Exercise in myositis: what is important, the prescription or the person?

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Abstract

Our aim for this narrative review was to undertake a search of studies into exercise for people living with Idiopathic Inflammatory myopathies (IIM). We explored the strength of existing evidence with a particular consideration for the implications for people living with IIM and what is important to them. The search strategy from the 2021 Cochrane Physical Activity review in neuromuscular disease was used, and we selected articles that included people with IIM, including Dermatomyositis (DM), Inclusion Body Myositis (IBM), Immune Mediated Necrotising Myopathy (IMNM) [also known as necrotizing autoimmune myopathy (NAM)], and Polymyositis (PM). 2967 records were screened and 16 were included in this review.

Safety of exercise was demonstrated in nine articles, using a range of measures of disease activity, serum creatine kinase, indicators of inflammation, pain, or fatigue. Two studies that took muscle biopsies showed no evidence of increased inflammation. Aerobic exercise protocols were used in 8 studies across conditions and demonstrated improvements in cardiorespiratory fitness or exercise capacity. Six studies of strength training observed improvements in muscle function, with two studies reporting muscle biopsy results of amplified immune response and up regulation of genes related to recycling of damaged proteins. Nine of 13 studies that measures functional outcomes showed significant improvements, and evidence for behaviour change was observed in a study of a self-management intervention.

The evidence of safety and effect of training is reassuring and welcome, and we now need to explore how we support people to incorporate exercise and physical activity longer term into active lifestyles.

Background

Idiopathic Inflammatory myopathies (IIM) are a heterogenous group of diseases, falling into subsets with varying clinical and pathophysiological features: Dermatomyositis (DM), Inclusion Body Myositis (IBM), Immune Mediated Necrotising Myopathy (IMNM) [also known as necrotizing autoimmune myopathy (NAM)], and Polymyositis (PM)(1,2). Acute or subacute onset is observed in NAM, PM or DM with muscle weakness and wasting feature clinically or sometimes subclinically in DM. People with IBM report an insidious onset with progressive muscle weakness and wasting. It is hypothesised that systemic and local inflammation in the acute phase impairs muscle contraction, fatigability and function, though the correlation between weakness and disease activity is not clearly related(3). MRI analysis reveals increasing percentage fat fraction in PM, DM (4,5) and IBM(6), that correlates with muscle function and disability and explains more prolonged presentations of weakness.

High dose steroids and other immunotherapies are offered to people with DM, PM and IMNM. People with IBM do not usually respond to immunosuppression with physical therapy recommended as the main management strategy(2).

Physical inactivity and sedentary lifestyles can lead to disuse muscle atrophy that could cause additional detriment in conditions where primary muscle weakness and wasting are features (7,8). People living with IIM show very low levels of physical activity compared to controls (9,10) and there are correlations between physical activity levels and disease severity (9–11). There is evidence of deconditioning in some IIM cohorts. MRI demonstrated volume loss in muscles less affected by fatty atrophy due to primary disease in IBM (12).

Exercise can be an important intervention to address the consequences of low levels of physical activity and the associated secondary impairments and non-communicable diseases (8). There have been two Cochrane reviews of exercise and physical activity interventions in people living with neuromuscular diseases (NMD), that included studies in myositis (13,14). There is uncertain evidence of effectiveness of strength and aerobic training more generally in NMDs (13), with slight increases in strength in DM, PM and juvenile DM, and slight increases in aerobic capacity in DM and PM. The review of physical activity interventions, revealed that they mainly consisted of structured exercise or physical activity support (14). There was high variation in the components of the interventions and methodological limitations which meant that the authors remained uncertain of the effectiveness of interventions to promote physical activity.

It has been suggested that endurance and aerobic exercise programs for people with IIM could have a direct impact on muscle metabolism to slow the muscle atrophy process. Activation of anaerobic muscle fibre phenotype and muscle growth pathways have been hypothesized (15). In addition positive effects on immune responses, epigenetics and endocrine pathways have also been suggested (16).

There has been a recent excellent review of exercise interventions in IIM focusing on the mechanistic changes within muscle, recommended to the reader who wishes to explore at this level (16). The emphasis of our paper will be through a different lens. A study of people with rare neurological conditions, including neuromuscular diseases, explored the areas of importance for change with physical activity interventions (17). People living with rare neurological conditions identified 3 domains: physical well-being (e.g., physical functioning and independence), psychological well-being (e.g., mood, enjoyment, confidence) and participation in activities.

Our aim for this narrative review was to update the search from the recent Cochrane review of physical activity interventions in neuromuscular diseases (14), apply it to interventions with IIM

cohorts, understand if the existing evidence-base meets the domains of importance of people living with neuromuscular and rare conditions and, consequently, to present some suggestions for future research, where gaps have been found to be present. To ensure real-world applicability and preserve ecological validity, this paper has been co-written with an academic diagnosed with an IIM.

Method

Exercise and myositis search and screening

To consider the most recently published evidence, we ran an updated search of the published search strategy from the Cochrane Physical Activity review in neuromuscular disease, which originally ran on 30 April 2020 (table 1). On 12 February 2022, Farhad Shokraneh updated the searches for CENTRAL, Embase and MEDLINE, which identified 3,487 new records before deduplication.

