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COMPARATIVE STUDY OF BONE MINERAL DENSITY, PHENOTYPES OF EMPHYSEMA IN PATIENTS WITH OR WITHOUT ESTABLISHED DIAGNOSIS OF CHRONIC AIRWAY DISEASE

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ABSTRACT
Background: Bone thinning and emphysema are established diseases caused by tobacco-related products proven beyond doubt. A paucity of literature available to establish the association between them. **Objectives:** To explore the association between the different emphysema subtypes and the presence of low bone mineral density among a population of active or former smokers with and without an established diagnosis of chronic obstructive pulmonary disease (COPD). **Methods:** 100 active and former smokers with chronic airway disease attending the Pulmonology Outpatient Department were identified, and they were administered clinical questionnaires, pulmonary function tests, chest computed tomography, and DEXA scans. Appropriate statistical tests were performed to analyze the association between the different emphysema subtypes, low bone mineral density, and smoking in the study participants. **Results:** Out of 100 samples, 80 % of the patients had low BMD (25 had osteoporosis, and 55 had osteopenia). Emphysema was more frequent and severe in patients with osteoporosis (63.2 vs. 36.8%, p=<0.01). For analyzing significant co-factors, a multivariable analysis was done, which yielded Body Mass Index (Odds ratio of 0.89 with a 95% Confidence Interval of 0.67–1.23) and the presence of centrilobular emphysema as most commonly associated with osteoporosis. (Odds ratio of 35.25, with a 95% confidence interval of 3.23 to 401.63). **Conclusion:** Patients having increased Body Mass Index (BMI) and the presence of centrilobular emphysema are having osteoporosis irrespective of their smoking status, which implicates BMI, and centrilobular emphysema has to be considered while evaluating COPD patients.

INTRODUCTION

The usage of different tobacco products is identified as a contributing factor to the development of osteoporosis [1]. Existing literature suggests that there is a further decrease in bone density among smokers, and there is also more propensity of succumbing to fractures indeed with trivial trauma [2]. The risk of rapid deterioration of bone density is observed among

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active smokers compared to ex-smokers [3]. Smoking tobacco is one of the most common etiological factors identified in the causation of chronic airway disease; out of them, chronic obstructive pulmonary disease (COPD) is one of the most common diseases [4]. Most of the extensive epidemiological studies concluded that low mineral density in bone was identified in patients with COPD [5]. Steroid usage in patients with limitations in airflow always leads to the development of osteopenia [6,7]. Contrary to this observation, people who were smokers and not prescribed steroids also had low bone density, suggesting a different pathology existed between lung disease and skeleton density [8]. Destruction of lung parenchymatous tissue with or without airflow obstruction is called emphysema [9,10]. Two recent studies were conducted one in patients who are smokers having emphysema with an established diagnosis of COPD and another study done in smokers having emphysema without an established diagnosis of COPD, suggesting that both emphysema and osteoporosis are the results of loss of extracellular matrix (ECM) and the elevation of inflammatory mediators, such as TNF- α [11,12].

Significant outcome of these studies where emphysema is a significant predictor of decreased bone density. There is no correlation between airflow restrictions and the causation of low bone density; these findings were later proven beyond doubt in other studies [13,14]. Emphysema is classified into three subtypes based on clinical and radiological findings: centrilobular, para septal, and pan lobular [15,16]. Existing literature identified an established correlation between emphysema and low BMD, but no study done to date has been able to identify the type of emphysema that is associated with maximum bone density loss. Hence an attempt is made to study the correlation of emphysema with the highest loss of bone density.

METHODS

Participants

One hundred consecutive patients with established emphysema diagnosis attending the Pulmonology department of the Narayana Medical College and Hospital were invited to participate in the study between March 2023 and October 2023.

Inclusion criteria

1) Study subjects were 50 years of age or older
2) Both sexes
3) With a smoking history of ≥10 pack-years as suggested by the Indian Society of Chest Physicians to be met as a study parameter involving smokers
4) Patients having established COPD diagnosis
5) Willing to give informed consent.

