The role of diet and nutrition in the management of COPD

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Abstract

In 2014, the European Respiratory Society published a statement on nutritional assessment and therapy in COPD. Since then, increasing research has been performed on the role of diet and nutrition in the prevention and management of COPD. Here, we provide an overview of recent scientific advances and clinical implications. Evidence for a potential role of diet and nutrition as a risk factor in the development of COPD has been accumulating and is reflected in the dietary patterns of patients with COPD. Consuming a healthy diet should, therefore, be promoted in patients with COPD. Distinct COPD phenotypes have been identified incorporating nutritional status, ranging from cachexia and frailty to obesity. The importance of body composition assessment and the need for tailored nutritional screening instruments is further highlighted. Dietary interventions and targeted single or multi-nutrient supplementation can be beneficial when optimal timing is considered. The therapeutic window of opportunity for nutritional interventions during and recovering from an acute exacerbation and hospitalisation is underexplored.

Introduction

It has long been recognised that chronic respiratory disease including COPD is associated with disordered nutritional status. Importantly, the impact of nutritional disorders on the prognosis of COPD and the burden of symptoms it imposes on sufferers has been clearly demonstrated in seminal studies over recent decades. This has prompted intense interest in developing both an understanding of the mechanisms underpinning the phenomenon and therapies to address it. For many years, the focus of attention was on weight loss and muscle wasting in COPD but in line with trends in population health generally, obesity as well as sarcopenic obesity is becoming an increasingly prevalent problem for people with COPD presenting a different challenge for nutritional management.

In this review, we will outline the current state of knowledge in this field recognising the depth and volume of literature on the topic. To do this, we draw the reader's attention to the European Respiratory Society (ERS) statement on nutritional assessment and therapy in COPD published in 2014 [1]. This provides an expert summary of the scientific literature and clinical practice at that time and, therefore, the focus of the current article will be on scientific and clinical advances in the field subsequently rather than reviewing the literature in its totality.

Initially, we will summarise the evidence to support the role of nutritional status and dietary intake in the pathogenesis of COPD, followed by a review of up-to-date methods for screening for nutritional disorders and assessment of nutritional status including the use of imaging techniques. We will also discuss current

understanding of nutritional phenotypes with implications for the underlying mechanisms of disease and identification of novel therapeutic targets. Finally, we will consider the evidence to support the benefits of nutritional therapies including macro- and micro-nutrient supplementation, nutritional management during acute exacerbation and management of obesity in COPD. Throughout, we will seek to identify key gaps in our understanding and identify the key research questions that require answering to take the field forward.

Quality of dietary intake as a risk factor for COPD

In the last few years, increasing evidence is showing a potential role of diet and nutrition as a risk factor for the development of COPD [2]. Especially, the Western-style dietary pattern, characterised by high intake of red or processed meats, refined grains, saturated fat and sweets, is associated with an increased risk of developing COPD [3]. On the other hand, a Mediterranean-like dietary pattern, characterised by high intake of fruit, vegetables, oily fish and wholegrains, is associated with preserved lung function. The latter was especially observed in smokers and ex-smokers, suggesting that a healthy diet might protect against the deleterious effects of smoking [4, 5].

The beneficial or harmful effects of different dietary patterns might potentially reflect a combined effect of diverse but highly correlated foods, which can individually affect lung function. Among potential beneficial foods, consistent epidemiological evidence from cross-sectional and longitudinal studies report inverse associations between high intake of fruits and vegetables, wholegrains, and dietary fibres and the risk of developing COPD [6–14]. By contrast, high consumption of processed red meat increases the risk of COPD by 40% when compared to a lower consumption [15]. Furthermore, consistent evidence reports a diverse relation between alcohol consumption and COPD onset. Whereas heavy drinking was associated with pulmonary function decline, low to moderate alcohol consumption was associated with higher levels of forced expiratory volume in 1 s, a lower prevalence of COPD symptoms and a decreased risk of COPD compared to nondrinkers of alcohol [16–20]. Evidence for other nutritional components, including fish and omega-3 polyunsaturated fatty acids as well as vitamin A, C, D and E, is still very limited and inconsistent [2].

