***International Journal of Biomedical Research***
ISSN: 0976-9633 (Online); 2455-0566 (Print)
Journal DOI: 10.7439/ijbr
CODEN: IJBRFA

**Original Research Article**

# Use of DEXA Scan in Chronic Obstructive Pulmonary Disease (COPD) and Comparative Analysis of Pulmonary Hypertension with GOLD classification Versus BODE Index in COPD

**Shekhar G Kadam**[1], Dipti Gothi[2] and Jyotsna M Joshi[*1]

[1]*Department of Pulmonary Medicine, T.N. Medical College and B.Y.L. Nair Hospital, Mumbai-400 008, India*
[2]*ESI Hospital, Basaidarapur, New Delhi, Delhi 110015*

***Correspondence Info:**
Dr J.M. Joshi,
Professor and Head,
Department of Pulmonary Medicine,
T.N. Medical College and B.Y.L. Nair Hospital, Mumbai-400 008, India;
E-mail: drjoshijm@gmail.com

## Abstract

**Background:** Osteoporosis, sarcopenia, pulmonary hypertension are common with COPD. There are only few studies which have evaluated the relationship of these co-morbidities with COPD severity.
**Aim:** To study osteoporosis in terms of bone mineral density (BMD) and sarcopenia in terms of fat free mass index (FFMI) with dual energy x-ray absorptiometry (DEXA); and their relation with forced expiratory volume in one second ($FEV_1$%). To study relation of pulmonary hypertension (PH) with forced expiratory volume in 1 second (FEV1) and BODE index in COPD.
**Materials and Methods:** In 30 stable COPD patients, BMD and FFMI were calculated with DEXA scan. Two groups of $FEV_1$ ≥50% and $FEV_1$<50% and three groups of BODE index <5, 5-6 and ≥7 were compared with PH severity.
**Results:** All patients had low BMD (33% osteopenia & 66% osteoporosis) and 83.3% had sarcopenia. Chi-square test to assess the significance of osteoporosis and sarcopenia in relation to $FEV_1$ groups was statistically insignificant (p value=0.88).
5/7 had normal pulmonary artery pressure (PAP) and 2 had mild PH in group I i.e. $FEV_1$ ≥50%, whereas in group II i.e. $FEV_1$<50 %, 2 had normal PAP; 15, 3 and 2 had mild, moderate and severe PH respectively. Binary logistic regression to assess PH in relation to $FEV_1$ and BODE index showed odds ratio for $FEV_1$ ≤ 50% statistically significant (p value= 0.016).
**Conclusion:** Osteoporosis and sarcopenia are very common in COPD in Indian population but there is no correlation with $FEV_1$. Though BODE index is a good prognostic indicator, $FEV_1$ is more likely to correlate with severity of PH than BODE index.
**Keywords:** Osteoporosis, sarcopenia, fat free mass index (FFMI), BODE index.

## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent, underdiagnosed, undertreated disease [1]; hence have significant morbidity, mortality leading to substantial economic and social burden. COPD has been recognized as a systemic disease because of associated significant co-morbidities in the form of osteoporosis, sarcopenia, coronary artery disease, anemia, anxiety, and depression, pulmonary hypertension (PH)[2]. Presence of these co-morbidities affects prognosis significantly in COPD [3]. Thus it is crucial to be aware about them, screen for them and intervene appropriately to decrease morbidity, mortality and improve quality of life.

PH, an important sequel of COPD, has been correlated with $FEV_1$ [4]; however has not been studied in correlation with BODE index. BODE index a multidimensional severity score has been shown as prognostic marker in COPD in terms of predictor of mortality[5] and proved to be surrogate marker of the benefits of pulmonary rehabilitation as well[6]. It is considered to be better prognostic maker than $FEV_1$.

In the present study we studied the frequency of these co-morbidities (osteoporosis, sarcopenia, PH) and their relation with COPD severity. Osteoporosis and

sarcopenia studied with FEV1% and PH with both FEV1% and BODE index.

