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REVIEW

Muscle function in COPD: a complex interplay

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Abstract: The skeletal muscles play an essential role in life, providing the mechanical basis for respiration and movement. Skeletal muscle dysfunction is prevalent in all stages of chronic obstructive pulmonary disease (COPD), and significantly influences symptoms, functional capacity, health related quality of life, health resource usage and even mortality. Furthermore, in contrast to the lungs, the skeletal muscles are potentially remedial with existing therapy, namely exercise-training. This review summarizes clinical and laboratory observations of the respiratory and peripheral skeletal muscles (in particular the diaphragm and quadriceps), and current understanding of the underlying etiological processes. As further progress is made in the elucidation of the molecular mechanisms of skeletal muscle dysfunction, new pharmacological therapies are likely to emerge to treat this important extra-pulmonary manifestation of COPD.

Keywords: skeletal muscle, pulmonary rehabilitation, exercise, quadriceps, diaphragm

Introduction

Chronic obstructive pulmonary disease (COPD) is major health problem. By 2020, COPD is predicted to be the third leading cause of death and fifth leading cause of chronic disability worldwide.[1] Although a disease of the lungs, extra-pulmonary features of COPD are increasingly recognized as important contributors to morbidity and mortality.[2] Skeletal muscle dysfunction is of particular interest, as it directly influences exercise performance,[3] is associated with poor health status,[4] and is an independent predictor of health care utilization[5] and mortality.[6] Furthermore, respiratory muscle function plays a key role in the pathogenesis of breathlessness[7] and maximum inspiratory pressure is an independent predictor of survival in severe disease.[8]

The most commonly studied skeletal muscles are the quadriceps and the diaphragm. Cross-sectional studies, with careful matching of patients with controls, have revealed the complexity of muscle dysfunction in COPD. In turn, these have provided insight into the possible etiological factors and pathophysiological processes. This review describes the distribution and nature of changes to skeletal muscle function in COPD and how this relates to lung function. Possible etiological factors and mechanisms underpinning COPD muscle dysfunction will be discussed and how this may inform emerging non-pharmacological and pharmacological treatment approaches in this field.

The peripheral muscles

Compared with healthy controls matched for age and gender, isometric quadriceps strength – whether assessed by volitional[9,10] or non-volitional measures[11] – is reduced

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by about 20%–30% in patients with COPD. A marked increase in susceptibility to fatigue is also observed, with a more rapid decline in performance during continuous[12,13] or repeated bouts of exercise.[14,15]

The reduction in strength can largely be explained by a comparable reduction in quadriceps cross-sectional area (CSA) and mass, the latter being assessed by magnetic resonance imaging[16] and the former by ultrasound[17] or computed tomography.[9,18] Microscopically, atrophy of single muscle fibers has been observed with a predilection for type IIX fibers.[19] Quadriceps endurance is more likely to be related to the relative loss of fatigue-resistant type I fibers[20,21] and subsequent reduction in oxidative capacity. Matched case-control pairs of vastus lateralis samples reveal a shift in fiber type expression away from type I and toward type II/IIX fibers.[20] Concurrent structural changes include a reduction in capillary density,[22] number of capillary-muscle fiber contacts[21] and levels of oxidative enzyme activity.[23] Samples from patients with COPD consistently demonstrate reduced levels of aerobic enzyme activity – for example, citrate synthase and 3-hydroxyacyl CoA dehydrogenase[23,24] – together with lower concentrations of adenosine-5′-triphosphate and creatine phosphate.[25] The resultant impaired capacity for oxidative phosphorylation leads to a greater reliance on glycolysis during exercise and early accumulation of lactate that becomes limiting.[26] Indeed, the oxidative:glycolytic enzyme activity ratio correlates moderately with quadriceps endurance.[27]

Where other peripheral muscles have been studied, a preferential distribution of muscle wasting and weakness to the lower limbs is observed. Mathur et al found reduced volumes and CSAs in the hamstrings and adductors (21% and 30%, respectively) of patients with moderate to severe disease.[16] In contrast, relatively preserved or maintained strength has been found in upper-limb muscles, such as the adductor pollicis[11] and elbow flexors,[28] and grip strength.[29] Structural and histochemical studies support this pattern of dysfunction. Biopsies of the biceps[30] and deltoid muscles[29] reveal no differences between patients and controls in fiber type profile, nor single-fiber CSA. Gea et al[29] explored the metabolism in the deltoid muscle, with findings suggesting a preserved oxidative capacity with raised lactate dehydrogenase and citrate synthase activity and no differences in levels of phosphofructokinase or creatine kinase. In summary, distribution of peripheral muscle dysfunction is not uniform in COPD. Changes are most marked in the lower limbs, which are necessary for locomotion, providing evidence that local factors such as disuse/immobility may be more influential than any systemic process.