Types of studies	Randomised controlled trials, including randomised cross-over trials, and quasi-RCTs. Full text and abstract publications; no language restrictions (see Jones et al. 2021 review) (14). Although the search strategy is designed to identify RCTs we also included any single arm exploratory trials identified through the update search.
Types of participants	Adults, children or both with myositis diagnosed by any established criteria. We screened for the following conditions: myositis; sporadic inclusion body myositis; polymyositis; dermatomyositis; juvenile dermatomyositis; anti-SRP myositis; necrotising myositis.
Types of interventions	Any type of exercise, compared with no intervention or another intervention (see Jones et al. 2021 review for ACSM definition of exercise) (14). We did not restrict inclusion by the duration of exercise intervention although the duration is often at least 6 weeks (see Jones et al. 2021 review) (14). We included single arm exploratory trials in which the intervention is any type of exercise.

Table 1: Eligibility criteria for evidence for updated search

We planned for initial screening of titles/abstracts to be completed by Katherine Jones (first author of the Cochrane PA review that published the original search strategy)(14) and at least 20% of the search results to be dual screened independently by GR.

We imported search results into Covidence to facilitate dual, independent screening of titles and abstracts. Covidence automatically removed 520 duplicate records, which left 2967 records for screening. KJ and GR screened titles and abstracts for inclusion based on the predefined eligibility criteria outlined above. As a narrative review, they also decided to consider search results of potential relevance to a broader neuromuscular or neurological population, and other types of evidence, such as reviews and non-interventional studies. However, it is important to note that the search strategy was primarily designed to capture RCTs and interventions for promoting physical activity. If there was any discrepancy for inclusion, the authors planned to resolve this by discussion.

Of the 676 records dual screened (23%), we found only five discrepancies (<1%), which were resolved through discussion in relation to the eligibility criteria. We agreed to exclude two studies that related to creatine supplementation, and provisionally included the three other studies for further consideration.

In total, we excluded 2934 of the 2967 records through screening of titles and abstracts. Two duplications of included records were also subsequently excluded, and full text publications were sought for the 31 remaining records (see list of records in Excel doc). KJ and GR retrieved 27 full text publications as two were conference abstracts and two were entries on a trials registry. One paper was translated from German to English using the translation option on the journal webpage.

GR (and MA) reviewed full text publications against the eligibility criteria and excluded 17 further publications because they did not include people with myositis (N=8); did not include an exercise intervention (N=6); protocol or commentary papers (N=4). Six papers were identified from two previous Cochrane reviews (13,14), and two additional papers were identified from the reference lists of included papers. In total, 16 articles were included in this review (18–32).

MA and GR consider the implications of the recently published evidence about exercise for people living with myositis, clinical practice and education.

Results

The main features of the articles included in the review are presented in table 2. We have considered the studies in terms of safety of exercise interventions, physiological change, functional change and behaviour change.

Safety of exercise interventions

Historically there was problematic advice telling people with IIM not to exercise to avoid worsening muscle damage. Secondary, disuse atrophy can be detrimental to function on top of the physical effects of primary disease. An important outcome from exercise research in this field is exploring the safety of exercise programmes.

A core outcome set for exercise trials in IIM was developed by the International Myositis Assessment and Clinical Studies (IMACS) group (33) that included a patient and physical global disease activity rating, using a 100 point visual analogue scale (VAS), Health Assessment Questionnaire (HAQ) and laboratory assessment of serum creatine kinase (CK). Four studies adopted the core outcome set (21,22,32,34), and of those that didn't, serum CK levels was also used in four other studies as an indicator of muscle damage (18,27,28,30). In addition, some studies measured additional indicators of inflammation, such as aldolase (28), erythrocyte sedimentation rate, serum C-reactive protein, creatine kinase, lactate dehydrogenase, myoglobin, and selected inflammatory cytokines, tumour necrosis factor or chemokines (32). No significant changes were observed with possible reductions in some inflammatory markers (32).

Symptoms were monitored using global activity scales (21) or visual analogies scales (VAS) for specific impairments such as pain and fatigue (27). Across the studies, there were no group changes in symptoms, though there were some individual reports of temporary symptoms, such as joint pain or delayed onset muscle soreness at the start of training programmes (27,32,35).

Muscle biopsy was used in two studies, one to explore changes in inflammatory infiltrates before and after exercise in people with early onset PM and DM (18), and another reported as a separate paper from the primary exercise intervention article in IBM (30) , that allowed a more in depth

exploration of inflammatory responses (23). Reassuringly, both studies did not show any signs of increasing inflammation.

Interventions studies targeting physiological change

The majority of included studies designed exercise protocols to promote changes in cardiopulmonary fitness or muscle structure and function. Aerobic exercise protocols were used to train a combined total of 92 people with myositis across 8 studies. They included a total 11 people with junior DM (19,22), 31 with DM (18,20,28,34,35), 25 people with IBM (27,31,35), 19 with PM (18,28,34) and 6 with IMNM (20). The training programmes were either as a stand-alone intervention (27,28,35) included as part of a combined training and strength regime (19,20,22,34) or combined with another intervention, e.g. energy conservation (26) or activity and balance training (32). The duration of training varied from 6 to 16 weeks, with a range of frequency of 2-5 times per week. Exercise intensity was set with some programmes using heart rate, e.g. at 60% of maximum heart rate, and was progressed with some training protocols across the intervention period (27,31).

