Combined chronic obstructive pulmonary disease assessment, body composition and muscle strength

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Abstract. Body composition, respiratory and skeletal muscle function have not been studied in patients with chronic obstructive pulmonary disease (COPD) using the combined COPD assessment recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). An assessment was carried out on 27 COPD patients to relate body composition and muscle strength, with the combined COPD assessment. Fat free mass (FFM) was estimated using bioelectrical impedance analysis (BIA) and body mass index (BMI). Percentage body fat was estimated by plicometry and muscle strength by hand dynamometry. For the women studied, the average FFM was 35.6 kg and for the man, this was 45.1 kg. 55.5% of the population was normal, 11.1% was underweight and 33.3% was overweight or obese in terms of BMI but 92.6% of the participants were at risk of hyperadiposity-associated diseases. Dynapenia was found in 59.3% of patients. There were no differences in body composition or muscle strength between the groups created with combined COPD assessment categories or their components except in FFM among patients with less than 2 vs those with 2 or more exacerbations. There were no differences in body composition or muscle strength between the combined COPD assessment and its components except in FFM in patients with different numbers of exacerbations.

1. Introduction
Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in the world [1]. In 2008, a prevalence of 8.9% was found, in 5 Colombian cities, significantly higher in people over 60 years of age [2]. This disease has the potential to trigger or worsen acute or chronic pathological conditions that increase morbidity, mortality, and cost of care [3]. In addition, there is a loss of skeletal muscle mass and a decrease in body weight [4].

Taking into account the above and as predictive tools, multidimensional COPD assessment systems such as BODE index and combined COPD assessment have been developed which, in addition to symptoms, include functional and nutritional assessment [1, 5]. Thus, interventions are important for secondary prevention and rehabilitation of patients with COPD [6].

In Asian populations exposed to risk factors for COPD, people with low BMI had a higher degree of bronchial obstruction [7] and worse values of forced expiratory volume in the first second (FEV1), in the ratio of forced expiratory volume in the first second and in forced vital capacity (FEV1/FVC) [8]. In a similar European population, spirometry results were worse in patients who increased their BMI but this was reversible by decreasing it [9]. In another study, a weak correlation was found between BMI
and FEV1 and between a dyspnea severity test and FEV1 [10]. However, obesity has been associated with poorer performance in functional tests [6] and greater prevalence of comorbidities [11].

Bioelectrical impedance analysis (BIA) has been shown to be a practical and low-cost tool that provides more accurate values of fat-free mass (FFM) than anthropometry in patients with COPD [12]. However, some results would be different compared to dual X-ray absorptiometry (DEXA) [13].

Low FFM is associated with a decrease in quadriceps strength and a decrease in the strength of the expiratory musculature [14]. In a Latin American population, it was found that the variations in FFM were homogeneously distributed among the different groups of severity in the classification of COPD and were not related to performance in the 6-minutes-walking test [15]. In another study, the decrease in FFM was associated with worse pulmonary function, more frequent exacerbations and continuity of smoking [16].

Evaluation of strength in patients with COPD is very useful [17]. When this parameter decreases with respect to controls, some alterations in inspiratory muscles are more frequent [18] and this is related to low lean muscle mass but not to performance in functional tests [19] even after training the strength of the upper extremity [20]. However, reductions in strength are also related to worse values of respiratory tests such as FEV1 [21], reduced exercise capacity and increased mortality [22].

The relationships between FFM and anthropometry with respiratory and skeletal muscle function tests have been studied in patients with COPD but not using the combined COPD assessment recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for risk assessment and therapeutic decision making [1]. Thus, the main objective of this research was to relate the body composition evaluated by BIA and anthropometry, and the muscular strength evaluated by dynamometry, with combined COPD assessment and its components: COPD assessment test (CAT), frequency of exacerbations and airflow limitation.

2. Methods

2.1. Subjects

This was an observational study with an analytical cross-sectional design. Patients belonged to a population with a medical diagnosis of COPD from a health service in Manizales and listed in a database with 2716 people on September 2013. The criterion of inclusion was to be in this database and the main criterion of exclusion was to have a pre- and post-bronchodilator spirometry not compatible with COPD. Other exclusion criteria covered patients with pathologies influencing body water distribution, anatomical or neurological alterations, presence of prosthesis or other conditions affecting BIA and/or dynamometry. However, the contact information on the database was wrong in most cases. Finally, 84 patients were evaluated, of which 14 had spirometry with restrictive pattern, 5 with reversible obstructive pattern, suggestive of asthma, 38 with normal spirometry and 27 with spirometric pattern compatible with COPD. These 27 were the population studied. The Bioethics Committee of the University of Caldas approved the study and all the participants signed the informed consent.

