Systemic Effects in COPD*

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The pathogenesis and clinical manifestations of COPD are not restricted to pulmonary inflammation and structural remodeling. Rather, this disorder is associated with clinically significant systemic alterations in biochemistry and organ function. The systemic aspects of COPD include oxidative stress and altered circulating levels of inflammatory mediators and acute-phase proteins. Indeed, an impaired endogenous oxidant-antioxidant balance has been reported in patients experiencing exacerbations of COPD, and others have observed altered circulating levels of several cytokines and adhesion molecules in patients with stable disease. As in other chronic inflammatory conditions, weight loss, muscle wasting, and tissue depletion are commonly seen in COPD patients. Selective wasting of fat-free mass coupled with impaired respiratory and peripheral muscle function and a reduced capacity for exercise occur in COPD patients. Indeed, weight loss may directly impact poor prognosis in COPD patients. The mechanisms underlying weight loss and muscle wasting are incompletely understood but likely involve an imbalance in ongoing processes of protein degradation and replacement. This may include alterations in the relative levels or activities of endocrine hormones such as insulin, growth hormone, testosterone, and glucocorticoids. Furthermore, chronic systemic inflammation involving cytokines such as interleukin-1 and tumor necrosis factor-α may be associated with these hormonal changes and muscle wasting in COPD patients. This review includes a discussion of the mechanisms of skeletal muscle fiber protein metabolism/catabolism, the potential roles of endogenous cytokines in protein loss, and the possibility that novel drugs that inhibit cytokine signaling may provide benefits by reducing muscle wasting and cachexia, thereby improving the prognosis and quality of life among COPD patients.

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Abbreviations: BCM = body cell mass; BMI = body mass index; FFM = fat-free mass; GH = growth hormone; IFN = interferon; IGF = insulin-like growth factor; NF-κB = nuclear factor-κB; sICAM = soluble intercellular adhesion molecule; TNF = tumor necrosis factor

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COPD is a disease state characterized by airflow limitation that is not fully reversible. This airflow limitation usually is both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. This largely pathophysiologic definition does not reflect insights into the cellular mechanisms of this heterogeneous disease, encompassing chronic obstructive bronchitis and emphysema.

Based on the generally accepted management goals for COPD patients (ie, improvement in quality of life and in functional status in the absence of progression of the disease) and the limited outcomes that are possible with present pharmacologic treatments, which are directed to improve airflow limitation to achieve these management goals, there is at present a revival of research on the mechanisms of COPD, not limited to the local organ involvement but extending to the patient as a whole. The latter mechanisms are generally considered to be the systemic effects of the disease. Systemic effects of disease processes such as COPD are generally approached by an assessment of changes in a variety of circulatory mediators. More strictly, the systemic effects of a disease condition like COPD have to be considered, such as those structural or biochemical alterations in the nonpulmonary structures or organs related to primary disease characteristics.

Systemic Manifestations of COPD

Many COPD-related articles have reported changes in levels of oxidative stress, circulating cytokines, and acute-phase response proteins or in the activation levels of circulating cells. An imbalance between oxidants and antioxidants is widely hypothesized as being the pathogenesis of COPD. Reactive oxygen species, which are generated by neutrophils, whether circulating or sequestered in the pulmonary vasculature, are scavenged by blood antioxidants and antioxidant enzymes, indicating that the ability of an individual to prevent the injurious effects of oxidative stress depends on the antioxidant capacity of the blood and the tissues. At least in smokers and during acute exacerbations of COPD, a marked oxidant-antioxidant imbalance could be demonstrated. Other studies have reported increased circulating levels of a variety of cytokine mediators even under conditions of stable disease. Others have investigated the expression of adhesion molecules in circulating neutrophils and endothelial cells in COPD patients. Compared with control subjects, stable patients with disease showed an increased expression of Mac-1 (CD11b/CD18) in circulating neutrophils with lower levels of soluble intercellular adhesion molecule (sICAM)-1. Increased sICAM-1 levels were reported by other investigators. Plasma levels of sICAM-1 in these studies are considered to be a surrogate of its expression on the endothelium. Even the expression of two G-protein subunits in circulating neutrophils has been studied. Ga subunits are key proteins in the activation and adhesion of human neutrophils to tissues. In one study, it was demonstrated that the expression of one Ga protein subunit, Gas, was down-regulated irrespective of the clinical condition of the patient. However, the pathogenic implications of most of these findings remain unclear.

Further-
more, these findings need confirmation in well-characterized patient groups and in different phases of the disease process.

