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Review Article

ASSOCIATION OF COPD AND OSTEOPOROSIS --A CLINICAL REVIEW

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ABSTRACT
Osteoporosis, with resulting fractures, is one of the systemic effects associated with chronic obstructive pulmonary disease (COPD). The etiology for the bone loss is diverse but includes smoking, vitamin D deficience, low body mass index, hypogonadisms, sedentary lifestyle, and use of glucocorticoids. However many patients remain undiagnosed until their fracture because of the lack of recognition of the disease. There is remarkable paucity of interventional studies targeting osteoporosis in patients with COPD. Effective strategies to prevent bone loss and to treat osteoporosis include calcium and vitamin D supplementation, hormone replacement when indicated, calcitonin, and biphosphonate administration. The results of some of the studies on the treatment of osteoporosis in COPD are reviewed here. With the increased awareness by the chest physicians and increased use of preventive strategies, the impact of osteoporosis on those patients with COPD should decrease.

Key Words: *COPD, Osteoporosis, Risk Factors, Treatment*

INTRODUCTION
Global initiative for chronic obstructive pulmonary disease (GOLD) (Klaus et al 2007) defines chronic obstructive pulmonary disease (COPD) as a "preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lung to noxious particles or gases". ATS/ERS (Viegi et al 2007) defines COPD as "a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences".
COPD is responsible for early mortality, high death rates and significant cost to health systems. The projection for 2020 indicates that COPD will be the third leading cause of death worldwide (from sixth in 1990) and fifth leading cause of years lost through early mortality or handicap in terms of disability-adjusted life years(DALY) (12^{th} in 1990) (Raherison and Girodet 2009). It is estimated that there are around 1.49 crore cases of COPD in India in the age group of 30 years and above, and these are projected to increase by nearly 50% by the year 2016, including 'severe' cases, some of whom may require greater levels of care, including hospitalization (Murthy and Sastry 2005). COPD is a costly disease. In developed countries, exacerbations of COPD account for the greatest burden on the health care system. In the European Union, the total direct costs of respiratory disease are estimated to be about 6% of the total health care budget, with COPD accounting for 56% (€ 38.6 billion) of the cost of respiratory diseases (National Heart, Lung, and Blood Institute 1998). In India roughly Rs 32,000 is the annual cost of treatment for acute cases of COPD that involve hospitalization (Murthy and Sastry 2005).
Comorbidities, defined as other chronic medical conditions, including coronary artery disease, diabetes mellitus, osteoporosis and muscle weakness, are common in chronic obstructive pulmonary disease .Van Manen et al., (2001) reported that over 50% of 1,145 patients with COPD had 1 to 2 comorbidities, 15.8% had 3 to 4 comorbidities, and 6.8% had 5 or more comorbid conditions. Older patients frequently have multiple chronic health conditions and the severity of comorbid conditions and their impact on a

patient's health status will vary between patients and in the same patient over time. Here we have reviewed osteoporosis, which is one of the important co-morbid conditions in COPD that leads to impaired quality of life in these individuals.

Osteoporosis in COPD

Osteoporosis in patients with COPD is a consequence of various factors: some of these factors have been present throughout the life of the patient, others exists due to the disease process itself and some factors are specific to the lung disease like smoking, increased alcohol intake, Vitamin D levels, genetic factors, treatment with corticosteroids, reduced skeletal muscle mass and strength, low BMI and changes in body composition, hypogonadism, reduced levels of insulin-like growth factors, chronic systemic inflammation (Ionescu and Schoon 2003).

Prevalence of Osteoporosis in COPD

The prevalence of osteoporosis in COPD varies between 4% and 59%, depending on the diagnostic methods used, the population studied, and the severity of the underlying respiratory disease (Lehouck A et al., 2011). Overall, a higher prevalence of osteoporosis is generally found in patients with COPD when compared with healthy control subjects. Jorgenson et al., (2007) examined the relationship between the severity of COPD and osteoporosis and found increased incidences of osteopenia and osteoporosis with advancing COPD stage. Only COPD stage III and IV patients were included in the study, and patients with already known osteoporosis were excluded. Of the 62 evaluable patients, 68% had either low bone mass (osteopenia or osteoporosis) or a previously undiagnosed vertebral fracture, with 25% of the included patients having a vertebral fracture. Thus, a large number of the COPD patients in this study had established osteoporosis and were in need of anti-osteoporotic treatment – this was the case for both glucocorticoid-treated patients and glucocorticoid-naive patients. Based on these findings it seems reasonable to screen all stage III and IV COPD patients for osteoporosis. Analyzing the results from the TORCH study (Ferguson GT et al 2009), it was observed that there was higher prevalence of osteoporosis and osteopenia in patients with COPD. A total of 658 patients (a subset of 6,184 international subjects in TORCH) from 88 US centers were involved in the study. At baseline, the overall prevalence of osteoporosis and osteopenia was high (65%). More women (30%) than men had osteoporosis (18%). In contrast the prevalence of osteopenia was comparable between men (42%) and women (41%). In a recent study by Forli L (2008), patients with advanced pulmonary disease who were considered for lung transplantation were subjected for DEXA scan. Of the total 40 patients, 59% of the patients had osteoporosis and 38% had osteopenia. Mineo et al (2005) studied BMD in similar group of patients who were awaiting lung volume reduction surgery in COPD patients. Of the 70 male patients, 49% of them had osteoporosis and 35% of them had osteopenia. The patients in both the above two studies belong to advanced stage of COPD. Two other studies (Incalzi RA et al 2000, Katsura H and Kida K 2002) also found a relatively high prevalence of osteoporosis in COPD patients (49% and 60% respectively). Karadag et al (2003) compared bone mineral density (BMD) in COPD patients receiving regular therapy and tried to identify the patients for BMD screening. Twenty-eight male, clinically stable COPD patients (mean age, 63 ± 9 years) and 20 male volunteer subjects with normal pulmonary function, as a control group (mean age, 63 ± 5 years) were admitted to the study. The BMD of the COPD patients and control subjects was measured by dual X-ray absorptiometry. It was observed that in COPD patients, 35% and 10% of patients had lumbar and femoral osteoporosis, while another 42% and 62% of patients had osteopenia respectively. The prevalence of osteoporosis and osteopenia in control subjects were 40% and 15% for lumbar and femoral osteoporosis respectively, while for osteopenia the rates were 40% and 50% respectively. Thus there was no statistically significant difference between the BMD values of the COPD and control groups. Lumbar BMD was 0.871g/cm2 in the COPD patients and 0.853g/cm2 in the control group (P <0.682); femoral BMD was 0.790g/cm2 in the COPD patients and 0.795g/cm2 in the control group (P < 0.909). They have concluded that the risk of osteoporosis is not increased in appropriately treated patients with moderate degree COPD, and there is no indication for bone mass screening in this group.

