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ORIGINAL PAPER

Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary disease

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Background: Overweight and obesity have been associated with better survival in patients with chronic obstructive pulmonary disease (COPD). On the other hand, excess body weight is associated with abnormal metabolic and inflammatory profiles that define the metabolic syndrome and predispose to cardiovascular diseases. This study was undertaken to evaluate the impact of overweight and obesity on the prevalence of the metabolic syndrome and on the metabolic and inflammatory profiles in patients with COPD.
Methods: Twenty-eight male patients with COPD were divided into an overweight/obese group [$n = 16$, body mass index (BMI) = $33.5 \pm 4.2\,kg/m^2$] and normal weight group ($n = 12$, BMI = $21.1 \pm 2.6\,kg/m^2$). Anthropometry, pulmonary function and body composition were assessed. The metabolic syndrome was diagnosed according to waist circumference, circulating levels of triglyceride and high-density lipoprotein cholesterol levels, fasting glycemia and blood pressure. C-reactive protein, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), leptin and adiponectin plasma levels were measured.
Results: Airflow obstruction was less severe in overweight/obese compared with normal weight patients (forced expiratory volume$_1$: $51 \pm 19\%$ versus $31 \pm 12\%$ predicted, respectively, $P < 0.01$). The metabolic syndrome was diagnosed in 50% of overweight/obese patients and in none of the normal weight patients. TNF-α, IL-6 and leptin were significantly higher in overweight/obese patients whereas the adiponectin levels were reduced in the presence of excess weight.
Conclusions: The metabolic syndrome was frequent in overweight/obese patients with COPD. Obesity in COPD was associated with a spectrum of metabolic and inflammatory abnormalities. *Chronic Respiratory Disease* 2008; **5**: 35–41

Key words: cardiovascular diseases; COPD; diabetes; inflammation; metabolic syndrome; obesity

Introduction

Loss in body weight and in muscle mass is a significant event in the course of chronic obstructive pulmonary disease (COPD) because it is associated with premature mortality, poor functional status and quality of life.[1–3] Conversely, overweight and obesity are said to be protective in COPD, a statement based on the inverse relationship between mortality and body mass index (BMI) in this patient population.[2,4–6] This observation has also been reported in other chronic diseases such as heart failure and is being referred to as the obesity paradox.[7,8]

The concept that fat accumulation may be protective in COPD does not take into account the potentially negative consequences of obesity as a risk factor for cardiovascular diseases. Obesity, particularly when associated with visceral fat accumulation, is associated with the metabolic syndrome whose main features include atherogenic dyslipidemia, inflammation, insulin resistance and increased for developing diabetes mellitus and cardiovascular diseases.[9–11] On the other hand, COPD is now recognized as a risk factor for cardiovascular diseases, increasing the risk for these diseases two to three-fold, independent of traditional risk factors such as, hypertension, dyslipidemia and smoking.[12] We also reported a high prevalence

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(61%) of the metabolic syndrome in men with COPD participating to a pulmonary rehabilitation program.[13] In comparison, the reported prevalence of the metabolic syndrome in age-matched men without COPD is 44%.[14] Lastly, COPD may predispose to insulin resistance and type-II diabetes.[15] It therefore emerges that, although obesity may protect against mortality on the short term, the concomitant presence of COPD and obesity may define a clinical phenotype at a high risk for cardiovascular diseases. Before making recommendation about weight management in COPD, there is a need to better understand the implication of obesity in this specific patient population.

We hypothesized that in the presence of overweight/obesity, patients with COPD would exhibit a metabolic and inflammatory profile associated with a higher risk of cardiovascular diseases. This hypothesis was tested by evaluating the prevalence of the metabolic syndrome and characterizing the metabolic and inflammatory profile in overweight/obese patients with COPD in comparison to normal weight patients with COPD.