Assuming that a dietary pattern characterises a habit that has been going on for years, these potential dietary risk factors might reflect the general dietary intake of patients with COPD. Indeed, a large cohort study in The Netherlands including 564 patients with COPD referred for pulmonary rehabilitation (PR) showed that patients had insufficient intake of protein, carbohydrate, vitamins (especially vitamin D) and calcium, combined with an excessive intake of (saturated) fat [21]. Furthermore, studies have consistently shown that COPD patients consume less dietary fibre, vegetables and fruit compared to controls subjects [22, 23]. This typical Western-style diet might be associated with the progression of COPD as well as extra-pulmonary disease manifestations and comorbidities.

Despite the generally poor dietary quality of patients with COPD and the increasing evidence of dietary quality as a risk factor for COPD, nutritional guidelines include no specific recommendations for prevention of COPD. This might be related to the methodological issues of the current evidence. Most evidence is coming from observational studies, either cross-sectional or, to a lesser extent, from longitudinal studies in both the general population and at-risk subjects. Additionally, most studies have been performed in Europe and North-America, limiting the generalisability of the study findings towards other countries. Randomised controlled trials (RCTs) investigating the long-term effects of specific nutritional components or adherence to certain dietary patterns are still lacking. Therefore, additional large longitudinal cohort studies and RCTs with long-term follow-up are needed to clarify the role of nutrition in maintenance of lung function and prevention of respiratory disease. Additionally, these studies should also take into account other well-known risk factors for COPD and adjust their models accordingly. These covariates should not be limited to smoking, but should also include other risk factors such as early life risk factors (*e.g.* premature birth and asthma), individual and social factors (*e.g.* socioeconomic disadvantage), and general external environmental risk factors (*e.g.* built environment and climate) [24].

Nutritional screening

There is now wide acceptance of the value of the assessment of nutritional status in the broader management of COPD. Nutritional status is an important predictor of clinical outcome (including mortality) and importantly can be modified through nutritional and rehabilitation interventions [25, 26]. It is also clear that single time-point measures of weight or body mass index (BMI) are insufficient to identify the presence of nutritional disorders and do not provide detailed body composition information to inform treatment choices. The ERS statement describes the tools available to assess nutritional risk and to identify nutritional phenotypes that might be of prognostic and therapeutic importance [1]. These include body composition measures to allow quantification of lean and bone mass (collectively fat-free mass (FFM)) and fat mass, which can be integrated with performance measures to identify nutritional

syndromes such as sarcopenia. Thresholds for these measures to allow categorisation of nutritional status (for example, cachexia, pre-cachexia, overweight, obesity) are available. These are inevitably arbitrary but offer the opportunity to standardise definitions and compare patient populations. Such measures provide assessments of "risk" where this refers to adverse health outcomes associated with disordered nutritional status. These measurements require the availability of technologies such as bio-electrical impedance (BIA) and dual energy X-ray absorptiometry (DEXA) in routine healthcare settings, which limit their wide implementation, especially in resource-limited health economies.

More recently, there has been an appreciation of the need to develop screening instruments that identify patients who might have such nutritional disorders and, therefore, might be prioritised for more detailed nutritional assessment. The European Society for Clinical Nutrition and Metabolic Care (ESPEN) published consensus statements in 2015 and 2017 suggest that simple nutritional screening instruments should be incorporated in all clinical settings to identify those at risk of malnutrition [27, 28]. This was re-enforced by the Global Leadership Initiative on Malnutrition (GLIM) in a subsequent consensus report [29]. There are a number of candidate instruments that have been tested in a wide range of clinical settings including the MUST (malnutrition universal screening tool), NRS 2002 (Nutritional Risk Screening 2002) and MNA (mini nutritional assessment) short (SF) and long forms (LF) [30]. Data on their utility in COPD populations are limited but have been reported more recently. Most studies report one or more of these screening instruments as part of a suite of nutritional assessments, comparing and correlating the presence of nutritional disorders identified by such measures in comparison with conventional measures of weight and body composition. Proportions of volunteers identified as malnourished using these different measures have been presented. For example, Marco *et al.* [31] reported 51% of a cohort of 118 patients with COPD attending PR were identified as malnourished using the MNA-SF (cut-off <11). Negative and positive predictive values were not presented but only 24% were identified as malnourished from BIA (ESPEN criteria) suggesting poor specificity of the instrument. Similarly, Ingadottir *et al.* [32] reported the performance of the NRS 2002 in a cohort of 137 patients hospitalised for COPD. Based on the ESPEN criteria using multi-frequency BIA, 19% of the entire cohort were identified as malnourished. The NRS 2002 identified 55% as "at risk", but less only 34% of those screening positive using this instrument were categorised as "malnourished" by ESPEN criteria. Formal positive and negative predictive value (NPV) data were not presented.