Cardiopulmonary exercise testing (CPET) was used in six studies, using incremental protocols with a bicycle ergometer (20,22,27,28,34,35). All measured maximum or peak oxygen uptake (VO_2 max or VO_2 peak) during the exercise test, with some also recording work rate (WR), maximum heart rate (HR_{max}) and time or VO2 at anaerobic threshold. All studies, with the exception of the pilot study by Habers et al. (22), demonstrated significant effect of exercise on CPET variables (18,20,34,35) or a large effect size (27) indicating improved cardiorespiratory fitness or exercise capacity.

Muscle strength training protocols were instigated by six studies, either as stand-alone programmes (21,23,29,30) or as part of combined intervention with aerobic training (18–20,22,34). Strength training protocols were used to train a total of 144 people with myositis across 8 study cohorts. They included 53 people with juvenile DM (19,22), 33 with DM (18,20,32,34), 26 people with PM (18,32,34), 21 with IBM (23,29,30) and 11 with IMNM (20,32). Most regimes aimed to increase peak muscle strength and were either prescribed as a programme of strength training using body weight (18,19) or using weight resistance, though the method of resistance training was not clear in one study (32). Endurance training of the muscles was included as part of a combined programme with aerobic training where the aim was to increase the strength of 5 repetitions rather than peak strength (34). Innovative methods of training were introduced in two cohorts: resistance training with blood flow resistance in 21 people with IBM (23,29,30) and water based plyometric training in 16 people with juvenile DM (21). Plyometric training involves fast, explosive movements and the adaptation to water could help to reduce the impact of forces in people with muscle disease (21). In this study, water based plyometrics were compared against a standard, out-patient exercise regime to ascertain superiority of this method of training. This was not the case with studies of resistance training with blood flow occlusion, as the control was a passive group of no exercise (23,29,30).

Changes in muscle function were assessed most frequently by manual muscle testing, as recommended for inclusion in the IMACS core outcome set of exercise interventions (33). It was the primary outcome measure in one study (32) but most often included as a battery of secondary outcomes (19,30,34). The one repetition maximum (1RM) method was used by Borges et al. (20) and other studies used quantitative muscle testing with handheld dynamometry (21) and isokinetic and/or isometric dynamometry (27,29,30). Voluntary muscle activation using twitch interpolation was used in combination with dynamometry in an IBM cohort (29). Interestingly one study that incorporated resistance training as a significant element of a combined programme did not measure

muscle function but performed muscle biopsies to explore changes in inflammation (18). Improvements in muscle function were observed with resistance training (stand alone or as part of a combined program) across all studies included in this review (table 2) compared to baseline (20), compared to control groups (20,29,32,34) or compared to a control condition in a cross-over trial (21).

The immunological reaction to exercise was examined in detail by Jensen et al. (23) in a paper reporting separate results for the cohort of people with IBM who underwent resistance training with blood flow occlusion (BFRE) in the study by Jørgensen et al. 2018 (30). Muscle biopsies were performed in 21 of the original cohort, 11 who underwent training and 10 no exercise controls. Biopsies were taken from either the tibialis anterior or vastus lateralis muscles for evaluation of CD3-, CD8-, CD68-, CD206-, CD244- and FOXP3-positive cells by three-colour immunofluorescence microscopy and Visiopharm-based image analysis quantification. The analysis found an upregulation in CD3−/CD8+ expressing natural killer cell content, suggesting an amplified immune response with training. However, there were no changes in macrophage or T cell infiltration. The authors concluded that these findings indicate no risk of intensified inflammatory activity with BFRE. The same study group also reported changes in muscle structure as well as function in the participants with IBM (30) using DEXA scanning to measure thigh lean muscle mass, but no response to the BRFE training was found.

Muscle biopsy was also used by Borges et al. 2021 (20) to investigate the effect of combined exercise programme on the ubiquitin-proteasome system (UPS) and genes related to autophagy on the skeletal muscle in people with DM and IMNM. In addition to the improvements in muscle strength reported earlier, genes related to UPS were downregulated, whereas genes related to autophagy, mitochondrial pathways, and antioxidative systems were upregulated. The authors suggested that this indicated an increase in the recycling of damaged proteins and organelles, which may also contribute to the performance and endurance of skeletal muscles in these patients.

Interventions targeting functional change

With improvements in muscle function and cardiopulmonary fitness, improvements in function and daily activities are assumed. A large variety of functional measures were used as secondary outcomes in many of the studies presented in this review, but only two trained functional activities specifically.

Špiritović at al. (32) included specific balance training and practice of activities of daily living (ADL) in addition to resistance training in this combined program. Balance was assessed using stabilometry (force vector area) and ADL using the Functional Index-2 score. Significant improvements were observed in both measures that accompanied the improvements in muscle strength.

