Chronic obstructive pulmonary disease: extrapulmonary manifestations, pulmonary rehabilitation programs and the role of nutritional biomarkers on patient outcomes

Melissa McDonald
Second Year Student (Undergraduate)
James Cook University

Melissa has always had a strong interest in health and initially pursued this interest by undertaking a Bachelor of Biomedical Science. As she has a passion for lifestyle and preventative medicine, she completed her third year research project on chronic obstructive pulmonary disease. As a doctor Melissa would like to focus on preventative medicine and research.

Until recently, chronic obstructive pulmonary disease (COPD) received little research attention, as it was perceived as a self-inflicted condition that was difficult to treat. As COPD now affects one in seven Australians over 40 and is a leading cause of disease burden and death, research into this condition has intensified. Traditionally, research focused on the pulmonary effects and yet it is starting to emerge that the condition encompasses a range of extrapulmonary manifestations, such as weight loss and skeletal muscle dysfunction, which significantly affect the health and functioning capacity of COPD patients. There are many unanswered questions about the disease process and the role of the extrapulmonary manifestations. The aim of the current review is to explore two critical extrapulmonary manifestations of COPD: weight loss and skeletal muscle dysfunction, to investigate how pulmonary rehabilitation aims to improve these pathological processes and, lastly, to investigate the role of nutritional biomarkers and how these may predict outcomes in the pulmonary rehabilitation programs. Ultimately, it is anticipated that research into nutritional biomarkers may lead to the development of a screening tool that can be used to identify COPD patients who may benefit from nutritional supplementation prior to the commencement of a pulmonary rehabilitation program. It is hoped that identifying and managing those patients that require nutritional support will lead to greater improvements in rehabilitation and overall quality of life.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic obstructive lung disease, primarily caused by smoking. It affects one in seven Australians over 40 [1] and is a leading cause of disease burden and death. [2-4] The morbidity and mortality rates associated with COPD are continuing to increase, and it has been predicted that COPD may be the third most common cause of death worldwide by 2020. [5,6] In the past, COPD has been perceived as a self-inflicted condition, which was difficult to treat. Although the perceptions surrounding COPD have changed and research has shed more light on the disease processes, there are still many gaps in the scientific knowledge regarding this condition.

One such gap, which has only recently been explored, is the role of extrapulmonary manifestations associated with COPD. Previously, clinicians and researchers solely focused on the structural and functional changes occurring in the pulmonary system of patients with COPD. However, in recent years, it has become increasingly evident that the disease encompasses a range of other manifestations outside the lungs, including weight loss and skeletal muscle dysfunction. [7] Weight loss, which is a very common manifestation in patients with COPD, causes a reduction in respiratory and skeletal muscle function, which is associated with reduced quality of life and increased mortality rates. [8] Weight loss, skeletal muscle dysfunction and some of the other manifestations associated with COPD can be managed through pulmonary rehabilitation programs, although these are costly, time consuming and individual success is highly variable. [9] Furthermore, there is currently no dedicated funding for these programs in Australia. [10]

In order to improve the effectiveness and outcomes achieved

through pulmonary rehabilitation programs, researchers have begun investigating the role of nutrition in COPD patients. Ultimately, it is anticipated that the identification of important nutritional biomarkers that predict improved outcomes in pulmonary rehabilitation, may lead to the development of nutrient supplementation strategies to improve success in rehabilitation programs and optimise the quality of life of patients with COPD. The aim of the current review is to explore two critical extrapulmonary manifestations of COPD: weight loss and skeletal muscle dysfunction, to investigate how pulmonary rehabilitation aims to improve these effects and lastly, to investigate the role of nutritional biomarkers in COPD and how these may predict outcomes in the pulmonary rehabilitation programs.

Extrapulmonary manifestations

Recent research has found that patients with COPD suffer a range of extrapulmonary manifestations that were not previously related to the condition. Two of the major extrapulmonary manifestations seen in COPD patients that have a critical impact on quality of life and prognosis are weight loss and skeletal muscle dysfunction.

