

Peripheral Muscle Dysfunction in Interstitial Lung Disease: A Scoping Study

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Abstract

Purpose: To characterize the state of the evidence for peripheral muscle dysfunction in individuals with interstitial lung disease (ILD).

Method: A scoping study was performed by searching multiple electronic databases for published papers and conference abstracts of any study design that included a measure of peripheral muscle dysfunction and/or structural and metabolic characteristics of muscle. All sub-types of ILD were eligible.

Result: Forty-five studies representing 2522 individuals with 34 sub-types of ILD were included in this study. Data were charted using descriptive numerical analysis of study characteristics. Peripheral muscle dysfunction was predominantly reflected by reduced volitional isometric strength (17 studies), whereas the evaluation of muscle endurance was rare (2 studies). Volitional muscle force or torque was measured in the quadriceps (14 studies) and handgrip (8 studies), with strength preferentially reduced in the lower limbs. Eight studies measured structural or metabolic characteristics and found evidence of reduced muscle size and oxidative stress. Findings of muscle injury and muscle inflammation (e.g. serum markers, electromyography and muscle biopsies) were reported primarily in individuals with idiopathic inflammatory myopathies and connective tissue diseases.

Conclusions: Reduced volitional muscle strength was the most common finding of peripheral muscle dysfunction in ILD. Further quantification of peripheral muscle dysfunction and identification of structural and metabolic characteristics are needed to target specific interventions and optimize muscle function.

Keywords: Interstitial lung disease; Muscle dysfunction; Scoping study

Introduction

Interstitial lung disease (ILD) represents a large group of chronic respiratory disorders of known and unknown causes. Interstitial lung disease varies in histology and radiology, as well as clinical presentation including severity and progression of lung disease, response to medications and prognosis (Figure 1) [1,2].

Individuals with ILD can present with respiratory symptoms of dyspnea and fatigue, impaired exercise capacity, reduced health-related quality of life (HRQOL) and decreased life expectancy. Little is known about peripheral muscle dysfunction in ILD, however individuals with ILD have impairments and risk factors that have been proposed to contribute to peripheral muscle dysfunction including inactivity, hypoxemia, hypercapnea, side effects of corticosteroids, age-related changes, systemic inflammation, oxidative stress and malnutrition [3].

Peripheral muscle dysfunction is defined as an alteration in muscle strength and/or muscle endurance resulting from structural and metabolic changes in the muscle [4]. In the context of this study, muscle inflammation and muscle injury were included as alterations in muscle that may contribute to muscle dysfunction (Figure 2).

Specific factors related to the ILD sub-type may contribute to peripheral muscle dysfunction. Sarcoidosis is a multisystem disorder that can involve muscle inflammation or myositis and muscle granulomas [5]. Idiopathic inflammatory myopathies (IIMs) are a group of rare systemic immune-mediated disorders that lead to chronic muscle inflammation accompanied by proximal muscle weakness [6].

There are a number of myositis-specific autoantibodies strongly associated with ILD involvement in individuals with IIMs [7,8]. Collagen vascular diseases, also known as connective tissue diseases (CTDs), are a heterogeneous group of autoimmune disorders affecting a variety of organs such as the lungs and skeletal muscle, and include rheumatoid arthritis (RA), scleroderma/systemic sclerosis (SSc), systemic lupus erythematosus (SLE), Sjorgren's syndrome and mixed connective tissue disease (MCTD) [9].

