Bone mineral density changes in male patients with chronic obstructive pulmonary disease:clinical and biochemical variables in correlation with glucocorticoids use

Abdelmoneim M. Barrak*, Atef Abulfotoh*, Essam Mousa*, Sherif Alsayed, and Mahmoud Rosasy*****

* **Department of Internal Medicine, Al-Azhar university,** Department of chest, El fayoum university**

***** Department Orthopedic , Tanta University**

Abstract

Recent studies have shown that osteoporosis and vertebral fractures are quite common in postmenopausal women with chronic obstructive pulmonary disease (COPD). Few data are available in correlation between bone mass density (BMD) and men with COPD.

This study was designed to investigate the prevalence of osteoporosis in men with COPD. With special regards to the role of glucocorticoids (GCs) use in these patients. We aimed to determine factors that influencing bone metabolism and the clinical variables of this group of patients. We also tried to answer the arising question: should COPD patients be routinely evaluated for BMD?

Methods: The study included 56 male patients with documented COPD for at least two years, their age ranged 24-66 years. Subjects were divided into 3 groups: group 1. consisted of 18 patients, who were oral GCs users, group 2. consisted of 18 patients who were inhaled GCs users and group 3. consisted of 20 patients, never GCs users (this group was considered as the control group). All subjects underwent measurement of BMD. Pulmonary function tests (PFTs) and a number of biochemical markers of bone metabolism. The associations between BMD. PFTs. GCs use. Biochemical markers and clinical variables were analyzed.

Results: of all 56 patients with COPD. the prevalence of osteopenia and osteoporosis. As defined by WHO criteria was 26.8% and 21.4% at the lumber spine. 30.4% and 23.2% at total hip. 35.7% and 28.5% at femoral neck and 32.1% and 28.8% for total body respectively. Patients included group 1 had the lowest BMD at any site ($p< 0.0001$). group 2 patients had over all bone mass loss, that was indistinguishable from those who were received oral GCs. group 3 patients had less bone mass reduction than the other two groups. Of the clinical and biochemical markers measured. N-telopeptide was significantly correlated with bone mass ($P<0.01$), but there was no correlation with other markers. The lowest mean of FEV1 (Forced Expiratory Volume in one second) was observed in group 1 patients. BMI (Body Mass Index) was weakly correlated with bone mass in the 3 studied groups.

Conclusion: Bone mass loss is a common problem in male patients with COPD. while the use of oral GCs increase the frequency of osteoporosis, inhaled GCs therapy offered no protection from bone loss. COPD patients who had never treated with GCs had also a substantial risk for osteoporosis. We advocate early screening and preventive intervention.

INTRODUCTION:

It is well known that hone mass loss is a major complication of chronic illness, but the magnitude of the effect in patients with COPD is not well defined. COPD is a complex disease; the most clinically important manifestations are the decrease in body weight with loss of skeletal muscle mass and osteoporosis (1). Although much has been learned about the factors that contribute bone loss, most of this information has been derived from studies of postmenopausal women; much less studies were directed to men with COPD. Recent epidemiologic data suggested that, the relative risk of osteoporosis and vertebral fracture is doubled by chronic illness. (2) For men with chronic lung disease, osteoporosis associated with loss of independence and increased mortality were reported (3), (4)

Corticosteroids are frequently prescribed for patients with COPD. Secondary osteoporosis is an important and well documented side effect of long-term GCs therapy in patients with COPD (5). Several studies have shown an association between chronic systemic steroid use and lower bone mineral density in COPD patients (6).(7). However it is not yet known whether patients with COPD who never received GCs have a high incidence of osteoporosis and whether these patients require treatment strategies to decrease the risk of bone mass loss recently it is reported that the incidence of osteoporosis in patients with COPD who had never received GCs remains controversial (8). (9).

The pathophysiology of bone mass loss in patients with COPD is unclear. BMD is related to markers of disease severity such as BMI, FEVI. C-reactive protein and physical activity. (10) Although several serum and urine biochemical markers of bone formation and bone resorption are available and useful in clinical trials, researches had revealed little correlation or predictive value for future bone loss or risk of fracture at the level of the individual patient. (11)

The present study directed to evaluate the contribution of clinical and biochemical variables to bone loss in male patients with COPD. these subjects had received chronic treatment with oral, inhaled GCs or no GCs. We aimed to identify the prevalence of osteoporosis and to determine the clinical and biochemical correlates in these patients.

Patients Materials and Methods:

♦Study Design:

This study was designed to evaluate bone mineral density (BMD) in men with COPD and to study the effect of oral and inhaled GCs on bone mass and bone metabolism in these patients. The study was carried out at Al Amen and Eladwany General Hospitals in Saudi Arabia. Male patients with COPD were only participated in the study, females were excluded from the study to avoid the postmenopausal effects on bone mass and bone metabolism in these patients. Previous uses of oral and inhaled GCs were carefully assessed from hospital patient's records.

*Subjects:

The study included 56 male patients with documented COPD for at least two years. Their age ranged 24-66 years. The criteria for diagnosis of COPD were based on the standards of the European Respirator)- Society Standards. (12) All patients were classified into one of three groups, according to their GCs treatment history.

