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Sarcopenia and Sarcopenic Obesity in Chronic Obstructive Pulmonary Disease Patients with Different Levels of Severity

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ABSTRACT

Background: Sarcopenia is defined as loss of muscle mass with attendant loss of muscle strength and physical function and is associated with advancing age. Inflammatory condition of chronic disease leads to more rapid progression of this syndrome, which may adversely affect quality of life. The aim of this study was to determine the relationship between chronic obstructive pulmonary disease (COPD) and sarcopenia. **Methods:** This study included 108 COPD patients who were treated in the pulmonary clinic at Masih Daneshvari Hospital. Patients were categorized into three groups based on Global Initiative for Obstructive Lung Disease criteria. Sarcopenic parameters including muscle mass, muscle strength, and physical performance were measured by Bioimpedance Analysis, hand grip dynamometer, and the Short Physical Performance Battery test, respectively. According to the European Working Group on Sarcopenia in Older People cutoff points and the definition of sarcopenic obesity, sarcopenic patients were diagnosed and categorized based on different COPD severity scores. **Results:** The relationship between sarcopenia and COPD grading, which was assessed using multiple regression models with adjustment of confounding factors, including age, chronic diseases, and smoking, was statistically insignificant. However, by using forced expiratory volume in 1 second (FEV1) or ratio of FEV1 to forced vital capacity in this model, the results were significant (P = 0.026). A positive linear correlation was observed between skeletal muscle index (SMI) and spirometric data, which was assessed by Spearman's correlation test. By exploring the association between sarcopenia and obesity with the one-way analysis of variance test, sarcopenic patients represented to have the minimal spirometric measures. However, this difference was only significant for actual measurements. **Conclusion:** This study showed that sarcopenic COPD patients had smaller spirometric measurements and that sarcopenia and magnitude of SMI were positively correlated with obstruction severity.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic disease associated with several systemic and pulmonary comorbidities. In particular, loss of muscle mass is a principal comorbidity that is frequently observed in COPD patients (1-3) and results from several factors, including improper nutrition, chronic use of corticosteroids, and systemic inflammatory mediators (4). Additionally, muscle depletion may adversely affect respiratory muscle function and exercise capacity and may even increase mortality (5-7).

In 1989,(8) sarcopenia was defined as age-related loss of skeletal muscle mass; however, it now indicates any depletion of muscle mass that occurs with aging and with any condition, such as chronic disease including COPD, which causes a catabolic state (9,10). Loss of muscle can begin at age 35 and accelerates with increasing age (11,12). Although sarcopenia is known as a geriatric syndrome, it can occur in young people after chronic disease and from malnutrition as well. Sarcopenia characterized by depletion of muscle mass is a common feature of all chronic diseases that are accompanied by inflammation; moreover, it can be associated with preserved fat mass that leads to a specific body composition state known as sarcopenic obesity. Koo and colleagues (13) showed that the COPD patients with sarcopenic obesity presented with the lowest pulmonary function test parameters, yet they had a better quality of life compared to patients who

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experienced other body composition changes. Although this syndrome has attracted considerable interest, as yet it has no universally accepted definition. However, the description of this syndrome by the European Working Group on Sarcopenia in Older People (EWGSOP) as loss of muscle mass accompanied by one of two other elements of physical function and muscle strength is most commonly used in research settings. Early identification of sarcopenia and sarcopenic obesity would enable appropriate preventive and therapeutic interventions.

To date, most have studies examined body mass index (BMI) and fat-free mass in COPD patients (14-17). To our knowledge, ours is the first to study both the quantity (muscle mass) and the quality (muscle strength and physical performance) aspects of sarcopenia in COPD patients.

In this study, we hypothesized that the chances of COPD patients developing sarcopenia increase with the severity of the disease. Also, we measured the prevalence of sarcopenia in COPD patients and comprehensively investigated lean body mass in relation to different lung function indexes.

METHODS

This cross-sectional study included 108 stable COPD patients who were seen for follow-up from April to August 2015 at the pulmonary clinic of Masih Daneshvari Hospital in Tehran, Iran. Written and informed consent was obtained from all patients, and the ethics committee of Masih Daneshvari Hospital approved this study. Basic information, including age, smoking history, other comorbidities (e.g. other chronic diseases), last hospital admission, severity of dyspnea (by the Medical Research Council [MRC] dyspnea scale) (18), and medication history, were obtained from patient records. If patients were experiencing an exacerbation of COPD or had any sign or symptom of systemic infection, they were excluded from the study. Additionally, because very few women presented at the clinic at the time, women were also excluded.

