Nutritional Support in Pulmonary Diseases

Module 38.4
Evidence Based Management of Pulmonary Cachexia
Current Evidence for Nutritional support, Multimodal Approaches and Future Directions

Dr Peter Collins, APD, PhD,
Senior Lecturer, Course Coordinator,
Nutrition & Dietetics, School of Exercise & Nutrition Sciences,
Faculty of Health, QUT, Brisbane, QLD, Australia;
Chronic Conditions Management Program,
Institute of Health and Biomedical Innovation (IHBI),
QUT, Brisbane, QLD, Australia;
Visiting Research Dietitian,
Department of Nutrition & Dietetics,
Princess Alexandra Hospital,
Woolloogabba, QLD, Australia

Learning Objectives

• Impact of malnutrition and nutritional depletion in COPD;
• Body composition abnormalities and complexities in identification of nutritional risk in patients with COPD;
• Role of nutritional interventions in patients with COPD during different phases of the disease (acute infective exacerbations versus stable outpatients);
• Multimodal interventions.

Content

1. Introduction
2. Nutritional interventions in stable COPD
   2.1. Ferreira meta-analyses
3. Nutritional interventions in acute COPD
4. Multimodal interventions in COPD
5. Summary
6. References

Key Messages

• Malnutrition is common in COPD but has a complex aetiology presenting clinical challenges in its identification and management;
• Two meta-analyses in 2012 and 2013 have shown the efficacy of ONS in treating malnutrition in stable (non-exacerbating) COPD in terms of nutritional intake, nutritional status, functional capacity and quality of life;
• Nutritional support delivered alongside exercise programs is associated with enhanced outcomes however, improvements in fat-free mass are difficult to achieve;
• Integrated multimodal interventions in depleted COPD constitute the present standards of care, where nutritional interventions have acquired a key role.
1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide and is expected to be the third leading cause of death globally by 2030 (1). Malnutrition is a common problem in patients with COPD with prevalence rates between 30% and 60% in inpatients and 30% and 45% in outpatients reported (2). Malnutrition in COPD has been found to present both a clinical and economic burden to healthcare systems. Compared to nourished COPD patients, those identified as malnourished had significantly poorer survival at 1-year, required emergency hospitalization more often, remained hospitalized for twice the duration and at almost double the cost (3). With malnutrition independently associated with poor clinical and economic outcomes, attention has understandably shifted to the effectiveness of nutritional support. However, the aetiology of malnutrition in COPD is incredibly complex and multi-factorial. The identification and treatment of malnutrition in this patient group is further complicated by the presence of both different nutritional (4) and respiratory phenotypes under the umbrella term COPD (5).

These different nutritional and respiratory phenotypes influence the ease at which malnutrition can be identified and treated. For example, patients presenting with the traditional emphysema phenotype (‘pink puffer’) are often visibly thin with depleted fat-free mass (FFM) stores. Whereas patients with chronic bronchitis are generally larger with elevated fat mass (FM) stores which can make mask sarcopenia. COPD patients with emphysema and hyperinflation may experience anorexia and early satiety compromising nutritional intake. Indeed, lung volume reduction surgery has been found to be associated with significant increases in body weight in the absence of subsequent improvements in pulmonary mechanics (6). Despite malnutrition being common in COPD, a high proportion are overweight or obese. Sarcopenic obesity as well as overweight and obese patients who are also malnourished, present very real clinical challenges to the detection and management of nutritional depletion. Losses of FFM is common in COPD (7) and can be masked by an expansion of FM which impacts on the sensitivity of measures such as body mass index (BMI) as a marker of nutritional status. This was highlighted in a study of 300 outpatients with COPD where a BMI of <20 kg/m² was reported in 17% of patients but more than double were found to have FFM depletion (38%) (8). It is now widely acknowledged that assessment of FFM is likely to be a more sensitive predictor of clinical outcomes in COPD (9).

