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Impact of pre-sarcopenia and sarcopenia on biological and functional outcomes in individuals with chronic obstructive pulmonary disease: a cross-sectional study

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ABSTRACT

Introduction: The impact of pre-sarcopenia, sarcopenia on important clinical and biological outcomes in individuals with Chronic obstructive pulmonary disease (COPD) have not been fully investigated.

Objective: To analyze the impact of pre-sarcopenia and sarcopenia on balance, muscle mass, peripheral and respiratory muscle strength and inflammatory and oxidative stress biomarkers in individuals with COPD.

Methods: sixty-one patients diagnosed with COPD were included, stratified into three groups: without sarcopenia (n = 33; 69 ± 6 years), with pre-sarcopenia (n = 15; 66 ± 6 years) and with sarcopenia (n = 13; 71 ± 7 years), according to the European Working Group on Sarcopenia in Older People. It was assessed respiratory muscle strength, through maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP), handgrip strength (HGS) and body composition analysis with bioimpedance. Inflammatory and oxidative stress biomarkers were analysed from peripheral blood.

Results: The prevalence of pre-sarcopenia and sarcopenia in individuals with COPD was 36% and 25%, respectively. Individuals with sarcopenia exhibit inferior muscle mass, peripheral muscle strength, respiratory muscle strength, and balance compared to their counterparts ($p<0.05$ for all). In addition, individuals with sarcopenia presented lower levels of protein oxidation ($p=0.015$) and higher levels of interleukin-1ϐ ($p=0.035$) compared to those without sarcopenia. Individuals with pre-sarcopenia presented lower levels of antioxidant activity ($p=0.045$) and higher levels of C-reactive protein ($p=0.035$).

Conclusion: Individuals with COPD who have sarcopenia exhibit diminished muscle mass, impaired balance, and reduced peripheral and respiratory muscle strength in comparison to those with pre-sarcopenia or without sarcopenia. In addition, the presence of sarcopenia and pre-sarcopenia is probably linked by biological mechanisms related to systemic inflammation and oxidative stress.

KEYWORDS

COPD; Sarcopenia; Muscle Strength; Inflammation; Oxidative stress.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an airflow limiting disorder caused by inhalation of toxic gases and particles[1] that is characterized by extra pulmonary changes that negatively affect physical function and quality of life[2–5]. The presence of such factors is also closely related to sarcopenia[6],

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a condition defined as the presence of low muscle mass, muscle strength and physical performance[6]. Sarcopenia is a significant contributor to frailty and disability in older people, and it is associated with increased rates of falls, hospitalization and mortality[7,8].

Various clinical and biological factors have been identified as significant contributors to sarcopenia in individuals with COPD[9–11]. These factors encompass the advanced stage of the disease, diminished levels of physical activity, smoking status, as well as heightened levels of oxidative stress and inflammatory biomarkers[9–11]. Sarcopenia has a negative impact on a range of clinical outcomes, physical function, exercise capacity, physical activity levels, quality of life, dyspnea and prognosis in individuals with this respiratory disease[12–16]. Additionally, current studies reported that individuals with this respiratory disease who have sarcopenia presented more chronic inflammation and oxidative stress[10,11].

Sarcopenia exhibits a high prevalence among individuals with COPD, ranging from 15% to 34%[17]. Its presence is strongly linked to a worsened prognosis and more health costs associated with hospitalization[18]. For this reason, health strategies to early diagnose and detect sarcopenia are important[6,19]. Therefore, considering the large prevalence of sarcopenia in individuals with COPD and its negative clinical impact[20], the identification of previous stages of sarcopenia (pre-sarcopenia) is necessary to prevent functional disorders in this population. However, according to a current systematic review in this field[17], there is a lack about the clinical impact of pre-sarcopenia on functional and biological factors in individuals with COPD. Thus, the present study aimed to analyze the impact of pre-sarcopenia and sarcopenia on clinical outcomes not fully studied by the literature[17] such as balance, respiratory muscle strength, inflammatory and oxidative stress biomarkers in individuals with COPD.

