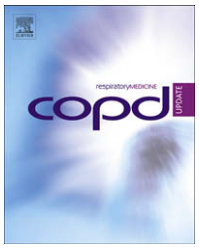

Skeletal muscle dysfunction in chronic obstructive pulmonary disease

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SUMMARY

Skeletal muscle dysfunction is considered to be one of the key systemic co-morbidities in chronic obstructive pulmonary disease (COPD) influencing exercise capacity and quality of life. The loss of skeletal muscle bulk and skeletal muscle strength are now recognised as important predictors of mortality in this patient group. The mechanisms involved in the development of muscle weakness are likely to be multifactorial, and systemic factors including inflammation and oxidative stress are thought to interact with local factors such as muscle inactivity. A greater understanding of the molecular pathways involved in muscle weakness may provide target areas for future treatments as an adjunct to pulmonary rehabilitation, which remains the mainstay of current therapy. Further research is required to increase and sustain the benefits of pulmonary rehabilitation and to develop novel interventions for this chronic, debilitating condition.

Although chronic obstructive pulmonary disease (COPD) has been considered primarily in terms of its effects on lung parenchyma, airways and vasculature, in recent years increasing attention has been focussed on its systemic effects.[1,2] This is driven by the fact that indices of pulmonary function are poorly predictive of patient symptoms and outcomes[3] and by the hope that greater understanding of these effects may lead to alternative therapeutic approaches to improve outcomes in this patient group. In this article, we outline the evidence that depletion of skeletal muscle is a major co-morbidity in COPD as well as address the mechanisms by which it occurs and the possible therapeutic strategies.

1. Importance of skeletal muscle impairment in COPD

Impairment of skeletal muscle can be considered in terms of muscle bulk and muscle function, though these are, of course, related. Weight loss has long been recognised as a feature of COPD[4] occurring in 10–15% of mild and 25% of moderate-to-severe COPD patients[5–7] and is associated with a poor prognosis.[8–17]

Different patterns of depletion occur depending on whether there is a loss of fat mass, fat-free mass (FFM) or both.[6] It is clear that preservation of fat-free mass as opposed to body weight is most important – normal-weight patients with nutritional depletion (fat-free mass index $<15\ kg\ m^{-2}$ for women or $<16\ kg\ m^{-2}$ for men) are more disabled than underweight patients with a preserved fat-free mass.[18,19] Skeletal muscle is a major component of FFM, and FFM depletion in COPD is associated with reduced exercise performance, increased dyspnoea and impaired health-related quality of life.[20–22] Leg fatigue makes a significant contribution to exercise limitation in patients with COPD,[23,24] and where quadriceps fatigue occurs after exercise, bronchodilation has not been found to increase exercise capacity.[25]

Skeletal muscle weakness does not occur equally in the upper versus lower limbs, limb versus respiratory muscles

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and proximal versus distal muscles with different 'compartments' responding to the particular demands placed on them.[26] The quadriceps is one of the main muscles of ambulation and has been the focus of much of the work around impairment of skeletal muscle in COPD. In moderate-to-severe COPD, the mean reduction in quadriceps strength is approximately 30%,[22,27–29] with significant weakness present in about 30% of patients.[30] Quadriceps weakness has been shown to be related to impaired quality of life,[31] exercise limitation[21] and increased health-care consumption[32] and predicts survival more powerfully than does age, FFM or forced expiratory volume in 1 s (FEV_1).[30] A reduction in quadriceps endurance has also been demonstrated in COPD using both volitional and non-volitional techniques of assessment.[33,34]

2. Scientific background and pathogenesis

Skeletal muscle atrophy and hypertrophy can be influenced by a number of processes that are relevant to patients in COPD. Systemic factors including inflammation and oxidative stress are thought to interact with the local pattern of use or disuse in a particular muscle. Some of the medications used to treat COPD, particularly corticosteroids, may also have a deleterious effect. In addition, genetic susceptibility[29,35,36] might explain why some COPD patients demonstrate greater peripheral weakness than others do.

