OSTEOPOROSIS IN PATIENTS WITH COPD AND IMPACT ON QUALITY OF LIFE

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Abstract
Chronic obstructive pulmonary disease (COPD) is a progressive disease parenchyma destruction. Smoking is a major risk factor for this disease with frequent comorbidities. Osteoporosis is a common comorbidity in patients with COPD. Osteoporosis is characterized by lower bone density and changes in bone microarchitecture, leading to increased sensitivity and bone fractures occur. Fractures cause pain, further worsen already damaged pulmonary ventilation, reduced mobility and disability, and increased risk of thromboembolic disease, and even death. Osteoporosis in patients with COPD is probably evolving as the basis for both diseases there is systemic inflammation, but also because of the influence of inhaled tobacco smoke, reduced mobility of patients, vitamin D deficiency, lower body weight and older age. The use of systemic corticosteroids in the treatment of exacerbations of COPD increases the risk of developing osteoporosis. In addition, exacerbation of the intensification of inflammation, hypoxia and oxidative stress, as well as the imbalance between protease and anti-protease may contribute to increased bone resorption in patients with COPD. Osteoporosis can lead to kyphosis, which limits physical activity, leads to dyspnea, exacerbations and inadequate ventilation, which leads to a decrease in pulmonary function parameters. Osteoporosis can cause fractures that further limit movement, increasing the risk of thromboembolism and death. All of that have large impact on the quality of life COPD patients. Early prevention, timely diagnosis and treatment of osteoporosis are very important for patients with COPD. It is necessary significantly increase awareness of the connection between these two diseases.

Keywords: COPD, osteoporosis, fracture, vitamin D, pulmonary function

Introduction:

Chronic obstructive pulmonary disease (COPD) is a progressive pulmonary disease characterized by persistent respiratory symptoms, broncho-obstruction (which is usually irreversible), hyperinflation, loss of lung elasticity and parenchymal destruction. It is caused by exposure noxious gases or particles and smoking (1). According to the World Health Organization, the prevalence of COPD is 4-10% (1,2). The prevalence of COPD increases in smokers, but also in non-smokers, it is about 4%, which suggests that smoking is main risk factor for the development of COPD (1,3). This disease is one of the leading causes of mortality, what was observe during decades of follow-up. COPD is now one of the top three causes of death worldwide (1). Risk factors for the development of chronic obstructive pulmonary disease include both host-derived factors and external factors, and the disease usually occurs as an interaction of these two types of factors. The first, most common and therefore the most important cause of the development of COPD is smoking, active or passive. Cigarette smoke causes both systemic and airway inflammation, systemic oxidative stress, changes in endothelial functions, and increases the concentration of pro-coagulant factors (4). Chronic inflammation is characterized by an increase in the number of inflammatory cells and inflammatory mediators. Changes occur in all lung tissue structures - airways, lung parenchyma and lung vascular tissue. There is an irreversible restriction of air flow, hyperinflation and loss of elasticity of the lungs, hypersecretion of mucus, accumulation of secretions, thus creating favorable conditions for bacterial infection (1,4). Because of this, main symptoms of COPD are dyspnea, cough, expectoration and fatigue.

As mentioned above, in COPD pathophysiology is inflammation, either due to an increase in the number of inflammatory cells or mediators, and the main risk factor is smoking. Therefore, we should think of numerous associated diseases that have the same pathophysiology or same risk

factors. The most common of these diseases are cardiovascular, skeletal muscle dysfunction, pneumonia, diabetes and metabolic syndrome, osteoporosis, lung cancer and other diseases (Figure 1). Those comorbidities are present in all stages of COPD, regardless of the severity of the disease and the age of the patient (1, 5). These comorbidities have a negative impact on the quality of life of patients, on the worsening of the symptoms, exacerbations/hospitalizations and mortality. Quality of life of patients with COPD or other diseases are evaluated by questionnaires such as ACT, CAT and with the help of them we get an objective state through the subjective answers of the patients (6,7). They may be asymptomatic or the symptoms may not be specific to chronic obstructive pulmonary disease. Therefore, the search for comorbidities need to be a part of the standard examination in medical practice (chest radiography, ECG, BMI, blood tests, echocardiography). While measuring bone density, computed tomography (CT), hormone status and vitamin D levels are not routine tests, they should be done in patients with COPD.