## 2. Materials and methods

### 2.1 Study design

It was a prospective cross-sectional observational study done over a period of 1 year. After obtaining ethic committee approval, thirty COPD patients attending outpatient department of our tertiary care centre over 1 year period, diagnosed based on global initiative for obstructive lung disease (GOLD) guidelines were included. Their written informed consent was obtained prior to inclusion. Patients with exacerbation in last 6 weeks and those on long term oral steroid therapy, calcium supplements, neoplastic disease or any disease with an inflammatory or metabolic component (CKD, rheumatoid arthritis, cirrhosis of liver) and cardiac failure were excluded from the study. Spirometry was performed as per American Thoracic Society (ATS) guidelines. Patients were classified into stage I, II, III and IV as per the GOLD guidelines. Further they were divided into 2 groups based on $FEV_1$%, that is $FEV_1$ ≥50% and $FEV_1$<50% for the purpose of statistical analysis. Bone mineral density (BMD) and fat free mass index (FFMI) were calculated with the help of dual energy x-ray absorptiometry (DEXA) scan (Lunar Expert XL Bone densitometer). DEXA scan measured BMD at hip (Left femoral neck), lumbar spine (L1-L4) and left forearm. For the diagnosis of osteopenia and osteoporosis lowest BMD at lumbar spine (L1-L4) or hip (femoral neck) was considered, as per the International Society for Clinical Densitometry (ISCD)[7] recommendations. BMD was recorded as t score in terms of standard deviations (SD) in relation to reference population. (T score - The patient's bone mineral density as compared to the peak bone mass in normal young adults). Osteopenia and osteoporosis was defined as per WHO [8] based on t score as mentioned in table 1.

**Table 1: WHO Criteria for Osteoporosis**

| Category | T score |
|---|---|
| Normal | >-1 SD |
| Osteopenia | <-1 and >-2.5 SD |
| Osteoporosis | <-2.5 SD |

FFMI was calculated with the help of lean body mass. DEXA scan gives total body mass and fat mass. Lean body mass (fat free mass) is total mass minus fat mass. The formula applied for calculating FFMI was: lean body mass (in kg)/height $(m)^2$. It was labeled sarcopenia if FFMI was <16 $kg/m^2$ for men, <15$kg/m^2$ for women as per Schols *et al*[9]. 2 groups of COPD patients, FEV1 ≥50% and $FEV_1$<50%, were compared with each other for BMD and FFMI.

BODE Index calculated after obtaining all necessary variables (body mass index in $kg/m^2$, post bronchodilator $FEV_1$%, dyspnoea modified medical research council index, 6 minute walk distance in meters).The sum of the variables corresponds to a BODE index score from 1 to 10. BODE Index was calculated for 26 out of 30 patients. In 4 patients 6 minute walk test could not be performed as there was desaturation during the exercise. BODE index scores were divided into 3 groups :< 5, 5-6 & ≥7 based on predicted mortality of each group [10].

Pulmonary artery pressure (PAP) was measured by 2 dimensional echo cardiography (2D Echo) by TR jet estimation. PAP was considered normal when the pressure was <30 mm of Hg. PH was scaled mild, moderate and severe if the PAP was 30-45 mm of Hg, PAP >45 mm of Hg but without RV dilated and cor pulmonale (RV dilated) respectively. The severity of PH was compared with $FEV_1$<50, $FEV_1$≥50% and 3 BODE groups.

Data analysis was performed with the help of SPSS Software ver. 15 and Sigmaplot Ver. 11. Mean, standard deviation, median and interquartile range (IQR) were calculated for the quantitative data. Frequency and percentage table were charted for the qualitative data. Comparison among study group was done with the help of unpaired t test as per the results of normality test. Binary logistic regression was applied to pulmonary hypertension as dependent variable and GOLD Staging & BODE Index as independent variable. Association among study group was assessed with the help of Chi-Square test. P value less than 0.05 was taken as significant level.