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Pathogenesis of Osteoporosis in COPD

Bone is generally classified into two types. Cortical bone is a dense and strong bone found primarily in the shaft of long bones. Trabecular bone is more porous or weak and typically occurs at the ends of long bones and within the interior of vertebrae and flat bones. Bone tissue is continuously renewed throughout life and it is estimated that in adults, approximately 25% of trabecular bone and 3% of cortical bone is replaced every year. After reaching peak bone mass at the age of 25 to 30 years, remodeling is associated with an imbalance between formation and resorption, resulting in a mean annual bone loss of 0.5% to 1%, which differs by sex, skeletal site, and age. Key determinants of the rate of bone remodeling and bone loss are parathyroid hormone (PTH), vitamin D, and sex hormones (Sambrook P and Cooper C 2006). At the cellular level, bone remodeling is a complex interplay in which osteoblasts, osteoclasts, and osteocytes work together. Basically, osteoclasts resorb bone and osteoblasts replace bone by forming an osteoid protein matrix that subsequently mineralizes, whereas osteocytes and their canalicular network serve as sensors to adjust bone response to mechanical stimuli. On their surface, osteoblasts constitutively express the receptor activator of nuclear factor- k B ligand (RANKL). When binding to its receptor (receptor activator of nuclear factor- k B [RANK]) on the surface of preosteoclast cells, the latter differentiate into mature and activated osteoclasts. Additionally, osteoblasts but also stromal cells secrete a soluble decoy receptor, osteoprotegerin (OPG), which blocks the RANK/RANKL interaction, thereby acting as a physiologic regulator of bone turnover (Lacey DL et al 1998). Imbalance between RANKL and OPG results in excessive activity of osteoclasts and is considered a major cause of osteoporosis (Leibbrandt A and Penninger JM (2008). Another pathway that is less well understood is the Wnt/ b -catenin signaling cascade downstream of a number of osteoblast-activating proteins and receptors. Wnt signaling activates osteoblasts and bone formation, whereas reduced Wnt signaling may lead to osteoporosis (Patel MS and Karsenty G 2002). Several factors that have often been described in COPD patients (i.e. systemic inflammation, use of corticosteroids, and vitamin D deficiency) clearly interact with these pathways which are diagrammatically represented below (Schellevis FG 1994) (Fig-1).

Systemic inflammation: Systemic inflammation is thought to play an important role in the development of osteoporosis in COPD (Biskobing DM 2002). Key inflammatory cytokines such as tumor necrosis factor a and IL-6 are known to induce expression of RANKL and RANKL-mediated bone resorption (Hardy R and Cooper MS 2009). In addition, many other cytokines have been found to interact with the OPG/RANKL system, supporting the concept that inflammatory mediators contribute to the regulation of bone remodeling (Lorenzo J et al 2008). Recent data from the arthritis field also demonstrate that inflammation can also trigger the Wnt/ b -catenin pathway (Diarra D et al 2007).

Use of Corticosteroids: Several in vitro and in vivo studies have demonstrated profound effects of glucocorticosteroids (GCSs) on bone turnover by different mechanisms. GCSs preferentially affect trabecular bone because of its higher metabolic activity, but with prolonged use, cortical bone is also affected (Canalis E et al 2007). Briefly, GCSs rapidly increase the expression of RANKL and macrophage colony-stimulating factor, while decreasing the expression of OPG. Along with reduced apoptosis of mature osteoclasts, enhanced and prolonged resorption occurs, which gradually slows down during continued use of GCSs because of the inhibition of osteoclast precursors (Weinstein RS et al 2002). In a second phase, inhibition of proliferation, differentiation, and maturation of osteoblasts leads to long-lasting impairment of bone formation (Eijken M et al 2007). In this process, inhibition of the Wnt/b -catenin pathway is likely to be involved (Ohnaka K et al 2005). GCSs also exert negative effects on osteocytes, resulting in a modification of their microenvironment that may alter their mechano- sensor function and render the bone more susceptible to fragility fractures.

