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REVIEW ARTICLE

# Nutritional supplementation in patients with chronic obstructive pulmonary disease

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Malnutrition in patients with chronic obstructive pulmonary disease (COPD) is associated with cachexia, sarcopenia, and weight loss, and may result in poorer pulmonary function, decreased exercise capacity, and increased risk of exacerbations. Providing nutritional supplementation is an important therapeutic intervention, particularly for severely ill COPD patients with malnutrition. Higher calorie intake through nutritional supplementation significantly increases body weight and muscle strength, and improves quality of life in malnourished COPD patients. Difficulties may be experienced by these COPD patients, who are struggling to breathe and eliminate $CO_2$ from the lungs, resulting in dyspnea, hypercapnia, hypoxia, and respiratory acidosis, which exacerbates muscle loss through oxidative stress and inflammatory responses. To overcome these problems, nutritional supplements should aim to reduce metabolic $CO_2$ production, lower respiratory quotient, and improve lung function. Several studies have shown that high-fat supplements produce less $CO_2$ and have lower respiratory quotient value than high-carbohydrate supplements. In addition, high-fat supplements may be the most efficient means of providing a low-volume, calorie-dense supplement to COPD patients, and may be most beneficial to patients with prolonged mechanical ventilation where hypercapnia and malnutrition are most pronounced. Further studies are required to investigate the optimal nutritional supplements for COPD patients according to their disease severity.


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## Introduction

Chronic obstructive pulmonary disease (COPD) is a life-threatening lung disease caused mainly by long-term exposure to cigarette smoke and other harmful airborne pollutants. Permanent damage to the lung parenchyma with loss of elastic recoil causes emphysema and inflammatory cell infiltration of the walls of the small airways, resulting in chronic bronchiolitis and bronchitis. The severity of COPD was classified according to measurements of airflow obstruction by determining the degree of $FEV_1$ (forced expiratory volume in the 1st second) reduction. However, $FEV_1$ alone does not reliably identify severity of breathlessness, exercise limitation, or impairment of health. The Global Initiative for Obstructive Lung Disease has published the classification system for COPD disease severity with revising the staging system based on $FEV_1$ alone.[1] This classification may allow diagnoses of 60—85% of undiagnosed patients who have mild to moderate disease.[1,2] The new Global Initiative for Obstructive Lung Disease guidelines categorize COPD patients into four groups by combining the spirometric measurements with symptomatic assessments, using established questionnaires (COPD Assessment Test, Clinical COPD Questionnaire, or modified Medical Research Council Dyspnea Scale), and the evaluation of the risk of future exacerbations, based on the patient's history of exacerbations in the previous year.[1]

There is no cure for COPD patients, and the major goals of treatments involve management of the patients' symptoms. As well as reduced lung function, patients with COPD tend to have poor health related quality of life, with approximately a third of these patients suffering from malnutrition. Their breathing difficulties not only affect their exercise capacity but also cause a loss of appetite and decreased nutritional intake, resulting in a spiraling malnourished state. Malnutrition is more common in patients with emphysema than chronic bronchitis, and may be either a cause of further degeneration of the disease or a consequence of disease progression.[3,4]

There is mounting evidence that in COPD patients with low body mass index and/or fat-free mass index (FFMI) are associated with a poorer prognosis and impaired long-term survival.[3] Malnutrition further aggravates the problems in COPD patients as respiratory muscle strength is reduced leading to cachexia, with a significant loss of appetite and exercise intolerance.[5—7] Furthermore, COPD patients tend to be elderly, and the loss in skeletal muscle mass as part of the natural aging process, may be further exacerbated by COPD as a result of malnutrition, sarcopenia, and cachexia.[6]

Sarcopenia is defined as the loss of skeletal muscle mass through the inability to generate new muscle cells, and also through the atrophy of existing muscle fibers.[6,8] The relationship among sarcopenia, physical performance, and respiratory function test was investigated in 71 patients with COPD aged $>$ 65 years.[9] In these well-nourished COPD patients, linear regression analysis revealed that respiratory function was a better predictor of physical performance compared with body muscle mass parameters. However, in sarcopenic COPD patients with moderate disease severity, the proportion of fat-free mass (FFM) was significantly reduced compared with healthy matched controls, although the fat mass was similar between the two groups, suggesting a similar lipolytic rate.[10]

It is widely accepted that COPD patients who are malnourished with low body weight are at greatest risk of further exacerbations,[11] with increased risk of hospital readmittance,[12] and have higher mortality rates.[13] Interestingly, in COPD patients who were considered to be overweight or obese, there was evidence of a reduced risk of hospitalization, and reduced mortality rates.[11—13] The reason that these overweight/obese patients have a better prognosis is probably attributable to the physiological advantages.