2.2. Study protocol

Patients were assessed at 6:30 am with minimum fast of 8 hours and a minimum physical exercise for 12 hours before the tests. The previous day, they were asked about the presence of acute pathological conditions that would contraindicate the performance of any of the tests. Measurements were performed by two trained physiotherapists. All subjects were examined barefoot, wearing underwear and a disposable hospital gown. After measuring the weight and height of each patient, pre and post-bronchodilator spirometry were performed. Then, BIA, dynamometry and plicometry were also carried out.

2.3. Body Composition

Weight was measured with a digital balance PP2000 (± 0.1 kg, Icob-Detecto, A&D Co, Japan) and height using a digital wall stadiometer Heighronic-235 (± 1 mm, Seca, Hamburg, Germany).
Measurements were performed twice [23]. BMI (weight in kilograms/height in meters\(^2\)) was categorized according to the World Health Organization criteria [24]. The percentage body fat was estimated by measuring skin folds three times on the non-dominant side using the electronic plicometer Skyndex ISM1000A (+/-0.5% USA) according to the Durnin and Womersley formula [25]. The results were classified according to the groups by Heyward [26]: malnutrition with (≤ 5% and ≤ 8%), below average (6-14% and 9-22%), average (15% and 23%), above average (16-24% and 24-31%) and at risk of diseases associated with obesity (>25% and >32%) for men and women respectively. For FFM estimation, a Hydra ECF / ICF 4200 body composition analyzer (0.01 Ω, 0.01° and 10 ml of Xitron Technologies Inc, San Diego, USA) was used under standard techniques [27]. Raw data of resistance, reactance, impedance and phase-angle were obtained at 50 kHz. For FFM estimation a formula for evaluation of patients with COPD and validated by the deuterium dilution method was used [12, 13]. The results were classified according to FFM percentiles for healthy white adults [28].

2.4. Muscle strength
Muscle strength was assessed by hand grip strength measurement on the dominant side. A hydraulic dynamometer Baseline, (±1 kg, Fabrication Enterprises Inc, USA) was used following the recommendations of the American Society of Hand Therapists [29]. The results were interpreted according to the values recommended by the European Consensus on the definition and diagnosis of sarcopenia to determine lower muscular strength: < 30 or < than 20 kg/f for men and women [30].

2.5. Combined COPD Assessment
Patients were assigned to categories A, B, C or D of the combined COPD assessment according to CAT results, number of exacerbations, and post bronchodilator FEV1[1]. Patients completed the CAT and exacerbations were quantified by self assessment of acute episodes of worsening symptoms, change in the treatment or hospitalization within the last year. Spirometry was performed with a Quark PFT-2 (±0.01 L COSMED, Italy) as standardized by the American Thoracic Society and European Respiratory Society [31]. Briefly, patients were given a basal spirometry test with three acceptable and repeatable FVC maneuvers for FVC and FEV1 (difference between the two highest values of FVC or FEV1 <0.15 L). For the bronchodilator test, 400 μg of salbutamol were administered after 15 minutes of rest and three new acceptal and repeatable maneuvers were obtained. FEV1, FVC and FEV1/FVC results were interpreted according to GOLD 2016 and the Latin American Association of Thorax, using reference values for Mexican American women and men [1, 32] acceptable for a Colombian population [33]. The severity of airflow limitation was categorized using post bronchodilator FEV1 as recommended by GOLD [1].

2.6. Statistical analysis
SPSS version 15.0 software licensed for the University of Caldas was used. A value of p < 0.05 was considered significant for all cases. Values were reported as mean ± standard error (SE). The Shapiro-Wilk test was used for the definition of normality and the Levene test for the equality of variances. ANOVA was used to compare body composition between categories of airflow limitation and t-student for the other comparisons.

3. Results

3.1. Subjects
The 2,716 patients diagnosed with COPD who were on the database were contacted by telephone. Between April 2015 and April 2016, 88 patients were recruited but 4 had exclusion criteria. Of the 84 patients finally evaluated, 14 had spirometry with restrictive pattern, 5 with reversible obstructive pattern suggestive of asthma, 38 with normal spirometry and 27 with spirometric patterns compatible with COPD (10 women and 17 men). Of these 27 patients, 88.0% were between 60 and 86 years old,
92.6% lived in urban areas, 85.0% had a history of smoking and 44.4% had previous exposure to biomass smoke.