Vitamin D Deficiency: Vitamin D plays a key role in the regulation of calcium and bone homeostasis (Lips P 2001). Low levels of vitamin D stimulate the parathyroid glands to increase secretion of PTH to compensate for the low bioavailability of calcium. More importantly, PTH induces renal 1-alphahydroxylase expression, with consequent production of active 1,25 dihydroxyvitamin D (1,25[OH]2D). 1,25(OH)2D enhances intestinal calcium absorption. It also acts on the immature

osteoblastic cells to stimulate osteoclastogenesis through the RANKL/RANK regulatory system, finally resulting in enhanced bone resorption and mobilization of calcium from the bone compartment. Resulting higher levels of calcium and 1,25(OH)2D then downregulate PTH secretion and prevent unlimited resorption of bone. In addition, several reports indicate that 1,25(OH)2D enhances OPG expression in mature osteoblasts, thus further reducing osteoclastogenesis in vivo (Baldock PA et al 2006).

Risk Factors For Osteoporosis In COPD

There are numerous risk factors that contribute to the pathophysiology of osteoporosis seen in COPD patients. These risk factors include smoking, vitamin D deficiency, low body mass index (BMI), hypogonadism, decreased mobility and glucocorticoid use as the disease progresses[21]. Most of the risk factors for osteoporosis coincide with COPD, especially at more severe stages of COPD, thus it is obvious that COPD and osteoporosis are strongly linked (Lehouck A et al 2011). (Fig- 2).

i) ***Smoking:*** Smoking has been shown to be an independent risk factor for osteoporosis in both men and women. Slemenda et al (1989) reported that lumbar spine BMD was 12% lower in smokers who have smoked 20 pack-years compared to nonsmokers. Seeman et al (1983) reported a 2.3-fold increased risk of vertebral fractures among long term smokers. Cooper et al (1988) reported a 1.7-fold increased risk for hip fractures among smokers. The pathophysiologic mechanism for the lower bone mass and increased fracture risk in smokers is unclear. One study by Krall EA and Dawson-Hughes B (1991) has shown evidence of decreased calcium absorption in the GI tract in smokers compared to nonsmokers. The combination of tobacco and alcohol use markedly increases the risk for osteoporosis. Alcohol use has been shown to be independently related to bone loss in a dose-dependent manner (*ie*, greater rates of bone loss are seen in those persons who consume higher amounts of alcohol) (Slemenda CW et al 1992).

ii) ***Vitamin D Deficiency*****:** Vitamin D plays a vital role in the normal mineralization of bone matrix (Reid IR 1996). Vitamin D deficiency, which may lead to decreased mineralization of bone and contribute to decreased BMD, appears to contribute to the declining BMD that is associated with COPD. Riancho et al (1987) reported significantly decreased 25-hydroxyvitamin D levels in a group of men with COPD who were not receiving long-term glucocorticoid therapy compared to control subjects of a similar age. In another study by Shane E et al (1996), it was observed that 35% of severe COPD disease had markedly low 25 hydroxyvitamin D levels (*ie*, $\leq$ 10 ng/mL). Thus, vitamin D deficiency may contribute to the decreased BMD associated with COPD due to less sun exposure and poor nutrition as a result of decreased functional status.

iii) ***Body Mass Index*****:** Bone mass is directly correlated with BMI. Both men and women with higher BMIs have higher BMD. This is thought to be partially due to the effect of the greater weight-bearing load on the bone. In addition, estrogen levels tend to be higher in obese people due to the increased aromatization of testosterone to estrogen in adipose tissue (Cauley JA et al 1996). The resulting higher estradiol levels may help to explain the higher BMD in obese persons, since estradiol levels in both men and women correlate with BMD (Khosla S et al 1998). Malnutrition, as well, may contribute to the low BMD associated with low BMI. Many patients with end-stage COPD lose weight as the disease progresses due to decreased intake and increased energy requirements (Coin A et al 2000). Iqbal et al (1999) reported that the lowest BMD was seen in a group of patients with BMI below the normal median and reported an independent correlation between BMI and BMD ($r \geq 0.34$; $p < 0.05$). Another recent study by Adachi JD (1997) has observed that BMI was the strongest predictor of osteoporosis, in COPD patients, with a BMI $\leq$ 22 having an odds ratio of 4.18 (95% CI, 1.19 to 14.71).

iv) ***Hypogonadism:*** Hypogonadism is a significant cause of osteoporosis. Chronic illness, as well as glucocorticoid therapy can cause hypogonadism in both men and women (Lane NE and Lukert BP 1998). Studies of healthy young men treated with high-dose glucocorticoids have demonstrated up to a 47% suppression of testosterone levels (Doerr P and Pirke KM (1976). The mechanism for the hypogonadism is an effect of corticosteroids on both the pituitary gland and the gonads. Corticosteroid use decreases gonadotropin (*ie*, leutenizing hormone and follicle-stimulating hormone) secretion from the pituitary gland. In addition, there is a direct effect of glucocorticoids to decrease estrogen and testosterone

production in response to gonadotropins (Hsueh AJW and Erickson GF (1978). The combination of these effects results in hypogonadism. If left untreated, this will contribute to accelerated bone resorption as well.

