

# Study the impact of chronic obstructive pulmonary diseases on bone mineral density of biomass fuel smoke exposed population and its association with hs-CRP in Rural Haryana



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## ABSTRACT

**Background:** Chronic obstructive pulmonary disease (COPD) has deleterious systemic impact due to spillage of inflammatory mediators in the circulation though its association with highly sensitive C-reactive protein (hs-CRP) considers as surrogate marker of inflammation is not much explored hitherto. **Aims and Objectives:** This study aims to study the impact of COPD on bone mineral density (BMD) and its association with hs-CRP in rural population of Haryana. **Materials and Methods:** Tertiary care hospital-based case-control multigroup study conducted in the Department of Respiratory Medicine, BPSGMCW, Khanpur Kalan, Sonapat, Haryana, India. A total of 150 female study subjects included and comprise in three groups, G1: Biomass exposed COPD patients; G2: Biomass smoke exposed non-COPD subjects; and G3: Non-biomass exposed healthy control. Bone density measured using dual-energy X-ray absorptiometry, hs-CRP considers as surrogate marker of inflammation. Statistical software SPSS Version 23 used to measure Chi-square/Fisher's exact test, Student's t-test, and Pearson/Spearman's rank correlation as test of significance,  $P < 0.05$  considered as statistically significant. **Results:** Mean total t-score of COPD subjects was  $-1.81 \pm 1.15$ , significantly lower than healthy control  $-0.66 \pm 1.69$  ( $P = 0.000$ ), however, it is near to biomass exposed non-COPD subjects  $-1.74 \pm 1.14$  ( $P = 0.625$ ). Odds ratio for the risk of osteoporosis in the lower limb among COPD group (Lt leg: 7.07; Rt leg: 4.51) was significantly high compare to other study subjects. Mean titer of hs-CRP ( $7.905 \pm 9.60$ ;  $P < 0.001$ ) was significantly high in study group (G1), though its correlation with t-score was very weak ( $r = -0.024$ ;  $P = 0.867$ ). **Conclusion:** COPD has significant impact on BMD of affected population predominantly on lower limb compare to other study subjects, however, no significant association was found with inflammatory biomarkers in the decrement of bone density despite high mean titer of hs-CRP among COPD patients.

**Key words:** Biomass fuel smoke; Bone mineral density; Obstructive airway diseases; Osteoporosis; Tobacco smoke

## INTRODUCTION

It was cited that indoor air pollution, arising from the use of biomass fuel could be one of the most important risk factors for chronic obstructive pulmonary disease (COPD) in addition to tobacco smoke and it is higher among women cooking with open fire stoves in unventilated rooms in the developing countries.<sup>1,2</sup>

According to global initiative for chronic obstructive lung disease (GOLD) report, COPD defined as a disease state characterized by airflow limitation that is not fully reversible, while the airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.<sup>3</sup>

Since the past decade, COPD has been considered as a complex, multicomponent disease associated with

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pulmonary and extra pulmonary manifestations by eminent researchers.<sup>4-6</sup> However, the origin of systemic inflammation present in COPD remains poorly understood and correlations in the regulation of inflammation in the pulmonary and systemic compartments are not well-documented, yet, it is clearly established that some inflammatory markers are risen in systemic circulation,<sup>7,8</sup> while on the other hand, few researchers also linked COPD with the risk of developing osteopenia and osteoporosis which is characterized by a low bone mineral density (BMD) or microarchitectural deterioration resulting in an increased bone fragility which further potentiate the fracture risk among women.<sup>9-11</sup>

Although known risk factors for developing osteoporosis are ageing, female sex, impaired nutritional status, corticosteroids, and tobacco smoking.<sup>12-17</sup> However, limited studies conducted hitherto which were suggestive of COPD itself a risk factor for osteoporosis due to increased oxidative stress and other (pro-) inflammatory mediators in systemic circulation.<sup>18-22</sup>

### Aims and objectives

Therefore, the present study has been designed to assess the risk of osteoporosis among biomass fuel smoke exposed women of rural India suffering from COPDs.