A more recent study formally assessed three screening instruments (MNA-SF, NRS 2002 and MUST) in a cohort of 124 patients with COPD presenting to PR [33]. Performance was assessed against GLIM definitions of nutritional status using BIA as a measure of body composition. Overall, sensitivity of these instruments was relatively low (58.3, 47.9 and 47.9% for MNA-SF, NRS 2002 and MUST, respectively). Specificity was more than 80% for MNA-SF and MUST but significantly lower (32%) for NRS 2002. Importantly, the NPV was 80% for MUST and MNA-SF indicating that 20% of patients with impaired nutritional status (according to the GLIM definition) would be missed using these instruments alone as screening tools.

In summary, indications from recent studies suggest the performance of general screening instruments may be sub-optimal in COPD populations. However, in keeping with GLIM recommendations, the use of a nutritional risk screening instrument in combination with more detailed measurements of nutritional status is favoured. However, caution interpreting the literature on specific instruments or protocols is required because studies in COPD are limited and conducted predominantly in selected populations where the prevalence of malnutrition may be relatively high. Whether these instruments can be used effectively to select patients from broader populations (for example those managed in primary care) who would benefit from more intensive nutritional assessment using body composition technologies remains to be determined.

Computed tomography (CT) assessment of muscle mass and body composition

As outlined in the ERS statement, a number of technologies have been widely deployed in COPD populations to measure muscle mass and body composition. More recently, the wider availability and routine use of thoracic CT imaging has prompted the use of CT indices of extra-thoracic muscle mass as markers of nutritional status. O'Brien *et al.* [34] reported that pectoralis major (PM) cross-sectional area (CSA) was related to DEXA measures of FFM in both a cross-sectional and longitudinal analysis. A number of studies have suggested that PM CSA is related to other clinically relevant indices such as physical activity and disease severity [35–37]. Other studies have suggested that PM CSA is linked to subsequent exacerbation frequency [38] and mortality [39, 40]. Interestingly, some studies have suggested that intermuscular fat infiltration may be an indicator of poorer outcome, whereas higher subcutaneous fat deposition may confer a better prognosis [41], in alignment with the favourable effect of whole-body obesity on survival. Therefore, CT measures of differential fat deposition may offer insight into the mechanisms explaining the impact of nutritional phenotypes in future studies.

Whilst CT imaging is unlikely to be a widely used diagnostic for broad populations of COPD, its increased use in patients managed in specialist care and its deployment in lung cancer screening programmes may provide insightful nutritional information and such measures could provide accessible biomarkers in the testing of anabolic drug interventions. Studies determining whether risk associated with these CT indices (such as intra- and extra-muscular fat deposition) is modifiable will be a key question for future research. At present, quantification of these CT indices is semi-automated, requires trained analysts and is still very labour intensive. Fully automated segmentation and analysis through artificial intelligence algorithms are being developed and will provide the potential to move these analyses from research settings to routine practice [42, 43].

Phenotypes in COPD

To capture the complexity and heterogeneity of COPD and to individualise nutritional intervention as an integrated part of disease management, phenotyping has been proposed.

