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REVIEW

Exercise and muscle dysfunction in COPD: implications for pulmonary rehabilitation

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ABSTRACT

Skeletal muscle dysfunction in COPD (chronic obstructive pulmonary disease) patients, particularly of the quadriceps, is of clinical interest because it not only influences the symptoms that limit exercise, but may also contribute directly to poor exercise performance and health status, increased healthcare utilization, and mortality. Furthermore, unlike the largely irreversible impairment of the COPD lung, skeletal muscles represent a potential site to improve patients' level of function and quality of life. However, despite expanding knowledge of potential contributing factors and greater understanding of molecular mechanisms of muscle wasting, only one intervention has been shown to be effective in reversing COPD muscle dysfunction, namely exercise training. Pulmonary rehabilitation, an intervention based on individually tailored exercise training, has emerged as arguably the most effective non-pharmacological intervention in improving exercise capacity and health status in COPD patients. The present review describes the effects of chronic exercise training on skeletal muscles and, in particular, focuses on the known effects of pulmonary rehabilitation on the quadriceps muscle in COPD. We also describe the current methods to augment the effects of pulmonary rehabilitation and speculate how greater knowledge of the molecular pathways of skeletal muscle wasting may aid the development of novel pharmaceutical agents.

INTRODUCTION

In a related review [1], we have described the current knowledge of the structural and functional abnormalities of skeletal muscle in patients with COPD (chronic obstructive pulmonary disease) and the possible aetiological factors. Despite increased knowledge and awareness of the importance of skeletal muscle dysfunction in COPD, only one intervention has been shown to be effective in reversing some of these abnormalities, namely exercise training. Although there was initial scepticism that COPD patients with their pulmonary impairment could achieve exercise levels necessary to produce a true physiological training effect [2], pulmonary rehabilitation, an intervention based on individually tailored exercise training, has emerged as arguably the most effective non-pharmacological intervention in improving exercise capacity and health status in COPD patients. These improvements occur without changes in lung function. Pulmonary rehabilitation is supported by a number of randomized-controlled trials and meta-analyses [3] and, quite appropriately, it has become the

Key words: chronic obstructive pulmonary disease, exercise, muscle dysfunction, pulmonary rehabilitation, quadriceps, skeletal muscle.

Abbreviations: AICAR, monophosphate (5-aminoimidazole-4-carboxamide-1-β-D-furanosyl 5′-monophosphate); AMPK, AMP-activated protein kinase; CaMK, Ca^{2+}/calmodulin-dependent protein kinase; COPD, chronic obstructive pulmonary disease; CSA, cross-sectional area; GH, growth hormone; GLUT, glucose transporter; IGF, insulin-like growth factor; MEF, myocyte-enhancer factor; MuRF-1, muscle ring finger-1; NFAT, nuclear factor of activated T-cells; NIV, non-invasive ventilation; PCr, phosphocreatine; PPAR, peroxisome-proliferator-activated receptor; PGC-1α, PPAR-γ co-activator 1α; TNF-α, tumour necrosis factor-α.

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cornerstone in the management of COPD [4]. Indeed, the magnitude of improvement in health-related quality of life observed in many trials of pulmonary rehabilitation far exceed the effects observed in clinical trials of bronchodilators, inhaled corticosteroids or combination products [5]. However, this should not detract from some of the limitations of rehabilitation. First, exercise training does not fully reverse all of the abnormalities observed in the quadriceps muscle [6]. Secondly, clinical trials and cohort studies reveal that up to a quarter to a third of COPD patients may not improve exercise capacity following pulmonary rehabilitation. Thirdly, improvements and gains from pulmonary rehabilitation decline towards baseline within 12–18 months [7,8]. Furthermore, a proportion of patients fail to take up or complete the offer of pulmonary rehabilitation, and, finally, at least in the U.K., provision of pulmonary rehabilitation is not universal, so some patients do not have access to this therapy [9]. A better understanding of the mechanisms of muscle disease in COPD would allow prophylactic strategies to be introduced at an earlier stage in the condition and may allow the development of therapies that could be used as an adjunct to exercise training.

