Fat-free mass index in patients with chronic obstructive pulmonary disease

R A Díaz-Sanabria¹, C H González-Correa², F Marulanda-Mejía¹, C D Aguilar-Díaz¹, L E Sepúlveda-Gallego³, L M Duque-González⁴ and M C Pineda Zuluaga²

¹Clinical Department, Universidad de Caldas, Manizales, Colombia
²Department of Basic Health Sciences, Research Group on Nutrition, Metabolism and Food Security, Universidad de Caldas, Manizales, Colombia
³Public Health Department, Research Group on Health Promotion and Disease Prevention, Universidad de Caldas, Manizales, Colombia
⁴Human Movement Department, Body and Movement Research Group, Universidad Autónoma de Manizales, Manizales, Colombia

E-mail: *maria.22919131551@ucaldas.edu.co

Abstract. Chronic Obstructive Pulmonary Disease (COPD) is a public health problem because it is a major cause of death in the world. Approximately 25% of patients with moderate disease and 35% with severe disease show a reduced fat-free mass (FFM). Thus, the objective of this study is to define the correlation between fat-free mass index (FFMI), muscle function, respiratory symptoms, number of exacerbations during the last year, and degree of airflow obstruction in patients with COPD. It is a prospective and cross-sectional study. The FFMI was below 32.7% (n=18) and the strength diminished by 56.4% (n=31). In the sample, we found a direct and significant correlation between the FFMI and the FEV₁ (predicted %), (p= 0.045). When analysed by sex, men had a direct correlation between FFMI and the FEV₁ (predicted %), (p=0.019), an inverse correlation between FFMI and the spirometric classification of the Global Initiative Obstructive Lung Disease (GOLD) (p=0.008), and between the muscular function and the symptoms (p=0.03). In women, no significant correlation was found. In conclusion, the conditions in mass and muscular function were correlated with clinical variables and pulmonary function in men. We did not find a correlation between corporeal composition and the number of exacerbations.

1. Introduction
COPD is characterized by persistent limitation of the air flow. It is the third leading cause of mortality and the first of chronic morbidity in the world, due to the increase in life expectancy, the tobacco consumption, and the increase in environmental factors [1,2]. Latin America reported a prevalence between 7.8% and 19.7% [1], and Colombia 8.9% [3]. COPD can cause significant systemic effects like muscular dysfunction and a loss of muscle mass. There are several factors that contribute to this reduction, such as insufficient energy intake due to the loss of appetite, an increase in energy expenditure secondary to increased respiratory work and a systemic inflammatory state with increased production of inflammatory cytokines [4,5]. On the other hand, it is proposed that the etiology of musculoskeletal dysfunction is due to hypoxia and chronic hypercapnia, the use of steroids, oxidative
stress, and physical deconditioning [6,7]. Additionally, the muscular dysfunction is characterized by reduced muscle strength and physical performance [8].

Alterations in FFM and muscle function have been associated with variables that determine the severity of COPD, such as respiratory symptoms, increase in the frequency of exacerbations and the level of obstruction of the airway, in addition to limitation in exercise performance and decrease in quality of life [9-11]. Therefore, multidimensional COPD rating systems have been developed that include functional and nutritional assessments in addition to the evaluation of respiratory function such as the BODE Index (body mass index, airflow obstruction, dysnea and exercise capacity) [12].

In Latin America there have been no studies that evaluate body composition, muscle function and its correlation with COPD severity variables according to Global Initiative Obstructive Lung Disease (GOLD) [1]. This is how the present study used FFMI to analyze body composition, hand grip strength (HGS) and gait speed to evaluate the muscular function of people with stable COPD who had different degrees of disease with the aim to define the correlation between these and the COPD severity variables defined by GOLD.

2. Methodology

2.1 Design of the Study and subjects

It is a prospective and cross-sectional study. A sample of 47 patients was calculated that allowed to detect correlation coefficients higher than 0.4 with a 95% safety and a statistical power of 80% according to findings in previous studies with similar characteristics [13-15]. The study population included subjects with a clinical diagnosis of COPD, managed by ambulatory services of pulmonology or internal medicine of the city of Manizales, during January 1st to November 30th, 2018.