## MATERIALS AND METHODS

A hospital-based cross-sectional, multigroup, case-control study was conducted in the Department of Respiratory Medicine, of BPS GMC for Women, Khanpur Kalan, Sonapat, Haryana in between May 2017 and June 2019, by included the patients visiting the OPD of department of respiratory medicine as well as patients admitted in the ward and respiratory ICU besides this control was selected through attendants of the patients. A total of 150 non-smoker female subjects included in the study and comprise into three groups. Each group having 50 subjects.

1. Biomass fuel user, diagnosed COPD patients (N=50);
2. Biomass fuel users, non-COPD asymptomatic subject (N=50);
3. Non-biomass fuel user, healthy subjects (N=50)

Sample size calculated using Kelsey et al., (<http://openepi.com/SampleSize/SSCC.htm>) methods in observational epidemiology, with 95% confidence interval and 80% power. Subjects with diagnosed COPD included except those who have diabetes, pregnancy, not fit on criteria to perform PFT, HIV, renal failure, ischemic heart diseases, age <35 years, BMI <18 kg/m<sup>2</sup>, on oral steroid therapy for more than 3 months, sputum-positive pulmonary tuberculosis, and not given written consent.

Written informed consent of all study subjects as well as approval of the institutional ethics committee was taken before starting of the project.

All subjects were evaluated by taking detailed clinical history. If the subject has any respiratory complaint, detailed clinical examination and PFT were performed by the trained technician in the department of respiratory medicine using pulmonary function equipment (BTL-08 Spiro PC, manufactured by Health and Medical Industry, United Kingdom, calibration 03-Jun-13/003-0031080), with pre- and post-bronchodilator reports to confirm the diagnosis and staging based on the criteria of Global Initiative for GOLDs 2016 guidelines (<http://www.goldcopd.org/>) in required subjects.

- Stage 1: Forced expiratory volume in one second (FEV1)  $\geq 80\%$  of predicted – Mild  
 Stage 2: FEV1  $50 \leq \text{FEV1} < 80\%$  of predicted – Moderate  
 Stage 3: FEV1  $30 \leq \text{FEV1} < 50\%$  of predicted – Severe  
 Stage 4: FEV1  $< 30\%$  of predicted – Very severe

All routine as well as specific investigations were done such as ECG, lipid, profile, PFT, ABG, blood sugar, KFT, CRP, serum electrolyte (Na<sup>+</sup>, K<sup>+</sup>, and Ca<sup>++</sup>), skiagram of chest in PA view, and CT thorax (in required patients).

CRP levels were measured quantitatively in all study subjects by taking peripheral venous blood and centrifuging it and then using Tina-quant CRPHS immunoturbidimetric assay for quantification on Roche automated clinical chemistry analyzers (ACN 217) based on the principle of measuring turbidimetrically the agglutination titer after addition of anti-CRP antibodies in the sample.<sup>23</sup>

BMD was calculated using dual-energy X-ray absorptiometry scan. T-scores were calculated by taking the difference between a patient's measured BMD and the mean BMD in healthy young adults, matched for gender and ethnic group, and expressing the difference relative to the young adult population standard deviation. As per the WHO, osteopenia is defined as a T-score of between  $> -1$  and  $< -2.5$  and osteoporosis  $> -2.5$  of standard deviation or  $< -2.5$  with multiple fracture.<sup>24,25</sup>

### Statistical analysis

Data were collected, compiled, and analyzed using standard statistical software SPSS (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: USA), by applying Chi-square test/Fisher's exact test on categorical variables, Pearson's correlation/Spearman's rho and regression test to assess relation in between study variables, Student's t-test/Rank test on continuous variable to compare the mean, and odds ratio calculated to measure the risk,  $P < 0.05$  was considered as statistically significant.

## RESULTS

Mean age in all study groups (G1: 56.38±10.19; G2: 54.6±11.12; G3: 54.14±10.72; P≥0.05) was matched (Table 1). Body mass index of study subjects was significantly lower than control group (Table 1). Mean total t-score as well as Z score significantly lower among Group 1 and Group 2 in relation to Group 3, though no significant difference observed in between Group 1 and Group 2 subjects (Table 1).