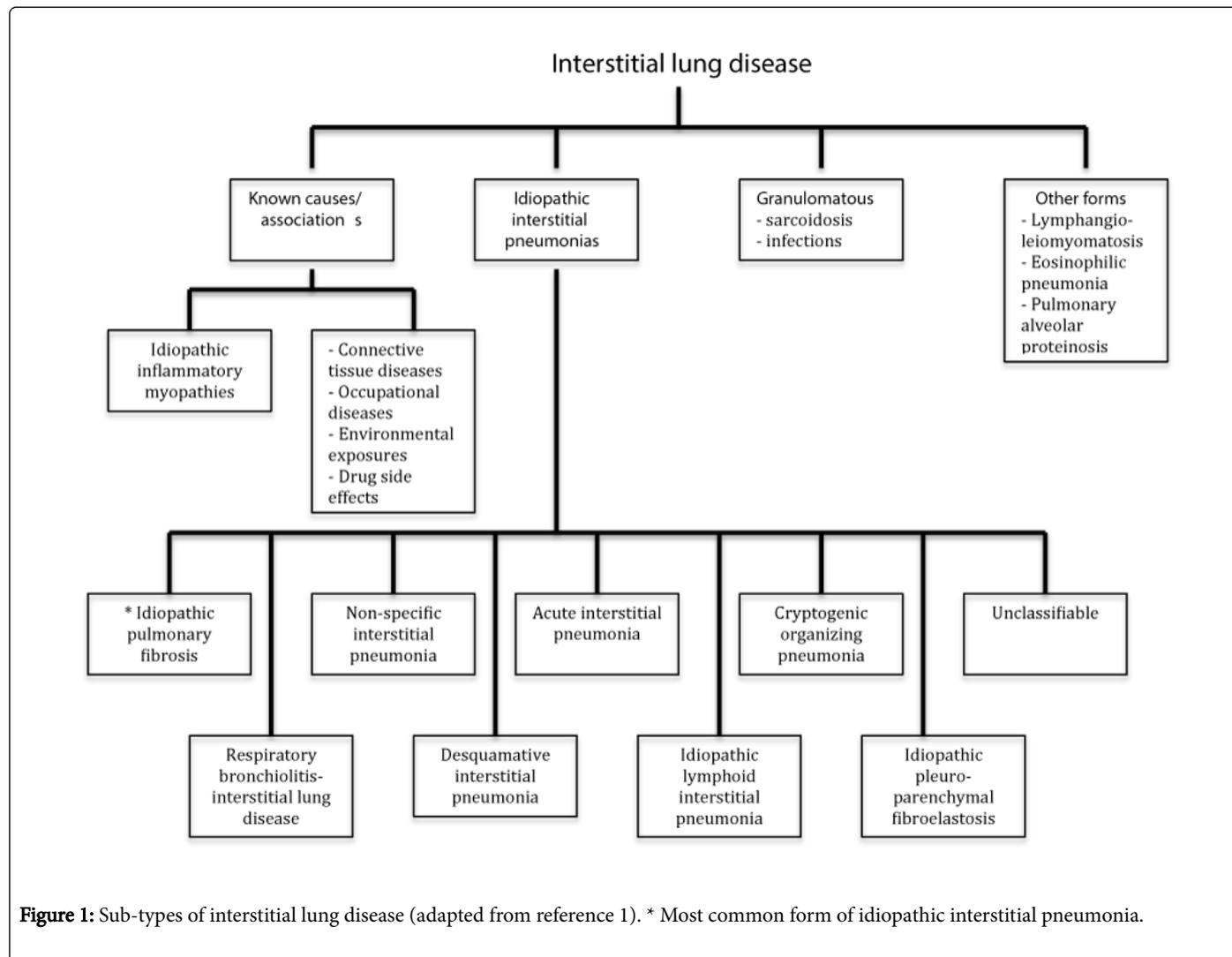
These conditions can result in myositis and be associated with IIMs in overlap syndromes. In addition, oral corticosteroids are often administered long-term in IIM, CTD and sarcoidosis to reduce systemic inflammation, and prolonged use can lead to a chronic steroid myopathy [10].

Although loss of muscle mass contributes to a decrease in muscle strength, other factors including qualitative changes in the contractile

properties of muscle (e.g. morphology, architecture, composition and biochemistry) can impact the force-generating capacity relative to the size of the muscle [11].

Peripheral muscle dysfunction (e.g. reduced force-generating capacity or weakness and reduced muscular endurance and/or contractile fatigue) can impact physical performance, functional capacity, levels of physical activity, activities of daily living, and may

have important implications for morbidity and mortality in ILD as has been documented in other chronic lung diseases [12]. Peripheral muscle dysfunction is potentially remediable through exercise, nutritional supplementation and pharmaceutical interventions. A better understanding of the structural and metabolic characteristics of muscle that can potentially contribute to peripheral muscle dysfunction in ILD is warranted.



Given the heterogeneity of ILD, the broad definition of peripheral muscle dysfunction and contributing factors, and a lack of randomized controlled trials in this area, a scoping study (rather than a systematic review) were performed to characterize the state of evidence for peripheral muscle dysfunction in ILD.

This methodology is an exploratory, iterative form of knowledge synthesis involving many types of evidence that systematically maps the breadth and depth of research activity of a broad and diverse topic

to provide greater clarity, identify gaps in the existing literature and inform practice and policy [13].

The aims of this scoping study were to 1) describe findings of peripheral muscle dysfunction in adults with all sub-types of ILD 2) describe alterations in muscle structure and muscle metabolism that could contribute to peripheral muscle dysfunction and 3) clarify what is lacking in the current literature and identify areas for future research.

