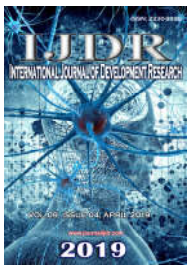
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 09, Issue, 04, pp.26978-26983, April, 2019



RESEARCH ARTICLE OPEN ACCESS

RISK OF OSTEOPOROSIS IN SMOKERS

***Dr. Ahmed Zuhair Younis Al-Dabbagh and Dr. Maha Abdulrazaq Mohammed**

Directorate of Nineveh Health, Iraq

ARTICLE INFO

Article History:
Received 18th January, 2019
Received in revised form
08th February, 2019
Accepted 30th March, 2019
Published online 29th April, 2019

Key Words:
Osteoporosis; Dual-energy X- ray Absorptiometry; Smoking.

ABSTRACT

The study was conducted on 2 groups including smokers group and nonsmokers control group at the outpatient clinic of Ibn Sina teaching hospital in Mosul during the period between 1/11/2010 and 1/5/2011. The first group consists of 100 subjects, and the second group also consists of 100 nonsmoker subjects matched for age and gender were kept as control group. The aim of this study was to assess whether there is an increase in the risk of osteoporosis in smokers compared to that in healthy age-matched control subjects. All the study groups were subjected to assessment of medical and drug history, measurement of weight and height to derive body mass index, biochemical tests, and dual-energy X- ray absorptiometry. The data obtained from the study revealed that smokers have a significantly increased risk of osteoporosis as compared to that in healthy age-matched control subjects, 34(34%) versus 13(13%), respectively. Most patients with osteoporosis did not receive pharmacological treatment. Age, body mass index, menopausal duration and number of cigarettes were significant independent correlates for osteoporosis.

Citation: Dr. Ahmed Zuhair Younis Al-Dabbagh and Dr. Maha Abdulrazaq Mohammed. 2019. "Risk of osteoporosis in smokers", *International Journal of Development Research*, 09, (04), 26978-26983.

INTRODUCTION

Osteoporosis is the most common metabolic bone disease and represents an increasingly serious problem, particularly as the population ages. Elderly white women are the most affected group by osteoporosis. However, osteoporosis is commonly seen in both sexes, all races and all age groups (Naghshin *et al.*, 2004). Osteoporosis can result in devastating psychosocial, physical, and economic consequences. Despite its great importance, osteoporosis often remains overlooked and undertreated, mainly because it is a clinically silent disease until it manifests in the form of a pathologic fracture (Kado *et al.*, 1999). It is important to define causes and risk factors of osteoporosis. Some of these causes are determined, including female sex, advanced age, hormonal disturbances, alcohol, smoking, genetic factors, and low calcium intake (Wasnich, 1996). Smoking has long been acknowledged to be a risk factor for poor bone health as it affects the metabolism of hormones, body weight, vitamin D levels, calcium absorption, blood circulation and increases oxidative stress thus disrupting healthy bone resorption and formation, leading to osteoporosis. Consequently, smokers have a 25% increase in fracture risk and are nearly twice as likely to experience hip fractures. Smoking also delays bone healing following operations to repair fractures.

Corresponding author: **Dr. Ahmed Zuhair Younis Al-Dabbagh**
Directorate of Nineveh Health, Iraq

