LITERATURE REVIEW

The Role of Macronutrients in Chronic Obstructive Pulmonary Disease: A Review

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ABSTRACT

The incidence of chronic obstructive pulmonary disease (COPD) is rising and is still regarded as one of the challenging medical issues. Regardless of the main relationship between tobacco smoking and toxic particle exposure with COPD, factors like nutritional status also play an important role in COPD progression and outcome, as the factor is an adaptable aspect. Malnutrition, sarcopenia, and obesity are nutritional problems that are often encountered in COPD patients. Macronutrients, namely carbohydrates, fat, and protein, support the adjunctive treatment options for COPD. The ideal dietary pattern includes low carbohydrates, medium fats preferably polyunsaturated fatty acids (PUFA), and high proteins to improve COPD symptoms, preserve muscle mass, and delay disease progression. High carbohydrate intake might also increase the respiratory quotient (RQ) which results in higher carbon dioxide (CO_2) production and oxygen (O_2) demand compared to fat and protein intake. Daily calorie intake should be adjusted to personal nutritional status. Higher calories in malnourished, sarcopenic patients and targeted weight loss in obese patients show improvements in lung function, frequency of exacerbations, and hospitalization rate. In obese individuals with COPD, however, maintaining a slightly higher body mass index (BMI) of 25-30 kg/m^2 was associated with lower mortality. This literature review summarized the significant role of macronutrients in COPD patients and the practical approach to macronutrient intervention in individuals with different nutritional statuses.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease caused by heterogeneous lung conditions that result in persistent and progressive airflow obstruction.[1] COPD was reported globally with a prevalence of about 10% in the adult population and was within the top three causes of mortality.[1,2] In 2013, National Registry Data of the Republic of Indonesia displayed that the prevalence of COPD in Indonesia was 3.7%.[3] COPD was classically linked to smoking and exposure to toxic pollutants, but the newest studies reported that many other factors, such as lung aging and development, contributed to this disease.[4] A study found a strong association between nutritional status and COPD in terms of pathogenesis, risk factors, exacerbations, and potential in therapy.[5] Nutritional-related problems that are often encountered in COPD patients include malnutrition, sarcopenia and obesity.[6,7] Macronutrients, particularly carbohydrates, protein, and fat, play a significant role in COPD.[8,9] A poor macronutrient diet leads to an increased risk of COPD and declined lung function which relate to disease symptoms such as dyspnea, fatigue, anorexia, and weight loss.[10] Therefore, macronutrient intervention might benefit populations with COPD in general and be adjusted to individuals' nutritional statuses. However, the recommendation of macronutrients for different nutritional statuses in COPD patients still has conflicting results.

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The Relationship between Nutritional Status and COPD

Malnutrition, loosely associated with undernutrition, was previously linked primarily to intake disorders and starvation. However, the growing evidence shows that prolonged inflammation could be the important culprit.[11] The number of malnutrition cases in COPD patients ranged from 17% to 47.6% and was found to be higher in developing countries.[12,13] COPD is known to be more prevalent in the elderly above 60 years old, and the growth of malnutrition in the Indonesian elderly population varies from 8-26% based on the body mass index (BMI) criteria.[14,15] Malnutrition has a direct impact on lung function and lower quality of life that is caused by alteration in metabolic function resulting in frequent exacerbations and prolonged hospitalization. Eventually, this will increase healthcare costs and produce a poor prognosis.[16] Malnutrition of COPD patients tends to have lower body mass than normal, overweight, or obese patients.[12] Fat-free mass (FFM), which contains the active metabolic organs is considered a better measurement of malnutrition than BMI in COPD patients. FFM is defined as the difference between total body mass and fat mass.[12] When used to measure physical activity, a low FFM index was linked to a shorter 6-minute walking test (6MWT). FFM index was also reported to worsen in patients whose COPD later progressed as measured by lower forced expiratory volume in the first second (FEV_1).[14] COPD patients who were underweight and suffered from acute weight loss had more frequent episodes of exacerbations even though contrary results from previous studies existed.[12,13] A lower FFM index also raises the risk of mortality by 17 times and also longer length of hospital stay by 9 days compared to the control group.[17] Ineffective muscle contraction in COPD patients might relate to a raised metabolic rate caused by excessive respiratory compensation effort and routine use of bronchodilators.[12] Furthermore, weight loss and muscle loss in COPD patients were associated with a prolonged inflammatory state and elevated cytokines levels such as tumor necrosing factor alpha (TNF α) and interleukin-1 (IL-1).[18,19] These might also contribute to the increased metabolic rate and energy expenditure.[17]