The present review summarizes the effects of exercise training on molecular pathways in skeletal muscle and the currently known effects of pulmonary rehabilitation on the quadriceps muscle in COPD patients. We will describe existing methods to augment pulmonary rehabilitation and speculate how a further understanding of muscle-wasting mechanisms may aid in the design of interventions as adjuncts to pulmonary rehabilitation.

EFFECTS OF CHRONIC EXERCISE TRAINING ON SKELETAL MUSCLE

Industrialization and technological advances over the last century have inevitably led to a major change in lifestyle, notably the drastic reduction in physical activity, and the associated marked increase in the incidence of obesity and chronic diseases. Physical inactivity is a risk factor for many chronic diseases, including pulmonary disease, cardiovascular disease, Type 2 diabetes, musculoskeletal disorders, such as osteoporosis, immune system dysfunction and even certain types of cancer. In COPD, physical inactivity has been shown to be a major independent risk factor for hospitalization and mortality [10]. Increased physical activity is associated with major improvements in numerous chronic health conditions. For example, there is strong epidemiological evidence that increased physical activity delays (or even prevents) the onset of Type 2 diabetes [11]. Despite the obvious clinical benefits of exercise, the molecular mechanisms underlying these effects, particularly on skeletal muscle metabolism, are only beginning to be unravelled.

Considerable debate continues with regards to the relative merits of additional strength training over traditional endurance training adopted during pulmonary rehabilitation [12]. The type of training may activate independent signalling pathways that result in different skeletal muscle adaptations. For example, chronic endurance exercise enhances the fatigue resistance of skeletal muscle, allowing more efficient utilization of substrates needed for ATP production. This is achieved by promoting a muscle fibre-type shift from fast-twitch fatigable type IIb and type IIx fibres to slow-twitch fatigue-resistant type I fibres [13], increasing mitochondrial content and activity, and improving skeletal muscle glucose transportation through activation of the glucose transporter GLUT4. These actions and the putative molecular pathways are summarized in Figure 1. Strength training reduces sarcopaenia [14] and promotes substantial hypertrophy of type IIb and IIx muscle fibres [15].

The adaptations to endurance training are likely to be partly mediated by motor neuron firing patterns, characterized by frequent release of small amounts of Ca^{2+} from the sarcoplasmic reticulum [16]. Changes in Ca^{2+} concentrations in the cytosol activate the protein phosphatase calcineurin and members of the CaMK (Ca^{2+}/calmodulin-dependent protein kinase) family, which appear to be important regulators of the fast-to-slow twitch transformation of muscle fibres. For example, cyclosporine, a commonly used immunosuppressant that is a calcineurin inhibitor, promotes a slow-to-fast muscle fibre transformation [16], whereas transgenic mice that overexpress active calcineurin have a vast increase in type I muscle fibres [17]. Calcineurin may also be involved in promoting mitochondrial biogenesis as it activates a large number of genes involved in mitochondrial energy metabolism [18], but animal studies have not shown an effect of cyclosporine on exercise-induced mitochondrial biogenesis [19,20]. Similarly, although transgenic mice that overexpress active calcineurin have increased skeletal muscle GLUT4 protein [21], completely blocking calcineurin activity with cyclosporine does not influence exercise-training-induced GLUT4 protein expression [22]. A role for CaMKs in exercise-induced muscle fibre type switching and mitochondrial biogenesis remains hotly debated [23,24], but an intermittent caffeine model of increased cytoplasmic Ca^{2+} levels induces increased GLUT4 protein, which is blocked by treatment with KN-93 (an inhibitor of CaMK) [25].