Osteoporosis is one of the most common comorbidities of COPD. The prevalence of osteoporosis varies from 9 to 69% and it is 2 to 5 times higher in a person of the same sex and age who do not have bronchial obstruction (8). Bone destruction in patients with COPD is enhanced by: systemic inflammation (cytokines), vitamin D deficiency, use of systemic corticosteroids in exacerbations and smoking. The main role of cytokines in bone adaptation lies in the fact that the receptor for pro-inflammatory cytokines such as IL-6 and tumor necrosis factor-alpha (TNF-a) are present on osteoblasts and osteoclasts, involved in osteoclastogenesis and bone resorption (9.10). Catabolic mechanisms can increased effect of pro-inflammatory cytokines and induce the activation of the immune system, which can trigger differentiation of osteoprogenitor cells from monocytes to macrophages and the formation of osteoclast. This disruption of bone homeostasis leads to osteoporosis, increased bone fragility and fractures (9). There are several common causes that link osteoporosis and COPD, the most common of which are oxidative stress, vitamin D deficiency, reduced physical activity, and corticosteroids.

Despite the interest in osteoporosis as part of various disorders confirmed by numerous papers published on this topic, many aspects of osteoporosis remain unclear. Therefore, the purpose of this systematic review is to indicate the impact of the early detection and treatment of osteoporosis, the consequences of untimely treatment on the quality of life and mortality of our patients with COPD.

Pathophysiology of COPD and osteoporosis

Oxidative stres:

It is believed, that oxidative stress is the basis of numerous disorders. Oxidative stress is caused by reactive oxygen species (ROS) that can initiate autocatalytic reactions. They turn target molecules into free radicals and cause a chain of damage (11). Reactive oxygen species have short half-lives and are difficult to measure, but it is possible to measure the damage they cause to proteins, lipids and DNA (11,12). This damage is manifested as chronic diseases, such as osteoporosis and emphysema. Oxidative stress, apart from direct damage to cells, can disrupt the balance of proteases and anti-proteases through the inactivation of anti-proteases (such as alpha 1-antitrypsin) or the activation of proteases- matrix metalloproteases (MMP). Matrix metalloproteinase family of endopeptidases, are an important factor in the metabolism of many tissues, such as lungs and bones. Their imbalance with tissue metalloproteinase inhibitors (TIMPs) has been proven in patients with COPD. MMP is a good predictor or biomarker for evaluating the severity of COPD (13). That is mechanism for alveolar and parenchymal destruction in pulmonary emphysema COPD type patients.

Bone loss with aging is due to a decrease in the number of osteoblasts. This decrease of osteoblasts is caused by an increase in mitochondrial ROS in osteoblast cells under oxidative stress, autophagy is activated with an increase in osteoclast differentiation and bone resorption. On that way ROS increased osteoclastogenesis and bone loss-osteopenia or osteoporosis (14). This plays a key role in cellular homeostasis. Inhibition of autophagy can slow osteoclast activation resulting from excess ROS. That is why antioxidants, either from food or endogenous, play an important role in the mechanism of protection against loss of bone mass and lung tissue (14,15).

