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## IATROGENIC OSTEOPOROSIS

**Summary.** The literature review provides information on the major calcium-regulating hormones and their role in the regulation of bone remodeling. These processes are also influenced by sex steroids, growth hormone, insulin, cortisol, thyroid hormones and various local growth factors. In this regard, osteopenia and osteoporosis are closely linked to a number of endocrine diseases, some of which are common (diabetes mellitus, hyperthyroidism), others – quite rare (endogenous hypercortisolism). Osteoporosis associated with diabetes, steroid osteoporosis, osteoporosis in thyroid function abnormality are considered in detail. It is emphasized that timely diagnosis and adequate treatment of endocrine diseases associated with a decrease in bone mineral density, contribute to slowing or stopping bone loss, normalization of bone remodeling, enables to reduce the incidence of fractures and to improve the quality of life of the patient.

**Key words:** osteoporosis, risk factors.

### Introduction

Osteoporosis is a metabolic bone disease characterized by a deterioration of bone microarchitecture which conduces to fragility fractures. It is a heterogeneous and multifactorial etiological disease. About 20 to 30 % of osteoporotic postmenopausal women and more than 50 % men have a secondary induced etiology, namely the medications (Table 1).

**Table 1. Drugs more frequently associated to bone mass loss and/or development of osteoporosis and/or osteoporotic fractures**

Corticosteroids	Serotonin selective re-uptake inhibitors	Aromatase inhibitors
Anti-epileptics	Proton pump inhibitors	GnRH agonists
Anti-retroviral drugs	Somatostatin analogs	Immunosuppressants (tacrolimus; cyclosporine A)
Antipsychotics; Lithium	L-thyroxine	Metotrexate
Unfractionated heparin	hiazolidinediones	Cyclophosphamide
Warfarin	Medroxyprogesterone acetate (depot)	Imatinib
Loop diuretics (furosemide)	Oral retinoids	Tetracyclin

**Note: GnRH agonists – gonadotropin-releasing hormone agonists.**

The actual increase in human longevity is possible due to the public health care and to polimedication, mainly of the oldest people. Unfortunately, some of the most prescribed drugs to chronic diseases may have negative effects on the skeleton, not only decreasing bone mass, but also increasing the risk for fragility fractures.

In the recent years, the list of such drugs and their potential mechanisms for reducing bone mass and bone quality and/or of inducing fractures, is becoming bigger, exceeding the classic glucocorticoids actions in the bone tissue.

More, the population with multiple and chronic medications has already an increased risk of osteoporosis and fractures. So, the clinicians must be aware and the potential risks and benefits of such medications should be balanced.

### Corticosteroids

Glucocorticoids are the main drug-induced bone loss and secondary cause of osteoporosis; their mechanism of action includes primarily the reduction in bone formation, as well as the increase in bone resorption, induction of hypogonadism, decrease in calcium absorption with augmented parathyroid hormone (PTH) and increase in calcium excretion [1]. More recent data suggest that the glucocorticoid-induced metabolic disruption, which is responsible for central obesity, diabetes mellitus, hyperlipidemia and insulin resistance are mediated by the inhibition of osteocalcin secretion in the osteoblasts; however it does not explain the decrease in bone formation rate and low bone mass. The bone loss is predominantly at the axial skeleton and bone mineral density (BMD) can decrease between 5 and 15 % per year, being more pronounced in the first 3 to 12 months. The fragility fractures risk is increased in the first 3 to 6 months after the beginning of the chronic therapy reaching about 30 to 50 % [2].

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The use of inhaled corticosteroids especially in moderate to high doses, can also induce bone loss (although less than oral and intra-articular use) and those patients should always be evaluated mainly if they have other risk factors for osteoporosis and fragility fractures and/or falls [3].

The myopathy induced by these drugs can also contribute to increase the falls frequency and consequently to the osteoporotic fractures.

Some factors which increase the risk for the fragility fractures in patients on glucocorticoids have been identified: reduced body mass index, patients older than 60 years, prevalent fracture(s), diseases that need corticosteroid treatment and actual and cumulative dose of corticosteroid (above 5 mg/day of oral prednisone or equivalent for more than 3 months).

Usually, the anti-osteoporotic treatment is indicated if one or more of the above risk factors are present and the patient will be on corticosteroids for 3 months or more with a daily prednisone or equivalent dose > 7.5 mg. It is controversial to treat women with childbearing potential.