3.2. Body composition and muscle strength

The mean FFM for women was 35.63 kg (±35.63) and 45.12kg (±1.54) for men. These figures were between the 5th and 10th percentile and below the 5th percentile of the group between 65 and 74 years of age of healthy individuals respectively. According to BMI, 11.1% of the population was underweight, 55.5% had normal BMI and 33.3% were overweight or obese. However, when body fat percentage was assessed by plicometry, 92.6% of the subjects were above the normal body fat percentage. The average hand grip strength was found to be in the range of dynapenia for both sexes. Table 1 shows characteristics of subjects (Table 1).

| Table 1. General characteristics and body composition measurements. |
|---------------------------|---------------------------|---------------------------|
| Characteristics          | Male n=17                 | Female n=10               |
|                          | Mean value | SE  | Mean value | SE  |
| Age (years)              | 73.8       | 2.1 | 69.3       | 3.4 |
| FFM (kg)                 | 45.1       | 1.5 | 35.6       | 1.2 |
| BMI (kg/m²)              | 24.0       | 0.9 | 24.1       | 1.4 |
| % of fat                 | 24.4       | 1.2 | 33.2       | 1.7 |
| HGS (kg)                 | 29.3       | 1.6 | 16.5       | 2.4 |

Abbreviations: SE, standard error; BMI, body mass index; FFM, fat-free mass; HGS: hand grip strength-dominant side

3.3. Combined COPD assessment

Most patients were classified in categories B and D of the combined COPD assessment, and only one was classified in category C (Figure 1). 88.9% of the patients had CAT ≥ 10 and 88.9% had less than two exacerbations in the previous year. The percentage of patients with mild airflow limitation was 22.2%, 51.9% had moderate limitation and 22.2% presented severe limitation. Only one patient had very severe limitation (Table 2).

3.4. Relationship between body composition and muscle strength with the combined COPD assessment and its components.

Considering that there was only one patient in the very severe category of airflow limitation and the GOLD C category of the combined COPD assessment, the following adjustments were made to search for differences between the combined COPD assessment categories and each one of its components with the variables of body composition and muscle strength:

1 - Patients in the severe and very severe categories of airflow limitation were put together.
2- Four groups were created with the GOLD categories.
Group 1: A+B. Group 2: C+D. Group 3: A+ C. Group 4: B + D.
Categories A and B and categories C and D are similar to each other in the severity of airflow limitation and in the frequency of exacerbations. Categories A and C and categories B and D are similar to each other in symptomatology.

Table 2. Combined COPD assessment components.

| Characteristics                              | Male n=17 | Female n=10 |
|----------------------------------------------|-----------|-------------|
| CAT ≥ 10                                     | 15        | 9           |
| Exacerbations ≥ 2 a                         | 3         | 0           |
| Severity of airflow limitation              |           |             |
| Mild FEV1 ≥ 80% predicted                   | 4         | 2           |
| Moderate 50% ≤ FEV1 < 80% predicted         | 9         | 5           |
| Severe 30% ≤ FEV1 < 50% predicted           | 3         | 3           |
| Very Severe FEV1 < 30% predicted            | 1         | 0           |

Abbreviations: CAT, COPD assessment test; FEV1, forced expiratory volume in 1 second. a ≥ 1 leading to hospital admission

Quantitative variables had normal distribution and equal variances. In the comparison of the means of body composition and muscle strength between the new GOLD groups and between the groups generated by the components of the combined COPD assessment, no differences were found except between the FFM of patients with less than 2 exacerbations vs those who were 2 or more. The CI 95.0% of the mean difference was (-21.39; -7.00) with a p-value of 0.000. Table 3 shows the evaluation of body composition and muscle strength in each group by categories of the combined COPD assessment and its components.
The population consisted mostly of elderly people living in urban areas and having high symptomatology, low frequency of exacerbations and moderate airflow limitation. Their FFM was under the 5th percentile. In about half of the cases, BMI was normal and, in almost all cases, the average percentage of body fat was in the obesity-associated disease risk category. Three fifths of patients had abnormal handgrip strength. As far as we know, this is the first study comparing body composition and muscle strength among combined COPD assessment categories.