Calcineurin and the CaMKs express their actions by activation of several important transcription factors, including MEFs (myocyte-enhancer factors) and members of the NFAT (nuclear factor of activated T-cells) family. Among the targets of MEFs and NFATs are exercise-regulated muscle genes, including PGC-1α [PPAR (peroxisome-proliferator-activated receptor)-γ co-activator 1α) or PPAR-γ], a powerful transcriptional co-activator that is implicated in fast-to-slow muscle

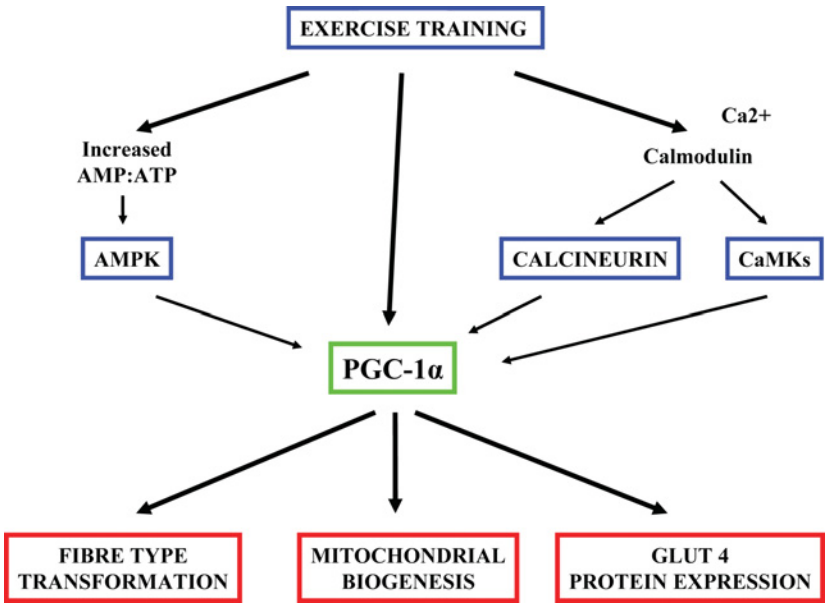

Figure 1 Skeletal muscle adaptations to chronic exercise training

fibre type transformation [26], mitochondrial biogenesis [27] and fatty acid metabolism [28]. Evidence for the pivotal role of PGC-1α in muscle adaptations to exercise training has been observed in both animal and human studies. Rat skeletal muscle PGC-1α mRNA and protein levels are increased following swimming exercise [29], whereas transgenic mice with increased expression of PGC-1α have increased proportions of type I and IIa muscle fibres, are more resistant to fatigue and have increased exercise endurance [26,30]. Meanwhile, mice with a muscle-specific deletion of PGC-1α have more type IIb and IIx muscle fibres and have a lower capacity for endurance exercise [31]. In healthy humans, 6 weeks of endurance training were sufficient to induce significant increases in vastus lateralis PGC-1α mRNA and protein levels [32]. Of clinical interest, reduced PGC-1α activity has been observed in several chronic diseases, and a recent study has demonstrated that a small cohort of COPD patients had significantly lower PGC-1α mRNA levels than age-matched controls [33].

Apart from calcineurin, another relevant upstream signalling molecule involved in the activation of PGC-1α is AMPK (AMP-activated protein kinase). AMPK is a heterotrimeric protein that is activated by a complex mechanism involving low-energy status signals (an increase in AMP/ATP ratio) and upstream kinases, such as LKB1, and has been implicated in exercise-induced skeletal muscle adaptations. For example, addition of AICAR [monophosphate (5-aminoimidazole-4-carboxamide-1-β-D-furanosyl 5′-monophosphate)], an AMPK activator, causes a significant decrease in the percentage of type IIb fibres and a concomitant increase in the percentage of type IIx fibres in the extensor digitorum longus muscle [34], and an increase in quadriceps and soleus muscle mitochondrial enzymes and GLUT4 [35]. Transgenic mice with chronic activation of AMPK have a significant increase in triceps muscle type IIa/x fibres and mitochondrial markers [36], whereas mice with inactive AMPK have reduced fibre-type shifting following endurance exercise compared with wild-type mice [36]. Chronic AICAR injections induce PGC-1α RNA expression [34,37], and recent findings have shown that 4 weeks of AICAR treatment enhanced running endurance in sedentary mice by 44 % [38]. AMPK has been shown to enhance the binding of PGC-1α to its promoter by direct phosphorylation of the PGC-1α protein [39]. Whether AMPK has an effect on exercise-induced muscle adaptations independent of PGC-1α is unknown, but appears unlikely given that transgenic mice deficient in PGC-1α have no response to AMPK [39]. It is also possible that AMPK may have a negative effect upon muscle as it has been shown to inhibit the activity of mTOR (mammalian target of rapamycin) [40], an integral part of the muscle hypertrophy pathway, and to increase the expression of MuRF-1 (muscle ring finger-1) [41], an atrogene implicated in muscle atrophy.

