Muscle mass and strength in obstructive lung disease: a smoking gun?

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Over the past 2 decades, there has been increasing interest in the extrapulmonary manifestations of chronic obstructive pulmonary disease (COPD). This is supported by the clinical observation that patients show significant improvements in functional performance and health-related quality of life with pulmonary rehabilitation in the absence of lung function changes. Furthermore, the forced expiratory volume in 1 s is an imperfect predictor of mortality in severe patients with COPD, and when forced expiratory volume in 1 s is correct after double lung transplantation, peak exercise remains only approximately 50% of predicted up to 1–2 years after surgery. This limitation in exercise and functional capacity has led to a particular focus upon the skeletal muscle compartment. Certainly, a surprisingly high proportion of patients with COPD terminate exercise complaining of muscle effort. Cross-sectional studies have typically demonstrated muscle weakness and reduced endurance, particularly of the lower limbs, in COPD compared with age-matched controls. This is corroborated by biopsy findings of muscle fibre atrophy and muscle fibre shift from type I to type II fibres. Skeletal muscle dysfunction seems to be clinically relevant in COPD, as loss of skeletal muscle mass and strength are associated with poor health status, increased healthcare use and even mortality. Independent of lung function parameters.

Debate continues as to the relative importance of systemic and local factors in the aetiology of skeletal muscle dysfunction in COPD. Potentially relevant factors include blood gas abnormalities, corticosteroids, nutritional depletion, anabolic–catabolic hormone imbalance, systemic or local inflammation, oxidative stress, genetic susceptibility and reduced daily physical activity. Studies in patients with COPD have been either cross-sectional or longitudinal without an adequate control group, and it has been difficult to tease out the influence of confounding factors.

In this issue of Thorax, van den Borst and colleagues present data from the Health ABC study. This longitudinal study was designed to document the extent of change in body composition (including muscle mass, fat mass and bone mineral composition) in older men and women, identify possible clinical conditions that accelerate these changes and examine the health impact of these changes on strength, endurance, disability and weight-related diseases of old age. In older people, as in COPD, sarcopenia (loss of muscle mass and strength associated with ageing) is independently associated with disability and mortality. The investigators retrospectively used baseline lung function criteria to divide the Health ABC cohort into those with obstructive lung disease (OLD) and controls. Patients with restrictive spirometry were excluded from analysis. The controls were then further divided according to self-reported cigarette smoking status. This study is therefore both novel and welcome in that it provides longitudinal data about decline in body composition and physical functioning in both patients with presumed COPD and well-matched (smoking, never-smoking and formerly smoking) controls. Although some of the longitudinal data are conflicting between the genders, the overall message is that downward trajectories in body composition and physical function are largely comparable between those with OLD, current-smoking controls and never-smoking controls. The implication is that neither COPD nor smoking accelerates sarcopenia.

However, caution is required in the interpretation of the results. First, the diagnosis of OLD was based on spirometry rather than a clinical diagnosis, and almost a quarter of the women in this group were never-smokers. Second, the men with OLD seemed to have significantly slower decline in lung function than the never-smoking controls, which raises doubt as to whether the group with OLD is representative of COPD. Lastly, the study population was selected on the basis of age (between 70 and 79 years) with good baseline functioning and hence subject to survivor bias. This cohort is therefore unlikely to be representative of either older adults or the patients typically seen by healthcare professionals. However, the most striking observation in this study was the reduced baseline difference in body composition and physical functioning in the OLD and smoking control groups compared with the former/never-smoking controls. There may be multiple contributing factors such as early life developmental influences, less-than-optimal diet, certain medications, hospitalisations or reduced daily physical activity, but the data might also suggest that smoking causes a common and early insult to the skeletal muscles.

Could smoking be the unifying aetiological factor for COPD-related skeletal muscle dysfunction? In support of this, smoking causes a reduced proportion of type I fibres, type I and IIa fibre atrophy in the soleus muscle and type I and IIb fibre atrophy in the extensor digitorum longus of rats. In humans, increased quadriceps muscle fatigability has been observed in young healthy smokers. Smokers without COPD also have vastus lateralis biopsy evidence of oxidative fibre atrophy and increased glycolytic capacity. Seymour et al recently demonstrated that 8% of healthy subjects with normal lung function have evidence of significant quadriceps weakness with smoking history an independent risk factor. Longitudinal studies are required to explore this relationship further. The differential effects of acute and chronic cigarette smoke exposure on skeletal muscle have also not been clarified. Furthermore, interventional (smoking cessation) studies with a focus on the effect upon skeletal mass and functioning would be of particular interest. The current study in Thorax demonstrated no differences in body composition and physical functioning between former smokers and never smokers at baseline. If smoking does indeed induce an early insult to the skeletal muscles, these data provide hope that the damage is potentially reversible.
A confounding factor for studies in body composition and physical functioning is reduced daily physical activity. Smoking, for example, is negatively associated with physical activity levels. Although technologies to objectively measure energy expenditure and physical activity are rapidly improving, activity monitors remain expensive, time-consuming and not suitable for routine clinical use. Unsurprisingly, there is a paucity of long-term longitudinal studies examining the relationship between physical activity and body composition, particularly in populations before the development of COPD or sarcopenia. At a cross-sectional level, objective or subjective measurements of physical activity at a single time point cannot hope to quantify decades of sedentary lifestyle. Although van den Borst and colleagues found no difference in subjective physical activity levels at baseline between the groups, quadriceps weakness was observed in the group with OLD and current-smoking controls in the presence of preserved handgrip strength. These data are corroborated by non-volitional muscle strength studies in patients with COPD, supporting the localisation of skeletal muscle dysfunction to the underused muscles of ambulation (ie, quadriceps) with preservation of strength in the muscles of ambulation (ie, quadriceps) and diaphragm.

Existing data no longer support the concept that skeletal muscle dysfunction is a manifestation of severe COPD but rather a problem that can exist before the onset of symptoms. Apart from this current study, Seymour et al demonstrated that a substantial proportion of patients with COPD in Global Initiative for Obstructive Lung Disease stages 1 and 2, or with an MRC dyspnoea score of 1 or 2, had significant quadriceps weakness (28% and 26%, respectively). These data are further supported by Watz and colleagues who, using objective activity monitoring, demonstrated that only 26% of patients with Global Initiative for Obstructive Lung Disease stage 1 had a physical activity level considered ‘active’. Whether one believes that smoking induces a direct early insult to the muscle or whether it is merely contributing to physical inactivity, van den Borst’s study raises the question (and challenge) of how to identify asymptomatic people at risk of declining body composition and physical functioning and whether we should be providing effective interventions, such as pulmonary rehabilitation, at a much earlier stage than present.

Funding W D C. Man is funded by a National Institute for Health Research Clinician Scientist award and the MRC. The views expressed in this editorial are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, the Department of Health or the MRC.

Competing interests None.

Contributors Dr Samantha Kon and Dr Man both reviewed the accompanying manuscript. Dr Kon wrote the first draft of the editorial and agreed to the final version. Dr Man takes responsibility for the accuracy and views of the final version of the editorial.

Provenance and peer review Commissioned; internally peer reviewed.


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Thorax  published online August 3, 2011

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