Exclusion criteria:

1) Those who had a previous diagnosis of osteoporosis
2) Those who were using preventive treatment for osteoporosis.
3) Using systemic corticosteroids for the treatment of COPD, as steroid usage causes decreased bone density and osteoporosis.
4) Not willing to give informed consent.

All subjects signed informed consent before enrollment, and the protocol was approved by the Institution's ethics committee (NMC/ADM/ETHICS/approval/003/02/2023). The sample size was calculated at a 95% confidence level, assuming the prevalence of emphysema at 16.3%, as per the seed article by Wong AW [4]. At the absolute allowable error of 7%, 93 emphysema patients are required for the study, which is further rounded off to 100 patients as the final sample size to avoid attrition. Patients were recruited into the study during their initial visit to the OPD. The study population does not represent the general population, and emphasis was given to studying the relationship between emphysema and bone mineral density but not to studying the prevalence of emphysema in diverse populations. After obtaining informed consent from the patients by disclosing the details of study protocol, they were enquired about details of a prefixed questionnaire comprising details of demographic data, medical history including substance abuse history, medication usage including details about the usage of inhalational steroid usage for symptom improve, and details of acute exacerbations in those with an already known diagnosis of COPD done by spirometry. The recruited study population will undergo a physical examination and measurement of BMI. Patients underwent Spirometry, a 6-minute walk test, BMD measurement, and chest computed tomography to classify emphysema using Fleischer Society guidelines [17].

Bone Density by Dual X-Ray Absorptiometry

A dual X-ray absorptiometry (DEXA) technique with a Lunar iDXA scan (General Electric Co) was used to measure the bone mineral density of the lumbar spine (L1 to L4), femoral neck, total hip and in some cases non-dominant forearm (33%). Diagnosis of osteoporosis was based on the lowest T-score of

these locations and defined according to the World Health Organization (WHO) criteria (osteoporosis: T-score≤- 2.5; osteopenia or low bone mass: T-score <-1.0 and >-2.5; and average bone mass: T-score ≥ −1.0). All DXA scans were interpreted by a physician certified by ISCD and following standard quality control procedures, including daily phantom scanning. The coefficient of variation was 1% for L1-L4 BMD and 1.1% for total hip BMD

Statistical Analysis

Quantitative data are represented as mean ± SD or median (IQR). Student t-tests and nonuniform data Mann-Whitney U-tests were used for uniformly distributed data variables. The Chi-square test was used to study the categorical variable. To investigate the association between low BMD and the other studied parameters, logistic regression analyses were done using the SPSS statistical software package (SPSS version 25.0 for Windows, Armonk, NY: IBM Corp.)

RESULTS

Out of 100 patient samples, 20 patients had normal BMD, and 80 had low BMD, comprising 55 subjects with osteopenia and 25 with osteoporosis. Low bone density is identified in women Subjects with lower body mass index. Between the two groups (regular vs. low BMD), no statistically considerable differences emerged in smoking status, steroid usage, and percentages of COPD patients. (Table 1). The presence of emphysema was more commonly found in patients with low BMD.

Among the low mineral density group of patients, Centrilobular alone and Centrilobular and paraseptal types were more widely observed. Compromised lung function with lower values of forced vital capacity and lung diffusion capacity and reduced performance on the six-minute walking test is identified in patients with a low mineral density group (Table 1).

On performing the univariate statistical analysis test, the low bone density group showed more numbers for both the presence and severity of emphysema. Among all emphysema subtypes, the centrilobular alone group had shown low BMD compared to other groups: centrilobular, para septal, and para septal (Table 2). Other predictive factors for the causation of low BMD identified were male gender, body mass index, forced vital capacity and lung diffusion capacity, and a six-minute walking test. There is no relationship observed between COPD diagnosis and low bone density. Clinical factors found to be significant on univariable analysis conducted on the study sample or established risk factors for causation of low bone density are considered for Multivariable logistic regression analysis. Risk factors include age, gender, emphysema type and severity, body mass index, and forced vital capacity. Out of these identified risk factors, only body mass index and centrilobular emphysema were identified as significant risk factors with low bone density (Table 3). Results also noted that patients with centrilobular or both centrilobular and para septal emphysema subtypes have low bone density but not in patients with isolated para septal emphysema.