Prevalence of osteoporosis among COPD group was 28% (14), compare to unexposed healthy individuals 10% (5; P=0.039), however among biomass fuel smoke exposed subjects, osteoporosis is slightly higher 30% (15; P=0.022) (odds ratio 3.85; CI: 1.27, 11.64) than COPD subjects (odds ratio 3.5; CI: 1.15, 10.63) though occurrence of unaffected bone density among biomass fuel smoke exposed subject was significantly higher 34% (17) than subjects suffering from COPD 16% (8), in addition to this total number of subjects with affected BMD in terms of osteoporosis as well as osteopenia (T-score >-1) was also found significantly higher among subjects with COPD (N=42; 84%; odds ratio: 4.47; CI: 1.75, 11.43; with t-score >-1) in compare to biomass smoke exposed individual (N=33; 66%; P=0.032; odds ratio: 1.65; CI: 0.73, 3.7; with t-score > -1) (Figure 1).

On differential analysis of BMD score, it was revealed that lumbar spine as well as limbs are markedly affected

anatomical site among COPD as well as biomass fuel smoke exposed group (Table 2 and Figure 2). Odds ratio for lower limb BMD was significantly higher among subjects with COPD (Lt leg: 7.07; Rt leg: 4.51) in compare to healthy control, while for biomass smoke exposed subject, this figure is slightly lower (Lt leg: 5.06; Rt leg: 3.27) (Table 3).

In different stages of COPD (GOLD 1 and GOLD 2) as well as (GOLD 3 and GOLD 4), t-score was significantly lower than healthy control, however not affected much by the severity of diseases (r= -0.018; P=0.901) (Figure 3). Prevalence of osteoporosis among mild-to-moderate COPD subjects was 26.66%, odds ratio 2.4 (CI: 0.56, 10.12; P=0.40), however, in severe to very severe stage of COPD, it was 28.57%, odds ratio 2.57 (CI: 0.80, 8.2; P=0.17) (Table 2). Mean value of highly sensitive C-reactive protein (hs-CRP) was significantly high among COPD (Group 1) in compare to biomass exposed non-COPD (Group 2) subjects as well as Group 3 (Healthy individual), however, it fails to show any significant correlation as well as dependency on BMD indices, t and z score (r=-0.024; P=0.867) (Table 4 and Figure 4).

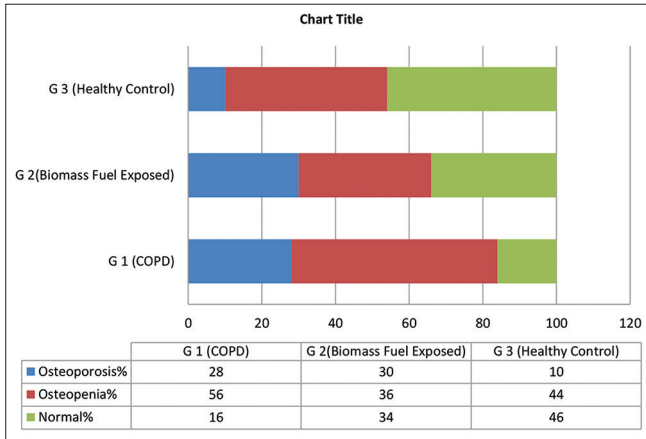
## DISCUSSION

Osteoporosis currently recognized as an important comorbidity in COPD patients by eminent researchers, which drag the attention of scientific fraternity to explore

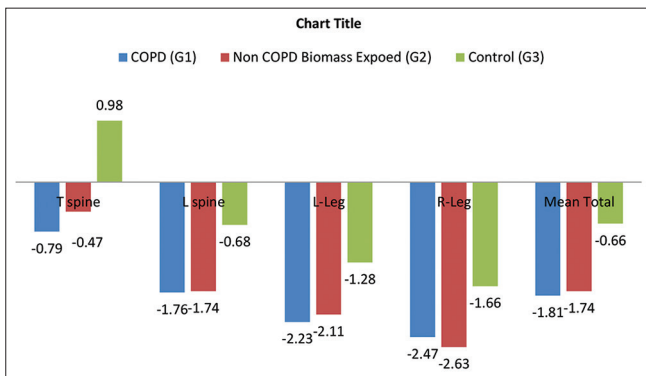
**Table 1: Mean value of indices with standard deviation in study and control groups**

