



Malnutrition in chronic obstructive pulmonary disease^{1,2}

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Loss of body cell mass is a common and serious problem for patients with end-stage chronic obstructive pulmonary disease (COPD), especially those with emphysema. COPD patients with emphysema have lower body mass indexes and greater depletion of lean body mass than do COPD patients with chronic bronchitis (1). Nonetheless, skeletal muscle weakness is associated with wasting of extremity fat-free mass (FFM) in COPD patients, independent of airflow obstruction and COPD subtype (2). Indeed, body weight and body mass index are independent risk factors for mortality in COPD patients (3, 4). Not only are COPD patients often malnourished on hospital admission but many are subject to further decline during hospitalization.

Poor nutritional status in COPD patients has been related to adverse effects that may contribute to complications and increased mortality. Patients with low body weights have greater gas trapping, lower diffusing capacity, and less exercise capacity than do persons with similar respiratory mechanics but normal body weights. Loss of body cell mass is associated with a reduction in the mass of the diaphragm and of the respiratory muscles, resulting in declines in strength and endurance. A malnutrition-related decline in immune status may further blunt airway defenses. These effects can contribute to undesirable clinical sequelae that include hypercapnic respiratory failure, difficulty with weaning from mechanical ventilation, and nosocomial lung infections.

Although astute clinicians have long recognized that weight loss portends an ominous prognosis for patients with COPD, there has been little investigation of the underlying mechanisms of malnutrition in this setting. A variety of contributing factors have been proposed and it is likely that more than one factor is often at play. Disturbances in energy balance may reflect both the mechanical inefficiency of breathing and the reduced dietary energy intakes of these patients. In COPD patients, resting energy expenditure (REE) has been reported to be 15–20% above predicted values and the increased energy required for breathing has been suspected to account for the difference. Under controlled chamber conditions, the basal metabolic rate was found to be elevated in patients with stable COPD even though the daily total energy expenditure (TEE) was normal (5). It appeared as though the patients compensated by reducing their level of spontaneous physical activity and related energy expenditure. In contrast, independent of resting metabolic rate, the TEE was elevated in COPD patients as measured by the doubly labeled water method (6).

Complex changes in metabolism are ultimately the result of inflammation, hypoxia, hypercapnia, nutritional deprivation, and pharmacologic therapy. Stressors like nosocomial infection may exacerbate the situation by promoting hypermetabolism. Muscle

proteolysis in the setting of systemic inflammatory responses appears likely in deteriorating patients. The ubiquitin-proteasome pathway is activated in catabolic states to accelerate the breakdown of muscle proteins. Cytokine-mediated cachexia, similar to other end-stage organ failure syndromes, is possible in COPD patients. Elevated concentrations of soluble tumor necrosis factor receptors and acute phase proteins have been observed (7) and anorexia and decreased dietary intakes are common. Steroid therapy may further stimulate proteolysis and promote gluconeogenesis through inhibition of both protein synthesis and the transport of amino acids into muscle.

One might think that there would be abundant data to support the efficacy of nutritional interventions for COPD patients but this is not the case. Although modest improvements in respiratory and limb muscle functions have been reported with nutritional repletion of ambulatory COPD patients, a recent meta-analysis of 9 randomized controlled intervention trials found that nutritional support had no effect on anthropometric measures, lung function, or functional exercise capacity among patients with stable COPD (8). A recent nutritional intervention trial found improvements in body weight and respiratory muscle strength in some COPD patients (3). Weight gain was a significant predictor of survival, but there were many nonresponders. Another study characterized the nonresponse to nutritional intervention among COPD patients as being related to aging, anorexia, and systemic inflammatory response (9).

In this issue of the Journal, Engelen et al (10) present an informative study of amino acid profiles in the quadriceps femoris muscle and arterial plasma of patients with COPD ($n = 28$) and of healthy, age-matched control subjects ($n = 28$). Of particular interest is the differentiation between the COPD patients with (Emph+; $n = 14$) and without (Emph-; $n = 14$) emphysema on the basis of macroscopic evidence of lung parenchyma destruction by high-resolution computed tomography. Low concentrations of plasma branched-chain amino acids were observed in COPD patients, which was attributed to a decline in leucine. The muscle-to-plasma leucine gradient was also elevated in COPD patients, as were plasma insulin concentrations. Additionally, concentrations of most amino acids in muscle were lower in the EMPH+ group than in the EMPH- group. Muscle glutamine was higher in EMPH- patients than in either the

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EMPH+ or the control subjects. REE measured by open-circuit indirect calorimetry, FFM measured by dual-energy X-ray absorptiometry, and REE:FFM were lower in the EMPH+ than in the EMPH- patients. Engelen et al suggested that alterations in leucine metabolism occur in patients with COPD and that there were striking differences in muscle amino acids between those with and without parenchymal destruction.

These findings indicate the need to carefully characterize the subtype of COPD when studying amino acid metabolism. Variation in the degree of parenchymal destruction may account for previously conflicting findings. Patients with severe parenchymal destruction tend to be the most malnourished and the least responsive to nutritional intervention. It is likely that COPD patients with macroscopic emphysema manifest the sequelae of both the inflammatory process and semistarvation. The result may be a combination of alterations in intermediary metabolism and negative energy balance that culminate in loss of body cell mass.

Engelen et al appropriately highlight the need for further investigation of several key observations.

- 1) Inflammatory response is known to promote a decline in plasma branched-chain amino acids. What effect might cytokines have on leucine flux?
- 2) High postabsorptive insulin concentrations were found in both COPD subtypes (Emph+ and Emph-). What role does hyperinsulinemia play in reduced plasma leucine concentrations?
- 3) Muscle glutamine concentrations decline during many states of inflammation and injury. What accounts for the higher muscle glutamine concentrations observed in the Emph- than in the Emph+ patients?

Better understanding of the mechanisms leading to malnutrition in COPD patients should guide the development of improved interventions and help clinicians learn who should be targeted. By the time weight loss occurs in patients with end-stage emphysema, there is often little benefit of currently available nutritional support modalities. Can subjects at risk for malnutrition be identified early in the course of inflammatory responses before loss of body cell mass occurs? There is a need to develop novel inter-

ventions to augment nutritional support. Possible interventions include the use of anticytokines to blunt inflammatory responses and trophic agents to facilitate the accrual of muscle mass. 

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