Methods

Subject characteristics

Twenty-eight male patients with COPD volunteered to participate in the study. These patients were recruited consecutively from a cohort of patients previously engaged in pulmonary rehabilitation in our institution. Only men were recruited to avoid the possible influences of gender differences on body composition and metabolic and inflammatory profiles. The diagnosis of COPD was based on past smoking history, clinical evaluation and pulmonary function tests, showing irreversible airflow obstruction [post-bronchodilator forced expiratory volume at 1 s (FEV_1) $<80\%$ of predicted value and FEV_1/forced vital capacity (FVC) $<70\%$]. All patients with COPD were in a stable state at study entry with no exacerbation of their disease and exposure to systemic corticosteroids within two months of their participation to the study. Patients with COPD were divided in two groups according to BMI: overweight to obese (BMI $\geq 25\,kg/m^2$, range 28.2–44.7 kg/m^2) and normal to low body weight (BMI $<25\,kg/m^2$, range 16.5–25 kg/m^2). The institutional ethics committee approved the research protocol and a written consent form was obtained for each patient.

Pulmonary function testing

Standard pulmonary function tests including spirometry, lung volumes with body plethysmography and diffusion capacity were obtained according to previously described guidelines[16,17] and related to the normal values of Quanjer *et al.*[18] These results were used to define disease severity according to the GOLD classification[19]: GOLD I (mild): FEV_1/FVC $<70\%$ and $FEV_1 \geq 80\%$; GOLD II (moderate): FEV_1/FVC $<70\%$ and $FEV_1 < 80\%$ and $\geq 50\%$; GOLD III (severe): FEV_1/FVC $<70\%$ and FEV_1 $<50\%$ and $\geq 30\%$; GOLD IV (very severe): FEV_1/FVC $<70\%$ and FEV_1 $<30\%$ or FEV_1 $<50\%$ and arterial partial pressure of O_2 (PaO_2) <60 mmHg.

Anthropometric measurements and body composition

Body weight and height were measured, and BMI was calculated as weight divided by height squared (kg/m^2). Blood pressure measurements were obtained in the supine position after 15 min of resting period. Blood pressure was taken from both arms and the highest measurement was used for analysis. Waist circumference was measured according to the procedures of the Airlie Conference.[20] Regional assessment of fat mass (FM) and fat-free mass (FFM) were obtained by dual-energy X-ray absorptiometry (General Electric Healthcare, PRODIGY, Chicago, IL, USA). Fat-free-mass index (FFMI) was calculated by dividing FFM by height squared (kg/m^2).

Blood sampling and analyses

Arterial blood was drawn from a radial artery while the subject was breathing room air in a seated position. Arterial blood gas was analysed with a blood gas analyser (AVL 995, AVL Scientific, Roswell, GA, USA). After a resting period of 30 min, antecubital venous blood was sampled between 8:00 AM and 10:00 AM in overnight fasted subjects. Blood was centrifuged for 15 min, put into aliquots and stored at $-80°C$ until further analysis. Fasting plasma glucose and lipids [cholesterols, triglycerides and high-density lipoprotein (HDL)-cholesterol] were measured by enzymatic assays using an automatic Roche Diagnostics MODULAR system (Roche Diagnostics, Indianapolis, IN, USA). Low-density lipoprotein (LDL)-cholesterol levels were calculated using the Friedewald equation.[21] Fasting plasma insulin was measured by an electrochemiluminescence immunoassay using an automatic Roche Diagnostics MODULAR system (Roche Diagnostics). Insulin sensitivity was estimated from the homeostasis model assessment-insulin resistance (HOMA-IR) index (fasting insulin X fasting glucose/22.5).[22] Commercial enzyme-linked immunosorbent

assay (ELISA) kits (RD Systems, Minneapolis, MN, USA) were used to measure the plasma levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). C-reactive protein (CRP) plasma levels were measured with a nephelometer immunoassay using a Dade Behring BN ProSpec instrument (Dade Behring, Deerfield, IL, USA). Fasting plasma adipokine concentrations (Leptin, adiponectin) were determined with commercial ELISA kit (B-Bridge International, Inc., San Jose, CA, USA).

The metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).[23,24] To diagnose the metabolic syndrome, the presence of three or more of the following criteria is required: waist circumference >102 cm for men, raised triglycerides level ≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality, reduced HDL-cholesterol <40 mg/dL (1.03 mmol/L) in men, raised blood pressure: systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension, raised fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or a previously diagnosed type-2 diabetes.

Statistical analysis

All values are reported as mean ± standard deviation. Differences between groups were tested with unpaired *t*-test or Chi-square test or with non-parametric statistics (*U-test* Mann–Whitney) when appropriate. Stepwise regression analyses were used to identify the variables contributing to the variance in proinflammatory cytokines and adipokines plasma levels. In these models, indices of lung function [FEV_1, FVC, total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV) and diffusion capacity (DLCO)] and of body composition (FFM, FM, BMI) were entered as independent variables. Statistical analyses were performed using STATISTICA (version 6.1) (Statsoft Inc.). A *P*-value of <0.05 was considered significant.

Results

The characteristics of the two groups of patients are reported in Table 1. All overweight/obese patients had abdominal obesity with a waist circumference >102 cm. BMI and FFMI were significantly greater in the overweight/obese group compared with the normal weight group. Similar observation was made for FM and FFM (Figure 1). In comparison to normal weight patients, the overweight/obese group were less severely obstructed and hyperinflated. They also had a greater inspiratory capacity to TLC ratio. Accordingly, the distribution of disease severity was different between the two groups with a greater number of normal weight patients showing stage II and III disease (GOLD II, $n = 6$; GOLD III, $n = 6$) while a greater proportion of overweight/obese patients had stage I disease (GOLD I, $n = 8$; GOLD II, $n = 4$; GOLD III, $n = 4$) (Figure 1). Cardiovascular diseases and diabetes were frequent in the overweight/obese group (Table 1).

Table 1 Characteristics of the two groups of patients with COPD[1]

	Overweight/obese n = 16	*Normal weight n = 12*
Age (years)	65.1 ± 4.2	65.5 ± 6.3
Smoking status (pack/year)	69 ± 33	65 ± 36
BMI (kg/m^2)	33.5 ± 4.2	21.1 ± 2.6[2]
Waist circumference (cm)	119 ± 10	85 ± 10[2]
FFM of two legs (kg)	19 ± 4	15 ± 4[3]
FFMI (kg/m^2)	21.1 ± 3.1	16.4 ± 1.3[2]
FEV_1 (% predicted)	51 ± 19	31 ± 12[4]
FEV_1/FVC (%)	45 ± 11	36 ± 9[3]
IC (% predicted)	84 ± 21	76 ± 24
FRC (% predicted)	115 ± 24	157 ± 29[2]
RV (% predicted)	131 ± 36	178 ± 59
TLC (% predicted)	102 ± 12	118 ± 10[2]
IC/TLC (%)	38.7 ± 9.2	28.7 ± 7.6[4]
DLCO (% predicted)	64 ± 13	59 ± 12
PaO_2 (mmHg)	74.1 ± 9.5	73.7 ± 3.7
$PaCO_2$ (mmHg)	41.9 ± 4.6	42.5 ± 3.7
Co-morbid conditions (*n*)		
Diabetes	5	0
Hypertension	6	2
Coronary artery disease	6	1
Cerebrovascular accident	1	0
Medication (*n*)		
β2-agonists	11	10
Anti-cholinergics	4	9
Inhaled steroids	13	10
Calcium channel blocker	7	0
β-blockers	1	0
ASA	7	1
Oral hypoglycemic medications	5	0
Statins	9	2

[1]Values are mean ± SD.
[2]$P < 0.001$.
[3]$P < 0.05$.
[4]$P < 0.01$ between overweight/obese and normal weight patients with COPD.
BMI, body mass index; FFM, fat-free mass; FFMI, fat-free mass index; FEV_1, force expiratory volume at 1 s; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DLCO, diffusion capacity; PaO_2, arterial partial pressure of O_2; $PaCO_2$, arterial partial pressure of CO_2; ASA, acetylsalicylic acid.

