

## Review Article

# Osteoporosis in frail patients

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### Abstract

Frailty, a condition that many people share nowadays, is connected to both the modern way of life and also age, physical and mental condition of a person. Sometimes, it is characterized by rapid weight alterations, slow walking speed and extreme tiredness, symptoms which vary according to the patient. It is a condition that can be altered or in other cases treated and thus it is can be a challenge for both the doctor and patient. Osteoporosis in such patients can be a riddle - sometimes it is not discovered or it is not treated properly leading to more problems. Sarcopenic patients, namely those with severe anorexic disorders, people with transplants and malignant tumors can be harmed even more because their conditions allow osteoporosis not only to grow but also become harder to be traced by the doctors. Bone loss appreciation is an urgent process because it can prove to be supportive to the patients and doctors and by all means improves the problems that may occur to people suffering from frailty.

**Keywords:** Frailty, Osteoporosis, Anorexia Nervosa, Cancer, Oldest Old

## Introduction

Frailty is a condition connected to slow walking speed, loss of weight, exhaustion, weakness and low physical activity; the combination of at least three of them can be an indication that a patient should be examined for the specific syndrome.

It is the inability of the analysis of homeostasis following a stress, which lead to adverse outcomes (falls and/or disability). However, frailty is not to be found in all seniors. It may be connected with aging but it can also be prevented and treated accordingly<sup>1-6</sup>.

In osteoporosis, a condition that causes bones to become fragile due to the fact that the tissue weakens, calcium and vitamin D are low, factors that inevitably lead to fractures.

Bone Mineral Density (BMD) however is not the only reason that could indicate and measure the risk for fractures<sup>1,7</sup>. Physical, mental and social well-being are three main specifications to be considered and evaluated accordingly. First is physical well-being related to the individuals' health assessment and included morbidity, second comes the pain and third refers to the level of physical functionality. In addition, mental well-being consists of self-esteem and general satisfaction along with anxiety, depression and adaptability. Social well-being on the other hand is connected not only to the general satisfaction - whether he or she appreciates life and its gifts - but also reflects the degree of participation in social activities.

The FRAX (acronym for the Fracture Risk Assessment

Tool) (Figure 1) has been introduced by the World Health Organization (WHO) in 2008 has proven to be an extremely supportive tool because it has the potentials to indicate the patients who can receive treatment for osteoporosis. Through an algorithmic process one can determine probable osteoporotic fractures (vertebral, humerus and forearm) and hip breaks with a prospect of about a decade; it refers to both males and females and takes into consideration the density of femoral neck (BMD) and other factors that can be considered clinically risky<sup>8,9</sup>.

In addition, youngsters can also be in danger due to low bone density and their aBMD ( areal Bone Mineral Density) that can be calculated with dual-energy X-ray absorptiometry (DXA) for more accurate results. However, it is ambiguous whether cortical Volumetric (vBMD) and/or bone size and structure are connected to such a condition<sup>7-10</sup>.

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Figure 1. FRAX questionnaire.

## Osteoporosis and Anorexia Nervosa

Anorexia Nervosa (AN) or else food aversion is a mental disorder of psychiatric origin, in which the patient can force him or herself to starvation. With a 0.5 to 1% of teenage American women to be directly affected, it is proven that this problem is connected to thousands of people; millions if we count the cases in other countries around the world as well.

Numerous comorbidities and medical drawbacks are connected with AN and loss of bone strength is one of the most projected. An estimated of 50% of women with AN have osteopenia with an additional 35% having evidence of osteoporosis<sup>11</sup>. Bone loss in AN is linked with many problems and it is affected by various factors. Deficiency of estrogens and the negative results of severe malnutrition are directly connected to bones' quality. Also, it is persistent to some degree even after weight recovery proving the complexity of the problem<sup>12</sup>.

Relevant measurements and tests have proven that youngsters with AN have differences in weight and bone growth compared to their peers, showing that 50% of AN patients, females in particular, have -1 Z-scores and about 11% of them have -2 in the same index. On the other hand, young men data are fewer but they show that 70% of them score -1. In young female population, BMD has

proven to be rather different, with AN patients reaching the lowest numbers while in adulthood 92% and 38% of the same group of people have osteopenia and osteoporosis respectively<sup>12-16</sup>.

Osteoporosis is a common problem among people with AN. There are two factors connected to this result: time and duration. Firstly, the syndrome generally begins while patients are teenagers and deeply affects their growth and their bones strength and quality. Malnutrition slows down their physical development and respectively all their body balance is at stake. Secondly, AN continues or relapses in early adulthood, right after their growth has stopped, resulting in a weak skeleton due to the inability of bones to recover the past major losses<sup>17</sup>.