Group l: consisted of 18 patients who received prednisolone orally in a daily dose *of* at least 5mg/ day in the past 6 months, of which the cumulative dose administered was not less than 1000mg and not more than 2000mg.
Group2; consisted of 18 patients who were currently stabilized on doses of inhaled GCs not less than 800 µg/day during the past 6 months. GCs prescribed in the study were beclomethasone and budesonide.
Group 3: consisted of 20 patients with mild to moderate COPD who never treated with GCs. This group was considered as the control group. Full history and clinical data were obtained including age. race, duration of respiratory illness, smoking. Consumption of coffee, concurrent illness, fracture history and family history of osteoporosis. Information of the clinical data and history of GCs treatment were derived from subject interviews and medical record reviews. Patients of the three groups were balanced for age and duration of COPD.
Subjects were excluded if they had a coexisting medical disorder that might affect bone metabolism such as renal, hepatic thyroid or non-osteoporotic metabolic bone disease. Patients were also excluded if they have received medications known to affect bone metabolism apart from GCs such as bisphosphonate. Calciotrophic hormones, phenothiazine, D-penicillamine. Methotrexate or gold therapy.

* **Laboratory Measurements:**
Blood samples were collected in the morning under fasting conditions. Plasma concentrations of calcium, phosphorus, total protein, albumin, blood urea and creatinine were measured by routine assays. Total testosterone. Free testosterone, total serum alkaline phosphatase and bone specific alkaline phosphatase were measured by radio immunoassay. Serum osteocalcin levels were measured by immunoradiometric assay (ELSA - Osteo - CIS Bio International, Cedex - France). Urinary concentrations of calcium, phosphate and creatinine were measured by routine assays. Urinary excretion of type 1 collagen cross links (N - telopeptide), was measured in a day spot urine sample (Ostex International. Portland OR).

***Measurement of BMD:**
BMD was measured by using dual energy x-ray absorptiometry (DEXA) (Osteocore 3. Bone densitometer. MEDILINK. Carnon -France "Release date May 20th. 2002) Measurements were made of the lumber spine (LI - L4). femoral neck, total hip and total body. Measurements were express as grams of bone mineral per square centimeter of bone. BMD was also expressed as a Z score and T score. The Z score is a SD from the weight-adjusted average of BMD of each age based data of the same race in the Osteocore 3 densitometer. The T score is a SD from peak bone mass. Calibration procedures were performed at least every day and again after each series of eight scans using the appropriate phantoms provided by the manufacture. All scans were performed and analyzed by the same operator.

Pulmonary Function Tests: (PFTs)
PFT data were obtained from the medical records and were all measured within one week prior to inclusion into the study. PFTs were performed using Jaeges Masterlab (Erich Jaeges Gm BH. Wneszbng Germany) and the included normal values were based on the European Respiratory Society standards (12). Total lung capacity (TLC) Residual volume (RV), and forced expiratory volume (FEV) in absolute values and in percentages of predicted values were recorded.

Statistical Analysis:

Unpaired student tests **were used to compare the three studied patient groups. For** continuous variables, the differences between the groups were compared using analysis of variance, post hoc multiple comparisons were done using rising Schejje's method. X2 analysis was used to compare categorical variables. Using predefined criteria for osteoporosis logistic regression was used to calculate adjusted odds ratio for the presence of osteoporosis.

RESULTS:

***Patient Characteristics:**

As shown in Table 1. patients were divided into 3 groups according to their GCs history intake. The mean ages of patients in the 3 groups were similar, but BMI was lower in group 1. Smoking habit was expressed in Cigarette per day, it was 28 ± 5.6 Cigarette per day, 26 ± 5.1 Cigarette per day and 25 ±4.3 pack-year in the 3 groups respectively. These values did not differ significantly.

Results showed that the lowest mean of FEVI was observed in the oral GCs group (group 1). but there was no significant differences between the 3 groups. The mean duration of GCs intake was not also significantly differ between group 1 and 2. Table 2 shows the results of BMI and the cumulative doses of GCs in the 3 studied groups.

Table 1: patient characteristics, and previous steroid use.

Variables	Group 1 COPD Plus oral steroids(mg)	Group2 COPD Plus inhaled Steroids(µg)	Group3 COPD No steroids
Number of patients	18	18	20
Age (Years)	61±1.6	60 ±1.9	69 ±2.1
Smoking history (Number)	14	13	9
Cigarette per day	28 ±5.6	26 ± 5.1	25±4.3
Body weight /Kg	63.7±12	65 ± 14	64±16
Body height /cm	165±1.5	168±1.3	167± 1.1
BMI .Kg /m^2	23.6±8"	28±0.6	30.1±0.2
Duration of steroid intake	**10.9** ± 3.2	11 ± 5.4	NO
Total steroid doses	3.123 ± 617	430±64	NO
FEV!	49.6 ± 2.8"	59±1.7	66 ± 4.7