***Vitamin D deficiency*:**

Vitamin D is produced by photosynthesis in the skin, but it can also be obtained from food (fish, dairy products, eggs) (16). Ultraviolet rays convert de novo synthesized 7-dehydrocholesterol, followed by hydroxylation into 25-hydroxy vitamin D (25-OHD) in the liver. This form of Vitamin D has a long half-life and circulates in the blood, so determining its concentration is used to analyze the vitamin D status of patients. Numerous studies show a link between low levels of vitamin D and diseases such as tumors, skeletal muscle weakness, autoimmune diseases, diabetes, tuberculosis, osteoporosis, COPD (17). Vitamin D deficiency (<15 ng/Ml) leads to secondary hyperparathyroidism. The body requires vitamin D in order for calcium to be absorbed. When we don't get enough vitamin D, the calcium we need for our bones and making them thick and strong can't be absorbed. Excess calcium in the urine is a common finding in osteoporosis. Vitamin D is most important for bone and calcium homeostasis, Calcium and vitamin D supplementation effectively reduce the risk of osteoporosis and fractures (17,18). Randomized controlled trials (RCTs) have tested the importance of vitamin D and calcium. The main outcomes were any fracture. It has been proven that supplementation reduce the risk of any kind of fracture, especially hip fracture (19,20).

The roles of vitamin D are cellular proliferation, differentiation and regulatory of host defense and inflammation. And we know that COPD is inflammatory disorder in nature. Vitamin D deficiency in patients with CODP is mainly, a consequence of malnutrition, an imbalance between energy intake and expenditure. Insufficient intake is caused by difficulty breathing due to effort in obtaining, preparing food and during the meal itself. Malnutrition is more dominant in patients with emphysema.

***Corticosteroid use*:**

Recommend maintenance therapy for patients with COPD are bronchodilators, mainly as dual therapy, and corticosteroids are not first line therapy. According to the GOLD guidelines, the use of inhaled corticosteroids (ICS) is suitable for patients with frequent exacerbations due to their strong anti-inflammatory and immunosuppressive effect, with a mixed type of disease, i.e. asthma and COPD-ACO, or in COPD patients who have a higher number of eosinophils (1,21). Bone mineral density (BMD) according to literature and many studies, was significantly lower in COPD patients using inhaled corticosteroids as main therapy, measured at the hips and in the lumbar region (22).

In addition to ICS, a special bigger problem is the use of oral corticosteroids. Glucocorticoids change the secretory dynamics of parathyroid hormone, inhibit the production of insulin-like growth factor-I (IGF-I). Glucocorticoids will increase bone resorption by reducing the secretion of androgens and estrogens, which leads to a decrease in calcium concentration, a decrease in osteoblastic activity and a decrease in bone density (23, 24). Glucocorticoids exert their effect on gene expression through cytoplasmic glucocorticoid type 2 receptors and inhibit the proliferation

and differentiation of osteoblasts and increase apoptosis of mature osteoblasts and osteocytes. High levels of glucocorticoids also stimulate pre-osteoblast/stromal cell RANKL synthesis, stimulating osteoclast differentiation and bone resorption (25). Glucocorticoids reduce intestinal calcium absorption by reducing the expression of calcium channels in the duodenum. Glucocorticoids can also increase renal excretion of calcium (26). All these are the reasons why corticosteroids play a role in the development of osteoporosis in patients with COPD. Their use need to be only in exacerbations or in corticosteroid-dependent patients (1). If corticosteroids are used in chronic therapy, it is necessary to anticipate their side effects and choose a preventive plan for the treatment of osteoporosis based on that.

***Physical (in)activity, anxiety and depression*:**

Muscle mass and strength loss and physical inactivity are factors which reduce the quality of life and mobility in patients with COPD. In patients with a lower BMI and with low physical activity may have bone formation reduction because there is a relatively low mechanical load on bones. An example is astronauts who lose as much bone mass in 1 month of spaceflight as a woman in 1 year of post-menopause (27). A study by Harding and Beck showed that bone-targeting exercises have a positive effect on BMD. Regular physical activity leads to an increase of bone mass, contributes to the maintenance of bone mass and reduces the reduction of bone mass loss, in that way preventing osteoporosis (28).