METHODS

Study Design and sample

This study is a cross-sectional design, with a convenience sample composed of sixty-one individuals with diagnosis of COPD[21] aged between 60 and 79 years from the University Hospital of Londrina, Paraná, Brazil. The inclusion criteria were COPD diagnosed at least 3 years, with peripheral baseline oxygen saturation> 90%, who did not have neurological, orthopedic, cardiovascular, or psychiatric diseases that incapacitated them testing. Individuals who had exacerbations of COPD and decompensated metabolic disorders in the last two months were excluded, as well as chronic respiratory failure during the data collection or who were unable to perform the tests. The research project was approved by the Research Ethics Committee of the State University of Londrina and authorized by the Education Department / Londrina / PR (1.830.048).

Functional measurements

Muscle mass was quantified with bioelectrical impedance (Biodynamics 310TM; Biodynamics Corp., USA) with measurements of fat-free mass (FFM) and fat-free mass index (FFMI-FFM/ height^2). FFM was calculated by the formula of Kyle et at[22].

Handgrip strength (HGS) was assessed using a hydraulic dynamometer (Jamar Plus + Digital 563213; Lafayette Instrument Company, USA). The highest value from tree attempts (1-minute rest each) was used as a maximal force value[6].

Physical performance was evaluated with 4-meter gait speed test (4MGS). The best time of two walks was used for analysis[6].

Respiratory muscle strength was measured as maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) using a digital manovacuometer (MVD 300, GlobalMed, Brazil) following previously standardized procedure[23]. Maneuvers were maintained for at least 2 seconds and the peak value was recorded. The best of 3 acceptable and reproducible maneuvers was used for analysis.

Balance was measured using the Timed Up and Go (TUG) test[24]. The best time of two walks was used for analysis.

Blood biomarkers

All individuals underwent a 12-hour fasting blood collection and were classified into their respective groups. The collected peripheral blood serum was analyzed. Blood samples were centrifuged for 30 minutes at 3000 rpm (2100 xg) at 20°C, to obtain serum, plasma and concentrated of red blood cells to ensure the analysis of inflammatory markers and oxidative stress biomarkers, and then, frozen at -80°C. Serum levels of inflammatory markers were analyzed: C-reactive protein, interleukin 6, 8, 10, 1β, 12P70, tumor necrosis factor-α (TNF-α). The reaction was read on a microplate reader using a flow cytometer. Total radical-trapping antioxidant parameter (TRAP)[25], paraoxonase 1 activity (PON1)[26], superoxide dismutase activity (SOD) in erythrocytes[27], catalase activity (CAT) in erythrocytes[28], advanced oxidation protein products (AOPP)[29] and nitric oxide metabolites (NOx)[30] were used as oxidative stress biomarkers. According to protocol previously published[11]. All collections and tests were performed in the graduate laboratory of the University Hospital of Londrina, Paraná, Brazil by properly trained professionals.

Sarcopenia diagnosis

Sarcopenia definition was following the European working group of sarcopenia in older people (EWGSOP)[6]. Individuals diagnosed with COPD were separated into 3 groups: without sarcopenia, with pre-sarcopenia and with sarcopenia. Low muscle mass was detected according to a specific cutoff point

for the Brazilian population with COPD using FFMI (14.65 kg / m2 for women and 20.35 kg / m2 for men)[31], low muscle strength using HGS (<20 kg for women and <30 kg for men)[6] and low physical performance using 4MGS (<0.8 m /s was adopted for both sexes)[6]. Sarcopenia was defined as the presence of low muscle mass plus low muscle strength and/or decreased physical performance, and pre-sarcopenia as the presence of only low muscle mass (Figure 1)[6].

Statistical analysis

Descriptive statistics were used to describe the demographic and clinical characteristics of the patients and other potentially confounding variables. Continuous variables were presented as the mean and standard deviation (SD), and categorical variables were presented as number and percentage. The normality of data distribution was analyzed using the Shapiro-Wilk test. Intergroup analysis (COPD separated into without sarcopenia with pre-sarcopenia, and with sarcopenia) was performed using the Student´s T-test or Mann-Whitney test. A value of p <0.05 was adopted as statistical significance with 95% confidence intervals (95%CI). For statistical analysis, SPSS-IBM version 20 software was used.

RESULTS

Sixty-one individuals were stratified into three groups: without sarcopenia (n = 33; women: 51%), pre-sarcopenia (n = 15; women: 20%) and sarcopenia (n = 13; women: 62%) (Figure 1). Sociodemographic characteristics were reported in Table 1. Individuals without sarcopenia presented lower weight, body mass index (BMI), fat-free mass index (FFMI), muscle mass index (MMI) and abdominal circumference when compared to those with sarcopenia. Age, height, and GOLD variables did not show statistically significant differences. Individuals with COPD and sarcopenia presented lower MIP, TUG and HGS compared to those with pre-sarcopenia and without sarcopenia (Table 1).

