups; mRNA, messenger RNA; NA, not assessed; NHP, Nottingham Health Profile; NR, not reported; PM, polymyositis; Phsp90, plasma heat shock protein 90; Pts, patients; RCP, respiratory compensation point; RCT, randomized controlled trial; max, maximum; Resp., responder; RM, repetition maximum; ROM, range of motion; SF-36, Short Form 36; SF-36 PF, Physical Function; GH, General Health; V, Vitality; MH, Mental Health; PSC, SF-36 Physical composite score; MSC, SF-36 Mental composite score; TNF, Tumor Necrosis Factor; VAS, visual analogue scale; VO<sub>2max</sub>, maximal oxygen uptake; VO<sub>2peak</sub>, peak oxygen uptake; VRM, voluntary repetition maximum.

**Table 2** Exercise Effects on Physiological, Physical and Psychological Health Outcomes in IBM

Study/Design	Diagnosis/Patients, n/Disease Activity/HCs, n	Exercise Duration, Intensity, Frequency	Physiological	Physical	Psychological
Spector et al 1997 <sup>84</sup> Open study	IBM Established n = 5	Dynamic 12 weeks 50–70% of max 3 d/week	CK: 0	<b>Muscle strength</b> Isometric PT: 0 <b>3VRM: +</b> MMT8: 0 <b>Fatigue: 0</b>	ADL: 0
Arnardottir et al 2003 <sup>85</sup> Open study	IBM Established n = 7	Dynamic, home based 12 weeks NR 5 d/week	CK: 0 <u>Biopsy</u> CD3+ T-cell 0	Muscle strength: 0 Muscle endurance: 0	NA
Johnson et al 2007 <sup>86</sup> Open study	IBM Established n = 7	Dynamic, home based 16 weeks NR Twice a day	CK: 0	<b>Muscle strength: +</b> <b>Physical capacity: +</b>	NA
Johnson et al 2009 <sup>87</sup> Open study	IBM Established n = 7	Aerobic, stationary cycling + resistance, home-based 12 weeks 80% of max HR NR 7 d/week	CK: 0	<b>Aerobic capacity: +</b> <b>Muscle strength: +</b> Physical capacity: 0	NA
Jørgensen A et al 2018 <sup>88</sup> RCT	IBM Established n=22 EG n=11 CG n=11	EG: BRF (110 mmHg) BRF (100 mmHg) on 30–35% / IRM (progressive), 3 45-sec sets, quadriceps CG: no exercise	<u>6-item core set</u> <b>EG-CG</b> PGA: 0 PatGA: VAS 0 MMT 0 HAQ: 0 ↑ <b>CK: –</b> MDI: 0	<b>Knee extensor maximal strength: EG-CG: +</b>	<b>ADL</b> <b>IBMRFS, 10- item EG-CG: +</b> QoL SF-36 all domains EG-CG: 0

<p>Yde Jensen K et al 2019<sup>20</sup> RCT, same exercise protocol as Jorgensen<sup>88</sup></p>	<p>IBM Established n=21 EG n=11 CG n=10</p>	<p>EG: BRF (110 mmHg) BRF (100 mmHg) on 30–35% / IRM (progressive), 3 45-sec sets, quadriceps CG: no exercise</p>	<p>Inflammatory infiltrates CD3+ T-cells, CD8+ T-cells, CD28<sup>null</sup>T-cells EG: 0 <b>CG: ↓+</b> <b>EG-CG: + in favor for CG</b> <u>T<sub>reg</sub> (FOXP3<sup>+</sup>)</u> EG-CG: 0 M1 and M2 macrophages EG: 0, CG: 0 <u>NK-cells</u> <b>EG: ↑-</b> CG: 0 <b>EG-CG: - in favor for CG</b></p>	<p>NA</p>	<p>NA</p>
<p>Jorgensen 2022<sup>21</sup> RCT, same exercise protocol as Jorgensen<sup>88</sup></p>	<p>IBM Established n=21 EG n=8 CG n=11</p>	<p>EG: BFR (110 mmHg) on 30–35% / 1 VRM (progressive), 3 45-sec sets, quadriceps CG: no exercise</p>	<p>Thigh lean mass: 0</p>	<p>Max knee ext strength (Nm × kg<sup>-1</sup>) <b>Stronger leg</b> <b>EG: +</b> <b>CG: -</b> EG-CG: + <b>Weaker leg</b> EG: 0 <b>CG: -</b> <b>EG-CG: +</b> Rate of force development 0–50ms (Nm × kg<sup>-1</sup> × s<sup>-1</sup>) <u>Stronger leg</u> EG and CG: 0 <b>EG-CG: +</b> <u>Weaker leg</u> EG and CG: 0 EG-CG: 0</p>	

(Continued)

Table 2 (Continued).

