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A Review On the Occurrence, Causative Factors and Pattern Of Malnutrition In Patients With Chronic Obstructive Pulmonary Disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a disease of the respiratory system characterised by extra pulmonary manifestations that includes nutritional depletion, which is known to have negative consequences on morbidity and mortality. Chronic malnutrition results in reduced lung and respiratory muscle function secondary to loss of lean body mass, multiple nutrient deficiencies and cachexia when chronic in nature. A literature review was performed on the prevalence and trend of malnutrition, reported in COPD patients. Increased resting energy expenditure, thermic response to food, early satiety, increased pro inflammatory cytokines are known to lead to loss of appetite, weight loss and cachexia on a long term. Under nutrition among various study populations is reported between 20-70% and cachexia in 27-33% of subjects with COPD. Malnourished individuals are exposed to higher risk of mortality, morbidity and poor prognosis by the reduced pulmonary function and risk of infections due to the loss of fat free mass, skeletal muscle strength, lower immune function secondary to malnutrition. Pre-existing oxidative stress can be further worsened by deficits in micronutrient intakes. Anthropometric assessment including fat free mass is important in evaluating nutritional depletion as some COPD patients may lose fat free mass without any alterations in fat mass. Thus, COPD patients can suffer from malnutrition, further aggravated by the severity of symptoms, biochemical alterations and severity of disease. Further, under nutrition can negatively affect the prognosis necessitating a thorough assessment of body composition along with somatic status among patients losing weight and those with a history of weight loss.

Keywords: Cachexia, Fat free mass, Malnutrition, Nutritional depletion, Oxidative stress.

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INTRODUCTION

The Global initiative for chronic obstructive lung disease (GOLD) report defines chronic obstructive pulmonary disease (COPD) as 'a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases'. The limitations are a result of several airway diseases namely obstructive bronchiolitis and emphysema characterized by parenchymal destruction[1]. The inflammation of the cells in the bronchial tubes or the destruction of the alveoli are the major reasons for limitation of the airflow and these conditions are known to co-exist together and include few common clinical manifestations such as reduced sir flow rates, dyspnoea and hypercapnia. Chronic hypoxemia is seen in patients with bronchitis but in patients with emphysema, it is observed in the advanced stage of the disease. The symptoms and its severity are related to the effects of these conditions and vary on from one individual to another [1,2].

Nutritional status and pulmonary function are interdependent. Weight loss and muscle wasting are extra-pulmonary effects of COPD that are caused by deficits in nutrient intake due to anorexia, early satiety, dyspnoea, bloating and fatigue combined with increased energy requirements[2]. Pulmonary inflammation and tissue hypoxia are also known to mediate weight loss. An increase in the levels of leptin and its interaction further with orexigenic and anorexigenic components is suspected to have a role in loss of fat and fat free mass combined with the presence of anorexia[3].

Malnutrition is affirmative in worsening the clinical outcome of these patients. Malnutrition is known to negatively impact the strength and endurance of respiratory muscles, thus causing reductions in lung parenchyma (respiratory bronchioles, alveoli, and capillaries) [2]. Muscle wasting reflects the disorder of nutritional status, which has negative consequences on the skeletal muscle functioning and exercise capacity. Further, wasting is also a determinant of mortality in patients with COPD[4]. Body mass index and fat free mass are validated and accepted as independent predictors of mortality in COPD patients. Higher COPD related mortality rates have been observed in underweight patients and patients with normal weight compared to overweight and obese individuals.

Assessment of nutritional status for the presence and grading of malnutrition by the use of body mass index (BMI) is a widely used approach in nutritional practice. The changes occurring in the body compartments vis., fat free mass and fat mass can be found only through analysis of the body compartments by various techniques such as bioelectrical

impedance analysis, dual energy x-ray absorptiometry etc. The evidence for loss of fat free mass without any changes in the fat mass among weight losing patients with COPD adds more importance to the analysis of body composition[5,6]. The use of fat free mass is also recommended as a systemic marker for disease severity that can be used along with BMI during assessment to detect and define the state of nutritional depletion as 'cachexia', 'semi-starvation' or as 'muscle atrophy'[6].