Aside from malnutrition, sarcopenia is also frequently reported in COPD patients. Sarcopenia is defined by the European Working Group on Sarcopenia in Older People (EWGSOP) which consists of low muscle mass quantity, low strength, and low physical performance.[20] It leads to poorer outcomes with a rising incidence of falls, length of hospitalization, and death rate.[21] The EWGSOP criteria consist of gait speed, grip strength, and low muscle mass and are used to diagnose sarcopenia.[21] One study reported that 24% of COPD patients suffer from sarcopenia.[22] Factors like age, cytokines marker, and nutritional status are linked to sarcopenia in COPD patients. Lower FEV_1 reflects severe airflow obstruction, physical endurance limitation, and reduced daily activity performance.[23,24] Malnutrition is known as an important factor contributing to the development of sarcopenia, and muscle mass reduction is a significant criterion in both. Furthermore, malnutrition also causes exacerbations, more severe dyspnea, deterioration of lung function, and poorer performance in physical exercise tests.[25] Although malnutrition and sarcopenia are common findings in COPD patients, some patients did not meet both conditions according to the European Society for Clinical Nutrition and Metabolism (ESPEN) and EWGSOP criteria.[7,26] This strongly suggests that these two malnutrition-related states are not similar. Thus, routine assessment of both conditions should be performed in COPD patients.[26]

The pathogenesis of sarcopenia and COPD is primarily correlated with inflammation, oxidative stress, reduced muscle endurance due to muscle disuse and dystrophy, prolonged hypoxemic state, and steroid exposure in COPD patients.[27] As previously mentioned, TNF α and IL-1, along with IL-6, play a big role in the inflammatory process linked to a lower muscle mass count. TNF α and IL-1, which are released during inflammation, can damage lung tissue and trigger the inflammatory response of neutrophils, macrophages, type 1 helper T-cells (Th1), and type 1 cytotoxic T-cells (Tc1).[18,19] IL-6 level was also reported to be elevated in patients with poor 6MWT results, indicating a possible association between sarcopenia and inflammation markers released.[28] The increased production of reactive oxygen species (ROS)/nitrogen (RONs) can negatively affect deoxyribonucleic acid (DNA) changes and cell structure, resulting in poor protein and muscle function.[27]

Oxidative stress due to excess production of oxidants or insufficient amount of antioxidants may trigger a response in COPD patients by modulating transcription factors and kinases. The results of this oxidative stress are a generation of proteolytic pathways and muscle cell death.[29] This will eventually lead to the shifting of type I muscle fiber to type IIx, which is inefficient, causing a higher oxygen demand.[27,30] Prolonged hypoxemia is commonly found in COPD patients because of airway obstruction and alveoli damage reported to increase oxidative stress. A previous study showed that hypoxemia causes a reduction in muscle endurance and muscle strength, primarily in the quadriceps muscles.[30] Decreased physical activity as the disease progresses will result in loss of muscle mass due to disuse atrophy. The diminished muscle mass,

endurance, and strength produce earlier muscle fatigue and limit the daily activity and exercise capacity. This results in poorer muscle preservation and, thus, a vicious cycle.[30] The shrinkage of muscle fibers, function, and endurance are also related to the long-term use of anti-inflammation drugs, specifically glucocorticoids (GC). GC affects the production of insulin-like growth factor 1 (IGF-1), the eukaryotic translation initiation factor 4E (EIF4E) binding protein 1, and ribosomal protein S6 kinase 1 (S6K1), which also contribute to lowering protein synthesis.[27]

The obesity paradox in COPD patients is a well-known irregularity in which obesity might provide beneficial outcomes.[31] Obesity in COPD patients, termed by BMI exceeding 30 kg/m^2, has been increasing worldwide. Data reported that the prevalence of obesity, with some variations worldwide, may be due to different measurement methods and body composition. One recent study reported a 21.8% coexistence between COPD and obesity. Generally, obesity leads to various cardiovascular, metabolic, gastrointestinal, and neurological disorders and raises the risk of malignancy.[32] However, mild to moderate obesity with a BMI of 30-40 kg/m^2 in COPD patients has been proven to have a protective outcome in mortality rate and reduced hospitalization. Lean and fat mass distribution have mechanical effects on respiratory physiology. Functional residual capacity (FRC) and expiratory reserve volume (ERV) decline with BMI increment while inspiratory capacity (IC) increases. Mild to moderately obese people with COPD interestingly have relative benefits due to these changes.[33] This is supported by a previous study that obese people with COPD showed no worse exercise capacity or symptoms of breathlessness compared to those with normal BMI and with a comparable reduction in $FEV_{1.}$[34] Unfortunately, this is not the case in people with a BMI above 40 kg/m^2, in which rates of respiratory-related death increase.[33]