## 3. Results

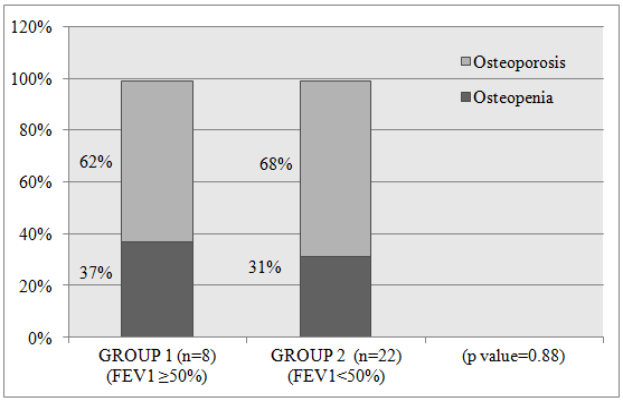
**Table 2: Baseline Characteristics of the Study Group**

| Variables | |
|---|---|
| Total no. of patients | 30 |
| Mean Age | 66 yrs |
| Mean Pack Year Smoking | 18 pack yrs |
| Average $FEV_1$(post) % | 40.9 |
| Gold Class<br>1<br>2<br>3<br>4 | (No. of patients)<br>0<br>8<br>12<br>10 |
| No. of patients with Osteopenia | 10 (33.3%) |
| No. of patients with Osteoporosis | 20 (66.6%) |
| No. of patients with Sarcopenia (FFMI<16 $kg/m^2$) | 25 (83.3% ) |
| Mean BMI (in $kg/m^2$) | 19.03 |
| Mean FFMI (in $kg/m^2$) | 15.05 |
| Mean BODE Index score | 5 |

The study group consisted of 30 men with mean age of 66yrs (45 to 84yrs), with mean smoking history of 18 pack years. There were no female patients. Their average $FEV_1$ was 40.9% predicted. None of the patients were in GOLD class I, 8 belonged to class II, 12 to class III and 10 in class IV (table 2). All patients were found to

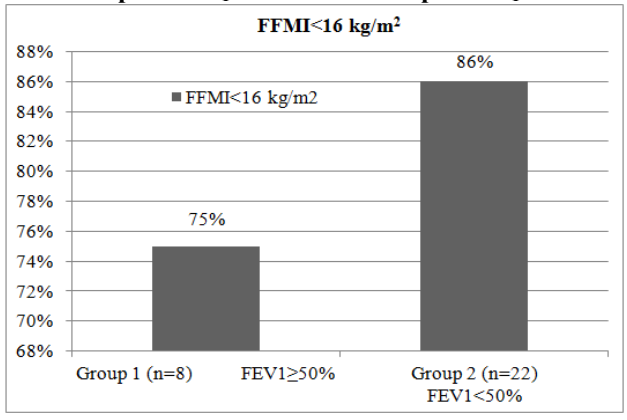
have low BMD, 10 had osteopenia and 20 osteoporosis. Amongst 8 patient of group 1 i.e. $FEV_1 \geq 50\%$ 3 (37%) had osteopenia and 5 (62%) had osteoporosis (figure1). In group 2 ($FEV_1 < 50\%$) out of 22, osteopenia and osteoporosis was found in 7 (31%) and 15 (68%) patients respectively (figure 1). However the difference in osteoporosis in two groups was statistically not significant (chi-square test, p value=0.88).

**Figure 1: Proportion of osteopenia and osteoporosis in Group 1=$FEV_1 \geq 50\%$ and Group 2=$FEV_1 < 50\%$**




19 (63.3%) out of 30 patients had BMI < 21 $kg/m^2$ and 25 (83.3%) out of 30 patients had FFMI<16 $kg/m^2$ (sarcopenia). Average BMI was 20.3 $kg/m^2$ in group 1 and 18.77 $kg/m^2$ in group 2. Average FFMI was 15.81 $kg/m^2$ and 14.3 $kg/m^2$ in group 1 and 2 respectively. In group 1, 6 (75%) out of 8 and in group 2, 19 out of 22 (86%) patients had sarcopenia (figure 2).

**Figure 2: Proportion of patients with FFMI<16 $kg/m^2$ in Group 1=$FEV_1 \geq 50\%$ and Group =$FEV_1 < 50\%$.**




The difference in sarcopenia in two groups was statistically not significant (chi-square test, p value=0.85)

6 out of 30 (20%) patients had normal BMI with low FFMI. The difference of BMI and FFMI in group 1 and 2 was statistically not significant (chi-square test, p value 0.324 and 0.095 respectively).

The result of severity of BODE index (<5, 5-6, ≥7) in comparison with PH is given in table 3.