S. No.	Indices Mean±SD	Group 1 COPD N=50	Group 2 Non-COPD biomass smoke exposed N=50	Group 3 Non-biomass exposed healthy control N=50	P value G1 versus G3	P value G2 versus G3	P value G1 versus G2
1.	Age	56.38±10.19	54.6±11.12	54.14±10.72	0.287	0.834	0.406
3.	BEI	42.84±12.92	47.68±31.36	-	-	-	0.315
4.	BMI	20.94±4.51	23.04±5.54	25.90±4.16	0.000	0.004	0.038
5.	FEV1%	44.87±21.67	65.03±21.49	100.12±22.06	0.000	0.000	0.000
6.	FVC%	61.74±24.50	67.89±21.91	99.02±19.50	0.000	0.000	0.189
7.	FEV1/FVC	68.08±14.22	101.91±7.55	106.67±9.09	0.000	0.005	0.000
8.	FEF25-75	14.11±13.04	42.65±19.94	75.11±26.50	0.000	0.000	0.000
9.	hs-CRP	7.905±9.60	3.58±5.27	2.87±4.74	0.001	0.527	0.006
10.	T spine t-score	-0.79±1.55	-0.47±1.65	0.98±2.68	0.000	0.002	0.327
11.	T spine z score	-0.010±2.23	0.118±1.53	1.44±2.77	0.005	0.004	0.739
12.	L spine t-score	-1.76±1.61	-1.74±1.30	-0.68±2.16	0.006	0.004	0.935
13.	L spine z score	-1.18±1.62	-1.09±1.18	-0.25±2.23	0.019	0.020	0.748
14.	L leg t-score	-2.23±1.08	-2.116±1.06	-1.28±1.15	0.000	0.000	0.585
15.	L leg Z score	-1.62±1.09	-1.48±0.90	-0.83±1.23	0.001	0.003	0.50
16.	R leg t-score	-2.47±1.15	-2.634±1.18	-1.66±1.18	0.001	0.000	0.496
17.	R leg Z score	-1.83±1.20	-2.01±1.09	-1.21±1.28	0.014	0.001	0.447
18.	Total t-score	-1.81±1.150	-1.74±1.14	-0.662±1.69	0.000	0.000	0.625
19.	Total Z score	-1.16±1.34	-1.11±0.99	-0.21±1.78	0.000	0.000	0.778

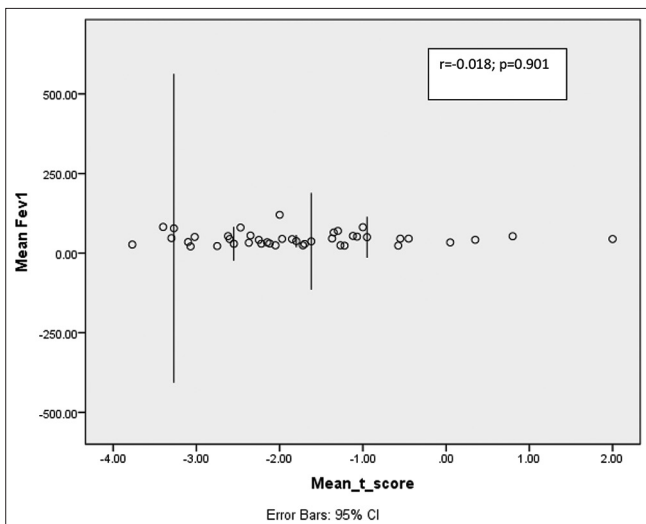
BEI: Biomass exposure index (Biomass average hours spent on cooking per day multiplied by the number of years of cooking; Developed by Behera et al.,<sup>41</sup>), BMI: Body mass index, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, FEF25-75: Forced expiratory flow at 25-75% of forced vital capacity, hs-CRP: Highly sensitive C-reactive protein. T: Thoracic, L-Spine: Lumbar spine, L leg: Left leg, R leg: Right leg, COPD: Chronic obstructive pulmonary disease



**Figure 1:** Bar diagram shows distribution of subjects in percentage (n=50 in each group) on basis of grading of bone mineral density