A bibliographic search of published national and international scientific articles was performed in PubMed and Google Scholar with an objective to review the available literature on COPD depicting presence of malnutrition, the pattern of malnutrition based on somatic and body compositional changes in these patients and the inter relationship between COPD and nutritional status from both randomized controlled trials and non-randomized trials.

Prevalence of COPD

COPD is the third leading cause of mortality in the world in 2012 and World Health Organisation (WHO) estimates 65 million people diagnosed with moderate to severe COPD. COPD was responsible for 5% of deaths in 2005 and total deaths from COPD were projected to increase to 30% by 2015[7]. The wide variations seen in the prevalence of COPD across countries can be due to the differences in the methods of diagnosis and classification of COPD. The prevalence of patients with stage II (moderate) or higher stages of COPD classified as per GOLD criteria globally, is estimated to be 10.1%; 11.8 % in males and 8.5 % in females as reported by a multi centric study involving 22 centres[8]. Prevalence of COPD in adults aged more than 40 years is 9–10% and pooled prevalence estimates for COPD were found to be 4.5%, 8.3%, 12.5% and 10.6% in America, Europe, South East Asia and Western pacific respectively[9]. WHO estimates for age adjusted deaths per lakh and disability adjusted life years (DALY) due to COPD for China, India, Japan, France, USA, UK, and Russian federation which are among the most populous nations in the world[10] are presented in table 1.

The prevalence of COPD in India is varied widely. Several single centre studies across North and South India have estimated the prevalence rates ranging from 2-5% in men and 1-4.5% among women in the study group[11,12]. An overall prevalence of 7.1% has been reported among both the gender groups in selected rural areas in Mysuru city[13]. The Indian study on epidemiology of asthma, respiratory symptoms and chronic bronchitis in adults (INSEARCH) study has reported chronic bronchitis to be prevalent in 3.49% among adults aged more than 35 years and the national burden of chronic bronchitis is estimated at 14.84 million[14].

Table 1: World Health Organisation estimates for Age adjusted deaths per lakh and disability adjusted life years due to COPD

Countries	China	India	Japan	France	United States of America	United Kingdom	Russian federation
Age adjusted deaths/1,00,000	130.5	73.2	4.4	12.0	27.2	23.1	16.2
Disability adjusted life years	622	667	120	270	426	442	242

MALNUTRITION IN COPD – CAUSATIVE FACTORS AND MAGNITUDE

Malnutrition in COPD appears to be multifactorial in aetiology and the two crucial factors that lead to malnutrition are inadequate consumption of food and increased energy expenditure, the latter attributed to the increased effort of breathing. Resting energy expenditure (REE) of patients is known to be elevated to 120% of normal resting metabolic rate. This increase can be due to the hyper metabolism subsequent to an increase in respiratory muscle work, which results in greater demand for oxygen. This demand further stimulates the respiratory muscles to perform increased activity, finally presenting a decreased mechanical efficiency as the condition progresses[15]. Medications used to treat COPD including bronchodilators by their thermogenic effect may also elevate the REE[2]. Malnourished COPD patient's exhibit elevated resting energy expenditure due to enhanced thermic response to nutrients compared to malnourished subjects without COPD suggesting this effect as one of the factors for elevation in energy expenditure[16].