Pinto *et al.* [44] systematically reviewed the literature until 2013 for studies that derived phenotypes among patients with COPD using validated statistical analyses free of definitive pre-determined hypotheses. Most studies appeared to be biased; patients were more likely males, with severe disease and recruited in tertiary care settings. The number of phenotypes ranged from two to five. Two phenotypes, with poor longitudinal health outcomes, were common across multiple studies: young patients with severe respiratory disease, few cardiovascular comorbidities, poor nutritional status and poor health status and a phenotype of older patients with moderate respiratory disease, obesity, cardiovascular and metabolic comorbidities. All of the studies derived phenotypes with cross-sectional data; the stability over time of these phenotypes and the effect of medications and interventions remain unknown and needs to be studied in prospective studies.

To investigate COPD specificity of comorbidity clusters, Triest *et al.* [45] compared, in a tertiary setting, 208 patients with COPD with 200 non-COPD controls matched for age. Comorbidities were more prevalent in patients with COPD compared to controls. A "psychological" and "cachectic" cluster was only present in the COPD population while "less comorbidity", "cardiovascular" and "metabolic" clusters were also observed in controls. Pikoula *et al.* [46] identified COPD subtypes in a large primary care population (n>30 000) based on electronic health records using data-driven approaches and related these to episodes of acute exacerbation of COPD (AECOPD) in primary care, AECOPD hospitalisation and mortality. Five COPD clusters were identified, including 1) anxiety/depression 2) severe airflow obstruction and frailty, 3) cardiovascular disease and diabetes, 4) obesity/atopy, and 5) a low prevalence of most comorbid conditions. The anxiety/depression cluster composed predominantly of young female smokers and a high score on socioeconomic deprivation. This cluster was also most at risk for AECOPD and hospitalisations. Patients in cluster 3 had the highest rate of AECOPD hospitalisation, most likely due to circulatory system diseases and less likely due to respiratory related causes. Cluster 4 showed low rates of AECOPD in primary care but high rates of AECOPD hospitalisations.

In summary, all studies to date show distinct COPD phenotypes with poor nutritional status ranging from cachexia and frailty to obesity. Since poor nutritional status is a treatable trait, this underlines the importance of body composition assessment as an integral part of the diagnostic work-up and as a target for preventive or therapeutic intervention.

Obesity in COPD

In patients with advanced COPD, it is well known that overweight and obese patients have better survival compared to normal weight patients. Previous studies showed that obesity was associated with an increased risk of all-cause mortality in patients with mild-to-moderate COPD compared to normal BMI patients with comparable disease severity. However, the relative risk of all-cause mortality and COPD-related mortality was 0.62 and 0.31, respectively, in obese patients with severe COPD compared to normal-weight patients with severe disease [47–50]. This epiphenomenon is called the "obesity paradox" and might be related to the direct effect of adipose tissue on lung mechanics. Although the mechanism is unclear, obese patients have relatively reduced static lung volumes, which are an independent predictor of increased respiratory and all-cause mortality in patients with COPD [47]. On the other hand, it could be speculated that major components of body composition (*e.g.* excessive fat mass and/or greater muscle mass) contribute to the survival advantage in chronic disease [51]. However, since the phenomenon of reduced mortality with obesity did not persist at BMI $\geqslant$40 kg·m^{-2}, the latter might not be applicable.

Based on the evidence, it can be hypothesised that obesity exerts divergent effects on COPD prognosis based on patient characteristics and disease severity. Obesity may protect against mortality in patients with advanced COPD, in which loss of FFM is a particularly important short-term risk factor for death. By

contrast, in earlier stage COPD, the harmful long-term effects of obesity-related conditions such as metabolic syndrome may result in increased cardiovascular and all-cause mortality. Despite the divergent effects on COPD prognosis, a data analysis by LAMBERT *et al.* [52] revealed that obesity in COPD is associated with worse COPD-related outcomes, including decreased quality of life and 6-min walking distance, and increased dyspnoea and greater odds of severe AECOPD. These associations were strengthened by an increasing obesity class. In addition, during hospitalisation for AECOPD, obesity is associated with increased use of noninvasive and invasive ventilation and increased hospital length of stay [53].

