Original article

Association of sarcopenia with osteoporosis in patients with chronic obstructive pulmonary disease

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A R T I C L E   I N F O

A B S T R A C T

Objectives: Systemic consequence of Chronic Obstructive Pulmonary Disease (COPD) is associated with progressive loss of muscle mass and function. Preliminary studies showed presence of sarcopenia in COPD leads to reduced pulmonary function and quality of life; studies on whether this condition results in consequent loss of bone mineral density (BMD) is still inconsistent. This study aims to examine the association of sarcopenia in COPD with osteoporosis.
Methods: This is a *post-hoc* analysis of a study on forty-one (n = 41) participants with COPD seen in a tertiary public hospital in Manila, Philippines who underwent pulmonary function test and dual-energy x-ray absorptiometry. Sarcopenia was defined using a Philippine-based criteria of low fat free mass index (FFMI) and low muscle strength - hand grip strength, and osteoporosis using World Health Organization T-score diagnostic criteria.
Results: The prevalence of osteoporosis among COPD is 44%, and 63% in COPD with sarcopenia. There was no statistical difference seen in pulmonary function variables between COPD with and without osteoporosis. Significant positive correlations were observed between Forced Expiratory Volume in 1 s, FFMI, and appendicular lean muscle with total body BMD. Sarcopenia in COPD was associated with significantly increased risk for osteoporosis.
Conclusions: High prevalence rate of osteoporosis, and even higher among sarcopenic Filipino COPD patients should be further studied. The findings also suggest that sarcopenia in COPD is associated with increased risk of osteoporosis, and osteoporosis alone does not seem to affect lung function.

1. Introduction

Osteoporosis and sarcopenia are 2 disorders that predominantly affect elderly patients and are related to major clinical and financial burdens. There is a growing body of evidence that links the biology of bone and muscle with constant biochemical channel communication [1]. Clinically, osteoporosis and sarcopenia share similar risk factors, highlighting muscle-bone interactions, which may result in debilitating consequences, such as falls, fractures, and hospitalizations [2]. In Chronic Obstructive Pulmonary Disease (COPD), the chronic inflammatory state inherent to lung pathology arising from increased oxidative stress is thought to cause multi-organ dysfunction (i.e., muscle, bones, heart, metabolism),

ultimately leading to increased morbidity and mortality [3]. Further, airflow limitation inherent to COPD pathology contributes to patients' breathlessness resulting in physical inactivity, consequently leading to reduction of muscle mass and strength, termed as sarcopenia. Likewise, reduced muscle load on bones can reduce bone formation and increase bone resorption.

Osteoporosis is prevalent among COPD patients [4], and is more common in persons with COPD compared to age matched controls without airflow limitation [5]. Roughly one-third of patients with COPD have osteoporosis (range 9—69%), about 38% have osteopenia (range 27—67%) [4,5]. Just as in osteoporosis, older age, smaller waist circumference, smoking, and alcoholic beverage drinking were significant predictors of sarcopenia [6]. Sarcopenia has been

identified in 46% of COPD patients, resulting in impaired pulmonary function and lower quality of life score [7]. Osteoporosis and sarcopenia have similar risk factors, and both contribute to higher risk of disabilities, falls, fractures and impaired physical mobility [8].

However, there are limited studies on the association between sarcopenia and osteoporosis in COPD patients. Initial studies showed that the prevalence of sarcopenia and osteoporosis increases, as the severity of airflow limitation increases [9,10]. In this study, we aim to evaluate the association between sarcopenia, as measured by fat-free mass index and osteoporosis, and examine the relationship of body composition indices and lung function with bone mineral density.

2. Methods

2.1. Study design

This is a *post-hoc* analysis of a study on body composition among Filipino COPD patients [7]. All procedures were reviewed and approved in compliance with the ethical standards of the University of the Philippines Manila-Research Ethics Board (Study code 2018-270). Written informed consent and/or assent was obtained from all participants in accordance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. Forty-one adult Filipino COPD patients older than 40 years-old consulting at the Philippine General Hospital − outpatient pulmonary clinic consented and were included in this study. Clinico-demographic information, measurements for anthropometrics, body composition, lung function test, COPD assessment test (CAT) score, hand grip strength (HGS) and 6-min walk distance (6MWD) were recorded and performed (full protocol as seen on original study) [7]. Fat-free mass index (FFMI), appendicular lean muscle mass (ALM), and total body bone mineral density (BMD) were measured using whole body dual energy X-ray absorptiometry (DXA) scan (STRATOS DR, DMS-Imaging, Maugio, France).