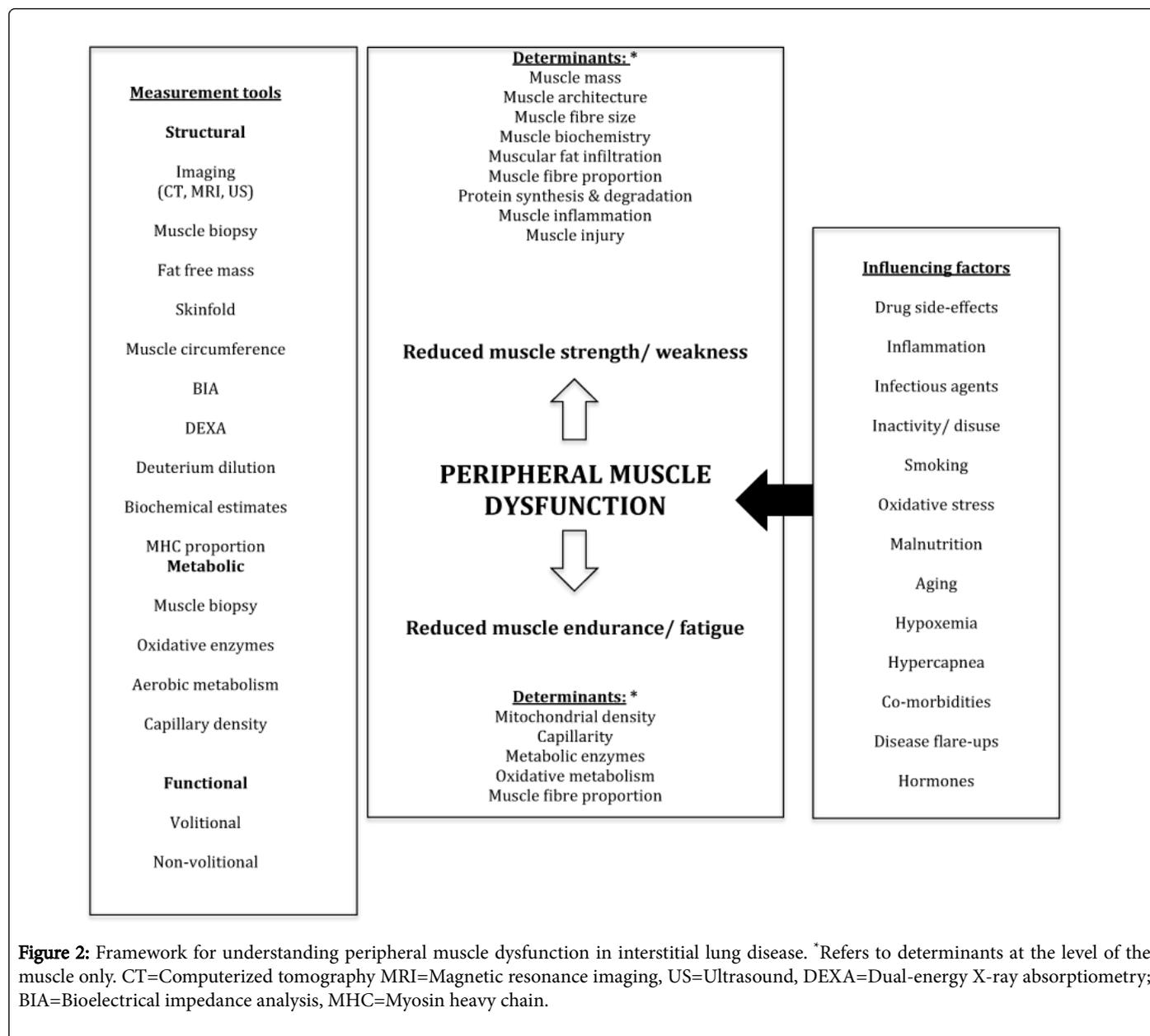


Figure 2: Framework for understanding peripheral muscle dysfunction in interstitial lung disease. *Refers to determinants at the level of the muscle only. CT=Computerized tomography MRI=Magnetic resonance imaging, US=Ultrasound, DEXA=Dual-energy X-ray absorptiometry; BIA=Bioelectrical impedance analysis, MHC=Myosin heavy chain.

Method

This study was conducted utilizing established frameworks for scoping studies, including identifying the research question, searching and selecting relevant studies, charting the data, and summarizing and reporting the results [13,14].

Identifying the research question

Is ILD associated with findings of peripheral muscle dysfunction (e.g. reduced muscle strength or muscle endurance) or structural and/or metabolic alterations that can lead to peripheral muscle dysfunction?