v) ***Immobility and Decreased Muscle Strength:*** Normal weight-bearing activity has been shown to be required for maintenance of bone mass. Complete immobilization such as in paralysis or in experimental settings has been shown to accelerate bone turnover, resulting in decreased BMD (Kiratli BJ 1996). Most patients with COPD are not completely immobilized; however, advanced COPD often is associated with decreased functional status and mobility. The decreased exercise tolerance is due to multiple factors, including dyspnea and deconditioning due to respiratory and peripheral skeletal muscle weakness. The decreased activity and muscle strength may increase their risk for falls and fractures, and various studies (Slemenda CW et al 1989) have demonstrated an inverse correlation between hip fracture risk and activity level. Decreased activities such as standing, walking, stair climbing, and housework, as well as decreased grip strength and ability to rise from a chair, have been shown to be associated with a significantly increased risk for hip fracture in postmenopausal women (Gregg EW et al 1998).

vi) ***Glucocorticoids :*** Glucocorticoid-induced osteoporosis is well documented in the literature. Patients placed on high-dose glucocorticoid therapy exhibit a rapid loss of BMD within the first 6 months. Normal bone metabolism is a result of the equilibrium between bone formation by osteoblasts and bone resorption by osteoclasts (Hurley DL and Khosla S 1997). The mechanism of bone loss induced by glucocorticoids is twofold, with decreased bone formation and increased bone resorption. Bone formation is decreased through the inhibition of osteoblast function (Canalis E 1996). This has been demonstrated on histomorphometric analysis of bone biopsy specimens and with decreased levels of osteocalcin, a biochemical marker of bone formation (Ebeling PR et al 1998). The level of the biochemical marker osteocalcin was lower than the control level in men with chronic bronchitis who did or did not have a history of glucocorticoid use (Praet JP et al 1992). The accelerated bone resorption seen with glucocorticoid therapy appears to be due to secondary hyperparathyroidism. Glucocorticoids decrease intestinal calcium absorption and increase urinary calcium excretion, causing a rise in parathyroid hormone levels, which stimulates bone resorption. The elevation in parathyroid hormone level activates osteoclasts and accelerates bone resorption (Lane NE and Lukert BP 1998). Many studies have been done till date for evaluation of various correlates for development of osteoporosis in COPD. Bolton et al (2004) have observed that BMI (OR: 0.79) and % ideal body weight (OR: 0.93) were significantly associated with development of osteoporosis in COPD patients. Another study by Dubois et al (2002) analyzed 1222 COPD patients for the evaluation of osteoporosis. They observed that cumulative dose of steroids >1000mg (OR: 0.48) and low BMI (OR: 0.65) to be the independent risk factors for development of osteoporosis in COPD. In another recent study by Graat-Verboom L (2009), independent predictors of osteoporosis in COPD observed were: cachexia (OR: 12.1; 95% CI: 4.5-32.7; $p < 0.001$), age between 55 - 65 years (OR: 6.0; 95% CI: 2.2-16.3; $p < 0.001$), and over 65 years (OR: 11.7; 95% CI: 4.1-33.1; $p < 0.001$). Overweight (OR: 0.1; 95% CI: 0.05-0.4; $p < 0.001$) and obesity (OR: 0.78; 95% CI: 0.02-0.4; $p < 0.002$) showed a substantial protective effect against development of osteoporosis. Vrieze et al (2007) observed that the patients having COPD with Stage III (OR: 2.4), and Stage IV (OR: 7.6), and those with low fat free mass (OR: 4.9) and low BMI (OR:4.7) were independent correlates for development of osteoporosis in COPD.

DIAGNOSIS OF OSTEOPOROSIS

Dual X-ray absorptiometry (DEXA) is now established as the state-of the-art technology for noninvasive determination of bone density. Clinical usefulness of DEXA stems from its role in the diagnosis of osteoporosis, assessment of fracture risk, and monitoring of treatment. Because measurement of bone mineral density is the only method of diagnosing osteoporosis in asymptomatic people, DEXA scans are widely used for that purpose and because bone mineral density (BMD) is the best predictor of risk of fracture, measurement of BMD allows estimation of this risk. DEXA scanners are very precise; therefore,

BMD measurements obtained with DEXA allows monitoring of patients receiving treatment. In 1994, WHO defined the threshold levels for the diagnosis of osteopenia and osteoporosis with DEXA. As a consequence, DEXA measurements are currently the standard of reference for the clinical diagnosis of osteoporosis with bone densitometry.

A DEXA scanner (GE Health care lunar prodigy advance, software version ENCORE 2008, version 12.2), consists of a mobile x-ray source, a couch for the patient, and a detection system that detects radiation emerging from the bones being examined. The x-ray source is under the couch and moves together with the detection system, which is located opposite the x-ray source and over the patient's body. DEXA has the distinguishing feature of making use of an x-ray beam composed of two different photon energies (constant and pulsed). The energy used is selected to compensate for the different attenuation coefficients of the mineralized bone and soft tissues of the skeletal site being analyzed. Practically, the intensities of high-energy and low-energy photons are analyzed separately after the protons have passed through bones and soft tissue. With use of a particular computing algorithm, the attenuation values of soft tissues are subtracted, leaving only the attenuation values of bone. The relationship between the attenuation of the skeleton and its BMD is determined by comparing the attenuation values obtained with standard values in phantoms of known density (higher attenuation indicates higher density). The original DEXA scanners used a pencil-width x-ray beam and a single detector and scanned in a rectilinear fashion across the anatomic site. Technical developments in DEXA in recent years include fan-beam x-ray sources and a bank of detectors. Fan-beam scanners use wider beams that permit more rapid scanning, improved image quality, and a spatial resolution of 0.5–0.7 mm.