All patients should receive calcium and vitamin D supplements. Assessing the baseline fracture risk and incorporate the dose and anticipated duration of glucocorticoid therapy into treatment decisions are in the prevention and treatment of glucocorticoid-induced osteoporosis of the American College of Rheumatology recommendations. The preferred drugs for treatment are the bisphosphonates (oral and intravenous) and more recently, teriparatide and denosumab [1].

## Sex steroid hormone inhibitors

Drugs causing hypogonadism such as aromatase inhibitors and GnRH agonists are one of the main causes of bone mass loss and fractures. Hypogonadism is the most important cause of osteoporosis in men, occurring in up to 20 % of men with symptomatic vertebral fractures and 50 % of old men with hip fractures [4].

The hormonal therapy with aromatase inhibitors and with GnRH agonists is based in originating an estrogen depletion state; consequently, a down-regulation of osteoprotegerin expression occurs, causing increased osteoclastic bone resorption, which leads to decreased bone mass.

## Aromatase inhibitors

The aromatase inhibitors (anastrozole, letrozole, exemestane) are used in postmenopausal women with positive estrogen-receptor breast tumors. These medications inhibit the enzyme aromatase, which aromatises the androgens produced in the adrenal glands to estrogens, originates approximately 95–99 % reduction in the circulating estradiol levels. This effect is beneficial to control the disease, but originates about 2 %/year bone mass loss (double of the normal postmenopausal), low BMD and osteoporosis.

The disease and also other treatments like surgery, chemotherapy and radiotherapy may contribute to the bone mass loss; thus, these women have a higher risk for fragility fractures, especially at the lumbar spine.

The ATAC study showed that the anastrozole group alone (versus the anastrozole and tamoxifen combined

group) had an augmented incidence of osteoporotic fractures and decreases in baseline BMD (from 6.98 % at the lumbar spine and 7.24 % at the hip after 5 years [5]).

Oral bisphosphonates, zoledronate and denosumab may prevent the aromatase inhibitors-related bone loss.

## GnRH agonists

GnRH (or luteinizing hormone-releasing hormone) agonists (leuprolide and goserelin) are widely used in the treatment of hormone-dependent cancers therapy such as the prostate and the breast, acting through the inhibition of the pituitary gonadotropins.

In premenopausal women with estrogen-receptor positive breast tumors, these medications are used to inhibit estrogens production, inducing hypogonadism. The reduction in circulating estrogens can reach 98 % and BMD decreases from 6 to 10 % in the first 2 years, with a recovery after drug discontinuation. The data regarding osteoporotic fractures are scarce and it does not seem to be increased in women with normal BMD.

In prostate cancer the aim of this therapy is to inhibit the testosterone production, which is a very important hormone maintaining bone health, mainly at the bone formation. However, a secondary decrease in estrogens is also detected and appears to be primarily responsible for the skeletal adverse effects of these drugs. An increase in PTH-mediated osteoclast activation can contribute to the physiopathology of the bone loss. In the first year of therapy, men on these drugs have a maximal «acute» loss of bone mass; in the first year of therapy, the bone loss rate is about 2–8 % at the lumbar spine and 1.8–6.5 % at the hip. The BMD decrease at the distal radius is about 5.3 % in 12 months. The occurrence of fractures is also increased and is correlated with the duration of the treatment and it has been described that patients treated during with at least 9 doses of these drugs are more prone to fractures in the first year.

The efficacy of both oral and intravenous bisphosphonates (pamidronate and zoledronate) as well the selective estrogen-receptor modulators (raloxifene, toremifene) and denosumab has been shown in men with non-metastatic prostate cancer, preventing bone loss and inducing increases in BMD, thus reducing the fracture risk [6–9].

## Thiazolidinediones (Glitazones)

Thiazolidinediones used in type 2 diabetic patients have major insulin-sensitizing effects in the liver, in the muscle and in the adipose tissue through the activation of the peroxisome proliferator-activated receptor gamma. However, their ability to deviate the differentiation of the stem cells from osteoblasts to adipocytes increases the adipogenesis and reduces the osteoblastogenesis, thus reducing the bone formation. So, the previous studies showed an association of these drugs to the BMD reduction in both lumbar spine and hip and osteoporotic fractures, mainly in women with type 2 diabetes mellitus.

Rosiglitazone and pioglitazone have been associated to an increase in the incidence of fragility fractures at the humerus, hands and feet; the risk seems to be higher in postmenopausal women and is also dose-dependent. However,

more recent studies suggest that the risk of osteoporotic fractures is similar in patients using thiazolidinediones or insulin, and so, it remains unclear if the association between these medications and fracture risk is related to the drug or to the diabetes itself [10].