Osteoporosis can lead to kyphosis, which limits physical activity, leads to dyspnea, exacerbations and inadequate ventilation, which leads to a decrease in pulmonary function parameters in patients with COPD. Osteoporosis can cause fractures that further limit movement, increasing the risk of thromboembolism and death (29,30). Also, compression fractures of the vertebrae of the thoracic spine and rib fractures further aggravate the impairment of pulmonary function in patients with COPD (31). It's a vicious circle so we have to ask ourselves is it physical inactivity a cause or a consequence of osteoporosis? The activity level of COPD patients decreases significantly in the earlier stages of the disease, starting with the GOLD 2 stage. GOLD stage 3 patients (FEV1 less than 50% of predicted values) are mostly inactive with a predominantly sedentary regime and a smaller number of steps taken (32). Improving lung function is necessary for increasing physical activity. In patients with COPD, treatment with dual bronchodilator therapy, it significantly improved the tolerance of effort during physical activity, the functioning and the general condition of the patients with great satisfaction from the treatment. Improvements were observed in all GOLD groups (33). In addition to pharmacological treatment, non-pharmacological treatment is equally important, including physical rehabilitation of patients with COPD (1).Physical activity is need to incorporation of recommendations and strategies into daily practice in patients with COPD. Pulmonary rehabilitation with exercise decreased dyspnea and fatigue, improves quality of life, reduces exacerbations, hospitalizations and mortality for COPD patients (34). Pulmonologists, physiatrists, psychologists have an important influence in encouraging physical activity, they must raise the self-confidence of these patients. The personal perception of the illness, habits, motivation and social environment play an important role in physical (in)activity.

The existence of COPD and osteoporosis with limitation in walk and daily activities, in some patients may be associated with a higher frequency of anxiety or depression. The psychological condition is affected by the number and length of exacerbations and hospitalizations, as well as the quality of life. Manifestations of the mental state are characterized in the form of weakness, sadness, lack of interest in activities and pessimism (35). Numerous studies have described the

association between depression and osteoporosis through hormonal status, inflammatory factors, and numerous other mechanisms. In osteoporosis, main cause for depression is pain, difficulty in daily routine, dependency to others and immobilization in case of fracture (36). All this leads to worsening of the general condition, loss of independence of patients with COPD and osteoporosis. Gold is to identify physical problem and referral to the adequate professional specialist and treat of both psychic and somatic comorbidities.

Fractures:

Main diagnostic method for osteoporosis is dual-energy X-ray absorptiometry (DXA) examinations in the assessment of BMD in the lumbar spine and hip. The World Health Organization defined osteoporosis as a BMD more than 2.5 SDs (Figure 2). Osteoporosis is a skeletal disorder characterized by low bone density and micro architectural deterioration of bone tissue (37). According to a literature, the total burden of osteoporosis is growing by 50% with more than 3 million incident fractures by 2025. By 2050, hip fractures may exceed 21 million cases in world and that is alarming (38). The risk of fracture increases with age. One in 3 women over the age of 50 years and 1 in 5 men will experience osteoporotic fractures in their life (37). Women with one or more vertebral compression fractures have a 1.2 times higher mortality rate. These patients report a lower quality of life 1 to 2 years after the fracture (39). Fractures are that that occur spontaneously or fall from a standing height.

Osteoporosis leads to chronic pain, reduced height, kyphosis, difficulty breathing. Fractures increase morbidity in people with COPD due to intense pain, reduced mobility, decrease a lung volume, possible occurrence of pneumonia, which leads to disability, poorer quality of life and even death. A painless compression fracture presents a special problem because it is detected late. In case of hip fracture (Figure 3), there is an increased operative risk in people with COPD due to impaired lung function and usually respiratory insufficiency (39). If they are not operated for the above reasons, they remain practically immobile, which in turn further impairs the quality of life and causes numerous complications.

Fractures of the thoracic vertebra require bracing with corset, which additionally restricts the chest mobility and accelerate lung function decline, although it is necessary in the non-pharmacological treatment of patients with osteoporosis. Therapeutic options include medications, limited bed rest, bracing, physical therapy and nerve root blocks (40).