However, stopping smoking has been shown to partially reverse the risk of suffering fractures, and smoking cessation is therefore advised in national guidelines for the prevention and treatment of osteoporosis (Hippisley-Cox *et al.*, 2007). Bone health is primarily determined by peak bone mass achieved (usually around 30 years of age) and the rate of bone loss in the succeeding years (Wark, 1996). While the former is largely dependent on untreatable factors such as genetics, the latter is not only determined by non- modifiable causes like age but also by modifiable risk factors such as physical inactivity (Cummings, 1996). Among treatable causes of osteoporosis, smoking has long been established as a contributing risk factor, Wong *et al.*, 2007, as it affects the balance of the naturally occurring processes of bone resorption and bone formation, resulting in low BMD as the amount resorbed is not fully replaced (Szulc *et al.*, 2002; Vogel *et al.*, 1997). Smoking is thought to cause low bone density through various pathways: (1) Smoking has been linked to changes in hormone household, leading to a decrease in parathyroid hormone (thus reducing calcium absorption) and oestrogen levels as well as to an increase in the level of cortisol and adrenal androgens, changes that have been linked to an increased risk of osteoporosis (Kapoor and Jones, 2005); (2) Smoking reduces body mass, which is postulated to provide an osteogenic stimulus and is linked to higher BMD (Daniel *et al.*, 1992); (3) Smoking reduces the level of Vitamin D in the body, which is

required for good bone health (Brot *et al.*, 1999); (4) Smoking increases free radicals and oxidative stress which affects bone resorption (Duthie *et al.*, 1991); (5) Smokers are more likely to suffer from peripheral vascular disease, reducing blood supply to the bones (Vestergaard and Mosekilde, 2003); (6) As smokers are weaker, have poorer balance and impaired neuromuscular performance, smoking may also increase the risk of falls (Nelson *et al.*, 1994); (7) Finally, there may also exist direct toxic effects of many of the constituents in tobacco smoke on bone cells (Broulik and Jarab, 1993). There is a significant effect of smoking on overall fracture risk – in particular for the hip, spine and heel bone (Vestergaard and Mosekilde, 2003; Ward and Klesges, 2001; Kanis *et al.*, 2005; Law and Hackshaw, 1997).

Overall, risk of any fracture is increased by about 25% in current smokers and for hip fractures risk is increased between 40–84% and there is an increase in risk to over a 100% in those over 85 years of age (Vestergaard and Mosekilde, 2003; Ward and Klesges, 2001; Kanis *et al.*, 2005; Law and Hackshaw, 1997). The pathophysiology underlying the development of osteoporosis in smokers is largely unknown, but during the last few years a number of studies have shed light on the possible mechanisms involved. Smokers appear to be under a state of continuous systemic inflammation, (Jorgensen and Schwarz, 2008) and this inflammatory state seems to be associated with the production of a number of chemoattractants and inflammatory markers as well as markers of destruction, including members of the matrix metalloproteinase (MMP) enzyme family (Jorgensen and Schwarz, 2008). Osteoporosis is found in a proportion of smokers and confirms the view that long-term epidemiological studies which would take into account the degree and number of cigarettes smoked are required in order to identify the person who have a high risk to develop osteoporosis (Biskobing, 2002).

Aim of the study

The aim of this study was to assess:

- The risk of osteoporosis in smokers compared to that in healthy age-matched control subjects, who are nonsmokers.
- The correlations of age, body mass index and number of cigarettes with the degree of osteoporosis.

MATERIALS AND METHODS

The study had approved from regional committee of Mosul health administration and conducted at the outpatient clinic of Ibn Sina teaching hospital in Mosul during the period between 1/11/2010 and 1/5/2011.

Study design: It is a clinical case controlled study. One hundred known cases of smokers followed at the respiratory outpatient clinic by their physicians in Ibn Sina teaching hospital in Mosul participated in the study are included in the study.

Inclusion criteria included

1- Age ranges between 20 - 60 years.
2- Smokers for 20 to 30 cigarettes per day.

Exclusion criteria included

1- Nonsmokers.
2- Diabetic patients.
3- Rheumatic diseases.

Controls: One hundred apparently healthy nonsmoking individuals matched for age and sex with the cases were kept as control group. They denied respiratory symptoms like dyspnoea or chronic sputum production, or diagnosed respiratory diseases.

Data collection: The main source of data was obtained directly from all the studied subjects during interviews with them. The study was designed as a case controlled study, based on historical data on concomitant medication combined with clinical data and a questionnaire obtained at the study visit at the outpatient clinic. Basic demographic and clinical data were collected during the study using a questionnaire concerning: age, gender, body weight in (kg), height in (m), previous bone fractures, present and previous medication, tobacco consumption (pack-year), daily exercise, daily diet and characteristic symptoms of both COPD and osteoporosis.