EFFECT OF PULMONARY REHABILITATION ON COPD MUSCLE DISEASE

The clinical benefits (both physiological and psychological) following pulmonary rehabilitation in COPD are well documented [3,42]. Despite initial scepticism that COPD patients with their considerable ventilatory limitation were able to achieve a sufficient training

Table 1 Effects of pulmonary rehabilitation on quadriceps muscle abnormalities in COPD

Effect	
Clinical	Increases strength and endurance
	Reduces fatigability
	Small increase in mid-thigh CSA
	Small increase in fat-free mass
Structural	No significant change in fibre type proportion
	Increases muscle fibre CSA
	Increases capillary contact for each muscle fibre type
Metabolic	Increases oxidative enzyme capacity
	Reduces lactic acid production during exercise
	Normalizes decline in PCr/P_i ratio during exercise

Table 2 Potential strategies to augment pulmonary rehabilitation

Strategy	
Reducing ventilatory limitation	Bronchodilators
	Oxygen
	Heliox
	Non-invasive ventilation
	Inspiratory muscle training
Improving muscle bulk and function	Neuromuscular electrical stimulation of the locomotor muscles
	Nutritional supplements
	Anabolic hormones
	Anti-inflammatory drugs
	Antioxidant drugs
	Novel agents (e.g. muscle atrophy pathways antagonists and exercise mimetics)

intensity to induce physiological improvements [2], it is now clear that exercise training is the only intervention to date that consistently improves skeletal muscle function and morphology, giving further credence to the view that inactivity is the principal driving force for COPD muscle dysfunction. Some of these improvements are summarized in Table 1. Quadriceps strength, endurance and fatigability all improve significantly following exercise training [8,12,43–46], with smaller, but significant, improvements in mid-thigh CSA (cross-sectional area) [43] and fat-free mass [47,48]. Morphologically, although exercise training has not been shown to convincingly reverse the fibre-type shift observed in the quadriceps muscle [6], it does improve CSA of muscle fibres by at least 20 % [6]. Furthermore, metabolic improvements observed after training include an increase in oxidative capacity [49], reduced lactic acid production during exercise [49,50] and normalization of the decline in the PCr (phosphocreatine)/P_i ratio during exercise [51]. As yet, no studies have examined skeletal muscle molecular adaptations following pulmonary rehabilitation in COPD and this is likely to be a fruitful area of future research.

The benefits of exercise training in COPD have to be tempered by several observations. In some studies, the training occurred in motivated research volunteers during heavily supervised laboratory exercise sessions. Whether these benefits can be anticipated following pulmonary rehabilitation in the general outpatient setting has not been firmly established. Certainly, it has been observed in cohort studies that up to a quarter to a third of COPD patients may not improve their exercise capacity following pulmonary rehabilitation. In addition, almost all studies have looked at short-term or immediate changes in muscle structure and function, without due attention to the duration of improvements; many clinical improvements and gains from pulmonary rehabilitation decline towards baseline within 12 months [7]. Furthermore, exercise training even in the laboratory setting does not appear to fully reverse all of the abnormalities observed in the quadriceps muscle [6,43]. Some investigators have used these observations to argue that inactivity may explain only part of the abnormalities observed in the peripheral muscles [52], whereas others have argued that the duration of general pulmonary rehabilitation programmes is inadequate [8] or that the considerable ventilatory limitations associated with COPD impose constraints on the level of training [53]. For example, training strategies that exercise small muscles without requiring the patient to breathe maximally demonstrate the same peak muscle oxygen consumption in COPD patients as healthy controls [54]. Although there does not appear to be a clear dose–response effect, some authorities consider that longer pulmonary rehabilitation programmes are associated with prolonged benefits [8,55], although this is not a universally held view [56]. Recent evidence suggests a shorter programme is sufficient to induce a measurable change in maximal exercise performance, but that a longer programme is required to induce long-term lifestyle changes in daily physical activity levels when measured using accelerometry [57].