There is mounting evidence from large, multicenter studies demonstrating that in patients with moderate to severe COPD, low FFMI was a statistically significant predictor of mortality, independent of other factors.[14—17] In the elderly COPD population, sarcopenia is accelerated by as much as 30% in patients with mild to moderate COPD.[16] This is in addition to skeletal muscle loss due to the natural process of aging. The results from these studies support the assessment of body composition as a very important diagnostic marker of disease severity in COPD.

## Inflammation in COPD

There is evidence to suggest that, in addition to inflammatory responses to the respiratory tissues, inflammation may be an important factor affecting the loss of skeletal muscle mass in COPD patients. The detection of high levels of circulating proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-6, and IL-1$\beta$ in COPD patients with cachexia, have led to claims that COPD is a "chronic systemic inflammatory syndrome."[18] Systemic inflammation and oxidative stress do play a role as pathological mechanisms involved in muscle dysfunction in COPD.

Chronic inflammation may have a detrimental effect on muscle catabolism. The action of inflammatory cytokine TNF binding to its receptor on muscle cells results in apoptotic muscle cell death. Furthermore, muscle anabolism may be affected during chronic inflammation as the available amino acid pool may become depleted, through synthesis of acute phase proteins, thus preventing replenishment of muscle protein stores.[19] Indeed, glutamate, the amino acid salt form of glutamic acid, has been shown to be low in concentration in the plasma of COPD patients.[19] Cachectic COPD patients with moderate disease have lower plasma concentrations of glutamate and branched-chain amino acids (BCAAs) than those in the control and noncachectic COPD groups, and demonstrate a higher whole-body myofibrillar protein breakdown.[19]

## Oxidative stress in COPD

In addition to chronic inflammation, oxidative stress may further aggravate muscle degeneration and other symptoms in COPD patients. There may be an imbalance between $O_2$ and $CO_2$ levels in the blood, creating hypoxic conditions in the cells and muscles, leading to the production of reactive oxygen species. It has been proposed that the loss of muscle mass in COPD patients may not solely result from physical inactivity, but that hypoxia, oxidative stress, and muscle dysfunction also play a significant role.[20] The

production of reactive oxygen species activates the expression of inflammatory mediators resulting in muscle cell death through apoptosis and the degradation of actin and myosin.[21] Evidence for this has been shown with an increase in lipid peroxidation, a marker for oxidative stress, and reduction in antioxidants (reduced glutathione, catalase, and glutathione peroxidase) in COPD patients compared with healthy control individuals.[22]

## Nutritional supplementation benefits body weight control in COPD patients

Overall, 10–45% of patients with COPD are malnourished, and it is evident that malnutrition and undernutrition are important prognostic factors for COPD patients.[23] A growing number of studies looking at nutritional supplementation in COPD patients have been performed and wished to improve current clinical practice.[3,24,25] A meta-analysis of 17 studies assessing the impact of nutritional support on weight gain, respiratory function, muscle strength, exercise capacity, and quality of life revealed that nutritional supplementation promoted weight gain, with an increase in FFM, fat mass, improved 6-minute walk distance, and skinfold thickness in malnourished COPD patients.[3] There were also significant improvements in respiratory muscle strength and overall quality of life in malnourished COPD patients. A systematic review and meta-analyses of nutritional support also found that in 12 randomized controlled trials, nutritional supplements significantly improved respiratory muscle strength, handgrip strength, weight gain ($\geq$2 kg), exercise performance, and quality of life.[24] In another meta-analysis of 13 randomized controlled trials of nutritional supplements, nutritional advice, or enteral tube feeding, a significant increase in mean total protein and energy intake were observed with improvements in body weight and handgrip strength.[25] The results from these meta-analyses clearly indicate that additional nutritional supplementation together with nutritional advice, provides significant increases in body weight, muscle strength, and improved quality of life, which may lead to improved mortality rates.