Sarcopenia was defined using Philippine based normative value criteria of low fat-free mass index (FFMI) by Tee et al. [11] of < 12.50 kg/m^2 (male) and < 8.33 kg/m^2 (female), and low muscle strength defined as hand grip strength of < 24.54 kg (male) and < 16.10 kg (female). Prevalence of sarcopenia in this study population was based on the original study [7]. Using the lowest T-score of either lumbar spine (L1-L4) or total hip, we defined osteoporosis and osteopenia according to the World Health Organization (WHO) criteria [12] of *T-score of > -1.0* as normal; *-1.0 to -2.5* as osteopenia and *< -2.5* as osteoporosis.

2.2. Statistical analysis

Statistical analyses were performed using STATA (version 15.1; StataCorp, College Station, TX, USA). The quantitative variables - age, body mass index, pulmonary function variables (FEV1, FEV1 % predicted, PIF, PEF), 6MWD, HGS, DXA variables - FFMI, ALM, total body BMD were expressed as mean ± SD. The qualitative variables - 2018 COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity of airflow limitation classification and osteoporosis/osteopenia diagnosis were expressed as count (with proportion). For comparisons of quantitative variables (6MWD, HGS, body composition indices, and pulmonary function tests) between 2 groups (osteoporosis and no osteoporosis groups), we used Mann-Whitney U test. Spearman rank correlation was used to assess correlations of BMD with FEV1, FFMI, SSMI, ALM (2 quantitative variables), and Fisher's exact test to test association between sarcopenia and osteoporosis (2 qualitative variables). Values of P < 0.05 were considered statistically significant.

3. Results

3.1. Subject characteristics

The baseline subject characteristics are summarized in Table 1. The mean age between COPD with and without osteoporosis is similar (P = 0.889). Majority of participants were male and belonged to 2018 GOLD stage 2 and 3. The mean total BMD was 1.295 g/cm^2, and only 2 participants had normal total bone mineral density. The overall prevalence of osteoporosis was 43.9%. Based on the established prevalence of sarcopenia in the study population (46.3%, 19/41)[7], osteoporosis was seen in 63.2% (12/19) COPD patients with sarcopenia.

Osteoporotic COPD group (n = 18) had significantly lower mean HGS (P = 0.0341), BMI (P = 0.0033), appendicular lean mass (P = 0.0027) and FFMI (P = 0.0011), compared to non-osteoporotic COPD. There was no statistical difference in CAT score, 6MWD, and pulmonary function variables including actual FEV1, FEV% predicted, PIF and PEF between the COPD patients with and without osteoporosis (Table 1).

3.2. Relationship and association of sarcopenia, lung function, and osteoporosis/bone mineral density

Table 2 shows the correlation of FFMI, FEV1 and ALM with total BMD in COPD. Results showed FFMI, ALM and FEV1 significantly positively correlated with total BMD (r = 0.4542, 0.5828, 0.3312, all P < 0.05, respectively).

Table 3 shows that the diagnosis of sarcopenia in COPD patients was significantly associated with osteoporosis (odds ratio 4.57, [95% CI 1.22−17.15], P = 0.024).

4. Discussion

This *post-hoc* analytic study highlighted several important findings: the higher prevalence of osteoporosis in COPD with sarcopenia; the positive correlations between airflow limitation (FEV1) and BMD, body composition indices (FFMI, ALM) and BMD; diagnosis of osteoporosis did not seem to affect lung function alone, and lastly, the strong association of sarcopenia and osteoporosis.