Search strategy

A librarian from the University health network (UHN), Toronto, Canada was initially consulted to refine the key concepts and search strategy. We systematically searched multiple electronic databases including MEDLINE, MEDLINE In-Progress, EMBASE, CINAHL, PEDro, cochrane database of systematic reviews and controlled clinical trials and clinical trials registries (Figure 3). Interstitial lung disease medical subject headings [exp. lung diseases, Interstitial or pulmonary fibrosis] were combined (AND) with terms focusing on muscle dysfunction [exp. muscular diseases, muscle fatigue, exp. neuromuscular manifestations] and selected keywords [sarcopenia, myositis, grip adj 2 weak*, muscle or muscular, quadriceps, rectus femori*, vastus intermedi*, vastus mediali*, vastus laterali*, tibialis anterior, limb, arm or leg (weak* or atroph* or fatigue or dysfunction)]. The search was limited to humans, the adult population (>18 years) and studies published in English from inception to June 2015. A

citation manager RefWorks™ was used to eliminate duplicates. References of relevant articles were manually searched.

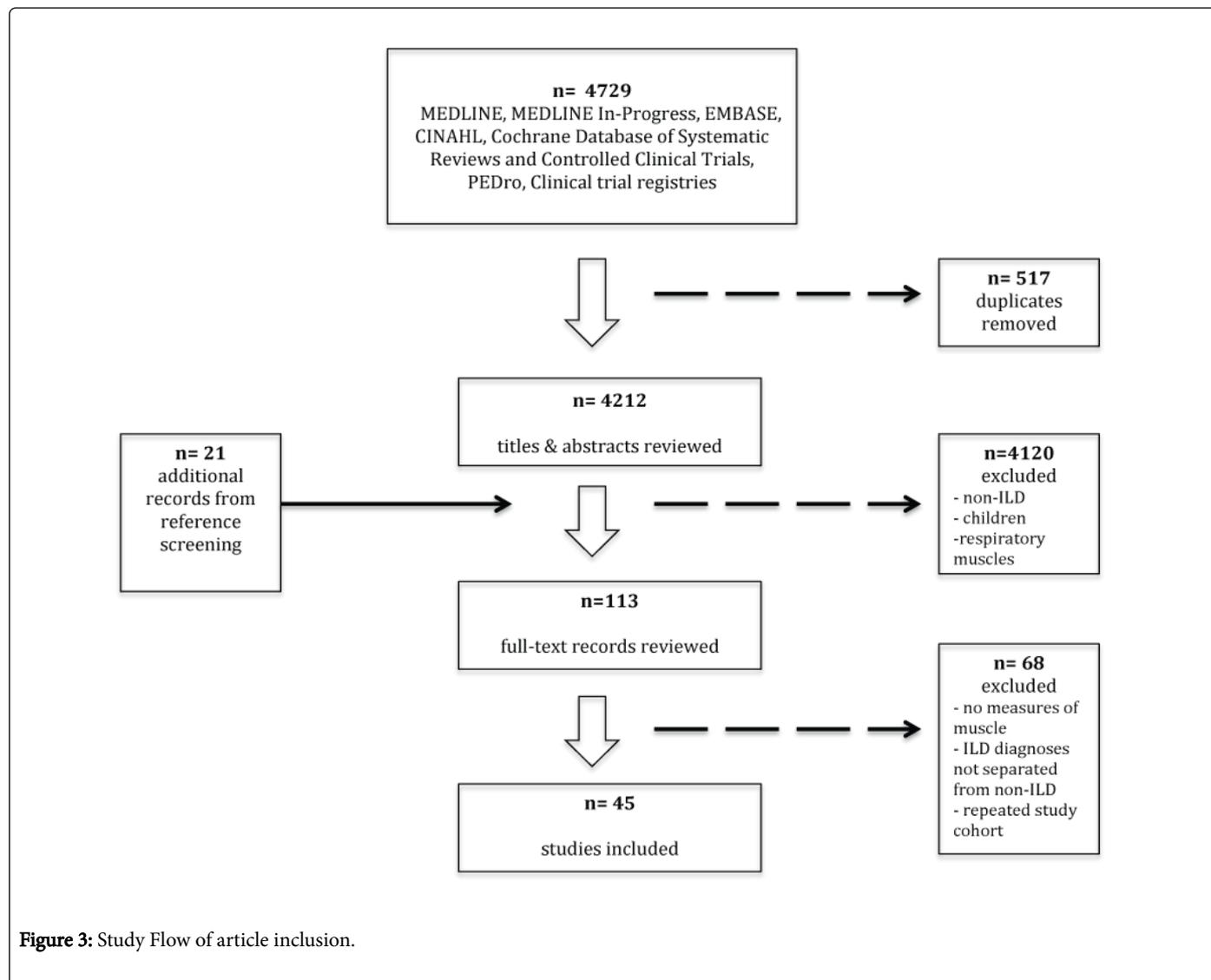


Figure 3: Study Flow of article inclusion.