Weight loss

Although traditionally research focused on the pulmonary effects of the disease, it was evident as early as the 1960's that a low body weight and weight loss were associated with an increased mortality rate in COPD patients. [11] However, at the time weight loss was believed to be only associated with the terminal phase of the disease, and hence it was considered inevitable and irreversible. [11] Currently, excessive weight loss, especially loss of fat-free mass, is very common in COPD patients and is associated with poor functional capacity, reduced quality of life and increased mortality. [8] Although the exact cause of excessive weight loss in COPD remains unclear, the proposed mechanisms include low testosterone levels, increased pro-inflammatory cytokines and increased catecholamine synthesis. [12-14]

Skeletal muscle dysfunction

A common extrapulmonary manifestation that significantly affects the quality of life of a COPD patient is skeletal muscle dysfunction. Skeletal muscle dysfunction is characterised by increased muscle fatigability, and a reduction in muscle endurance and strength. [15] In many studies, body mass index (BMI) (which is calculated as weight/height squared in kg/m^2) is used as a basic indicator of weight loss

or possible muscle alterations, although these measures can be further investigated by evaluating skeletal muscle strength and body composition. [16] COPD patients with skeletal muscle dysfunction have increased mortality rates and are likely to place a significant burden on healthcare resources. [17,18] The precise mechanisms causing skeletal muscle dysfunction in COPD patients are still unclear, although several factors that may contribute include sedentary lifestyle, nutritional abnormalities, tissue hypoxia, systemic inflammation, skeletal muscle apoptosis, oxidative stress, tobacco use and medications. [7] In patients with COPD, skeletal muscle dysfunction is characterised by two different phenomena: (1) net loss of muscle mass; and (2) dysfunction or malfunction of the remaining muscle. [7] One of the key features involved in the loss of muscle mass is increased protein catabolism. The major pathway involved in the degradation of proteins, which relates to muscle wasting, is the ATP-ubiquitin dependent proteolytic system (Figure 1). [19] This system can be activated by several factors such as cytokines, glucocorticoids, acidosis, inactivity or low insulin levels. [20-22] Following the activation of this pathway, proteins are marked for degradation by ubiquitination, and then they are recognised and processed in the proteasome. [4] Pro-inflammatory cytokines may also play a role in muscle deterioration by producing reactive oxygen species, which modify skeletal muscle proteins allowing them to be easily degraded by the proteasome. [4]

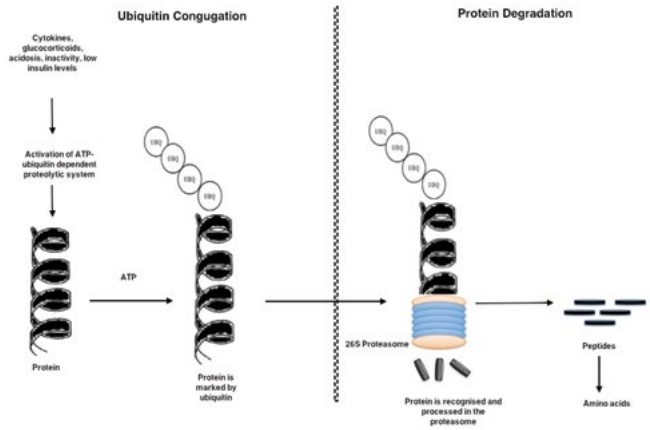

Figure 1. *ATP-ubiquitin dependent proteolytic system. A trigger such as cytokines, glucocorticoids, acidosis, inactivity or low insulin levels causes the activation of this pathway. Initially, proteins are conjugated with ubiquitin and then they are recognised and bound to the proteasome. The protein enters the proteasome, which contains multiple proteolytic sites. Peptides are then released from the proteasome and are rapidly degraded into amino acids by peptidases in the cytoplasm. The ubiquitin is released and is reused. [23]*

The exact trigger for the development of the extrapulmonary manifestations is unknown, although it is thought that the process is mediated by systemic inflammation. [24] As COPD is a condition primarily caused by smoking, it could be questioned whether smoking is the major cause for the development of systemic inflammation and in turn the extrapulmonary manifestations. As multiple studies have found that persistent inflammation is still present in ex-smokers, [25] it is possible that tobacco smoke may initiate the inflammatory process, however it does not explain the sustained inflammatory state evident in COPD patients. [24] Instead, it is possible that the systemic inflammation arises from pathological changes occurring within the lungs of COPD patients. [24] This is supported by other studies that have found that inflammation is still present in COPD patients who have ceased smoking. [26,27] In light of these observations, some researchers have speculated that part of the COPD pathogenesis process involves an autoimmune component. [28]

The discovery that COPD encompasses both pulmonary and systemic manifestations has created new possibilities for rehabilitation and treatment targets. As weight loss and skeletal muscle dysfunction are reversible and treatable, pulmonary rehabilitation programs have been reorientated in order to focus on improving skeletal muscle function and the overall quality of life of COPD patients.