An innovative method of gait training was used for people with neuromuscular diseases (including one person with IBM) using the HAL-HN01 cybernetic device N, which is a robot assisted gait training triggered by motor unit detection (25). The study demonstrated improvements in 2 metre timed walk function compared to a control group who practiced walking in a hoist. There was only one person with myositis in the cohort who actually showed a decline in walk time, so the effect of this intervention would need to be replicated in a larger myositis cohort.

Where functional measures were secondary to aerobic or resistance training, functional improvements were observed in most trials (18,21,22,28,30,31,34) but not all (19,27,29). Often trials

are powered for physiological or muscle performance outcomes, rather than functional activities, so this may account for where change is not observed, but it may also be due to lack of training specificity for more complex functions.

Interventions targeting behaviour change

Veenhuizen et. al. (26,31) developed the Energetic intervention of group self-management, aerobic exercise, energy conservation and relapse prevention. They included facilitated sessions with Occupational Therapists and Physiotherapists to provide support with the different elements of the program. Here the focus was on educating and empowering the person living with neuromuscular disease to adopt these positive behaviours. This 16-week programme was compared to usual care and demonstrated a significant improvement in the Canadian Occupational Measure (COPM) across all time points in participants receiving the Energetic programme.

Discussion

For many years, people with myositis were told not to exercise for fears of increasing inflammation and muscle damage. With exercise being recommended more often, it is of utmost importance for the person living with IIM to know what type and dosage of exercise is safe and effective. Some of the studies reviewed included people with myositis in larger studies of people with other muscle wasting diseases (25,27,31). The question for people living with IIM could be whether a more generic application of exercise programmes is appropriate or safe for people with IIM, with inflammation a key feature of these myositis, but not in other muscle diseases, e.g. muscular dystrophy.

What is striking from this review is that a large variety of exercise types, durations and prescriptions have been investigated with no increases in serum CK (refs) or inflammatory markers (32), with anti-inflammatory effects (18) and increased recycling of damaged proteins (20) suggested. Another important finding from comparisons with no-exercise control groups is that a decline in muscle strength in IBM continues with no intervention (30) and exercise interventions improve muscle function parameters. These two conclusions support the premise that most activity is good for disease management and these studies provide a wider “menu” of exercise types that people may wish to engage with. For a person living with IIM, knowing that exercise can have a real effect on muscle function, as well as the other more generic benefits, is positive and motivating. Furthermore, with the increasing number of different exercise types that are being shown to yield positive effects, people living with IIM with particular exercise preferences can select what is more motivational for them while also understanding the strengths and limitations relating to how successful their chosen approach could be. We are moving towards a time where people living with IIM will be able to be presented with greater and more informed choice of how to manage their own treatment, which could lead to greater engagement with exercise and physical activity.

The safety monitoring data in these studies is reassuring and of particular interest are the muscle biopsy methods used to explore this. Not only is there no evidence of increasing inflammation with exercise, but there may even be an anti-inflammatory effect. Could this provide a disease modifying effect? Further longitudinal studies would be required to understand if disease trajectories are altered with people who exercise or are physically active, as has been observed in small cohorts of people with muscular dystrophy (36). We should be cautious, however, to ensure that longitudinal studies not only focus on the effect on the muscle, but also physical functioning that is meaningful to

people living with the conditions. This adds complexity, as larger cohorts will need to be recruited, but required to understand the effect sizes and minimally clinically important differences.

Disease modifying drugs are being developed for some types of myositis so it is important to understand the effect sizes of strength training interventions in particular. For example, drugs targeting protein homeostasis may have potential to increase muscle mass (37). The question is whether the effects of those drugs are greater than the effect of resistance training, and could their effect actually be enhanced by a well thought out, individualised and targeted exercise programme?

There has been an assumption that engagement in structured exercise programmes will automatically lead to greater engagement in physical activity and exercise beyond the supportive environment of participation in a trial. Wallace et al. (27) stated their aim to improve self-management by participants training in their local leisure facilities. Astley et al. (19) responded to restrictions from the Covid-19 pandemic with a home based, virtually supported programme, and other studies included extended follow up or open-label periods to explore longer term effects (32,34). Exercise effects tended to tail off on cessation of the active elements of the programmes (32,34) with active "washout" periods included in two cross-over trail designs (21,27). This indicates that continued engagement is required to sustain beneficial effect but one study in IBM and other studies in NMDs find that a minority of participants continue to exercise independently beyond the training periods (8,27,38,39). Three studies included in this review incorporated qualitative methodologies to understand the experiences of participation in the trials (19,26,27). A consistent finding was that the support from trainers and coaches was very important for motivation and engagement.

We should now start to shift our focus from trials that focus on just changing the structure and function of muscle, but how can people living with IIM bring exercise and physical activity into their day to day lives. Voorn et al. (35) took an important step in co-designing the Be-FIT exercise programme with people living with muscle diseases with an aim to carrying over into the home or community. People living with IIM are best placed to tell us what will work best for them to achieve that aim. The Energetic study by Veenhuizen et al. (26,31) is the only one in this review that incorporates more psychological approaches to improve self-management through support and education. It has been argued that behaviour change theories need to underpin physical activity interventions for long term implementation and benefit (8), with increased engagement as the goal.