**Table 3: BODE index score and pulmonary hypertension (PH)**

| PH / BODE SCORE | Normal | Mild (PASP 30-45 mm of Hg) | Moderate (PASP >45 mm of Hg) | Cor pulmonale | Total |
|---|---|---|---|---|---|
| <5 | 6 (46%) | 6 (46%) | 1 (8%) | 0 | 13 |
| 5-6 | 1 (16%) | 3 (50%) | 2 (34%) | 0 | 6 |
| ≥7 | 0 | 5 (71%) | 0 | 2 (29%) | 7 |
| Total | 7 (27%) | 14 (54%) | 3 (11%) | 2 (8%) | 26 |

All patients with more severe BODE index score (≥7) had PH, 5 (71%) had mild PH and 2 (29%) had cor pulmonale, amongst 6 patients in second group (BODE index score 5-6) 5 patients had PH. Lastly, of 13 patients with low BODE index (<5), 6 patients (46%) did not have PH. The relation between BODE index and PH was statistically not significant (chi-square test, p value=0.07). On comparison of $FEV_1$ with PH, 5 (71.4%) out of 7 patients in group I ($FEV_1 > 50$) had normal PAP and 2 had mild PH, whereas amongst group II ($FEV_1 < 50$ %) patients 2 (9%) had normal PAP, 15 (68.8%) had mild PH, 3 (13.6%) had moderate PH and 2 (9%) had cor pulmonale. It was not possible to measure PH in one of the patients due to technical reasons.

Binary logistic regression was applied to assess association among PH, as a dependant variable and GOLD class, BODE index as independent variables. It was observed that the odds ratio for GOLD class was 0.025 which is statistically significant (p value= 0.016). It indicates that patients with GOLD class 3 and 4 are more likely to have PH.

## 4. Discussion

Osteopenia and osteoporosis are common in COPD with prevalence of 35-72% and 36-60% respectively [11,12]. In our study all the patients (100%) had reduced BMD, 33.3% had osteopenia and 66.6% had osteoporosis. These results are similar to the only another study from India [13] which have used DEXA scan for studying bone loss in COPD patients. In this study out of 102 patients 88 (86%) had low BMD; 68 patients (66.6%) had osteoporosis and 20 patients (19.6%) had osteopenia. So far, the highest reported prevalence of osteoporosis in COPD has been 69%[14]. This study was done in

pretransplant patients i.e. end-stage pulmonary disease. Another study reported from India on osteoporosis performed on 37 patients belonging to stages III, and IV COPD with ultrasound bone densitometer also showed a high, 73%, prevalence of osteoporosis and osteopenia[15]. The risk of osteoporosis and osteopenia are reported to be as high as 35.1% (men-24.6%, women-42.5%) and 49.5% (men-54.3%, women-44.9%) respectively in healthy Indian population aged 50 years and above [16]. This suggests that osteoporosis prevalence in normal population is also very high in India. This high prevalence of osteoporosis has been linked to high prevalence of vitamin D deficiency reported from India [17,18]. The high prevalence of osteoporosis/osteopenia in our study may be partly due to reflection of general population. However, even after considering for overall high risk of osteoporosis/osteopenia, the prevalence is very high in our study. Since no other study has been done with DEXA scan in COPD from India, a larger scale studies with vitamin D levels are required to address the problem of this magnitude for appropriate management strategy.

When osteoporosis/osteopenia were correlated with $FEV_1$, the difference in osteoporosis in two groups of $FEV_1$ was statistically not significant, though osteoporosis was more in patients with $FEV_1$<50% (62% in group1 and 68% in group2). The association between COPD and osteoporosis is well established, however the association between low lung fuction ($FEV_1$) and low BMD is not well established. The relationships between lung function parameters and BMD are complex and not yet clear [19]. Certain studies have shown a correlation between $FEV_1$ and BMD, others have not. Vrieze *et al*[20], Bolton *et al*[21], Hattiholi *et al*[13] involving 115, 81 and 102 patients respectively, showed that BMD was related to severity of COPD. However the EOLO study [22] involving 3030 patients of COPD showed that osteoporosis had only a tendency, not statistically significant, for very severe COPD.