Subjects were included according to the following criteria: age over 40 years, clinical diagnosis of COPD and acceptance to participate in the study. Subjects with exacerbations in the last month who did not comply with spirometric criteria for COPD according to GOLD [1], as well as those with active pulmonary infections or disability that prevented any of the measurements necessary for the study were also excluded.

Once included, they were called in for evaluation at the nutritional assessment laboratory of the University of Caldas. The project was evaluated and endorsed by the ethics committee of the University of Caldas. This committee considered this study to be low risk. All patients signed informed consent.

From the outpatient department of internal medicine and pneumology, 142 patients who met the inclusion criteria were recruited, of whom 19 were excluded because they presented clinical conditions that limited the performance of the tests necessary for the study (5 paraplegia, 7 osteosynthesis material, 3 chronic use of oral steroids, 2 hemodialysis, 2 exacerbations in the last week) leaving a total of 123 patients who were examined. After carrying out the tests, 68 patients who did not comply with the diagnosis of COPD with post-bronchodilator spirometry confirmation were excluded, resulting in a total of 55 patients for the statistical analysis, a number that exceeded the calculated sample of n=47 to find significant correlations.

2.2 Body composition assessment

Anthropometric measurements such as weight, height, and body mass index (BMI) were performed. FFM and FFMI were estimated from BIA, using Kiton Technologies Hydra 4200® bioimpedanciometer at a frequency of 50 kHz. The patients were placed in supine position with four surface electrodes on the wrist and near the ankle [16].

The validated formula by Schols et al in 1991 was used as a calculation formula in patients with COPD [17]. The FFMI (kg/m²) was determined according to the FFM/ height² equation. In COPD, a low FFM was defined when it was less than 15 kg/m² in women and less than 16 kg/m² in men [18,19].
2.3 Muscular Function

The muscular function was evaluated by means of HGS and gait speed in four meters. The HGS was measured with a Baseline® digital dynamometer, (±1 kg) following the recommendations given by the American Therapeutic Society. A total of three efforts were made, one at the beginning, the next at 35 seconds and the last at 1 minute and 10 seconds with the dominant arm, resulting in the largest of the three efforts recorded, expressed in Kg/force [20].

The reference values used were according Mathiowetz and Cols. in 1985, for the different age groups and sex [21]. We used the gait speed test in 4 meters, due to its easy application in the clinical and research settings. It has a good interobserver and reproducibility correlation [22], being considered normal values as those equal to or higher than 0.8 m/sec.

2.4 Pulmonary Function

Spirometry was performed with the equipment to measure lung function Quark PFT-2 (± 0.01 L COSMED, Italy) calibrated daily before starting the evaluation [23]. Patients were examined in a sitting position, and they had to complete a basal spirometry with three forced vital capacity manoeuvres (FVC) acceptable and repeatable for FVC and the forced expiratory volume in the first second (FEV₃) (difference between the two highest values of FVC or FEV₃<0.15 L).

The FEV₁, FVC and the relation between FEV₁/FVC were measured before and 15 minutes after a bronchodilator test with a 400 mcg dose of salbutamol. The FEV₁ and FVC values are expressed in liters and the predicted percentage for the patients of the same genre and age.

The relationship between FEV₁/FVC was calculated with the highest values of each of the parameters in at least 3 spirometry maneuvers with an acceptable technical curve. For the COPD diagnosis, a relation between FEV₁/FVC < 0.7 post-bronchodilator was considered as a cutting point [1].

2.5 Symptoms and exacerbations

The COPD Assessment Test (CAT), (an 8-item unidimensional questionnaire format) specific for COPD and validated in Spanish, was used to determine the symptomatology. The score goes from 0 to 40. It has an adequate correlation with the St George Respiratory Questionnaire (SGRQ) [24,25] and is easier to interpret, which allows for a higher reproducibility in the test-retest procedure [26]. The results were expressed as discrete variables, values greater than 10, represent the patients with the most symptoms and the worst quality of life, using a lower value than 10 as a dichotomous variable representing the minimally symptomatic according to the GOLD guides [1].