3. Disuse

Patients with COPD are breathless when they exercise, and this is reflected in a reduction in physical activity which may be very pronounced.[37] Quadriceps weakness can occur with relatively brief periods of bed rest (10 days) in healthy elderly subjects[38] or indeed other medical conditions,[39] so it is unsurprising that quadriceps weakness is described within a week of hospital admissions with COPD.[40] Weakness in COPD is most pronounced in the locomotor muscles,[27,28] and, at biopsy, a classic disuse pattern of change is observed in the quadriceps with a shift towards a preponderance of 'fast' type II fibres,[41–43] reduced capillarity[44] and oxidative capacity.[43] This pattern is not seen in the deltoid muscle[45] and the reverse effect, a shift towards a preponderance of slow fibres, is seen in the diaphragm which exhibits increased activity in COPD patients.[46]

4. Systemic inflammation and oxidative stress

Systemic inflammation is present in patients with COPD as evidenced by increased levels of tumour necrosis factor (TNF)-alpha and CRP.[47] However, although early data supported a role for increased serum levels of cytokines such as TNF-alpha in muscle wasting in severe COPD,[48] a review incorporating the more recent studies of circulating plasma TNF-alpha levels has concluded that there has been no difference found between cachectic and non-cachectic COPD patient groups.[49] The diminished role for TNF-alpha in COPD peripheral muscle dysfunction has been supported by the Barreiro et al.[50] study identifying that levels of quadriceps muscle TNF-alpha actually fall with decreasing strength. This study also found no difference in interleukin (IL)-6, interferon-gamma or transforming growth factor (TGF)-beta protein expression between COPD patients and controls suggesting that the quadriceps muscle does not exhibit a pro-inflammatory environment in patients with severe COPD. It did, however, identify markers of quadriceps muscle oxidative stress in this patient group and, importantly, depletion of reduced glutathione levels has also been observed in COPD patients when compared to controls.[51] It is well established that free radicals are capable of causing tissue damage, and therefore this may play a role in the muscle atrophy seen in COPD. Recent work has also demonstrated that chronic endurance exercise leads to nitrosative stress in the quadriceps of severe COPD patients.[52] Interestingly, recent work also indicates that COPD patients exhibit different quadriceps muscle gene expression patterns in response to training when compared to controls.[53] In particular, oxidative stress gene pathways had higher expression in COPD after training. Further work is needed to establish if attenuation of these pathways can enhance training responses in this patient group. The role of oxidative stress was reviewed in more detail recently by Couillard et al.[54]

5. Corticosteroids

Steroid-induced myopathy classically affects the proximal muscles with atrophy of fast-twitch fibres, and frank myopathy has been described as a complication of corticosteroid use in COPD.[55] However, interpretation is confounded by the effects of frequent exacerbations, which are the classical indications for steroid therapy in this patient group. It has been shown that a 2-week course of prednisolone in stable COPD patients had no effect on skeletal muscle parameters,[56] and cross-sectional studies have not demonstrated a link between muscle depletion and steroid use in COPD[6,29] although there are other reasons to avoid chronic steroid therapy.[57]

6. Molecular mechanisms

The key molecular biology underlying the skeletal muscle dysfunction observed in COPD remains to be determined. The nuclear factor kappa B (NFκB) is a transcription factor modulating inflammation, and it has been shown that NFκB[58] and its downstream products[59] are over-expressed in the lungs in patients with COPD. Aside from its role in the regulation of inflammation, NFκB expression causes muscle atrophy, and it has been established in murine models that this is associated with over-expression of downstream transcription factors linked with atrophy, including muscle RING finger protein-1 (MuRF-1).[60] In an unloading model, while wild-type mice developed a slow-to-fast shift in myosin isoform expression which mirrors that which is seen in the quadriceps in COPD patients,[43] NFκB-1 knockout