The causative factors for deficits in food intake are difficulty in mastication and swallowing resulting from dyspnoea, cough, hyper secretion and fatigue. On a long term, these can lead to inadequate ingestion of food, consequently leading to weight loss in these patients. Cachexia is frequently diagnosed in patients with COPD. It is associated with reduced functional capacity and increased mortality. The prevalence of cachexia in patients with COPD is reported between 27 - 33 %[17,18]. It has been observed that 10 to 15 per cent of patients with mild to moderate COPD have significant weight loss which increases to 50 per cent in patients with severe COPD[11]. The proportion of patients with malnutrition among the out-patients and hospitalized patients is reported to be 25% and 50% respectively. This figure increases to 70% in COPD patients with acute respiratory failure. Malnutrition specifically undernutrition varies between 20% and 70% among different patient groups with COPD[3,19]. Available Indian studies on evaluation of nutritional status of COPD patients also have reported similar trends. Nutrition assessment using subjective global assessment tool revealed 83% of the 106 hospitalised COPD patients to be malnourished[20]. A case control study on

100 elderly COPD patients and 100 healthy controls aged above 50 years using mini nutrition assessment reported 55% of the subjects with COPD as malnourished, 46% of the malnourished subjects were underweight and 18% of them to be at risk of malnutrition. The mean BMI of disease group (20.67 ± 5.68 kg/m^2) was significantly lower than the control group (23.34 ± 4.7 kg/m^2, p<0.001)[21]. The proportion of muscle mass loss is found to range from 20-35% in clinically stable COPD patients[22].

Cachexia is understood as the end result of low testosterone levels combined with increased pro-inflammatory cytokines such as C-reactive protein (CRP) and increased catecholamine synthesis in COPD. Systemic inflammatory molecules that have been studied in higher details include Tumor necrosis factor-α (TNF- α), Interleukin-1β (IL-1β), Interleukin-6 (IL-6) and C-reactive protein (CRP). Inflammatory mediators have the potential to alter leptin metabolism, thereby contributing to weight loss. Clinically stable patients with weight loss have been evaluated with significantly higher serum TNF - α concentrations compared to patients without weight loss[23]. Reduced forced expiratory volume in one second (FEV_1), decreased respiratory endurance and poor health status have been associated with increases in CRP and IL-6[24]. The Bergen COPD cohort study reported elevation in CRP and soluble tumor necrosis factor receptor-1 among 409 COPD patients[25]. In a case control study on 33 subjects involving 15 subjects (7 male and 8 female subjects) with emphysema and 18 healthy controls (9 male and 9 female subjects), men had a mean BMI of 22 ± 3 kg/m^2 compared to 25 ± 4 kg/m^2 among healthy controls, the mean BMI of female subjects were similar (25 ± 3 vs 25 ± 2 kg/m^2). The lean body mass index was lower in subjects with COPD (Men – 16 ± 3 vs 18 ± 1 kg/m^2; Women -15 ± 2 vs 16 ± 1 kg/m^2). The plasma transthyretin levels also followed a similar trend, (Men – 0.28 ± 0.03 vs 0.35 ± 0.05 g/L; Women -0.28 ± 0.1 vs 0.38 ± 0.08 g/L) and indicate the early stage of malnutrition evident sub-clinically in subjects with COPD[26]. Overall, weight loss in COPD is a result of loss of lean body mass, fat free mass or both resulting from increase in resting metabolic rate accompanied by decreased food intake owing to hypoxia, hyperinflation etc, effect of inflammatory cytokines, reduced activities of enzymes involved in muscle oxidative metabolism and long term corticosteroid use .

Can malnutrition worsen the scenario?

The alterations in the basal metabolism as a result of nutrient deficiencies further may deteriorate the disease status. Evaluation of REE in stable COPD patients revealed significantly higher REE in patients experiencing >10% of weight loss (n=34) in the past six months compared to weight stable COPD patients (n=34)[27]. A state of malnutrition in COPD patients can lead to decreased lung elasticity, pulmonary function as well as respiratory

muscle mass, force and resistance. Studies on body composition have shown that weight loss accompanied by significant loss of fat-free mass or muscle mass is the primary factor responsible for impaired skeletal muscle strength and exercise capacity[28]. A low BMI has been proven to be an independent indicator of poor prognosis in these patients. Supporting data on marked prognostic influence of muscle mass on mortality has necessitated the assessment of body composition along with other anthropometric indicators in identifying and malnutrition in patients with COPD[29].