The work to date indicates improvement in aerobic capacity and functional improvement, reflecting the more in depth metanalysis performed (40). However, this and other systematic reviews in muscle disease have highlighted methodological issues with studies in this field. There are particular issues with small sample sizes in trials of rare diseases so incorporating core outcome sets, such as the measures recommended by IMACS (33) will aid future metanalysis. With the suggested shift of focus to the individual, we would also recommend inclusion of co-designed core outcome sets that prioritise what is important to people living with rare neurological diseases, relating to the real life situations they encounter every day (17). If engagement is the key ingredient, then pragmatic trials using wearable technologies could be designed where activity and physical effort is tracked as an intervention goal as well as an outcome measure (41–43).

The research community in this field needs to build on this change of focus to further a paradigm shift to include people living with IIM in the design of programmes (35), outcome measurement (17) and support of the person rather than just focus on the muscle (26,31).

Study citation	Design & methods	Participants	Interventions	Outcomes	Results
Alexanderson et al. 2014	Single blinded, randomised, controlled trial for 24 weeks, with 80-week open label follow up	Polymyositis (PM) or Dermatomyositis (DM) N=19 [10 intervention group, 9 control group] Onset <3 months Median age 60 years (52-67)	Intervention group (EG): 12 weeks, 5 times per week, supported resistance training and brisk walking at home, followed by 12 weeks, twice a week, home/gym combined with immunosuppression. Control group (CG): range of motion exercises plus immunosuppression	Disease-Specific Functional Index (FI), Aerobic capacity, Nottingham Health Profile, CPK levels, Muscle biopsy (inflammation)	N=6 dropouts. Improved FI and aerobic capacity in both groups at 24 and 52 weeks, exercise group at 104 weeks. No increase in inflammation through CPK and muscle biopsy analysis
Astley et al. 2021	Quasi-experimental, mixed methods study for 12 weeks	Juvenile DM N=11 Mean age 13.2 years (±3.2 years)	12 week aerobic and bodyweight exercise training program, 3 times per week. One session per week with live, online supervision (1-5 participants), 2 sessions with feedback to the trainer via messaging app. Online instructional materials.	Strength & Difficulties Questionnaire (SDQ), Paediatric Quality of Life inventory (PedsQL), Pittsburgh Sleep Qquality Index (PSQI), Manual Muscle Test (MMT), Childhood Muscle Assessment Scale (CMAS), Disease Activity Score (DAS), qualitative data (text or voice message)	N=2 dropouts. No change in SDQ, PedsQL and PSQI with the exercise intervention. Some perceived health benefits from qualitative data, e.g., improved energy, mood and sleep. The online format was mostly received positively, and the trainer support was valued by participants.

Borges et al. 2021	Quasi-experimental, longitudinal	Systemic Auto-immune Myopathies: N=7 with DM, N=6 with Immune Mediated Necrotising Myopathy (IMNM). Health control group N=10 Mean age: DM 49.8 (±2.3), IMNM 58.5 ±10.6), control 48.7 (±3.9) years	12 weeks, twice a week combined program of resistance, aerobic and stretching exercises.	Muscle biopsy: identification of auto-antibodies RNA integrity & concentration, Maximal cardiopulmonary exercise test (CPET). Variables: VO_2 peak, time of ventilatory anaerobic threshold (VAT), point of respiratory compensation (RCP), time to exhaustion. 1 repetition maximum test, Timed-up-and-go (TUG), Timed stands test (TST)	Post exercise, several genes related to UPS were downregulated, whereas genes related to autophagy, mitochondrial pathways, & antioxidative systems were upregulated in the DM and IMNM groups. DM: improvement in time to VAT and exhaustion, leg & bench press loads, TST & TUG. IMNM: improvement in time to RCP, bench press load & TUG
Elnaggar et al. 2021	Single-blind, randomised, cross-over pilot study	Juvenile DM N=16 [8 intervention group, 8 control group] Mean age: 13.44 (±2.85)	Training condition: 45 minutes of supervised water-based, plyometric exercise, 3 times a week for 4 weeks Control condition: standard outpatient care consisting of 45 minutes of supervised, combine flexibility, aerobic and resistance exercises, 3 times	Maximum Isometric Force (MIF) using hand-held dynamometry (make-test) for hip flexors & abductors, knee flexors & extensors, PedsQL Multidimensional Fatigue Scale, Childhood Health Assessment Questionnaire (CHAQ), Patient/parent	Improvement in all outcome measures following both water-based and standard exercise training. Greater improvements were observed in muscle strength, fatigue, functional ability & disease activity with plyometric training.