The respiratory muscles

Although the capacity of the diaphragm to generate transdiaphragmatic pressure is reduced in COPD, this is largely the product of hyperinflation, which places the muscle at a mechanical disadvantage. Indeed, when corrected for lung volume, the contractile strength of the diaphragm in COPD is not reduced compared with controls[11] and may even be enhanced in some cases.[31] The maintenance of strength in this muscle is probably due to persistent involuntary training secondary to the increased work of breathing. As a result, the diaphragm adapts by remodeling its fiber type profile toward a fatigue-resistant phenotype with a relative increase the proportion of type I fibers. Relative to controls, samples reveal increases 20%–50% in the overall proportion of type I fibers,[32,33] matched by reductions in type IIX fibers.[34]

Less is known about change in single diaphragm fibers and debate exists as to whether their CSA or force-generating capacity is altered. Some studies report no change in fiber size,[35] while others observe selective atrophy of type I fibers.[36] Similarly, lower isometric force-generating capacity (normalized for CSA) has been reported among patient fibers tested in vitro,[36,37] while others have found no difference between patient and control fibers.[38] More established is the intrinsic resistance to fatigue that occurs via an increased concentration of mitochondria,[38] capillary density,[34] and capacity to generate adenosine-5′-triphosphate through oxidative pathways, marked by an increased succinate dehydrogenase activity.[39] In COPD patients, no fatigue of the diaphragm is seen with maximum voluntary ventilation or exhaustive treadmill exercise.[40,41] Diaphragm fibers from patients are also more efficient than those from controls, with a lower adenosine-5′-triphosphate cost to maintain a similar isometric force.[36] The reduced energy cost may be accounted for by the number of cross-bridge formations within each fiber, with COPD diaphragm muscle fibers having fewer active cross-bridges and each exerting a greater force than in control muscle.[35,36]

Where other accessory respiratory muscles have been studied, these appear to adapt in the same manner in response to the increased work of breathing. The shift in fiber type from II to I observed in the diaphragm is also seen in the parasternal intercostal muscles of patients with severe disease.[42] A contrasting shift in fiber type expression has been observed in the external intercostal muscles, which may reflect their postural role in this group.[43] Functionally, pectoralis major and latissimus dorsi strength are preserved relative to the quadriceps,[9] as is abdominal strength, presumably due to the additional activity of expiratory muscles in COPD.[10]

In summary, the changes seen in the respiratory muscles are in stark contrast to those in quadriceps muscle in COPD. Whereas the quadriceps muscle is characterized by a reduced mass and loss of fatigue-resistant type I fibers and oxidative capacity, which impairs strength and endurance, the diaphragm remodels toward a fatigue-resistant profile, with a relative increase in type I fibers and resultant increase in oxidative capacity (Table 1), a pattern reflected in other accessory muscles of respiration. These observations support muscle disuse being a major etiological factor for the differential adaptation of peripheral and respiratory muscles in COPD.

Muscle function and COPD severity

The traditional paradigm is that skeletal muscle dysfunction is a feature of severe or end-stage disease. Certainly, Bernard et al demonstrated a significant relationship between quadriceps strength and forced expiratory volume in 1 second (FEV_1) percentage of predicted value, with the more flow-limited patients being weaker[9] and the prevalence of quadriceps weakness rises with increasing Global initiative for chronic Obstructive Lung Disease (GOLD) stage.[44] Others have also shown a moderate relationship between FEV_1 and quadriceps endurance;[45] whereas, in the diaphragm, muscle-fiber proportion shift advances with increasing disease severity.[37] However, the literature is far from being unequivocal and several studies have not found any correlations between airflow obstruction and muscle dysfunction.[46,47] Very recent data supports the presence of muscle dysfunction, even in the early stages of the disease. Seymour and colleagues showed that quadriceps weakness is common across all disease stages with a mean (95% confidence interval [CI]) prevalence of 31% (25%–38%) in GOLD stage I/II, rising (though not sufficiently to achieve statistical significance) to 38% (31%–46%) in GOLD stage IV.[44] Endurance is compromised even in patients with mild disease performing low-intensity tasks,[15] while invasive evaluation of diaphragm contractile function, structure, and biochemistry demonstrated that cellular and molecular alterations occur, even in GOLD I/II patients.[48] These data suggest that the relationship between airway obstruction and muscle dysfunction in COPD is modest at best and, certainly in some patients, muscle abnormalities may occur before any drop in FEV_1 is detected.[49] This could be attributed to potential etiological factors such as smoking[49] or reductions in physical activity.[50,51]

Table 1 Quadriceps and diaphragm structure and function in patients with COPD compared with controls

	Quadriceps	Diaphragm
Strength	Reduced	Unchanged
Endurance	Reduced	Increased
Overall CSA	Reduced	Unchanged
Single-fiber CSA	Reduced in type IIX	Reduced in type I
Fiber type shift	Type I to II	Type II to I
Capillary and mitochondrial density	Reduced	Increased
Metabolism – oxidative: glycolytic ratio	Reduced	Increased

Abbreviation: CSA, cross-sectional area.