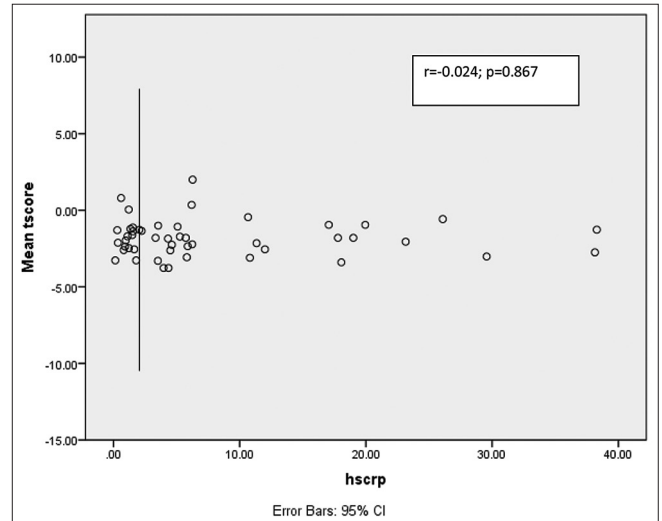


**Figure 2:** Bar diagram shows t-score of bone mineral density at different anatomical site in study groups



**Figure 3:** Scattered plot of correlation in between mean FEV1 and mean t-score in chronic obstructive pulmonary disease. FEV1: Forced expiratory volume in one second

the idea in a more comprehensive way.<sup>26,27</sup> In the present study, we found that BMD markedly affected by the presence of COPD in study subjects, however in a parallel group, those exposed to biomass fuel smoke without



**Figure 4:** Scattered plot of correlation in between mean t-score and highly sensitive C-reactive protein in chronic obstructive pulmonary disease

COPD, have similar presentation on BMD analysis. In both study groups, the mean t value; which is considered as diagnostic criteria for the osteoporosis, was significantly lower than healthy control group. In a recent cross sectional study conducted in Japan revealed significant association of COPD with decrement in BMD. However statistical robustness of the results lacking due to the absence of control group.<sup>28</sup> Another cohort study conducted by Goto et al., in Japan by including 103 patients with COPD found contrary results, as progression of COPD is not directly related with progression of osteoporosis.<sup>29</sup> A similar case-control study conducted by Nayyar et al., found significant association of COPD with osteoporosis, however, they have not analyzed the impact of smoke produced by biomass fuel or tobacco on bone health as a major confounder, unlike the present study.<sup>30</sup> On analyzing the data of various study groups in the present study it was observed that COPD may have very little independent role in the decrement of bone mineral density, as it will enhance the risk of osteoporosis among subjects with COPD, equal to non-COPD biomass smoke exposed study population, however, risk of decrement in BMD as a manifestation of osteoporosis including osteopenia, was found significantly higher among subjects suffering from COPD compare to other study subjects. While prevalence of osteopenia among controlled group of healthy individual was nearly similar to other study groups may be due to ageing. In a prospective study conducted by Hattiholi and Gaude included 102 COPD subjects observe that 66% cases were osteoporotic and predominantly they belongs to stage three and four of COPD.<sup>31</sup> However in present study there was no significance difference in the decrement of BMD among various stages of airway obstruction (Table 3). According to Inoue et al., in a previous systematic review including

a total of 775 COPD patients from 13 studies, the overall prevalence of osteoporosis defined by low BMD was 35.1% on average, ranging from 8.7% to 69%. In addition to this, COPD significantly increased the risk of osteoporosis (low BMD) 1.9-fold.<sup>32</sup> However, in the present study, the prevalence of osteoporosis is 28% in COPD subjects with 3.5-fold increased risk, which is slightly higher to above cited studies somehow due to inclusion of only female subjects; more prone to osteoporosis after menopause while COPD somehow expedites the process of decaying during the course (Figure 1).