Macronutrient Factors in COPD

The role of macronutrients, known as carbohydrates, fat, and protein, has been studied in COPD patients. These factors potentially affect the presence of a disease and the potential target of disease treatment. A balanced proportion of macronutrients must be attained for optimal health, but the exact recommendation data is still debatable.[8] Though malnourished COPD patients aim to gain weight, a high intake of carbohydrates in the patients is likely to accelerate the metabolic production of CO_2 and eventually increase the oxygen demand, resulting in high levels of CO_2 and respiratory acidosis.[31,35] One study reported that <130 grams of carbohydrate intake daily led to fewer dyspnea episodes.[35] This suggests that consuming fewer carbohydrates has a beneficial effect on COPD patients. On the other hand, calorie substitution with a high-fat diet is more favorable because it leads to less CO_2 production.[35] The high-fat diet also contributes to better exercise endurance, which is determined by FEV1. The body will likely produce more ketone bodies, which relate to a declined nucleotide-binding oligomerization receptor 3 (NLRP3), known as one of the inflammatory receptors in COPD.[31,35]

Increased metabolic rate in COPD patients results in higher resting energy expenditure (REE) and would influence daily calorie intake.[36] Furthermore, resting carbohydrate oxidation is also found to be elevated in COPD individuals, probably because of increased anaerobic metabolism in a slightly hypoxic state.[37] Determining REE and respiratory quotient (RQ) could measure changes in energy metabolism in individuals.[31,36] RQ measures the body's basal metabolic rate between the volume of CO_2 released and the volume of oxygen absorbed. The calculation of RQ is determined by the mixture of the main macronutrient substrates, such as carbohydrates, fats, and proteins.[38] An RQ value of <1.0 was proved to be ideal in COPD patients due to less CO_2 being exhaled.[31,38] The measurement of RQ in carbohydrate oxidization was equal to 1.0, while the measurement of RQ in fat oxidation was equal to 0.7.[38] Furthermore, the measurement of protein substrates resulted in an RQ equal to 0.9. These reports showed that a high-fat and protein diet is preferable diet to a high-carbohydrate diet in COPD patients.[38] COPD patients who experienced symptoms of dyspnea were also proved to be more comfortable when assigned to a low carbohydrate diet.[39]

Saturated fatty acids (SFA) and trans fats induce systemic inflammation. The generation of ROS after fat intake is reported to induce atherogenesis.[40] Impaired lung function is associated with increased systemic inflammation. Types of fatty acids have different effects on lung function. Pentadecanoic acid, a type of fatty acid, has been found to have advantages in terms of reduction in BMI, low-density lipid to high-density lipid (LDL-HDL) index, plasma triglycerides, body weight, and metabolic and cardiovascular benefits in general. Pentadecanoic acid has been suggested to improve mitochondrial dysfunction seen in COPD patients and thus may improve respiratory function measured with FEV_1/FVC.[41] Omega 3 fatty acids (eicosapentaenoic acid/EPA) and docosahexaenoic acid (DHA) are also linked to the improvement of respiratory function because of lower systemic inflammation effect and reduced inflammation markers such as Il-6, C reactive protein, and tumor necrosis factor α, but this hypothesis

would need further studies.[40,42] Polyunsaturated fatty acids (PUFA), including EPA, docosapentaenoic acid (DPA), and DHA, have been found to improve lung function, while plasma monosaturated fatty acids (MUFA) and SFA had an inverse association. The hypothesis suggested the role of PUFA in enhancing the production of epidermal growth factor receptor agonist amphiregulin (AREG) which promotes lung repair in animal studies.[42]

A high-protein diet with amino acids has been observed in COPD patients and reported to increase protein synthesis, leading to improved muscle metabolism and a better quality of life.[37,40] COPD patients were found to have increased protein turnover with negative nitrogen balance, decreased protein synthesis, and altered amino acid profile in plasma and muscle, especially in those with later stages of the disease and frequent exacerbation.[43] Branched-chained amino acid (BCAA) levels are lower in COPD patients, suggesting impairment in protein metabolism. Alteration in this BCAA happens due to a reduced level of leucine and is associated with a lower FFM index. Elevated inflammation markers in COPD, such as IL-1 and TNF α, stimulate the liver's BCAA catabolism and amino acid (AA) uptake.[44] Dietary protein intake is also needed to prevent muscle wasting and maintain adequate protein synthesis.[43] FEV_1 decreases with increased urinary nitrogen excretion, suggesting that COPD patients might need sufficient protein supplementation.[45]