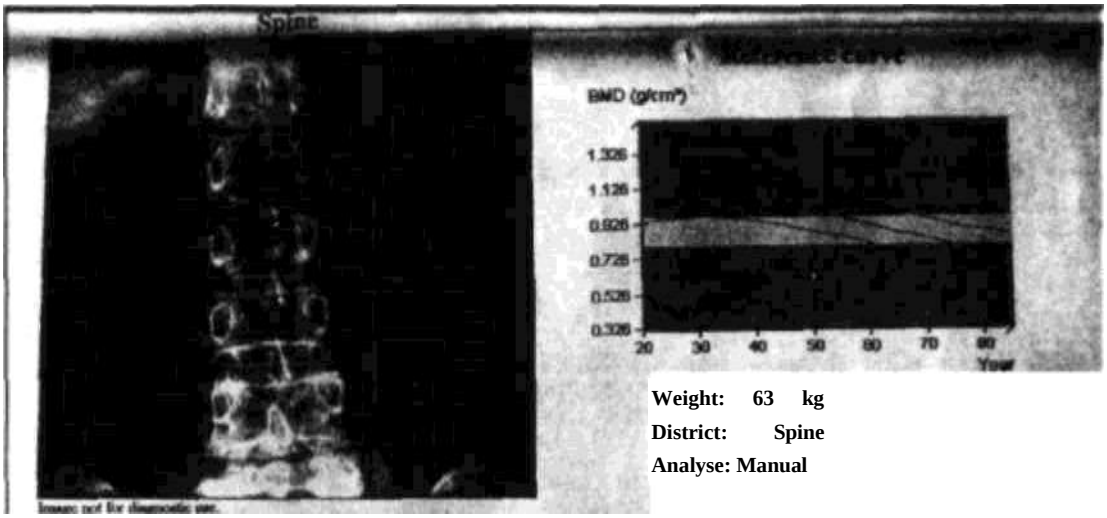
Data are presented as mean (SD). P <0.001 (Lower BMI values than group 2 and 3)

P <0.0001(lower FEV1 values than group 2 and 3)

Table 2: Cumulative

Groups	Age - **Year**	**BMI**	Cumulative steroid dose (mg)
Group ! (n= 18)	61.2±(1.6)	23.6±8	3.123±617
Group 2 (n = 18)	60.0±(1.9)	28±0.6	430 ±64
Group3 (n -20)	63.0±(2.1)	30.1 ±0.2	0

Data are presented as mean (SD). BMI = Body Mass Index
P <0.001 (Lower BMI values than group 2 and 3)



R.O.I	BMI(g/m²)	BMC(g)	Area(cm²)	Z score	T score
L1	0.482	4.468	9.28	-438 (-51%)	-5.39(-55%)
L2	0.581	5.919	10.19	-3.69(-41%)	-4.50(-46%)
L3	0.604	7.364	12.50	-3.47(-38%)	-4.29(-44%)
L4	0.768	10.845	14.12	-2.00(-22%)	-2.81(-28%)
Total	0.6254.468	28.786	46.09	-3.23(-36%)	-4.10(-42%)

Figure 1 - B: Shows bone mass loss of a male patient with chronic obstructive pulmonary disease on oral glucocorticoids. (LI through L4).

The percentages of patients meeting the criteria for osteopenia and osteoporosis as defined by World Health Organization (WHO) criteria for the diagnosis of osteopenia and osteoporosis are shown in Table 3. Of all 56 patients with COPD the prevalence of osteopenia and osteoporosis was 26.8% and 21.4% at the lumber spine. 30.4% and 23.2% at total hip. 35.7% and 28.5% at femoral neck and 32.1 and 26.8% for total body, respectively.

Table 3: Prevalence of osteopenia And osteoporosis in 56 male patients with COPD.

Site	**Osteopenia**	**Osteoporosis**
- Lumber spine (LI - L4)	15(26.8)	12(21.4)
- Total hip	17(30.4)	13(23.2)
- Femoral neck	20 (35.7)	16(28.5)
- Total body	18(32.1)	15(26.8)

Data are presented as percentages (%). osteopenia was defined as -2.5 SD and osteoporosis was defined as < 2.5 SD.

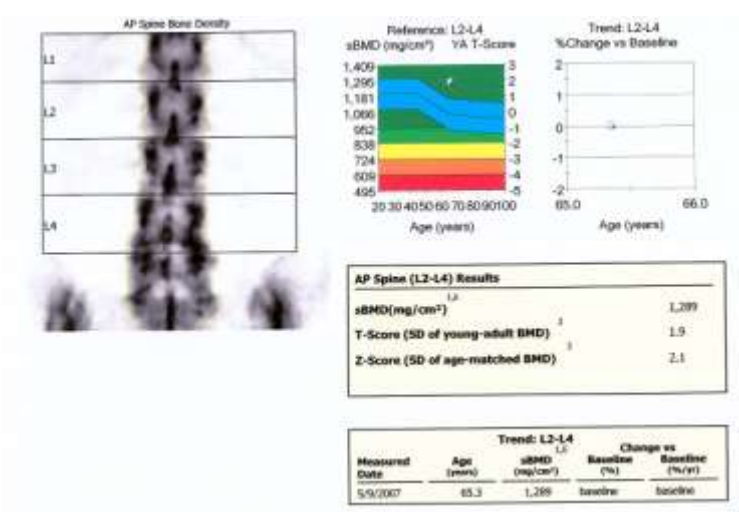
BMD outcomes of the 3 groups are listed in Table 4.

patients included group 1 (oral GCs) had the lowest BMD at any site compared to the other two groups (P O.0001). Group 3 (patients with COPD. who never used GCs). showed less reduction in BMD than group 1 and 2 (P <0.04).

*Bone Mass Measurements:
Bone mass at the lumber spine (LI - L4). total hip. femoral neck and total body was evaluated as a real mineral density (BMD. gm/cm2). It is represented as SD from mean age. gender and site specific (Z score), and

as SD from peak bone mass (T Score). Figure 1 (A and B). Figure 1 - A: Shows the quality control and die standard DXA scan during the study. (From 26/10/2003 to 08/03/2004). Figure 1 - B shows sever bone mass loss in a 52 years old male patient with COPD on oral GCs therapy using Osteocore III absorptiometry

Figure 1 - A: The DXA scan of osteopenic and osteoparotic patient.