Instruments and materials

- Weight and height scale (seca; made in Germany).
- Dual-energy X-ray absorptiometry (DEXA) (Hologic; made in China).
- Three kits for serum calcium, phosphorus and alkaline phosphatase (Biolabo; made in France).
- Disposable syringes.
- Plastic tubes.
- Micropipettes.
- Centrifuge (Kukusan; made in Japan).
- Stethoscope.
- Spectrophotometer (C-cil; made in France).
- Nebulizer (Atomizer; made in France).

Figures (3-1) and (3-2) show the way of measurement of bone mineral density using DEXA scanner

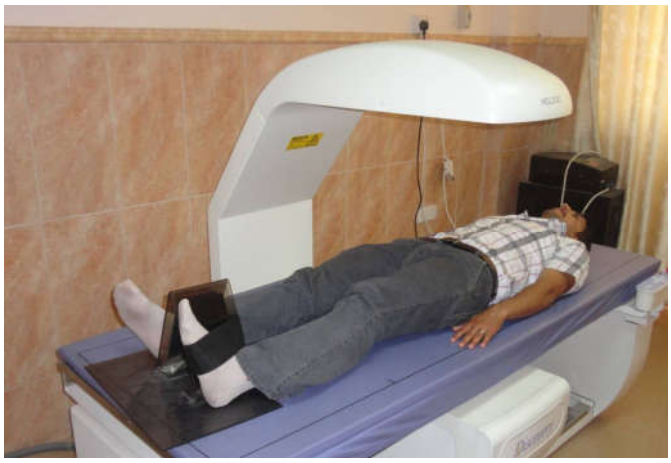


Figure 3-1. Dual-energy X-ray absorptiometry of the hip (DEXA unit in Ibn Sina Teaching Hospital)

Methods: All the study groups were subjected to the following clinical assessment:

Weight was measured with barefoot and light clothes by weighting scale with fixed tape for height measurement.

Figure 3-2. Dual-energy X-ray absorptiometry of the lumbar spine (DEXA unit in Ibn Sina Teaching Hospital)

Body mass index was calculated according to the following equation: BMI=weight (kg) /height (m^2). Low BMI was defined as 18.5 kg/m2 or less, based on WHO criteria. A person's smoking intensity is measured in pack-years. "One pack-year" means that a person has smoked approximately 1 pack (20 cigarettes) per day for 1 year; smoking 1/2 pack a day for 1 year is equivalent to 1/2 pack-year; and smoking 2 packs a day for 1 year is equivalent to 2 pack-years. Dual-energy X-ray absorptiometry (DEXA) method is considered to be the gold standard to measure bone mineral density (BMD) (Mautalen, 2001; Sadat-Ali *et al.*, 2004). So in this study, the BMD was measured by DEXA method of both lumbar spine and hip to diagnose osteoporosis based on the lowest T-score of the measured locations and conducted in the DEXA unit of Ibn Sina teaching hospital in Mosul.

According to the WHO criteria for diagnosis of osteoporosis in concern to T-score for BMD, we categorize the patients and control subjects to osteoporosis, osteopenia, or normal bone mass. The lowest T-score at either region determined the diagnosis. Thus, if the T-score at either region was below -2.5, the individual was diagnosed as having osteoporosis. If the lowest T-score at either region was between -2.5 and -1.0 the subject was diagnosed with osteopenia. If both hip and lumbar spine T-score was above -1.0 the study subject was grouped as having normal bone mass. The type of dual-energy X-ray absorptiometry was Hologic. For more accurate way to reflect the day-to-day variance is to establish the baseline phantom value would be to scan the phantom once a day for 15 to 25 consecutive days and then averaging these scans. After baseline value established subsequent BMD results should not vary by more than 1.5% of the established baseline. If any single measurement is more than 1.5% from the baseline, the phantom measurement should be repeated. If the second measurement is more than 1.5% from baseline, the equipment service representative should be contacted for a more detailed system evaluation. Basic laboratory parameters were analyzed in order to exclude patients with other causes of osteoporosis. The following parameters were determined: ESR (m.m./H), S. alkaline phosphatase (u/L), S. calcium(mmol/L), S. phosphorus(mmol/L).