AUGMENTING THE EFFECTS OF PULMONARY REHABILITATION

Aside from addressing the organizational, methodological and psychological elements of general exercise training, there are two broad strategies to augment the effects of pulmonary rehabilitation in COPD patients: (i) reducing ventilatory limitation in order to reduce the constraints on exercise training; and (ii) pharmacological interventions to improve muscle bulk and function (Table 2).

Reducing ventilatory limitation

All patients should receive optimal medical management before starting pulmonary rehabilitation [4]. In particular, bronchodilator therapy not only reduces

airflow resistance, but also resting and dynamic hyperinflation [58–60], which are considered to be major limiting factors of exercise capacity in COPD [61]. The use of the long-acting anticholinergic bronchodilator tiotropium in conjunction with a general pulmonary rehabilitation programme was associated with significant improvements in exercise endurance, health-related quality of life and breathlessness [62]. However, it should be noted that patients who develop quadriceps fatigue following symptom-limited cycling exercise may fail to benefit from bronchodilators [63].

The use of supplementary oxygen during rehabilitation remains contentious. In the research setting, oxygen supplementation improves symptoms, increases exercise endurance, reduces minute ventilation and decreases lactic acid production in COPD patients [64–67]. Furthermore, oxygen delivery to the locomotor muscles is also improved [68]. Theoretically, this should enable higher training intensities and improve the degree and duration of gains from pulmonary rehabilitation. This has not been the case in clinical studies, where oxygen supplementation during exercise training has not been shown to be better than room air in improving exercise capacity, health-related quality of life or dyspnoea, even in hypoxic patients [69,70]. Admittedly, these studies have been under-powered to demonstrate a significant change, but there is insufficient evidence to routinely use oxygen during pulmonary rehabilitation programmes. However, most operators use oxygen supplementation during rehabilitation in exercise de-saturators (from a safety point of view) and in those already on domiciliary long-term oxygen therapy. Helium/oxygen mixtures (Heliox) have also been postulated as having a potential role for augmenting rehabilitation. The low density reduces airflow resistance, thus decreasing the development of dynamic hyperinflation and improving exercise endurance [71,72]. However, there have been few trials of Heliox in exercise training or pulmonary rehabilitation, principally because of the high cost of providing sufficient gas mixture for each patient throughout a rehabilitation programme [73].

The use of NIV (non-invasive ventilation) has been a major development in the management of COPD, particularly in the treatment of acute exacerbations [74]. Inspiratory pressure support decreases the load placed on the inspiratory muscles, hence, reducing the work of breathing [75], and has been shown to improve breathlessness and exercise endurance [76,77]. Unsurprisingly, investigators have tested the potential of NIV to enhance training intensity and duration, with mixed results. In very severe COPD patients, proportionally assisted ventilation has been shown to improve training intensity and maximum exercise capacity [78,79], but this was not observed in more typical patients referred for outpatient rehabilitation [80]. Further limitations of NIV include the need for expert supervision to ensure optimal patient–ventilator interaction [80] and the bulk of the ventilator (even ambulatory ventilators), which may limit the type of exercise training [81]. Although there is little evidence for routine application in the outpatient setting, NIV may be potentially beneficial in the rehabilitation of selected patients. Examples may be the acute exacerbation setting, where there is increasing evidence that rehabilitation is important [82,83], or the home setting, particularly in severe patients who are unable to regularly attend outpatient programmes. Certainly, in severe patients with chronic respiratory failure, the addition of domiciliary NIV to outpatient rehabilitation led to improvements in exercise capacity and health-related quality of life compared with rehabilitation alone [84].