Oxidative stress and inflammatory blood biomarkers of individuals with COPD were described in Table 2. In individuals with COPD, AOPP levels were lower in those with sarcopenia compared to those with pre-sarcopenia and without sarcopenia. SOD activity was lower in individuals with pre-sarcopenia compared to those without sarcopenia. IL-1β was detected only in individuals with sarcopenia. CRP was higher in those individuals with pre-sarcopenia compared to those with sarcopenia. The main results were summarized in Figure 2, which presents clinical variables that were increased or reduced in individuals with pre-sarcopenia and sarcopenia compared to individuals without sarcopenia.

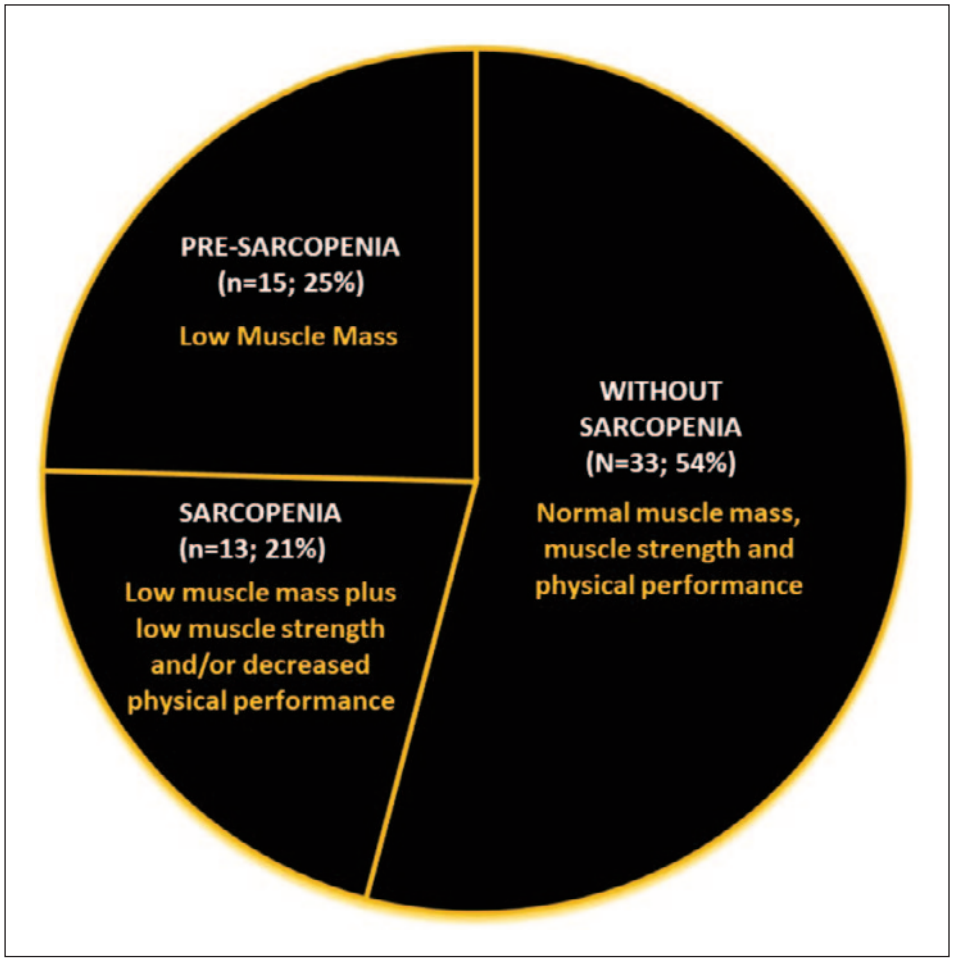

Figure 1. Diagnosis and prevalence of pre-sarcopenia and sarcopenia in individuals with COPD included in this study

DISCUSION

This study contributes novel insights to the field by delineating specific clinical characteristics in individuals with COPD afflicted by either sarcopenia or pre-sarcopenia. Our findings reveal that individuals with sarcopenia exhibit inferior muscle mass, peripheral muscle strength, respiratory muscle strength, and balance compared to their counterparts. Moreover, we observed that the presence of sarcopenia and pre-sarcopenia is probably linked by biological mechanisms related to systemic inflammation and oxidative stress.