Overall, undernutrion compared to western studies was more common in terms of both BMI (83.3%) and FFMI (63.3%). 4/8 (50%) in group I i.e. FEV1> 50%and 15/22 (68.3%) in group II i.e. FEV1 <50% had BMI <21 $kg/m^2$. BMI in other Indian studies also show similar results [23]. Studies from western countries show low BMI in 10-15% of mild to moderate COPD and in 37 % of severe COPD [24].

Sarcopenia was seen in 6/8 (75%) in group I and 19/22 (86%) in group II. Western counterpart show reduced FFMI in about 17 % to 32.5% of moderate to severe COPD and 50% of very severe COPD [6,25,26]. There are no other Indian studies which have evaluated sarcopenia in COPD. Poor FFMI in our study is an isolated phenomenon or is due to different body composition in Indian population needs to be determined. Hence, more studies are required to define normal fat free mass index for Indian population. A "hidden" loss of fat free mass i.e. normal BMI with low FFMI has been shown in many studies [27- 30]. In our study too it was observed in 20%, prevalence similar to other studies [31-34]. BMI and FFMI both were low in patients with $FEV_1$<50% compared to those with $FEV_1$>50%, however the difference in two group was statistically not significant. This may be due to overall, small number of patients included in the study or because group I had very few patients.

Sarcopenia in COPD is treatable and treatment significantly improves the survival in COPD. Sarcopenia has been linked to mortality of COPD as well[9].We used DEXA scan for calculating FFMI of COPD patients. The other two methods available for calculating FFMI are body impedance anthropometry (BIA) and skin anthropometry. None of the method is gold standard[35], however DEXA scan is simple, non invasive and considered a reference method. BIA has been shown to underestimate while skin anthropometry overestimates FFMI [35]. Though, DEXA scan is costliest among the three methods, it is accurate in calculating FFMI. Similarly prevention and treatment of osteoporosis is an important part of management of COPD. DEXA scan is considered to be the gold standard for the diagnosis and management of osteoporosis [34]. Since, DEXA scan measures both BMD and FFMI accurately, and it is important to screen for both sarcopenia and osteoporosis, this common diagnostic tool should become as essential and as widely available as spirometry for the management of COPD.

BODE index, a multidimensional prognostic index has been proved to be a better prognostic marker for mortality[6], a predictor of hospitalization[36], a predictor of outcome of exacerbation[37] than GOLD classification. Mild-to-moderate pulmonary hypertension, a common complication of chronic obstructive pulmonary disease (COPD) is also considered to be a good prognostic marker for risks of exacerbation and survival [38]. However, to the best of our knowledge no study has been performed to study correlation between two good prognostic indicators i.e. BODE index and PH. In the present study we attempted to study association of BODE index with PH. All patients with more severe BODE index score (≥7) had PH. This compared to patients with low BODE index score, 6 out of 13(46%) did not have PH. However, BODE index did not correlate with severity of PH. Contrarily binary logistic regression to assess PH in relation to $FEV_1$ showed odds ratio for $FEV_1$ ≤50% statistically significant (p value= 0.016). Thus, though BODE index is a good prognostic indicator; GOLD staging (stage III and IV) is more likely to correlate with PH. Since, PH correlated

better with $FEV_1$ and not with BODE index we propose that combination of BODE index and PH would a better prognostic indicator than BODE index alone. Our study however, needs to be confirmed with the larger sample size.

There are certain limitations to present study. There were no female patients in our study; hence prevalence of osteoporosis in females could not be studied. However both male and female are at risk of osteoporosis, the risk is higher in postmenopausal women because of additional risk factors for osteoporosis. Secondly cut off values used for calculating sarcopenia based on FFMI, is subject to change with the availability of cut off parameters of Indian population. Third limitation in our study can be small sample size, hence association between osteoporosis and sarcopenia with $FEV_1$%, and also between BODE index and PH should be confirmed and validated with a large sample size study. Fourthly we have used 2 D echo instead of more accurate right heart catheterisation (RHC) for measurement of PAP [39].

2 D echo is more likely underestimate than overestimate PAP[39]. RHC though invasive and accuracy of results varies with the expertise doing it[40], it is found to be more accurate than 2 D echo[39]. Thus, present concept can be studied with RHC for more accurate results.