Study selection

Two authors (LW and SM) independently screened the titles and abstracts to identify potential studies to screen as full-texts. A third reviewer (DB) was available for consultation in cases of disagreements during the screening process. All study designs were included and conference abstracts were accepted.

Studies including individuals with all sub-types of ILD were eligible, however the criteria were adapted throughout the course of the study to include study participants with IIM, CTD or sarcoidosis only if there was reported evidence of lung involvement on chest X-ray or pulmonary function tests.

Charting the data

Data extraction was performed by one reviewer (LW) on eligible full-text studies using a pre-defined data abstraction form that was initially pilot-tested by two reviewers (LW and SM) on three studies and further refined.

Data extraction included study design, publication type, sample size, subject demographics, ILD sub-type, and diagnostic criteria for lung disease, measures and findings of peripheral muscle dysfunction, muscle structure and metabolism. The choice of muscle measures was based on previous work on peripheral muscle dysfunction in chronic obstructive pulmonary disease (COPD) and also incorporated markers of muscle inflammation and injury that are commonly observed in IIMs and CTDs [3,15]. Results were exported to Microsoft Excel.

Data synthesis

A descriptive, numerical analysis of the study characteristics was performed and findings of peripheral muscle dysfunction and alterations of muscle structure and metabolism were synthesized into categories. A quality assessment was not performed, and there was no consultative stage with stakeholders [13]. Evidence gaps were identified as well as future opportunities for practice and research.

Result

The flow of article review, selection and inclusion are detailed in Figure 3. The majority of studies (n=4120) were excluded for the following reasons: non-ILD population, children and/or only respiratory muscles were assessed. Of the 113 studies that underwent a full-text review, 68 were excluded due to no reported findings of peripheral muscle dysfunction or alterations in muscle structure or

metabolism, results from individuals with IIM, CTD and sarcoidosis with evidence of ILD were not separated from individuals without ILD, or a repeated study cohort was used in more than one study. The final number included in the scoping study was 45 articles [8,16-59]. Table 1 describes the characteristics of the included studies. There were 34 journal articles including brief communications and correspondence and 11 conference abstracts.

Characteristic	Non-idiopathic inflammatory myopathies	Idiopathic inflammatory myopathies
ILD Subtype*	No. of studies (proportion)	No. of studies (proportion)
IPF	8 (29%)	
Mixed Population (IIP, CTD, IIM)	8 (29%)	
Scleroderma	3 (10.5%)	
Sarcoidosis	3 (10.5%)	
Other (occupational, SLE, NSIP)	6 (21%)	
PM		3 (18%)
DM		5 (29%)
PM and DM		6 (35%)
Other IIM		3 (18%)
Type of Control Group*	No. of studies (proportion)	No. of studies (proportion)
No control	16 (57%)	13 (76%)
Healthy matched control	8 (29%)	2 (12%)
No rehabilitation intervention	3 (10.5%)	
IIM without ILD		2 (12%)
COPD	1 (3.5%)	
Participant characteristics**		
Age in years (range)	42-71	30-77
Sex:		
Males (n)	397	109
Females (n)	204	123
PFTs (range):		
TLC (% pred)	56-78%	
FVC (% pred)	49-78%	
D _{LCO} (% pred)	39-59%	
6-minute walk distance in meters (range)	157-710	
Daily prednisone dose in mg (range)	1-30	11-60
COPD: Chronic obstructive pulmonary disease; MRC: Medical Research Council (dyspnea scale); IPF: Idiopathic pulmonary fibrosis; IIM: Idiopathic inflammatory myopathy; ILD: Interstitial lung disease; RCT: Randomized controlled trial; PM: Polymyositis; DM: Dermatomyositis; IIP: Idiopathic interstitial pneumonia; CTD: Connective tissue disease; IIM: Idiopathic inflammatory myopathy; SLE: Systemic lupus erythematosus; NSIP: Non-specific interstitial pneumonia; ILD: Interstitial lung disease TLC: Total lung capacity; VC: Vital capacity; FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide.		

Table 1: Characteristics of included studies.

There was a wide variety of study designs including retrospective (n=11), case study (n=9), prospective cross-sectional (n=7), prospective cohort (n=6), randomized controlled trial (n=3), non-randomized controlled trial (n=3), non-randomized or controlled trial (n=1), case series (n=1), case-control (n=1) and unspecified study design (n=3). Eleven studies of non-IIM examined peripheral muscle dysfunction in the context of pulmonary rehabilitation.