Using the normative reference for Filipinos, we identified 46% of our COPD population to have sarcopenia [7]. This is higher than the reported prevalence of 21.6% (95% CI 14.6−30.9%, I^2 = 94%), among patients with COPD [13]. The same systematic review and meta-analysis of 10 articles involving 2565 COPD patients, however, also reported that up to 63% of COPD patients residing in nursing homes may have sarcopenia [13]. Likewise, the prevalence of osteoporosis in our COPD population was higher at 43.9%, compared to the global prevalence of 38% (95% CI, 34−43) as established by a meta-analysis of 58 studies [4]. COPD itself is an independent risk factor for osteoporosis, and increases the likelihood of osteoporosis by an odds ratio of 2.6−2.83 [4,14] compared to age matched control subjects. Existing data points to the inflammatory milieu in COPD as the main factors that promotes imbalances in normal bone homeostasis, ultimately leading to osteoporosis: elevated levels of receptor activator of nuclear-factor kappa-B (RANK) and RANK/osteoprotegerin (OPG) ratio, increased interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α) [15]. Additionally, the use of inhaled corticosteroids, vitamin D deficiency, and hypogonadism seems to contribute to the increased predisposition [15].

In our study, there is an increased prevalence (63%) of osteoporosis in the sarcopenic COPD group, which is consistent with the literature of a Korean sarcopenic COPD population, in which the reported prevalence is 60.8% [10]. COPD patients are invariably

Table 1
Baseline characteristics of study participants according to diagnosis of osteoporosis (n = 41).

Variable	Osteoporosis n = 18 (44%)	No osteoporosis n = 23 (56%)	P-value
Age, yr	69.38 (7.26)	69.21 (6.78)	0.889
Male gender, n (%)	15 (83%)	22 (85%)	–
Comorbidities			
DM/HTN/CV/Others	0/4/5/2	3/9/5/0	–
2018 GOLD classification			
A/B/C/D	8/7/0/3	9/7/2/5	–
2018 GOLD severity of airflow limitation classification			
I/II/III/IV	0/6/9/3	1/10/10/2	–
CAT score[a]	10.55 ± 6.26 (3–22)	12.65 ± 6.7 (4–30)	0.3915
6MWD, m	383.94 (82.86)	378.35 (98.35)	0.9267
Hand grip strength, kg	14.54 (6.97)	19.51 (6.97)	*0.0341
Body mass index, kg/m^2	18.85 (0.90)	22.32 (0.59)	*0.0033
Appendicular lean mass, kg	15.41 (4.02)	18.33 (2.48)	*0.0027
Fat free mass index, kg/m^2	13.21 (2.16)	15.40 (1.82)	*0.0011
Total body bone mineral density, g/cm^2	1.202 (0.12)	1.369 (0.10)	*0.0001
Pulmonary Function			
Post FEV1, liters	1.01 (0.32)	1.17 (0.33)	0.1340
FEV1, % predicted	44.37 (12.21)	50.00 (15.66)	0.3308
PIF, liters/min	153.93 (51.76)	172.38 (64.88)	0.2614
PEF, liters/min	162.44 (58.99)	173.47 (71.63)	0.5833

Values are presented as mean ± standard deviation. Mean (SD). [a] Mean ± SD (range). *Indicates statistical significance.
DM, Diabetes Mellitus; HTN, Hypertension; CV: Cardiovascular; CAT, COPD Assessment test; 6MWD, 6-min walk distance; FEV1, Forced Expiratory Volume in 1 s; PIF, Peak Inspiratory Flow; PEF, Peak Expiratory Flow.

Table 2
The correlation of total bone mineral density (g/cm2) with FEV1, Fat-free mass index, and total appendicular muscle mass.

Variable	Spearman rank correlation	P-value
FEV1	0.3312	0.0344
Fat-free mass index	0.4542	0.0029
Appendicular lean mass	0.5828	0.0001

FEV1, Forced Expiratory Volume in 1 s.

Table 3
Association between sarcopenia and osteoporosis in COPD (n = 41).