Metabolic and proinflammatory markers

Group mean values for the different metabolic variables are presented in Table 2. Insulin levels and

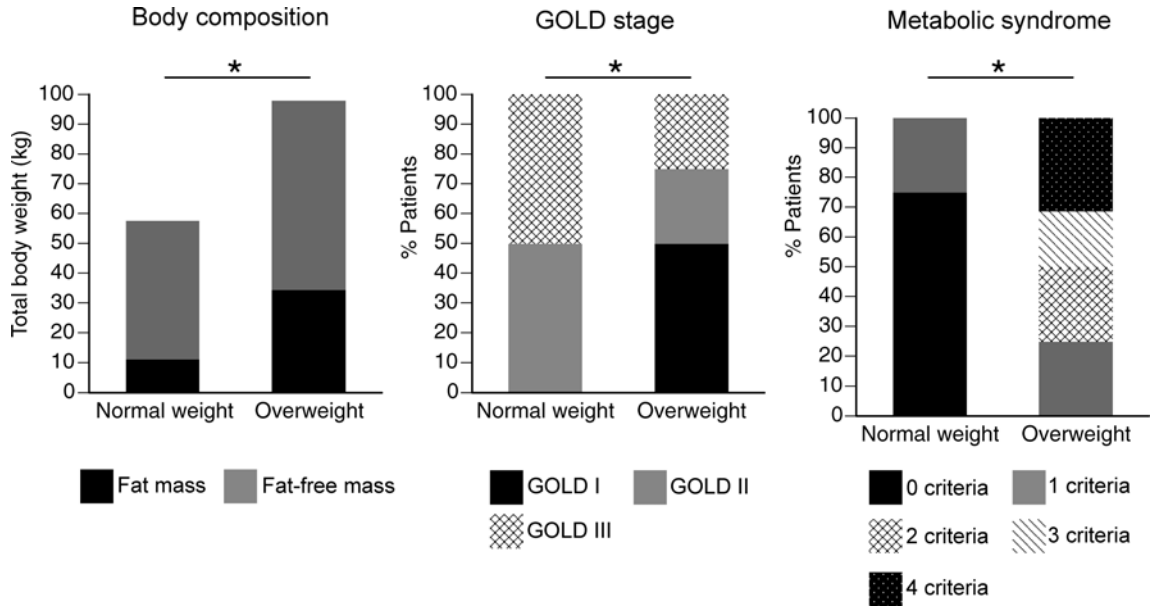

Figure 1 Body composition (left panel), distribution of disease severity according to the GOLD classification (middle panel) and number of criteria of the metabolic syndrome (right panel) in normal weight and overweight/obese patients. Values are in mean ± SD, $*P < 0.05$.

the HOMA-IR index were higher while the HDL-cholesterol and LDL-cholesterol levels were lower in the overweight/obese group in comparison with the normal weight group. All patients of the overweight/obese group exhibited at least one criteria of the metabolic syndrome whose presence (3 diagnostic criteria or more) could be established in 50% of these patients. Twenty-five percent of the normal weight patients had one criteria of the metabolic syndrome; none had more than one criteria (Figure 1).

TNF-α and IL-6 plasma levels were significantly increased in overweight/obese patients compared with normal weight patients ($P < 0.001$ and $P < 0.05$, respectively) (Figure 2). CRP was also increased in the presence of excess weight, but the difference between the two groups for this inflammatory mediator did not reach statistical significance. Plasma adiponectin concentration was reduced and leptin plasma concentration was increased in the overweight/obese group compared with the normal weight group ($P < 0.001$) (Figure 2).