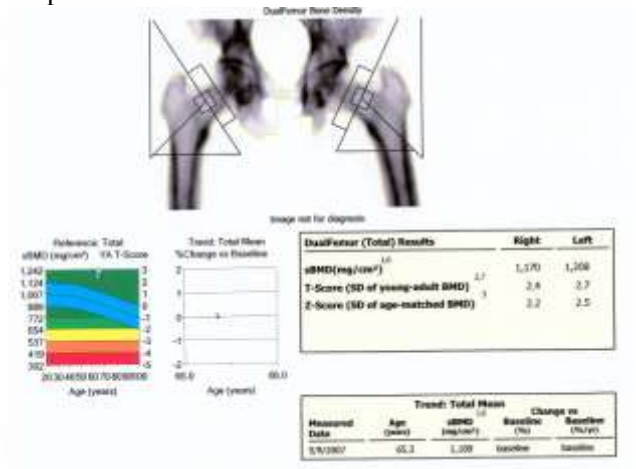


Table 4: BMD outcomes in the three studied groups.

Groups	BMD/ cm^2	P values
Group 1 (n= 18)	0.683±0.115	< 0.0001
Group 2 (n= 18)	0.759-±0.238	< 0.001
Group 3 (n = 20)	0.928±0.176	<0.04

Data are presented as means + SD
BMD - Bone mass density, n = Number
Data are presented as (SD) of predicted values

The results of BMD at the lumber spine, total hip. Femoral neck and total body of the 3 studied groups, revealed that patients included in group 1 had the lowest BMD at any site compared to group 2 and 3 (P <0.0001).

The results also showed that patients who were prescribed chronic GCs inhalation therapy had an overall loss of bone mass (P O.001). That was indistinguishable from those who were received oral steroids (group 1). Patients with COPD who never treated with GCs (group3), also showed bone mass loss. Thus our results suggested that bone mass loss in these subjects occurred whether or not they were received steroid therapy as obvious in table 5

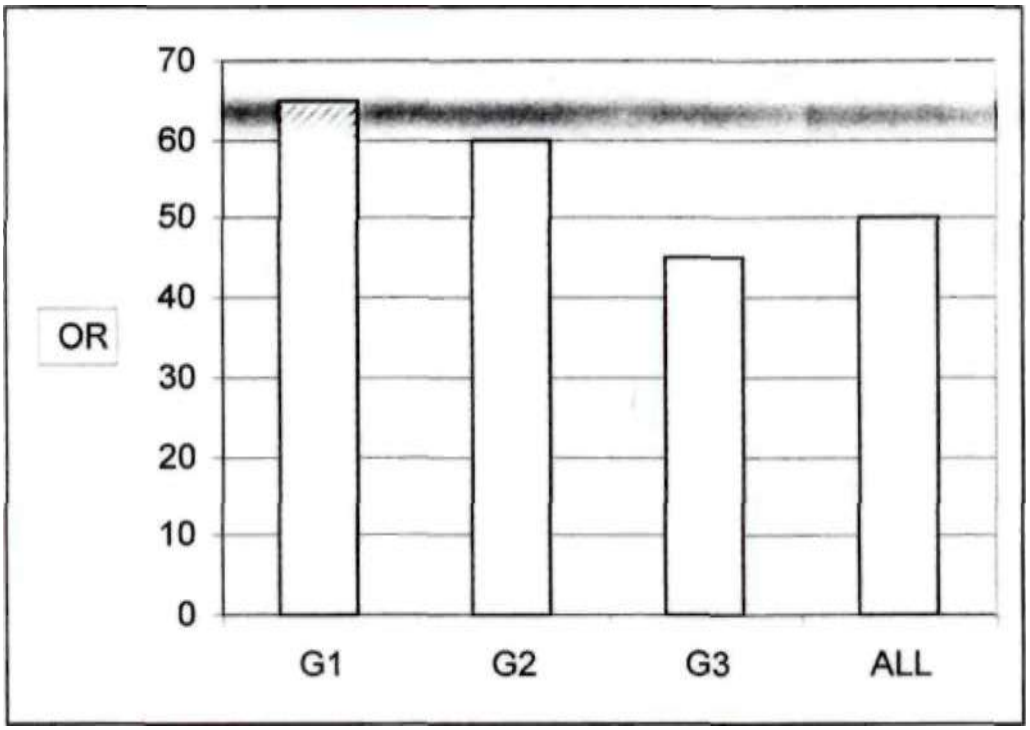
As shown in figure 2. The calculated odds ratio for meeting (WHO) criteria for the diagnosis of osteoporosis (T score < 2.5). After adjusting for BMI were calculated with their 95% confidence intervals (Cls), the subjects with COPD were more than five times as likely to meet the criteria for osteoporosis as were the standard control.

Table 5: BMD in lumber spine, total hip, femoral neck and total body in male patients with COPD.