Newer scanners have the capacity to perform lateral scanning. This is permitted by a C-arm structure on which the x-ray tube is mounted and that can be rotated 90°. Lateral scanning increases measurement accuracy, avoiding the superimposition of posterior vertebral elements, marginal osteophytes, and vascular calcifications that may artificially increase bone density at posteroanterior imaging of the lumbar spine. DEXA examination yields monoplanar bone density. The measurements provided by DEXA are bone mineral content (in grams) and the projected area of the measured site (in square centimeters) (Gugliemi G 2011). Dividing bone mineral content by the area yields BMD (in grams per square centimeter). Consequently, the measurement of areal BMD is significantly affected by bone size, resulting in systematic overestimation of density in larger bones and underestimation of density in smaller bones. BMD is expressed in terms of standard deviation (SD) as a T score and a Z score. The T score describes the difference between the BMD of the patient being examined and the mean BMD of a standard young adult population (30 years of age), and refers to the peak of bone mass. The Z score shows the difference between the patients's BMD and the mean BMD of age- and gender-matched controls. DEXA results are reported as numeric values for the T score and Z score and as a graphic curve normalized for gender and age (Kanis JA et al 2008).

Table 1: WHO Osteoporosis Definition according to DEXA Scan

T-score	**What the score means**
2.5SD to -1 SD	Normal bone density
Between -1SD and -2.5SD	Osteopenia (low bone density)
Below -2.5SD	Osteoporosis

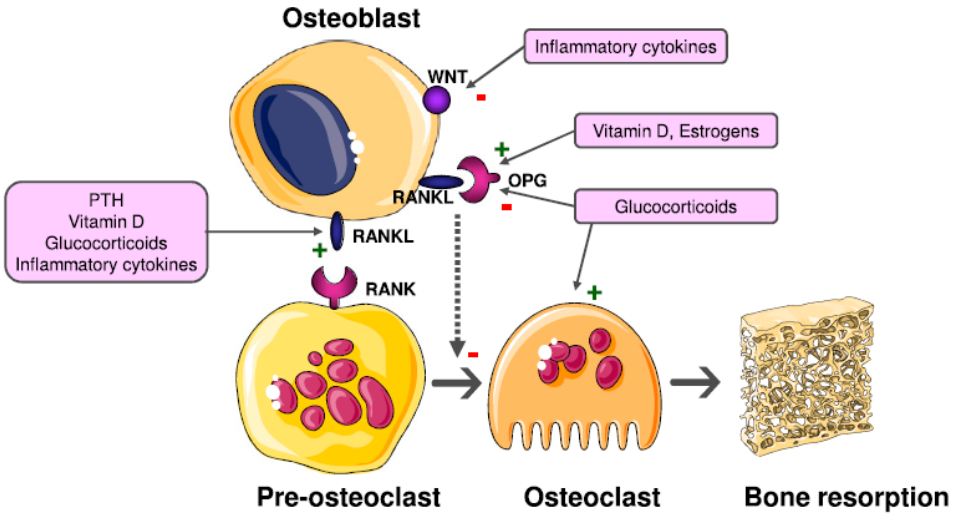


Figure 1. Key mechanisms in the formation of osteoporosis in COPD.
(OPG =osteoprotegerin; PTH =parathyroid hormone; RANK =receptor activator of nuclear factor kB; RANKL =receptor activato of nuclear factor-kB ligand; WNT =Wnt signaling pathway) *(Adapted from Patel MS and Karsenty G[19])*