Overall there were 34 different subtypes of ILD examined in the studies. Seventeen studies examined IIM and represented 214 individuals with IIM and evidence of existing ILD. The remaining 28 studies included 2308 individuals with IIP, CTD and sarcoidosis. Where reported, the time from diagnosis was variable, from newly diagnosed to up to eleven years post diagnosis. Individuals with IIM had a variable disease status including acute, chronic stable or chronic with an acute flare. Both sexes were represented, however the exact number of males and females could not be calculated in every study since in some studies participants with IIM and CTD with co-existing ILD were not separated from participants without ILD, or sex was not reported (Table 1). The presence of interstitial lung disease was reported in the studies if participants had values of less than 70-80% predicted for total lung capacity, vital capacity or forced vital capacity. The most commonly reported medication was prednisone, and there was no information on other medications known to affect muscle (e.g. statins) in study participants.

Findings of muscle strength and endurance

In non-IIM; peripheral muscle dysfunction was reflected predominantly by reduced muscle strength. (Table 2) Reduced force or torque was reported in the quadriceps (11 studies), handgrip (7 studies), elbow flexors (2 studies) and hamstrings, plantar flexors and dorsiflexors (1 study). Reduced lower extremity volitional muscle strength based on comparisons to healthy matched controls or predicted values and ranged from 62-82% predicted. One study did not find reductions in volitional quadriceps muscle strength compared to healthy controls, however did report reduced non-volitional quadriceps muscle strength and endurance. [37] Quadriceps force or torque was reduced to a greater extent than handgrip force, which was reported to be normal in some studies, or marginally reduced (range: 84-97% predicted). Muscle strength and lower extremity function was also measured using short functional tests targeting muscle strength (3 studies); and lower performance in individuals with ILD compared to healthy controls or predicted values was reported. In IIM, proximal muscle weakness against gravity was reported as well as self-reported difficulty when rising from a chair (Table 2). In IIMs, studies reported either similar or reduced muscle strength in individuals with IIM and ILD compared to a control group of individuals with IIM and no evidence of ILD.

	Non-Idiopathic inflammatory myopathies (n:17)	Idiopathic inflammatory myopathies (n:5)
	# studies (proportion)*	# studies (proportion)
Reduced volitional muscle strength		
Computerized dynamometry	4 (24%)	1 (20%)**
-isometric	4 (24%)	
-isokinetic		
Handgrip dynamometer	8 (48%)	Not tested
Handheld dynamometry	4 (24%)	Not tested
Strain gauge	1 (6%)	Not tested
Manual muscle testing	Not tested	3 (60%)
Isotonic test	Not tested	1 (20%)
Functional tests***	3 (18%)	Not tested
Reduced non-volitional muscle strength		
Supra-maximal magnetic femoral Stimulation	1 (6%)	Not tested
Reduced non-volitional muscle endurance		
Magnetic stimulation of quadriceps	1 (6%)	Not reduced**

*Some studies measured more than one measure of peripheral muscle dysfunction; therefore the total proportions exceed 100%.
 **Study participants with IIM were not separated into groups with and without ILD. 18
 ***Functional tests included the Timed up and go, the Short Physical Performance Battery, the 4-metre walk time and speed and the 30-second chair stand.

Table 2: Findings of muscle strength and muscle endurance in ILD in individuals with and without idiopathic inflammatory myopathies.

Alterations in peripheral muscle structure and metabolic characteristics

and fat free mass index measured using bioelectrical impedance analysis was reported as either normal 34 or impaired [37].

In five studies; muscle size was measured using fat free mass; muscle cross-sectional area and muscle layer thickness (Table 3). Fat free mass