All patients underwent spirometry during their last visit. Based on their spirometric results, they were categorized according to Global Initiative for Obstructive Lung Disease (GOLD) guidelines (19) into mild, moderate, and severe/very severe groups. Spirometry was conducted according to American Thoracic Society guidelines (20); pneumotachograph (Master Lab, E. Jaeger, Würzburg, Germany) results and all parameters were recorded as percentage of predicted and actual measurements.

Muscle mass measurements were taken using a Bioimpedance Analyzer (body mass analyzer, model 359. GAIA, Jawon, Korea) in the standard condition based on National Institutes of Health guidelines (21). Patients with pacemakers were excluded from the study. Skeletal muscle index (SMI) was calculated as appendicular muscle mass (kg) divided by height squared (m^2). Appendicular muscle mass was calculated as the sum of the lean soft tissue of four limbs. Based on EWGSOP recommendations, muscle mass index less than 8.87 was considered a cutoff point for sarcopenia.

Patients were classified as underweight if their BMI was less than 21 kg/m^2; they were classified as normal weight if their BMI was between 21 kg/m^2 and 25 kg/m^2; they were classified as overweight if their BMI was greater than or equal to 25 kg/m^2 and less than 30 kg/m^2; and they were classified as obese if their BMI was greater than 30 kg/m^2 (22).

Grip strength in the dominant hand as an indicator of muscle strength was measured using a dynamometer (model DHD-3, GH1003, Sachon, Korea), based on American Society of Hand Therapists protocols (23). The test was performed three times in 20-second intervals, and the highest measurement was recorded. Measurements lower than 30 were considered as reference value for sarcopenia.

To examine physical function, we evaluated patients using the Short Physical Performance Battery (SPPB) test. This test assesses balance, gait, strength, and endurance by examining individuals' ability to stand with their feet together in side-by-side, semi-tandem, and tandem positions; time to rise from a seated position five times; and time to walk 8 feet (24). Each part of the test has four scores, and the maximum score for the whole test is 12. Scores were calculated based on the time needed to complete each part of the test.

Patients were considered to have sarcopenia according to EWGSOP guidelines if they had an SMI less than 8.87 plus at least one grip strength or SPPB test measurement less than the cutoff point determined for sarcopenia. They were considered sarcopenically obese if, in addition to being sarcopenic, their BMI was greater than 25 kg/m^2.

To begin, we analyzed the distribution of study variables. All continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as frequency (%). Comparison between variables was determined by an unpaired t-test, Fisher's exact test, and the chi-squared test, when appropriate. The Mann-Whitney test was used to compare dyspnea function class in four groups that were categorized based on obesity and sarcopenic status.

Significant variables were introduced in a multiple regression model to determine development of sarcopenia in relation to lung function values.

One-way analysis of variance (ANOVA) and Kruskal-Wallis tests were used to determine differences in spirometric parameters, BMIs, and MRC scores in four groups of patients with various obesity and sarcopenia statuses and with different stages of COPD. A post-hoc test was used for multiple comparisons between groups.

Pearson correlations were evaluated between SMI and BMI and pulmonary function variables after checking for normal distribution of SMI and BMI. Correlation between dyspnea severity and measures of SMI and BMI were assessed using Spearman's correlation bivariate test.

P values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 23 software.

RESULTS

All 108 patients met the inclusion criteria. Their mean age was 60.7 years (SD, 11.13). Following the proportions recommended by the GOLD guidelines, 28 patients (25.9%) comprised

the mild COPD group, 44 patients (40.7%) comprised the moderate COPD group, and 36 patients (33.3%) comprised the severe/very severe COPD group. Of the patients, 55 (50.9%) were active smokers, 16 (14.8%) were former smokers, and the rest were exposed to secondhand smoke. Thirty-six (33%) of 108 patients were identified as having sarcopenia. Detailed clinical characteristics and test parameter measurements of patients with and without sarcopenia are outlined in Table 1.

The correlation between SMI and spirometric parameters is presented in Table 2. SMI was weakly but significantly correlated with parameters of diffusion capacity; however, when we assessed SMI in different COPD GOLD stages, it did not reach statistical significance (P = 0.067). Additionally, there was negative correlation between SMI and MRC scores using Spearman's correlation test, although the results were not significant (P = 0.058).

As shown in Table 1, no significant relation was observed between COPD stage and whether a patient developed sarcopenia (P = 0.65). Therefore, to assess the relation between sarcopenia and COPD severity further and also because of the high correlation of SMI with parameters of lung diffusion, we used a multiple regression analysis model with sarcopenia as a dependent variable and adjusted for age, smoking status, and chronic disease as contributing factors (Table 3).

