Chronic obstructive pulmonary disease

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Sarcopaenia in chronic obstructive pulmonary disease

Michael C Steiner

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Lower limb muscle strength may be a predictor of mortality in patients with chronic obstructive pulmonary disease

Human beings are designed to move. Despite changes in modern lifestyles that have led to a reduction in habitual physical activity in the developed world, this remains an important human biological function. The skeletal muscles, forming one of the largest tissue compartments of the body, are dedicated to this end. The ability to move in the form of athletic performance peaks in the third and fourth decades of life and then progressively declines. Skeletal muscle mass declines by around 30% by the seventh and eighth decades and further losses of up to 50% may occur by the ninth decade and above.[1] This age-related loss of muscle mass has been termed "sarcopaenia", of Greek origin, meaning "poverty of the flesh". Sarcopaenia and the loss of muscle strength that is associated with it have important health consequences. Muscle mass and strength are independent predictors of mortality and disability in the elderly,[2] and are important aetiological factors in falls in frail older people.[3] Some loss of muscle mass and strength is almost universal in older people, but varies widely between individuals, particularly in relation to habitual levels of physical activity. The prevalence of "pathological" sarcopaenia in older people is uncertain. Using a cutoff for muscle mass (measured by dual-energy x ray absorption) of two standard deviations below the mean for young healthy adults (analogous to the T score for bone mineral density), a recent study suggested the prevalence to be 13–24% in 60–70-year-olds and over 50% in older people aged ≥80 years.[4]

Loss of skeletal muscle mass and strength is a particular problem in many chronic diseases affecting older people, particularly diseases such as chronic obstructive pulmonary disease (COPD), where exercise intolerance is an important and disabling feature. In COPD, there is abundant evidence that muscle mass, particularly in the lower limbs, is reduced when compared with healthy individuals of similar age, and that this is an independent predictor of mortality and disability.[5][6] Weight loss in COPD may present as part of a cachexia-like syndrome with severe tissue wasting in both fat and fat-free compartments. Others show selective muscle atrophy with relative preservation of the fat compartment.[7] Interestingly, recent evidence in weight-losing patients with COPD has suggested that it is muscle atrophy that exerts the most prognostic influence and has heightened interest in understanding the epidemiology and biology of this phenomenon.[5]

The paper by Swallow et al in this issue of Thorax[8] provides another piece of the jigsaw of evidence in this area **(see page 115)**. They demonstrate, in a cohort of patients with COPD, that lower limb muscle strength is a predictor of mortality, independent of the severity of the underlying lung disease. This complements other studies that have indicated that lower limb muscle strength is an important predictor of physical functioning in COPD.[9][10] Muscle strength is considered to be largely determined by muscle size, but Swallow et al found that total body muscle mass did not contribute to their predictive model. In other words, muscle quality rather than quantity seems to be more important. This is consistent with recent studies carried out in the elderly and on heart failure, which showed a similar distinction between the prognostic influence of muscle strength and mass.[11][12]

The finding of Swallow et al that neither body mass index nor fat-free mass index predicted survival contrasts with previous reports on COPD.[5][13] As the authors suggest, lower limb strength may be more predictive than whole-body measurements because of preferential loss of muscle function in the muscles of ambulation due to inactivity. An additional explanation may lie in the characteristics of the cohort. Overall mortality was not especially high, and patients with rapidly advancing cachexia and global tissue wasting who have a particularly poor prognosis may have been under-represented compared with previous studies. This would have the effect of dampening the predictive effects of measurements of whole body muscle mass on outcome.