DISCUSSION

In the present study, emphasis was given to find out any correlation existed between any specific type of emphysema and BMI, which were used as endophenotypes for decreased bone density. It was found that the association is not dependent on the majority of the common risk factors for reduced bone density, and it was not reliant on either the presence of airway disease or the severity of airway disease. Existing literature reveals that body mass index strongly influences bone density. Elderly subjects who have high BMI have lower chances of developing osteopenia or osteoporosis when compared to individuals having lower BMI, which in turn is reflected in the prevalence of fractures [18].

Another study done by Barnes PJ concluded that intentional weight loss in obese or overweight individuals leading to loss of bone mass suggests there is a correlation between body weight and bone density [19]. In a study done by Barrera G revealed that any loss of tissue in body such as weight, muscle wasting, lung tissue loss was dependent on low bone density [20].

Several existing studies suggest the association of emphysema was evident on imaging is associated with decreased bone density. In our study we found there is a correlation between decreased muscle mass, destruction of lung parenchyma leading to emphysema and loss of bone mineral density, similar to our study, a study done by Kaenmuang [21] also found emphysema is more commonly associated with decreased bone density. In both human and animal models it was proposed that bone resorption by osteoclast and loss of pulmonary tissue are mediated by activation of immune mediated auto immune reaction, inflammatory cells and interleukins [22].

Table 1: Depicting the details of the patient's demographic, Radiological, Clinical, and pulmonary Characteristics of Patients with and without low bone mineral density

Characteristics	Low bone mineral density (n=80)	Normal bone density (n=20)	p-value
Demographic			
Age Mean (SD)	65.3 (8.1)	64.1 (8.7)	0.169
Men, No (%)	37 (51.2)	18 (74.2)	0.009
BMI Mean (SD)	27.2 (3.5)	27.8 (3.9)	<0.001
Radiological parameters			
Total emphysema, No (%)	80(80.0)	20 (20.0)	<0.001
Sub-type of emphysema, No (%)			
Centrilobular alone	38 (44.2)	3 (3.1)	<0.001
Centrilobular and paraseptal	31 (30.0)	9 (10.3)	
Paraseptal alone	11 (5.8)	8(6.6)	
Severity of emphysema, by NETT (0–4)	2	1	0.09
Clinical parameters			
Current smoker, No (%)	60 (52)	14 (40.0)	0.371
Pack-years, Median with IQR	46 (27.8)	42(29.7)	0.572
Diagnosed COPD, No (%)	61 (75.25)	11(54.9)	0.187
Patients on Inhaled steroids, No (%)	31(29.7)	9 (21.5)	0.403
Pulmonary function tests			
Forced vital capacity Mean (SD)	4.8 (2.4)	5.7 (1.2)	0.081
Forced expiratory volume one second, Mean (SD)	79.7 (31.9)	91.5 (19.2)	0.231
Forced expiratory volume one second/forced vital capacity, Median (IQR)	61.2(21)	71.1 (16.3)	0.081
Diffusing capacity for carbon monoxide -%, Mean (SD)	71.3 (25.1)	81.5 (19.2)	0.061
Six minutes walking test, Median (IQR)	467 (123.7)	601.2 (145.6)	0.063

Table 2: Depicts the results of Low bone mineral Density Predictors in active and Ex-Smokers by doing univariate analysis

