

COPD is a systemic disease – the extrapulmonary manifestations

The extrapulmonary manifestations of COPD may not always be obvious.

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COPD is defined as a preventable and treatable respiratory disease characterised by partially reversible chronic airflow obstruction.¹ There is abnormal inflammation of the lungs in response to the inhalation of noxious particles, particularly cigarette smoke.

Although COPD predominantly affects the lungs, there are numerous systemic manifestations related to this disease (Table I).²⁻⁴

Table I. What are the extrapulmonary manifestations of COPD?

- Loss of weight
- Muscle dysfunction
 - Respiratory muscle
 - Peripheral muscle
- Osteoporosis
- Cardiovascular diseases
 - Coronary artery disease
 - Cerebrovascular disease
- Co-morbidities
 - Gastro-oesophageal reflux
 - Anaemia
 - Depression and anxiety

The mechanism of these effects is not known, but is believed to be related to enhanced systemic inflammation and oxidative stress.⁵ The pathophysiology of both the local and systemic manifestations of COPD is shown in Fig.1.

The rest of the article covers the individual systemic manifestations.

Weight loss

This has been noted to be associated with poor survival in patients with COPD since the 1960s.⁶ Malnutrition varies from 26% to 47% in patients with COPD.^{7,8} Reduction in body weight by more than 10% of the ideal weight is an independent negative prognostic factor. Loss of lean body mass also results in peripheral muscle dysfunction, reduction in effort tolerance and poorer quality of life. The exact mechanisms are uncertain,⁹ but decreased food intake and increased energy expenditure in breathing are the most important.¹⁰

In patients with severe COPD and body mass indices lower than 25 kg/m² survival rates improve after weight gain.²

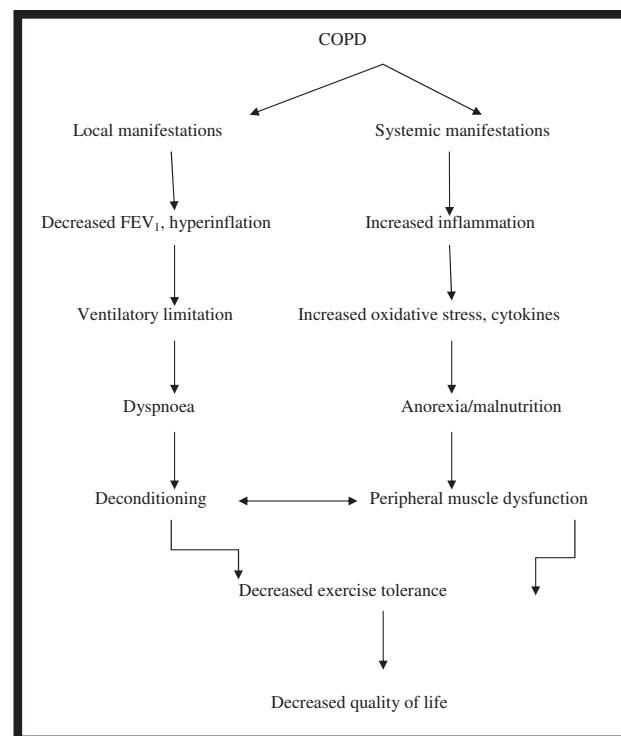


Fig. 1. The pathophysiology of both local and systemic manifestations of COPD.

The hypermetabolism that is present in patients with COPD may be caused by the liberation of inflammatory mediators, such as TNF- α and interleukin-1 β . Leptin is a signalling protein that regulates caloric intake and body weight. Leptin metabolism can be altered by the systemic inflammation in COPD.¹¹

We should also take into account that many patients have hypoxia, which has been shown to stimulate the production of inflammatory mediators and to contribute to the development of malnutrition in COPD patients.²

Muscle dysfunction

Peripheral skeletal muscle dysfunction is an established systemic feature of COPD.¹² This affects effort tolerance, leads to disability and causes poor quality of life, as well as adversely influencing the outcome of these patients. The weakness is predominantly in the lower limbs due to gait-related limitation from dyspnoea. The cause may relate to an intrinsic reduction in the number of mitochondria in the muscles, and is contributed to by nutritional depletion, corticosteroid use, systemic inflammation, deconditioning, hypoxia, and diminished anabolic hormone levels.^{2,13} A local

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extrinsic factor contributing towards muscle weakness includes chest wall expansion from changes in lung volume.

