Nutritional Support in Pulmonary Disease

Module 38.2
Issues Related to Obesity in COPD

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Learning Objectives
- Create insight in the epidemiology of obesity in patients with chronic obstructive pulmonary disease;
- Understand the impact of obesity on lung function, symptoms and exercise capacity in patients with chronic obstructive pulmonary disease;
- Learn about the obesity paradox in patients with chronic obstructive pulmonary disease;
- Receiving insight in the importance of nutritional counselling for both obesity and chronic obstructive pulmonary disease;
- Acquire the latest insights in the role of fat mass in the pathophysiology of chronic obstructive pulmonary disease;
- Learn about management of obesity in patients with chronic obstructive pulmonary disease.

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Key Messages
- The number of COPD patients with obesity is expected to increase, in line with the world wide obesity pandemic;
- For accurate clinical assessment and disease management it is essential to understand the effects of excessive fat mass in patients in which COPD and obesity collide;
- Contrary to expectations, obesity is not necessarily associated with worse patient-related outcomes in COPD;
• Besides other modalities, efforts to adapt a healthy food pattern is an effective strategy to limit both COPD progression and obesity risk;
• The role of adipose tissue dysfunction in COPD pathophysiology and increased cardiovascular risk is a hot research topic;
• The effects of weight loss and the optimal BMI for obese patients with COPD are currently unknown.

1. Introduction

While traditionally considered a wasting disease, there is an increasing focus on the impact of obesity in patients with COPD. In this section, the epidemiology of obesity, defined as body mass index (BMI) ≥ 30 kg/m², and its impact on symptoms, lung function, exercise performance, morbidity and survival in COPD will be described. Also, the potential role of metabolic syndrome and adipose tissue dysfunction in COPD pathophysiology will be evaluated. Finally, nutritional management and the effects of pulmonary rehabilitation will be discussed.

2. Epidemiology

Whereas the worldwide prevalence of obesity has more than doubled in the last three decades (1), there are only limited data on trends in prevalence of obesity in patients with COPD. In the Canadian National Health Survey, the prevalence of obesity in subjects with self-reported COPD increased by 5% over a 14 year period, while it rose by 38% in non-COPD subjects over the same period (2). In the same study, the prevalence of obesity in COPD and non-COPD subjects was 24.6% and 17.1%, respectively. An even higher prevalence of obesity was reported in an adult multi-ethnic cohort of early stage COPD patients from Northern California, USA (3). In this study, 54% of subjects met criteria for obesity compared to the 20-24% reported prevalence for the general adult population of that region. However, not all studies report an increased prevalence of obesity in COPD compared to non-COPD subjects. In the multi-centre population-based epidemiologic ‘Proyecto Latinoamericano de Investigacion en Obstruccio´n Pulmonar’ (PLATINO) study, the prevalence of obesity among those meeting spirometric criteria for COPD (FEV₁/FVC < 0.7) was 23%, compared to 32% in subjects without COPD (4). In another study from the Netherlands, based on a large primary care population of COPD patients the prevalence of obesity was 18% (5). In that cohort, obesity was found to be more prevalent (16–24%) in patients with milder disease severity (GOLD 1 and 2) and was lowest (6%) in those with severe disease (GOLD 4) (6). This is compared to the national prevalence of obesity in the general adult population in the Netherlands at that time of approximately 11% (6).

As such, available data indicate that the prevalence of obesity in COPD is variable and may be related to differences in general risk factors for obesity among populations, such as gender, diet, level of daily physical activity and education (2). In addition, factors related to COPD disease severity, including the severity of airflow limitation, frequency of exacerbations and hospitalizations, co-morbidities, use of systemic glucocorticosteroids and smoking status, may also contribute to the observed differences in prevalence of obesity between studies.
3. Symptoms

It has long been recognized that obese individuals experience increased symptoms from dyspnoea and more exercise limitation than non-obese individuals, independent of the presence of airflow limitation (7). In a study including adult subjects without an established diagnosis of COPD, obesity and not airflow limitation was associated with productive cough, exercise-induced dyspnoea, poor self-reported health and decreased functional performance (8). Also in a COPD population, obese patients reported increased dyspnoea and poorer health-related quality of life than normal weight patients (9). Remarkably, the number of inhaled medications was higher in obese patients compared to normal weight patients despite having less severe chronic airflow limitation (9). Also, the level of fatigue seems to be increased in obese compared to non-obese COPD patients (10).