Study/Design	Diagnosis/Patients, n/Disease Activity/HCs, n	Exercise Duration, Intensity, Frequency	Physiological	Physical	Psychological
Wallace A et al 2019 <sup>89</sup> Randomized single-blinded cross-over design	IBM Established n=17	Exercise period: Aerobic exercise, ergometer biking on 60%/VO <sub>2peak</sub> , increasing to 80%, aiming at 30 min. Control period, non-exercising: exercise/activity diary	CK: 0	<u>Exercise period vs control period</u> VO <sub>2peak</sub> (+17%) vs (1.3%) Watt: (+17.3%) vs (+0.4%) Physical activity: 0 Dysphagia: 0	NA
Mohannak N et al 2020 <sup>90</sup> Open study	IBM Established n=10	Breathing exercise using an Expiratory Muscle Strength Trainer (EMST) 30 min, 5 d/week, 12 weeks	NA		QoL. SF-36: 0 Dysphagia: 0

**Notes:** +, statistically significant within-group improvement; 0, no statistically significant change/no statistically significant difference between groups; -, statistically significant within-group worsening, (+ %); change in percentage without statistical analysis.

**Abbreviations:** ADL, activities of daily living; BFR, blood flow restricted; CK, creatine phosphokinase; CG, control group; d/week, days/week; EG, exercise group; EG-CG +, statistically significant improvement in EG vs CG; FOXP3, forkhead box P3; IBM, inclusion body myositis; M1, activated macrophage; M2, alternately activated macrophage, inflammatory cytokine; M2, max, maximal; MDI, Myositis damage index; MMT8, Manual muscle strength 8 muscle groups; PT, peak torque; SF-36, SF-36 Short Form; PatGA, Patient global assessment; PGA, Physician global assessment; QoL, quality of life; T<sub>reg</sub>, regulatory T-cell; VAS, visual analogue scale; VRM, voluntary repetition maximum; VO<sub>2peak</sub>, Peak oxygen uptake.

improve muscle function, aerobic capacity, and activity limitation (limited evidence ++) in patients with established, low-active IIM.<sup>92</sup> There is less evidence to support positive effects on muscle function and aerobic capacity in patients with recent onset, inflammatory active IIM (insufficient evidence +). There is also insufficient evidence supporting that submaximal blood-flow restricted resistance training can improve quadriceps muscle strength in patients with inclusion body myositis (+). The limited scientific evidence is mainly due to the still low number of RCTs. However, the results from additional open-designed studies all indicate safety of exercise in all subtypes of IIM as well as positive effects on improved aerobic capacity and muscle function in both recent onset and established non-IBM IIM, strengthening the scientific evidence supporting exercise as an effective treatment to improve physical health. Studies indicate that aerobic exercise improves aerobic capacity in patients with inclusion body myositis,<sup>87,89</sup> however, results are somewhat diverging regarding effects of exercise on muscle function in these patients. Twice daily home exercise was reported sufficient to improve muscle strength in the quadriceps and finger flexors as well as improving short walking distance and ability to stand up from sitting.<sup>86</sup> A RCT reported 6% improved quadriceps strength by twice-a-week blood-flow restricted submaximal strength training compared with a near 10% worsening in the non-exercising control group.<sup>88</sup> Other studies have reported unchanged muscle function by exercise in this group of patients.<sup>84,85,87,89</sup> Detailed information on exercise programs and their effects on physical health outcomes are presented in Tables 1 and 2.

## Physical Activity

The effects of physical activity, e.g., everyday movement on at least a moderate level, such as walking, biking, gardening, have not been evaluated in patients with IIM. However, convincing data on general populations reveal that recommended levels of physical activity, i.e., 150–300 minutes of physical activity/week, or 75–150 minutes of physical activity on a high intensity in combination with strength training twice a week can reduce the risk of early death, cardiovascular disease (CVD), type-II diabetes (T2D), osteoporosis, obesity, cancer, anxiety/depression and improve quality of life.<sup>93,94</sup> Since patients with IIM have an increased risk of CVD, T2D, osteoporosis and cancer, it is recommended for individuals with IIM to strive towards these physical activity recommendations to optimize health.