Table 1. Baseline characteristics of individuals with COPD with different body composition phenotypes

Variables	Without sarcopenia (n=33)	Pre-sarcopenia (n= 15)	Sarcopenia (n=13)	*p*
Age (years)	68 ± 7	66 ± 6	71 ± 7	0,142
Women, n (%)	17 (51%)	3 (20%)	8 (62%)	0.056
Weight (kg)	74 ± 14	77 ± 14	58 ± 15 [a,b]	0,004*
Height (m)	158 ± 10	162 ± 10	158 ± 9	0,299
BMI (Kg/m^2)	29,8±4	26±4	20±3 [a,b]	0,0002*
Abdominal circumference (cm)	107±12	97±12	81±9 [a,b]	0,0001*
FFMI (Kg/m^2)	19±3	19±2	16±2 [a]	0,0003*
MMI (Kg/m^2)	10±2	10±1,6	7±1,4 [a]	0,0004*
A.A Charlson Comorbidity index	4±1,5	3,7±1	5±1	0,29
Pulmonary function				
FEV_1 (% predicted)	50 ± 16	54 ± 15	47 ± 10	0,434
FVC (% predicted)	82 ± 20	89 ± 20	88 ± 15	0,552
FEV_1/FVC (%)	48 ± 9	49 ± 9	43 ± 9	0,230
MIP (cmH_2O)	82 ± 23	91 ± 29	61 ± 14 [a,b]	0,010*
MEP (cmH_2O)	113 ± 34	131 ± 40	99 ± 26	0,095
GOLD, I, II, III, IV, n	(1/17/11/3)	(0/6/5/3)	(0/5/8/0)	0,39
Balance, strength and functionality				
TUG (m/s)	7,1 ± 1,1	7,3 ± 1,3	8,3 ± 1,3 [a]	0,036*
4MGS (m/s)	1,2±0,11	1,1±0,13	1,04±0,2	0,1
HGS (Kg)	33 ± 7	38 ± 9	25 ± 6 [a,b]	0,002*

The values were described as mean ± SD, with the exception of the GOLD class. BMI: body mass index; COPD: chronic obstructive pulmonary disease. FFMI: fat-free mass index; GOLD: Global Initiative for Obstructive Lung Disease; FEV1: final expiratory volume in 1 sec; FVC: forced vital capacity; HGS: handgrip strength; MMI: muscle mass index; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; TUG: Timed Up and Go test; 6MWT: 6-minute walk test; 4MGS: 4-meter gait speed. Comparison between without sarcopenia, pre sarcopenia and sarcopenia (a, b, c respectively). P * ≤0.05 was used.

In our study, we observed a sarcopenia prevalence of 21% and pre-sarcopenia at 25%, which are comparatively lower than those reported in other studies involving the Brazilian population (4,9% and 12,4%, respectively)[32]. However, our study differs from the investigations by Costa et al 2017[32] in the methodology used to diagnose sarcopenia, because we detected sarcopenia and pre-sarcopenia according to international recommendations[6]. The prevalence observed in our study is in accordance with the worldwide prevalence of sarcopenia in this population[17].

We observed a negative clinical impact among individuals with COPD and sarcopenia, characterized by lower muscle mass, peripheral, respiratory muscle strength and balance. The decrease in muscle mass in individuals with COPD is already known and it is prevalent in around 35% of the individuals with COPD[31]. This reduction is linked to alterations in both peripheral and respiratory muscle strength[33]. In our study, individuals with COPD and sarcopenia exhibited notably poorer respiratory muscle strength compared to the other groups. While a decline in respiratory muscle strength has

Table 2. Inflammatory and oxidative stress biomarkers in individuals with COPD with different body composition phenotypes