2. Nutritional Interventions in Stable COPD

Historically, malnutrition was often thought to be an inevitable consequence of the progressive pathophysiology of COPD. The progressive irreversible nature of the disease suggesting that malnutrition was an epiphenomenon not amenable to extra-pulmonary interventions such as exercise and nutrition. This view was reinforced over the period of a decade with numerous systematic reviews and meta-analyses including three Cochrane Collaboration reviews published in 2000, 2003 and 2005 that concluded nutritional support did not lead to significant improvements in body weight or other anthropometric measurements (10). However, two systematic reviews and meta-analyses published in 2012 and 2013 involving thirteen randomised controlled trials (RCTs) highlighted important methodological differences compared to the previously completed reviews which resulted in misinterpretation and an underestimation of the true effect of nutritional support (11, 12). Of the 13 RCTs, eight were performed completely within the outpatient setting, 3 in inpatients, 2 RCTs involving both inpatient and outpatient components and intervention durations varied from 16 days to 6 months. The more recent analyses found that nutritional support consumed orally (diet + oral nutritional supplements (ONS) or dietary advice and supplementation) was associated with a significant improvement in energy intake (+236 kcal/d ± 71 kcal/d; p <0.001). Similar results were found when a study involving nocturnal enteral tube feeding was included (+318 ± 157 kcal/d; p =...
0.004) or when only those RCTs involving ONS were analysed (+413 ± 175 kcal/d, p = 0.006). Nutritional support was also found to significantly increase protein intakes (+16.5 ± 10.3 g/d; p = 0.023), with similar findings when only those studies involving ONS were included (+18.2 ± 7.0 g/d; p = 0.014). These significant improvements in energy and protein intakes were accompanied with significant increases in body weight. When analysis was performed according to outpatient nutritional status (malnourished (‘depleted’) and normally nourished (‘non-depleted’) compared to control) both groups showed significant increases in weight in favour of nutritional support (depleted: +1.94 SE 0.26 kg; p <0.001 and non-depleted: +1.32 SE 0.37; p <0.001). Whilst the malnourished patients had a more pronounced response to nutritional support it should be noted non-deplete patients also had a significant response but nutritional support was received as part of an exercise rehabilitation program (13, 14).

The second meta-analysis published by Collins et al. (11) explored the effectiveness of nutritional support in improving functional capacity and quality of life in COPD patients. Nutritional support had no impact on forced expiratory volume in 1 second (FEV₁), which could be expected given the irreversible pathological changes that occur in the lung with COPD. Nutritional intervention was associated with significant improvements in respiratory muscle strength, measured by maximal inspiratory and expiratory pressures (PI and PE max (cm H₂O)) as well as non-respiratory (handgrip/quadriceps) muscle strength. Importantly, these functional improvements were accompanied with a significant improvement in body weight of more than 2 kg (2.1–3.1 kg). Despite no RCTs included in the review involving individualised dietary counselling alone, one study did intervene with dietary counselling by a dietitian alongside 6 month supplementation of the diet with milk power (15). After 6 months there was a significant difference in the change in weight between the intervention and control groups (2.99 SE 1.2 kg; p = 0.014). At the end of the intervention, the intervention group not only achieved an increase in body weight of 2 kg, they were able to maintain the elevated weight status 6 months after the intervention. These improvements in nutritional status were also associated with significant and clinically meaningful improvements in quality of life, suggesting individualised dietary counselling and supplementation may have resulted in lasting behaviour change. Despite being rather arbitrary, a 2 kg improvement in body weight does appear to be the threshold at which functional and quality of life improvements are seen at a group level. In addition, Schols et al. have also previously reported an improved maximal inspiratory pressure and weight gain of >2kg to be associated with improved survival (16). This needs to be confirmed in adequately powered prospective studies.

2.1 Ferrerira et al. Meta-analyses

Following three negative reviews on nutritional support in COPD (10, 17, 18), the Cochrane Collaboration published an update to its 2005 review concluding moderate quality evidence exists that nutritional supplementation promotes significant weight gain in patients with COPD (12).
Fig. 1. Meta-analysis of the influence of nutritional support on weight (kg) change from baseline in 13 studies grouped according to nutritional status (nourished = non-depleted; malnourished = depleted), *p < 0.0005. Overall summary effect (depleted + non-depleted) = 1.69 ± 0.30, SE kg, p< 0.001, adapted from (12).