Malnutrition leads to decreased oxygen carrying capacity, pulmonary edema, compromised surfactant function, decreased synthesis of collagen. Atrophy of the lymphoid tissues resulting from malnutrition leads to reduction in the number of T-lymphocytes, lymphokines and monokines. Inadequate removal of respiratory secretions, alveolar collapse secondary to reduction in tidal volume due to malnutrition can increase the risk of pulmonary infections in these patients[30].

In addition to smoking, vitamin D deficiency, low body mass index (BMI), hypogonadism, and decreased mobility with disease progression and chronic use of corticosteroids may lead to the development of osteoporosis. Osteopenia is reported in 35-72% and osteoporosis in 36-60% of patients with stable COPD patients[31]. Prevalence of vitamin D deficiency ranges between 33-77% percent and the deficiency is known to increase with progression of disease[32]. Vitamin D deficiency is also associated with prevalence of osteoporosis and decreased skeletal muscle strength in these patients[33]. Among 158 subjects with COPD, 30.3% have been reported with serum phosphorus levels less than 2.5 mg/dl. A higher magnitude of deficiency was observed in patients taking more than one drug for COPD management known to have a negative effect on renal handling of phosphorus, suggesting the possibility of phosphorus deficiency in patients with COPD[34].

COPD is characterised by increased oxidant burden owing to an imbalance in oxidant and antioxidant balance as a result of the causative factors and impaired antioxidant defence mechanism secondary to a state of malnutrition. Significantly lower mean serum vitamin C and higher malondialdehyde (MDA) levels have been observed in 50 COPD subjects (Vitamin C- 0.54 ± 0.12 mg/dl; MDA- 5.43 ± 0.74nmol/ml) compared to 50 healthy controls (Vitamin C -1.09 ± 0.16 mg/dl; MDA-2.64 ± 0.52 nmol/ml)[35]. Similarly, observations of lower plasma concentrations of vitamins A, C, and E; α- and β-carotene; total carotenoids and higher levels of endogenous and hydrogen peroxide induced white blood cell DNA damage is reported in 34 COPD patients as compared to healthy controls. The dietary intake of the assessed micronutrients were lower in the COPD group[36]. In a cross sectional study on 73 subjects, among whom 41 subjects had moderate COPD (n=41) and 32 subjects had mild

COPD. Significantly lower serum levels of catalase (8.95 ± 0.06 vs 8.88 ± 0.07 units/mg serum protein, p<0.01), superoxide dismutase (9.19 ± 0.09 vs 8.95 ± 0.08 units/mg serum protein, p<0.01) and glutathione peroxidase (54.32 ± 0.38 vs 52.95 ± 0.32 units/mg serum protein, p<0.01) were found in the subjects with moderate COPD compared to mild COPD. The serum concentration of MDA was inversely correlated to these enzymes[37]. These studies show that COPD patients have a deranged oxidant: antioxidant balance. Malnutrition, further can worsen the scenario by hindering the required action of antioxidants in the body by causing a deficiency of nutrients required for cellular antioxidant synthesis.