4. Lung Function

A reduction in functional residual capacity (FRC) as a result of a reduction in lung compliance (11) is the most prominent effect of obesity on respiratory function, both in normal subjects (12) and in patients with COPD (13). In a study of moderate-to-severe COPD patients, there was no difference in diffusion capacity or maximum inspiratory mouth occlusion pressure between normal weight and obese patients with a comparable degree of airflow limitation (13). Although resting hyperinflation was present in both groups, FRC and expiratory reserve volume (ERV) were significantly lower in obese patients compared to normal weight patients (13). This was likely due to the effects of obesity on static lung volumes in COPD causing less hyperinflation. Similarly, total lung capacity (TLC) (% predicted) was smaller and the ratio of inspiratory-to-total lung capacity was significantly increased in obese compared to normal weight COPD patients. In line with isolated obesity, increasing BMI was associated with decreasing static lung volumes in COPD, resulting in less hyperinflation. The association between BMI and plethysmographically measured lung volumes was shown to be independent of the severity of COPD (14). However, increasing BMI was associated with increasing FEV₁/FVC ratio, especially in patients with severe to very severe disease (14). Moreover, presence of the metabolic syndrome also affects lung function impairment and increases the risk of COPD exacerbations, although the exact mechanism behind this remains unclear (15). Whether the observed effects of obesity on lung function in COPD patients differ based on the distribution of fat mass (i.e. central versus peripheral obesity) has not yet been studied.

5. Exercise Performance

Despite the increased resting and exercise-induced metabolic needs, peak cycling exercise capacity has been shown to be normal in healthy obese subjects compared to normal-weight age-matched controls (16). In patients with obesity and COPD, peak oxygen uptake and peak work rate during symptom-limited cycle exercise were higher in obese patients than in normal weight patients matched for FEV₁ (13). Although both patient groups had ventilatory exercise limitation, minute ventilation and ventilatory efficiency at any given work rate were greater in the obese patients. The intensity of dyspnoea at any given level of ventilation was also lower in obese COPD patients compared to normal weight patients (13), despite higher respiratory rates in the obese patients. This lowered dyspnoea intensity in the obese COPD subjects is probably the result of improved ventilatory
mechanics. Although the magnitude of dynamic hyperinflation was comparable to the normal weight COPD patients, obese patients had a higher maximal minute ventilation (13).

In contrast to cycling, which is a non-weight bearing exercise, important impairments in weight-bearing exercises were reported in obese COPD patients. In COPD patients referred for pulmonary rehabilitation, six-minute walking distance and functional status were significantly reduced in obese patients compared to non-obese patients with even more impaired lung function (10). This is likely to be due to increased metabolic and ventilatory requirements associated with weight-bearing exercise, given comparable physiological responses, i.e. dyspnoea and leg fatigue during six-minute walking test between obese and non-obese COPD patients (17). In a retrospective study, weight bearing exercise (e.g. 6 minute walking distance) was compared with non-weight bearing exercise (peak cycling exercise) in obese patients with COPD and non-obese patients with COPD with the same degree of FEV₁ impairment (18). Despite comparable exercise related symptoms and peak cycling capacity between the groups, the obese patients had a lower walking capacity. Thus, the potential beneficial influence of obesity on exercise tolerance related to decreased resting hyperinflation, may be offset by the increased metabolic load associated with weight-bearing exercise in obesity. Future studies need to clarify the influence of obesity on activities of daily life in COPD.

6. Nutritional Intake

It has been shown that the nutritional intake of patients with COPD is not optimal and reflects a typical western food pattern. From an analysis of moderate to severe patients with COPD admitted for pulmonary rehabilitation, three quarters of the patients have a vitamin D and calcium intake below the adequate daily intake, and more than one third of the patients have low intake of protein, vitamins A, E and C (19). It is well known that this western food pattern is a major risk factor for obesity and the metabolic syndrome. Moreover, epidemiological studies show an association between the western food pattern and a higher risk of developing COPD (20, 21). On the contrary, nutritional components of a healthy food pattern such as dietary fibre, unsaturated fatty acids and vitamin D have been shown to have a protective effect on both the development and progression of COPD (22, 23). Nevertheless, data point out that the effects of these nutritional components are more effective when approaching them as a whole compared to isolated supplementation. These data suggest that a healthy food pattern in obese patients with COPD may be effective to prevent the progression of COPD, but also to limit cardio-vascular risk (24).