Groups	BMDg/cm^2	P values
Group 1 (n= 18)		
lumber spine (LI - L4)	0.779 ± 0.288	< 0.001
Total hip	0.663 ± 0.155	< 0.0001
Femoral neck	0.687 ± 0.213	< 0.001
Total body	0.669 ± 0.165	< 0.0001
Group 2 (n = 18)		
lumber spine (LI -L4)	1.269 ± 0.227	<0.01
Total hip	0.749 ± 0.218	< 0.001
Femoral neck	0.667 ± 0.215	< 0.001
Total body	0.692 ± 0.219	< 0.001
Group 3 (n = 20)		
lumber spine (LI - L4)	1.007± 0.080	NS
Total hip	0.664 ± 0.211	<0.01
Femoral neck	1.098 ± 0.103	< 0.5
Total body%	0.769 ± 0.299	<0.01

Data presented as mean ± SD
BMD = bone mass density, n = number. NS = not significant
Data are presented as (SD) pv predicted values

Figure 2: Odds ratio (OR) for achieving WHO criteria for the diagnosis of osteoporosis (T score < 2.5) in patients with COPD. With and without steroid therapy.



OR = Odds ratios. G 1 = group 1 (COPD + oral steroids). G2 = group 2 (COPD + inhaled steroids), G3 = group 3 (COPD with no steroids), all = all 56 patients with COPD.

Results show the calculated OR±95% confidence intervals (C1 s) for each group. The relationship between BMD and BMI is shown in Figure 3.

It is revealed that for all patients with COPD with and without steroid therapy, bone mass was positively correlated with BMI vs. Z score. Parason correlation coefficients (r) between BMI and BMD were 0.04 at the lumber spine. 0.06 at the total hip. 0.5 At the femoral neck and 0.01 for total body ($r = 0.346$. $P < 0.001$ for all sites) .

The subjects with the lowest BMI tended to have the lowest BMD. The correlation between bone mass and BMI was stronger at total hip and total body than the spine and femoral neck, but it was significant at all sites for all the studied groups as a whole.

Table 6: PFT results in 56 male COPD patients.

Variables	Data	P values
Group l(n= 18)		
FEVl °o predicted	0.682±0.:~4	**NS**
TLC °o predicted	1.050±0.224	**NS**
RV % predicted	1.045±0.34-1	**NS**
Group 2 (n= 18)	-	**-**
FEVI% predicted	0.797 ±0.268	**NS**
TLC Vo predicted	1.007±0.103	**NS**
RV % predicted	1.104±0.207	**NS**
Group 3 (n = 20)	-	**-**
FEVI % predicted	0.691 ±0.259	**NS**
TLC % predicted	1.009±0.133	**NS**
RV % predicted	1.102±0.216	**NS**

PFT = pulmonary function tests. FEVI = forced expiratory volume in one second TLC = total lung capacity, RV = residual volume. NS = not significant Data are presented as % of predicted values (SD).

Results of Biochemical Markers:

The biochemical markers osteocalcin, bone specific alkaline phosphatase and total alkaline phosphatase in serum in addition to the bone resorption marker N-telopeptide in a day time urine sample were measured as showed in table 7

BMD was negatively correlated with N-telopeptide levels ($P<0.01$). The relationship between bone mass and N-telopeptide is shown in Figure 4.

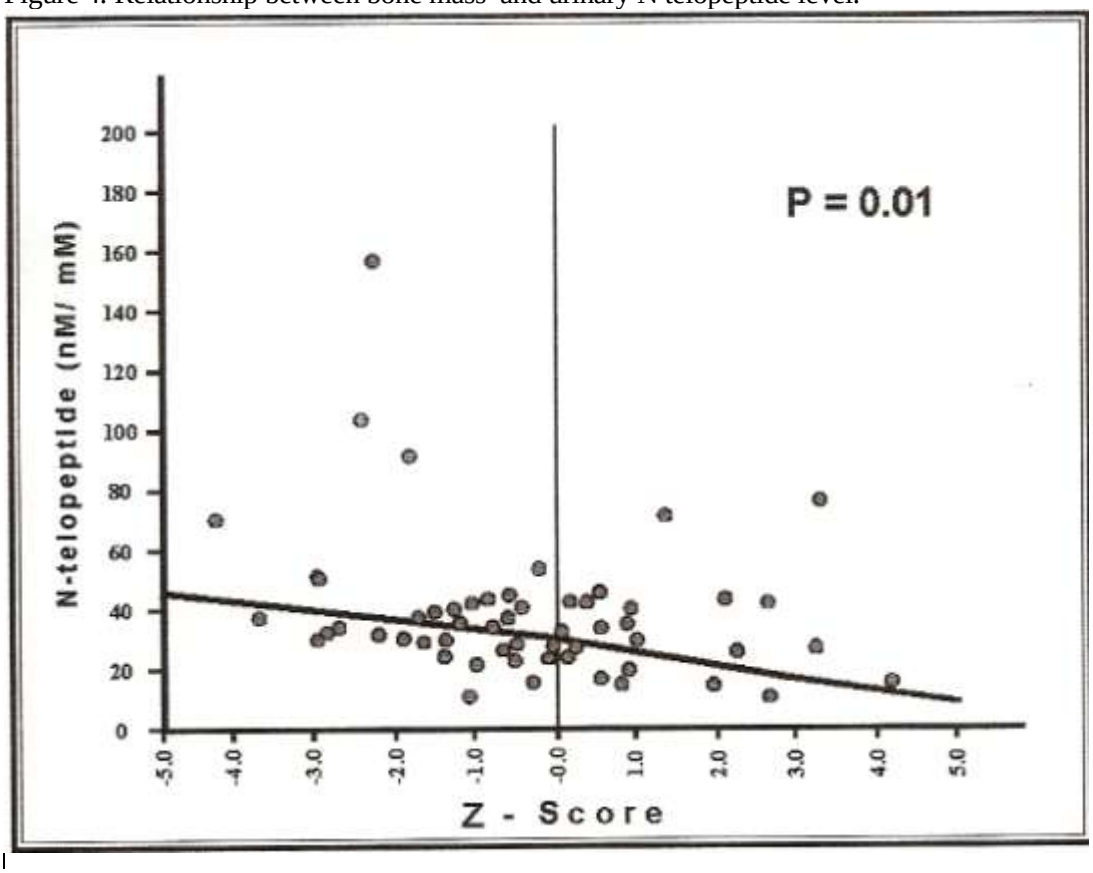
Our results also showed that N-telopeptide was significantly correlated with bone mass ($P <0.01$) but not significantly correlated with other biochemical markers.