Variable	Sarcopenia	No sarcopenia	Total	Odds ratio
Osteoporosis	12	6	18	4.57
No osteoporosis	7	16	23	(95% CI 1.22–17.15,
Total	19	22	41	*P = 0.024)

Fisher's exact test P-value = 0.0296.
*Indicates statistical significance.

characterized by long smoking history and exposure to bronchodilators with or without inhaled corticosteroids, which contribute to the increased development of osteoporosis. Further, this study showed that sarcopenia is an independent risk factor of a decreased BMD regardless of bodyweight. The presence of sarcopenia seems to be additive to the baseline increased risk of osteoporosis among COPD patients [15]. The consequential effects on bones, skeletal muscle loss and dysfunction were all linked to persistent chronic inflammatory response in COPD [16]. Our study also observed a significant reduction in muscle strength (HGS) and body composition indices (FFMI, ALM) in the osteoporotic group, and a positive correlation between body composition indices and BMD, all of which were consistent with studies showing interrelationships between components of sarcopenia and osteoporosis [10,14,15].

Our initial study concluded that low FFMI results in reduced lung function (PIF, PEF) and upper limb muscle strength (HGS) in Filipino COPD patients [7]. However, in this current study, lung function variables were not different between osteoporotic and non-osteoporotic COPD patients. Indeed, in several studies, it is the muscle quality that has been found to be significantly associated with the clinical outcome of patients with COPD [17]. This study also observed a weak positive correlation between actual FEV1 and total BMD. Data on the relationship between osteoporosis or BMD score and lung function have been inconsistent and contradicting; a large study on a Korean general population aged ≥ 50 years old showed that reduced BMD is not associated with airway obstruction [18], while a Chinese general population cohort concluded otherwise [19]. A meta-analysis on COPD patients showed that a lower FEV1 value was not a significant risk factor for osteoporosis [4]. This is congruent with a small study conducted on a Taiwan COPD population where similar lung function results were observed between osteoporotic and non-osteoporotic groups. Our findings however, can neither support nor dispute the relation of airflow severity and BMD as this study is limited by its sample size and study design. Nevertheless, we believe that lung function severity is independent of BMD levels.

Lastly, we conclude that osteoporosis is strongly associated with sarcopenia in COPD with an odds ratio of 4.57, higher than previously reported of 3.65 [4]. Body composition derangements such as reduced BMI (malnutrition) and FFMI (cachexia) are highly prevalent in COPD and have potential effects on mechanical load on bones resulting in reduced bone formation. These changes, on top of physiological effects of muscle strength and function loss seen in sarcopenia, and airflow limitation inherent to COPD, can lead to synergistic reduction and limitation of physical activity, thus resulting in overall general frailty and increased risk of falls and subsequent fractures. Osteoporosis-related fractures are associated with several adverse health outcomes in COPD, including an increase in hospitalization and mortality rates [20], further decline in lung function from immobility, and poor quality of life [21].

The need for timely recognition and prevention of sarcopenia before its detrimental effects on the bones cannot be overemphasized. Early recognition of this new geriatric syndrome is crucial for the prevention of its sequelae, and novel studies should pay attention to identifying the associated modifiable factors that underlie mechanisms of sarcopenia. Exercise and dietary programs that are suited to the lifestyles of the Asian COPD population, as well as optimizing treatment regimens to address airflow limitation, would be beneficial for these patients [22].

This study has the following major limitations: mainly this is

limited by its study design being a post hoc analysis, the study population is limited to the sample size of the original study (n = 41), where our study findings might be insufficiently powered to generate definite conclusions. Lastly, investigation for risk factors contributing osteoporosis (use of inhaled corticosteroid, vitamin D insufficiency, hypogonadism, anemia, hypoxia, smoking) cannot be explored due to insufficient data. Therefore, prospective analytic studies with sufficient powered sample size and exploratory risk factors contributing to development of osteoporosis in this population are needed to validate our initial findings.

5. Conclusions

The high prevalence rate of osteoporosis, and which is even higher in Filipino COPD patients with sarcopenia should be further studied. No statistical difference was seen in lung function variables (actual FEV1, FEV1 %predicted, PIF, PEF) among COPD with and without osteoporosis, however, a weak positive correlation was observed between FEV1 and total BMD. Fat-free mass index and appendicular lean muscle mass positively correlated with total BMD. Sarcopenia in COPD is associated with 4.6-fold increased risk of osteoporosis.

Conflicts of interest

CRediT author statement

Jamie R. Chua: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Michael L. Tee:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing - review & editing, Visualization, Project administration, Funding acquisition.

Acknowledgements

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