## Nutritional supplementation with high-fat and high-carbohydrate formulations

Although it is desirable to increase the body weight of malnourished COPD patients, challenges may exist as these patients have a higher resting energy expenditure resulting in a greater calorie requirement than in mild COPD patients. Furthermore, these patients may have increasing fatigue, dyspnea, and early satiety, which affect their ability to eat and consume enough calories. Therefore, under these circumstances, it is important to provide nutrition that has high calorie density. This will also help to minimize abdominal distention that may cause discomfort while eating.

It has been proposed that increasing the calorie intake of COPD patients through a higher fat content diet may be more beneficial, as fat produces less metabolic $CO_2$ ($VCO_2$) per $O_2$, and has a lower respiratory quotient (RQ) compared with carbohydrate (CHO) metabolism. This may be particularly important in COPD patients with hypercapnia and those suffering from shortness of breath. Several studies have been performed to investigate the beneficial effects of different types of nutritional supplements in COPD patients, and the results of these studies are summarized in Table 1.

**Table 1** Summary of effects of nutritional supplementation on clinical outcomes in COPD patients.

| Nutritional supplement | COPD status | Clinical outcomes | References |
|---|---|---|---|
| High fat | Stable ambulatory COPD | Lower $Paco_2$, RQ, $V_E$, higher $Pao_2$ | Frankfort et al[27] |
| | COPD with hypercapnia | Lower $Paco_2$, RQ<br>Improved lung function | Cai et al[28] |
| | Moderate to severe COPD | Lower $Paco_2$, RQ<br>Higher $Pao_2$<br>Improved lung functions | Kane et al[26]<br>Angelillo et al[30]<br>Akrabawi et al[33] |
| | Severe COPD with artificial ventilation | Lower $Paco_2$<br>Reduced time on the ventilator | al-Saady et al[31] |
| High calories | Depleted COPD Patients | Increased body weight, FFM, increased handgrip strength, improved exercise capacity | Creutzberg et al[36] |
| | Mechanically ventilated COPD patients | Higher $Paco_2$ | Talpers et al[35] |
| Omega-3 | Stable COPD | Lower TNF | de Battle et al[40] |
| Protein (BCAA) | COPD Patients | Enhanced whole body protein synthesis | Engelen et al[43] |
| Protein (EAA) | Severe COPD | Increased FFM | Dal Negro et al[44] |
| | | Improved daily life performance, muscle strength, & energy metabolism<br>Improved cognitive function | Dal Negro et al[45] |
| Vitamin D | COPD patients | Reduced risk of exacerbations in the most deficient patients | Varraso & Camargo[47] |

BCAA = branched chain amino acid; COPD = chronic obstructive pulmonary disease; EAA = essential amino acid; FFM = fat-free mass; Ref. = reference; RQ = respiratory quotient; TNF = tumor necrosis factor; VE = minute ventilation.

Analysis of young cystic fibrosis patients with moderate to advanced pulmonary disease given low-, medium-, and high-CHO diets by enteral feeding, demonstrated that $CO_2$ production was significantly reduced in the high-fat formulation (28% CHO, 55% fat) compared with two higher CHO content formulations (53% CHO and 30% fat; 81.5% CHO and 0.70% fat), and also with a lower RQ.[26] The high-fat formulation also appeared to be less likely to impair exercise performance in these patients as determined by workload, $FEV_1$, and ventilation.[27]