In the general population, obesity is usually considered detrimental and weight loss is therefore always being encouraged. However, due to the divergent effects of obesity on morbidity and mortality in COPD and because unintended weight loss is associated with higher mortality in COPD [54], it is unclear whether weight loss should be stimulated in patients with COPD. At present, there is only one weight-loss intervention study describing obese patients with COPD [55]. In this study, 28 patients received a 12-week weight-reduction programme involving meal replacements, dietary counselling by a dietitian and resistance exercise training prescribed and supervised by a physiotherapist. After the 12 weeks, BMI was decreased by 2.4 $kg \cdot m^{-2}$ and, importantly, skeletal muscle mass was maintained. Additionally, clinical outcomes including exercise capacity, health status, dyspnoea, strength and functional outcomes also improved. Systemic inflammation, however, did not change as a result of the intervention. The intervention additionally lead to improved micronutrient intake and decreased intake of total and saturated fat [56]. Whether the beneficial effects of weight loss in obese patients with COPD prolong in the long term still needs to be investigated.

In the current obesogenic society, low muscle mass might be hidden in overweight to obese patients due to accumulation of fat mass. This specific phenotype is called sarcopenic obesity. Also, in COPD, a large proportion of the patients (up to 50%) is defined as sarcopenic obese [57, 58]. In patients with COPD, the sarcopenic obesity phenotype is characterised by worse physical performance and higher systemic inflammatory burden compared to patients with normal body composition, obesity or sarcopenia [59, 60]. When the relative abundance of fat mass is located in the abdominal region, it is associated with an increased cardiometabolic risk [22], even in normal-weight patients with COPD [61]. This strengthens the importance of body composition assessment in patients with COPD. According to the recent ESPEN and the European Association for the Study of Obesity, sarcopenic obesity should be considered in at-risk individuals who screen positive for a co-occurring elevated BMI or waist circumference, and markers of low skeletal muscle mass and function [62]. Subsequently, diagnosis should be based on an assessment of skeletal muscle function, followed by an assessment of body composition in order to define excess adiposity and low skeletal muscle mass or related body compartments.

Nutrition and exacerbations

An AECOPD is an important event in COPD management affecting patient and economic disease burden. Early identification of high-risk groups for readmission within 30 days were investigated in a Chinese study including more than 1000 elderly (60+ years) patients with COPD [63]. Poor nutritional status assessed by the MNA was identified as one of eight factors significantly affecting hospital readmission, next to education level, smoking status, cardiovascular disease, number of hospitalisations for acute exacerbation in the past year, seasonal factors, home oxygen therapy and regular medication. The risk of malnutrition and the incidence of malnutrition in this study group were 44.7% and 28.1%, respectively. Reduced BMI in itself was not discriminative for readmission in this Chinese study, but shown to be associated with more than 10 days hospitalisation in a different cohort study [64]. A smaller observational study by KARANIKAS *et al.* [65] prospectively followed 80 patients with COPD admitted to the hospital for AECOPD and showed that both low BMI and low FFM (assessed by BIA) were predictive for a new COPD exacerbation during 1-year follow-up. A systematic review and meta-analysis of observational studies was performed investigating the different methods of diagnosing undernutrition and their association with mortality, exacerbation, length of hospitalisation stay and quality of life in adults with COPD [66]. The common diagnostic method of undernutrition in the 49 included studies was BMI. Next to being associated with increased mortality and poorer quality of life, in this study low BMI was also associated with increased exacerbation.

One of the factors contributing to low BMI or low FFM index maybe a low protein intake. Using data from the 2007–2012 KNHANES survey, PARK *et al.* [67] showed an association between low protein intake and increased risk of exacerbations in mild-to-moderate COPD, as reflected by hospitalisation and emergency department utilisation. The low protein intake group was associated with older age, women, never-smokers and low socioeconomic status compared to the non-low protein intake group.

All these studies consistently show adverse effects of poor nutritional status, as a treatable trait, on incidence and outcome of AECOPD. However, limited studies have investigated the effects of nutritional

interventions on outcome. Zhang *et al.* [68] reported positive effects of 2 weeks standard enteral nutrition on nutritional biomarkers, markers of immunological functioning and systemic inflammation, and partial pressure of oxygen and carbon dioxide in AECOPD with respiratory failure. The NOURISH study, a multi-centre RCT, investigated the efficacy of a high protein, oral nutritional supplement in malnourished, older patients hospitalised for cardiovascular and pulmonary events. This study showed no effects on 90-days post-discharge incidence of death or nonelective readmission as the primary composite end-point, but improved indices of nutritional status up to 90 days after discharge and decreased mortality [69]. This discordant result might be related to the heterogeneity of the study population, the length of follow-up as well as competing events of readmission. Further studies are clearly indicated to investigate the efficacy and feasibility of nutritional intervention to prevent as well as improve the outcome of acute exacerbations in malnourished patients with COPD.