Impact of osteoporosis on patients with COPD:

We need to think about the role of common risk factors and common underlying mechanisms in COPD and osteoporosis. Factors which are associated in those two diseases, include female gender, smoking, lack of calcium and vitamin D intake, long-term corticosteroid use. Osteoporosis and the appearance of fractures significantly and in many ways affect the life of patients with COPD.

First of all, we need to fight with those risk factors. In daily clinical practice, we advise our patients with COPD to stop smoking because as You saw that is common factor for both diseases. There are many multidisciplinary teams within hospitals and clinics which can help them with this. Meal plan with nutritionists for a protein diet and one rich in vitamin D (eggs, fish). Along with nutrition, in the case of a major deficit, supplementation with vitamin D and calcium is required with regular endocrinologist checks. With physiatrists and physiotherapists, a plan of rehabilitation, breathing exercises and exercises for osteoporosis is made. If the chest scanner proves the existence of bronchiectasis, exercises for their drainage can be performed along with

regular controls of sputum for the bacterial flora of the fungus in order to prevent exacerbations. We advise patients to walk for at least 45 minutes on a flat surface every day, and if they get tired of sitting, rest and continue. They must not be passive and spend most of their time sitting or lying down because that can lead to a vicious circle of worsening of both diseases. Pulmonary rehabilitation with passive exercises to increase bone density are of great importance for this patient population. Physical rehabilitation improves the lung capacity of these patients, which has been damaged due to all of the above. Physical exercise with adequate nutrition and nutritional supplementations (proteins, Vitamin D with calcium) represent a significant strategy for treatment. Both non-pharmacological and pharmacological treatment have synergistic effect on osteopenia and osteoporosis (41). Also, pulmonary rehabilitation, affects on functional parameters such as lung mechanics, chest kinetics and peripheral and respiratory muscle function. It enables them to perform a larger volume of work, usual physical activities in house and reduce the number of exacerbations (42,43). We need to remember that comorbidities in COPD are common at any stage of the disease. In GOLD guidelines there is recommendations for treatment od COPD but also for comorbidities (1). Need to be treat together. Only in that way we can improve the disease outcomes for patients including pulmonary function, exercise capacity and rate of exacerbations, and reduce mortality.

The biggest problem is certainly corticosteroids. With good control of the disease, with good adherence to the use of inhalation therapy with an adequate technique of using the same, a stable condition is achieved and the possibility of subsequent exacerbation is reduced. The goal is maximum bronchodilation, symptom relief and COPD control (1). Oral corticosteroids are used in the worsening of the underlying disease, but frequent exacerbations increase the need for them, thus increasing the possibility of osteoporosis and, consequently, the possibility of a fracture. Exceptionally good control of the disease with regular and correct use of inhalation therapy can delay the next worsening and the application of oral corticosteroid therapy. Therapy must be personalized depending on the characteristics and habits of our patients with COPD. Different molecules, as well as the inhalers themselves, must be considered individually for each patient in order to achieve better drug deposition. The future will be smart inhalers that will be connected to smart phones (44)

Patients with COPD must be advise to undergo DEXA and an endocrinologist examination. The goal is to detect osteopenia or osteoporosis as soon as possible. It is also, mandatory to measure the height at check-ups when pulmonary function tests are performed, because in this way we can see if there is a decrease in height and possibly in this way suspect the existence of bone thinning, i.e. osteoporosis. The biggest loss of bone mass is in menopausal women, and this is our target group for DEXA above all. With multidisciplinary approach for screening, prevention, diagnosis and management of osteoporosis in postmenopausal treatment is recommending (45). Patients with osteopenia should be carefully monitored in order to start the fight against osteoporosis immediately before any fracture occurs. In the case of vertebral fractures due to osteoporosis, treatment need to start as soon as possible because in this way the risk of new fractures is reduced. If the patient is on therapy with oral corticosteroids, the treatment should start already when osteopenia is diagnosed.