### Serotonin selective reuptake inhibitors

The central nervous system has a recognized serotonin signaling: serotonin is synthesized in presynaptic neurons, accumulates in vesicles and stimulates the postsynaptic neurons through its receptor. Inhibition of this pathway prevents uptake of serotonin, resulting in its accumulation within the synaptic cleft and the prolonging of receptor activation.

Since some years ago the serotonergic system is known to play a role in bone metabolism, through functional serotonergic pathways in bone cells; indeed, osteoblasts, osteoclasts and osteocytes express the serotonin receptors and serotonin selective reuptake inhibitors (SSRI) inhibit serotonin uptake in bone cells in the same manner as in neurons [11, 12].

SSRI like citalopram, escitalopram, fluoxetine, paroxetine, sertraline, fluvoxamine, seem to originate bone mass loss and even change bone architecture. In a prospective study during 5 years, 5,008 patients taking serotonin selective reuptake inhibitors had a lower BMD at both hip and spine, increased falls and increased risk of clinical fragility fractures. Clinical longitudinal studies found about a 1.6-fold of greater decline in BMD in the SSRI users vs non-users. However, the Women's Health Initiative and the National Health and Nutrition Survey did not find association with a decrease in BMD [13].

Regarding osteoporotic fractures, some studies like MrOS and CaMOS from Canada showed, respectively, an increase in the risk of non-spine fractures and higher 5-years fracture rates for the SSRI users [12, 14].

Also regarding the classic tricyclic antidepressants, a meta-analysis showed they confer an increased risk of fragility fractures, independent of depression and BMD [15].

So, it is far from clarified the relative importance of the major depressive disease and its co-morbidities like reduced food ingestion, low body weight, hypogonadism, and/or its treatment in the bone mass loss and in the fractures observed in these patients [16].

### Second-generation antipsychotics

The second-generation antipsychotics like olanzapine, clozapine and risperidone are actually very used in clinical practice not only in adults with bipolar disorders and schizophrenia, but even in children with problems of irritability and autism. Their negative effect on insulin sensitivity is responsible for their induction of obesity, type 2 diabetes and dyslipidemia. Also in bone, negative effects have been found, namely reduced bone mineral density and increased fracture rate. Some studies showed that risperidone can cause hyperprolactinemia and secondary hypogonadism due to the blockade of dopamine receptors and that could be one of the mechanisms for bone loss. However, it is known that second-generation anti-psychotics have multiple targets like the serotonin, D2 and histamine receptors, and

so can indirectly and through many pathways influence the bone remodeling. Experimental studies on mice suggest that risperidone affects both bone formation and resorption, decreasing bone mass and changing bone microarchitecture. This is a very important issue mainly in children and adolescents, because there are still building their skeleton and acquiring the peak bone mass. Also, studies in humans are needed to clarify all these issues [17].

### L-thyroxine

The thyroid hormone is essential for the normal skeletal development and linear growth, so both deficiency and excess have negative skeletal consequences; also in adults the excess of thyroid hormones are detrimental for the skeleton because they increase bone turnover, shortening the bone remodeling cycle and causing up to 10 % loss of mineralized bone per cycle. More recently, studies revealed that thyroid stimulating hormone (TSH) alone is able to modulate the bone turnover; thus, when it is suppressed, the bone resorption also increases [18, 19].

The thyroid hormone (L-thyroxine) is usually prescribed in the treatment of hypothyroidism with a replacement dose; however, in thyroidectomized patients due to thyroid carcinoma, a higher dose is used in order to suppress the plasma TSH concentrations originating a subclinical hyperthyroidism. Thyroid hormone increases directly the bone resorption and indirectly by stimulating bone-resorbing cytokines decreasing the BMD predominantly at the cortical bone.

Some studies have shown that patients aged 70 or more years on chronic L-thyroxine therapy had a significantly higher risk for osteoporotic fractures with a strong dose-response relation, as the overtreatment results in very low TSH levels [20].

We have also showed that young men with endogenous hyperthyroidism have an increase in the prevalence of reduced bone mass and osteoporosis and even asymptomatic vertebral fractures detected by VFA (Vertebral Fracture Assessment) [21, 22].