Nutritional supplementation

Multi-nutrient supplementation

Overall, a healthy well-balanced diet should be promoted in patients with COPD. In case this is not sufficient, nutritional supplementation should be considered based on an expert dietician review. Due to the heterogeneity of COPD, the ERS statement of 2014 highlighted the need for multimodal intervention approaches including multi-nutrient supplementation that target impairments in multiple organs. Recently, a large RCT was performed among 45 cachectic patients with COPD that investigated the effect of 12-weeks targeted medical nutrition (TMN) on multiple outcome parameters including body composition, inflammation, muscle function and quality of life [70]. The TMN was enriched with whey protein, n-3 polyunsaturated fatty acids (PUFAs) and 25-hydroxyvitamin D3 and was compared with an isocaloric comparator including milk protein instead of whey protein and sunflower oil instead of n-3 PUFA-containing fish oil. After 12 weeks, the TMN group showed decreased exercise-induced fatigue and dyspnoea compared to the comparator group. Another recent RCT combined nutritional supplementation with PR and investigated if targeted nutritional supplementation enhanced outcomes of exercise training in 81 patients with COPD with low muscle mass [71]. In this NUTRAIN-trial, a multi-nutrient drink enriched with leucine, vitamin D and n-3 PUFAs significantly improved or maintained body weight, inspiratory muscle strength and physical activity but did not enhance the effects of a 12-week rehabilitation programme on muscle mass, muscle strength and physical performance.

While most study designs focused on short-term (1–3 months) efficacy in clinically stable disease or as adjunct to PR, limited studies investigated the benefits of nutritional supplementation during the maintenance phase after PR. The previously mentioned NUTRAIN-trial showed that during the 12 months after PR, nutritional intervention in muscle-wasted patients ameliorated total body weight, physical activity and generic health status, at an acceptable increase of costs for patients with high disease burden [72]. However, nutritional supplementation did not affect exacerbation rate. Thus far, the period during and after an acute exacerbation is still largely neglected. This is noteworthy as during an acute exacerbation, disease-related factors such as inflammation, hypoxia, physical inactivity and glucocorticoid treatment converge and intensify [73]. There is one ongoing study investigating the efficacy of 1-year targeted multi-nutrient supplementation on physical activity levels and health-related quality of life in patients with COPD. As an additional explorative aim, this study investigates the relative effect of targeted nutrient supplementation during the recovery phase after hospitalisation for a COPD exacerbation [74]. Therefore, more studies are needed to further investigate the window of opportunity for nutritional interventions during and after an exacerbation.

Single nutrient supplementation

In recent years, an increasing number of studies focused on single nutrients as an ergogenic aid to enhance the effects of exercise training. Especially, nitrate was expected to be such an ergogenic aid, since it has been shown to improve endurance exercise performance and decrease oxygen cost of exercise in healthy adults, without affecting resting metabolic rate [75]. Recently, several small-scale studies investigated the effect of dietary nitrate on exercise performance in patients with COPD, which have been summarised in a recent systematic review and meta-analysis [76]. This review concluded that there is no significant effect of nitrate-rich beetroot juice on exercise performance, measured using a 6-min walking test, cycling ergometry endurance time or maximum rate of oxygen consumption. However, it is worth highlighting the findings of one large double-blind, placebo-controlled, randomised cross-over study performed by Pavitt *et al.* [77], which was not included in the systematic review by Alshafie *et al.* [76]. This study included 165 patients with COPD and randomly assigned them to either a nitrate-rich beetroot juice (n=78) or placebo nitrate-depleted beetroot juice (n=87) group. Patients in this study followed a twice-weekly 8-week PR programme and 3 h prior to undertaking each PR session they consumed the study product. After the 8-week PR programme, exercise capacity increased more with active treatment than with placebo, suggesting that