Acute worsening of the respiratory symptoms is defined as exacerbation that leads the patient to additional treatment and whether or not they need hospitalization. As a frequent exacerbator, we defined those who presented one or more exacerbations in the last year that required of hospital admission, or two or more exacerbations that did not require hospitalization [1].

2.6 Combined COPD assessment

The patients underwent the combined evaluation according to the GOLD guide [1]. This evaluation consists of measuring the following parameters: a) the degree of airflow obstruction according to FEV₁ (predicted %); b) the CAT and c) the frequency of exacerbations during the past year. With b) and c) variables, four groups were generated:

Group A: low risk (0 or 1 exacerbation, without hospitalization); minimally symptomatic (CAT <10),
Group B: low risk (0 or 1 exacerbation, without hospitalization); very symptomatic (CAT ≥ 10),
Group C: high risk (≥2 or ≥1 with hospitalization); minimally symptomatic (CAT <10),
Group D: high risk (≥2 or ≥1 with hospitalization); very symptomatic (CAT ≥ 10).
2.7 Statical Analysis
For the statistical analysis, the SPSS program, version 24, licensed for the University of Caldas, was used. The Pearson correlation coefficient was used to evaluate the association between the variables.

3. Results
The average age population was 69 years, all had a risk factor for COPD, 88% had a positive history of smoking, 49% had exposure to wood smoke and 40% had a positive history of smoking plus exposure to firewood smoke. The BMI and the FFMI were low in 7.3% (n = 4) and 32.7% (n = 18) respectively (table 1).

Regarding the severity of COPD, most patients were in categories B and D; 72.7% had a CAT ≥ to 10 points; 25.4% had an average of exacerbations of 0.85 per year and 7.3% (n=4) of the population presented severe limitation of airflow. Muscle dysfunction was observed in most of the population, low HGS values were obtained in 56.4% (n=31) and low gait speed in 52.7% (n=29).

In the general population, a direct and significant correlation was found between the FFMI and the FEV\textsubscript{1} (predicted %) post bronchodilator, with a correlation coefficient of 0.271, an r\textsuperscript{2} of 0.074 and a p=0.045 (figure 1-A), no correlation was found between the FFMI and the other severity variables.

In the analysis done by subgroups according to sex, in men we found an increase in the direct correlation between the FFMI and FEV\textsubscript{1} (predicted %) post bronchodilator, with a correlation coefficient of 0.407, an r\textsuperscript{2} of 0.166 and a p=0.019 (figure 1-B).

Additionally, we found an inverse correlation between FFMI and the spirometric classification of the GOLD with a correlation coefficient of -0.456, an r\textsuperscript{2} of 0.216 and a p=0.008 (figure 1-C). We also found an inverse correlation between the muscular function and the symptoms according to the CAT. The correlation coefficient found was of -0.379, an r\textsuperscript{2} of 0.145 and a p=0.03 (figure 1-D). On the contrary, in women, no significant correlation was found between the FFMI, the muscular function and the severity variables found in COPD.

**Table 1.** Basic characteristics of the population.

| Basic characteristics                      | n (%)   | $\bar{x}$ ± (SD) |
|--------------------------------------------|---------|-----------------|
| **Age (years)**                            | 69 (12) |                 |
| **Sex**                                    |         |                 |
| Men                                        | 33 (60%)|                 |
| Women                                      | 22 (40%)|                 |
| **Smoking history**                        |         |                 |
| Negative                                   | 6 (11%) |                 |
| Positive                                   | 49 (88%)|                 |
| Former smoker                              | 41 (74%)|                 |
| Active smoker                              | 8 (14%) |                 |
| Index Packages / year                      |         | 40 (28)         |
| Exposed to wood smoke                      | 27 (49%)|                 |
| Years exposed to wood smoke                |         | 17 (16)         |
| Positive smoking history and exposure to wood smoke | | 22 (40%) |
| Weight (Kg)                                | 61 (12) |                 |
| Height (cm)                                | 158 (9) |                 |
| **FFMI**                                   |         |                 |
| Low                                        | 18 (33%)|                 |
| Normal                                     | 37 (67%)|                 |