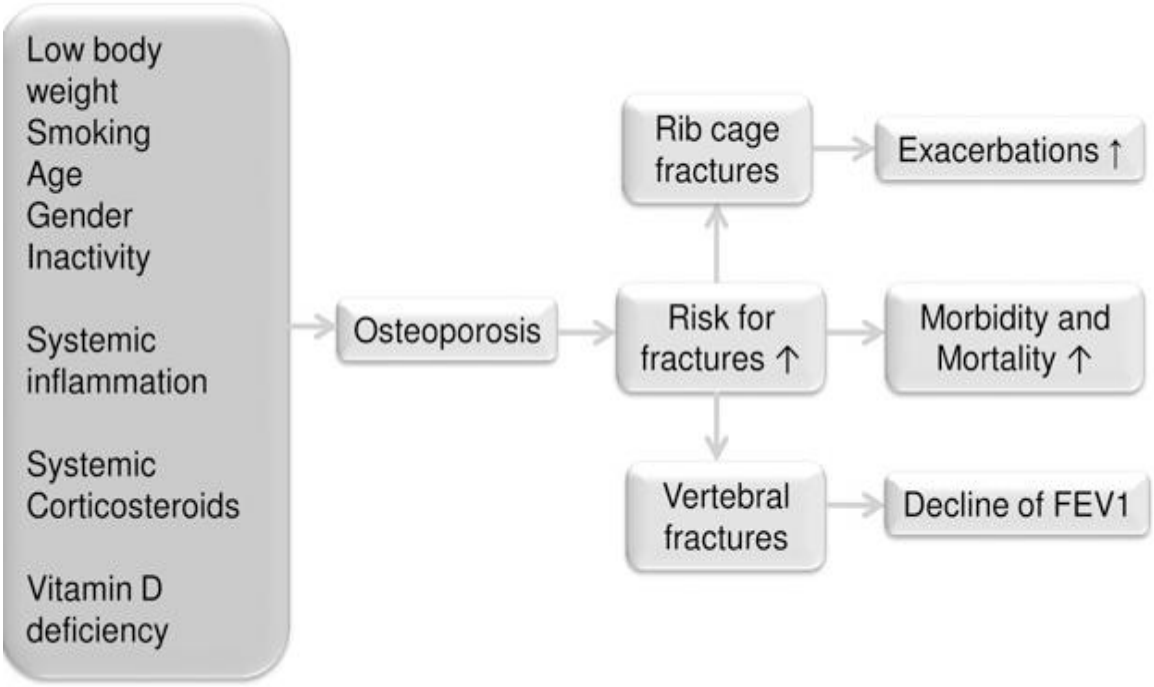


Figure 2. COPD-related risk factors for osteoporosis and its functional consequences.

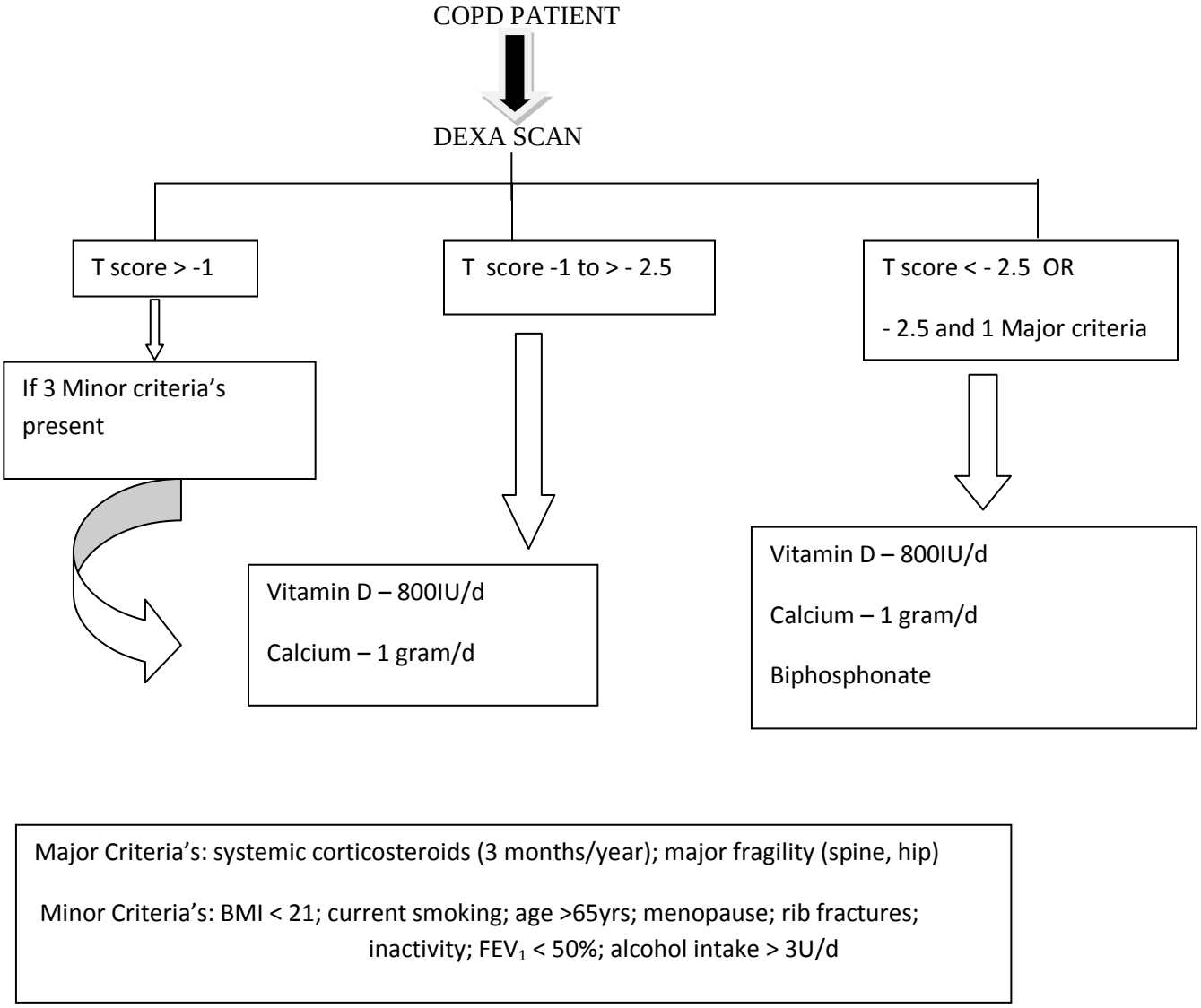
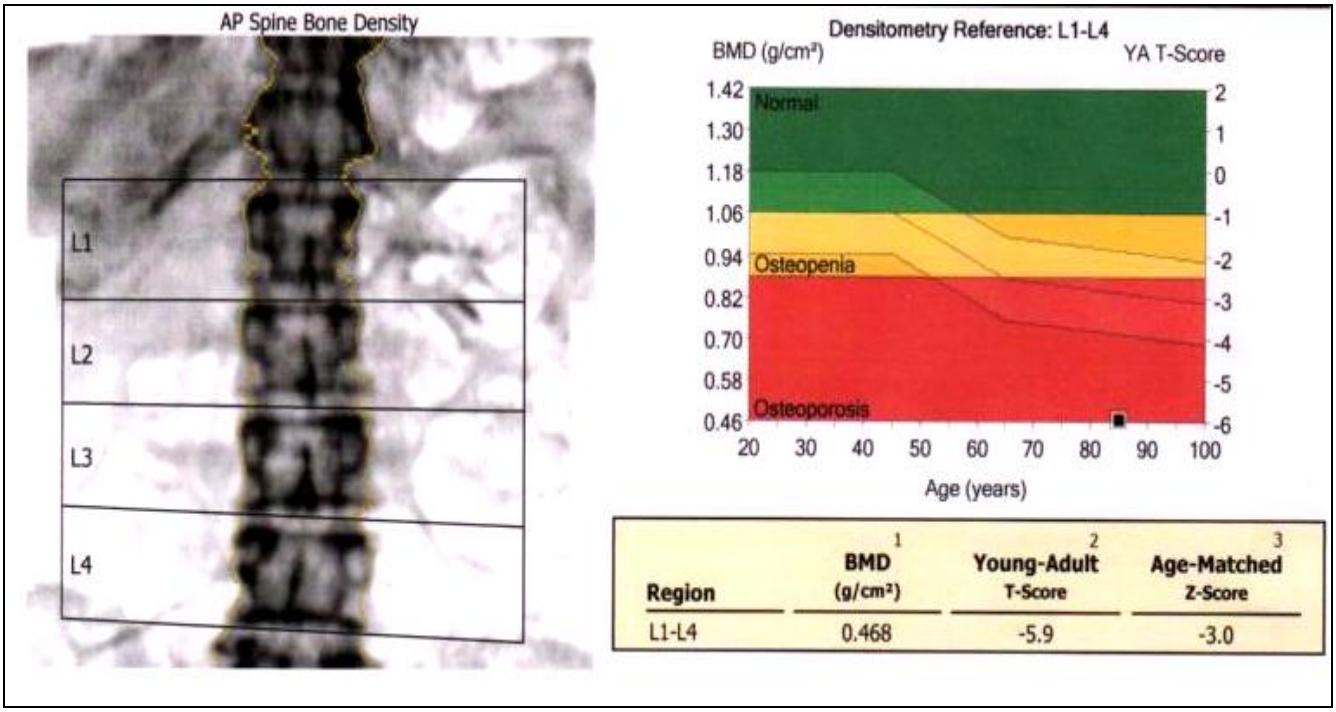