Statistical analysis

All variables were presented as means ± standard deviation (SD) and compared with analysis of variance, paired samples T-test. Some of data were calculated manually as strict number and percentage in relation to the same sample. Variables correlation by paired samples correlation was performed to know the direction and degree of affection of each variable. Univariate and multivariate multinomial logistic regression analyses (enter procedure) were performed to investigate determinants of osteopenia and osteoporosis based on DEXA findings. All study subjects were analyzed. Univariate analyses with osteoporosis, osteopenia and normal BMD as dependent variable were used to test for the potentially confounding effect of biomedical and demographic factors. If significant at $p<0.05$, the variables were included into the multivariate analyses. A p-value <0.05 was used to indicate statistical significance. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 17.0.

RESULTS

Table (4-1) shows the number and percentage of male and female in each group included in the study. There was no statistically significant difference between the smokers and healthy control groups (P-value= 0.497).

Table 4.1. The number and percentage of male and female in the smokers and the control groups

Sex	Smokers (n=100)	Control group (n=100)
Male	79(79%)	76(76%)
Female	21(21%)	24(24%)

Table (4-2) shows the number and percentage of the three degrees of bone mineral density (BMD) in both smokers and healthy control group included in our study. Thirty four (34%) smokers were shown to have osteoporosis by BMD, while 48(48%) were osteopenic and 18(18%) had normal bone mass. Again, 13(13%) control subjects were diagnosed as having osteoporosis by BMD, while 62(62%) were osteopenic and 25(25%) had normal bone density.

Table 4-2. The number and percentage of the three categories of bone mineral density in patients and control groups

T-score / BMD	Smokers (n=100)		Control (n=100)	
	No.	%	No.	%
Normal (≥-1)	18	18	25	25
Osteopenia (-1 < > -2.5)	48	48	62	62
Osteoporosis (≤-2.5)	34	34	13	13

Table (4-3) shows the number and percentage of each fragility fracture in both smokers and control subjects. There was increased percentage of fragility fracture in smokers (11%) in comparison to the control group (3%). In smokers, 2 of them had vertebral fracture, 3 had hip fracture, 4 had wrist fracture and lastly 2 smokers had chest fracture. In the other hand, the control group have developed only one fracture in each of hip, wrist and chest.

Table 4-3. Comparison of the fragility fractures between smokers and control group in number and percentage

Fragility fractures	Smokers No=100	Control No=100
Vertebral fracture	2(2%)	0(0.0%)
Hip fracture	3(3%)	1(1%)
Wrist fracture	4(4%)	1(1%)
Chest fracture	2(2%)	1(1%)
Total number	11(11%)	3(3%)

Table (4-4) shows the number and percentage of normal, osteopenia, osteoporosis in smokers regarding bone mineral density whether are males or females 3(3%), 8(8%), 10(10%)

versus15(15%), 40(40%), 24(24%), respectively. The number of osteoporosis in men patients was 24 while in women patients was 10.