Variables	Without sarcopenia (n=33)	Pre-sarcopenia(n= 15)	Sarcopenia(n=13)	*p*
Oxidant				
AOPP (µM/l)	80 (67-128)	86 (62-104)	58 (51-71) [a,b]	0.015
NOX (pmol/mg)	7.7±3	8.7±4	8.6±4	0.5
Antioxidant				
TRAP (µM/trolox)	985±134	987±178	889±150	0.1
SOD (U/mgHb)	49.5±15	39.7±9 [a]	41±12	0.045
CAT (U/mgHb)	51±11	49±11	46±11	0.4
PON-1 (U/ml)	194±52	172±51	195±68	0.4
Inflammation				
CRP (mg/L)	2.6 (1.1)	4.5(1.3-6) [a,c]	1.2(0.9-1.8)	0.035
IL6 (pg/mL)	2,542 ± 3,893	2,025 ± 2,152	2,297 ± 2,097	0,876
IL-8 (pg/mL)	12 ± 5,985	12 ± 4,860	15 ± 5,010	0,468
IL-10 (pg/mL)	0,117 ± 0,192	0,541 ± 1,990	0,118 ± 0,182	0,543
IL-1β (pg/mL)	0	0	0 (0-0.20) [a,b]	0.033
IL-12P70 (pg/mL)	0 ± 0	0,037 ± 0,112	0 ± 0	0,232
TNF-α (pg/mL)	946 (890-1080)	942 (882-1049)	845 (770-1062)	0.6

COPD: Chronic pulmonary obstructive disease; AOPP: Advanced oxidation protein product; PON-1: paraoxonase 1; SOD: superoxide dismutase activity; NOX: nitric oxide metabolites; TRAP: total radical trapping antioxidant parameter; CRP: C-reactive protein; IL-6: interleukin-6; IL-1ƃ: interleukin-1ƃ; TNF-α: tumoral factor-α; IL-12: interleukin-12. Comparison between without sarcopenia, pre-sarcopenia and sarcopenia (a, b, c respectively). P * ≤0.05 was used.

been observed in individuals with COPD[34], our study constitutes a pioneering investigation, as it delves into the specific comparison between individuals with and without sarcopenia and pre-sarcopenia in this context.

Muscle weakness is associated to chronic inflammation and oxidative stress in individuals with COPD[35,36]. Elevated levels of pro-inflammatory cytokines and oxidative stress biomarkers have been documented in this respiratory condition[35]. In our study, Individuals with COPD with sarcopenia and pre-sarcopenia showed high levels of circulating proinflammatory cytokines. These findings align with prior research indicating that individuals with COPD and sarcopenia exhibit elevated levels of inflammatory biomarkers[36] and diminished protein oxidation[37]. Chronic inflammation and oxidative stress biomarkers have been correlated with compromised muscle strength, reduced muscle mass, and slower gait speed in individuals with COPD[36]. The decline in peripheral muscle mass is directly associated with decreased protein synthesis, a consequence of oxidative stress and chronic inflammation[38].

While muscle mass and strength have received attention from previous authors in the context of individuals with COPD and sarcopenia, balance has been not totally investigated[17]. In our study, we addressed this gap by examining dynamic balance using the Timed Up and Go test. This particular test is widely recommended for assessing physical performance, dynamic balance, and fall risk in the elderly population[39], and it has found application in individuals with COPD[40]. Notably, a previous study has indicated that individuals with COPD exhibit compromised balance and an elevated risk of falls[40]. The potential association between impaired balance and sarcopenia in individuals with COPD is noteworthy, considering that muscle weakness is a known factor contributing to balance dysfunction and an increased risk of falls, particularly in older individuals[39]. As clinical message, the early diagnose of sar-