**Table 2: Comparative data of BMD indices among subjects with GOLD 1 and 2 and GOLD 3 and 4 stage of COPD**

	COPD N=50		Healthy control
	GOLD 1 and 2 N=15	GOLD 3 and 4 N=35	N=50
Mean	-1.79±1.10	-1.82±1.18	-0.66±1.69
t-score±SD			
Osteoporosis	4 (26.66%)	10 (28.57)	5 (10%)
Odds ratio	2.4	2.57	-
CI	0.56;10.12	0.80;8.2	-
P value	0.941		
GOLD 1 and 2 versus GOLD 3and4			
P value			-
case versus control	0.018	0.001	

GOLD 1 and 2 and 3 and 4: Stages of COPD, CI: Confidence interval, GOLD: Global initiative for chronic obstructive lung disease, BMD: Bone mineral density, COPD: Chronic obstructive pulmonary disease

According to researcher, smoke associated to alterations in the receptor activator of nuclear factor kappa-B (RANK), receptor activator of nuclear factor kappa-B ligand (RANKL), and osteoprotegerin (OPG) system (RANK–RANKL–OPG system), and direct cellular effects on bone cells in exposed population.<sup>33,34</sup> Similarly, in recent research conducted by Saha et al., by including 74 pre-menopausal women from East India using biomass and 65 control women who cooked with cleaner liquefied petroleum gas, reveal that the levels of CD4 (+) and CD19 (+) lymphocytes and circulating granulocytes with elevated levels of membrane-bound RANKL (receptor activator of nuclear factor-kappa ligand 1) were higher in biomass users. The serum levels of RANKL were increased by 41%, whereas serum osteoprotegerin (OPG) was reduced by 22% among biomass users, suggesting an increased risk of bone resorption and consequent osteoporosis in biomass exposed women of a child-bearing age.<sup>35</sup> Moreover, role of inflammation in COPD-associated osteoporosis, with lower BMD have been shown to exhibit higher levels of CRP and inflammatory cytokines such as TNF- $\alpha$ , IL-1, and IL-6.<sup>32</sup> In present study the titer of hs-CRP was significantly high among COPD group compared to healthy control as well as non COPD biomass smoke exposed individual. Though very weak negative correlation was found in between hs-CRP and mean total t-score among COPD. In an old meta-analysis, pooled data across 86 studies, enrolling 40,753 subjects reveal that smokers had significantly reduced bone mass compared with non-smokers (never and former smokers) at all bone sites. Smoking increases the lifetime risk of developing a vertebral fracture by 13% in women and 32% in men. At the hip, smoking is estimated to

**Table 3: Differential analysis of t-score among groups in relation to various anatomical sites of skeleton with odds ratio**

AS	Prevalence of osteoporosis (T-score>-2.5)			P-value			Odds ratio with CI		
	G1 N=50	G2 N=50	G3 N=50	G1 versus G3	G2 versus G3	G1 versus G2	G1 versus G3	G2 versus G3	G1 versus G2
TS	5 (10%)	6 (12%)	0 (00)	0.05	0.02	0.99	11.11 (0.59, 209.1)	13.5 (0.73, 248.6)	0.814 (0.23, 2.860)
LS	18 (36%)	17 (34%)	6 (12%)	0.007	0.017	0.99	4.31 (1.54, 12.06)	3.77 (1.34, 10.63)	1.09 (0.47, 2.48)
LL	22 (44%)	18 (36%)	5 (10%)	0.0002	0.003	0.54	7.07 (2.40, 20.81)	5.06 (1.70, 15.05)	1.39 (0.62, 3.11)
RL	28 (56%)	24 (48%)	11 (22%)	0.001	0.01	0.54	4.51 (1.88, 10.79)	3.27 (1.37, 7.80)	1.37 (0.62, 3.02)
MT	14 (28%)	15 (30%)	5 (10%)	0.039	0.022	0.99	3.5 (1.15, 10.63)	3.85 (1.27, 11.64)	0.90 (0.38, 2.15)

AS: Anatomical site, TS: Thoracic spine, LS: Lumbar spine, LL: Left leg, RL: Right leg, MT: Mean total, G1: Subjects with COPD, G2: Subjects exposed to biomass fuel smoke non-COPD, G3: Non-biomass fuel smoke healthy subjects, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease

**Table 4: Correlation and regression analysis of mean total T and Z score of bone mineral density with study indices among COPD subjects**