Pulmonary rehabilitation programs to improve patient outcomes

In response to the growing prevalence and burden of COPD, the Australian Lung Foundation and Thoracic Society of Australia and New Zealand developed clinical guidelines (COPDX) for the diagnosis and management of COPD. [29] One of the main aims of COPDX is to optimise patient function using pulmonary rehabilitation programs. [29] Pulmonary rehabilitation programs are composed of exercise training, behavioural and psychosocial interventions and nutritional therapy. [30]

Exercise training

Prior to the work by Barach *et al.* [31] in the 1950's, who suggested that exercise may be beneficial, the only recommendations for the management of respiratory conditions were rest and avoiding breathlessness. [32] Since this suggestion, there have been many experimental findings, randomised controlled trials and observations supporting the benefits of exercise training for patients with COPD. Based on the most recent evidence, patients with COPD undergoing pulmonary rehabilitation should participate in exercise training at least 2-5 days per week, for at least 20-30 minutes per session, over an 8-12 week period. [33, 34] Exercise programs involve endurance and strength training, mainly focusing on the lower limbs. [30] In patients with COPD, exercise training has been shown to significantly improve exercise tolerance and endurance time and it is also able to improve or reverse the physiological, metabolic and structural skeletal muscle abnormalities seen in COPD patients [35], suggesting that pulmonary rehabilitation is an anabolic stimulus. [36] Although, it is unknown how pulmonary rehabilitation improves skeletal muscle dysfunction and the role of specific nutrients during this process.

Nutritional approaches to improving muscle function and body composition in COPD

The role of nutritional therapy in the management of COPD has changed dramatically during the past twenty years. Although it was widely known that a large proportion of COPD patients experienced significant weight loss, it was viewed as irreversible and nutritional support was not considered. [37] This concept has been challenged by recent studies, which have revealed that nutritional depletion affects functional performance and exercise intolerance. [37] After this discovery, many trials have investigated the benefits and effects of nutritional support in patients with COPD, although the initial results from these studies were disappointing. A meta-analysis of the available literature conducted by Ferreira *et al.* [38] concluded that nutritional support, defined as any caloric supplement administered for more than two weeks, had no significant effect on 6-min walk distance, anthropometric measures, respiratory muscle strength, weight gain or FEV_1. These results led to the suggestion that in order to improve muscle mass and physiologic function, nutritional support must be combined with an anabolic stimulus such as exercise training. [39] In a large clinical trial combining nutritional therapy (daily high caloric supplement (420 kcal)) with an 8-week pulmonary rehabilitation program, patients showed an increase in body weight and a significant improvement in fat-free mass and respiratory muscle strength. [40] These results were further supported by a more recent study by Creutzberg *et al.* [39], who observed that the combination of nutritional therapy with pulmonary rehabilitation was effective in improving physiological measures such as body composition, muscle function, exercise capacity, serum protein, as well as the health status and well-being of patients with COPD. [39] Since the use of nutritional support has been shown to be beneficial, research needs to shift towards investigating the effectiveness of different types of nutrients and how these may be used in combination with pulmonary rehabilitation programs in order to maximise patient outcomes.

Protein supplementation

There are two main pathways involved in the synthesis and breakdown

of proteins (Figure 2) and recent research has shown that the loss of fat-free mass in patients with COPD is caused by an imbalance between these two pathways. A reduction in fat-free mass causes the loss of protein-rich tissues, particularly skeletal muscle [36] and the imbalance in protein metabolism leads to increased whole-body protein turnover. [41] This has led researchers to investigate the use of protein supplementation in improving fat-free mass in COPD patients.