	Non-idiopathic inflammatory myopathies (n:28)	Idiopathic inflammatory myopathies (n:17)
	No. studies (proportion)	No. studies (proportion)*
Muscle inflammation		
Elevated serum markers		
· CRP	2 (7%)	3 (18%)
· TNF- α	1 (3.5%)	1 (6%)
· Interleukin (sIL-2R; IL-6; IL-8)	1 (3.5%)	1 (6%)
· sCD163	Not reported	1 (6%)
· ESR	Not reported	1 (6%)
Necrotizing inflammation	Not reported	8 (48%)
Muscle edema	Not reported	1 (6%)
Muscle injury		
Elevated muscle enzymes		
· CK/CPK	4 (14%)	13 (76%)
· Aldolase	1 (3.5%)	2 (12%)
· ALT	Not tested	1 (6%)
· ADT	Not tested	1 (6%)
· LDH	Not tested	1 (6%)
· Matrix metalloproteinase 9	1 (3.5%)	Not tested
· Tissue inhibitor of metalloproteinase	1 (3.5%)	Not tested
Muscle size		
Lower FFM and FFM index	1 (3.5%)	Not tested
Reduced mid-thigh CSA	3 (11%)	Not tested
Decreased lower limb muscle thickness	1 (3.5%)	Not tested
Muscle fibre atrophy	1 (3.5%)	3 (18%)
Bioenergetics		
Diminished muscle oxygen extraction	1 (3.5%)	Not tested
Oxidant stress and lipid peroxidation	2 (7%)	Not tested
Shift to anaerobic energy production	1 (3.5%)	Not tested
CRP: C-reactive protein; TNF- α : Tumour necrosis factor alpha; CK: Creatine kinase; CPK: Creatine phosphokinase; FFM: Fat-free mass; CSA: Cross-sectional area; IL-6: Interleukin-6; IL-18: Interleukin-18; Sil-2R: Soluble interleukin-2 receptor; sCD163: Soluble cluster of differentiation 163; ESR: Erythrocyte sedimentation rate; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactic dehydrogenase		
*Some studies measured more than one alteration in peripheral muscle structure or metabolism; therefore the total proportions exceed 100%.		

Table 3: Alterations in peripheral muscle structural and metabolic characteristics in ILD in individuals with and without idiopathic inflammatory myopathies.

A smaller mid-thigh cross-sectional area using computerized tomography and ultrasound imaging, and reduced rectus femoris cross sectional area, calf and bicep muscle layer thickness using ultrasound imaging was observed in ILD compared to healthy controls [35,36,48]. There was also evidence of Type II muscle fibre atrophy on muscle biopsy in IIM. Alterations in muscle metabolism were reported in three studies and included decreased muscle oxygen extraction with exercise; and evidence of oxidant stress and lipid peroxidation in IPF [25,26,28] (Table 3). Oxidative enzyme concentrations or activity were not reported.

Muscle inflammation and muscle injury were predominantly measured in IIM, often for purposes of a differential diagnosis of the disease (Table 3). In addition to elevated serum markers of inflammation, evidence of inflammatory infiltrates, necrosis, phagocytosis, edema and regenerating myofibres were reported from muscle biopsy, and muscle irritability, fibrillations, bizarre repetitive discharges, low voltage and/or short duration potential during maximal contraction and sharp waves on EMG were documented. Elevated serum markers of muscle inflammation and injury were also reported in individuals with CTD, sarcoidosis and overlap syndrome, but not in other non-IIMs. The most commonly elevated muscle enzyme was creatine kinase (CK)/creatine phosphokinase (CPK) (Table 3).

In studies involving individuals with IIM with ILD and a control group of IIM without ILD, there was either no difference in muscle enzymes (CK/CPK and aldolase) or greater abnormalities in CK, C-reactive protein and erythrocyte sedimentation rate reported in individuals with co-existing ILD.

Discussion

Peripheral muscle dysfunction may be a systemic consequence of ILD. In non-IIM, peripheral muscle dysfunction was reflected by reduced quadriceps and handgrip muscle strength; however the extent of peripheral muscle weakness was variable. There is some evidence of reduced muscle size in non-IIM, specifically reduced muscle cross-sectional area and muscle thickness and lower fat-free mass.

Evidence of alterations in metabolic characteristics included diminished oxygen extraction, oxidative stress and a shift away from aerobic energy production. In IIM, alterations in peripheral muscle structural characteristics included markers of muscle inflammation and muscle injury. Factors that may contribute to peripheral muscle weakness have not been fully elucidated in ILD, as 80% of studies did not measure both peripheral muscle dysfunction and alterations in muscle structure and/or metabolism.

The focus on serum markers of muscle injury and muscle inflammation in IIM is not surprising as these markers are essential in the clinical diagnosis of IIM and monitoring the response to medical therapy. Diagnostic criteria for IIM include symmetrical proximal muscle weakness (e.g. shoulder girdle and hip musculature) progressive over weeks to months, elevation of serum levels of skeletal muscle enzymes, positive muscle biopsy findings of degeneration; regeneration and chronic inflammatory infiltrates within the muscle fibre, and abnormal muscle activation patterns on EMG [60,61].

Although muscle injury and muscle inflammation are present in IIM, little is known of the functional consequences on muscle weakness, muscle fatigue and exercise capacity. In non-IIM, peripheral muscle dysfunction has been quantified as reduced muscle strength;

with a tendency to measure muscles such as the quadriceps, elbow flexors and handgrip that could be considered more distal limb muscles, and therefore potentially different from proximal muscles assessed in IIMs.