The data are presented as percentage (%), mean ($\bar{x}$) and standard deviation (SD). Abbreviations: FFMI, fat free mass index.
Table 2. COPD severity according to the combined COPD assessment.

|                          | n (%) | ± (DE) |
|--------------------------|-------|--------|
| Number of exacerbations (patient/year) | 0.85 (1.1) |
| With admission to hospitalization | 0.07 (0.3) |
| Without admission to the hospital | 0.78 (1.1) |

**FEV₁ (predicted %)**
- >80: GOLD 1 | 9 (16.4%)
- 50-79: GOLD 2 | 25 (45.4%)
- 30-4: GOLD 3 | 17 (30.9%)
- <30: GOLD 4 | 4 (7.3%)

**Combined classification**
- A: low risk, minimally symptomatic | 10 (18.2%)
- B: low risk, very symptomatic | 28 (50.9%)
- C: high risk, minimally symptomatic | 5 (9.1%)
- D: high risk, very symptomatic | 12 (21.8%)

The data are shown as percentage (%), mean (X) and standard deviation (SD).

Abbreviations: GOLD, Global Initiative for Obstructive Lung Disease.

Figure 1. Correlation between Fat Free Mass Index (FFMI) with FEV₁ (% predicted) in all subjects (r² = 0.074, p: 0.045) (A); FEV₁ (% predicted) in men (r² = 0.166, p: 0.019) (B); Classification GOLD spirometry in men (r² = 0.161, p: 0.008) (C) and correlation between maximum dynamometry and COPD assessment test (CAT) in men (r² = 0.095, p: 0.03) (D).
4. Discussion
In this study, 37% of patients presented a low FFMI. It was a percentage slightly higher than those observed by Vermeren, et al in 2006 [27] who described a low FFMI in 27% of the population and of Norden et al, in 2015 who found 36% [28]. It is noteworthy in this study that only 7% of patients were underweight, while 44% were overweight or obese, different from the results of other studies such as those of Hallin, et al in 2006, which show percentages of low weight up to 26% and only 29% with overweight and obesity [10].

It is interesting to highlight the functional commitment of more than 50% of the patients, which could be indicating a deterioration of the muscular composition and its function, with risks of loss of autonomy, quality of life and that of the immune function, as different studies related to outcomes of sarcopenia show it. Jones et al in 2015, determined that up to 14.5% of patients with COPD have sarcopenia [29].

It is notable that the average of exacerbations was reduced and is below what other studies show, with the possible explanation that, perhaps, the phenotype of the patients, as it seems to be seen in the BMI, may be different from other populations studied, or that patients have not accurately reported the retrospective self-report of exacerbations. Zhenchao, et al in 2018 conducted a retrospective study with 744 patients with COPD, finding an average of 3.8 exacerbations per patient/year [30]. In contrast, Hallin et al in 2006 followed up a total of 42 patients with COPD for 12 months and found an average of 0.58 severe exacerbations per patient/year with a requirement for hospital admission [10].

It should be noted that the direct and significant correlation found between FFMI and lung function in the subgroup of men is comparable with the findings found in the study by Ischaki, et al in 2007 [15].

Additionally, the direct correlation between manual dynamometry and the clinical condition and quality of life evaluated by CAT confirms previous results of studies such as those of Bernad, et al. In support of the importance of muscle function [7]. Unlike what was reported by Hallin et al in 2006 [10] and Zhenchao et al in 2018 [30], correlation between body composition and number of exacerbations was not observed in this study, which could depend on the low degree of exacerbations reported in these patients.

It is necessary to point out the lack of correlation in women’s FFMI, muscle function and the severity of COPD, while other investigations such as those of Ischaki and cols in 2007 did observe it [15]. It would be worthwhile to get a bigger sample in former studies and compare different COPD phenotypes to specify if there is any gender inequality or is it a kind of COPD that marks the difference.