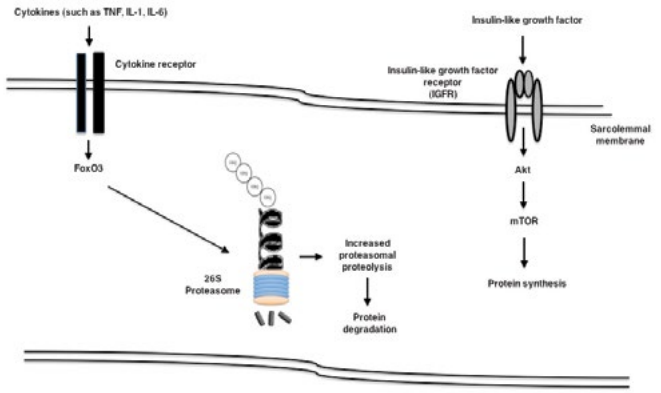

Figure 2. *Mechanisms of protein synthesis and degradation in skeletal muscle. The balance between protein synthesis and degradation determines whether muscles hypertrophy or atrophy. If hypertrophy occurs, protein synthesis exceeds degradation, as the Akt pathway stimulates protein synthesis and the FoxO pathway is inactivated. In certain disease states, such as muscle wasting, insulin signalling is suppressed, and therefore the Akt pathway is not activated and protein synthesis cannot occur. The FoxO pathway is activated and proteins are degraded in the proteasome. [42-44]*

In skeletal muscle, the regulation of protein initiation, translation and synthesis relies on the activation of two signalling proteins called the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK). [45] In a study by Fujita *et al.* [45] Protein supplementation, which provides the essential amino acids necessary for protein synthesis, alters the phosphorylation status of AMPK and mTOR signalling proteins, and increases the synthesis of proteins in healthy adults. As mentioned previously, for patients with COPD, nutritional supplementation must be combined with an additional anabolic stimulus in order to be effective and therefore recent studies have investigated the effectiveness of protein supplementation combined with exercise training. Laviolette *et al.* [46] conducted a study observing the effects of supplementation with pressurised whey or casein combined with an 8-week exercise-training program in patients with COPD. From the study, they concluded that combining whey supplementation with exercise training caused an improvement in exercise capacity (cycle endurance time), fatigue and emotional control. [46] Although these results are promising, there is emerging evidence that other nutrients such as vitamin D and B, calcium, zinc, magnesium, fatty acids and antioxidants can influence lung function and stimulate the anabolic pathways involved in protein synthesis and muscle function.

Vitamins

Vitamin D

One of the first studies to investigate the association between vitamin D and muscle metabolism was by Birge and Haddad [47], who observed that 25-hydroxy vitamin D altered muscle metabolism causing an accelerated incorporation of amino acids into muscle protein. They postulated that vitamin D acts directly on muscle [47] and this theory was confirmed in 1985, when a vitamin D receptor (VDR) was discovered in cultured rat myoblast cells. [48] Further research has discovered VDR in a range of tissues, and recently, it was isolated from human skeletal muscle. [49] Recent studies have shown that COPD patients, particularly those with severe COPD, have low levels of vitamin D. [50] In order to investigate the link between vitamin D depletion and muscle function, Bjerk *et al.* [51] performed a randomised pilot trial in which patients with COPD were supplemented with vitamin D for 6 weeks. Although the supplementation group had a significant increase in mean vitamin D levels compared to the control, there were no significant improvements in physical performance or respiratory symptoms. [51]

Vitamin B

A recent study examining hyperhomocysteinaemia discovered that COPD patients had reduced plasma concentrations of vitamin B, particularly folate [52], which is an essential co-factor involved in protein synthesis. [53] Another study found an association between folate intake and lung function. In this study, participants with COPD had lower folate levels than controls, and their folate intake was below the recommended dose. [54] Based on epidemiological data, it has been suggested that an increased folate intake could lead to reductions in the prevalence of COPD and breathlessness. [54]