Table 4.4. The number and percentage of the three categories of bone mineral density in women and men in smokers

T-score	Total number (n=100)	Women (n=21)	Men (n=79)
Normal (≥-1)	18(18%)	3(3%)	15(15%)
Osteopenia (-1< > -2.5)	48(48%)	8(8%)	40(40%)
Osteoporosis (≤-2.5)	34(34%)	10(10%)	24(24%)

DISCUSSION

Risk of Osteoporosis in Smokers: Osteoporosis is a systemic skeletal disease characterized by a low bone mass and/or microarchitectural deterioration of bone tissue leading to increased bone fragility and increased fracture risk (WHO, 2008). Osteoporosis was observed to be more prevalent among smokers than among healthy subjects (Agusti *et al.*, 2003; Kjensli *et al.*, 2007). In the present study, we define osteoporosis according to the WHO criteria of osteoporosis. Katsura and Kida, (2002) defined osteoporosis according to the Japanese guidelines whereas most other studies used the WHO criteria to define osteoporosis. Cigarette smoking was first identified as a risk factor for osteoporosis more than 20 years ago. Recent studies have shown a direct relationship between tobacco use and decreased bone density. Analyzing the impact of cigarette smoking on bone health is complicated. It is hard to determine whether a decrease in bone density is due to smoking itself or to other risk factors common among smokers. For example, in many cases Smokers are thinner than nonsmokers, tend to drink more alcohol, may be less physically active, and have poor diets. Women who smoke also tend to have an earlier menopause than nonsmokers. These factors place many smokers at an increased risk for osteoporosis apart from their tobacco use (Agusti *et al.*, 2003; Kjensli *et al.*, 2007). Interpretation of the results should be with caution as causality of the correlates needs to be confirmed. Some of these causes are determined, including female sex, advanced age, hormonal disturbances, alcohol, smoking, genetic factors, and low calcium intake (Wasnich, 1996). Furthermore, there are several factors reported to be responsible for the reduced bone density in patients with COPD, such as BMI (Iqbal *et al.*, 1999; Katsura and Kida, 2002; Kjensli *et al.*, 2007; Vrieze *et al.*, 2007), FEV_1 (Iqbal *et al.*, 1999; Vrieze *et al.*, 2007), smoking (Iqbal *et al.*, 1999), inactivity (Iqbal *et al.*, 1999), and corticosteroid therapy (Iqbal *et al.*, 1999; Kjensli *et al.*, 2007; Lee and Weiss, 2004). However, the effects of these factors, with the exception of BMI, are still controversial. The present study was performed to evaluate the risk of osteoporosis in smokers by measurement of bone mineral density (BMD) depending on the DEXA- scan findings. At the same time compare this group of smokers with a healthy group who are not smokers. The current study involved 200 individuals who were divided into 2 groups. The first group consists of 100 smokers and the second group consists of 100 healthy nonsmoker individuals. The two groups were matched concerning the number of males and females (table 4-1). This matching of individual groups number, sex may exclude any effect of these parameters on the results of the study.In this study the mean age of the patients was 40 years, regarding age group from 20 to 60 year. Higher age is a risk factor for osteoporosis in the general population (WHO, 2007). In the current study, the combination of DEXA-scan of both lumbar spine and hip and the clinical manifestations resulted in an osteoporosis percentage of (34%) in smokers according to the T- score reading of (≤ 2.5) on DEXA- scan findings (table 4-2). On the other hand, on contrast, the percentage of osteoporosis in control group was (13%). This is completely in line with the findings of Jorgensen *et al.*, (2007) who only included smoker outpatients and found (45%) of osteoporosis in the studied group. Also Katsura and Kida, (2002) have reported osteoporosis in 50% of their studied group. On average, in the present study, the percentage of osteoporosis and/or a low BMD was significantly higher in smokers patients than in healthy subjects (Table 4-2).