dietary nitrate might be an effective strategy to augment benefits of PR in COPD. Endogenous nitric oxide is produced through oxygen-dependent mechanisms, suggesting that the ergogenic benefits of the administration of exogenous nitrate might be greater in patients with sustained hypoxia. Support for this hypothesis was provided by the finding of positive benefits of beetroot supplementation in patients with COPD requiring long-term oxygen therapy [78]. Despite the diverse results of small-scale studies, we suggest that dietary nitrate might be an interesting ergogenic aid to be considered to enhance the effects of exercise training.

Another nutritional component that has substantially been investigated in patients with COPD is vitamin D. As already addressed in the ERS statement, there is compelling evidence that vitamin D deficiency, measured as serum levels of 25-hydroxyvitamin D, is often present in patients with COPD and increases with disease severity [79, 80]. The high prevalence of vitamin D deficiency in COPD might be related to the dysregulated vitamin D metabolism observed in COPD [81]. Therefore, vitamin D supplementation is highly recommended where deficiency is identified. Next to the beneficial effects on bone metabolism, vitamin D might also be relevant for pulmonary as well as extrapulmonary manifestations in COPD. Two recent systematic reviews and meta-analysis investigated the link between vitamin D supplementation and prevention of exacerbations in COPD [82, 83]. These meta-analyses revealed reduced rates of moderate and severe COPD exacerbations after vitamin D supplementation, especially in patients with baseline levels $<25\ nmol \cdot L^{-1}$. Another meta-analysis in healthy adults showed a positive effect of vitamin D supplementation on muscle strength only in subjects with plasma 25-hydroxyvitamin D levels $<25\ nmol \cdot L^{-1}$ [84]. Recently, a study reported regulating effects of vitamin D on mitochondrial function, dynamics and enzyme production, which might explain the beneficial effects on muscle strength [85]. A placebo-controlled RCT reported larger improvements in inspiratory muscle strength and maximal oxygen uptake after vitamin D supplementation combined with PR in patients with COPD [86].

Conclusions and directions for future research

Evidence continues to accrue that nutritional status has a significant impact on symptoms and future health risk in COPD. In addition to the well-documented impact of weight and muscle mass loss, obesity is becoming a more prevalent and important clinical association of COPD.

The subtleties of nutritional phenotypes that present in COPD raise the possibility of phenotype-driven, personalised nutritional interventions (both macro- and micronutrient supplementation and also weight reduction programmes) but the identification of patients suitable for such targeted intervention requires further research and prospective trials.

Incorporating the assessment of nutritional status into routine clinical practice remains highly variable internationally. Simple instruments to identify those with higher nutritional risk (beyond single timepoint measures of weight) need to be validated in COPD. We suggest that these instruments need to be practical for use in low-resource health economies.

There remains a significant potential to improve clinical outcomes through nutritional assessment and treatment. In the box, we suggest the practice and research questions that need to be addressed going forward. We urge clinicians, academics and research funding bodies to give these questions a high priority so that these benefits can be realised.

Points for clinical practice

- Consuming a healthy diet should be promoted in patients with COPD.
- Nutritional screening instruments informing the deployment of body composition measures should be part of a comprehensive assessment of COPD, but more research is needed on the positive and negative predictive values for these instruments.
- The role of nutritional support during and beyond exacerbation in malnourished patients in improving clinical outcomes such as mortality, frailty and readmission requires larger, multi-centric clinical trials.
- The benefit of a range of specific micronutrients has been demonstrated in small-scale efficacy studies but larger phase 3 clinical effectiveness trials are needed.
- The management of obesity, especially dietary and bariatric therapy, in COPD has yet to be defined.
- The period during and after an AECOPD includes a therapeutic window of opportunity for multimodal and personalised nutritional interventions beyond malnutrition, but optimised intervention strategies and composition of interventions needs to be elaborated in future studies.
- The potential role of diet and nutrition in the prevention of COPD, especially in people who smoke, requires further investigation and implementation in current nutritional guidelines.

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