Muscle function and physical inactivity in COPD

COPD patients often adopt sedentary lifestyles due to breathlessness and, in some, this can precipitate a downward spiral of disease (Figure 1).[52] Anaerobic quadriceps metabolism results in lactate and carbon dioxide production, which stimulates ventilation and worsens breathlessness. Daily activity has been documented to be lower in COPD patients than in healthy controls and lower than recommended international guidelines for physical health maintenance.[53] Recently, Watz et al[50] demonstrated that physical activity and steps per day were reduced even in those with less severe disease. Individuals with early COPD were predominately (although not significantly) more sedentary than the control group of patients with "chronic bronchitis."

Several lines of evidence support the important etiological role of physical inactivity in the development of COPD skeletal muscle dysfunction. With advancing airway obstruction severity, physical activity declines and matches the loss of muscle mass observed in COPD patients,[54] which correlates with muscle force.[55] Abnormalities in the quadriceps muscle in COPD patients are similarly observed in patients with other chronic diseases, such as heart failure,[56] suggesting a common etiological factor like physical inactivity and resultant deconditioning. Furthermore, as previously discussed, muscle dysfunction is most marked in the lower limb muscles

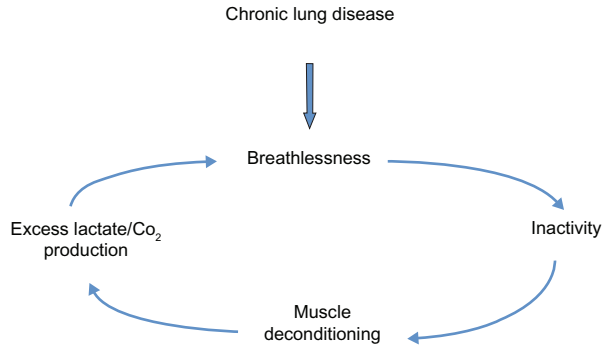

Figure 1 The downward spiral of disease.

of locomotion, again supporting the role of disuse. During hospitalization for an exacerbation of COPD, physical inactivity is marked and there is a corresponding reduction in quadriceps strength.[57] Exercise interventions, during or shortly after an exacerbation requiring hospitalization, result in significant improvements in quadriceps muscle strength.[58,59]

Large prospective population-based studies also support the relationships between physical inactivity and important clinical end-points in COPD. Physical activity is protective against hospital admissions[60] and all-cause and respiratory mortality[61] in COPD; furthermore, physical activity can also modify the smoking-related decline in lung function, therefore reducing the risk of COPD in those individuals.[62]

Other etiological factors

Low-grade systemic inflammation is thought to be reflected by higher levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α); interleukin (IL)-6, -8, -18; and acute-phase proteins in COPD patients. These are postulated to originate either from the peripheral lung or the respiratory muscles. Quadriceps strength has been related to IL-6 and TNF-α in a stable cohort of aged individuals[63] and IL-8 in those with COPD during an exacerbation.[57] Elevated IL-6 levels are also associated with radiological evidence of quadriceps wasting in COPD[64] and reduced lean body mass.[65] A similar association was suggested in early studies for TNF-α; however, a possible confounding factor includes changes in assays used to quantify cytokine levels.[66] Moreover, quadriceps biopsy findings have not shown increased muscle levels of pro-inflammatory cytokines, including TNF-α, IL-6, IL-8, interferon-gamma, and transforming growth factor-beta, in COPD,[67–69] and further work is required to determine the contribution of local inflammation to muscle dysfunction.

Hypoxemia and inflammation are thought to be the up-stream mediators of oxidative stress.[70] An increase in reactive oxygen species or reactive nitrogen species, and/or a reduction in antioxidant capacity, leads to local oxidative stress damaging cellular components. This can adversely affect muscle-fiber function via its contractile property[71] and mitochondria respiration. Furthermore, oxidative stress can alter protein catabolism and anabolism and induce cell death.[72] Peroxidation products from reactive oxygen species-induced lipid membrane damage can be detected peripherally and have been shown to be elevated in COPD patients at rest and during an exacerbation.[73] Studies of antioxidant capacity in COPD are less consistent. Some investigators have reported elevated antioxidant enzymes in patients with severe COPD with muscle wasting,[74,75] while others have shown no differences in levels in the quadriceps muscle between COPD patients and controls.[72,76,77] Antioxidant enzyme function may be inadequate in the muscles of COPD patients and unable to respond to the increased oxidant stress after exercise.[76] However, given that exercise generally improves muscle function in COPD, the observation that whole-body and localized-limb exercise induces increased oxidative stress in COPD patients[76,78] questions whether oxidative stress is indeed pathological or simply a physiological reflection of the muscle repair cycle.