It is remarkable that the prognostic influence of skeletal muscle wasting and weakness is so visible in COPD, particularly in a disease where the outcome will be considerably influenced by lung function impairment. Is the loss of skeletal muscle mass and function in COPD specific to the disease or is this merely accelerated sarcopaenia? There is no clear-cut answer to this question that can be generalised across the spectrum of COPD. A number of disease-related factors could plausibly contribute to muscle wasting and dysfunction in COPD, including hypoxia, negative energy balance, hormonal disturbances and medical therapy such as corticosteroids.[14] However, most of these have been explored in cross-sectional studies using age-matched healthy subjects as controls. A crucial confounding issue in these studies is habitual physical activity. This is a key factor in the development of sarcopaenia and is itself a predictor of mortality and disability in the elderly and in COPD.[15][16] Sarcopaenia can, at least in part, be averted in older people who maintain youthful levels of physical activity[17] and resistance training can increase muscle strength and mass in the elderly, even those in their 10th decade.[1][18] Patients with COPD are substantially less active than their peers and are therefore likely to be subject to more severe sarcopaenia. Despite these limitations, an important association of muscle wasting in COPD does seem to be systemic inflammation. The finding of elevated circulating inflammatory cytokines in patients with COPD has been consistent across several studies.[19] However, considerable uncertainty remains on the causes and prevalence of systemic inflammation and the mechanisms by which this leads to loss of muscle mass. Inflammation seems to be particularly associated with severe lean mass wasting leading to cachexia.[20][21] This syndrome may be a distinct form of muscle disease that differs from the one caused predominantly by inactivity, but at present reliable means to identify this phenotype of muscle wasting are not available. This is an important challenge because cachectic patients may respond less well to interventions aimed at improving muscle function such as rehabilitation and nutritional support.[22][23] At present we do not have much therapy to help these individuals.

The cellular and molecular mechanisms underlying muscle wasting remain largely unexplored in COPD. However, recognition of the importance of muscle wasting

to disability and frailty in the elderly has focused recent attention on these mechanisms in sarcopaenia. Muscle mass is determined by the relative balance of muscle protein synthesis and breakdown. These are in turn influenced by a number of factors, including exercise, dietary protein intake and the action of anabolic hormones such as testosterone, growth hormone and insulin. It is uncertain whether sarcopaenia is due to gradual changes in the relative rates of muscle protein synthesis and breakdown in the basal state. Moreover, the magnitude of any such changes may be too small to detect, given the slow pace of muscle loss during healthy ageing.[24] More important may be the responses of ageing muscle to diet and physical activity, which themselves change with age.

The responsiveness of ageing muscle to physical activity appears to be preserved, as there are numerous studies that have confirmed that resistance training can produce similar increments in muscle mass in the young and the old.[25] More recent data, however, suggest that older people are less able to use dietary protein for muscle protein synthesis.[26] These changes were associated with alterations in intracellular anabolic signalling pathways that may also be linked to inflammation-mediated proteolysis via the ubiquitin–proteosome system.[27] These pathways could therefore represent a common mechanism by which muscle protein synthesis and breakdown are uncoupled, leading to rapid loss of muscle mass such as that seen in cachectic individuals with COPD.

Muscle wasting in COPD may occur in some patients in a progressive linear manner, but the inability to build muscle effectively using dietary protein also suggests that ageing muscle may be more vulnerable to short-lived illnesses such as exacerbations where muscle breakdown is accelerated. Exacerbations are associated with extended periods during which patients are inflamed and inactive (particularly if hospitalised), and may be treated with therapy such as high-dose corticosteroids that have a potentially negative effect on muscle mass. In some patients therefore, muscle wasting could be more "events driven", where exacerbations cause brief but rapid losses of muscle protein from which the muscle fails to adequately recover. Support for this concept comes from studies showing that patients with COPD who have been hospitalised for an exacerbation may lose muscle strength rapidly (up to 5% in a few days) and that the effects of an exacerbation on physical activity and performance may be prolonged.[28 29] In addition, recent trials exploring the role of early rehabilitation after hospitalisation in COPD showed that patients allocated to standard care showed very little improvement in exercise performance after discharge.[30 31] This suggests that losses of fitness and muscle function after exacerbation are prolonged and may indeed not fully recover to the pre-exacerbation baseline. These trials did confirm the effectiveness of exercise training in this setting, providing hope that the damaging effects of exacerbations can be overcome by an effective rehabilitation strategy. Interestingly, the study of Swallow et al found that mortality was not increased in those who had been admitted for an exacerbation, suggesting that these events were less important in their cohort. However, the study may have lacked statistical power to examine this question and other studies have indicated that hospital admission in COPD is associated with a higher mortality.[32] Longitudinal studies measuring decline in muscle mass and function are needed to disentangle the effects of these multiple potential influences on the aetiology and progression of skeletal muscle disease in COPD.