In conclusion, prevalence of bone loss in the form of osteopenia/osteoporosis and under nutrition in the form of low BMI and low FFMI (sarcopenia) is very high in COPD in Indian population. FFMI is more sensitive than BMI in diagnosing under nutrition. As DEXA scan is accurate, simple, non invasive test which gives both BMD and FFMI, it is a cost effective investigation for COPD patients whenever available. GOLD classification is still an important part of management not only for treatment perspective but also from the prognosis perspective specially to predict the severity of PH.

## References


[1] Celli R B. Update on management of COPD. *Chest* 2008; 133; 1451-62.

[2] Barnes PJ, Celli BR. Systemic manifestations and co morbidities of COPD. *Eur Respir J.* 2009; 33: 1165–85.

[3] Sin DD, Anthonisen NR, Soriano JB, Agust AG. Mortality in COPD: Role of comorbidities. *Eur Respir J.* 2006; 28:1245–57.

[4] Gupta NK, Agrawal RK, Srivastav AB, Ved ML. Echocardiographic evaluation of heart in chronic obstructive pulmonary disease patient and its co-relation with the severity of disease. *Lung India* 2011; 28:105-9

[5] Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, *et al*. The body mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350:1005–12

[6] Cote CG, Celli BR. Pulmonary rehabilitation and the BODE index in COPD. *Eur Respir J.* 2005; 26:630-6.

[7] 2007 official positions of The International Society For Clinical Densitometry. 2008. 10-7-2008. Ref Type: Internet Communication

[8] WHO Scientific Group on the Prevention and Management of Osteoporosis. Prevention and Management of Osteoporosis: report of a WHO scientific group. http;//whqlibdoc who int/trs/WHO_TRS_921 pdf [ 2007

[9] Schols AM, Brokhuizen R, Weling-Scheepers CA, and Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005; 82:53–9.

[10] Robert A Wise. Chronic obstructive pulmonary disease: clinical course and management. In: Fishman's pulmonary diseases and disorders(Alfred P. Fishman, Jack A Elias, Jay A Fishman, eds), 4th edition, Mc Graw Hill Medical Ltd. 2008;732.

[11] Iqbal F, Michaelson J, Thaler L, Rubin J, Roman J, Nanes MS. Declining bone mass in men with chronicpulmonary disease: contribution of glucocorticoid treatment, body mass index, and gonadal function. *Chest* 1999; 116:1616–24.

[12] Incalzi RA, Caradonna P, Ranieri P, Basso S, Fuso L, Pagano F, *et al*. Correlates of osteoporosis in chronic obstructive pulmonary disease. *Respir Med.* 2000; 94:1079–1084.

[13] Hattiholi J, Gaude GS. Prevalence and correlates of osteoporosis in chronic obstructive pulmonary disease patients in India. *Lung India* 2014;31:221-7

[14] Tschopp O, Boehler A, Speich R, Weder W, Seifert B, Russi EW *et al*.Osteoporosis before lung transplantation: association with low body mass index, but not with underlying disease. *Am J Transplant* 2002; 2:167–72.

[15] Bhattacharyya P, Paul R, Ghosh M, Dey R, Rana Dey, Barooah N, *et al*. Prevalence of osteoporosis and osteopenia in advanced chronic obstructive pulmonary disease patients. *Lung India.* 2011; 28:184–6.

[16] Marwaha RK, Tandon N, Garg MK, Kanwar R, Narang A, Sastry A, et at. Bone health in healthy Indian population aged 50 years and above. *Osteoporos Int.* 2011; 22:2829-36.

[17] Arya V, Bhambri R, Godbole MM, Mithal A. Vitamin D status and its relationship with bone mineral density in healthy Asian Indians. *Osteoporos Int* 2004; 15: 56-61.

[18] Vupputuri MR, Goswami R, Gupta N, Ray D, Tandon N, Kumar N. Prevalence and functional significance

of 25- hydroxyvitamin D deficiency and vitamin D receptor gene polymorphisms in Asian Indians. *Am J Clin Nutr* 2006; 83: 1411-9.

[19] Graat-Verboom L, Wouters EFM, Smeenk FWJM, van den Borne BEEM, Lunde R, Spruit MA. Current status of research on osteoporosis in COPD: a systematic review. *Eur Respir J* 2009; 34:209–18.