This explains the stone impact of inflammatory process on the bone biophysiology with its consequences, that result from effect of smoking on the health of smokers in addition to other consequences like chronic obstructive diseases that itself leading to increased susceptibility to osteoporosis. There may be several explanatory mechanisms for our results. The first is the presence of systemic inflammation. It is found that reduced lung function is associated with increased levels of systemic inflammatory markers that lead to the inflammatory process in smokers and eventually cause acceleration and increase in bone resorption leading to osteoporosis. Increased concentrations of the circulating inflammatory mediators (tumour necrosis factor (TNF) - α, IL-6, IL-1α) have been reported (Gan *et al.*, 2004). Leukocyte-derived IL-1α and TNF-α stimulate bone resorption (Engelen *et al.*, 1998; Gowen and Mundy, 1986; Bertolini *et al.*, 1986) and IL-6 stimulates the formation of osteoclasts (Manolagas and Jilka, 1995). In addition, most studies on the effects of smoking suggest that smoking increases the risk of having a fracture. The longer you smoke and the more cigarettes you consume, the greater your risk of fracture in old age. Smokers who fracture may take longer to heal than nonsmokers and may experience more complications during the healing process. Significant bone loss has been found in older women and men who smoke. At least one study suggests that exposure to second-hand smoke during youth and early adulthood may increase the risk of developing low bone mass. Women who smoke often produce less estrogen (a sex hormone) and tend to experience menopause earlier than nonsmokers, which may lead to increased bone loss. Quitting smoking appears to reduce the risk of low bone mass and fractures. However, it may take several years to lower a former smokers risk. All these are facts that confirm our study about risk of smoking on bone. In addition to the advanced age of the patient, genetic factors and other environmental factors that all contribute to osteoporosis.
The elevated percentage in the osteoporosis in smokers in the present study may add some light on the fact that smoking is one of the most important risk factors that may contribute to the high morbidity and mortality in this group of patients in presence of this high percentage of osteoporosis especially if we regard to its consequences.

In Summary, the present study had several main findings

1. Thirty four % of smokers attending a regular visit at the respiratory outpatient consultation in the Ibn Sina teaching hospital in Mosul had evidence for osteoporosis depending on DEXA- scan findings.
2. Combining the results of dual energy X-ray absorptiometry (DEXA)-scans with clinical manifestations augmented the proportion of COPD patients with osteoporosis.

3. A large proportion of the osteoporotic smokers did not use physician prescribed bone medication.
4. There is increase in the prevalence of osteoporotic or fragility fractures in smokers by about 4 folds than controls, this will affect the quality of life which contributed to the high rate of morbidity and mortality in those patients.

Conclusion

On the basis of the results obtained in the present study, the followings can be concluded:

1. Smoking is a risk factor for osteoporosis.
2. Smokers showed a significantly increased risk of osteoporosis as compared to that in healthy age-matched control subjects.
3. The present study showed that smokers had about 3 times the risk of osteoporosis compared with nonsmokers age-matched control subjects.
4. Smokers developing osteoporosis even if they are not had any other health problem.
5. Low BMI, reduced physical activity, aging and number of cigarettes are well known additive risk factors in osteoporosis regarding osteoporosis development.
6. There was a higher risk of fragility fractures in smokers than in nonsmokers subjects by 3.7 times, so there will be bad effect on the quality of life in smokers and eventually increase the morbidity of the person.

Suggestions for Further Studies

- Longitudinal studies that investigate the contribution of potential factors leading to osteoporosis such as the nutrition, levels of physical activity, body habitus and composition, peripheral skeletal muscle mass and function.
- Future researches that explore the incidence of hypogonadism in patients with COPD and if hormone manipulation has long-term effects on the preservation of bone mass. Other possible hormonal changes will need to be investigated, such as the potential imbalance between anabolic (IGF-1) and catabolic (corticosteroids) hormones that may contribute to the loss of skeletal muscle and bone mass in COPD.
- The relationship between the persistent systemic inflammation and the depletion of skeletal muscles and bone in some smokers will need to be further explored, in order to clarify if circulating inflammatory mediators have an effect at the tissue level or if other factors stimulate increased inflammation in the peripheral tissues, including the bone tissue.
- Randomized placebo-controlled trials are required to assess the effects of bisphosphonates on the prevention and treatment of osteoporosis and fractures in various groups of patients. Such trials should have clear outcome measures, such as the change in bone mineral density (BMD) or the assessment of the fracture rates and should investigate potential short-term and long-term side effects of the treatment.