The latest review included 4 additional RCTs to the previous review however, three were excluded by Collins et al. One study was excluded due to data of interest being unavailable from published abstracts, two studies because nutritional support was delivered alongside exercise in the intervention arm but neither intervention was received by the control group (19, 20). One also involved comprehensive multimodal interventions in the intervention arm but not the control, in addition depleted patients that received nutritional support also accounted for a minority of a predominantly overweight patient group recruited with mild COPD (20). However, both studies reported significant improvements in body weight in their own right (Fig. 2) so would have only strengthened the findings reported had they been assessed as suitable for inclusion. The final study was not included by Collins et al. (11, 12) as it was published after the literature review but would have been excluded as it once again involved nutritional supplementation in combination with low intensity exercise (21). It could be argued these additional studies included in the 2012 review from the 2005 review should not have been included due to their study designs making it difficult to isolate the effect of nutritional support and therefore establish causality. Therefore the evidence base to date is based on research published from 1987 to 2009 (13 RCTs) and there has been no published research investigating nutritional support alone in stable COPD patients for over 8 years. Hopefully, with fresh interpretation of the evidence there will be renewed interest in this area.
Fig. 2. Nutritional supplementation versus placebo or usual diet, outcome: changes in weight (kg) from baseline; overall summary effect (undernourished and nourished) was 1.62 kg (95% CI 1.27 to 1.96), adapted from (30).

Fig. 3. Nutritional supplementation versus placebo or usual diet, outcome: change in fat-free mass / fat-free mass index from baseline; overall summary effect (undernourished and nourished) was SMD 0.57 (95% CI 0.04 to 1.09), adapted from (30).
3. Nutritional Interventions in Acute COPD

Evidence for the effectiveness of nutritional support in acutely unwell COPD patients is limited. Vermeeren at al. conducted a randomised double-blind, placebo-controlled trial in COPD patients admitted with an exacerbation and intervened with 3 x ONS/d. Whilst energy and protein intakes were significantly improved compared to control, no further benefits were observed however the mean duration of hospitalisation was 9 ± 2 days (22). This short timeframe highlights the challenge faced by nutritional support in demonstrating efficacy in the acute setting particularly in the face of marked inflammation, immobility due to worsened respiratory function and even the pharmacological management of infective exacerbations of COPD. Corticosteroids are often prescribed to treat inflammation however, one side-effect is they induce the ubiquitin proteasome pathway which is responsible for accelerated proteolysis in catabolic conditions (23). An earlier study also highlighted the difficulties in preventing weight loss in patients being treated with corticosteroids for an infective exacerbation but that nutritional intervention was able to improve energy and protein intake (24). In acutely unwell COPD patients, often experiencing frequent hospitalizations for infective exacerbations of the disease, systemic inflammation is common. Many of these patients could be diagnosed as having pre-cachexia according to the ESPEN definition: a) underlying chronic disease; b) unintentional weight loss ≥5% of usual body weight during the last 6 months; c) chronic or recurrent systemic inflammatory response; d) anorexia or anorexia-related symptoms (25). Response to nutritional support is likely to be effected during periods of elevated systemic inflammation and the time available to identify and intervene in hospitalised COPD patients is often limited. An abstract presented at the 2017 ESPEN conference by Collins et al. [ESPEN17-ABS-1788] titled ‘Treatment of malnutrition in hospitalised patients with COPD: is there opportunity?’ found the majority of hospitalised COPD patients stayed in hospital less than a week. Considering the variable availability of clinical expertise at the hospital ward level, the ability and time to identify those at nutritional risk, time to refer to the dietitian, initiation of treatment and subsequent review, the ability to meaningfully intervene is severely compromised. However, the hospital setting is a time-effective and opportune period to identify those at risk and who are often high service users. Coordinated nutritional support can be initiated and patients established on tailored nutritional care plans that continue post-discharge. Research involving retrospective analysis of healthcare use has found the use of ONS in hospitalised COPD patients to be associated with a 1.9 day reduction in length of stay, a reduction in hospital costs and reduced likelihood of readmission within 30 days (26). These findings need to be confirmed in adequately powered prospective studies which should include the exploration of the effectiveness of coordinated multimodal nutritional care started in hospital and continued post-discharge for an appropriate amount of time. During the acute phase prompt identification and initiation of nutritional support in those at risk will improve nutritional intake and help attenuate nutritional losses, and once stable the therapeutic target can shift to focus on nutritional repletion.