As more than 50% of very severe COPD patients have preserved quadriceps strength,[44] studies have sought to demonstrate a genetic predisposition to either loss of muscle mass or muscle resistance to the effects of long-term physical inactivity. The deletion (D) rather than the insertion (I) polymorphic variant of the angiotensin-converting enzyme (*ACE*) gene is associated with preserved quadriceps strength in COPD.[79] This is associated with higher tissue ACE and angiotensin II activity, which may affect muscle growth, and lower bradykinin levels. To establish whether the effects were mediated via increased *ACE*-related D allele kinin degradation, bradykinin receptor polymorphisms were later studied.[80] The +9/+9 (base pair repeat present) receptor polymorphism, which is associated with reduced gene transcription and lower mRNA, was more prevalent in COPD patients with low fat-free mass (FFM) index. However, this did not explain the previously identified *ACE* gene findings, as there was no interaction between the two genotypes on strength.[80] Polymorphisms of the vitamin D receptor are associated with reduced (*Fok*I polymorphism) or greater quadriceps muscle strength (*Bsm*I polymorphism) in COPD patients.[81] However, this association was not seen in healthy controls, suggesting a gene–environment interaction. Cachexia-associated polymorphisms of inflammatory cytokines such as TNF-α and IL-6 remain to be discovered. A -511 polymorphism of the *IL-1β* gene (the CC variant) has been shown to be associated with cachexia[82] but functional implications are unknown.

Cachexia or loss of muscle mass is well described in COPD, even in the presence of retained weight and fat mass.[83] Whether this process can be attributed directly to nutritional insufficiency or is secondary to a systemic inflammatory process remains unclear. Certainly, nutritional supplementation alone does not appear to improve measurements of FFM, lung function, or exercise capacity.[84] However, in combination with other anabolic stimuli, it can maintain or improve muscle mass but with undetermined effects on function.[85]

Imbalance between anabolic and catabolic hormones has also been suggested as contributing to muscle dysfunction

in COPD. Reduced circulating anabolic hormones such as testosterone and insulin-like growth factor-1 (IGF-1) have been reported in COPD patients.[64] Trials of testosterone have shown variable results; some have not been able to demonstrate an improvement in exercise capacity,[86,87] but others report an increase in muscle mass and strength with a combination of testosterone and resistance training in male individuals with low baseline testosterone levels.[88] Insulin resistance and changes in glucose metabolism have also been found in COPD patients, but this remains poorly studied in the COPD population therefore the relationship with skeletal muscle dysfunction remains inconclusive.[89] Similarly, although the effect of long-term, low-dose systemic corticosteroids on the proximal muscles is well described,[90]short-term use of higher doses (prednisolone 30 mg for 2 weeks) does not cause significant skeletal muscle dysfunction nor alter metabolic parameters during exercise.[91]

Potential molecular mechanisms and pathways

Cardinal molecular features of quadriceps muscle dysfunction include muscle-fiber atrophy and muscle-fiber shift. Muscle atrophy results in loss of muscle mass and can result from an imbalance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB), and/or individual fiber loss and gain. Muscle-fiber shift has been less extensively studied, but the loss of aerobic type I fibers classically results in a decrease in oxidative capacity, a reduction in mitochondria, and reduced muscle endurance. It is unclear at present whether these processes occur independently or are linked.

Animal models have identified key mediators in atrophy and hypertrophy signaling and therefore the control of muscle growth.[92] These are summarized in Figure 2. The anabolic hormone and growth factor IGF-1 stimulates the phosphoinositide 3-kinase/Akt (protein kinase B) pathway in skeletal muscle cells. Upon phosphorylation, Akt is able