In stepwise regression models, FM was the main predictor of TNF-α ($r = 0.73$, $P < 0.0001$) and of IL-6 ($r = 0.54$, $P < 0.005$) plasma levels. BMI was the main predictor of adiponectin ($r = -0.42$, $P < 0.05$) and of leptin ($r = 0.71$, $P < 0.0001$) plama levels. None of the pulmonary function parameters were retained in the stepwise regression models as significant predictor of the proinflammatory cytokines and adipokines plasma levels.

Table 2 Metabolic variables for the two groups of patients with COPD[1]

	Overweight/obese n = 16	*Normal weight n = 12*
Triglycerides (mmol/L)	1.3 ± 0.6	0.99 ± 0.4
HDL-cholesterol (mmol/L)	1.41 ± 0.42	1.92 ± 0.39[2]
Fasting glucose (mmol/L)	5.5 ± 1.1	5.0 ± 0.7
LDL-cholesterol (mmol/L)	2.2 ± 0.5	3.1 ± 1.2[3]
Insulin (pmol/L)	123.1 ± 221.2	26.4 ± 15.1[4]
HOMA-IR	26.8 ± 37.1	6.2 ± 4.0[3]

[1]Values are in mean ± SD.
[2]$P < 0.01$.
[3]$P < 0.05$.
[4]$P < 0.001$ between overweight/obese and normal weight patients with COPD.
HOMA-IR, homeostasis model assessment-insulin resistance; HDL, high-density cholesterol level; LDL, low-density cholesterol level.

Discussion

This study highlights the fact that the presence of obesity, specifically abdominal obesity, in patients with COPD, is associated with metabolic and inflammatory abnormalities typically associated with the development of cardiovascular diseases and diabetes such as, increased insulin levels, increased TNF-α and IL-6 plasma levels, reduced adiponectin plasma levels and