4. Multimodal Interventions in COPD

Whilst physiotherapy and exercise training and now viewed as key treatments in the longterm management of COPD patients, nutritional support also plays an important role. Significant numbers of patients (up to 30%) do not respond to nutritional rehabilitation, raising questions about the causes of non-response to intervention, amongst which systemic inflammation (27) and epigenetic controls due to hypoxia (28) may play a significant role. Research has focused on the effectiveness of multimodal interventions particularly immunomodulatory nutritional support alongside exercise. Sugawara et al. found a low-intensity home exercise program in combination with ONS for 12 weeks resulted in significant differences in body weight, FFM, \( P_{\text{max}} \), quadriceps muscle strength and walking distance compared to control (19). However, the significant differences in FFM were mainly attributable to losses of FFM in the control group.
Interestingly, the ONS regimen provided 2 x 200ml (1 kcal.ml) supplements per day enriched with 0.6 g omega-3 PUFAs and 248 µg vitamin A and was found to be associated with significant reductions in markers of inflammation (CRP, TNF-alpha, IL-6, IL-8). This study was followed by another from the same group investigating the effectiveness of exercise and whey peptide, n-3 fatty acid, vitamin A, C and E enriched ONS for 12 weeks (21). Despite achieving a significant improvement in energy and protein intake (protein: 1.76g/kg body weight/day; +31.6% from baseline, p <0.001) and body weight, the increase in weight was predominantly expansion of FM. Improvements in systemic inflammatory markers, respiratory muscle strength and exercise capacity were again observed. Nutritional support alongside exercise programs resulting in significant improvements in body weight but a failure to accrue significant amounts of FFM has been reported in other RCTs (13, 14). However, whilst publications often provide adequate detail on the composition of the nutritional intervention, few studies describe in adequate detail the aims, ‘dosage’ and types of exercises prescribed. The description of exercises provided by Sugawara et al. (19, 21) appear appropriate to enable the improvements in respiratory muscle strength and exercise capacity which were observed but not necessarily increases in FFM. Another challenge is the ability to establish causality and whether the results observed are a failure of the intervention or a failure to intervene. In order to do this assessment of compliance is needed, whilst Steiner and colleagues reported excellent compliance to ONS (97.6%) (13), it is difficult to establish accurate compliance to home-based exercise programs. In future studies, it is recommended that detailed reporting occurs not only of the nutritional intervention but also the type and amount of exercise undertaken. More recently, Dr Christophe Pison and colleagues as part of an international collaboration conducted an RCT exploring the effectiveness of a comprehensive multimodal home rehabilitation program and was able to achieve significant increase FFM over a 3 month period (+1.47 ± 3.04 kg, difference with control +1.75 SEM 0.64; p = 0.007) (29). However, the intervention group received seven 2 hour education sessions, 3 x 125 ml ONS per day (daily totals: 564 kcal, 28.2 g protein), a weekly phone call encouraging patients to perform the exercises and oral testosterone undecanoate (80mg twice daily in men and 40mg twice daily in women). These findings are incredibly positive and highlight that significant improvements in FFM can be achieved with multimodal interventions. It is important to note that this RCT did recruit patients based on fat-free mass index (FFMI) and/or a BMI ≤21 kg/m2 which also highlights the need for clinical expertise and comprehensive assessment in order to identify those at nutritional risk.

5. Summary

Malnutrition and body composition abnormalities are common in COPD patients and identification of individuals with depleted nutritional stores is challenging and requires skilled comprehensive assessment. Revised interpretations of the evidence base for nutritional support in COPD have again challenged traditionally held views that malnutrition in COPD is an irreversible epiphenomenon and in fact nutritional support does lead to improvements in nutritional intake, status and function. However, the evidence base to date is predominantly confined to stable (non-exacerbating) outpatients utilising ready-made liquid ONS. There is evidence that nutritional support can assist oral intake and attenuate losses in inpatients but in the face of marked inflammation, and often cachexia, attempting repletion during the acute phases of COPD appear to be futile. There have been positive findings for the use of multimodal interventions (nutrition + exercise and nutrition + exercise + testosterone) and the benefits are not confined only to the treatment of malnutrition in COPD but nutrition support appears to enhance the response to exercise. It is hoped with renewed interest in the field, there will be further research conducted exploring the potential immunomodulatory effects of nutrition as well as the impact of coordinated nutrition interventions between healthcare settings as COPD patients pass from community to hospital and back to the community.
6. References