When moderate to severe COPD patients were given the high-fat nutritional supplement (28% CHO, 55% fat, and 17% protein), they had significantly improved arterial oxygen levels, compared with those patients on a high-CHO diet (60—70% CHO, 20—30% fat, and 15% protein).[28] In a similar comparison of nutritional supplementation in clinically stable ambulatory COPD patients, high-fat diet was found to be more beneficial than a high-CHO diet. There were significantly higher levels of $CO_2$ production, $O_2$ consumption, RQ, and minute ventilation up to 1.5 hours after administration in those given the high-CHO diet, compared with the high-fat diet.[29] Comparison of a high-, medium-, and low-CHO diet (the low CHO contained 28% CHO and 55% fat) demonstrated that significantly lower $CO_2$ production, RQ, and arterial $CO_2$ were observed in COPD patients on the high-fat diet, and lung function improved with $FEV_1$ values increasing by 22%.[30]

People with COPD have difficulty inhaling enough $O_2$ and struggle to expire $CO_2$ from their lungs, resulting in elevated $CO_2$ levels in the blood and respiratory acidosis. Hypercapnia is a potentially fatal condition with symptoms including shortness of breath, drowsiness, dizziness, confusion, and headache. In patients who were on artificial ventilation as a result of severe chronic obstructive airway disease, those fed enterally with the high-fat formulation had significantly reduced $Paco_2$ levels and reduced time on the ventilator compared with patients in the standard feeding group.[31] These results suggest that a high-fat, low-CHO formula given by enteral feeding, may be beneficial to severe COPD patients on artificial ventilation. However, there were some studies that appear to provide contradictory evidence regarding the use of high-fat over high-CHO formulas. A retrospective review of six small studies with a total of 152 patients showed a lack of clinical benefit with high-fat formulas, suggesting that they should not be routinely used, but only be made available for severely malnourished COPD patients on ventilatory support.[32] When patients with moderate to severe COPD were given either a moderate-fat or high-fat enteral formula, individuals given the high-fat meal experienced significantly delayed gastric emptying.[33] Following both moderate and high-fat meals, $CO_2$ production and $O_2$ consumption both increased, with significantly higher levels at 30 minutes and 90 minutes after the moderate-fat meal (presumably because of earlier gastric emptying). Patients receiving the high-fat diet compared with a moderate-fat diet, had delayed gastric emptying and increased feeling of satiety, further exacerbating their malnourished state.[34] It has been suggested that hospitalized mechanically ventilated COPD patients do not benefit to the same extent as ambulatory patients when using high-fat formulas because of the increased gastric clearance time.[32] Further investigations are needed to determine the benefits of high-fat over high-CHO diets, especially when considering the different requirements of COPD patients according to their disease severities.

A diet high in carbohydrate compared to a diet high in fat is thought to increase the relative metabolic production of $CO_2$ ($VCO_2$) and the RQ and so increase the respiratory demand in COPD patients. The nutrition a COPD patient requires should be the appropriate amount of calories for that patient without increasing $VCO_2$. In mechanically ventilated patients given enteral formulations containing varying levels of carbohydrates or total calories (1, 1.5, or 2 times the basal energy expenditure), $CO_2$ production significantly increased with increases in total calories, but was unaffected by the different CHO regimens.[35] Avoidance of overfeeding may be a significant factor, rather than the amount of CHO intake, in avoiding hypercapnia.

In an attempt to prevent weight loss, sarcopenia, and cachexia in COPD patients, a number of studies have been performed to look at various nutritional supplements. When COPD patients were given an oral supplement containing a slightly higher calories (>10 kcal/kg/d) than standard hospital feeding, there was some improvement in lung function, but no significant effect on muscle strength or wasting.[28] COPD patients given nutritional supplementation drinks containing 61% carbohydrate (CHO), 19% fat, and 20% protein, up to three times a day for 8 weeks, had a significant increase in body weight, FFM, handgrip strength, and respiratory function compared with a historical placebo group.[36] Similarly, in a study where COPD patients were given a high-CHO oral nutritional supplement consisting of 83% CHO, given three times a day with pulmonary rehabilitation through exercise, significantly increased body weight, body mass index, FFMI, and also mid-thigh cross-sectional area were observed when both exercise and nutritional supplement were combined.[37] When COPD patients received dietary counseling and advice on nutritional supplementing for 6 months, they consumed more energy (194 kcal/d more than the control group), gained and maintained weight, but with no differences in respiratory and muscle function.[38] These studies confirmed that COPD patients benefitted from extra calories for a sustained period combined with exercise. It would be interesting to investigate what specific nutritional requirements can be tailored for COPD patients.