Patients' mean BMI was 25.6 kg/m^2 (SD, 5.31). The proportion of each subtype of BMI, including underweight, normal, overweight, and obese, was 17 (15.7%), 55 (59%), 28 (25.9%), and 8 (7.4%), respectively. Patients with moderate severity COPD had the highest BMI (27.15+-5.6; P=0.02) compared to the BMI of patients with mild and severe/very severe COPD (25.31+-5.36 and 23.97+-4.36, respectively). Patients with sarcopenia tended to have normal weight compared to patients who did not have sarcopenia, of whom most were overweight. As shown in Table 2, positive correlation was significant only between actual measures of pulmonary function parameters and BMI. Patients were compared in four groups: 1) non-sarcopenic non-obese(S-O-); 2) sarcopenic non-obese (S+O-); 3) obese non-sarcopenic(S-O+); and 4) sarcopenic obese(S+O+) (Table 4). They were also compared in post-hoc analyses to evaluate the differences between the actual number of spirometric parameters, which was significant in the ANOVA test (Table 4). The difference between S-O+ and S+O+ and the difference between S-O+ and S+O- was significant for forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and ratio of FEV1 to FVC (FEV1%) values.

Table 1. Patient characteristics (N=108)

	Non-Sarcopenia N=72	Sarcopenia N=36	*P*-value
Age (SD)	59.00 (10.52)	64.33 (11.61)	0.018
BIA outcome (SD)			
Weight, kg	77.79 (14.48)	57.11 (8.41)	<0.001
PBF	23.10 (7.86)	20.36 (11.28)	0.022
SLM/Ht	10.14 (2.58)	8.07 (0.51)	<0.001
Hand grip, kg (SD)	30.93 (7.51)	24.07 (5.39)	<0.001
SPPB score (SD)	11.35 (0.84)	10.33 (2.16)	
GOLD stage (%)			0.66
Mild	20 (27.8)	8 (22.2)	
Moderate	30 (41.7)	14 (38.9)	
Severe/very severe	22 (30.6)	14 (38.9)	
Dyspnea FC (%)			0.65
1and 2	41 (57.8)	17 (45.2)	
3 and 4	30 (42.2)	19 (52.8)	
Smoking YP (SD)	24.30 (30.77)	26.29 (28.05)	0.57
Chronic disease (%)	30 (41.7)	9 (25)	0.089
BMI (SD)	27.61 (5.05)	21.64 (3.22)	<0.001
Type of BMI (%)			<0.001
Underweight	2 (2.8)	7 (19.4)	
Normal weight	18 (25)	22 (61.1)	
Overweight	36 (50)	7 (19.4)	
Obese	16 (22.2)	0 (0)	

GOLD: Global Initiative for Chronic Lung Disease; SD: Standard deviation; PBF: Percent body fat; SLM: Soft lean mass; SPPB: Short physical performance battery; FC: Function class; YP: Year pack; BMI: Body mass index

Table 2. Pearson bivariate correlation coefficient of SMI and BMI with spirometric variables (N=108)

Variable	SMI	*P*-value	BMI	*P*-value
FVC				
Predicted	0.08	0.399	0.115	0.23
Actual	0.305	<0.001	0.22	0.02
FEV1%				
Predicted	0.225	0.02	0.23	0.01
Actual	0.228	0.018	0.26	0.006
FEV1				
Predicted	0.123	0.209	0.15	0.11
Actual	0.319	<0.001	0.23	0.01
Dyspnea (FC)	0.184	0.058	-0.115	0.23

FVC: Forced vital capacity; FEV1,: Forced expiratory volume in 1 second; FEV1%: ratio of FEV1 to FVC; FC: Function class; SMI: Skeletal muscle index; BMI: Body mass index

DISCUSSION

In this study, 34% of COPD patients were sarcopenic. As we investigated the prevalence of sarcopenia in different stages of COPD based on GOLD guidelines, we found no significant difference between groups, but we did find that pulmonary function values were significantly worse in sarcopenic patients. Although we found that sarcopenia status, depleted muscle mass, and reduced BMI were associated with decreased diffusion pulmonary indexes, these associations were mainly in relation to the actual value of pulmonary function parameters rather than percent of predicted values.

Additionally, we found that higher BMI and higher SMI were both associated with better pulmonary function values and worse lung diffusion indexes in sarcopenic obese patients. However, we found significant differences only between sarcopenic and obese patients and between

Table 3. Multiple regression analysis with sarcopenia as a dependent variable

(95% CI)	Sarcopenia	Non-sarcopenia	P-value*	≤ Adjusted OR
FVC (SD)				
Actual	1.95 (0.99)	2.9 (1.15)	0.002	1.99 (1.16-3.4)*
Predicted	63.22 (24.56)	75.54 (22.07)	0.047	1.02 (0.99-1.04)
FEV1 (SD)				
Actual	1.39 (0.77)	1.95 (0.99)	0.002	2.11 (1.11-4)*
Predicted	52.72 (22.9)	63.22 (24.56)	0.035	1.021 (1-1.04)*
FEV1% (SD)				
Actual	60.10 (11.75)	64.83 (11.50)	0.048	1.03 (0.99-1.07)
Predicted	78.78 (15.54)	84.43 (16.50)	0.084	1.02 (0.99-1.056)