Variables	OR	IC 95%	p-value
Age in years	1.54	0.91–1.87	0.367
Men	0.45	0.21–0.86	0.001
Body mass index	0.95	0.85–1.45	<0.001
Current smoker	1.46	0.57–2.93	0.409
Pack-years	2.0	1.11–2.32	0.97
Using Inhaled steroids	2.43	2.43–5.43	0.705
Established COPD	2.89	2.45-4.23	0.762
Bone density.	2.34	1.65–3.25	0.088
FEV1 after bronchodilator use	0.68	0.45–1.12	0.009
Diffusing capacity for carbon monoxide	1.24	0.67–1.32	0.976
Six minutes walking test	1.1	1.23-1.45	0.045
Emphysema	6.73	3.54–17.23	<0.001
Severity of emphysema, by NETT (0–4)	2.51	2.54–3.45	0.009
Type of emphysema			
Centrilobular alone	7.98	3.75–32.87	0.001
Centrilobular and paraseptal	6.56	2.75-16.73	0.007
Paraseptal alone	2.21	1.12–8.91	0.607

Table 3: Results of low bone mineral density predictors in active and ex-smokers by conducting Multivariate analysis

Variables	OR	IC 95%	P value
Age in years	1.54	0.79–1.81	0.623
Men	0.45	0.12–1.56	0.234
Body mass index	0.89	0.67–1.23	<0.001
FEV1 after bronchodilator use	0.75	0.35–2.12	0.457
Severity of emphysema, by NETT (0–4)	0.65	0.24–2.67	0.653
Type of emphysema			
Centrilobular alone	35.25	3.23-401.63	0.034
Centrilobular and paraseptal	27.64	3.72–281.75	0.023
Paraseptal alone	5.85	1.95–61.43	0.364

Our study found that the centrilobular emphysema phenotype was explicitly associated with loss of bone density compared to another type of emphysema independent of many other risk factors. These findings are similar to the study done by Lippi [23]. Centrilobular emphysema is commonly seen in people with chronic and heavy tobacco smoking and presents with severe respiratory symptoms when compared to other types of emphysema [24]. A study by Reid [25] identified increased WBC counts, matrix metalloproteinase, and TGF-B, which were also elevated in people with low bone density.

CONCLUSIONS

Patients having increased Body Mass Index (BMI) and the presence of centrilobular emphysema are having osteoporosis irrespective of their smoking status, which implicates BMI, and centrilobular emphysema has to be considered while evaluating COPD patients, and emphasis should be given on bone density in these subsets of the population.

Strengths: The main strength of the current study is that we have considered all the important variables that can contribute to low BMD in smokers. Another strength is recruiting equal male and female patients in the study sample.

Limitations: The current study is done in a relatively small sample population with fewer patients with established osteoporosis; hence, the findings cannot apply to the general population. The current study's findings require confirmation in other studies with diagnoses of emphysema.

Future implications: A well-designed study in patients with COPD and osteoporosis incorporates inflammatory mediators such as interleukins in the evaluation and the timing of introducing measures for bone mass protection.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

NCS Reddy collected data and interpreted the statistical values. He and Sushmita designed the study and contributed to drafting and editing the manuscript. Both authors wrote the final draft of the manuscript, which was read and approved by the authors.

REFERENCES

[1] Nathan SD, Waxman A, Rajagopal S, Case A, Johri S, DuBrock H, De La Zerda DJ et al. Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study. *Lancet Respir Med* **9**, 1266-74 (2021)

[2] Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. *N Engl J Med* **383**, 958-68 (2020)

[3] Katzen J, Beers MF. Contributions of alveolar epithelial cell quality control to pulmonary fibrosis. *J Clin Invest* **130**, 5088-99 (2020)

[4] Wong AW, Liang J, Cottin V, Ryerson CJ. Diagnostic Features in Combined Pulmonary Fibrosis and Emphysema: A Systematic Review. *Ann Am Thorac Soc* **17**, 1333-6 (2020)

[5] Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis--FDA review of pirfenidone and nintedanib. *N Engl J Med* **372**, 1189-91 (2015)