Evidence for Alterations In Somatic Status and Body Composition

The direct impact of malnutrition and increased REE makes these patients more prone to negative changes in body compartments such as loss of lean body mass and fat mass. Patients with COPD are at risk of loss of fat free mass (FFM) even with a normal BMI at the time of diagnosis. Muscle wasting, defined as a fat-free mass index (FFMI) <16 kg/m^2 (in males) and <15 kg/m^2 (in females)[38]. The BMI and FFMI levels together can be used to categorize the state of nutritional depletion as defined by Schols as 'No impairment (BMI ≥ 21 kg/m^2 and FFMI ≥16 kg/m^2), 'Semistarvation' (BMI < 21 kg/m^2 and FFMI ≥16 kg/m^2), 'Muscle atrophy' (BMI ≥ 21 kg/m^2 and FFMI <16 kg/m^2) and as 'Cachexia' (BMI < 21 kg/m^2 and FFMI <16 kg/m^2)[6]. In a multi-centre study on 389 out patients with moderate to severe COPD, 27% were found to have evidence of nutritional depletion, 15% had muscle atrophy and 11% had cachexia. The prevalence of low BMI as well as low FFMI was significantly higher in female than in male COPD patients, 18% and 40% vs. 10% and 20%, respectively (P<0.01)[17]. A cohort study on random population sample of 1898 subjects with COPD, 26.1% had low fat free mass index values (Less than 10th percentile value)[5]. Screening of 106 hospitalised COPD patients for nutritional status showed 59.5% of them to be moderately malnourished and 23.5% as severely malnourished based on classification by the patient generated subjective global assessment tool (PGSGA)[20]. Lower mean BMI 19.38 ± 3.10 kg/m^2) and MUAC (21.18 ± 2.31 cm) values were observed in 100% (83) of subjects with COPD who were evaluated on admission to hospital for management of exacerbation. Another cohort study on COPD patients (n=25) hospitalized for management of exacerbation found below normal mean values of BMI (19.1±3.1 kg/m^2), mid arm circumference (23.8 ± 3.91 cm) and triceps skin fold thickness (7.65 ± 3.92 mm). 15 patients, who had BMI <20 kg/m^2 had a significant longer duration of hospital stay suggesting nutritional status to be an important predictor of treatment outcome in hospitalised COPD patients[39]. Presence of low BMI (<20 kg/m^2) and on-going weight loss are considered to be independent risk factors that can lead to occurrence of an exacerbation in subjects with COPD[40].

Patients with emphysema are known to have more prominent signs of malnutrition than patients with bronchitis. In a cross sectional study on 18 subjects, significantly lower somatic status was found in emphysematous patients compared to patients with chronic bronchitis, while the emphysematous group exhibited lower values for percentage of ideal body weight (88 ± 15.1 vs 124 ± 13.2 %), arm muscle circumference (91±0.09 vs 125 ± 0.37 cm), triceps skin fold (85 ± 0.45 vs 168 ± 0.69 mm) and mean creatinine height index value (80 ± 29.58 vs 112 ± 32.2). A strong correlation was found between forced expiratory volume in 1 second and low somatic status (r=0.699) in the emphysematous group[41]. BMI was found to be significantly lower in 81 subjects (20.2 ± 2.8 kg/m^2, $P<0.05$) with emphysema dominant phenotype compared to 21 subjects (23 ± 2.6 kg/m^2) with airway dominant phenotype, suggesting different effect on nutritional status between the two phenotypes and association of low BMI with the presence of emphysema[42].

These studies indicate that alterations in BMI alone cannot define the nature and extent of negative changes in the nutritional status of patients with COPD. Analysis of fat free mass and combined analyses of BMI and FFM can be beneficial to get an insight into the state of nutritional depletion.

CONCLUSION

The loss of body weight and muscle mass in COPD patients places them at an increased risk of morbidity and mortality compared to normally nourished or weight stable patients. Malnutrition is one of the extra-pulmonary complications of COPD and development of malnutrition chiefly undernutrition can worsen the prognosis of the disease. This effect is more pronounced in weight losing patients compared to patients with stable weight. Nutritional depletion is evident in a considerable fraction of the diseased population characterised by the loss of both fat free mass and fat mass or fat free mass alone. The degree of malnutrition is more pronounced in emphysematous patients and patients who have a low BMI have changes in biochemical markers such as plasma transthyretin that indicate early stage of malnutrition. Malnutrition can further worsen lung function, respiratory muscle function, oxidative stress and impair immune function. Assessment of body compartments apart from the usual somatic status indicators and BMI is useful in determining the impact of disease on the fat free mass as it is also accepted as a determinant of prognosis of the disease.

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