The results of serum total testosterone and free testosterone were not statistically significant for the 3 studied groups.

The difference between all COPD subjects with and without steroid therapy for total and free testosterone were not significant.

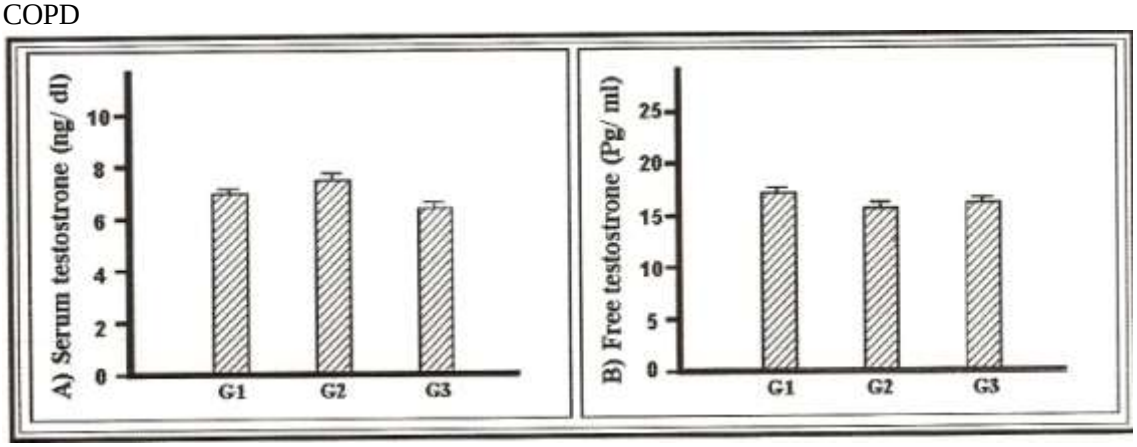
Figure 5. (A and B) represents the results of total and free testosterone in the 3 studied groups. Serum levels of calcium and phosphorus were not associated with bone mass in all subjects with COPD.

Figure 4: Relationship between bone mass and urinary N telopeptide level.



The solid line represent the most fit between the z score and urine- N-telopeptide level for all study group(P<0.O1)

Figure 5 (A+B): Serum total testosterone and serum free testosterone in all subjects with COPD



Results are represented as means±SD P value not significant. G = group

DISCUSSION:

- It is known that patients with chronic lung disease are at risk for osteoporosis, and it is also well known that GCs are frequently prescribed for patients with COPD. Osteoporosis is one of the most serious complications of patients receiving GCs. Among postmenopausal women with COPD as many as 30 to 72% have been reported to be osteopenic and 26 to 60% have been osteoporotic. (13). (14). Although, in men with chronic illness, osteoporosis continues to be a major problem. but the prevalence and criteria for bone mass loss in these patients remain unclear. These may be because most studies on osteoporosis focused postmenopausal women rather than men. In men with COPD. osteoporosis may be particularly disabling and vertebral fractures, when occur reduce the lung vital capacity which further compromises ventilation. (15). An increased prevalence of vertebral fractures has been documented in men with chronic lung disease on the evaluation of lateral spine films. (16) In the current study we aimed to identify' the prevalence of osteoporosis in male patients with COPD and to study the effect of GCs using bone densitometry screening, based on clinical and biochemical measures.

In a study on men with chronic lung disease, using the WHO criteria of T score < -1.0 for osteopenia and < - 2.5 for osteoporosis, data showed that the prevalence of osteopenia and osteoporosis was 72% and 36 % respectively. (17). The study of Dubois et. al. in 2002. showed that the prevalence of osteoporosis in male patients with COPD. who received continuous oral GCs. at the lumber spine, total hip and femoral neck regions was 31 %. 36 % and 29% respectively. (18). In our study the prevalence of osteopenia and osteoporosis meeting the criteria of WHO was 26.8% and 21.41% at the lumber spine. 30.4% and 23.2% at total hip. 35.7% and 28.5% at the femoral neck and 32.1% and 26.8% for the total body respectively. Our results showed that patients with COPD who received GCs had the lowest BMD at any site compared to patients who never received GCs. Although the prevalence of osteoporosis was higher in patients received GC therapy, our patients with COPD who had never treated with GCs had also risk of osteoporosis. Patients with inhaled GCs had no protection from bone loss compared to those treated with oral GCs.