			a week for 4 weeks 1 month washout prior to crossover	global disease activity assessment	
Habers et al. 2016	Multicentre, randomised controlled trial, parallel group	Juvenile DM N=26 [14 intervention group, 12control group] Median age: 12.3 years (range 8.3-17.6)	Intervention group: interval training on a treadmill, resistance exercise. Supervision every other week. Waiting list control group:	Feasibility: tolerability, safety & adherence; Aerobic fitness: VO2 peak, VO2 at ventilatory anaerobic threshold, endurance time. Visual Analogue Scale (VAS) for pain, muscle function subscale of Bruininks-Osteretsky Test of Motor Proficiency, Childhood Myositis Scale, 6 Minute Walk Test (6MWT), Physical Activity Enjoyment Scale, PedsQL Generic Core Assessment, Childhood Health Assessment Questionnaire, VAS global disease activity, physical activity (accelerometery)	N=8 dropouts. 75% of remaining participants completed median 30/32 sessions. No adverse events. No difference between groups in aerobic fitness or secondary measures except for 3 items of the Bruininks-Osteretsky scale (long jump, push ups and sit ups) in favour of the training group.

Jensen et al. 2019	Randomised, controlled trial. Single Blinded.	Same cohort as Jørgensen et al. 2018 and 2021 Sporadic Inclusion Body Myositis (SIBM) N=21 [11 intervention group, 10 control group]. One participant of the original 22 refused repeat biopsy	Intervention group: 12 weeks, twice a week, low load (25 repetition maximum), blood flow occluded resistance training. Blood flow occlusion using inflatable pneumatic cuff on proximal thigh or calf. Control group: no exercise	Muscle biopsy: immunological markers for T cells, natural killer (NK), M1 and M2 macrophages.	Increase in CD3 and CD8 NK cells in the intervention group. Decrease in CD28 T cells in the control group. No changes in cytotoxic or regulatory T cells, M1 or M2 macrophages in either group.
Jørgensen et al. 2018	Randomised, controlled trial. Single Blinded.	Same cohort as Jensen et al. 2019 and Jørgensen et al. 2021 Sporadic Inclusion Body Myositis (SIBM) N=22 [11 intervention group, 11 control group]	Intervention group: 12 weeks, twice a week, low load (25 repetition maximum), blood flow occluded resistance training. Included muscles: knee extension, flexion, plantarflexion & dorsiflexion. Blood flow occlusion using inflatable pneumatic cuff on proximal thigh or calf. Control group: no exercise	Short Form Health Survey (SF36); 2-minute walk test (2MWT), Timed-up-and-go (TUG), 30 seconds sit to stand test (STS), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Myositis Disease Activity Assessment Tool (MDAAT), Patient & Physician Global Activity & Damage VAS, Myositis Damage Index (MDI), Creatine Kinase levels (CK), Health Assessment Questionnaire (HAQ), Manual	N=2 dropouts from intervention group. Low training adherence with 1 participant (<66%). No between group differences in SF36, 2MWT, TUG or STS. Between group difference in IBMFRS in favour of the intervention group. Increased decline in knee extensor torque in the control group with per protocol analysis.

				Muscle Test for 8 muscles (MMT-8), isokinetic dynamometry for knee extensor torque.	
Jørgensen et al. 2022	Randomised, controlled trial. Single Blinded.	Same cohort as Jørgensen et al. 2018 and Jensen et al. 2019 Sporadic Inclusion Body Myositis (SIBM) N=22 [11 intervention group, 11 control group]	Intervention group: 12 weeks, twice a week, low load (25 repetition maximum), blood flow occluded resistance training. Included muscles: knee extension, flexion, plantarflexion & dorsiflexion. Blood flow occlusion using inflatable pneumatic cuff on proximal thigh or calf. Control group: no exercise	Training load (kg) and volume (load x reps), isometric dynamometry: maximum knee extensor strength & rate of force production, maximum knee extensor muscle power, thigh lean mass (DEXA scan), voluntary activation of knee extensors (twitch interpolation), index of limb asymmetry, 2-minute walk test (2MWT), Timed-up-and-go (TUG), 30 seconds sit to stand test (STS),	N=3 dropouts, and 1 insufficient adherence to program (<66%). Per protocol analysis. Between group differences observed: Increase in knee extensor strength and rate of force development with training in the stronger leg with a decline in the control group, decrease in knee in extensor power in control group with no change in training group. No between group differences observed in weaker leg, lean mass, voluntary activation, or functional measures.

Munters et al. 2013	Multicentre randomised, control trial, single blinded	N=21 PM (9) and DM (12) patients (n = 11 in the intervention group and n=10 in the control group)	Intervention group: 12-week, supervised endurance training program. 1 hour, 3 times a week. Exercise bicycle training for 30 minutes then muscle endurance exercises at 30-40% of 1 repetition maximum. Control group: 12-weeks of no exercise. Invited to participate in exercise after 12 weeks. 52-week open extension follow up	Primary outcome: VO2 max from incremental cycling test. Secondary outcomes: Short form 36 (SF36), McMaster Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR), Myositis Activities Profile (MAP), 5 repetition maximum (RM) for knee extensors, patient's & physician's global disease activity (VAS; range 0–100), MMT in 8 groups, Health Assessment Questionnaire, serum CPK, Myositis Intent-to-Treat Activity Index and global extra-skeletal muscle activity VAS	N= 2 dropouts Between group effects were observed favouring the intervention group for the following measures: VO2 max (O2 uptake & work, Physical function & Vitality domains of the SF36, physician's global disease activity,), 5RM for the left leg, 'moving around' domain of the MAP. Participants were identified as responders, if they improved by ≥20% in 5 VRM or by ≥10% in VO2 max compared to baseline: 8 in the intervention group & 2 in the control group. Some indication of reduced disease activity in the intervention group.