## Pain and Fatigue

No study has so far designed protocols to evaluate efficacy of exercise or other treatments with pain and fatigue as primary outcomes. However, some studies have included assessment of pain and/or fatigue primarily as safety measures of exercise. Fatigue assessed by the SF-36 domain “Vitality” was significantly reduced after 12 weeks of intensive combined aerobic and muscle endurance training in established, inflammatory low-active disease compared with the non-exercising control group, while SF-36 Bodily pain remained unchanged.<sup>42</sup> An individual 1-month in-patient rehabilitation program consisting of moderate intensity resistance training and aerobic exercise with additional breathing exercise and range of motion exercise resulted in significantly reduced fatigue assessed by SF-36 Vitality in patients experiencing a flare in their polymyositis. However, this improvement was not sustained during 6- and 12-months home exercise follow-up.<sup>83</sup> Reduced fatigue was observed after a 12-week moderate-intensity home exercise program in patients with recent onset non-IBM IIM within the exercise group assessed by the Nottingham Health Profile Energy domain but without between-group difference with the control group performing only range of motion exercise. This improvement was sustained also at 1- and 2-years follow-up. Interestingly, the exercise group was significantly more physically active and had better muscle function and aerobic capacity at long-term follow-up compared with the control group who was offered the same home exercise program with a 24-week delay.<sup>76</sup> These data are supported by reduced fatigue and pain levels after 12 weeks of the same home exercise program in a smaller, open-design study also in patients with recent onset, active non-IBM IIM.<sup>72</sup> A 7-week intensive resistance training study in established, inflammatory low-active IIM with adaptations in loading due to hand arthritis reported unchanged pain assessed by the Borg CR-10 symptom scale, 0–10 (Borg) indicating safety of this type of exercise.<sup>75</sup>

## Improving Psychological Outcomes

A number of studies have reported poorer psychological outcomes in patients with IIM compared with the general population.<sup>95–98</sup> Among outcomes that have been shown to be impaired in patients with IIM are health-related quality of life, functional disability, general health, depression and anxiety. For instance, in a large cohort of 45,800 patients with IIM in Germany a higher frequency of psychiatric disorders such as depression and somatoform disorders were reported in the cohort compared with a control group.<sup>98</sup> In another cross-sectional study of untreated depression and anxiety in patients with cutaneous lupus erythematosus and dermatomyositis, 43.9% of the patients diagnosed with DM met criteria for depression or anxiety.<sup>99</sup>

Several studies have reported a poorer health-related quality of life in patients with myositis compared with the general population.<sup>46,95–97,100–109</sup> In 2016, a systematic review of 10 studies including 654 patients with IIM on health-related quality of life demonstrated a significantly impaired health-related quality of life in all subsets of IIM compared with the general population.<sup>95</sup> Disease activity, disease damage and chronic disease course were associated with poorer health-related quality of life. The impact of IIM on health-related quality of life was investigated in a more recent study of an Australian cohort of 50 patients diagnosed with IIM.<sup>97</sup> They reported significantly lower health-related quality of life outcome scores for patients with IIM in most of the SF-36 domains when compared with the most recent population norm. This was also confirmed in a study of 1715 patients with IIM from the Myovision registry where health-related quality of life was measured using SF-12.<sup>96</sup> In this study significantly lower SF-12 score in the physical domain was observed in patients with joint and lung involvement, polypharmacy, older age, and the inclusion body myositis phenotype than in a normative population with a diagnosis of rheumatoid arthritis, and also compared with the general population.

Although there is an unmet need to improve psychological outcome in patients with IIM, only a limited part of myositis research has been focused on improving psychological outcomes. Several non-pharmacological intervention studies in patients with IIM have investigated psychological outcome measures as primary or secondary outcomes. To the best of our knowledge, we are not aware of any pharmacological intervention study where improving psychological outcome has been the primary outcome.

## Patient Reported Outcome Measures in Patients with IIM

In the studies that measure psychological outcomes such as depression, anxiety, disability, general health, and quality of life in patients with IIM the psychological outcomes are usually measured using patient-reported outcome measures (PROMS). PROMs are subjective measures of the patient's perceived health reported directly by the patient without interpretation of the response by a clinician. They provide important information about subjective health status beyond objectively verified health measures. In fact, PROMs are considered to be of such importance that the Food and Drug Administration (FDA) has listed PROMs as one of the important outcome measures in clinical trials and incorporating PROMs in clinical research has gained increased attention in recent years. PROMs can be divided into generic PROMs considering general aspects of health or disease-specific PROMs tailored to capture disease-specific symptoms and impact of function. Today, no myositis-specific PROMs are used as a standard in clinical research, but effort is ongoing through the Outcome Measures in Rheumatology Clinical Trials (OMERACT) consortium to develop myositis-specific PROMs and incorporating them in clinical research in the future.

