Nutritional status and airflow obstruction: two independent contributors to CO diffusing capacity impairment in COPD

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ABSTRACT: Nutritional status and airflow obstruction: two independent contributors to CO diffusing capacity impairment in COPD. S. Baldi, G.D. Pinna, P. Crotti, S. Montemartini, E. Dacosto, F. Fanfulla, C. Fracchia, C. Bruschi.

Background. The association between weight loss and Chronic Obstructive Pulmonary Disease (COPD) has been recognised from many years. Based on the evidence that nutritional status reflects metabolic disturbances in COPD, the relationship between body mass index (BMI), severity of airflow obstruction and CO diffusing capacity (DLCO), that is the functional hallmark of emphysema, is relevant to the management of COPD phenotypes.

Methods. We reviewed 104 patients with COPD (82 males), aged 66±9 years (mean±SD). Height averaged 165±8 cm, weight 71±16 Kg, FEV1 50±18 (% of predicted), RV 169±49%, and DLCO 56±26%. Multiple linear regression was performed using BMI, FEV1 and RV, as explanatory variables for DLCO. Patients were also classified into four groups according to BMI ≤18.5 (low), >18.5 and ≤25 (ideal), >25 and ≤30 (overweight), >30 (obese), and post-bronchodilator FEV1 < 50%. Using this categorisation, a two-factor analysis of variance, testing for interaction and main effects (BMI and FEV1) was performed as confirmatory analysis for the association between BMI (kg/m2), FEV1% and DLCO%.

Results. FEV1 and BMI were significantly and independently associated to DLCO according to the equation: DLCO = -18.32 + 0.65·FEV1 + 1.59·BMI (R2 = 0.40, p<0.0001). The contribution of RV % to DLCO % was largely non-significant (p=0.16). A close relationship was found between BMI (kg/m2) and DLCO %, for all of the four BMI groups segregated by post-bronchodilator FEV1 %, (p<0.001). No interaction was found between these two factors (p=0.30).

Conclusion. Nutritional status as assessed by BMI contributes substantially to impairment of DLCO independently of the severity of airflow obstruction. This data confirms the association between emphysematous process and weight loss in advanced COPD, independent of the airflow obstruction severity.

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Keywords: CO diffusing capacity, body mass index, airflow obstruction, COPD.

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Introduction

The association between weight loss and COPD, particularly the emphysematous type, has been recognised for almost one century [1]. Weight loss has been regarded as a determinant of course and prognosis of COPD [2-4], and a marker for more severely impaired lung function [5-7]. Body mass index (BMI), the ratio of body weight to height2, is a crude index reflecting complex metabolic disturbances in COPD [8]. Recent studies have provided evidence that nutritional abnormalities and weight loss are relevant contributors to disability and handicap experienced by the patients [9], and represent key points for better definition of rehabilitation programmes [10-12]. Therefore, the clinical assessment of patients with COPD should take into consideration body mass index along with respiratory function parameters, such as residual volume and forced expiratory volume in one second (FEV1), which almost exclusively targets the lung.

In the present study, we reviewed a group of 104 patients with COPD with either emphysema or chronic bronchitis, defined according to functional criteria. The study was designed to investigate the association between CO diffusing capacity and nutritional status based on BMI, in order to elucidate the role of a low BMI in COPD. In particular, we wanted to assess whether weight loss is a marker independent of the degree of airflow obstruction and/or hyperinflation, that in and of itself targets the COPD wasting syndrome.

Material and methods

Subjects

For the study we considered all the patients who had been consecutively referred to our Insti-
tute for respiratory rehabilitation between January 2000 and January 2002. They had a diagnosis of COPD based on international guidelines criteria [13, 14], with a clinical course consistent with chronic bronchitis and/or emphysema and a long history of cigarette smoking. All patients were clinically stable at the time of examination, and were receiving a standard treatment regimen. Exclusion criteria were: diagnosis of neoplasm, fibrosis and sleep apnea syndrome.