Recommendation

- Chest physicians should be aware of the high risk of osteoporosis in smokers, especially in elder patients with a low body mass index.
- It is necessary for pulmonologist to accentuate for preventive and cure strategies to reduce morbidity of osteoporosis in these patients.
- Prevention of osteoporosis should be a part of family medical care for smokers.
- BMD measurement should be considered in smokers and regarded them at high risk for osteoporosis.
- Patients should be encouraged to participate in physical therapy programs to increase exercise endurance and to maintain muscle strength.
- Awareness of the problem and of strategies to prevent the development of osteoporosis are essential to increase BMD and, likely, to decrease the incidence of fractures in these patients.
- It is recommended to suggest a minimum daily intake of 1,200 mg of calcium in adults older than 50 years.
- Replacement therapy is beneficial for the preservation of bone mass in smokers, only after considering potential risks of such treatments.
- Without appropriate diagnosis and treatment, these patients remain at substantial risk for recurrent, debilitating and life threatening osteoporotic fractures.

Abbreviations

Abbreviation	The original form
ACR	American college of rheumatology
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CS	Corticosteroid
DEXA / DXA	Dual energy X-ray absorptiometry
ESR	Erythrocyte sedimentation rate
FEV1	Forced expiratory volume in one second
FDA	United States Food and Drug Administration
FIT	Fracture Intervention Trial
FVC	Forced vital capacity
SD	Standard deviation
TNF	Tumor necrosis factor

REFERENCES

Agusti, A.G., Noguera, A., Sauleda, J., Sala, E., Pons, J., Busquets, X. 2003. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J*., 21(2):347–360.

Bertolini, D.R., Nedwin, G.E., Bingman, T.S., Smith, D.D., Mundy, G.R. 1986. Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factor. Nature; 319:516–518.

Biskobing, D.M. 2002. COPD and Osteoporosis. Chest; 121:609–620.

Brot, C., Jorgensen, N.R., Sorensen, O.H. 1999. The influence of smoking on vitamin D status and calcium metabolism. *Eur J Clin Nutr;* 53(12):920–926.

Broulik, P.D., Jarab, J. 1993. The effect of chronic nicotine administration on bone mineral content in mice. *Horm Metab Res;* 25(4):219–221.

Cummings, S.R. 1996. Treatable and untreatable risk factors for hip fracture. Bone 1996; 18(3 Suppl):165S–167S.

Daniel, M., Martin, A.D., Drinkwater, D.T. 1992. Cigarette smoking, steroid hormones, and bone mineral density in young women. *Calcif Tissue Int;* 50(4):300–305.

Duthie, G.G., Arthur, J.R., James, W.P. 1991. Effects of smoking and vitamin E on blood antioxidant status. *Am J Clin Nutr*; 53(4 Suppl):1061S–1063S.

Engelen, M.P., Schols, A.M., Does, J.D., Wouters, E.F. 2000. Skeletal muscle weakness is associated with wasting of

extremity fat-free mass but not with airflow obstruction in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr.,* 71:733–738.

Gan, W.Q., Man, S.F., Senthilselvan, A., Sin, D.D. 2004 Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 59 (7):574–580.

Gowen, M., Mundy, G.R. 1986. Actions of recombinant interleukin 1, interleukin 2 and interferon γ on bone resorption in vitro. *J Immunol;* 136:2478–2482.

Hippisley-Cox J, Bayly J, Potter J, Festy J, Parker C. 2007.Evaluation of standards of care for osteoporosis and falls in primary care. Leeds, The Information Centre for Health and Social Care. Ref Type: Report

Iqbal, F., Michaelson, J., Thaler, L., Rubin, J., Roman, J., Nanes, M.S. 1999. Declining bone mass in men with chronic pulmonary disease: contribution of glucocorticoid treatment, body mass index, and gonadal function. Chest; 116:1616–1624.

Jørgensen, N.R., Schwarz, P. 2008. Osteoporosis in Chronic Obstructive Pulmonary Disease Patients. *Curr Opin Pulm Med.;* 14(2):122-127.

