Extra-thoracic muscle wasting in exacerbations of COPD: No longer outside the region of interest

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While airflow limitation is used to diagnose chronic obstructive pulmonary disease (COPD) it is well established that FEV_1 alone relates poorly to mortality[1] or health related quality of life[2]. Skeletal muscle dysfunction has been shown to be a better predictor than lung function for both prognosis[3], and risk of hospitalisation[4]. Moreover, skeletal muscle weakness is increasingly recognised as an important component of both frailty and sarcopenia. Acute exacerbations of COPD (AECOPD) are a feature of many patients with COPD, with intermittent worsening of symptoms contrasting to many other chronic conditions. The impact of exacerbations is well established, with prevention and treatment an important goal for therapy with COPD.

Therefore the interaction between exacerbations and skeletal muscle dysfunction is of great interest. A reduction in both exercise capacity and quadriceps strength has been reported in patients admitted with acute exacerbation of COPD[5] and to a lesser extent amongst patients treated as an outpatient[6] but the longer-term impact on muscle mass is unknown. Similarly, how therapies such as pulmonary rehabilitation (PR) may impact on future exacerbations risk in the longer term is less clear, although the short term benefits of this therapy after AECOPD are established[7].

In this issue of Thorax, Mason *et al* report an association between exacerbation frequency and accelerated muscle loss in patients with COPD (add reference). Using CT images of 5,700 patients from the ECLIPSE and COPDgene cohorts over 3 or 5 years, and collecting exacerbation data in a standardised prospective fashion, the authors show that pectoralis major cross-sectional area (CSA), used as a surrogate for whole body muscle mass, falls more rapidly in those patients who have an exacerbation. Furthermore, this effect was cumulative

with each exacerbation accounting for six months of age-expected muscle mass decline and severe (hospitalised) exacerbations relating to greater muscle loss.

Strengths of the study include its size, the prospective and standardised nature of the data collection and the reproducibility of the findings in two separate cohorts. Weaknesses include the fact that the muscle studied was not a locomotor muscle; indeed we speculate that because inactivity may be a driver of muscle atrophy[8] that the findings might have been more dramatic if a locomotor muscle had been studied. Secondly whilst the strength of the association is strong they do not assess causality; specifically the study leaves unanswered the question whether muscle loss increases susceptibility to exacerbation, or the reverse or whether both are driven by some third process.

However, two key findings from this report help us to develop a better understanding of the process of sarcopenia in patient with COPD. First, more severe airflow obstruction as graded by GOLD stage was associated with excess muscle loss over the follow up period and secondly, as expected, muscle loss was less in participants who attended PR including for those who suffered exacerbations. Taken together these findings highlight the likely and unsurprising role of deconditioning and reduced physical activity in driving muscle loss. Inevitably in an observational study, some caution with this interpretation is required, since PR only occurred in a small subset of the study population (4.8%) and the observed difference may be confounded with other factors; for example poor PR uptake and increased drop out may be more prevalent in patients with rapidly progressive disease and increased exacerbations. Conversely in some countries PR provision may be a marker of socioeconomic advantage, associated with improved outcome. PR predominantly focusses on the muscles of ambulation, with programmes having limited upper limb exercises that would directly affect

the muscle measured in this study. Another cohort, recruited from a PR programme, did not see a greater number of previous self-reported in past exacerbations in those with sarcopenia[9].

It is also unfortunate that Mason *et al* reported only two time points several years apart. As a consequence there is an inevitable loss of clarity on the nature of the interaction that may between exacerbations and the skeletal muscles. Several data[5], include that of McAuley *et al* (also in this issue of Thorax- "NB: At editor's discretion"), show a profound impact on the quadriceps during hospitalisation for an exacerbation (add reference). Consistent with the current data those that were not readmitted there was partial recovery of muscle mass or function at three months, while those that were readmitted had continued muscle loss, suggesting readmission as a key event.

Identifying skeletal muscle weakness in COPD in clinical practice remains potentially problematic as there is limited commercially manufactured equipment available to measure maximum voluntary contraction force, and while ultrasound that could measure rectus femoris CSA is more widely available[4], the expertise is not. Here the authors used pectoralis major, one of the accessory muscles, as the region of interest and since CT is commonly undertaken in COPD this has the advantage of being applicable to commonly collected data in large numbers of unselected patients. Alternatively, a field test such as the short physical performance battery (SPPB) could be used. This has the advantage of being quick, safe and easy; and has been shown to predict both all cause mortality[10] as well as frequency and duration of hospital admission in unselected stable patients with COPD[11].

The findings from Mason et al also suggest preventing exacerbations may have unintended benefits outwith the airways, but not recognised within the confines of the limited outcome

measures typically performed in clinical trials. This may provide important links to that are important to patients, such as the ability to walk further and improved quality of life, as well as a potential modifiable prognostic risk factor.

Taken together the data remind us that exacerbations, whether through inactivity, inflammation or medications (especially corticosteroids) are associated with muscle loss, which is now established to be a marker of poor future outcomes. Clinical efforts should focus on reducing exacerbation frequency, especially in those with good skeletal muscle function and reversing muscle and functional weakness through the use of PR both to reduce admission and mortality risk but also to improve quality of life. Pectoralis major CSA could be a useful market in that regard especially of analysis of scans undertaken for other reasons could include this data as an automated read out, but readers should be aware that other screening approaches exist.

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+ 2 new references (Mason & McAuley)

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