## Effects of Exercise on Disability and Quality of Life in Patients with IIM

Effort has been made to investigate the effects of non-pharmacological interventions on disability and quality of life in patients with IIM. The most common PROM that has been used to measure limitations in daily activities in these studies is the Health Assessment Questionnaire (HAQ),<sup>110</sup> consisting of eight sections assessing self-reported appraisal of difficulties regarding dressing, arising, eating, walking, hygiene, reach, grip and activities. The most commonly used tool to assess quality of life is the Short Form 36 Health Survey Questionnaire (SF-36), measuring eight scales including physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental



health.<sup>111</sup> It can be discussed whether HAQ is in fact a psychological outcome measure but since HAQ is a crucial determinant of quality of life, HAQ has been included in this section.

Disability (as measured by HAQ) and quality of life (as measured by SF-36) have been investigated as outcome measures in patients with IIM in several studies. The results regarding improvement of disability have been somewhat conflicting. HAQ has been reported to improve in patients with polymyositis after a 4-week standardized hospital-based rehabilitation program.<sup>83</sup> In that study, the intervention group also improved compared with the control group in the general health and physical function domains of SF-36. HAQ has also been reported to improve in patients with polymyositis after a 12-week supervised exercise programme, and in patients with polymyositis or dermatomyositis after low-intensity resistance training.<sup>77,112</sup> In both studies, there was an improvement in all components in SF-36 as well as in HAQ score. In another study, where the effects of a 24-week training program for patients with IIM were evaluated, the intervention group improved 39% in HAQ score.<sup>79</sup> However, in that study there was no significant improvement in quality of life as measured by SF-36.

On the other hand, no improvement in HAQ scores was reported after isotonic muscle training in ten patients in an acute phase of PM or DM compared with 11 patients with a chronic phase of PM and DM.<sup>74</sup> Similar results were reported in 22 patients with IBM who were randomized into 12 weeks of low-load blood-flow restricted resistance training or a non-exercising control group.<sup>88</sup> In that study, neither HAQ scores nor the Inclusion Body Myositis Functional Rating scale improved, nor did the physical function domain of SF-36. This was also the case in a twice a week exercise training program for 12 weeks including 9 patients with IIM where no improvements in HAQ scores were reported.<sup>31</sup> Lack of improvement in HAQ scores was also reported in another study where patients with polymyositis or dermatomyositis were randomized into a 12-week endurance exercise program. However, the exercise group improved in the physical function domain of SF-36 and vitality compared with the control group.<sup>42</sup> In another study no changes were found in SF-36 after a 12-week aerobic training program.<sup>89</sup> It is possible that the discrepancy in results of the interventions partly can be due to small study groups, different lengths of the interventions and also due to different subgroups of IIM patients being included in the different studies which makes comparison and interpretation more difficult. Thus, the results regarding the effect of exercise on improving functional disability as measured by HAQ scores and quality of life as measured by SF-36 show conflicting results and this effect needs to be further investigated in standardized interventions, preferably with functional disability and health related quality of life as primary outcomes.

## Effects of Exercise on Depression in Patients with IIM

Only a few studies have investigated depression as a psychological outcome measure in non-pharmacological intervention studies. The effect of a 24-week training program focused on activities of daily living, muscle strengthening and stability for patients with IIM was evaluated in a study by Spiritovic et al.<sup>79</sup> In the intervention group, depressive symptoms as measured by the PROM Beck's Depression Inventory-II (BDI-II) improved by 24%. Depressive symptoms were also assessed as a secondary outcome in a 6-month 2-center double-blind randomized controlled trial where patients followed a home exercise program and were randomized either to creatine supplements or placebo.<sup>28</sup> Oral creatine supplements combined with exercise improved physical performance, but depressive symptoms as measured by Hospital Anxiety and Depression scales were not affected. Solid scientific evidence supports physical activity and exercise as effective to treat mild to moderate depression regardless of diagnosis,<sup>113</sup> and thus could be assumed to be effective also in individuals with myositis. Further research is needed to tailor suitable interventions aimed at improving depressive symptoms in patients with IIM. Detailed information on exercise programs and their effects on psychological health outcomes are presented in [Tables 1 and 2](#).

In summary, in most of the non-pharmacological intervention studies, exercise demonstrated positive effects on psychological outcome measures in patients with myositis. The improvement of psychological outcomes such as anxiety and depression as well as other aspects of quality of life such as fatigue and pain by increased physical activity has several possible explanations. First, exercise can lead to better muscle function and thereby a better quality of life. Second, intensive exercise reduces the systemic inflammation and may thereby improve quality of life. A third explanation could be that kynurenine otherwise passing the blood-brain barrier causing depression, is converted to kynurenine acid by physical activity and exercise.