Minerals

Calcium, Zinc and Magnesium

Currently, there is very limited human research on the role of minerals in muscle function and most of the available data is based on experimental animal models. Early evidence of the role of calcium in protein synthesis emerged from experimental rat studies, which revealed that maintenance of optimal rates of protein synthesis was dependent on the availability of calcium. Furthermore, calcium depletion led to the inhibition of protein synthesis, which was characterised by a reduced rate of peptide chain initiation. [55] Recently, it has been identified that an increase in the concentration of intracellular calcium triggers the activation of the mTOR pathway, leading to skeletal muscle hypertrophy. [56]

Zinc and magnesium are essential minerals required for growth in humans. [57,58] Both minerals play an important role in the synthesis of proteins, with deficiencies leading to the down-regulation of protein synthesis. [59] An experimental study revealed that protein synthesis in muscle was inhibited in zinc deficient rats [60] and a more recent study confirmed these results, by finding a reduction in protein synthesis and enhanced protein degradation in muscle tissue from zinc-deficient rats. [59] Unfortunately, the literature on the calcium, zinc and magnesium levels of COPD patients is limited and further research is warranted.

Fatty acids

In order to prevent or reverse muscle loss, interventions must target the abnormal anabolic pathways. The dysfunctional anabolic pathway is partly caused by defects in the anabolic signalling cascade in muscle, such as decreased activation of the mTOR signalling pathway. [61,62] In various animal studies, fish-oil-derived omega-3 fatty acids have been used to target the protein synthesis pathways. In one study, growing steers received feed enriched with menhaden oil, which increased the activation of anabolic signalling proteins in muscle. [63] In a more recent human study, omega-3 supplementation in older adults increased the rate of muscle protein synthesis, which suggests that omega-3 fatty acids reduce anabolic resistance. [64] It is not entirely clear how omega 3-fatty acids act on the muscle protein synthesis pathway, although it may be partially mediated via increased activation of the mTOR signalling pathway. [64] Based on the limited evidence, supplementation with fatty acids may be a beneficial treatment, although as of yet there are no published studies exploring this. [65]

Antioxidants

Antioxidants are considered to be protective factors in the lungs as they can scavenge endogenous and exogenous reactive oxygen species. [66] There is increasing evidence that oxidative damage and the failure of antioxidants to protect lung tissue are partly responsible for the development of COPD. [67,68] Studies examining the effect of antioxidant supplementation on oxidative damage and pulmonary function are incredibly conflicting. Habib *et al.* [69] observed that vitamin E supplementation had no effect on pulmonary function. Another study found that when used in addition to standard therapy,

an antioxidant supplement (containing vitamin A, C, E, zinc, copper, selenium and manganese) had a positive effect on the oxidant-antioxidant balance in COPD patients, however it had no effect on pulmonary function tests. [70]

Although research has focused on oxidative stress caused by the production of free radicals in the lungs in patients with COPD, there is emerging evidence that exercising skeletal muscle may also produce free radicals and contribute to oxidative stress. [71] Free radicals produced during exercise depress muscle force production [72] and increase the discharge frequency of thin-fibre muscle afferents [73] and thus, targeting oxidative stress may improve exercise tolerance and reduce the development of fatigue.

Based on all of the available evidence, it is apparent that patients with COPD suffer from nutritional abnormalities, which may contribute to muscle dysfunction and weight loss. An altered nutritional status may affect a patient's ability to synthesise protein and lead to less effective outcomes in pulmonary rehabilitation programs. Although some studies have shown that protein supplementation combined with exercise training can be beneficial, evidence is limited and somewhat conflicting. Apart from protein and amino acids, other nutrients have a direct effect on the synthesis of protein and the function of skeletal muscles, although research into these effects is lacking. Nutritional support is an important part of COPD management, however there is no definitive evidence about what types of nutrients should be used and how they may influence the outcome of rehabilitation programs. Ongoing and future research is expected to provide further insight in this area, and hopefully improve the quality of life and survival of COPD patients.

Acknowledgements

This literature review was first written as part of a Bachelor of Biomedical Science third year research project at the University of Newcastle. I would like to give special thanks to my project supervisor Associate Professor Lisa Wood, who provided valuable guidance and support. I would also like to thank my research partner Jennifer Latham for her participation in the research project.

Conflict of interest

None declared.

Correspondence

M McDonald: melissa.mcdonald1@my.jcu.edu.au

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