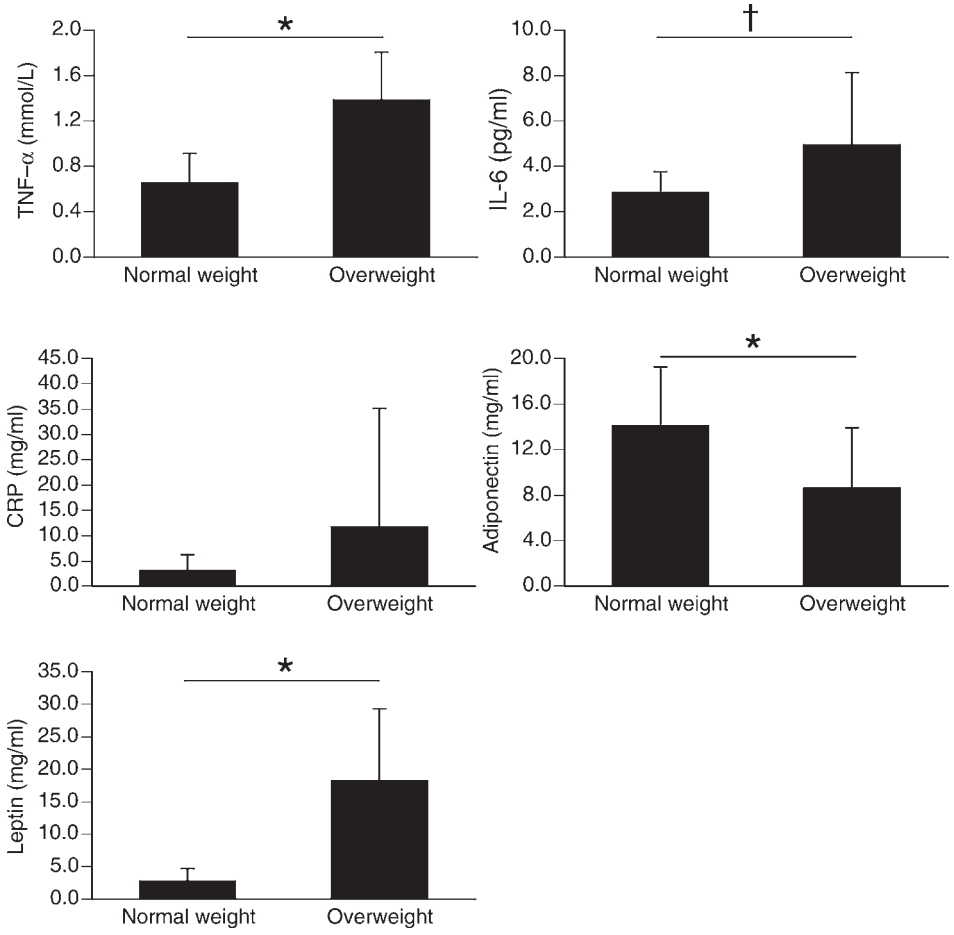

Figure 2 TNF-α, IL-6 and CRP, adiponectin and leptin plasma levels in normal weight and overweight/obese patients. Values are in mean $\pm$ SD, $^{*}P < 0.001$, $^{\dagger}P < 0.05$.

reduced HDL-cholesterol. We also found that the prevalence of the metabolic syndrome, a major determinant of cardiovascular morbidity and mortality,[11] was increased in obese patients compared with their normal body weight counterparts. Overall, obesity may add several detrimental long-term effects on the development of cardiovascular disease and survival in COPD.

These data might be surprising in view of the observation that increased BMI seems to protect against mortality in COPD[2] and other chronic diseases such as heart failure.[7] This apparent discrepancy between the present findings and the epidemiological studies showing that excess weight is associated with lower death rate in several chronic diseases can be explained in several ways. One has to consider that demonstrating excess weight, as a predictor of better survival, does not imply that accumulation of adipose tissue is beneficial. First, in epidemiological studies, body composition was not taken into account as a potential confounder in the relationship between survival and BMI. This is crucial since overweight individuals do not only exhibit excess in fat tissue, but also larger muscles as observed in the present study. Three studies, including one of ours, have recently confirm that increased muscle mass is a better predictor of survival than BMI.[3,6,25] The distribution of fat accumulation is another confounder of the association between BMI and mortality that should also be considered given that it is the abdominal or visceral fat that substantially increase the risk for cardiovascular diseases as opposed to subcutaneous fat. Another issue to consider is the relatively short follow-up period (3–5 years) in epidemiological studies.[2,7] Cachexia is a rapid killer while the detrimental impact of obesity on survival will likely become apparent after a much longer period of time. Lastly, the optimal BMI has not been defined in COPD; this value may also vary according to the severity of airflow obstruction.[5] For example, overweight/obesity seems to exert its protective effect on survival mostly in patients with advanced disease whereas in patients

with milder disease, the relationship between BMI and mortality has a *U*-shape, with mortality hazard ratio starting to increase with BMI over 30 kg/m^2.[5]

Caution is warranted before concluding that adipose tissue accumulation is beneficial to patients with COPD and other chronic disorders. Precise recommendation about weight management in these disorders should await studies in which the independent impact of muscle mass and distribution of obesity is accounted for in the observed statistical positive relationship between BMI and survival. This is not a trivial issue when considering that cardiovascular mortality is an important cause of death in COPD.[26] Furthermore, COPD increases the risk of cardiovascular diseases by two to three-fold, independent of traditional risk factors,[12,27] an effect possibly mediated by a low-grade systemic inflammation reported in COPD. The significance of this possible interaction of COPD and obesity in terms of cardiovascular mortality remains to be seen, but this situation is particularly worrisome in view of the current obesity epidemic. In Canada, 35 and 15% of the general population is respectively overweight or obese,[28] physicians will therefore be commonly challenged by the association of the two diseases.

