Respiratory Disease and Muscle

Nutritional Interventions to Support our Patients

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On face value, links between respiratory (or lung) illness and skeletal muscles may seem tenuous. However, the scientific literature is abundant with studies providing good evidence of links between respiratory diseases and skeletal muscle health deterioration.[1] Moreover, the importance of muscle health in morbidity and mortality is actually observed broadly across both non-communicable and infectious diseases alike.

Diseases associated with muscle ill-health are typically defined as either 'sarcopenia' or 'cachexia'. While not an exhaustive list, sarcopenia has been the terminology adapted for use to describe that seen with advanced ageing, chronic kidney disease (CKD), inflammatory bowel diseases (IBD) and chronic obstructive pulmonary disease (COPD). Instead, cachexia, for instance, has been used to describe muscle dysfunction in cancers and rheumatoid arthritis (RA). By definition, sarcopenia is specifically associated with a loss of lean tissue. In contrast, cachexia is often described as a more generalised wasting of body compartments, including fat stores – such as seen in cancers. Noteworthy to readers is that disease-specific use of these terms reflects how each of the clinical specialisms have adapted their use. Most importantly therefore, to the reader, both cachexia and sarcopenia are associated with muscle wasting and dysfunction and do not necessarily relate to the broader myriad of altered body composition often accompanying muscle wasting conditions.

Let us first consider the structure and homeostasis of muscle biology. Skeletal muscles are made up of very long cells each containing thousands of nuclei (or myonuclei; myo- as in muscle). These many myonuclei provide a large quantity of DNA for which to provide adequate template to sustain the large protein synthesis required to maintain housekeeping in a cell of such a large size. The other key characteristic of muscle is that each cell is connected to a motor nerve that provides a two-way connection to the brain via the spinal cord. This allows excitation of cells via the brain and thus movement and also a means for sensory feedback to the brain.

Muscle cells undergo constant protein 'turnover' (meaning, make new proteins to replace old ones) at a rate of ~1.5% per day. This is achieved through food intake (enteral or parenteral), and specifically, dietary proteins or their (amino acid; AA) constituents. Upon intake, dietary proteins are broken down into short chains of their constituent AAs in the stomach and small intestine before being transported across the gut into the hepatic portal system and then the systemic circulation. After this point, resulting AAs are circulated to tissues, such as muscle, where they enter cells at the capillary-muscle cell interface through specific AA transporters that permit entry into the cell. Intracellular AA are then incorporated into new muscle cell proteins to replace old and damaged ones. It is for this reason that nutrition, and dietary proteins especially are central to muscle health in development, life-long wellbeing, and in ageing and diseases.

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Precisely what is muscle wasting and dysfunction can be broken down into two parts. The first of these is altered handling of nutrients. Protein intake for example, may be in deficit due to malnutrition. However, other biological changes in ageing or disease may lead to inefficient digestion/absorption, altered splanchnic use of AA, or reduced delivery or cellular capacity for utilisation of available intracellular AA in terms of protein synthesis processes. Muscle-nerve communication can also literally breakdown rendering a muscle fibre at risk of death and irreversible loss. It is these processes most broadly that govern muscle wasting (loss of both muscle fibre size and fibre number) and resulting dysfunction in both sarcopenia and cachexia syndromes.

Respiratory conditions are one such major cause of such skeletal muscle health declines. In particular, COPD with a root cause of chronic pneumonia or emphysema remains a very common clinical burden due to sometimes frequent exacerbations and associated mobility limitations and frailty. In this patient group, impairments in respiratory gas exchange limit mobility due to feelings of significant exertion even with low-level physical tasks. This renders individuals chronically sedentary, further contributing to muscle wasting driven by the disease. Indeed, even in healthy individuals, sedentary behaviours or acute loss of limb function – e.g. limb fractures – leads to rapid wasting. So, conditions themselves associated with muscle wasting but also inducing inactivity (such as COPD) represent a double whammy.

SARS-CoV-2 (COVID-19) is an ongoing pandemic that has now been brought under control by large-scale natural immunity through viral exposure, and an unprecedented vaccination rollout. The initial care of COVID patients in acute medicine, respiratory wards or the ICU was stabilisation and respiratory support through oxygen therapy or ventilation (now amongst other drug/care protocols depending on severity). However, there is now a shift towards an understanding of best practices for avoiding severe disease (and hospitalisation) and potentiating recovery. The growing diagnosis of what has been termed 'long-COVID' is also a major concern in terms of best care. Long-COVID poses striking similarities in some instances with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a complex condition of extreme fatigue and myalgic symptoms.

Further compelling are the striking symptoms being reported between patients with lung conditions like COPD and COVID. Indeed, whether of similar or distinct aetiology, it is clear that proportions of COPD and COVID patients have been diagnosed with malnutrition, inflammation, physical inactivity and/or low of muscle mass and strength.