					Open extension between group effects in favour of the intervention group for the 'Vitality' domain of the SF36, the 'Work' domain of the MAP and a trend to continued improvement in 5RM for the left leg.
Nakajima et al. 2021	Multicentre randomised, crossover trial. Open label but blinding of assessors of gait parameters	N=24 participants with slowly progressive neuromuscular diseases including SIBM. N=24 (N = 13 in the intervention group and N=11 in the control group) Only 1 participant with myositis (IBM) assigned to intervention group	HAL-HN01 cybernetic device: robot assisted gait training triggered by motor unit detection. Intervention condition: 40 minutes gait training with a walking hoist plus HAL-HN01 device Control condition: 40 minutes gait training with a walking hoist	Primary outcome: 2 MTW. Secondary outcome: 10MTW (speed, cadence), VAS 0-100 for perception; Rivermead Visual Gait Assessment; Manual Muscle Testing (MMT), Barthel Index; 12 lead ECG,	The participant with IBM showed a negative change in 2MTW with the intervention, but the magnitude of negative change was greater with the control condition.
Špiritović et al. 2021	Prospective, controlled, assessor-blinded, non-randomized, single-centre trial	Idiopathic Inflammatory Myopathy N=57 (N = 30 in the intervention	48-week inclusion in the study. All participants given educational materials on activities of daily living and	Primary outcomes: manual muscle resting (MMT-8) & Functional Index-2 (FI-2).	Significant improvement in MMT-8 in the intervention group at 24 weeks, with a decline in the

		group and N=27 in the control group) Allocated according to proximity to the centre running the trial	exercise as usual treatment (TAU) Intervention group: 24 weeks, supervised activities of daily living, resistance, and stability training (ADLRSp) followed by 24 weeks of TAU Control group: 48 weeks of TAU	Secondary: Health Assessment Questionnaire (HAQ), Short Form 36 (SF-36), Fatigue Impact Scale (FIS), Beck's Depression Inventory-II (BDI-II), static balance: force vector area (FVA) basal metabolic rate (BMR) and muscle fitness (extracellular mass to body cell mass ratio [ECM/BCM]) assessed by bioelectric impedance.	control group over that period. The effect of the intervention was not sustained at 48 weeks. Significant improvement in FI-2 with exercise. Significant between group effects at 24 weeks with improvements in HAQ, BDI0II, FVA, BMR and ECM/BCM in the intervention group. No difference in SF-36. No increase in inflammatory markers
Veenhuizen et al. 2019	Multicentre, single blinded RCT Assessment prior to randomisation (T0), after intervention period (T1), 3 months follow up (T2) and 11 months follow up (T3)	Participant with NMDs, including IBM. N=29 in the invention group (including 3 people with IBM), N=24 in the control group (including 2 people with IBM).	Intervention group: 16 week Energetic intervention: 9 weeks aerobic exercise training (AET)(twice a week supervised, once a week at home), 7 weeks AET (once a week supervised, twice a week at home) using bicycle, treadmill or rowing training at 50-70% or maximum heart rate.	Primary outcome: Canadian Occupational Performance Measure COPM) Secondary outcome: Checklist Individual Strength-Fatigue Subscale, 6-minute time walk (6MTW), Activity card sort (ACS,	N=3 dropouts but included in Intention to Treat Analysis (ITT) Significant between group effect with significantly higher COPM performance at T1, T2 and T3. Significant improvements in 6MTW (T1-

			Education sessions on exercise, energy conversation, relapse prevention, support to apply exercise at home. Additional booster session 2 months after the end with Physiotherapist or Occupational Therapist. Control intervention: Treatment as usual (TAU)	Hospital Anxiety and Depression Scale (HADS) and Generalised Self-efficacy Scale (GSES	T3) HADS-Depression (T1 and T2) and ACS (T1). No significant differences in Checklist Individual Strength, GSES or HADS-Anxiety.
Veenhuizen et al. 2021	Mixed methods evaluation of trial reported in Veenhuizen et al. 2019	Participant with NMDs, including IBM. N=29 in the invention group (including 3 people with IBM), N=24 in the control group (including 2 people with IBM).	Intervention group: 16 week Energetic intervention delivered in small groups: 9 weeks aerobic exercise training (AET)(twice a week supervised, once a week at home), 7 weeks AET (once a week supervised, twice a week at home) using bicycle, treadmill or rowing training at 50-70% or maximum heart rate. Education sessions on exercise, energy conversation, relapse prevention, support to apply exercise at home. Additional booster session 2	Satisfaction questionnaire for participants Qualitative interviews (individual and focus groups) to explore the experiences of patients and healthcare professionals and into facilitators and barriers regarding the Energetic programme.	N=25 completed satisfaction questionnaire N=7 individual interviews, N=12 focus groups, N=2 partner interviews 96% of the participants were entirely or largely satisfied with the results of the intervention. Mean satisfaction score 8.7 (± SD 1.1). Management of the impairments was perceived as 'entirely' or 'largely'