**Measurements.** Pulmonary function tests were obtained in all the patients as part of the respiratory rehabilitation programme. Patients were asked to abstain from bronchodilators for at least 12 hours prior to lung function measurements. They included spirometry (post-bronchodilator FEV1, vital capacity) and maximum inspiratory and expiratory flow rates, single breath CO diffusing capacity (DLCO) and alveolar volume (VA). Single breath DLCO was measured (Baires System Bienmedin, Padua, Italy) according to ATS criteria [15]. Lung volumes were measured while the patients were sitting in a body plethysmograph (Jaeger Masterlab, Jaeger, Würzburg, Germany), and panting against a closed shutter at a frequency slightly < 1 Hz with their cheeks supported by hands [16]. Total lung capacity (TLC) was obtained as the sum of thoracic gas volume (TGV) and the linked inspiratory capacity. Functional residual capacity (FRC) was obtained from TGV corrected for any difference between the volume at which the shutter was closed and the average end-expiratory volume of the four preceding regular tidal breaths. RV was the difference between TLC and vital capacity (VC). All measurements were expressed as percentage of the predicted values according to the respective reference equations [17]. The presence of emphysema was defined according to functional criteria (FEV1/FVC < 70%, DLCO < 60%).

Body mass index was calculated as the ratio of body weight (in Kilograms) to height2 (in metres) [18]. Besides considering BMI and post-bronchodilator FEV1 as continuous variables, they were also categorised according to the following cut-off points: BMI ≤ 18.5 (low), > 18.5 and ≤ 25 (ideal), > 25 and ≤ 30 (overweight), > 30 (obese), based on previously used standards [18], and post-bronchodilator FEV1 < 50% (severe airflow limitation) versus FEV1 ≥ 50%.

**Statistical analysis**

Descriptive statistics are expressed as a mean, standard deviation (SD) and range. The univariate association between BMI, post-bronchodilator FEV1 and DLCO was assessed by linear correlation analysis (Pearson correlation coefficient). In order to test the ability of the first two variables to predict CO diffusing capacity, we applied multivariate regression analysis. As confirmatory analysis, the association between BMI, post-bronchodilator FEV1 and DLCO was also assessed expressing BMI and post-bronchodilator FEV1 as categorical variables, according to the cutoff points described above. This analysis was carried out by a two-factor analysis of variance (ANOVA), testing for interaction and main effects (BMI and FEV1). A p value < 0.05 was considered statistically significant.

**Results**

Anthropometrical characteristics and pulmonary function data of the 104 patients enrolled in the study are shown in table 1. The frequency distribution of patients according to categorised BMI and post-bronchodilator FEV1 is shown in table 2.

DLCO % of predicted correlated significantly with BMI (Kg/m²), (r = 0.40, p < 0.0001), post-bronchodilator FEV1 %, (r = 0.53, p < 0.0001) and RV %, (r = -0.47, p < 0.0001). No correlation was found between BMI (Kg/m²), and post-bronchodilator FEV1 %, (r = 0.14, p = 0.16.), indicating that they represented independent characteristics in the study population.

Multivariate regression analysis showed that DLCO % was independently and significantly associated to both post-bronchodilator FEV1 %, (p < 0.0001) and BMI (Kg/m²), (p < 0.0001), according to the equation:

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DLCO = -18.32 + 0.65 \cdot FEV1 + 1.59 \cdot BMI
\]

\[(R^2 = 0.40, p < 0.0001)\]

**Table 1.** Anthropometrical characteristics and pulmonary function data in 104 patients (82 males and 22 females) with COPD

| Age (years) | Mean | SD | Range |
|-------------|------|----|-------|
| 66          | 9.4  | 41-86 |
| Height (cm) | 165  | 8.2| 144-190|
| Weight (Kg) | 71  | 15.8 | 41-139|
| FEV1 (% pred.) | 50 | 18.3 | 17-76|
| VC (% pred.) | 81  | 18.7 | 42-134|
| FEV1/VC (% pred.) | 47 | 13.2 | 21-85|
| TLC (% pred.) | 112 | 17.8 | 70-162|
| FRC (% pred.) | 144 | 34.5 | 83-240|
| RV (% pred.) | 169 | 48.7 | 103-328|
| PaCO2 (mmHg) | 39  | 6.4 | 27-65|
| PaO2 (mmHg) | 66  | 8.7 | 42-93|
| DLCO (% pred.) | 56  | 25.8 | 9-114|

*SD = standard deviation; § post-bronchodilator value of FEV1.