Importantly some of these factors have already been shown to impact clinical outcomes. The presence of low muscle mass (sarcopenia), for instance, has been associated with both reduced pulmonary function (as in forced expiratory volume [FEV1]), exercise intolerance, and premature mortality in COPD patients. Presence of diagnosed malnutrition also increases mortality in COPD patients. In terms of COVID, hospitalised patients exhibiting higher handgrip strength would tend to have a shorter stay than those with lower grip strength.[2] Given that handgrip strength commonly links to poor health outcomes this suggests a direct link to muscle functional decline being linked to outcomes in in-patients with COVID. This is also a thesis supported by lower thigh cross-sectional areas also linking to longer hospital stays in COVID. Finally, malnourishment in hospitalised COVID patients is associated with a greater probability of severe disease[3] until very old ages when age itself likely becomes the key factor.

The question arises what can be done to intervene and mitigate muscle wasting and associated dysfunction in respiratory diseases, but also in all age/disease catabolic states – meaning where tissue breakdown predominated tissue regeneration. No effective and safe drugs target this in a clinical setting. Physical activity promotion is important but can be impractical, especially for the in-patient. That leaves nutrition. Targeted or precision nutrition, is the concept or providing nutrients specific to a patient group needs. Nutritional interventions have, over decades, provided good evidence of benefit in terms of muscle health and related reductions in morbidity and mortality across the continuum of care, i.e. in primary care, in hospital for acute/chronic catabolic disease(s) and in relation to the processes of incipient muscular ageing.

As stated, and explained at the outset of this article, protein nutrition is among the most intensely studied areas of clinical nutrition since dietary proteins are

indispensable for tissue maintenance in both sickness and health. In terms of ageing – even healthy ageing – the recommended daily allowance has been suggested to be higher than originally suggested (0.8 g/kg/day), and perhaps instead 1.2 g/kg/day or beyond.[4] Consistent with this, one of the few available longitudinal observational clinical trials revealed that those consuming higher protein intakes, in a step-wise manner, show improved retention of lean body mass.[5] It follows that adequate protein nutrition is likely key in staving off poor outcomes. Intervention studies would support this, with oral nutritional supplements (ONS) favouring improved survival on systematic review and meta-analysis in medical in-patients who are malnourished or at nutritional risk.[6]

Returning to respiratory diseases, such as COPD and COVID, it is notable that age coupled to low muscle mass and malnutrition are amongst some of the most decisive factors of disease severity. Of one of the largest studies of its kind,[7] the NOURISH study, was an interventional trial in hospitalised older adult patients (a large sub-group with COPD) treated with a specialised ONS, containing high-protein and another key anabolic constituent β-hydroxy-β-methylbutyrate (HMB), a breakdown product of the most muscle anabolic essential AA, leucine. The ONS outperformed the placebo and standard of care in terms of survival underlining a reduced mortality risk. While association rather than interventional studies insofar dominate COVID research, valuable data illustrate that low protein and energy intake are associated with in-hospital mortality and critical illness in COVID patients.[8] While somewhat preliminary given the unique and rapid research circumstances, these data suggest that higher energy/protein intakes could protect against negative COVID health impacts. Muscle-specific work linked to outcomes of interventions will no doubt follow, and will be likely to feature heavily.

To highlight key potential nutritional regulators of muscle beyond dietary proteins (without being exhaustive), HMB in addition to vitamin D warrant discussion – also in the context of potential future interventions for respiratory diseases. HMB has been shown to attenuate muscle loss under conditions of both sarcopenia and cachexia through its pro-anabolic (protein synthesis), and anti-catabolic credentials. HMB, like dietary proteins, stimulates muscle protein synthesis but also suppresses muscle protein breakdown at the same time.[9] Hence, HMB is sometimes a component of ONS adjuvant to protein nutrition and one which underlies its efficacy under meta-analysis (10) to positively impact muscle health outcomes when taken alone, or within ONS in older adults. Future studies will determine the role of HMB in COVID but the research basis for such is founded given promising results in COPD and beyond when it comes to muscle health.

Of additional note is vitamin D. Vitamin D deficiency remains, unfortunately, highly prevalent due to imbalanced diet, lack of outdoor exposure, and geographical weather conditions. Vitamin D is a hormone converted to its active form by hepatic and renal systems following absorption from the diet (via rich-sources or supplements) or sunlight exposure. It targets a cellular receptor, the vitamin D receptor (VDR), and many elements of DNA exhibit recognition of the activation of the VDR to regulate gene expression accordingly. While originally associated with bone ill-health in the earlier ages of poor diets – rickets – it has since had an increasingly recognised role in muscle health. The majority of data focuses upon associations between vitamin D status and health. Yet, strikingly, vitamin D deficiency in COPD and COVID have been associated with poor muscle health and/or disease severity.[11, 12, 13] This leaves the door open to further study how modulation of vitamin D biology might impact care in respiratory conditions, such as COPD or COVID; amongst others.

While muscles are not intrinsically subject to all but rare diseases (mostly genetic or neural) it is a tissue that represents insight into extant health transcending specific disease(s) and often being unexpectedly linked to clinical outcomes. That muscle is a biomarker of such is worthy of major pursuit, as are nutritional therapies and how they might be bolstered by, e.g. drug or physical therapies. The links and plasticity of muscle biology in respiratory and all major illnesses warrants significant further attention.

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