Jorgensen, N.R., Schwarz, P., Holme, I., Henriksen, B.M., Petersen, L.J., Backer, V. 2007. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study. *Respir Med;* 101:177-185.

Kado, D.M., Browner, W.S., Palermo, L., Nevitt, M.C., Genant, H.K., Cummings, S.R. 1999. Vertebral fractures and mortality in older women: a prospective study. Study of Osteoprotic Fractures Research Group. *Arch Intern Med;* 159 (11): 1215-20.

Kanis, J.A., Johnell, O., Oden, A., Johansson, H., De Laet, C., Eisman, J.A. *et al*. 2005. Smoking and fracture risk: a meta-analysis. *Osteoporos Int;* 16(2):155–162.

Kapoor, D. and Jones, T.H. 2005. Smoking and hormones in health and endocrine disorders. *Eur J Endocrinol;* 152(4):491–499.

Katsura, H., Kida, K. 2002. A comparison of bone mineral density in elderly female patients with COPD and bronchial asthma. *Chest* 122(6):1949–1955.

Law, M.R., Hackshaw, A.K. 1997. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. *BMJ;* 315(7112): 841–846.

Lee, T.A., Weiss, K.B. 2004. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 169, 855-859.

Manolagas, S.C., Jilka, R.L. 1995. Bone marrow, cytokines and bone remodelling. *N Engl J Med;* 332:305–317.

Mautalen, C.A. 2001. Osteoporosis in Argentina. Clin Calcium 11 (4):496–498.

Naghshin, R., Javadzadeh, A., Mousavi, S.A.J., Adeli, S.H., Heydari, A. 2004. Comparison of the Osteoporosis between Male Smokers with and without Chronic Obstructive Pulmonary Disease; 3(9): 13-18.

Nelson, H.D., Nevitt, M.C., Scott, J.C., Stone, K.L., Cummings, S.R. 1994. Smoking, alcohol, and neuromuscular and physical function of older women. *Study of Osteoporotic Fractures Research Group*. JAMA; 272(23):1825–1831.

Sadat-Ali, M., Al Habdan, I.M., Al Mulhim, F.A., El Hassan, A.Y. 2004. Bone mineral density among postmenopausal Saudi women. *Saudi Med J* 25(11):1623–1625.

Szulc, P., Garnero, P., Claustrat, B., Marchand, F., Duboeuf, F., Delmas, P.D. 2002 Increased bone resorption in moderate smokers with low body weight: the Minos study. *J Clin Endocrinol Metab*., 87(2):666–674.

Vestergaard, P., Mosekilde, L. 2003. Fracture risk associated with smoking: a meta-analysis. *J Intern Med*; 254(6):572–583.

Vogel, J.M., Davis, J.W., Nomura, A., Wasnich, R.D., Ross, P.D. 1997. The effects of smoking on bone mass and the rates of bone loss among elderly Japanese-American men. *J Bone Miner Res;* 12(9):1495–1501.

Vrieze, A., de Greef, M.H., Wkstra, P.J., Wempe, J.B. 2007. Low bone mineral density in COPD patients related to worse lung function, low weight and decreased fat-free mass. *Osteoporos Int* 18, 1197-1202.

Ward, K.D., Klesges, R.C. 2001. A meta-analysis of the effects of cigarette smoking on bone mineral density. *Calcif Tissue Int*; 68(5):259–270.

Wark, J.D. 1996. Osteoporotic fractures: background and prevention strategies. Maturitas; 23(2):193–207.

Wasnich, R.D. 1996. The epidemiology of osteoporosis. In: Primer on the metabolic bone diseases and disorders of mineral metabolism. 3rd ed.: 249-251.

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

WHO Scientific Group on the Prevention and Management of Osteoporosis (2008) Prevention and Management of Osteoporosis: report of a WHO scientific group.

Wong, P.K., Christie, J.J., Wark, J.D. 2007. The effects of smoking on bone health. *Clin Sci (Lond);* 113(5):233–241.

****