In the study of Karadage et al. on 28 male patients with clinically stable COPD. they found that there was no statistically difference between the BMD values of COPD patients and the control group. The authors concluded that the risk of osteoporosis is not increased appropriately in patients with moderate degree COPD. and there was no indication for bone mass screening in this group. (19) In a recent Chinese study. COPD was detected to be a risk factor for osteoporosis and it is concluded that early measures of BMD should be considered to prevent osteoporosis in COPD patients. (20) Smith and colleagues demonstrated that clinically important bone density reduction was found in up to 29% of patients with COPD and asthma who received daily oral GCs at various bone sites. (21) It is also reported that bone density reduction occurred in patients with COPD in the absence of GCs therapy. (22) In our study we determined that GCs therapy (oral or inhaled) was associated with a significant reduction on BMD at all bone sites. We also found that subjects with COPD who had not been treated with GCs had a relatively greater reduction in bone mass at the hip than at the spine. This is agreement with Yen and coworkers who found a significant relationship (P=0.0045).Between COPD and osteoporosis. independent of GCs use. (23)

In the current study a number of clinical and biochemical variables were assessed aiming to determine their correlation with bone mass. Of these. BMI was positive!)

correlated with bone mass independent of other variables. It is found that patients who received chronic GCs had lowest BMI. this may explained by the fact that bone mass loss occurred once the disease is sever enough to cause weight loss. Our results support the conclusion that bone mass is directly correlated with BMI and that both men and women with high BMIs have higher BMD C24). (25)

Biochemical markers measured in our study included, calcium, phosphorus, total serum alkaline phosphatase, bone specific alkaline phosphatase, total testosterone. free testosterone, osteocalcin and urinary N-telopeptide. Our results showed that, only N-telopeptide. as a marker of bdhe resorption, was significantly ($P<0.01$) correlated with bone mass, thus it may represents one predictor of low bone mass in our study. Aderson et al.. reported that N-telopoptide accurately showed the early response to therapy in men receiving testosterone replacement. (26)

It is known that gonadal hormones have an important determinant of skeletal health. several recent reports have suggested that estrogen, rather than testosterone. may be the active gonadal hormone that maintains a positive formation, resorption balance. (27)

In the current study we measured total and free testosterone to determine if contributed to bone mass loss, however, in our COPD subjects, as a group, we did not observe a difference in these markers between the three studied groups. Our observation agreed with the hypothesis of Slemenda and coworkers who reported that estrogen, rather than total or free testosterone. is the most predictor of bone mass in elderly men. (28).

In our study, as regards to osteocalcin assay, there was no correlation between osteocalcin concentrations and bone density, although, Antoni et al.. in their study found that women used inhaled steroids had significantly low serum osteocalcin concentrations. (29). In fact this finding of lower osteocalcin levels among patients with chronic lung diseases, using inhaled steroids, is consistent with other studies. (30), (31). which may explained by the fact that osteocalcin levels reflect recent change in bone turnover. Other bone density studies (32), (33) demonstrated initial rapid onset of bone loss within the first 12 months, in patients received chronic steroid therapy, without evidence of further bone loss later on. On the basis of these observations, we speculate that mutable courses of steroid are correspondingly associated with multiple episodes of bone loss.

In our study PFTs including TLC. RV and FEVI were measured, the outcomes showed that patients with COPD who received oral steroids had the lowest mean of FEVI. but there were no differences in other PFTs between the 3 studied groups. Our data also revealed that there was no correlation between PFTs and BMD outcomes in our subjects as a group. Davies and Coworkers in their study in patients with COPD. who received chronic oral steroids, noted that there was a significant reduction in BMI and FEVI compared to the control group. (34)

In summary, data reported in our study indicate that patients with COPD comprise a high risk group for osteoporosis. In comparison to postmenopausal women, men with COPD have also an almost identical burden of the disease. While the use of GCs increases the frequency of osteoporosis, the problem is also seen in patients who never treated with steroids, thus COPD patients should be considered for bone densitometry screening regardless of glucocorticoids.

Reference:

(1) Grassi V. Carminati L. Cossi S. et al.: Chronic obstructive lung disease. Systemic manifestations. Recenti prog Med 94(5): 217 - 26. 2003

(2) Mussolino ME. Looker AC. Madans JH. et al. Risk factors for hip fractures in white men: the NHANES I Epidemiologic. J Bone Miner Res. 13:918-924.2002.

(3) Orwoll ES and Klein RF. Osteoporosis in men. Endocr Rev. 16: 87 -116. 1995.

(4) Myers AH, Robinson EG. Van Natta ML. et al.: Hip fractures among the elderly: Factors associated with in-hospital mortality. Am J Epidemiol' 134: 1128-1137. 1991.

(5) Hougard DM, Peterson GM. Bleasel MD et al.: Is enough attention being given to the adverse effects of corticosteroid therapy?. J Clin Pharm Ther. 25(3): 227 - 34. 2000.

(6) Shane E. Silverberg SJ. Donovan D. et al. Chronic systemic steroids and osteoporosis in patients with chronic obstructive pulmonary disease Am J Med. 101:262- 269. 1996

(7) Kado DM. Browner WS. Palermo L. et al. Vertebral fractures and mortality in older women. .Arch Intern Med. 159: 1215 - 1220. 1999.

(8) Riancho JA. Gonzales. Del Arco C. et al. Vertebral compression fractures and mineral metabolism in chronic obstructive lung disease. Thorax 42: 962 - 960. 2002.