Peripheral muscle dysfunction has been evaluated and described in COPD and has been correlated to decreased exercise capacity HRQOL and survival [3,12,15]. There are similarities and differences in peripheral muscle dysfunction between ILD and COPD. Studies in both populations report reduced voluntary strength of the quadriceps as the most common finding of peripheral muscle function; preferential muscle weakness in the lower versus upper extremities; and have a smaller body of evidence of reduced non-volitional quadriceps strength and endurance [3,18,35,37].

In contrast, studies in people with COPD report a 20-30% reduction in voluntary quadriceps muscle strength [3,15]. Whereas muscle strength showed greater variability in ILD with some studies not reporting any muscle weakness. As postulated in COPD; primary and secondary impairments such as hypoxemia; inactivity; systematic inflammation; malnutrition and side effects of medications may play a role in the development of peripheral muscle dysfunction in ILD. Little is known about the mechanisms and effects of hypoxemia on peripheral muscle oxidative stress in ILD. In COPD; chronic hypoxemia has been associated with increased muscle oxidative stress at rest and exercise compared to non-hypoxemic individuals [63]. Individuals with non-IIM; particularly idiopathic pulmonary fibrosis (IPF); can exhibit significant hypoxemia; and evidence of oxidative stress has been recently examined in this population (e.g. increased plasma 15-F2t0 isoprostanes) [25,26].

Systemic corticosteroids have been shown to lead to steroid myopathy in other populations [10], however they play a role in the first-line clinical treatment of IIM to reduce muscle inflammation; normalize muscle enzymes and improve muscle strength [7]. If sarcoid muscle involvement is present; corticosteroids may also be beneficial. However steroid-induced myopathy and other side effects such as osteoporosis can occur if corticosteroids are not tapered to the lowest dose in order to keep myositis in remission and steroid-sparing medications are not utilized [53,62,63]. This may further impact peripheral muscle dysfunction; and should be investigated.

Identifying patients with ILD who have peripheral muscle dysfunction has implications for rehabilitation practice. Reduced muscle strength and endurance may be responsive to interventions such as exercise training. There are studies showing improvements in muscle strength and function following aerobic and resistance exercise programs in individuals with IIM; some involving creatine supplementation. Exercise training has not resulted in increased in muscle inflammation in this population [64]. However these studies are not specific to individuals with IIM with ILD involvement. In addition; there is limited information on the safety and efficacy of exercise in individuals with active or recent onset disease; it is important to consider that exercise training may not be indicated until the active muscle inflammation is under control to prevent further muscle injury.

The heterogeneity of ILD may make it difficult to make broad recommendations for interventions such as exercise training (e.g. timing; type; intensity and progression of exercise; disease-specific modifications; functional expectations and goals) as different ILD subtypes may have different muscle alterations leading to peripheral muscle dysfunction (e.g. muscle inflammation vs. disuse).

Gaps

Our understanding of the mechanisms and contributing factors to the development and progression of peripheral muscle dysfunction in ILD is limited based on the literature to date. This scoping study identified the following gaps in the literature relating to ILD and peripheral muscle dysfunction: description of the structural and metabolic characteristics of peripheral muscle that can contribute to dysfunction (e.g. muscle and fibre size, muscle quality, muscle fibre type distribution, protein turnover, capillary density, mitochondrial density, oxidative enzymes and oxidative capacity), the examination of muscle endurance, objective clinical measures of measuring muscle strength in IIMs and the relationship of peripheral muscle dysfunction to important clinical outcomes such as exercise capacity, HRQOL and survival in ILD.

Limitations

The research question varied in the included studies; and peripheral muscle dysfunction was often a secondary rather than primary question. This study included conference abstracts that did not contain detailed information on the population sub-types, peripheral muscle dysfunction findings or alterations of structural and metabolic characteristics. Restricting IIM and CTD to studies where findings of peripheral muscle dysfunction in individuals with existing ILD could be separated out could have limited the available findings in IIM and CTD. The focus of this study was muscle factors that could lead to reduced muscle strength and endurance, and we did not consider neurological factors or musculoskeletal conditions such as arthritic articular changes and pain that can contribute to peripheral muscle dysfunction. A consultation stage was not performed for feasibility reasons; however collaborating with experts particularly in the area of IIM may have directed the study question; search strategy and interpretation of the data.

Conclusion

There is evidence of reduced volitional muscle strength and reduced muscle size in non-IIM. In IIM and CTD with co-existing ILD, the impact of muscle inflammation and muscle injury on peripheral muscle dysfunction has not been elucidated. A further quantification and understanding of factors and mechanisms may inform potential therapeutic interventions in this heterogeneous population.

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