The findings found in this work represent an important event for COPD patients in our region for various reasons. The first of these is that in our region there is an important gap in knowledge related to research in patients with COPD, in addition, the investigations carried out focus on the pharmacological treatment of these patients and do not address the need to inquire about the Comprehensive evaluation of these patients in routine consultations as a disease prevention strategy.

The comprehensive assessment of the patient with COPD will allow health professionals to identify the real condition of the patient, not only based on their lung function, but also on her muscle function and body composition. Well, as this study shows, there are variables that are related to lung function and symptoms. The timely identification of extra-pulmonary systemic effects derived from COPD would contribute to timely and effective care to improve the quality of life of these patients.

5. Conclusions
COPD patients in our region present lower FFMI values compared to those registered in studies carried out elsewhere. Furthermore, in approximately half of them, overweight and obesity prevailed, which is an unusual finding in these patients who generally present alterations in body composition related to malnutrition. Low FFMI values were related to greater airflow obstruction in the general population, but not to body composition and the number of exacerbations. The results found show us the importance of including in the routine check-ups of these patients, the evaluation of the quantity
and quality of the muscles, since, as we have seen, they are related to lung function and can determine
the independence and functionality of the patient to a greater extent.

Acknowledgement
We want to acknowledge the volunteers who responded to the call. We also want to make a special
recognition to the working team of the Nutrition, Metabolism and Food Safety group, which actively
collaborated in the realization of this research.

Conflict of interest
The authors declare no conflicts of interest.

References

[1] Global Initiative for Chronic Lung Disease (GOLD) 2021 GOLD Report – 2021 [Internet] 12–9
[2] Menezes A M, Pérez-Padila R, Jardim J R, Muiño A, López M V and Valdivia G 2005 Chronic
obstructive pulmonary disease in five Latin American cities (the PLATINO study): a
prevalence study Lancet. 366 (9500) 1875-81
[3] Caballero A, Torres-Duque C A, Jaramillo C, Bolivar F, Sanabria F, Osorio P, et al 2008
Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude
(PREPOCOL study). Chest. 133 (2) 343-9
[4] Barnes P J and Celli B R 2009 Systemic manifestations and comorbidities of COPD Eur Respir
J 33 (5) 1165-8
[5] Takao T and Kenji N 2013 Undernutrition in Patients with COPD and Its Treatment Masayuki
Itoh Nutrients 5 1316-3
[6] Robles P G, Mathur S, Janaudis-Fereira T, Dolmage T E, Goldstein R S and Brooks D 2011
Measurement of peripheral muscle strength in individuals with chronic obstructive
pulmonary disease: a systematic review J Cardiopulm Rehabil Prev. 31 (1) 11
[7] Bernard S, Leblanc P, Whittom F, Carrier G, Jobin J, Belleau R, et al 1998 Peripheral Muscle
Weakness in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care
Med 158 629–634
[8] Ischaki E, Papatheodorou G, Gaki E, Papa I, Koulouris N and Loukides S 2007 Body mass and
fat-free mass indices in COPD: relation with variables expressing disease severity Chest. 132
(1) 164-9
[9] Gupta B, Kant S and Mishra R 2010 Subjective global assessment of nutritional status of
Chronic obstructive pulmonary disease patients on admission Int J Tuberc Lung Dis. 14 (4)
500-5
[10] Hallin R, Koivisto-Hursti U K, Lindberg E and Janson C 2006 Nutritional status, dietary
energy intake and the risk of exacerbations in patients with chronic obstructive pulmonary
disease (COPD) Respir Med 100:561e7
[11] Hallin R, Gudmundsson G, Suppli-Ulrik C, Nieminen M M, Gislason T, Lindberg E, et al 2007
Nutritional status and long-term mortality in hospitalized patients with chronic obstructive
pulmonary disease (COPD). Respir Med. 101(9) 1954–60
[12] Celli B R, Cote C G, Marin J M, Casanova C, Montes de Oca M, Mendez R A, et al 2004 The
body-mass index, airflow obstruction, dyspnea, and exercise capacity index in obstructive
pulmonary disease. N Engl J Med 350 (10) 1005-12
[13] Pértegas-Díaz S and Pita F S 2001 Determinación del tamaño muestral para calcular la
significación del coeficiente de correlación lineal Aten Primaria 9 209-211
[14] Dias F D, Gomes-Evelim L F D, Stirbulov Roberto, Alves-Vera L S and Costa D 2014
Assessment of body composition, functional capacity, and pulmonary function in patients.
with Chronic Obstructive Pulmonary Disease Fisioter. Pesqui. 21 (1) 10-15
[15] Ischaki E, Papatheodorou G, Gaki E et al 2007 Body mass and fat-free mass indices in: relation
with variables expressing disease severity. Chest 132 164-9