Osteopenia ( $-1.0 \text{ SD} \geq \text{T-score} > -2.5 \text{ SD}$ ) in the anterior-posterior spine scored 50%, 57% for the lateral spine and 47% for the total hip; while for the same points osteoporosis ( $\text{T score} \leq -2.5 \text{ SD}$ ) scored 13%, 24% and 16% respectively. In addition, 92% of the patients has reduced BMD by at least 1.0 SD at more than one skeletal sites while 38% showed a decrease of 2.5 SD. It worth mentioning that weight has been critical in the prediction of BMD. Estrogen was prescribed and taken by 23% of the patients and 58% of the people in the aforementioned research had used using estrogen in the past<sup>18</sup>.

## Osteoporosis in transplanted patients

Transplantation is a reliable treatment option in treating patients with end-stage lung, heart, liver, kidney and hematologic patients. Increased doses of glucocorticoids and calcineurin-calmodulin phosphatase inhibitors are the proper treatment for transplant patients so their new organs not be rejected by their body. While necessary, these substances harm the structure and density of the bone affecting its mineral balance and leading to fast bone loss; when this happens to people who already have health problems the damage is more severe. During the first year from the transplantation, fractures of about 8% to 65% have been reported; with the second half of the first year to be the most problematic and risky. Fracture rates are higher among people who proceeded to organ substitution and suffered from biliary cirrhosis and lower among patients with renal transplantation.

The bone reduction is a multifactorial pathogenesis; among others, bone resorption seems to be partially accountable for the problem<sup>7,19,20</sup>.

### *Kidney transplantation*

Osteoporosis and Osteonecrosis (avascular necrosis) are the two main bone illnesses that affect kidneys; they cause problems and are connected with high percentages of morbidity<sup>21</sup>. Patients after renal transplantation had fast bone reduction that varies from 28 to 88% with about 6.8% of it taking place during the year after the operation. In other cases, there was an 1.7% gradual decrease for the first 10 years after the transplantation; the numbers are the results of histological analyses and show cases of extensive osteoporosis. However, the highest number of bone fractures take place about 2 years after the operation<sup>22</sup>.

Kidney bone disease 4 also known as renal osteodystrophy, is categorized in four sections: (1) bone illnesses with high turnover, (2) bones makes as adynamic or have lower turnover rates, (3) those with blended osteodystrophy and (4) osteomalacia. Recent researches show that renal osteodystrophy, including the problems caused in parathyroid and the problematic dissemination of vitamin D and FGF-23, are directly connected with cardiovascular illnesses and high mortality<sup>23</sup>.

### *Liver transplantation*

OLT that already exists and fast post-transplant bone reduction are connected to symptomatic osteoporosis. Post-transplant bone reduction takes place in people who transplanted solid organs; this is probably connected to their preparation before the surgery and their recovery in the post-transplant period. One cannot completely understand the functions if there is no connection with the functions of liver along with the calcium and vitamin D indexes and how they affect metabolism or osteocalcin levels.

Significant is the fact that hormonal balance improves

by about six months after OLT when bone structure and strength improves<sup>24</sup>.

### *Lung transplantation*

Lung transplantation is directly correlated with osteoporosis and has a negative affect on the quality of life of lung recipients<sup>25</sup>. While in the first six to twelve months after the operation the patients receive vitamin D and calcium supplements that should be of support; on the contrary, BMD decreased significantly at LS and FN levels (more or less at at about 5%). Post-transplant osteoporotic fractures are found in high numbers and they are relevant to BMD dropping prices. Thus, the numbers show that most patients who wait for transplantation suffered from osteoporosis or osteopenia. Antiresorptive therapy (pamidronate or hormone-replacement therapy (HRT) halted rapid LS bone reduction right after the procedure<sup>26</sup>.

### *Cardiac transplantation*

Common side effects of cardiac transplantations are vertebral fractures and osteoporosis. Bones' rates of replacement are increased in most patients, according to the biochemical indications. Secondary hyperparathyroidism was considered to be directly correlated to biochemical proofs but this is connected to only half of the cases of renal failure. Osteocalcin (OS) and alkaline phosphatase (AP) are two of the main substances responsible for the density and strength of bones despite that histomorphometric evidences did not connect with biochemical changes. The main knowledge emerged is that numerous factors affect osteoporosis in patients who received a transplant. OS and AP respectively proved to be two highly important indicators that can offer insight of the fracture risks<sup>27</sup>.