## Discussion

Medical treatment reduces inflammation and can to some extent improve physical capacity, pain, fatigue, and quality of life in patients with IIM, except for inclusion body myositis.<sup>114</sup> Although medical treatment reduces inflammation in most patients with IIM, it may often cause side-effects such as muscle atrophy, osteoporosis, type-2-diabetes, elevated liver enzymes or fatigue.<sup>115,116</sup> Exercise is emerging as a treatment modality that significantly improves health from physiological, physical, and psychological perspectives.

A physically active lifestyle might lead to milder symptoms at diagnosis of rheumatoid arthritis.<sup>117</sup> As of today, it is not known if physical activity can have the same effects in patients with IIM. Still, we recommend that patients with IIM should be physically active according to recommendations for the general population but with individual adaptations to optimize physiological, physical and psychological health.

In contrast to pharmacological treatment, a correct dose of exercise can be a beneficial, and cost-effective treatment to restore and optimize muscle health as well as muscle function and aerobic capacity without any side-effects. Although our knowledge on molecular mechanisms that lead to reduced muscle function has increased substantially over recent years, there is still a knowledge gap on how early in the disease course mitochondrial changes, ER-stress, and vasculopathy occur. Furthermore, it is not explored if mechanisms for muscle weakness differ between subsets of non-IBM IIM patients.

We now know that exercise improves muscle function in patients with IIM; however, we do not know which type of exercise is the most efficient to optimize physiological, physical and psychological health in different IIM subsets. Multi-center studies including large and well-characterized cohorts of patients with IIM as well as relevant outcome measures are needed to be able to compare efficacy of different exercise programs in individuals with all subsets of IIM. Since most exercise studies have focused on patients with established, inflammatory low-active IIM, there is also a lack of knowledge on safety and efficacy of exercise in patients with recent onset or refractory IIM. The only RCT evaluating exercise in patients with recent onset, active non-IBM IIM could not show short-term improvements in the group that exercised and received immunosuppressive treatment compared with only immunosuppressive treatment.<sup>76</sup> The home exercise was safe, but probably not intensive enough. However, at 1- and 2-year follow-ups the exercise group was more physically active and had better muscle function and aerobic capacity than the control group. These data suggest that it is important to start a supervised exercise program early in the disease course with follow-ups to initiate and sustain a physically active lifestyle. Further, previous exercise studies have excluded patients with clinical interstitial lung disease and cardiac involvement, indicating an urgent need to evaluate safety and efficacy of exercise in these patients. Although there is consensus in the literature on the safety of exercise in inclusion body myositis, data on efficacy of exercise on physical capacity is somewhat diverging, especially the effects of exercise on the most affected muscle groups, such as the quadriceps and finger/wrist flexors. The paucity of exercise studies in this group of patients also contributes to the insufficient evidence.

A combination of aerobic exercise and resistance training can reduce pain and fatigue in patients with RA<sup>118</sup> and reduce fatigue in SLE and IIM (Limited evidence ++).<sup>91</sup> Pain in IIM is an understudied area and current evidence suggests that adapted exercise results in unchanged pain levels. As in RA, exercise can also reduce pain in other populations,<sup>119,120</sup> thus the hypothesis is that exercise can also contribute to reduced pain in IIM. There is a need for future, well-designed exercise studies using validated measures of pain and fatigue as primary outcomes. Recently, the PROMIS pain interference 6a and PROMIS Fatigue 7a were reported as valid and reliable measures in adults with non-IBM IIM.<sup>121</sup> As shown from studies in IIM as well as in other inflammatory rheumatic conditions, a longer exercise duration might be needed to show significant and clinically relevant improvement in pain and fatigue. Reduced anxiety and depression were also observed in non-IBM IIM patients IIM.<sup>79</sup> This is not surprising, as regular physical activity and exercise is an effective treatment for mild to moderate depression in populations.<sup>122</sup> Furthermore, there are no studies exploring efficacy of water-based exercise or telerehabilitation in adult patients with IIM, indicating that these are important areas for future research.

## Conclusion

Exercise is a treatment with potential to improve all aspects of health, including physiological changes in muscle tissue, physical capacity, and psychological impact in persons with IIM. Given in the correct, and individually adapted dose, exercise does not impose negative side effects, but rather only health benefits. Further research needs to focus on effects of exercise in patients with recent onset and refractory IIM as well as in different subgroups of IIM. In addition, future exercise studies need to be designed with PROM such as pain, fatigue, depression, and quality of life as primary outcomes.

## Disclosure

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