**Body Cell Mass Alterations in COPD**

Wasting is a generally occurring manifestation in a wide variety of different chronic conditions and can be considered to be an important systemic manifestation as a loss of > 40% of actively metabolizing tissue is incompatible with life. The body cell mass (BCM) represents the actively metabolizing (organs) and contracting (muscles) tissue. This BCM cannot be measured directly. Changes in BCM can be clinically recognized by weight loss in general and by loss in fat-free mass (FFM) in particular. FFM can be subdivided into the intracellular compartment or BCM, which represents the energy-exchanging part, and the extracellular compartment, which represents substances outside the cells. Tissue depletion occurs commonly in COPD patients, its prevalence increasing from 20% in clinically stable outpatients up to 35% in patients who are eligible for pulmonary rehabilitation. In addition, the selective wasting of FFM, despite relative preservation of fat mass, has been reported in COPD patients. Loss of FFM adversely affects respiratory and peripheral muscle function, exercise capacity, and health status. In addition, several reports have provided evidence that weight loss negatively affects prognosis in COPD. In a retrospective study of 400 patients with COPD, Schols et al demonstrated that low body mass index (BMI), age, and low PaO₂ were significant independent predictors of increased mortality rates. After stratification of the group into BMI quintiles, a threshold value of 25 kg/m² was identified below which the mortality risk was clearly increased.

A subsequent study by Landbo et al prospectively examined whether BMI was an independent predictor of mortality in subjects with COPD from the Copenhagen City Heart Study.

An imbalance in the continuously ongoing process of protein degradation and replacement can be hypothesized as a mechanism contributing to this wasting condition. Limited data are available to date about overall body protein synthesis and breakdown in COPD patients. At least in nondepleted COPD patients who were assessed under stable conditions, a balanced increase in protein breakdown and synthesis has been demonstrated. Especially in acute exacerbations, a disturbance in this tightly regulated equilibrium can be hypothesized. Hormonal changes are closely linked to overall protein turnover. Insulin, growth hormone (GH), insulin-like growth factors (IGFs), and anabolic hormones favor protein synthesis, while glucocorticoids stimulate proteolysis, especially in muscle tissue. In the absence of fasting, insulin normally suppresses the breakdown of protein. GH also increases FFM and generates a positive nitrogen balance as well as a depletion of fat mass. The activity of GH is mediated by a receptor that is expressed at high levels on liver cells but also on muscle and fat cells. GH stimulates the liver production and secretion of IGF-1, which circulates in plasma bound to IGF-1-binding proteins 1, 2, and 3. IGF-1 regulates GH release but is also sensitive to nutritional and metabolic changes. In starvation and anorexia, the IGF-1 levels are low, thereby stimulating the release of GH. Circulating IGF-1 levels are used as a marker of GH action because IGF-1 has a longer half-life than GH, and its concentration integrates the pulsatile release of GH.

Evidence is present in the literature to suggest a GH resistance under conditions of catabolism, as occurs in inflammation. Fasting and catabolic states are associated with reduced GH receptor binding, reduced IGF-1 gene expression, and low levels of IGF-1-binding proteins. The changes in IGF-1 during catabolism may be explained either as an adaptive mechanism to facilitate the reduction of anabolism at a time of stress or by the fact that IGF-1 levels in tissue are increased but circulating levels of IGF-1 are reduced to counteract the catabolic effects at tissue level. The association between inflammation and hormonal changes also has been supported by data from studies in vivo and in vitro. The infusion of interleukin-1 and tumor necrosis factor (TNF)-α in animals is associated with low plasma levels of IGF-1 and reduced protein synthesis. Others have reported that protein synthesis in myoblasts is stimulated in a dose-dependent manner by exposure to IGF-1. However, this IGF-1-stimulated protein synthesis is inhibited in a dose-dependent fashion when these myoblasts are exposed to TNF-α.

Endocrine changes in COPD patients are poorly documented. Most attention has focused on decreased levels of anabolic hormones as aggravating factors in the failing anabolic response. Anabolic hormones like testosterone act on muscle tissue via the following two pathways: (1) by inducing protein anabolic effects mediated by the androgen receptor; and (2) by inhibition of the protein catabolic processes via neutralizing the effects of endogenous glucocorticoids. The effects of testosterone on muscle tissue, which are mediated by the androgen receptor, can be attributed to increases in the fractional synthesis rates of actin and myosin heavy chains via somatomedin, resulting in fiber hypertrophy. Evidence for decreased levels of total and free testosterone has been reported in the literature. Furthermore, despite the complete absence of evidence-based data, the administration of low-dose systemic glucocorticoids as maintenance anti-inflammatory medication is still common practice in a substantial number of patients. Systematic analysis of the endocrine anabolic and catabolic balance in COPD is required in order to establish adequate intervention strategies.

**Muscle Protein Degradation in Muscle Wasting**

In response to stimuli such as acidosis or infection or in states of inadequate caloric intake, it is a general finding that the overall breakdown of cell proteins, especially in muscles, increases to provide the essential amino acids required for protein synthesis and energy metabolism. During these conditions, the muscles and probably the skin preferentially lose proteins, while visceral organs lose little or no protein and the brain is unaffected. The preferential loss of skeletal muscles, especially in the lower
extremities in patients with COPD, has been confirmed in different studies. Gosker et al\textsuperscript{22} recently demonstrated a strong correlation between FFM and mean fiber cross-sectional area in biopsy specimens from the vastus lateralis muscle. Within fiber type categories, only the mean cross-sectional areas of IIA/IIX and IIX fiber types were reduced compared to those in control subjects.\textsuperscript{22} Predominant fiber type II atrophy has been found in such different medical conditions as anorexia nervosa, chronic heart failure, AIDS, and chronic renal failure.\textsuperscript{23–25} The depletion of FFM seems largely related to the level of systemic inflammation, as has been reported in different studies.\textsuperscript{3,26,27} Some evidence from studies in incubated muscles and muscle extracts has suggested that the adenine triphosphate-dependent ubiquitin-proteasome pathway is responsible for most of the increased proteolysis in various types of muscle atrophy.\textsuperscript{28,29} However, it remains unclear how most muscle proteins are ubiquitinated and degraded. Furthermore, variations in the underlying mechanisms leading to muscle atrophy need to be explored, particularly the rate or order of degradation of individual muscle proteins and the differences in activation of ubiquitination enzymes by different catabolic stimuli.\textsuperscript{29}