The implication of the link between muscle strength and prognosis is that we may be able to reduce mortality in COPD by interventions to improve muscle function. Indeed the skeletal muscles are a potential therapeutic target in a disease where the primary pulmonary pathology is largely irreversible. The benefit of this approach is illustrated by the success of pulmonary rehabilitation in improving symptoms and reducing disability.[33] The mechanism of this improvement is largely through skeletal muscle adaptation to physical training.[34 35] There is circumstantial evidence that rehabilitation also improves survival, although this has not been conclusively demonstrated in adequately powered clinical trials.[36] It is unlikely that such trials will now be conducted, as this would involve withholding pulmonary rehabilitation from patients who would clearly benefit from it on grounds of symptoms and quality of life.

Pharmacological interventions targeted at skeletal muscles such as anabolic and sex hormone supplementation are at an early stage of evaluation, but show promise and may have a place in selected patients.[37 38] Nutritional support for patients with weight loss has proved disappointing when applied across the board,[39] but may benefit selected patients when combined with an appropriate anabolic stimulus such as exercise.[23 37]

Muscle wasting is clearly of functional and prognostic importance in COPD, but we have much to learn about the natural history and underlying mechanisms of this aspect of the disease. The situation is complex because muscle atrophy in COPD occurs on a background of age-related sarcopaenia. The application of advances in our understanding of the biology of muscle growth in young and old humans may help us unravel these issues and direct us to new therapies aimed at reversing muscle wasting. Such developments are likely to have a wide application, given the importance of disabling chronic diseases in an ageing population.

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COPD exacerbation

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Chronic obstructive pulmonary disease exacerbation and risk of pulmonary embolism

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Pulmonary embolism is not a common feature in patients with chronic obstructive pulmonary disease with uncomplicated exacerbations

Exacerbations of chronic obstructive pulmonary disease (COPD) are episodes of acute deterioration in respiratory symptoms[1] that are accompanied by physiological changes[2] and associated with increases in airway and systemic inflammation.[3 4] These episodes are responsible for considerable morbidity and mortality, especially in patients with more severe COPD.[5] There is consequently much interest in understanding the underlying pathophysiology of exacerbations and determining their triggers, so that appropriate interventions can be designed to prevent these events, reduce their severity and thus improve health status.

We now recognise that respiratory infections are important triggers of exacerbation. Respiratory viral infections, especially with human rhinovirus (the cause of the common cold), influenza and respiratory syncytial virus may be isolated from up to 60% of exacerbations.[6 7] Exacerbations where a virus is isolated have increased airway and systemic inflammatory changes.[3 8] The role of bacteria at exacerbation has been more difficult to determine as airway bacteria are also found in stable patients with COPD, especially those with more severe COPD. However, we now know that bacterial strain change may play a part in triggering exacerbation.[9] Airway bacteria may be present in up to 70% of COPD exacerbations, and their isolation is accompanied by increased airway inflammatory changes.[10] Viruses and bacteria may also be co-isolated from the same exacerbation, and recent studies have suggested that the presence of both pathogens may have a synergistic effect on the degree of airway inflammation, especially when exacerbations are severe.[8 10–12] Thus, airway infection can be implicated as a trigger in most COPD exacerbations, even taking into account difficulties in sampling these patients that can lead to underestimating the significance of airway infection.

There is also interest in other causes of COPD exacerbation. Air pollution has been associated with an increase in hospital admissions in patients with COPD, although these effects are relatively small.[13] As COPD exacerbations are closely linked to respiratory infections, the hypothesis has been put forward that pollutants can increase susceptibility to viral infection. One study has suggested that with higher personal nitrogen dioxide exposure, there is a greater risk of an asthmatic exacerbation after respiratory infection.[14] Similar mechanisms might be operating in patients with COPD and further studies investigating the associations between pollution and infection are required.

Exacerbations therefore result from further insult to the COPD airway, but a number of conditions may mimic exacerbation by causing worsening dyspnoea in patients with underlying COPD. One such condition is pulmonary embolism, a disorder of the vasculature rather than the airway. Although pulmonary embolism is not thought to predispose to exacerbation, there have been a number of reports suggesting that the prevalence of deep venous thrombosis and pulmonary