[16] Kyle U G, Bosaeus I, De Lorenzo A D, Deurenberg P, Elia M, Gómez JM, et al 2004 Bioelectrical impedance analysis--part I: review of principles and methods. ClinNutr 23 (5) 1226-43

[17] Schols A M, Wouters E F, Soeters P B and Westerterp K R 1991 Body composition by bioelectrical-impedance analysis compared with deuterium dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease Am J ClinNutr 53 (2) 421-4

[18] Schols A M, Soeters P B, Dingemans A M, Mostert R, Frantzen P J and Wouters E F 1993 Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation Am Rev Respir Dis 147(5) 1151-56

[19] Creutzberg E C, Wouters E F, Mostert R, Weling-Scheepers C A and Schols A M 2003 Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease Nutrition 19 (2) 120-7

[20] Roberts H C, Denison H J, Martin H J, Patel H P, Syddall H, Cooper C, et al 2011 A review the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach Age Ageing 40 (4) 423-9

[21] Mathiowetz V, Kashman N, Volland G, Weber K, Dow M and Rogers S 1985 Grip and pinch strength: normative data for adults Arch Phys Med Rehabil 66 (2) 69-74

[22] Working Group on Functional Outcome Measures for Clinical Trials 2008 Functional for clinical trials in frail older persons: time to be moving J Gerontol A Biol Med Sci 63 160-4

[23] Rojas M X and Dennis R J 2010 Reference values for respiratory parameters in the adult of Bogota, D.C., Colombia Biomedica 30 (1) 82-94

[24] Jones P W, Harding G, Wiklund I, Berry P, Tabberer M, Yu R, et al 2012 Tests of the responsiveness of the COPD Assessment Test following acute exacerbation and pulmonary rehabilitation COPD assessment test responsiveness Chest. 142 134-40

[25] Tsili gianni I G, van der Molen T, Moraitaki D, Lopez I, Kocks J W H, Karagiannis K, et al 2012 Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). BMC Pulm Med 12: 20

[26] Jones P W, Harding G, Berry P, Wiklund I, Chen W H and Kline-Leidy N 2009 Development and first validation of the COPD Assessment Test Eur Respir J. 34 648-54

[27] Vermeeren M A, Creutzberg E C, Schols A M, Postma D S, Pieters W R, Roldaan A C, et al Prevalence of nutritional depletion in a large out- patient population of patients with COPD Res pir Med 2006 100 (8) 1349-55

[28] Norde’ n J, Gro’ nberg A M, Bosaeus I, Forslund H B, Hulthe’n L., Rothenberg E, et al 2015 Nutrition impact symptoms and body composition in patients with COPD Eur J ClinNutr 69 (2) 256- 61

[29] Jones S E, Maddocks M, Kon S S, et al 2015 Sarcopenia in COPD: prevalence, clinical, and response to pulmonary rehabilitation Thorax 70 213-8

[30] Yang Z, Mengdie Y N and Wu Y L 2018 Body mass index of patients with chronic obstructive pulmonary disease is associated with pulmonary function and exacerbations: a retrospective real world research J Thorac Dis 10 (8) 5086-99