Chronic obstructive pulmonary disease (COPD) affects various structural and functional domains in the lungs. It also has significant extrapulmonary effects, the so-called systemic effects of COPD. Weight loss, nutritional abnormalities, and skeletal muscle dysfunction are well-recognized systemic effects of COPD. Other less well-known but potentially important systemic effects include an increased risk of cardiovascular disease and several neurologic and skeletal defects. The mechanisms underlying these systemic effects are unclear, but they are probably interrelated and multifactorial, including inactivity, systemic inflammation, tissue hypoxia and oxidative stress among others. These systemic effects add to the respiratory morbidity produced by the underlying pulmonary disease and should be considered in the clinical assessment as well as the treatment of affected patients.

**Keywords:** extrapulmonary effects; multicomponent disease; oxidative stress; tissue hypoxia

Chronic obstructive pulmonary disease (COPD) affects various domains of lung structure and function, leading to airflow limitation (1). Besides these pulmonary abnormalities, COPD is also associated with significant effects in distant organs outside the lungs, the so-called systemic effects of COPD (2, 3). This article reviews the types, mechanisms, and clinical implications of these systemic effects. Understanding that COPD is more than a lung disease may open up new opportunities for the clinical management of this devastating condition.

**TYPES AND MECHANISMS**

Table 1 lists the systemic effects of COPD that have been best described to date. Although the mechanisms underlying these systemic effects are unclear, probably multiple, and likely interrelated, systemic inflammation, tissue hypoxia, oxidative stress, and sedentarism are the most relevant (Table 2).

**Nutritional Abnormalities and Weight Loss**

Nutritional abnormalities, including alterations in caloric intake, basal metabolic rate, intermediate metabolism, and body composition, are common in COPD (4). Unexplained weight loss occurs in about 50% of patients with severe COPD and chronic respiratory failure, but it can also be seen in about 10 to 15% of patients with mild to moderate disease (5). Loss of skeletal muscle mass is the main cause of weight loss in COPD, with loss of fat mass contributing to a lesser extent (4). Importantly, however, alterations in body composition can occur in COPD in the absence of clinically significant weight loss (4).

It is unlikely that these abnormalities are due to decreased caloric intake, which does not appear to be prominent in these patients except during episodes of exacerbation of the disease. In contrast, most patients with COPD have an increased basal metabolic rate, which often results in weight loss (4). This increased metabolic rate can, in turn, be due to several different mechanisms, including the increased work of breathing that characterizes the disease (4), drugs that are commonly used in the treatment of COPD (such as β2 agonists) (6), systemic inflammation (see below, Skeletal Muscle Dysfunction) (7), and/or tissue hypoxia (8).

**Skeletal Muscle Dysfunction**

Skeletal muscle dysfunction is common in patients with COPD (9). It is characterized by specific anatomic changes (e.g., fiber-type composition and atrophy) and functional changes (e.g., strength, endurance, and enzyme activities) and contributes significantly to limited exercise capacity and reduced quality of life (9). The respiratory muscles, in particular the diaphragm, appear to behave quite differently from skeletal muscles in patients with COPD, from both the structural and functional points of view (2, 9). The difference is probably due to the different conditions under which both work in these patients. The skeletal muscles are generally underused, whereas the diaphragm is constantly working against an increased load (10, 11).

The mechanisms of skeletal muscle dysfunction are unclear. Sedentarism, tissue hypoxia, and systemic inflammation are likely to be relevant pathogenic factors. The last of these has been the subject of intense research because cytokines, such as tumor necrosis factor (TNF)-α, and oxidative and nitrosative stress can contribute to protein inactivation and degradation, resulting in dysfunction, atrophy, and apoptosis (12–14). We now know that patients with COPD show increased levels of several circulating cytokines and acute-phase reactants including interleukins 6 and 8, TNF-α, TNF receptors 55 and 75, C-reactive protein, lipopolysaccharide-binding protein, Fas, and Fas ligand (3), as well as evidence of systemic oxidative stress (15, 16). In fact, circulating inflammatory cells appear to be “activated” in patients with COPD. Thus, peripheral blood neutrophils harvested from patients with COPD show enhanced chemotaxis and extracellular proteolysis (17), produce more reactive oxygen species (18), and have enhanced expression of several surface adhesion molecules, particularly Mac-1 (CD11b) (19). Interestingly, Mac-1 upregulation persists during the process of neutrophil apoptosis in vitro (20). This may interfere with the normal process of neutrophil clearance from inflamed tissues by macrophages.

Other circulating inflammatory cells are also abnormal in COPD. Sauleda and colleagues reported higher activity of cytochrome oxidase, the terminal enzyme in the mitochondrial electron transport chain, in circulating lymphocytes in COPD and also in patients with asthma and chronic arthritis (21). Therefore, elevated cytochrome oxidase activity suggests that it may be a nonspecific marker of lymphocyte activation in chronic inflammatory diseases (20).

The origin of this systemic inflammation in COPD is unclear. Apart from smoking itself (22), inflamed pulmonary parenchyma...
Other potential systemic effects
- Cardiovascular effects
- Nervous system effects
- Skeletal effects
- Bone marrow effects

Adapted from Agustí and coworkers (2).