## Nutritional supplementation with anti-inflammatory omega-3

Anti-inflammatory supplements may improve the prognosis for COPD patients. It has been shown that the balance between omega-3 levels and omega-6 levels determines whether these eicosanoids have anti- or proinflammatory effects in patients with COPD.[39] Omega-3 (n-3 PUFA) has an anti-inflammatory effect through its ability to compete with omega-6 (n-6 PUFA) to prevent production of proinflammatory eicosanoids.

In a study of 250 clinically stable COPD patients using dietary data from a 122-item questionnaire, it was shown that high levels of anti-inflammatory omega-3 fatty acid $\alpha$-linolenic acid in the patients' diet was associated with low

levels of the inflammatory cytokine, TNF.[40] Conversely, a diet high in a proinflammatory omega-6 fatty acid, arachidonic acid, indicated higher serum levels of the inflammatory cytokine, IL-6, and C-reactive protein.[40] These results suggest that COPD patients should be encouraged to increase dietary omega-3 fatty acids (e.g., herring, sardine, mackerel, salmon, halibut, tuna, sword fish, green-shelled mussels) to promote the anti-inflammatory benefits of this supplement, while avoiding foods dense in omega-6 fatty acids (e.g., poultry, eggs, nuts, cereal, palm oil, and sunflower oil, catfish) so that their condition does not worsen by elevating systemic IL-6 levels. There was no apparent association between IL-8 and omega-3 intake, possibly because it was difficult to measure serum IL-8 levels as it is a more localized cytokine involved in recruitment and activation of neutrophils in the lung (produced by activated, resident macrophages), rather than systemic, circulating cytokines (such as TNF and IL-6).[39,40] This was supported by data that smokers with emphysema have increased levels of IL-8 in bronchoalveolar lavage samples.[40] These results suggest that omega-3 supplementation may be beneficial in helping with an anti-inflammatory response in COPD patients.

## Nutritional supplementation—essential amino acids and BCAAs

Another area where supplementation may be useful is in the use of essential amino acids (EAAs) or BCAAs essential for building protein, as nutritional supplements. An imbalance between muscle protein synthesis and breakdown results in skeletal muscle cell wasting. Sarcopenia occurs as part of the normal aging process (>50 years) as muscle protein synthesis declines, along with a loss in muscle quality and strength (where muscle fibers are replaced with fat), with an increase in fibrosis, changes in muscle metabolism, oxidative stress, and degeneration of the neuromuscular junction. This loss of FFM and change to fat is accelerated in about 30% of patients with moderate to severe COPD.[41] This can exacerbate the problems that COPD patients have with a lack of exercise, and increases the risk of further deterioration in their respiratory and peripheral muscle function.[41] Skeletal muscle dysfunction may result from an array of pathophysiological conditions in COPD such as inflammation, malnutrition, and oxidative stress.[19,41]

In COPD patients with accelerated loss of FFM, there is a direct correlation between low plasma concentrations of BCAA and low FFM body composition and muscle energy metabolism.[19,42] The dietary supplementation of a soy protein meal with BCAA enhanced whole-body protein synthesis in patients with COPD.[43]

In a study of 32 severe COPD patients, oral supplementation with EAAs for 12 weeks increased FFM by 10% and had beneficial effects on muscle energy metabolism, cognitive function, and perception of health status.[44] In a subsequent study performed in 88 COPD outpatients, supplementation with EAAs for 12 weeks significantly improved their quality of life and their ability to perform their daily life routines, as well as increasing FFM, muscle strength, and cognitive function.[45] It appears that in all these studies, supplementing with EAAs and BCAAs provides significant nutritional benefits to COPD patients in terms of muscle cell growth and strength, especially in malnourished COPD patients.