If a hip fracture occurs, if the patient does not receive the approval of the pulmonologist for the operation due to the increased risk of complications because of severe COPD or respiratory insufficiency, he remains immobilized. That consequently complicates the course of the COPD, deterioration od lung function with the consequent possibility of pulmonary embolism and fatal outcome. If we confirm a vertebral fracture (Figure 4) due to osteoporosis, patients need to wear a

corset, which again impairs lung function, reduces chest movements and lung volumes. This is a way that patient becomes physically inactive due to pain and reduced lung capacity. Furthermore, there remains a high risk of new fractures and further complications. That's why we have to think about potential fractures as early as possible and prevent them by urgent treatment of osteoporosis, because when it occurs, operative treatment is often impossible.

Many studies showed relationship between osteoporosis and decline in pulmonary function test parameters. Forced vital capacity related to the degree of kyphosis due to osteoporotic vertebral fractures and bracing use (46). In Kakoullis study, reduction in pulmonary tests parameters such as FEV_1/FVC and forced expiratory volume in 1 second (FEV_1) was close to 5% of predicted values (43). Deterioration in pulmonary function affects on daily activities and quality of life. COPD patients with osteoporosis had significantly higher mMRC, CAT and SGRQ scores than patients without osteoporosis (47). These questionnaires compare their difficulties in daily functioning, the burden of COPD symptoms, how they perform physical activities (bathing, dressing, cleaning, going to the store) and walking on the level. All this affects their social life, they leave the house less and they spend less time with their friends. These questionnaires clearly show that patients with CODP are ashamed of their symptoms (cough and shortness of breath), that they cannot follow the activities of their friends and all what they could before. Due to these reasons, the appearance of mental disorders and the appearance of depression, sadness and fear follows (48).

It is likely that in patients with COPD compared to persons without respiratory problems, much more aggressive prophylactic treatment is required even before osteoporosis is proven, especially when it is considered that it is a consequence of the treatment of the underlying lung disease. Osteoporosis is a silent disease until it is complicated by fractures. Therefore, anamnestic information about the existence of COPD and long-term corticosteroid therapy or frequent exacerbations of COPD when the patient is treated with systemic corticosteroids is useful in thinking about the possible existence of secondary osteoporosis. Osteoporosis should be actively search for in patients with COPD who have some of the risk factors for this disease.

Conclusion

Chronic obstructive pulmonary disease is an inflammatory disease with numerous comorbidities, of which osteoporosis is one of the most common. It is necessary to significantly increase the awareness of the connection between these two diseases because almost 80% of patients with COPD do not receive treatment for osteoporosis precisely because this disease is unrecognized. Osteoporosis can cause fractures that further limit the movement of patients with COPD, increasing the risk of thromboembolic disease and death. Also, compression fractures of the thoracic spine vertebrae and rib fractures further worsen impaired lung function or cause exacerbation of COPD. Early prevention, timely diagnosis and adequate treatment of osteoporosis, with multidisciplinary approach are very important for patients with COPD.

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Figure 1- COPD and comorbidities