**TABLE 1. SYSTEMIC EFFECTS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

<table>
<thead>
<tr>
<th>Nutritional abnormalities and weight loss</th>
</tr>
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<tbody>
<tr>
<td>• Increased resting energy expenditure</td>
</tr>
<tr>
<td>• Abnormal body composition</td>
</tr>
<tr>
<td>• Abnormal amino acid metabolism</td>
</tr>
<tr>
<td>Skeletal muscle dysfunction</td>
</tr>
<tr>
<td>• Loss of muscle mass</td>
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<tr>
<td>• Abnormal structure/function</td>
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**TABLE 2. POTENTIAL MECHANISMS OF THE SYSTEMIC EFFECTS DESCRIBED IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

<table>
<thead>
<tr>
<th>Related to COPD itself</th>
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<tbody>
<tr>
<td>• Spillover of pulmonary inflammation/activation of inflammatory cells in the lungs</td>
</tr>
<tr>
<td>• Tissue hypoxia (reoxygenation? pH? PaCO2?)</td>
</tr>
<tr>
<td>• Sedentarism/inactivity due to dyspnea on exertion</td>
</tr>
</tbody>
</table>

Related to the cause(s) of COPD
- Smoking
- Genetic characteristics of the host
Other, as yet unidentified

limited exercise capacity (and muscle function) of these individuals. Finally, the prevalence of osteoporosis is increased in patients with COPD (34, 35). Because proinflammatory cytokines can alter bone metabolism significantly, excessive osteoporosis in relation to age could also be considered a systemic effect of COPD (36).

**CLINICAL RELEVANCE AND THERAPEUTIC OPTIONS**

The systemic effects reviewed above are likely to have a profound clinical impact on the management of COPD. First, weight loss and skeletal muscle dysfunction clearly limit the exercise capacity of these patients and, therefore, have a direct negative effect on their quality of life. Second, weight loss is a prognostic factor in patients with COPD that, importantly, is independent of other prognostic indicators, such as FEV1 or PaO2, that assess the degree of pulmonary dysfunction (37, 38). In this regard, Schols and colleagues showed that prognosis improved in patients with COPD if body weight could be regained, despite the absence of changes in lung function (37). Thus, weight loss identifies a new systemic domain of COPD not considered by the traditional measures of lung function (39).

These observations indicate, therefore, that in addition to the severity of lung disease, the clinical assessment of patients with COPD should take into consideration the extrapulmonary consequences of COPD, with weight loss being a critical indicator. This new approach underlies the creation of the BODE Index (body mass index [B], the degree of airflow obstruction [O] and functional dyspnea [D], and exercise capacity [E] as assessed by the 6-minute walking test), which has been shown to be better than FEV1 at predicting the risk of all-cause death and the risk of death from respiratory causes among patients with COPD (39). This multidimensional approach has now been formally recognized in the new COPD guidelines by the American Thoracic Society and the European Respiratory Society (1).

Because the pathogenesis of these systemic effects of COPD is still not well understood, we lack specific therapies for them. However, some recommendations can be made from what is known at present, and some predictions can be anticipated. First, because sedentarism (due to shortness of breath) and tissue hypoxia can play a relevant pathogenic role, it is clear that the minimization of these two consequences of COPD may have a beneficial effect on these systemic effects. In this regard, optimal drug therapy in combination with physical rehabilitation and domiciliary oxygen therapy (when needed) seems advisable (1, 39). Second, because systemic inflammation is likely to play a significant pathogenic role in many of the systemic effects described so far, particularly regarding skeletal muscle dysfunction and cardiovascular disease, appropriate systemic antiinflammatory therapy may also prove helpful. In this context, two reports are worth noting. The first (40), by Sin and coworkers, showed that withdrawal of inhaled corticosteroids increased systemic inflamm-
tion, and that 2 weeks of treatment with inhaled fluticasone reduced it by more than 50%. These effects were maintained after an additional 8 weeks of inhaled fluticasone. If low-grade, chronic, systemic inflammation is relevant in the pathogenesis of cardiovascular disease both in general and in COPD in particular, then these effects may well be clinically relevant.

The second study, by Huiart and coworkers (41), showed a 32% reduction in the risk of acute myocardial infarction in patients with COPD receiving low doses of inhaled steroids. These potentially beneficial antiinflammatory effects of inhaled steroids may not occur with oral steroid therapy, which is known to be associated with well-described, undesirable systemic effects (hypertension, glucose intolerance, and muscle atrophy, to name a few). Finally, although nutritional supplementation may seem a logical option in undernourished patients, a metaanalysis does not support its usefulness (42). It is possible, however, that the combination of more specific nutritional support with effective antiinflammatory therapy (and regular exercise training) may provide different results in future.

The role of more specific therapeutic alternatives needs to be further explored. For instance, it is possible that the use of antibodies directed against TNF-α may be beneficial in these patients, as has already been shown in other chronic inflammatory diseases (43). Inhibitors of the angiotensin-converting enzyme prevent weight loss in patients with chronic heart failure (44), but their usefulness in COPD has not been investigated. The potential role of inducible nitric oxide synthase inhibitors may also merit investigation (45). Finally, it is interesting to note that in the National Emphysema Treatment Trial, the patients who benefited the most (in survival) were those with poor exercise capacity after rehabilitation (46). Because these patients are likely to have skeletal muscle dysfunction, this observation suggests that skeletal muscle dysfunction (and perhaps other systemic effects of COPD) can be ameliorated by removing diseased lung parenchyma. The mechanisms underlying the improvement are unclear but may be related to the removal of a potential site of systemic inflammation and/or to the improvement in oxygen transport that occurs after surgery. These and other possibilities require additional investigation.

CONCLUSION

COPD is associated with numerous and significant systemic effects that impact a wide range of extrapulmonary tissues and organ systems. The clinical management of the disease should address these effects to ensure that significant improvement in both the health status and prognosis of patients with COPD is observed.

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References