Li et al\textsuperscript{30} have reported direct effects of TNF-\(\alpha\) on differentiated skeletal muscle cells. They demonstrated that TNF-\(\alpha\) treatment of differentiated myotubes stimulated time-dependent and concentration-dependent reductions in total protein content and a loss of adult myosin heavy chain content. These changes were evident at TNF-\(\alpha\) concentrations that were similar to those measured in the circulation of COPD patients. The TNF-\(\alpha\) signal was transduced in part by the activation of nuclear factor-\(\kappa\)B (NF-\(\kappa\)B), a process that involves ubiquitin conjugation and proteasomal degradation of I-\(\kappa\)B\(\alpha\). The authors demonstrated that TNF-\(\alpha\) stimulates ubiquitin conjugation to muscle proteins, suggesting that an existing ubiquitin pool is activated rather than the synthesis of new proteins. Furthermore, they found that proteasome inhibitors completely prevented this NF-\(\kappa\)B translocation, indicating that ubiquitin-proteasome interactions are obligatory for TNF-\(\alpha\)/NF-\(\kappa\)B signaling in skeletal muscle.

In addition to disturbances in the energy or anabolism-catabolism balance, muscle wasting may be a result of a decrease in the number of fibers or of changes in the regulation of skeletal muscle differentiation. The vertebrate skeletal muscle differentiation is under the strict control of the myogenic basic helix-loop-helix transcription factor family (ie, MyoD, myf5, myogenic, and MRF4) and of a second class of transcription factors termed myocyte enhancer factor-2 (MEF2A through MEF2D). MyoD is expressed in proliferating undifferentiated myoblasts and, on growth factor withdrawal, is activated to initiate skeletal muscle differentiation, ultimately leading to the fusion of myoblasts into multinucleated myotubes. MyoD therefore is essential for the repair of damaged tissue.\textsuperscript{31} Guttridge et al\textsuperscript{32} have demonstrated that in differentiating myocytes TNF-\(\alpha\)-induced activation of NF-\(\kappa\)B caused the inhibition of skeletal muscle differentiation by suppressing MyoD messenger RNA at the post-transcriptional level. Thus, TNF-\(\alpha\) caused a severe reduction in MyoD protein levels in these cells, and this rapid loss of MyoD protein was preceded by an equally rapid loss of MyoD messenger RNA.\textsuperscript{32} In contrast, in differentiated myotubes TNF-\(\alpha\) plus interferon (IFN)-\(\gamma\) signaling was required for the NF-\(\kappa\)B-dependent down-regulation of MyoD and dysfunction of skeletal muscle fibers. MyoD messenger RNA also was down-regulated by TNF-\(\alpha\) and IFN-\(\gamma\) expression in mouse cells in vitro. So, it seems that TNF-\(\alpha\) and IFN-\(\gamma\) are likely to affect skeletal muscle regulation during the following two phases: (1) by the inhibition of the formation of new myofibers; and (2) by the degeneration of newly formed myotubes and by the inability to repair damaged skeletal muscle.

Recently, Langen et al\textsuperscript{33} evaluated the effects of inflammatory cytokines, TNF-\(\alpha\) and interleukin-1\(\beta\), on myocytes. They reported that the TNF-\(\alpha\)-induced NF-\(\kappa\)B activation interfered with the expression of muscle proteins in differentiating myoblasts, with the activity of muscle creatine kinase and myosin heavy chain abundance decreasing markedly following 72 h of exposure to TNF-\(\alpha\). Thus, a causal link between NF-\(\kappa\)B activation and the inhibition of myogenic differentiation could be demonstrated clearly.

Based on the present findings, it can be hypothesized that inflammatory cytokines may contribute to muscle wasting through the inhibition of myogenic differentiation via a NF-\(\kappa\)B-dependent pathway, and that the direct inhibition of NF-\(\kappa\)B with novel therapies may prove beneficial in reducing the muscle wasting associated with cachexia. Present findings need to be supported by human data in vitro.

Programmed cell death, or apoptosis, can be another mechanism contributing to a reduction in muscle cells. Further studies are needed to unravel the complexity of muscle wasting in chronic inflammatory diseases or COPD. In addition, the unraveling of the molecular mechanisms underlying this wasting process may offer new intervention strategies in order to improve functionality as well as quality of life in patients with COPD and other wasting diseases.

**REFERENCES**