Macronutrients as a Nutritional Intervention for COPD

Improving nutritional status with nutritional intervention in COPD patients is linked to a better outcome. The intervention should be customized depending on each patient's clinical requirements, stability, physical activity, and COPD severity.[16,46] As mentioned previously, REE in COPD patients tended to be higher, resulting in physical endurance limitation.[46] Individuals with COPD are likely to be malnourished and sarcopenic, and thus macronutrient requirements are an essential aspect of nutritional intervention.[16] Studies suggest a high-fat, medium-protein, and low-carbohydrate diet for a favorable outcome in COPD individuals compared to a high-carbohydrate, medium-fat, and low-protein diet in achieving a daily calorie target.[46] One study reported that this dietary pattern could reduce symptoms of dyspnea and improve the FEV_1 by 22% in COPD patients, but no distinction of the COPD grade was noted.[47] A high-carbohydrate diet shows increased CO_2 production, O_2 demand, and RQ, which worsens COPD patients and induces CO_2 elimination.[43] A generally recommended daily caloric intake is 30 kcal/kgBW, but it may increase to 45 kcal/kgBW.[16,47] The medium-fat diet needs to be reached with an intake of PUFA, which shows an anti-inflammatory action.[46,47] Daily recommended protein substitution in COPD patients is 1.0-1.2 g protein/kgBW/day and may increase to 1.5 g/kgBW/day in patients with marked sarcopenia.[47] A high-protein diet, defined as above 1.0 g/day, also improved physical performance in COPD patients who participated in rehabilitation programs.[48] Nevertheless, the protein intake exceeding its recommended dose will lead to shortness of breath which is caused by a rising respiratory impulse.[40,43] Effects of macronutrient administration have also been proven to increase strength response after training in pulmonary rehabilitation.[34]

Table 1. The general daily recommendation of macronutrients in COPD patients[46,47]

	Composition	Comment
Calorie	30 – 45 kcal/kgBW	Depending on the individual's needs
Carbohydrate	30%	Limiting as much as 200 g/day
Fat	50%	Omega-3 fatty acid sources such as fish are preferable, about 50% or 4 servings per week. 30 grams of nuts/day are recommended alternatively.
Protein	1.2 – 1.5 g/kgBW	Three portions of white meat per week, one portion of red meat per week, one portion of milk and yoghurt per day, two servings of cheese and eggs, each, two to three portions of legumes per week, and four servings of fish per week

Malnutrition and sarcopenia are common nutritional-related issues in COPD, overweight, and obesity. These health issues also need a special approach with comprehensive nutritional and exercise intervention therapy.[32] Though the optimal therapy for obese patients still needs validation due to the "obesity paradox" concerning COPD, studies suggest benefits from losing weight and preserving muscle mass.[33,46] Managing the population with a low-calorie, high-protein diet with partial meal replacement (PMR) and resistance training would actualize clinical improvements in health status, reduced cardiac events, and metabolic disorders.[33] Therefore, to cope with the diet issue, a dietitian must participate in treating obese COPD patients. For patients with a BMI of 30-40kg/m^2, 920-1,200 kcal/day is recommended, and those with BMI >40kg/m^2, with 1400 kcal/day, need at least a three-course meal a day to achieve adequate nutrients. Patients should also receive daily protein of 1.2-1.5 g/kgBW to prevent muscle atrophy. Weight loss interventions must be combined

with resistance and endurance training programs believed to maintain bone density, muscle mass, and strength.[34,47]

Furthermore, maintaining a BMI in the overweight to obese class I range of about 25-35 kg/m^2 has been found to have a protective effect on mortality risk in the population with COPD in general. A previous study showed that a BMI of 30 kg/m^2 was associated with decreased mortality rates.[33] Therefore, good dietary habits and exercise can facilitate weight loss in COPD individuals, and keeping this population overweight was also proved to be ideal. Studies that investigate the exact mechanism need to be performed in the future.

SUMMARY

The correlation between COPD and nutrition has been a focus in recent years as it is one of the modifiable factors determining the outcomes of a disease. Malnutrition and sarcopenia are commonly found, especially in elderly patients with COPD with both cause-and-effect relationships. On the other hand, obesity possesses a detrimental effect on individuals with COPD. The general dietary pattern, in other words, the consumption of low carbohydrates, medium-protein, and high fat, could lead to favorable results in COPD patients, which include reducing symptoms, preserving muscle mass, and slowing disease progression. However, this macronutrient intervention should be adjusted by tailoring individual's needs considering their nutritional status, activity, and comorbidities. Further research should scrutinize the role of other nutritional interventions in patients with COPD.

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Conflict of Interest
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