[6] Kaner RJ, Bajwa EK, El-Amine M, Gorina E, Gupta R, Lazarus HM et al. Design of Idiopathic Pulmonary Fibrosis

Clinical Trials in the Era of Approved Therapies. *Am J Respir Crit Care Med* **200**, 133-9 (2019)

[7] Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med* **8**, 147-57 (2020)

[8] Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med* **8**, 453-60 (2020)

[9] Behr J, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* **9**, 476-86 (2021)

[10] Pompe E, Bartstra J, Verhaar HJ, de Koning HJ, van der Aalst CM et al. Bone density loss on computed tomography at 3-year follow-up in current compared to former male smokers. *Eur J Radiol* **89**, 177-81 (2017)

[11] Bon J, Fuhrman CR, Weissfeld JL, Duncan SR, Branch RA, Chang CC et al. Radiographic emphysema predicts low bone mineral density in a tobacco-exposed cohort. *Am J Respir Crit Care Med* **183**, 885-90 (2011)

[12] Nambu A, Zach J, Schroeder J, Jin G, Kim SS, Kim YI et al. Quantitative computed tomography measurements to evaluate airway disease in chronic obstructive pulmonary disease: Relationship to physiological measurements, clinical index and visual assessment of airway disease. *Eur J Radiol* **85**, 2144-51 (2016)

[13] Hersh CP, Washko GR, Estépar RS, Lutz S, Friedman PJ, Han MK et al. Paired inspiratory-expiratory chest CT scans to assess for small airways disease in COPD. *Respir Res* **14**, 42 (2013)

[14] Smith BM, Austin JH, Newell JD, D'Souza BM, Rozenshtein A, Hoffman EA et al. Pulmonary emphysema subtypes on computed tomography: the MESA COPD study. *Am J Med* **127**, 94.e7-23 (2014)

[15] Su ZQ, Guan WJ, Li SY, Feng JX, Zhou ZQ, Chen Y et al. Evaluation of the Normal Airway Morphology Using Optical Coherence Tomography. *Chest* **156**, 915-25 (2019)

[16] Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. *Eur Respir J* **49**, 1700214 (2017)

[17] MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. *Radiology* **284**, 228-43 (2017)

[18] Lynch DA, Austin JH, Hogg JC, Grenier PA, Kauczor HU, Bankier AA et al. CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society. *Radiology* **277**, 192-205 (2015)

[19] Barnes PJ. Endo-phenotyping of COPD patients. *Expert Rev Respir Med* **15**, 27-37 (2021)

[20] Barrera G, Bunout D, Gattás V, de la Maza MP, Leiva L, Hirsch S. A high body mass index protects against femoral neck osteoporosis in healthy elderly subjects. *Nutrition* **20**, 769-71 (2004)

[21] Kaenmuang P, Keeratichananont W, Geater SL, Chantamanee N, Srikaew P. Prevalence, predictors, dynamic bone change, and treatment efficacy of osteoporosis among chronic obstructive pulmonary disease patients: a prospective cohort study. *Front Med (Lausanne)* **10**, 1214277 (2023)

[22] de Sire A, Lippi L, Aprile V, Calafiore D, Folli A, D'Abrosca F et al. Pharmacological, Nutritional, and Rehabilitative Interventions to Improve the Complex Management of Osteoporosis in Patients with Chronic Obstructive Pulmonary Disease: A Narrative Review. *J Pers Med* **12**, 1626 (2022)

[23] Lippi L, Folli A, Curci C, D'Abrosca F, Moalli S et al. Osteosarcopenia in Patients with Chronic Obstructive Pulmonary Diseases: Which Pathophysiologic Implications for Rehabilitation. *Int J Environ Res Public Health* **19**, 14314 (2022)

[24] Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 Update. *Endocr Pract* **26**, 1-46 (2020)

[25] Reid IR. Revisiting osteoporosis guidelines. *Lancet Diabetes Endocrinol* **9**, 805-6 (2021)