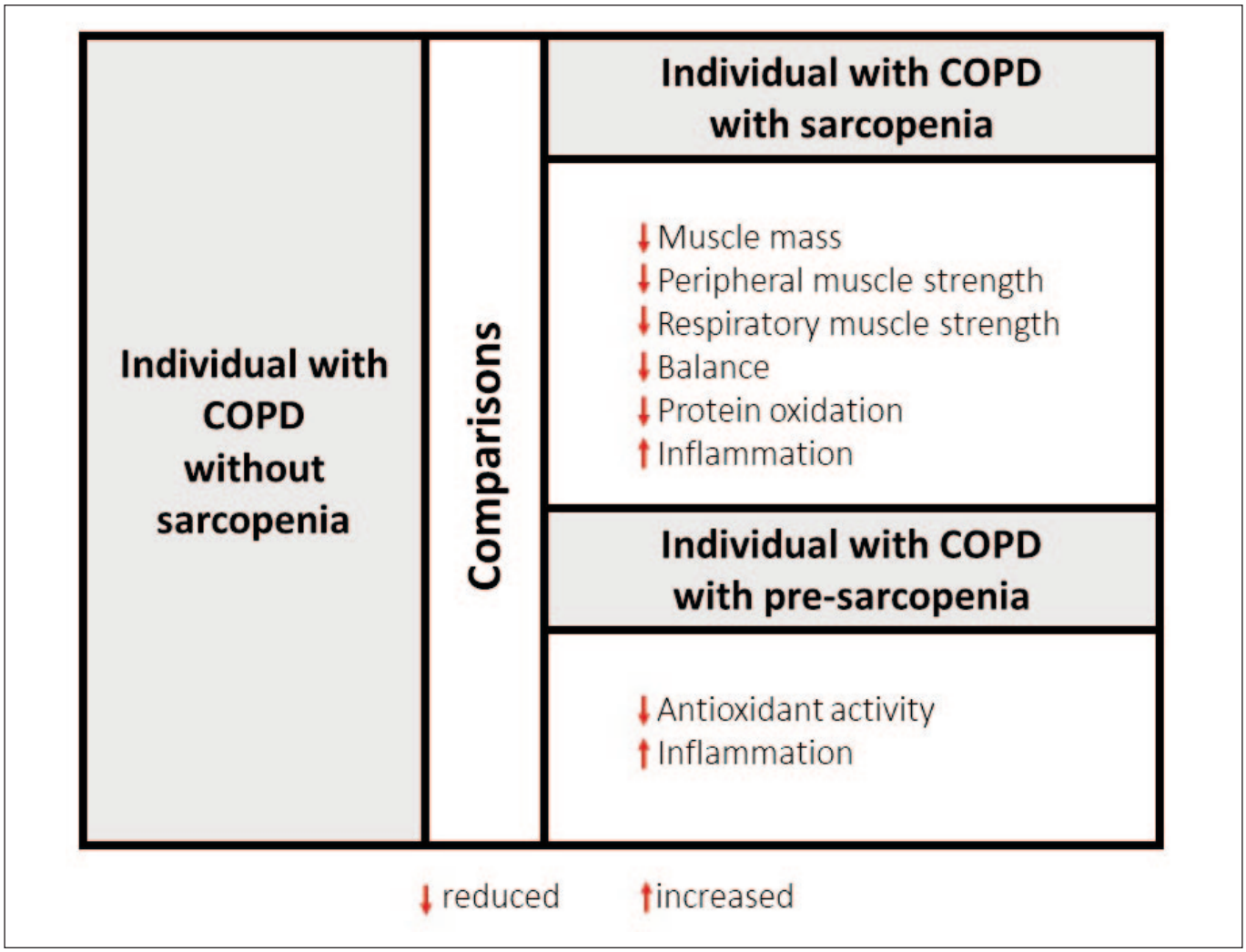

Figure 2. Comparison between individuals with COPD with pre-sarcopenia and sarcopenia: main results

copenia or pre-sarcopenia in individuals with COPD is beneficial to detect patients who need more intervention specially exercise program to improve the balance, muscle strength and muscle mass. One of the few studies to explore rehabilitation in individuals with COPD who have sarcopenia was conducted by Jones *et al.*[41], that included a multicomponent exercise-based intervention with aerobic exercise, lower and upper limb resistance training, and education classes. However, this exercise program[41] did not include balance training. Therefore, considering the negative functional impact of sarcopenia in individuals with COPD, it is necessary to incorporate other exercises modalities in the pulmonary rehabilitation which have not been fully considered by the international consensus in this respiratory disease[42,43].

The limitations of the study are related to the cross-sectional design, and the results cannot infer the causality of the data. Additionally, the sample was for convenience, not probabilistic, and some groups were left with the sample quantity decreased. However, we used the recommendation of European Working Group on Sarcopenia in Older People to diagnose sarcopenia. In addition, we analyzed clinical and biological biomarkers not fully investigated in the literature. Future studies could include a large sample size and explore longitudinally these and other variables in individuals with COPD and pre-sarcopenia or sarcopenia.

CONCLUSION

In conclusion, our study demonstrates that individuals with COPD who manifest sarcopenia exhibit diminished muscle mass, impaired balance, and reduced peripheral and respiratory muscle strength in comparison to those with pre-sarcopenia or without sarcopenia. Furthermore, our findings suggest a probable association between the coexistence of sarcopenia and pre-sarcopenia, indicating a connection through biological mechanisms linked to systemic inflammation and oxidative stress biomarkers.

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