Figure 3 A clinical guidance for the management of Osteoporosis in COPD is summarized in a flowchart.

A patient's BMD is given a T-score, which is derived by comparing it to an average score for a healthy 30-year-old of the same sex and race. The difference between the "normal young" score and the patient's score is referred to as a standard deviation (SD). The WHO classifies BMD on the basis of the T score as normal (< –1.0 SD), osteopenia (< –1.0 SD but > –2.5 SD), osteoporosis (< –2.5 SD) (Kanis JA et al 2008).
This definition is applied to DEXA measurements made in the lumbar spine, proximal femur, and forearm, but not to measurements made with other techniques (eg, quantitative CT) or to DEXA measurements made at other anatomic sites.



Patient:	*AAAAA*
Age:	*65 years*
Height / Weight:	*145.0cm 55.0 Kg*
Sex / Ethnic:	*Male White*

Figure 4. Typical DEXA Report of a COPD patient with Osteoporosis

Prevention And Treatment Of Osteoporosis In Copd Patients

a) ***Non-pharmacologic Interventions:*** Physical inactivity, smoking, and poor diet are accepted as important domains for intervention in COPD patients, and the benefits of multidisciplinary rehabilitation in symptomatic patients have been clearly established (Troosters T et al 2005). The beneficial effects of other lifestyle modifications, such as smoking cessation and healthy diet, on osteoporosis and osteoporotic fracture occurrence in established COPD should still be confirmed with intervention studies.

b) ***Calcium and Vitamin D Supplementation:*** Supplementation of calcium and vitamin D enhances bone density, suppresses bone remodeling, and reduces fracture risk in older individuals (Chapuy MC 1992). Higher doses of vitamin D (800IU/day) reduces non-vertebral fractures by approximately 20% and hip fractures by approximately 18%, aggressive repletion regimen are recommended when 25-OHD levels are below 10 ng/mL (Dawson-Hughes B 2010). Moreover, the effect of high doses of vitamin D supplementation is predicted to extend beyond the protection of bone because 1,25-(OH) 2 D may directly affect inflammation and interfere with other co-morbidities.