SD: Standard deviation; FVC: Forced expiratory volume; FEV1: Forced expiratory volume in first second; FEV1%: ratio of FEV1 to FVC; OR: Odds ratio; CI: Confidence interval
*P values<0.05 are statistically significant ≤: variables include chronic disease, age, and smoking

Table 4. Patients in four groups compared based on their BMI and sarcopenia status

	S-O-	S-O+	S-O-	S+O+	*P*-value
COPD %)					0.114
Mild	5 (25)	15 (28.8)	8 (27.6)	0 (0)	
Moderate	0 (0)				
Severe/very	3 (15)	27 (51.9)	9 (31)	5 (71.4)	
Severe	12 (60)	10 (19.2)	12 (41.4)	2 (28.6)	
FVC (SD)					
Actual	2.7 (1.15)	2.9 (1.15)	2.29 (0.92)	1.94 (0.67)	0.016
Predicted	70.05 (21.7)	77.23 (22.08)	67.07 (22.6)	65.25 (13.86)	0.148
FEV1% (SD)					
Actual	59.52 (15.53	66.46 (9.52)	60.8 (12.15)	57.66 (10.57)	0.029
Predicted	79.7 (23.54)	85.89 (13.57)	79.32 (15.11)	76.87 (13.06)	0.167
FEV1 (SD)					
Actual	1.79 (1.16)	2 (0.93)	1.47 (0.83)	1.08 (0.3)	0.017
Predicted	55.41 (26.8)	65.63 (23.56)	54.1 (25.34)	47.87 (10.42)	0.066
Dyspnea FC (%)					0.37
1	2 (10)	6 (11.8)	2 (6.9)	1 (14.3)	
2	8 (40)	25 (49)	13 (44.8)	1 (14.3)	
3	7 (35)	19 (37.3)	11 (37.9)	4 (57.1)	
4	3 (15)	1 (2)	3 (10.3)	1 (14.3)	

SD: Standard deviation; FVC: Forced vital capacity; FEV1: Forced expiratory volume in first second; FEV1%: ratio of FEV1 to FVC; FC: Function class; S-O, no sarcopenia, no obesity; S+O-, sarcopenia, no obesity; S+O+, sarcopenia, obesity; S-O+, no sarcopenia, obesity

sarcopenic and sarcopenic obese patients. This may indicate that soft lean mass provides information beyond BMI in predicting disease severity, although further studies are needed to investigate SMI and BMI separately for this purpose.

A previous study by Ischaki and colleagues (25) found that, based on GOLD staging and spirometric values, SMI was the only measurement related to COPD severity. Furthermore, this study found no relationship between BMI and disease severity indexes. Although in our study SMI correlated with the same spirometric parameters as shown in older studies (25,26), we could not demonstrate that SMI was reduced as COPD stage progressed.

Like the results reported in other studies (27,28), we found no significant relationship between SMI and dyspnea severity (expressed by MRC scores), which indicates that dyspnea is probably affected by factors other than muscle mass alone.

Our results are in line with the results reported in a study of Korean COPD patients (29), which also assessed patients in four groups with different obesity and sarcopenia statuses. In both studies, sarcopenic obese patients presented with the lowest spirometric parameters; however, differences between categories were also significant for FEV1% in our study, which was not found in the Korean study. Additionally, in the study of the Korean patients, the investigators

found that the difference between groups with the same obesity status and different sarcopenia status for all pulmonary function parameters was significant, whereas in our study reduction in pulmonary function values was significant between sarcopenic category and obese and sarcopenic obese patients. This difference between studies could be explained by different definitions of sarcopenia.

In our study, we considered both the qualitative and quantitative aspects of sarcopenia in COPD patients, which sets our study apart from previous studies. Nevertheless, our study has some limitations. First, since the number of women who met the inclusion criteria was small, women were excluded in our study, so we cannot extrapolate our study results to the general population of COPD patients. Second, we did not perform dual-energy X-ray absorptiometry, which is the best clinically available technique to measure lean muscle mass and fat mass. Third, for the diagnosis of sarcopenia, we used the EWGSOP cutoff point, which might need to be modified for Asian populations.

CONCLUSION

We conclude that spirometric indexes, specifically actual measurements, are better predictors of whether COPD patients will develop sarcopenia than GOLD staging of this disease. Sarcopenia and obesity have independent effects in pulmonary function values, and we recommend that both of these elements be assessed in all COPD patients.

The authors declare that there are no conflicts of interest.

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