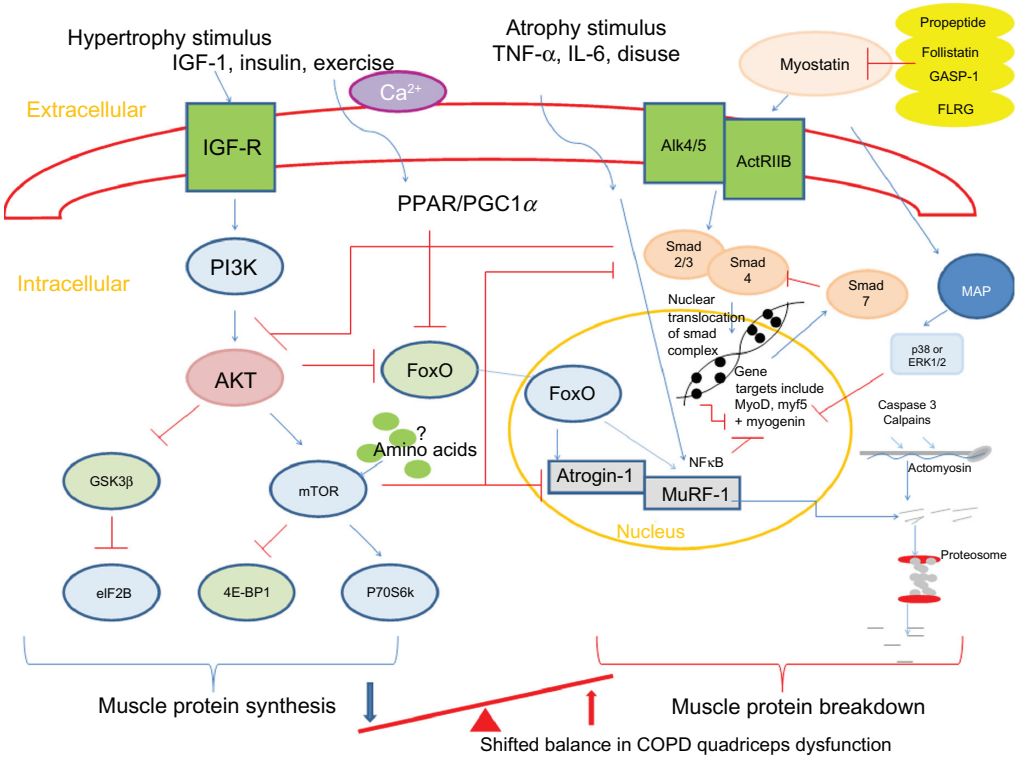

Figure 2 Summary of pathways controlling muscle protein synthesis (MPS) and muscle protein breakdown (MPB). The role of myostatin in MPS and MPB has also been included. Myostatin is held in an inactive state by its pro-peptide, follistatin, and inhibitory binding proteins – growth and differentiation factor-associated serum protein-1 (GASP-1) and follistatin-like related gene, (*FLRG*) as shown. Upon activation, it binds to its transmembrane receptor activin receptor type IIB (ActRIIB), which then forms homodimers with activin receptor-like kinase 4 or 5 (Alk 4/5). The SMAD signaling pathway is then activated and translocation of this transcription factor complex to the nucleus occurs, where MyoD production and therefore myoblast proliferation and fusion are blocked. Myostatin is also proposed to increase proteosomal activity in a FoxO-dependent manner. Activation of MAP kinase is mediated via myostatin either via p38 or ERK1/2, which leads to the blocking of genes involved in myogenesis.
Notes: → denotes stimulation; ⊣ indicates inhibition.
Abbreviations: 4E-BP1, eukaryotic translation initiation factor 4E binding protein-1; Akt, protein kinase B; ERK, extracellular signal-regulated kinase; eIF2B, eukaryotic initiation factor 2B; FoxO, forkhead box class O; GSK-3β, glycogen synthase kinase-3β; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; MAP, mitogen-activated protein; mTOR, mammalian target of rapamycin; MuRF, muscle-specific RING finger protein; p70S6k, 70-kD ribosomal S6 protein kinase; PGC1α, peroxisome proliferator-activated receptor gamma co-activator 1-alpha; PI3K, phosphoinositide 3-kinase; PPAR, peroxisome proliferator-activated receptor; SMAD, ;TNF-α, tumor necrosis factor-alpha; GASP-1, growth and differentiation factor-associated serum protein-1; IGF-R, insulin-like growth factor-1 receptor; Ca^{2+}, calcium ion; NFκB, nuclear factor κB.

to activate mammalian target of rapamycin (mTOR), which, in turn, activates 70-kD ribosomal S6 protein kinase[93] and inhibits eukaryotic translation initiation factor 4E binding protein-1/ PHAS-1;[94] these processes stimulate MPS. Another downstream regulator of anabolism, which is mTOR independent, is the phosphorylation of glycogen synthase kinase-3β (GSK-3β) by phosphorylated Akt.[95] This leads to the release of eukaryotic initiation factor 2B (eIF2B) which upregulates MPS. Phosphorylated Akt also plays a role in MPB pathways. It downregulates two muscle-specific E3 ligases, atrogin-1 (muscle atrophy F-box or MAFbx), and muscle-specific RING finger protein (MuRF)-1 via inactivation of the forkhead box class O (FoxO) family of transcription factors.[96] The muscle-specific ubiquitin ligases contribute to protein degradation via the ubiquitin-proteasome pathway.[97]

Ubiquitin-mediated protein degradation may play an important role in COPD skeletal muscle dysfunction. Two small studies found elevated atrogin-1[98,99] and MuRF-1[98] in quadriceps from COPD patients, but, in one of these, it was alongside elevated hypertrophy signaling. Although larger studies are required to confirm these observations, this may suggest COPD patients actually fail to restore muscle mass and therefore have some form of synthetic resistance. Indeed, tracer studies from immobilized individuals would support this theory of resistance to MPS to protein nutrition (termed "anabolic resistance").[100] MPS is greatly suppressed in the immobilized post-absorptive state,[101] while the contribution from MPB is minimal. Therefore, the relative contribution of MPB in the process of disuse-induced muscle atrophy remains under question.[102]