While 60.0% of our patients with CAT ≥ 10 had FFM under the 5th percentile, and almost all of them had normal or elevated BMI, the few patients with CAT <10 had FFM between the 5th and 50th percentiles and normal or high BMI. This study did not find any correlation between CAT and fat-free mass index (FFMI) [34]. In addition, differences in values from CAT or Medical Research Council (MRC) parameters, comparing patients with low vs normal FFMI were not significant [15, 35, 36]. Obesity determined by BMI has been associated with an increased risk of functional limitation in women [6] and the dyspnea score has not deferred significantly between patients with FFMI depletion determined by a combination of BMI and BIA-FFMI [36].

The total number of patients with FFM for BIA below the 5th percentile had less than 2 exacerbations. 58.3% of patients with less than 2 exacerbations had FFM lower than the 5th percentile while patients with 2 or more exacerbations had FFM between the 25th and 50th percentiles. The FFM average for the first group was 40.0 kg and the second 54.2 kg. The difference was significant. This differs from a study with more patients with low FFMI in the group of frequent exacerbations compared to those with fewer than 2 exacerbations the previous year, but without significant difference [35]. Patients with a low phase angle reported more exacerbations than those with low FFMI, and no difference was found in frequency of exacerbations in the previous year between groups with and without FFMI depletion [34]. However, in the follow-up of these patients, the FFM decline was associated with more frequent exacerbations.
[16] and patients with lower FFM presented greater hospital readmissions due to exacerbations [37]. Explanations as to why our patients with lower FFM had fewer exacerbations should emerge from studies with a larger number of patients in addition to the measurement of biochemical markers that reflect nutritional and inflammatory status.

In our study patients, 67.0 % of patients with less than 2 exacerbations had dynapenia and all those with 2 or more exacerbations had normal hand grip strength. Similarly, evaluation of quadriceps strength in patients from the United Kingdom, was not significantly correlated with frequent exacerbations [16] whereas, in some Spanish research, both, respiratory and peripheral muscle weakness were strongly associated with exacerbations [38].

In this study, patients with mild to moderate airflow limitation, FFM was below the 5th percentile in 60.0 % of cases as did 28.6% of those with severe and very severe limitation. In patients studied in different European countries, FEV1 has been positively correlated with FFM [34, 37]; however, differences in FFM between groups with different degrees of bronchial obstruction were of no statistical significance [16, 35, 39] except in patients with very severe obstruction in a Dutch investigation [39].

When evaluating BMI in patients with different degrees of airflow limitation, the tendency in several studies was to find a greater number of overweight and obese patients in degrees of mild and moderate bronchial obstruction and progressive decrease in their values as the limitation worsened. These findings place most of them with normal BMI in categories of severe and very severe bronchial obstruction in other studies [35,39,40]. 57.1% of participants with severe and very severe limitation were overweight or obese. Our patients with different degrees of airflow limitation had a similar proportion of dynapenia. In other research, quadriceps strength was not significantly correlated with the severity of airflow obstruction at baseline or at follow-up at one year when it decreased [16].

Although we only found differences in FFM between patients with different frequencies of exacerbations, this evaluation of body composition and muscular strength, using the Combined COPD assessment, opens the door to possible differences between GOLD categories. Different tests that do not require formulas for their determination, such as phase angle [34] or the impedance ratio to 5/250 KHz are also possible [41].

This study has limitations. Different BIA formulas for estimation of FFM could modify the final results of associations between different categories of patients with COPD [42,43]. An example is that the formula used in the present investigation for calculation of FFM underestimates the FFM by DEXA in Dutch patients with moderate and severe COPD but not the FFM estimated by a specific formula developed by the authors [44].

Last, but not least, is the need to mention the remarkable difference found between clinical diagnosis and spirometric diagnosis of COPD. 68% of the patients initially evaluated from a population database with a diagnosis and treatment for COPD had a spirometric pattern not compatible with this pathology, that is, their diagnosis was erroneous [45].

5. Conclusion
In this study there was a predominance of very symptomatic patients, with moderate limitation to the airflow and low frequency of exacerbations. Contrary to the expected results, patients with 2 or more exacerbations had a FFM, BMI, percentage of fat and manual dynamometry greater than those with less than 2 exacerbations. This could suggest that an increase in body mass could have a protective effect for these patients. On the other hand, the differences between groups created with the combined COPD assessment categories in terms of body composition and muscle strength were not statistically significant.

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Conflict of interest
The authors declare that there is no conflict of interest for this work.

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