Survivors of cardiac transplantation who received the organs as teenagers, show mild renal anomalies, secondary hyperparathyroidism and proofs that their bones have recovered remarkably. In addition, osteoporosis is a common condition for many patients. At a radius of one-third, they are affected deeply by the catabolic effects of sustained excessive PTH secretion. To sum up, it is obvious that adult survivors, who has received their heart while they were teenagers, must be examined and monitored for osteoporosis and hyperparathyroidism<sup>28</sup>.

### *Hematopoietic stem cell transplantation (HSCT)*

Hematopoietic cell transplantation refers to the process of intravenous infusion of hematopoietic stem and progenitor cells specifically structured to offer marrow and immune function. HSCTs, at a number of 25,000, take place every year as a way to treat patients with leukemia, lymphoma, immune deficiency diseases, congenital metabolic defects, hemoglobinopathies and myelodysplastic and myeloproliferative syndromes<sup>29</sup>.

Osteoporotic fragmentations have been a long-lasting problem that delivers various complications to the

patients. Corticosteroids, drugs that suppress the immune system, cytokines and hypogonadism based treatment are considered to be the reason for bone reduction after HSCT. Patients who actively use HSCT are likely to be younger than 50 years old; osteopenia and osteoporosis is about 20% after two years and 50% after a period of five years. The research showed that cortical bone is more affected than the trabecular one and in all cases, even more in allo-HSCT, bone reduction reaches extreme levels. One should notice that fragmentation risk is seven to nine times higher in people from 45 to 64 years old<sup>1</sup>.

### ***Osteoporosis in dialysis patients***

Researches have shown that patients who suffer from Chronic Kidney Disease (CKD) have also suffer from bone disorders. The guidelines issued (2016) by the International Kidney Disease : Improving Global Outcomes (KDIGO) introduced the term “Chronic Kidney Disease-Mineral and Bone Disorder” (CKD-MBD) as the most fulfilling in order to describe all bone illnesses and mineral abnormalities that CKD is directly connected with; hypocalcemia, hyperphosphatemia and secondary hyper or hypoparathyroidism are some of the most common problems<sup>1</sup>.

In addition, patients with CKD on dialysis (CKD-5D) often experience low bone mass and other bone disorders which are also common in renal osteodystrophy. Despite its importance, BMD does not seem to be a common method in the management of patients who experience CKD-5D. Kidney Disease Outcomes Quality Initiative (KDOQI) proposed DXA based on BMD calculations on patients who already suffer from bone breaks. On the other hand, KDIGO decided against BMD calculations in CKD-3 to CKD-5D patients because BMD is not able to predict clearly the fractures<sup>30</sup>.

### **Osteoporosis in cancer patients**

#### ***Breast cancer***

Osteoporosis and breast cancer are common diseases in postmenopausal women. Thus, the reports have shown that patients who suffer from breast cancer have higher potential to experience bone fragments and it seems that they cannot protect themselves from osteoporosis; thus, bone health should equally be examined when breast cancer is diagnosed. It seems that harsher therapies can have negative side-effects and inevitably lead to bone loss and increased percentages of fragmentation. To be more specific, after one year of therapy in a patient with breast cancer, the endocrine therapy (ovarian suppression) and the relevant chemotherapy can result in CTIBL, bone loss connected to chemo, and a reduction of the lumbar spine of up to 10%<sup>31,32</sup>.

#### ***Prostate cancer***

Men with prostate cancer who receive Androgen Deprivation Therapy (ADT) experience higher bone loss than other patients. Due to the decrease of androgens,

bones lose their density and strength and that leads to increased risks of fractures and skeletal morbidity as a result of bone metastases. While PSA level, namely the prostate-specific antigen, can offer important knowledge for the prospects of the disease, the absence of noninvasive tools to monitor the health of the skeleton create a gap in research and treatment. Maybe the biochemical markers found in serum and urine can offer some more support of the process<sup>33-35</sup>.

### ***Osteoporosis in sarcopenic patients***

The musculoskeletal system following general deterioration of an aging body experiences lower lean and bone and higher percentages in fat mass. In specific, women with the loss of estrogens suffer from over 50% loss of their bone mass while men prove to be less vulnerable against this process. Fat is a really important factor as it seems able to replace many tissues through aging, showing that even if someone keeps his or her weight at the same levels for an entire life, still fat takes over the body. The musculoskeletal system undergoes inevitable physiological changes of its structure, in terms of mass, geometry and composition that changes gradually impair functionality and at certain impoverishment threshold they promote the onset of pathological conditions, named osteoporosis and sarcopenia. So, both conditions co-exist in older people and share genetic, environmental and health-related intrinsic and extrinsic factors. Age-related sarcopenia and osteoporosis, when not recognized and treated, do increase the risk for falls and fractures, thereby making older individuals more susceptible to mobility limitations, that, ultimately, leads to severe disability<sup>36</sup>. Obesity however does not seem to be the main factor but probably it is sarcopenia that leads women to have higher mortality risks<sup>37</sup>.