Myostatin, or growth differentiation factor-8, is a member of the transforming growth factor-β (TGF-β) super-family and is a potent negative regulator of muscle mass, as demonstrated by naturally occurring mutations occurring in mice, cattle, and humans.[103–105] Myostatin can influence muscle wasting by affecting the number and size of muscle cells and by inducing muscle atrophy pathways. Myostatin upregulates p21 (cyclin-dependent kinase inhibitor), which negatively affects activated satellite cell/myoblast proliferation,[106] and downregulates myogenic differentiation factors (MyoD, myf5, and myogenin), which inhibit myoblast differentiation.[107] It can also exert an effect on muscle catabolism by activating the ubiquitin proteolytic system in a FoxO1-dependent manner[108] and may possibly inactivate Akt, affecting MPS.[108] Finally, myostatin has also been shown to inhibit satellite cell activation and self-renewal in a Pax7-dependent way.[109]

Several lines of evidence implicate a role for myostatin in COPD quadriceps dysfunction. Myostatin mRNA was elevated in weak COPD patients.[99] Following an in-patient resistance training program, hospitalized COPD patients had reduced myostatin transcripts, with a trend toward an increase in MyoD and myogenin.[59] Following exercise training, non-cachectic COPD patients demonstrated a reduction in myostatin protein, with a reduction in MuRF-1 and atrogin-1,[110] while a modest reduction in myostatin was found following resistance training with or without testosterone.[111] Our group have also demonstrated a negative association between quadriceps muscle myostatin mRNA expression and quadriceps muscle strength in COPD patients.[112]

Animal studies have shown that skeletal muscle-fiber phenotype appears to be regulated by several independent signaling pathways. Fiber type switching in mice can be induced by changes in nerve activity from differing electrical stimulations,[113] enabling the study of pathways that affect myosin gene expression and metabolic profiles.

Myofiber gene activation occurs via calcium signaling through calcineurin (Cn) and various kinases – for example, Ca^{2+}/calmodulin-dependent protein kinases II. Cn is a calcium/calmodulin-regulated protein phosphatase that acts on transcription factors of the nuclear factor of activated T cells (NFAT) family. Ca^{2+}/calmodulin-dependent protein kinases II regulate myocyte enhancer factor 2, via histone deacetylase (HDAC), and has been suggested to interact with NFAT.[114] Studies of transgenic mice[115] and those treated with Cn inhibitor[116] have implicated Cn signaling in activity-dependent maintenance of the slow gene program.[113]

Cn-NFAT signaling may also upregulate the transcription factor peroxisome proliferator-activated receptor (PPAR)-β/-γ and the transcriptional co-activator PPAR-γ(PGC-1α),[117] both of which have been implicated in the muscle dysfunction of COPD patients. PPAR signaling can affect oxidative signaling and fiber type composition,[118] in addition to having inflammatory properties via effects on the nuclear factor kappa-light-chain-enhancer of activated B cells pathway.[119] The three isoforms of PPARS (α, β/δ, and γ) are all present in skeletal muscle. PPAR-δ regulates fatty acid utilization and energy homeostasis[120] and higher levels are expressed in type I muscle fibers[121] and can be induced by acute exercise in healthy young men.[122] A transgenic "marathon mouse" model, in which PPAR-δ expression is increased, shows fiber shift opposite to that seen in COPD.[121] PGC-1α is a co-activator of PPAR-δ that can interact with transcription factors and basal transcriptional machinery[123] and can stimulate mitochondrial

and oxidative enzymes.[113] In one small study of 14 COPD patients and nine control subjects, PPAR-α and -δ protein levels and PGC-1α mRNA were significantly lower in the quadriceps of moderate/severe COPD patients than in controls with a similar smoking history[124] and PPAR-α mRNA expression was lower still in cachectic patients. These findings suggest that PPAR-γ or -α content and/or function may in some way be involved in the change in oxidative gene program and mitochondrial dysfunction.[125] However, as type I fibers have higher expression of PPARs, these results may simply represent an association rather causation.