(9) Shea JE. Miller SC. Poole DC. et al.: Conical bone dynamics, strength and densitometrv after induction of emphvsema in hamsters. JA ppl Physiol. 95 (2): 631 - 4.2003.

(10) Szymanski P. Mosiewicz J. Mvslinski W. et al. The influence of chronic obstructive pulmonary disease on the occurrence rate and intensification of osteoprosis. .Ann Univ Mariae Curie Sklodowska (Med). 57(1): 187-95.2002.

(11) Biskobing DM. Chronic Obstructive pulmonary disease and osteoporosis. Chest. 121: 609 - 620. 2002.

(12) Quanjer PH. Tammeling G. Cotes TE. et al.: Lung volumes and forced ventiiator> flows: Report Working Part) Standardization of Lung Functions Tests. European Community for steel and coal. Official statement of the European Respiratorv Society. Eur Respir J Suppl. 16: 5-40. 1993.

11?) Incalzi RA. Caradonna P. Ranieri P. et al.: Correlates of osteoporosis in postmonopausal women with chronic obstructive pulmonary disease. Respir Med. 94: 1079 - 1084. 2000.

(14) Estell R.: Treatment of postmenopausal osteoporosis N. Engl J Med 338:736-746,1998.

(15) Tattersflied AE. Town GI. Johnell O. et al.: Sever osteoporosis and vertebral fractures in men with end-stage pulmonary disease. Thorax 56-272-278.2001.

(16) Mc Evory CE. Ensrud KE. Bender E. et al. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. AM J Respir Care Med. 157: 704 -709. 1998.

(17) Farrukh I, Jeffrey M. Leonard T. et al.: Declining bone mass in men with chronic pulmonary' disease: Contribution of glucocorticoid treatment, body mass index and gonadal function Chest. 6, 1616 -1621. 1999.

(18) Dubois EF. Roder E, Richard D. et al.: Dual energy X-ray absorptiometry outcomes in male COPD patients after treatment with different glucocorticoid regimens Chest. 121.(5). 1456 - 1464, 2002.

(19) Karadag F. Cildag O. Yurekli Y. et al.: Should COPD patients be routinely evaluated for bone mineral density? J Bone Miner Metab. 21(4): 242-6. 2003.

(20) Wang G. Li TQ and Yang DZ.: Study in correlation between bone mineral density and syndrome type of TCM in patients with chronic obstructive pulmonary disease. Zhongguo Zhong Xi Yi Jie He 2a 2h: 23(4): 261 -4. 2003."

(21) Smith BJ. Phillips PJ and Heller RF.: Asthma and chronic obstructive airway disease are associated with osteoporosis and fractures: Respirology. 4(2): 101 -9. 1999.

122) Geltser BI. Kochetkova EA. Nevzorova \'A. et al.: Chronic obstructive pulmonary disease and osteoporosis. Ter Arkh. 72(11) 74- 7. 2002.

(23) Yeh SS. phanumas D. Hafher A. et al.: MW: Risk factors for osteoporosis in a subgroup of elderly men in a Veterans Administrations nursing home. J Investig Med. 50(6): 452 - 7. 2002

(24) Reid IR. Ames R. Evans MC et al.: Determinants o\ب total body and regional bone mineral density in normal postmenopausal women: a key-role for fat mass. J Clin Endocrinal Metab. 75: 45 - 51. 1992.

(25) Cauley J A, Salamone LM. Lucas Fl, et al.: Postmenopausal endogenous and exogenous hormones, degree of obesity, thiazide diuretics and risk of osteoporosis. In: Marcus R. Felman D. Kelsey J, eds. Osteoporosis. New York. NY: Academic press. 551 - 576. 1996.

(26) Aderson FH. Francis RM. Peaston RT. et al.: Androgen supplementation in eugonadal men with N/dth osteoporosis: effects of six months treatment on markers of bone formation and resoption. J Bone Miner Res 12: 472 - 478. 1997.

(27) Riggs BL, Khosla S. Melton L. et al.: A unitary model for evolutional osteoporosis: Estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res. 13: 736 - 773. 1998.

(28) Slemenda CW. Christian JC. Reed T, et al.: Long term bone loss in men: Effects of genetic and environmental factors. Ann Intern Med. 117:286-291. 1992.

(29) Antoni FW. Sarah A. Wendy M. et al.: Cross sectional investigation of the effects of inhaled corticosteroids on bone density and bone metabolism in patients with asthma. Thorax 52(10). 853 - 861, 1997.

(30) Hanania NA, Chapman KR. Sturtridge WC. et al.: Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. J Allergy Clin Immunol. 96: 571 - 9. 1995.

(31) Kerstjens HAM. Postma DS. Doormaal JJ. et al.: Effects of short term and long term treatment with inhaled corticosteroids on bone metabolism in patients with airways obstruction. Thorax. 49: 652 - 6. 1994.

(32) Sambrook PN. Cohen ML. Eisman JA. et al.: Effects of low dose corticosteroids on bone mass in rheumatoid arthritis: a longitudinal study. Ann Rheum Dis. 48: 535 - 538. 1989.

(33) Sambrook PN. Kelly PJ. Reogh AM, et al.: Bone loss after heart transplantation: a prospective study. J Heart Lung Transplant. 13: 116 - 121. 1994.

(34) Davies L. Angus RM. Calverly PM. et al.: Oral corticosteroids in patients admitted to hospital with excerptions of chronic obstructive pulmonary disease: a prospective randomized controlled trial. Lancet 354-456-460. 1999.