## Nutritional supplementation—vitamins and minerals

Unsurprisingly, malnourished COPD patients have also been shown to have decreased levels of vitamins, minerals, and antioxidants as a result of poor nutrition, smoking, and cachexia.[34] Vitamin D deficiency may be common among COPD patients as intake through food may be limited, and their exposure to the sun is reduced because of a decline in their outdoor activity. Skeletal muscles have vitamin D receptors, and it has been suggested that vitamin D deficiency causes muscle weakness.[46] Vitamin D deficiency can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and increase the risk of fracture.[46] Vitamin D is also thought to protect the body against viral and bacterial infections that can trigger COPD attacks.

It has been shown that performance speed and proximal muscle strength were markedly improved when 25-hydroxyvitamin D levels increased from 4 ng/mL to 16 ng/mL, and this continued to improve as the concentration increased above 40 ng/mL.[46] In COPD patients with less than 10 ng/mL of serum 25-hydroxyvitamin D, it was found that patients had a reduced risk of COPD exacerbations following vitamin D supplements.[47] Low serum levels of 25-hydroxyvitamin D were also shown to directly correlate with poor $FEV_1$ values.[46] By contrast, a longitudinal study of 356 moderate, severe, and very severe COPD patients were assessed for an association between serum levels of vitamin D and exacerbations, but no association was found.[48]

To study the effects of antioxidant and minerals, a comprehensive examination of the independent associations of a wide range of serum markers of nutritional status with lung function was conducted in 14,120 individuals. Using data from a cross-sectional population nutrition survey, serum levels of antioxidant vitamins (vitamin A, betacryptoxanthin, vitamin C, and vitamin E), selenium, calcium, chloride, and iron were independently associated with higher $FEV_1$ values. Higher concentrations of potassium and sodium were associated with lower $FEV_1$.[49] A study in older Chinese adults (>55 years) given daily doses of antioxidant vitamins and increased dietary fish intake, and supplementary omega-3 significantly improved lung function in these COPD patients.[50] The results from these studies suggest that additional supplementation with vitamins, minerals, and antioxidants would be beneficial to the outcome of COPD patients.

## Discussion

The goal of effective COPD management is to relieve symptoms, slow disease progression, improve exercise tolerance, prevent and treat complications, and improve nutritional status and overall quality of life. There is a mounting body of evidence to indicate that nutritional supplementation to increase body weight, FFM, and fat

mass, and to lower RQ and $CO_2$ levels in the blood provides significant benefits for the prognosis of COPD patients.

To achieve this, a high-fat supplement may be beneficial in providing low volume, calorie dense nutrition especially to malnourished COPD patients with satiety problems, as it has been shown to produce less $CO_2$ and result in a lower RQ value compared with high-CHO diets. In addition, increasing the amount of omega-3 in the diet or through supplementation may help provide important anti-inflammatory benefits to COPD patients. More specific supplements containing EAAs and BCAAs in combination with exercise may be helpful for increasing muscle strength and increasing FFM, together with vitamin D and other mineral supplements, which may improve the quality of life in COPD patients. Further studies to look at combining these nutritional supplements could be extremely useful and would provide a relatively cheap and simple method to improve clinical outcomes of COPD patients.