The mitogen-activated protein kinase (MAPK) pathway may have an influence on fiber shift via extracellular signal-regulated kinase (ERK) signaling. In muscle cell lines, a type I phenotype is induced when the ERK pathway is inhibited and a shift toward type I/IIa from IIx myosin heavy chain (MHC) results from MAPK phosphatase-1.[126] Recent data from COPD patients have been conflicting. Lemire and colleagues showed elevated ratios of phosphorylated to total level of p38 MAPK and ERK 1/2 in the quadriceps muscle compared with controls.[127] These ratios were negatively associated with mid-thigh muscle CSA, supporting the hypothesis that MAPK may contribute to the development of skeletal muscle dysfunction in COPD.[127] In contrast, data from a much larger cross-sectional study failed to show a role for p38 MAPK signaling.[128]

Emerging data suggest that microRNAs (miRNAs), small polynucleotides that can decrease mRNA translation or directly destabilize mRNA, may also be implicated in the control of skeletal muscle phenotype.[129] Muscle-specific miRNAs include those which affect myocyte proliferation and differentiation, for example, miR-1 and miR-206,[130] and others, such as miR-208b and miR-499,[130,131] that modulate the expression of slow MHC genes through regulation of transcriptional repressors.[132,133] In COPD, we have recently shown that the miRNA profile of the quadriceps muscle in COPD patients differs from that of controls, with a downregulation in the myocardin-related transcription-serum response factor axis and reduced expression of muscle-specific miRNAs, particularly miR-1.[134] Reduction in miR-1 has been reported in other models of inactivity resulting from denervation, nerve entrapment, or space flight and targets include myostatin[135] and IGF-1.[136] We found IGF-1 was elevated in the COPD group consistent with previous reports of the overexpression of muscle hypertrophy pathways.[98] MiR-1 may also contribute toward reduction in MHC I and fiber shift, via an increase of HDAC4. HDAC4 inhibits serum response factor, an important regulator of MHC1 expression, and the expression of follistatin,[137] which may activate the myostatin pathway.

Non-pharmacological treatments for muscle dysfunction in COPD

Exercise training remains the only known intervention to reverse some of the underlying skeletal muscle abnormalities seen in COPD, further supporting the notion that reduced daily physical activity is the major etiological factor. Exercise training, in the form of pulmonary rehabilitation (PR), has emerged as the most effective non-pharmacological intervention in improving exercise capacity, dyspnea, and health status in COPD patients, as evidenced by numerous randomized controlled trials and meta-analyses.[138] Given that PR does not directly improve lung mechanics or gas exchange,[139] it is likely that the main area of improvement with exercise lies in the skeletal muscle. Dysfunction of the locomotor muscles may limit exercise performance because of leg discomfort,[13] but also because early anaerobic metabolism leads to lactic acid production. Lactic acid, buffered by bicarbonate, causes production of carbon dioxide and an increased ventilatory stimulus. As expiratory flow limitation is commonly present in COPD, increased ventilation can exacerbate dynamic hyperinflation and promote premature exercise termination and dyspnea.[140]

Quadriceps strength, endurance, and fatigability all improve significantly following exercise training.[58,141,142] Even in the acute setting, resistance training during an exacerbation can prevent muscle function deterioration,[59] while PR shortly following hospital discharge can significantly accelerate recovery of quadriceps muscle strength.[58] Debate remains as to the most effective mode of exercise to induce not only different skeletal muscle adaptations but also long-term improvements in clinically relevant health outcomes. Typically, chronic endurance training enhances the fatigue resistance of skeletal muscle by promoting a muscle-fiber type shift from fast-twitch fatigable type II fibers to slow-twitch fatigue-resistant type I fibers, increasing mitochondrial content and activity and improving skeletal muscle glucose transportation. However, resistance training reduces sarcopenia and promotes hypertrophy of muscle fibers, especially of type IIx.[143]

Intensity of exercise training is an important determinant of the physiological training effect.[144] However, in patients with severe COPD, intolerable sensations of breathlessness may prevent sufficiently long periods of high-intensity training levels.[145] Strategies to augment exercise tolerance by

reducing dyspnea sensation or ventilatory limitation have included noninvasive mechanical ventilation,[146] oxygen,[147] and/or heliox supplementation,[148] all of which have been demonstrated to increase exercise tolerance in the laboratory setting. However, these are rarely systematically used as part of clinical PR programs. An alternative approach, which may be particularly suitable for patients with more severe COPD, is interval training, which allows patients to complete short periods of high-intensity exercise not possible with classical aerobic exercise training.[149]

Although the emphasis has so far been on the muscles of the lower limbs, there have been studies examining the effects of training the upper limbs or the respiratory muscles in COPD. A systematic review of upper-limb exercise-training studies in COPD showed improvements in arm exercise capacity, but the effects on symptoms, overall exercise capacity, and health-related quality of life were inconsistent.[150] Similarly, debate continues with regard to the role of inspiratory muscle training in the context of PR. Although most studies have demonstrated a positive effect on voluntary inspiratory muscle strength,[151] it remains unclear whether this is as a result of a genuine physiological improvement in the inspiratory muscles or a learning effect in performing the voluntary maneuver. Furthermore, the added benefit of inspiratory muscle training over a general exercise-training program seems relatively limited.[151]