Inspiratory muscle training has been postulated as a useful adjunct to general exercise training, particularly as COPD patients have long been observed to have reduced maximum inspiratory mouth pressures [85]. However, although the respiratory muscles may be functionally 'weak' due to being mechanically disadvantaged by the effects of hyperinflation in COPD, investigators have not demonstrated any intrinsic weakness of the inspiratory muscles when assessed non-volitionally and when lung volume is taken into account [86,87]. Indeed, as described previously, the diaphragm in COPD patients has very different characteristics (both structurally and functionally) to the quadriceps, with increased slow-twitch characteristics and resistance to fatigue [88,89]. Although controlled inspiratory muscle training has been demonstrated to produce favourable changes in inspiratory muscle fibre size and fibre-type proportion [90], meta-analyses have not shown additional improvement in exercise capacity compared with general exercise training alone [91]. Furthermore, there is some evidence that inspiratory loading, if uncontrolled, may cause damage to the diaphragm [92].

In some patients, ventilatory constraints are so severe, or peripheral muscles are so weak, that they are unable to participate in general aerobic exercise training. Neuromuscular electrical stimulation of the lower limbs has been shown to improve skeletal muscle strength and exercise capacity in stable patients with severe peripheral muscle weakness [93,94]. It has also been shown to be useful in bed-bound patients receiving mechanical ventilation [95]. The technique is safe, relatively inexpensive and with the added advantage that it is suitable for home use. However, existing studies have been small, and neuromuscular electrical stimulation has not been studied as an adjunct to general exercise training or in patients who do not have severe peripheral muscle weakness.

Pharmacological and nutritional interventions

Most interventions to date have focused on methods to promote anabolic pathways in view of the high prevalence of fat-free mass loss observed in COPD patients [96,97]. This may be particularly relevant during pulmonary

rehabilitation where exercise training is associated with increased energy expenditure [98]. Early nutritional intervention studies in underweight COPD patients were able to demonstrate improvements in body weight, but it is not known whether any of this gain consisted of useful muscle mass rather than simple fat mass [99]. More recent studies have not shown a demonstrable benefit with nutritional supplementation alone [100]. Although results are marginally more promising when combined with supervised rehabilitation, there is still insufficient evidence to recommend universal prescription of nutritional supplements. Steiner et al. [98] demonstrated an increase in weight following carbohydrate-rich supplementation to patients undergoing outpatient pulmonary rehabilitation, but were not able to demonstrate improvements in exercise capacity or health-related quality of life. Benefits appeared to be more marked in well-nourished patients [BMI (body mass index) >19] [98]. This is in contrast with the findings of Creutzberg et al. [101], who, in an uncontrolled study of depleted patients, were able to show improvements in weight, fat-free mass, exercise capacity, respiratory and peripheral muscle strength, and health-related quality of life when combining nutritional supplementation with in-patient pulmonary rehabilitation.

Body builders and athletes have long known the effects of anabolic steroids in promoting muscle bulk. Apart from simulating muscle hypertrophy pathways, anabolic steroids may have other potentially beneficial effects upon factors relevant to COPD, namely their antiglucocorticoid effect and erythopoietic action [48]. These drugs have been shown to increase body weight and fat-free mass in COPD patients either alone [102] or in conjunction with exercise training [48,102–104]. However, it is less conclusive as to whether there is an effect upon muscle strength or exercise capacity. Schols et al. [103] demonstrated an improvement in maximal inspiratory mouth pressure when nandrolone was combined with nutritional supplementation, but others have not found improvements compared with placebo in either skeletal muscle strength or exercise capacity [48,104]. Some investigators have studied the effect on selected patient subgroups; for example, hypogonadism is not uncommon in men with COPD [47,105,106]. The addition of testosterone to rehabilitation in hypogonadal COPD patients promotes the anabolic pathways, principally by activation of the muscle IGF (insulin-like growth factor) system [107], resulting in increased quadriceps strength and resistance to fatigue [47]. It remains to be seen whether these muscle functional improvements translate to improved exercise capacity and health-related quality of life in larger trials, and further studies are required to clarify the long-term side-effect profile of testosterone. As discussed in a related review [1], IGF-1 induces skeletal muscle hypertrophy through the PI3K (phosphoinositide 3-kinase)/Akt pathway, and may inhibit the muscle atrophy by suppression of the FoxO (forkhead box O) class of transcription factors. Mixed results have been observed with GH (growth hormone), a potent stimulator of systemic IGF-1 levels. In a small study of patients undergoing pulmonary rehabilitation, recombinant GH improved fat-free mass compared with placebo, but did not result in improvement in muscle strength or exercise capacity [108]. Furthermore, due to the ubiquitous expression of GH and IGF-1 receptors, a concern exists about unwanted side effects, and greater potential perhaps may be found with directed hormonal therapies to the muscle [109] or the addition of specific binding receptors [110].