## References


1. Global Initiative for Chronic Obstructive Lung Disease. *Global strategy for diagnosis, management, and prevention of COPD*. 2015. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf.
2. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *Lancet* 2012;**379**:1341—51.
3. Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;**12**. CD000998.
4. Mallampalli A. Nutritional management of the patient with chronic obstructive pulmonary disease. *Nutr Clin Pract* 2004;**19**:550—6.
5. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopenia Muscle* 2010;**1**:1—5.
6. Thomas DR. Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia. *Clin Nutr* 2007;**26**:389—99.
7. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. *Am J Clin Nutr* 2006;**83**:735—43.
8. von Haehling S, Morley JE, Anker SD. An overview of sarcopenia: facts and numbers on prevalence and clinical impact. *J Cachexia Sarcopenia Muscle* 2010;**1**:129—33.
9. Cesari M, Pedone C, Chiurco D, Cortese L, Conte ME, Scarlata S, et al. Physical performance, sarcopenia and respiratory function in older patients with chronic obstructive pulmonary disease. *Age Ageing* 2012;**41**:237—41.
10. Franssen FM, Sauerwein HP, Rutten EP, Wouters EF, Schols AM. Whole-body resting and exercise-induced lipolysis in sarcopenic [corrected] patients with COPD. *Eur Respir J* 2008;**32**:1466—71.
11. Hallin R, Koivisto-Hursti UK, Lindberg E, Janson C. Nutritional status, dietary energy intake and the risk of exacerbations in patients with chronic obstructive pulmonary disease (COPD). *Respir Med* 2006;**100**:561—7.
12. Zapatero A, Barba R, Ruiz J, Losa JE, Plaza S, Canora J, et al. Malnutrition and obesity: influence in mortality and readmissions in chronic obstructive pulmonary disease patients. *J Hum Nutr Diet* 2013;**26**:16—22.
13. Hallin R, Gudmundsson G, Suppli Ulrik C, Nieminen MM, Gislason T, Lindberg E, et al. Nutritional status and long-term mortality in hospitalised patients with chronic obstructive pulmonary disease (COPD). *Respir Med* 2007;**101**:1954—60.
14. Budweiser S, Meyer K, Jorres RA, Heinemann F, Wild PJ, Pfeifer M. Nutritional depletion and its relationship to respiratory impairment in patients with chronic respiratory failure due to COPD or restrictive thoracic diseases. *Eur J Clin Nutr* 2008;**62**:436—43.
15. Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med* 2006;**173**:79—83.
16. Vermeeren MA, Creutzberg EC, Schols AM, Postma DS, Pieters WR, Roldaan AC, et al. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. *Respir Med* 2006;**100**:1349—55.
17. Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005;**82**:53—9.
18. Aniwidyaningsih W, Varraso R, Cano N, Pison C. Impact of nutritional status on body functioning in chronic obstructive pulmonary disease and how to intervene. *Curr Opin Clin Nutr Metab Care* 2008;**11**:435—42.
19. Laveneziana P, Palange P, Faculty ERSRS. Physical activity, nutritional status and systemic inflammation in COPD. *Eur Respir J* 2012;**40**:522—9.
20. Couillard A, Prefaut C. From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. *Eur Respir J* 2005;**26**:703—19.
21. Rutten EP, Franssen FM, Engelen MP, Wouters EF, Deutz NE, Schols AM. Greater whole-body myofibrillar protein breakdown in cachectic patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 2006;**83**:829—34.
22. Vibhuti A, Arif E, Deepak D, Singh B, Qadar Pasha MA. Correlation of oxidative status with BMI and lung function in COPD. *Clin Biochem* 2007;**40**:958—63.
23. Schols AM. Nutrition as a metabolic modulator in COPD. *Chest* 2013;**144**:1340—5.
24. Collins PF, Elia M, Stratton RJ. Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respirology* 2013;**18**:616—29.
25. Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Am J Clin Nutr* 2012;**95**:1385—95.
26. Kane RE, Hobbs PJ, Black PG. Comparison of low, medium, and high carbohydrate formulas for nighttime enteral feedings in cystic fibrosis patients. *JPEN J Parenter Enteral Nutr* 1990;**14**:47—52.
27. Frankfort JD, Fischer CE, Stansbury DW, McArthur DL, Brown SE, Light RW. Effects of high- and low-carbohydrate meals on maximum exercise performance in chronic airflow obstruction. *Chest* 1991;**100**:792—5.
28. Cai B, Zhu Y, Ma Y, Xu Z, Zao Y, Wang J, et al. Effect of supplementing a high-fat, low-carbohydrate enteral formula in COPD patients. *Nutrition* 2003;**19**:229—32.
29. Kuo CD, Shiao GM, Lee JD. The effects of high-fat and high-carbohydrate diet loads on gas exchange and ventilation in COPD patients and normal subjects. *Chest* 1993;**104**:189—96.
30. Angelillo VA, Bedi S, Durfee D, Dahl J, Patterson AJ, O'Donohue Jr WJ. Effects of low and high carbohydrate feedings in ambulatory patients with chronic obstructive pulmonary disease and chronic hypercapnia. *Ann Intern Med* 1985;**103**:883—5.
31. al-Saady NM, Blackmore CM, Bennett ED. High fat, low carbohydrate, enteral feeding lowers $PaCO_2$ and reduces the period of ventilation in artificially ventilated patients. *Intensive Care Med* 1989;**15**:290—5.
32. Malone AM. Specialized enteral formulas in acute and chronic pulmonary disease. *Nutr Clin Pract* 2009;**24**:666—74.
33. Akrabawi SS, Mobarhan S, Stoltz RR, Ferguson PW. Gastric emptying, pulmonary function, gas exchange, and respiratory