In patients unable or unwilling to adhere to existing forms of exercise, neuromuscular electrical stimulation (NMES) may offer an alternative way of enhancing leg muscle strength.[152] NMES uses a battery-powered stimulator unit to produce a controlled contraction of the muscles via skin electrodes. A typical program consists of 30–60 minutes of quadriceps stimulation, 3–5 times weekly for 4–6 weeks. NMES can lead to improvements in muscle strength and exercise performance, with pooled data revealing mean between-group differences in peak quadriceps torque and 6-minute walking distance of 9.7 Nm (95% CI 1.2, 18.1) and 48 m (95% CI 9, 86), respectively.[153] Recent studies have also demonstrated favorable changes in markers of anabolism/catabolism[154] and the quadriceps fiber type profile following NMES.[155] However, studies remain small, follow-up data are lacking, and the patient phenotypes most likely to benefit have yet to be identified.

Pharmacological treatments for muscle dysfunction in COPD

Despite the many benefits of PR, there are limitations. Firstly, exercise training does not fully reverse all of the abnormalities observed in the quadriceps muscle. Secondly, a proportion of patients either has limited accessibility to PR or has issues with uptake and completion. Thirdly, improvements following PR decline toward baseline level within 12–18 months.[156] Hence, there is interest in pharmacologically augmenting (or even replacing) exercise training to bring about structural and functional improvements in the skeletal muscles. However, as well as the technical problems involved in creating a drug that specifically benefits the muscles, there are regulatory hurdles to be overcome before such a compound can reach the market.[157]

As previously discussed, systemic inflammation, oxidative stress, and anabolic/catabolic hormone imbalance have been postulated as etiological factors for muscle dysfunction in COPD. An early trial of infliximab, an anti-TNF-α therapy, found that it was largely ineffective in improving lung function, exercise capacity, or health-related quality of life,[158] although there did appear to be a trend for benefit in cachectic patients. Furthermore, antioxidant therapy with N-acetylcysteine led to a 25% increase in quadriceps endurance compared with placebo.[70] However, this was a very small study of nine COPD patients in a controlled laboratory setting. Studies of anabolic hormones have had mixed results. Anabolic steroids increase body weight and FFM in COPD, either alone[159] or in conjunction with exercise training,[87] but not muscle strength or exercise capacity. However, the addition of testosterone to resistance training in hypogonadal COPD patients promotes anabolic pathways that can result in improved quadriceps strength and endurance.[88] Recombinant growth hormone (GH) improves FFM compared with placebo but does not improve muscle strength or exercise capacity.[86] Ghrelin is a novel GH-releasing peptide that induces a positive energy balance by decreasing fat utility and stimulating feeding through GH-independent mechanisms. In a small open-label study, ghrelin increased FFM, muscle strength, and 6-minute walk distance in cachectic COPD patients.[160] Systemic side effects with hormonal drugs are a concern, hence there is current interest in the development of anabolic drugs without the unwanted side effects. An example is the selective androgen-receptor modulator class of drugs that have the benefits of anabolic/androgenic steroids with a hypothetically reduced risk of prostate cancer in men and virilizing effects in women.[161]

Another therapeutic approach is to use existing drugs for new indications. As previously discussed, common variations in the gene for the vitamin D receptor[81] and deletion of the allele of the ACE[79] have been demonstrated to influence muscle strength. Vitamin D supplementation or the administration of ACE inhibitors may have a future role in treating muscle

dysfunction in COPD, or at least augmenting the benefits of exercise training. Certainly, this approach has been used with positive results in elderly people with functional impairment.[162] Similarly, levosimendan, a calcium sensitizer used as a cardiac inotrope, has recently been shown to improve neuro-mechanical efficiency and contractile function of the human diaphragm in healthy subjects,[163] and conceivably it may also improve skeletal muscle dysfunction in COPD. However, with increasing understanding of the underlying molecular mechanisms, there is also hope that a number of novel pharmacological agents that address cachexia and skeletal muscle dysfunction in COPD will become available for clinical use. Already, prototype inhibitors of ubiquitin ligases and neutralizing antibodies to myostatin have been developed for cancer-related cachexia and muscle dystrophies.[164] PPAR-δ agonists have recently been shown to mimic and enhance exercise training and AICAR, an 5′ adenosine monophosphate-activated-kinase agonist, was sufficient to improve exercise endurance in mice alone.[165] Thus, there is much future promise that novel therapeutic agents will become available to address important extrapulmonary manifestations of COPD such as skeletal muscle dysfunction.

Future directions

A greater understanding of the etiology and basic mechanisms of skeletal muscle dysfunction should continue to underpin developments in the field, informing the identification and testing of new pharmacological agents and strategies to augment or optimize PR across community and in-patient settings. Phenotyping of patients according to skeletal muscle dysfunction will also enhance the identification of those most likely to response to specific treatments, thus should be embraced in clinical trial design and practice, where possible.

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Disclosure

The authors declare no conflicts of interest in this work.

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