Our patients were selected consecutively and randomly from a list of individuals involved in our rehabilitation program. Specifically, we did not try to match the overweight/obese and non-obese patients with COPD for lung disease severity and muscle mass. An interesting observation was that overweight/obese patients had substantially less airflow obstruction and hyperinflation compared with their normal weight counterparts, despite similar smoking history and age between the two groups. This observation may represent a selection bias; obese patients with severe airflow obstruction may be too sick or dyspneic to accept to be enrolled in clinical studies. On the other hand, the finding of less airflow obstruction in overweight/obese patients is consistent with other studies showing that disease severity distribution is not homogenous among the different BMI categories. In fact, disease severity distribution is strongly biased toward less severe disease in patients with excess body weight[6] raising the hypothesis that obesity may be associated with a reduced susceptibility to develop severe airflow limitation. Although FEV_1, the most widely used surrogate of disease severity, is usually included as a covariate in regression analyses between BMI and survival, it is likely that the impact of inhomogeneous disease severity distribution among the BMI classes cannot be entirely captured. For instance, indices of hyperinflation (FRC, RV, TLC, IC/TLC) predict mortality independent of FEV_1 in COPD[29] and have not been taken into account in the epidemiological link between BMI and survival in this disease. As such, it may well be that the so-called protective effect of obesity on survival may in fact reflect the impact of better preserved overall respiratory function and not some benefits related to fat accumulation.

A relevant observation of the present study was that FM was the main determinant of TNF-α and IL-6 plasma levels. This is not surprising given the inherent endocrine properties of adipose tissue that overexpresses and releases numerous cytokines and proinflammatory molecules, such as TNF-α, IL-6 and CRP among others.[11] One practical consideration of this finding is that obesity and body composition should be taken into account when interpreting the level of systemic inflammation in COPD. The role of systemic inflammation as a potential underlying mechanism of muscle wasting in COPD is the subject of intense research and the current literature is somewhat controversial on this topic. Some,[30] but not all investigators[31] found a link between proinflammatory plasma mediator levels and muscle mass. We were intrigued by the present finding that muscle mass was better preserved in overweight/obese patients despite higher TNF-α and IL-6 levels compared with those with normal weight. This finding suggests that systemic inflammation may not be sufficient in itself to induce muscle wasting in COPD.

Along with increased TNF-α and CRP, reduced adiponectin levels are commonly observed in obesity and have been associated with cardiovascular diseases, insulin resistance and hyperinsulinemia.[32] Increased TNF-α and reduced expression of adiponectin are highly important in relating adiposity to the development of metabolic syndrome, although such other adipokines such as leptin contribute to this pathobiology. In the present study, leptin plasma levels were significantly higher in the overweight/obese group compared with the normal weight group. Consistent with the fat tissue origin of leptin, our study and other's[33] found that this adipokine correlated positively with FM.

Some methodological limitations of our study should be discussed. The sample size was small and our study should be viewed as a pilot investigation about the impact of obesity in COPD. It will be important in future studies to minimize selection biases to ensure that the study population is representative of the entire range of COPD severity. The HOMA-IR was used as an index of insulin sensitivity since it shows good concordance with the euglycemic–hyperinsulinemic clamp, which is considered as the gold standard technique.[22] Although the HOMA-IR is usually used in large study population, it has also been utilised in smaller sample size studies.[15,34]

In conclusion, our findings suggest that metabolic syndrome is frequent in overweight/obese patients

with COPD. Abdominal obesity in patients with COPD was associated with a cluster of metabolic and inflammatory abnormalities concurring to the development of cardiovascular diseases and diabetes. Despite the notion that increased BMI is associated with better survival in COPD in short-term studies, final weight maintenance recommendations in this population have to await further studies in which important confounders, such as disease severity, body composition and distribution of obesity are taken into account.

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