Diaphragmatic muscle dysfunction occurs frequently in patients with COPD, and this is an independent determinant of survival.¹³ The mechanisms of diaphragm muscle atrophy are not certain.

The determination of muscle fatigue is very complicated, since there is no uniform definition of muscle fatigue and specific tests are not available. Elevated blood lactate during exercise is frequently used to monitor muscle fatigue during stress tests, and more recently blood ammonia levels have proven to be of some use.¹⁴ More specific tests other than exercise limitation and dynamic voluntary contraction tests are being investigated.

Osteoporosis

This is also frequently found in excess in patients with COPD and may be related to the use of corticosteroids. Both inhaled and oral corticosteroids can cause bone loss in patients, although there are studies showing decreased bone density in patients not receiving corticosteroids.² This suggests that other systemic factors also play a role.

Cardiovascular disease

COPD is an independent risk factor for cardiovascular disease, including coronary artery disease and cerebrovascular disease.¹⁵ Endothelial dysfunction, due to excessive systemic inflammation,¹⁶ is present in patients with COPD, which may be responsible for this. Endothelial dysfunction may be indirectly measured by the C-reactive protein level.¹³ This raises the possibility that the same mechanisms causing COPD may also cause cardiovascular disease and osteoporosis.

However, long-term inhaled corticosteroid use lowers the incidence of ischaemic heart disease (3% versus 5% in the placebo group) in patients with COPD.¹³ This suggests that

inhaled corticosteroids may reduce systemic inflammation in patients with COPD, but further evaluation is needed.

Gastro-oesophageal reflux disease

This is present in 57% of patients with severe COPD when monitored by oesophageal pH monitors, although many are asymptomatic.¹⁷ This may be related to concomitant medication such as steroids and theophylline, rather than to systemic inflammation.

Anaemia

This has been shown to be an independent risk factor that increases mortality in patients with COPD.¹³ In one review, anaemia was present in 70% and polycythaemia in 6%.¹⁸ The cause is uncertain and may relate to a systemic inflammatory response in the absence of bleeding.

Depression and anxiety

This is often attributed to the nihilism that both patients and caregivers associate with a diagnosis of emphysema or COPD. Appropriate treatment for the COPD and the associated psychological concerns improve the patient's quality of life.

Systemic inflammation in COPD

This concept has been firmly established, although the relationship to local inflammation has yet to be established.^{9,16} There is an imbalance in the reactive oxygen species and anti-oxidant capacity of the lungs. This can cause pulmonary inflammation through the activation of transcription factors.¹⁹

Serum C-reactive protein (CRP) levels are inversely related to FEV₁ and FVC. CRP is a strong predictor of COPD outcomes such as hospitalisation and death.²⁰

Treatment

Therapeutic interventions for the systemic manifestations of COPD include:

- Inhaled or, less commonly, oral corticosteroids, providing an incidental benefit when prescribed for pulmonary indications.
- Nutritional supplementation may be of benefit for patients with less accentuated nutritional changes.²¹
- Anabolic steroids are controversial and not recommended at present.
- Pulmonary rehabilitation therapy is an important mechanism to counter many of the systemic effects of COPD. This includes aerobic exercise and strength training, which results in greater exercise tolerance.² Aerobic exercise should be initiated regardless of the COPD stage. This training increases mitochondrial oxidative enzyme levels, capillarisation of the trained muscles, as well as decreasing creatine phosphate recovery time, thereby resulting in greater ability to exercise.²
- Investigative therapies not currently recommended include neuromuscular electric stimulus and antioxidant therapy.

Conclusion

COPD must be considered to be a systemic disease. Treatment of these manifestations does modify the prognosis of these patients. Further studies of the exact cause of these manifestations, especially those affecting nutrition and muscle dysfunction, are needed to develop new treatment strategies.

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In a nutshell

- Chronic obstructive pulmonary disease (COPD) is perceived primarily as an insult to the lungs, but numerous systemic manifestations have been described, including:
 - weight loss
 - muscle dysfunction
 - osteoporosis
 - excessive cardiovascular disease
 - gastro-oesophageal reflux disease
 - anaemia
 - depression and anxiety.
- Systemic inflammation may play a role in the aetiology of these manifestations.
- Management of these systemic extrapulmonary manifestations may improve the quality of life of COPD patients.

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