[20] Vrieze A, Greef M H G, Wýkstra P J, Wempe J B. Low bone mineral density in COPD patients related to worse lung function, low weight and decreased fat-free mass. *Osteoporos Int* 2007; 18:1197–202.

[21] Bolton CE, Inonescu AA, Shiels KM, Pettit RJ, Edwards PH, Stone MD, Nixon LS, Evans WD, Griffiths TL, Shale DJ. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170:1286–93.

[22] Maggi S, Siviero P, Gonnelli S, Schiraldi C, Malavolta N, Nuti R *et al*. Osteoporosis Risk in Patients With Chronic Obstructive Pulmonary Disease: The EOLO Study. *J Clin Densitom*. 2009;12:345-52

[23] Mathew JT, Veena GV, Kurpad AV, D'souza GA. Nutritional status predicts outcome in patients hospitalized with exacerbation of COPD. *Lung India* 2006; 23:143-6.

[24] Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis*. 1993; 147:1151–6.

[25] Palange P, Forte S, Felli A, Galassetti P, Serra P, Carlone S. Nutritional state and exercise tolerance in patients with COPD. *Chest* 1995; 107:1206-12.

[26] Vermeeren MA, Creutzberg EC, Schols AM, Postma DS, Pieters WR, Roldaan AC, Wouters EF. Prevalence of nutritional depletion in a large out-patient population of patients with COPD. *Respir Med.* 2006; 100:1349-55.

[27] Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.*1998; 157:1791–7.

[28] Montes de Oca M, Torres SH, Gonzalez Y, Romero E, Hernández N, Mata A, *et al*. Peripheral muscle composition and health status in patients with COPD. *Respir Med.* 2006; 100:1800–6.

[29] Creutzberg EC, Schols AM, Bothmer-Quaedvlieg FCM, Wouters EFM. Prevalence of elevated resting energy expenditure in patients with chronic obstructive pulmonary disease in relation to body composition and lung function. *Eur J Clin Nutr*.1998; 52:396–401.

[30] Ischaki E, Papatheodorou G, Gaki E, Papa I, Koulouris N, and Loukides S. Body Mass and Fat-Free Mass Indices in COPD: Relation With Variables Expressing Disease Severity Chest 2007;132:164-9.

[31] Schols AM, Soeters PB, Dingemans AMC, Mostert R, Frantzen PJ, Wouters EFM. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis.* 1993; 147:1151–6.

[32] Shoup R, Dalsky G, Warner S, Davies M, Connors M, Khan M, Khan F, ZuWallack R. Body composition and health-related quality of life in patients with obstructive airways disease. *Eur Respir J*.1997;10:1576-80

[33] Eid AA, Ionescu AA, Nixon LS, Lewis-Jenkins V, Matthews SB, Griffiths TL, Shale DJ. Inflammatory response and body composition in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1414–8.

[34] Bolton CE, Ionescu AA, Shiels KM, Pettit RJ, Edwards PH, Stone MD *et al*. Associated Loss of Fat-free Mass and Bone Mineral Density in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2004; 170; 1286-93.

[35] Lerario MC, Sachs A, Lazaretti-Castro M. Body composition in patients with chronic obstructive pulmonary disease: which method to use in clinical practice? *British Journal of Nutrition* 2006; 96:86–92.

[36] Ong KC, Earnest, Lu SJ. A Multidimensional Grading System (BODE Index) as Predictor of Hospitalization for Copd. *Chest* 2005; 128; 3810-6.

[37] Cote CG, Celli BR. Effect of exacerbations of COPD (AE) on the multidimensional body mass index (B), airflow obstruction(O), dyspnea (D) and exercise capacity (E), BODE index [abstract]. *Chest* 2004; 126:840S.

[38] Chaouat A, Naeije R and Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J* 2008;32:1371-85

[39] Fisher MR, Forfia PR, Chamera E, *et al*. Accuracy of Doppler Echocardiography in the Hemodynamic Assessment of Pulmonary Hypertension. *Am J Respir Crit Care Med* 2009;179:615

[40] Paterson I; Michelakis ED, The Role of Doppler Echocardiography in Pulmonary Artery Hypertension The Importance of Proving the Obvious, Editorials, *Chest*, May 2011; 139:5.