			months after the end with Physiotherapist or Occupational Therapist. Therapists trained in self-management and behaviour change Control intervention: Treatment as usual (TAU)		improved by 88% of participants. Themes from interviews: Combination of modules makes a complete picture; being prepared to change lifestyle is pivotal; sustainability of implementation in daily live is essential; sports performance in one's own environment is challenging; the program is physically and mentally intensive; the group setting is valuable; therapists are coaches, therapists need education
Voorn et al. 2021	Multi-centre, prospective pilot study to evaluate feasibility & preliminary effectiveness	N=31 (including N=3 with IBM & N=1 with DM)	BE-FIT training guides: therapist and participant manuals. Intervention: 5 visits to set goals, monitor progress and provide support. Additional telephone support.	Measures taken one week prior to the intervention (T0) and immediately afterwards (T1). Feasibility: completion rate of logbook.	N=5 dropouts. Of the participants who remained, >75% of training sessions were completed. Overall satisfaction from

			4-month home-based intervention with a combination of high and low intensity on a bicycle ergometer	Satisfaction questionnaires for participants and therapists. Change in HR_{max} with incremental exercise testing between T0 and T1. HR_{rest} and submaximal RPE (RPE_{submax}), and increased peak workload (W_{peak}), and workload at anaerobic threshold (WAT)	participants & therapists Mean HRsubmax reduced significantly by −6.5 beats per minute at baseline to after intervention. A significant reduction was also found for RPE_{submax} (−1.5 points on the Borg Scale, significant increases in W_{peak} & WAT
Wallace et al. 2019	Single-blinded, single centre, randomised, cross-over feasibility trial	N=17 people with IBM	Training condition: 12 weeks, 3 times per week training on a recumbent bicycle ergometer at a local, community gym. 30 minutes aerobic training starting at 60% maximum HR for 0-4 weeks, 70% at 4-8 weeks & 80% at 8-12 weeks. Weekly support from physical trainers trained in the protocol, monthly support from trial physiotherapist. Control condition: discouraged from	Primary outcome: VO_2 peak from incremental, cardiopulmonary exercise test (CPET) on a bicycle ergometer. Secondary outcomes: work rate with CPET testing (W), body mass index (BMI), percentage body fat, blood pressure, spirometry; Fatigue Severity Scale (FSS); VAS for pain; isometric & isokinetic	N=1 dropout, included in ITT. N=1 unable to complete exercise testing due to high blood pressure, but secondary outcomes assessed. Completion of 97% of exercise sessions. 17.4% improvement in VO_2 peak with training, 1.3% deterioration with control condition. Cohen's D

			increasing usual activity level. Monthly telephone calls Crossover: 8-week TAU between conditions	lower limb muscle strength; 6MTW & 10 metre timed walk (10MTW); Walk-12 scale; 7 days accelerometery; Self-efficacy for Managing Chronic Diseases Scale; Barriers to Activity & Exercise scale; Short Form–36; Pittsburgh Sleep Quality Scale; Epworth Sleepiness Scale; International Physical Activity Questionnaire Qualitative, semi-structured interviews & 3 month follow up telephone call on cessation of participation. Monitoring: exercise diaries, VAS for pain and fatigue, serum creatine kinase.	effect size: 1.72 (strong). Secondary outcomes: 17.3% improvement in work rate with training, 0.4% improvement with control condition. No major changes in other outcomes measured. No changes in serum CK levels, pain or fatigue. Qualitative interviews: participants reported finding the training acceptable but highlighted the importance of support from trainers % physiotherapists. Perceived improvement & wished to continue exercising. Telephone calls at 3 months: 5 participants still exercising. Reasons for cessation: gym costs, time, loss of confidence.

Wiesinger et al. 1998a	Randomised, controlled trial. Blinding not reported.	N=9 people with DM, N=5 people with PM 7 participants in each group	Intervention group: 6 weeks training, twice a week for weeks 1-2, 3 times a week for weeks 3-6. One-hour sessions of static cycling at 60% maximum HR for 30 minutes, followed by 30 minutes of step aerobic exercises. Training supervised by a physiotherapist. Control group: no training.	Primary outcome not identified. Functional assessment: Functional Assessment Screening Questionnaire for activities of daily living (ADL); isokinetic strength of knee extensors & flexors VO_2 max from incremental, cardiopulmonary exercise test (CPET) on a bicycle ergometer. Monitoring: Serum CK and Aldolase.	ADL: 20.5% improvement in ADL score in intervention group, 2.9% improvement in the control group with significant group effect. Lower limb muscle strength: 29.4% improvement in the intervention group, 11.1% improvement in the control group with significant group effect. VO2 max: 12% improvement in intervention group, 2.6% deterioration in control group. Significant group effect. No significant chank in serum CK or aldolase

Table 2: Summary of data extraction from

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