Indices	T-score					Z score				
	Correlation		Regression			Correlation		Regression		
	r	p	F	B	p	R	P	F	B	P
FEV1	-0.018	0.901	0.016	-0.018	0.901	0.022	0.881	0.022	0.022	0.881
FVC	0.026	0.860	0.031	0.026	0.860	0.053	0.715	0.135	0.053	0.715
FEV1/ FVC	-0.035	0.811	0.058	-0.035	0.811	-0.028	0.846	0.038	-0.028	0.846
FEF25-75	0.044	0.761	0.094	0.044	0.761	0.060	0.680	0.173	0.060	0.680
hs-CRP	-0.024	0.867	0.090	-0.043	0.766	0.093	0.52	0.001	-0.005	0.972
BEI	-0.102	0.479	0.508	-0.102	0.479	-0.046	0.749	0.104	-0.046	0.749
BMI	-0.108	0.453	0.572	-0.108	0.453	-0.117	0.420	0.661	-0.117	0.420

BEI: Biomass exposure index (Biomass average hours spent on cooking per day multiplied by the number of years of cooking, Developed by Behera et al.<sup>43</sup>), BMI: Body mass index, FEV<sub>1</sub>: Forced expiratory volume in one second, FVC: Forced vital capacity, FEF<sub>25-75</sub>: Forced expiratory flow at 25-75% of forced vital capacity, hs-CRP: Highly sensitive C-reactive protein, COPD: Chronic obstructive pulmonary disease

increase lifetime fracture risk by 31% in women and 40% in men.<sup>36,37</sup> Although in one prospective study conducted in Spain by including 248 patients over 2 years promulgate that vertebral column fracture is common in COPD patients.<sup>38</sup> In a similar recently published large retrospective population-based study conducted in Taiwan by including 11312 patients with COPD, found that the most common site specific fracture were vertebral, femoral, and forearm (32.4%; 31%; and 12%), respectively.<sup>39</sup> However, in the present study, lumbar spine as well as lower limb were significantly affected in subjects with COPD, compare to control, as well as risk of osteoporosis was quite higher than healthy subjects; perhaps be due to disuse atrophy of lower limb in debilitating moribund patients. Overall risk of osteoporosis was also found significantly high in compare to healthy subjects, however, similar risk was found among non-COPD biomass smoke exposed subjects at different anatomical level of skeleton except lower limb and lumbar spine. Moreover, titer of hs-CRP was significantly high among COPD subjects in compare to healthy as well as non-COPD biomass smoke exposed individuals; though it was not correlated significantly with the decrement in BMD. It was cited that smoking has been shown to increase cortisol level, leading to hypercortisolism, a high blood level of glucocorticoid in smokers alters bone metabolism and decreases bone mass either directly by changing the osteoblast and osteoclast activities or indirectly by altering the gastrointestinal as well as renal absorption of calcium. Besides this in women, tobacco smoking enhances estrogen metabolism resulting in a lower level of estradiol which may lead to early osteoporosis,<sup>40</sup> however, it is not yet proved in relation to biomass smoke; need further research for better understanding of its pathophysiology at molecular level. Therefore, according to the present study, it can be stated that COPD has significant impact on BMD in compare to other study subjects, however, risk of osteoporosis is similar among COPD and biomass fuel smoke exposed individual compare to healthy population though lower

limb involvement was predominant in COPD patients compare to other study subjects perhaps due to sedentary life style among them.

## CONCLUSION

COPD has significant risk of osteoporosis in compare to healthy population, as well as increase the risk of decrement of BMD of lower limb in compare to other study groups, though it was not proved as an independent risk factor for it. According to the present study, biomass smoke also has significant deleterious impact on bone health in pre-COPD stage similar to patients with diagnosed COPD. Moreover, systemic inflammation was pronounced in COPD subjects compare to other study groups, though there was very weak inverse correlation found in between decrement of BMD and titer of inflammatory mediator (hs-CRP) among COPD subjects. In addition to this, airflow limitation has no significant correlation with decrement in BMD, although risk of osteoporosis is slightly higher in advance stage compare to early stage of COPD.

## ACKNOWLEDGMENT

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**AA and KS** – Concept design of the study, prepared first draft of manuscript, statistical analysis, and interpreted results; **SK** – Review of literature, coordination, and preparation of manuscript; and **RR** – Review of literature and revision of manuscript.

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