### **Osteoporosis in the Oldest Old**

Osteoporosis is common to seniors and due to that fact they are also named Frail Elderly. In WHO's report on Aging, healthy aging is constituted by the ability of a person to maintain a well balanced life, namely be fully functional and self-contained. Totally connected with all aspects of life (mental, psychological, physical), functional ability is the ability of a person to live with balance in his personal moments (capacity to do errands etc) and also be a responsible and valuable person of the society. Sometimes people do not fully embrace their abilities and that adds up to their alienation from social groups and also from the deterioration of their mental and physical abilities; thus, they do not fully enjoy life and its potentials. Frailty is the decline of the physiological system that comes with age, it respectively leads to difficulties, vulnerabilities that affect deeply all stages of the life of a person; psychological and physical alike<sup>1</sup>.



## Treatment of osteoporosis in frail patients

### Supplements: vitamin D & calcium

Vitamin D and calcium are two of the main components that are proposed and widely used as supplements in order to increase the shortage found in many people of older age because they can halt bone loss and risk of fragmentation<sup>1</sup>.

There are several drugs to treat osteoporosis divided into two categories: one reduces bone loss while the other enhances bone production. Calcitonin, bisphosphonates and denosumab are in the first category, while parathyroid hormone in the second. There is also strontium ranelate, testosterone and mixed-action tibolone. The choice of the drug is based on the history, age, sex and severity of the disease. There is no complete cure for osteoporosis. However, there are ways of preventing the disease, reducing the rate of bone loss and, to a certain extent, reversing bone decay and improving bone density<sup>7,38,39</sup>.

### Prevention of falls

Preventing falls means preventing fractures. The main risk factors of falls are: environmental risks, ladders, low level lighting, non-stable carpets, obstacles on walkways, lack of auxiliary appliances in the bathroom, slippery external conditions.

### Fitness and frailty

It is commonly known and scientifically proven that sarcopenia, deficiency of muscles and strength, negatively affect skeletal muscle function and has an impact in functionality performance, especially in senior ages.

Muscle fibers, specifically the type II ones, are considered to be responsible for the reduction of muscle tissue when the first are found in lower percentages. People's life becomes more difficult as the lack of strength affects everyday tasks and they run their errands efficiently while at the same time physical imbalance (namely not able to carry weight or stand and balance properly) make them vulnerable to accidents and puts their life in danger. However, it seems that resistive training can increase the strength in really high levels, even in people that are considered too old to exercise. Through the production of fiber hypertrophy, neutral factors are improving and thus strength is advancing reaching in some cases the levels of a much younger person. As long as concerns physical activity is highly important for healthy aging people, the advancement in their strength makes them feel independent and able to continue enjoying their lives<sup>40-42</sup>.

## Discussion

Frailty is connected with aging and thus it is associated with elderly. While it is commonly accepted that when people grow their body ages irreversibly, the process can be slow down, treated or even prevented with the proper actions. Frailty also occurs in patients with chronic or devastating

diseases including patients with anorexia nervosa or other malignancies.

Osteopenia and osteoporosis is present in almost all frailty patient. The roots of bone loss is multifaceted and the biochemical approach proposes the disconnection of the creation of bone tissue from resorption may partially give a solution as it may be the root of the problem.

It is commonly accepted that age affects all the aspects of someone's life, including the muscles and bones as well. Aging deteriorates the performance of body parts leading to loss of strength, lower stamina and limited functionality; aspects that affect the psychological state of an elderly person. A partial but fulfilling solution can be found in resistive training as it seems to strengthen muscles at a high degree, even in people of advance age.

Preventing falls means preventing fractures. The main risk factors of falls are: environmental risk factors, ladders, low level lighting, non-stable carpets, obstacles to walkways, lack of auxiliary appliances in the bathroom, slippery external conditions.

Finally, treatment of osteoporosis is highly significant in keeping frail patients' metabolism, especially that of bones, in good or acceptable standards. Anti-osteoporosis medication, in combination with vitamin D and calcium supplements can lead to the reduction of bone loss and the risk for fragmentations in patients.

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