quotient after feeding a moderate versus high fat enteral formula meal in chronic obstructive pulmonary disease patients. *Nutrition* 1996;**12**:260—5.
34. DeBellis HF, Fetterman Jr JW. Enteral nutrition in the chronic obstructive pulmonary disease (COPD) patient. *J Pharm Pract* 2012;**25**:583—5.
35. Talpers SS, Romberger DJ, Bunce SB, Pingleton SK. Nutritionally associated increased carbon dioxide production. Excess total calories vs high proportion of carbohydrate calories. *Chest* 1992;**102**:551—5.
36. Creutzberg EC, Wouters EF, Mostert R, Weling-Scheepers CA, Schols AM. Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. *Nutrition* 2003;**19**:120—7.
37. Gurgun A, Deniz S, Argin M, Karapolat H. Effects of nutritional supplementation combined with conventional pulmonary rehabilitation in muscle-wasted chronic obstructive pulmonary disease: a prospective, randomized and controlled study. *Respirology* 2013;**18**:495—500.
38. Weekes CE, Emery PW, Elia M. Dietary counselling and food fortification in stable COPD: a randomised trial. *Thorax* 2009; **64**:326—31.
39. Giudetti AM, Cagnazzo R. Beneficial effects of n-3 PUFA on chronic airway inflammatory diseases. *Prostaglandins Other Lipid Mediat* 2012;**99**:57—67.
40. de Batlle J, Sauleda J, Balcells E, Gomez FP, Mendez M, Rodriguez E, et al. Association between Omega3 and Omega6 fatty acid intakes and serum inflammatory markers in COPD. *J Nutr Biochem* 2012;**23**:817—21.
41. Rutten EP, Spruit MA. Essential amino acids to treat sarcopenia in patients with COPD? *Monaldi Arch Chest Dis* 2010;**73**:2—4.
42. Kutsuzawa T, Shioya S, Kurita D, Haida M. Plasma branched-chain amino acid levels and muscle energy metabolism in patients with chronic obstructive pulmonary disease. *Clin Nutr* 2009;**28**:203—8.
43. Engelen MP, Rutten EP, De Castro CL, Wouters EF, Schols AM, Deutz NE. Supplementation of soy protein with branched-chain amino acids alters protein metabolism in healthy elderly and even more in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* 2007;**85**:431—9.
44. Dal Negro RW, Aquilani R, Bertacco S, Boschi F, Micheletto C, Tognella S. Comprehensive effects of supplemented essential amino acids in patients with severe COPD and sarcopenia. *Monaldi Arch Chest Dis* 2010;**73**:25—33.
45. Dal Negro RW, Testa A, Aquilani R, Tognella S, Pasini E, Barbieri A, et al. Essential amino acid supplementation in patients with severe COPD: a step towards home rehabilitation. *Monaldi Arch Chest Dis* 2012;**77**:67—75.
46. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;**357**: 266—81.
47. Varraso R, Camargo Jr CA. More evidence for the importance of nutritional factors in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2012;**95**:1301—2.
48. Puhan MA, Siebeling L, Frei A, Zoller M, Bischoff-Ferrari H, Ter Riet G. No association of 25-hydroxyvitamin D with exacerbations in primary care patients with COPD. *Chest* 2014;**145**:37—43.
49. McKeever TM, Lewis SA, Smit HA, Burney P, Cassano PA, Britton J. A multivariate analysis of serum nutrient levels and lung function. *Respir Res* 2008;**9**:67.
50. Ng TP, Niti M, Yap KB, Tan WC. Dietary and supplemental antioxidant and anti-inflammatory nutrient intakes and pulmonary function. *Public Health Nutr* 2014;**17**:2081—6.