7. Metabolic Syndrome

Patients with COPD are at high risk of hospitalization and death from cardiovascular disease (25) and at increased risk of diabetes (26). Although the mechanisms responsible for these associations remain largely unknown, obesity is associated with abnormal metabolic and inflammatory responses that may contribute to increased cardiovascular morbidity in COPD.

Metabolic syndrome is a cluster of risk factors (i.e. hypertension, dyslipidaemia, diabetes) for cardiovascular disease (27). Central obesity is one of the key factors in the pathogenesis of this syndrome, in addition to physical inactivity, nutrition, aging, genetics,
a proinflammatory state and hormonal changes all play a role (28). Metabolic syndrome is associated with restrictive lung function impairment, independently of waist circumference and BMI (29). In a large population based study, the risk of metabolic syndrome was 40% higher in subjects with restrictive lung function impairment than in subjects with normal lung function (30). Abdominal obesity, not BMI, was the strongest predictor of lung function impairment in that study.

Several studies have investigated the prevalence of metabolic syndrome in patients with COPD. In a small study of patients with severe COPD referred for pulmonary rehabilitation, 47% of patients fulfilled the diagnostic criteria for metabolic syndrome. This percentage was significantly higher compared to the age and gender matched control subjects, in whom the prevalence of metabolic syndrome was only 21% (31). Similar results were reported in a larger study including patients with chronic bronchitis and COPD (32). Although the prevalence of metabolic syndrome does not appear to vary based on the severity of lung disease, it is associated with increased circulatory levels of high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) and with physical inactivity. These associations were independent of lung function impairment (32). A recent review on the prevalence of the metabolic syndrome in COPD concluded with comparable results of a pooled prevalence of the metabolic syndrome in patients with COPD of 34%, significantly higher compared to controls (33). Overweight or obese patients with COPD and concomitant metabolic syndrome have more cardio-vascular co-morbidities and diabetes type II than overweight or obese patients without metabolic syndrome (34). Future studies should focus on whether this contributes to increased cardiovascular and all-cause mortality in these patients.

8. Systemic Inflammation

Low-grade systemic inflammation is considered a hallmark of COPD (35, 36) and may explain the increased cardiovascular morbidity and metabolic syndrome noted in patients with COPD. Indeed, increased levels of pro-inflammatory cells and mediators have been reported in the circulation of COPD patients, including increased plasma concentrations of fibrinogen, CRP, TNF-α and circulating leukocytes (36). Increased levels of IL-6 (37, 38), IL-8 (39), IL-10 (38), IL-18 (40) have also been reported. Although it is often hypothesized that inflammation in the systemic compartment is the result of spill-over of the inflammatory process in the airways, lung parenchyma and pulmonary vasculature, evidence from cross-sectional studies indicates no correlation between pulmonary and circulatory inflammatory markers in stable COPD (39, 41). In addition, it is becoming more and more evident, that systemic inflammation is not a characteristic of all patients with COPD. In the ECLIPSE study, only 16% of patients had persistent systemic inflammation during follow-up (42). Interestingly, patients with systemic inflammation were more obese, had more respiratory symptoms and lower health related quality of life, worse exercise tolerance and reported more cardiovascular disease (42). These ECLIPSE data suggest a systemic origin of inflammation and are in line with previous observations suggesting that adipose tissue is a potential source. Increased levels of systemic inflammation had been earlier reported in relation to excessive fat mass in COPD patients. Specifically, TNF-α, IL-6 and leptin plasma levels have been shown to be significantly increased in overweight/obese patients compared with normal weight patients, while plasma adiponectin concentrations were reduced (36). The likelihood of having elevated CRP is three times higher in obese patients than in normal weight patients, after adjusting for
relevant confounders (43), with abdominal fat mass being positively associated with plasma CRP levels in patients with COPD (44).