Other therapeutic possibilities include reversal of putative factors that influence muscle dysfunction in COPD, such as systemic inflammation and oxidative stress. In a related review [1], we have discussed the potential role of pro-inflammatory cytokines, such as TNF-α (tumour necrosis factor-α), in the pathogenesis of COPD muscle dysfunction. Anti-TNF-α treatments have been used successfully in conditions such as rheumatoid arthritis, inflammatory bowel disease and psoriasis, but early trials in COPD patients have not demonstrated improvements in lung function, exercise capacity or health-related quality of life [111]. No studies have looked specifically at the role of anti-TNF-α therapies in augmenting pulmonary rehabilitation, and there are also continued concerns about unwanted side-effects, including the possible increased risk of infections and malignancies [111]. Another candidate intervention includes antioxidant drugs, including vitamins and mucolytics, such as *N*-acetylcysteine and carbocysteine. These have few side effects, and there is evidence that some may play a role in preventing acute exacerbations of COPD [112]. There are results to suggest that antioxidant vitamin supplementation may increase exercise capacity in healthy humans with low antioxidant levels [113]. Studies in COPD are relatively sparse, but Koechlin et al. [114] were able to improve quadriceps endurance by 25 % with *N*-acetylcysteine compared with placebo in severe COPD patients. Whether this translates to the outpatient rehabilitation setting or has an effect upon exercise capacity and health-related quality of life warrants further study.

As understanding of the molecular mechanisms of muscle wasting increases, it is likely that there will be an increased focus on new therapeutic strategies, including pharmacological agents, that antagonize muscle atrophy pathways. This is relevant not only in COPD, but in other chronic disorders where muscle wasting is a feature [115]. As discussed previously [1], the ubiquitin ligases MuRF-1 and atrogin-1 are up-regulated in several animal models of muscle wasting, and transgenic mice deficient in these enzymes appear to be protected against muscle wasting [116]. Prototype ligase inhibitors have been developed for cancer-associated cachexia, but may also have a potential role in COPD [117]. Regulators of myogenic satellite cells may also be influential; for example, inhibitors of

myostatin have been shown to increase muscle mass and function in mouse models of muscular dystrophy [118], although human studies are in their infancy [119]. Aside from improving muscle bulk, other therapeutic strategies that require future consideration include pharmacological mimicking of exercise training. As discussed above, PGC-1α appears to play a pivotal role in muscle adaptations to exercise training, and pharmacological manipulation of this pathway may have an enormous potential clinical impact [120]. Recent gene-expression-based screening studies have identified small molecules that induce PGC-1α expression in skeletal muscle cells, including microtubule inhibitors and protein synthesis inhibitors [121]. Further encouragement also comes from the recent discovery that PPAR-δ agonists have been shown to synergize with exercise training, and that AICAR (an AMPK agonist) alone was sufficient to induce metabolic genes and significantly improve exercise endurance [38].

CONCLUSIONS

In recent years, the clinical importance of skeletal muscle dysfunction in COPD has led to a clearer description of the abnormalities and further understanding of the potential aetiological factors. Concurrently, exciting laboratory studies have started to unravel the molecular mechanisms of muscle wasting and adaptations to chronic exercise training. A major lesson has been that inactivity plays an important aetiological role, which explains the effectiveness of rehabilitation strategies. Furthermore, existing pharmaceutical interventions often appear to work more effectively as an adjunct to pulmonary rehabilitation. As new pharmacological agents are developed, it must be remembered that real progress to improve patients' quality of life requires a combined strategy with effective pulmonary rehabilitation and with psychosocial interventions to promote continued physical activity.

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