c) Pharmacologic Therapies

i) ***Hormone Replacement*:** Due to the high incidence of hypogonadism with glucocorticoid use, all premenopausal women and men should be monitored for the development of hypogonadism (Lukert BP 1992). In premenopausal women, a history of amenorrhea suggests the development of hypogonadism, which can be treated with oral contraceptives or hormone replacement therapy (HRT). Postmenopausal women should be considered for HRT unless there is a contraindication. HRT has been shown in a small

retrospective study (Lukert BP 1992) of 15 asthmatic women receiving oral corticosteroids to increase spine BMD by 4.1% compared to a 3.4% loss in the control group. An alternative to estrogen therapy is raloxifene, a selective estrogen receptor modulator (Clemett D and Spender CM 2000). Raloxifene has not been studied in patients with glucocorticoid-induced osteoporosis. Testosterone levels should be measured in all men who have osteoporosis. If the level is low, testosterone replacement therapy will be beneficial not only by improving BMD but also, possibly, by improving muscle mass and strength (Brodsky IG 1996). Testosterone therapy has been shown to improve BMD in a crossover study by Doerr P and Pirke KM (1976) of 15 asthmatic men receiving oral glucocorticoid therapy. The spine BMD improved 5% after 12 months of testosterone therapy compared to no change in BMD after the 12-month control period.

ii) ***Calcitonin*****:** Studies evaluating the effectiveness of calcitonin on glucocorticoid-induced bone loss have been mixed. Healey et al (1996) randomized patients who were beginning high-dose prednisone therapy to receive calcium plus vitamin D vs calcitonin plus calcium and vitamin D for 2 years. Neither group showed a significant loss in BMD in the spine or hip over the 2 years, nor there was no difference between the groups. Sambrook et al (1993) randomized patients who were beginning high-dose prednisone therapy (aver. 13.5 mg/d) to receive calcium alone, calcium plus calcitriol, or calcium plus calcitriol and calcitonin. After 1 year, the BMD in the spine was decreased 4.3 ± 5.5% in the calcium-alone group, 1.3 ± 5.6% in the calcium-plus-calcitriol group, and 0.2 ± 6.5% in the calcium-plus-calcitriol-and-calcitonin group. The groups receiving calcium plus calcitriol with or without calcitonin had significantly less bone loss than did those receiving calcium alone. However, there was no significant difference between patients receiving calcium plus calcitriol alone and those receiving calcium plus calcitriol with calcitonin added. Thus, the current data are not definitive regarding the benefits of calcitonin in preventing or treating glucocorticoid-induced osteoporosis.

iii) ***Bisphosphonates:*** There is now substantial evidence that the initiation of bisphosphonate therapy when glucocorticoid therapy is begun will prevent a significant loss of BMD. In two randomized prevention studies (Adachi JD 1997, Roux C 1998) of patients beginning long-term glucocorticoid treatment for rheumatologic diseases (aver. 10 to 23 mg/d prednisone), intermittent etidronate therapy, when started within 3 months of glucocorticoid treatment, prevented bone loss compared to calcium alone. In another study by Saag KG (1998) comparing the newer bisphosphonate alendronate vs calcium and vitamin D in patients receiving glucocorticoid therapy (aver. dose, 8.7 to 10 mg/d) for from < 4 months to > 12 months, alendronate significantly increased lumbar spine BMD by 2.9% compared to a 0.4% loss in the calcium-and-vitamin D group. More recently, risedronate has been shown to be effective in preventing bone loss in patients receiving glucocorticoid therapy (average dose, 11 mg/d prednisone) for ≤ 3 months. The lumbar spine BMD for the placebo group decreased 2.8%, whereas those patients receiving 5 mg risedronate showed a 0.6% gain in BMD (Cohen S et al 1999). Finally, there is one small study by Boutsen Y (1997) of 27 patients evaluating IV pamidronate for the prevention of glucocorticoid-induced bone loss. The groups receiving pamidronate showed a significant increase in BMD at all sites compared to a significant loss in BMD in the calcium-alone group. Thus there is evidence that bisphosphonate therapy can improve BMD in patients with established bone loss due to glucocorticoid therapy.

Recommendations for management of osteoporosis in COPD

Preventive strategies to decrease osteoporotic fractures in those patients with COPD should begin with screening for the disease. Ideally, BMD should be measured prior to initiating therapy, especially in those patients at highest risk such as postmenopausal women. BMD measurement also should be considered in COPD patients at high risk for osteoporosis such as those receiving high-dose inhaled glucocorticoid therapy, postmenopausal women, premenopausal women, or men with hypogonadism, low BMI, or a history of osteoporotic fracture. Following are the recommendations to decrease osteoporosis risk in COPD.

i) Measure BMD in the following high-risk patients at baseline:

- Those on chronic oral glucocorticoids or high-dose inhaled glucocorticoids
- Postmenopausal women
- Premenopausal women with amenorrhea
- Hypogonadal men
- History of fracture
- BMI < 22

ii) Follow BMD every 6–12 mo in those receiving oral glucocorticoids or every 12–24 months in those not taking oral glucocorticoids.
iii) Give supplements to ensure daily intake of 1,000–1,500 mg calcium and 400–800 IU vitamin D.
iv) Encourage an exercise program to improve strength and balance.
v) Offer gonadal hormone replacement to all postmenopausal women, premenopausal women with amenorrhea, and hypogonadal men (unless contraindicated).
vi) Consider bisphosphonates or calcitonin in patients with osteoporosis or in high-risk patients in whom HRT is not effective or indicated.

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