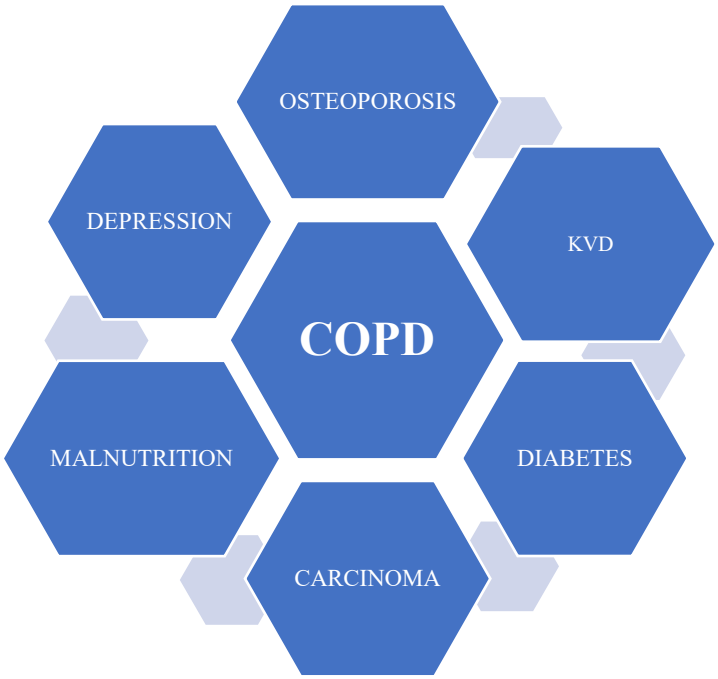

Figure 2- Dual-energy X-ray absorptiometry (DXA) of the hip in patient with osteoporosis

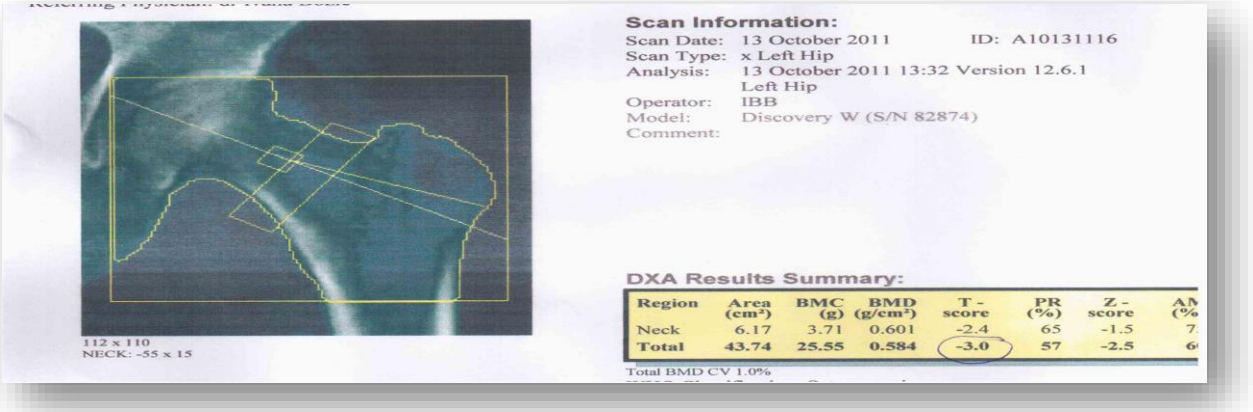

Figure 3- Osteoporosis of both hips with an right endo-prosthesis placed due to a hip fracture

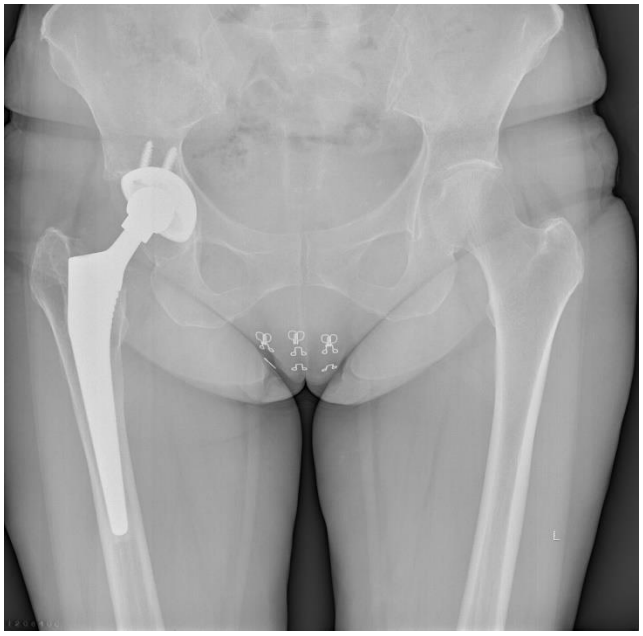

Figure 4- Osteoporosis with a compression fracture of the L4 vertebra on CT scan