**Table 2.** Frequency distribution of patients by categorised FEV1 and BMI

| BMI (Kg/m²) | ≤ 18.5 | > 18.5 | Total |
|-------------|--------|--------|-------|
| ≤ 18.5      | 8      | 4      | 12    |
| > 18.5 and ≤ 25 | 30   | 19     | 49    |
| > 25 and ≤ 30 | 13   | 17     | 30    |
| > 30        | 6      | 7      | 13    |
| Total       | 57     | 47     | 104   |

§ post-bronchodilator value of FEV1.
The contribution of RV % to DLCO % was largely non significant (p = 0.16).

Figure 1 shows the mean value ± SD of DLCO % in patients classified according to categorised FEV1 % and BMI. There was no interaction between these two factors (p = 0.30), suggesting that the effect of either of them was independent of the level of the other. Both factors were highly significant (p < 0.0001).

**Discussion**

The results of the study show that CO diffusing capacity is associated to nutritional status, based on BMI, independent of FEV1. This data confirms previous findings on the role of nutritional depletion in patients with COPD [5-7]. Furthermore, looking at the close relationship between BMI and CO diffusing capacity for all four BMI groups segregated by FEV1, it could be argued that reduction in body weight is related to emphysema, to the extent that DLCO represents the functional hallmark of destruction of alveolar capillary surface. A vast number of comparative studies between lung function and either pathology or radiological evaluation support this notion [19-25]. Alternatively, the relationship between CO diffusing capacity and BMI groups segregated by post-bronchodilator FEV1 shows a significant difference between weight-stable and weight-losing COPD patients for the same level of FEV1, and invites to look at weight loss as a systemic domain which may in and of itself contribute to the COPD wasting syndrome. In this context, weight loss and low BMI reflect complex metabolic alterations related to disturbed energy balance, systemic inflammation, hypoxia and metabolic adaptations targeting lung, as well as skeletal and respiratory muscles [14].

Recent studies looking at systemic effects of COPD have analysed the pathogenesis of differences in nutritional status in COPD phenotypes [8]. They support the notion of a link between factors responsible for parenchymal destruction and nutritional abnormalities. Firstly, body weight and composition were substantially different between chronic bronchitis and emphysema [26]. The emphysematous type of COPD has lower values not only for BMI, but also for fat free mass index and fat mass index, compared to chronic bronchitis type [26]. Secondly, nutritional intervention studies have documented positive outcome of nutritional intervention in the majority of COPD patients [27]. Moreover, the fact that elevated systemic inflammatory response determines a non response to nutritional therapy [28] leads to speculate on the possibility that the systemic inflammatory response directly impacts on the metabolism, thus leading to disturbed energy balance and wasting syndrome that might contribute to emphysematous dysfunction independent of the severity of functional impairment. Besides differences in energy balance between emphysema and chronic bronchitis types, the relationship between CO diffusing capacity and BMI may also reflect differences in muscular adaptation, consequent to reduced availability of oxygen or tissue hypoxia. The negative relationship between diffusing capacity and fast myosin heavy chain isoform content in musculus vastus lateralis of COPD patients [29], and the occurrence of arterial oxygen desaturation in patients with emphysema as reflected by impaired diffusing capacity [30], lead to speculate on this hypothesis. Furthermore, the relationship between BMI and DLCO would suggest a decrease in oxygen supply and nutrients to muscles, especially during exercise, due to loss of capillary bed and inability to accommodate cardiac output without increasing pulmonary artery vascular pressure [31]. Therefore, these findings reinforce the idea that metabolic impairment as assessed by BMI may contribute to emphysematous dysfunction.

All of the above considerations provide accumulating evidence that COPD is a multi-organ disease that would be better characterised by a mult-idimensional grading system assessing the respiratory and systemic expressions of COPD [32]. In this context BMI is an index of paramount importance to characterize the “wasting syndrome” of COPD.

In conclusion, nutritional status as assessed by BMI contributes substantially to the impairment of CO diffusing capacity independently of the severity of airflow obstruction. Thus, BMI and FEV1 in combination provide useful respiratory and systemic markers of emphysematous dysfunction in COPD.

Fig. 1. - DLCO % predicted by categorised BMI (≤ 18.5; > 18.5 and ≤ 25; > 25 and ≤ 30; > 30) and post-bronchodilator FEV1(<50 % predicted vs ≥ 50% predicted). No interaction was found between BMI and FEV1 (p=0. 30). Both factors were highly significant (p <0.0001).
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