Few studies have examined adipose tissue inflammation in COPD. Significant differences in subcutaneous adipose tissue mRNA expression of proinflammatory IL-6, TNF-α, and CD68 (macrophage cell surface receptor) were reported among cachectic, normal-weight, overweight and obese patients with moderate-to-severe COPD (45). However, there was no difference in serum levels of IL-6, TNF-α and high-sensitivity CRP (hsCRP) (45). Comparable adipokine and inflammatory gene expression was reported in subcutaneous adipose tissue of clinically stable normal-weight COPD patients and matched controls (46). However, independently of body composition, COPD patients with high CRP had significantly greater adipose tissue macrophage infiltration than did patients with low CRP, indicating a possible role of adipose tissue macrophages in the pathophysiology of systemic inflammation in COPD. Also, adipocyte size, adipose tissue macrophage infiltration and systemic adipokine concentrations were comparable. On the other hand, data from the Health ABC study showed that excessive abdominal visceral fat mass contributed to increased plasma IL-6 concentration (47). In conclusion, specific alterations in adipose tissue function in patients with concomitant COPD and obesity remain currently unknown.

9. Effect of Obesity on Prognosis in COPD

In the general population, obesity is associated with a decrease in life expectancy (47). In the Prospective Studies Collaboration the association between BMI and mortality was assessed by long-term prospective follow up of almost 900,000 participants (48). For each 5 kg/m² increase in BMI above the normal range, overall mortality was about 30% higher, mainly due to cardiovascular disease (48).

A recent data analysis revealed that obesity in COPD was associated with worse COPD-related outcome on a BMI dependent scale (49). Only a few studies have investigated the impact of obesity on prognosis in patients with COPD. In the epidemiological Copenhagen City Heart Study, obesity was associated with a 20-34% increase in the relative risk of all-cause mortality in patients with mild-to-moderate COPD compared to normal BMI patients with comparable disease severity (51). However, the relative risk of all-cause mortality and COPD-related mortality was 0.62 and 0.31, respectively, in obese patients with severe COPD compared to normal weight patients with severe disease (51). A possibly protective role for obesity in patients with severe COPD was also observed in early studies on the association between body weight and mortality (52, 53). In the ‘Association Nationale pour le Traitement a Domicile de l’Insuffisance Respiratoire Chronique’ (ANTADIR) network, the prognostic value of obesity in hypoxaemic patients with COPD treated with long-term oxygen therapy, was clearly demonstrated (54). During the 7.5 years follow up, the highest survival and lowest hospitalization rates were observed in obese COPD patients. The 5-year survival rates were 24%, 34%, 44%, and 59%, respectively, for patients with BMI’s < 20, 20 to 24, 25 to 29, and > 30 kg/m².

This possible association between obesity and improved survival in COPD thus contrasts with epidemiological data from the general population. Although not completely understood, this phenomenon known as the “obesity paradox” is not unique for COPD (55). One explanation, for the prognostic advantage of obesity, concerns the relative reduction in static lung volumes in obese COPD patients. During a three-year follow-up study, the
inspiratory capacity-to-total lung capacity ratio (IC/TLC), an index of static lung hyperinflation, was found to be an independent predictor of increased respiratory and all-cause mortality in patients with COPD (56). Although the mechanism underlying the association between hyperinflation and prognosis remains unclear, it can be speculated that increased IC/TLC in obese patients with COPD (13) may contribute to a benefit in survival.

In addition, obesity is associated with significantly lower annual decline in FEV₁ in men and not in women (57). Thus, there may be gender specific differences in the effect of obesity on the progression of chronic airflow limitation. Furthermore, it is not yet clear whether excessive fat mass or muscle mass contributes to the survival advantage in chronic diseases (55).

Based on the evidence outlined above, it can be hypothesized that obesity exerts divergent effects on COPD prognosis based on patient characteristics and disease severity. Obesity may protect against mortality in patients with advanced COPD, in which loss of fat-free mass is a particularly important short-term risk factor for death (58). By contrast, in earlier stage COPD, the harmful long-term effects of obesity-related conditions such as low-grade systemic inflammation and metabolic syndrome may result in increased cardiovascular and all-cause mortality.

10. Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) has been shown to improve symptoms, exercise tolerance, body composition and health status in patients with COPD in general (59). Given these beneficial effects, PR seems to be a useful adjunct in the comprehensive management of patients with COPD as well as obesity. However, few studies have addressed the effects of pulmonary rehabilitation in this patient category. In a retrospective study, similar improvements in six-minute walking distance, health status and functional activities (using the Pulmonary Functional Status Scale) were observed in obese and non-obese COPD patients after an outpatient pulmonary rehabilitation programme (10). However, obese patients improved less in unsupported arm exercise than non-obese patients (10). In another study, the magnitude of improvement in walking distance, cycling endurance time and health status after pulmonary rehabilitation was also comparable in normal weight, overweight and obese COPD patients (60). No significant changes in BMI were noticed after PR (60). Given the impact of obesity on weight-bearing exercise performance in patients with COPD (13), the ability to perform traditional exercise training may be limited. Water-based exercise training may provide an alternative mode of training for these patients with concurrent COPD and obesity. In a recent study, including not only COPD patients with obesity but also those with other musculoskeletal comorbidities limiting exercise capacity, water-based exercise training was more effective than land-based exercise training in increasing peak and endurance exercise capacity and improving symptoms of fatigue (61). Changes in body weight were not reported. Based on these limited studies, it appears that obesity per se does not have a negative impact on the outcomes of PR in patients with COPD. As yet, no studies have focussed on optimization of nutritional and lifestyle interventions as part of PR in obese COPD patients, in which losing excess fat may be an important goal. Studying the impact of weight reduction strategies in conjunction with exercise training in this specific patient population should be a research priority.
11. Summary

COPD and obesity are two heterogeneous chronic conditions with increasing prevalences all over the world. For accurate clinical assessment and disease management, it is important to understand the effects of excessive fat accumulation in patients with concomitant COPD and obesity. In COPD, obesity results in reductions in static lung hyperinflation, irrespective of the severity of airflow limitation. The impact of obesity on exercise capacity in COPD is likely dependent on the type of exercise, with obesity being associated with decreased tolerance to weight-bearing exercise while having beneficial effects on dynamic ventilatory mechanics during weight-supported exercise. Although obese COPD patients have higher levels of systemic inflammation and increased risk of metabolic syndrome, it is currently unknown whether and to what extent adipose tissue dysfunction and insulin resistance contribute to increased cardiovascular risk and extra pulmonary manifestations in COPD. In contrast to early stage COPD, obesity seems to protect against mortality and hospitalisation in patients with severe disease. Even though additional studies on the interaction between obesity and COPD are warranted, the current findings suggest that the presence of obesity has implications for interpretation of diagnostic measurements and management of patients with COPD. Future studies need to show the overall effects of nutritional interventions in obese COPD patients and determine the optimal BMI for an obese patient with COPD.

12. References

and International Association for the Study of Obesity. Circulation. Oct 20
2009;120(16):1640-1645.
28. Huang TT, Ball GD, Franks PW. Metabolic syndrome in youth: current issues and
29. Fimognari FL, Pasqualetti P, Moro L, et al. The association between metabolic
syndrome and restrictive ventilatory dysfunction in older persons. The journals of
gerontology. Series A, Biological sciences and medical sciences. Jul
syndrome: the critical role of abdominal obesity. Am J Respir Crit Care Med. Mar 15
bronchitis and COPD: frequency and associated consequences for systemic
33. Lipoveca NC, Beijers RJHCG, van den Borst B, Doehner W, Lainscak M, Schols AMWJ.
The Prevalence of Metabolic Syndrome In Chronic Obstructive Pulmonary Disease:
34. Breyer MK, Spruit MA, Hanson CK, Franssen FME, Vanfleteren LEGW, Groenen MTJ,
35. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive
pulmonary disease and systemic inflammation: a systematic review and a meta-
37. Yasuda N, Gotoh K, Minatoguchi S, et al. An increase of soluble Fas, an inhibitor of
apoptosis, associated with progression of COPD. Respir Med. Aug 1998;92(8):993-
999.
38. Koehler F, Doehner W, Hoernig S, Witt C, Anker SD, John M. Anorexia in chronic
obstructive pulmonary disease--association to cachexia and hormonal
patients with chronic obstructive pulmonary disease: soluble tumor necrosis factor
receptors are increased in sputum. Am J Respir Crit Care Med. Nov 1
2002;166(9):1218-1224.
40. Petersen AM, Penkowa M, Iversen M, et al. Elevated levels of IL-18 in plasma and
skeletal muscle in chronic obstructive pulmonary disease. Lung. May-Jun
2004.
42. Agusti A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is