### Proton pump inhibitors

Some studies in rats have shown that long-term administration of proton pump inhibitors like omeprazole originates reduced bone density. Also in humans using omeprazole, decreases in serum and urinary calcium levels were documented, because the gastric acid is important for the absorption of calcium supplements, especially the calcium carbonate.

Moreover, the protein content of the meal influences the calcium absorption. Some case-control studies in humans have shown an association between gastric acid suppression and fractures, with significant increase in hip fractures risk. The association was also dependent on duration of the proton pump inhibitors use and their different effect in men and women seemed to depend on calcium intake.

It seems that the use of a high dose more than one year can increase the risk of bone fractures in 10–40 %, especially hip and spine and that risk could reverse after one year of discontinuation [23, 24].

Also, studies with H2 receptor antagonists revealed conflicting results regarding the fracture risk.

So, at this time, the association of these drugs to reduced BMD and to fragility fractures is not completely clarified and more studies are needed to confirm the real negative skeletal effects of the proton pump inhibitors [25–28].

## Antiretroviral drugs

Acquired immune deficiency syndrome (AIDS) itself is associated to low BMD and fragility fractures, which have a multifactorial etiology, namely chronic immune activation and upregulation of pro-reabsorptive cytokines (tumor necrosis factor alfa, interleukin-6, receptor activator of nuclear factor kappa-B ligand), direct effects of human immunodeficiency virus 1 (HIV-1) viral proteins on bone cells, low body weight and hepatitis C coinfection [29, 30].

Moreover, the highly active treatments for AIDS have significantly decreased both morbidity and mortality associated with the disease; however, some side effects emerged, namely the bone disease. The prevalence of osteoporosis in men and premenopausal women HIV infected is already increased and is about 3 times higher than the non-infected population [31, 32].

The AIDS patients on antiretroviral drugs (both protease and reverse-transcriptase inhibitors) have higher prevalence of low BMD and osteoporosis. Within the first 1–2 years after initiation the anti-retroviral therapy, there is about 2–4 % loss BMD, both at the lumbar spine or hip detected by dual-energy x-ray absorptiometry (DXA). The peak bone loss occurs in the first 6 and 12 months, respectively, at the lumbar spine and at the hip. All the antiretrovirals and in different regimens seem to be similar, although most studies agree that tenofovir induces a more pronounced bone loss [33].

Despite the pathogenesis being controversial, the increased osteoclastogenesis seems to be an important mechanism originating an increase in the bone resorption. Furthermore, the impaired osteoblastic function through the Wnt signaling contributes to reduce the BMD. Also direct effects on vitamin D metabolism seem to be implicated [34, 35].

## Loop diuretics

These drugs, like furosemide, often used in the treatment of congestive heart failure, increase renal calcium excretion and originate an increased bone turnover, with reduced BMD and risk of fragility fractures [36].

## Anti-epileptics

These drugs have been associated to BMD reduction, changes in bone quality, osteoporosis and fractures. The pathophysiology includes various mechanisms, namely the induction of the liver cytochrome P450, increasing the catabolism of vitamin D into inactive metabolites and thus, secondary hyperparathyroidism and increase in PTH-mediated bone resorption. Also, the direct action in the osteoblasts, the changes in calcium absorption, the increase in homocysteine and the reduction in vitamin K and in sex steroids, are possible mechanisms implicated in the bone loss. The drugs that have been studied and associated to the bone disease are the phenytoine, the phenobarbital and the carbamazepine. Valproate, despite being an inhibitor of the liver cytochrome P450, can reduce the BMD at several skeletal sites [37–39].

## Anticoagulants

The unfractionated heparin can both activate the osteoclasts because it binds to osteoprotegerin, and also inhibit the differentiation and function of the osteoblasts decreasing bone formation. About one third of patients on heparin can have reduced BMD, however fractures are rare. By opposite, the patients on low-weight heparin have even less fractures [40, 41].

Oral anticoagulants, like warfarin, antagonize the vitamin K and inhibits the gamma-carboxylation of osteocalcin. Despite that, the patients with reduced BMD and fractures are not so evident [42].

The new generation anticoagulants like dabigatran and rivaroxaban do not seem to be associated to bone disease. However, studies in vitro with rivaroxaban show that it may reduce the function of the osteoblasts [43, 44].

## Imunosuppressants

The patients undergoing transplantation are prone to bone mass loss and fractures relatively frequently. That is usually due to the use of imunosuppressants like calcineurin inhibitors, namely tacrolimus and cyclosporine A; they can originate bone mass loss and osteoporosis, but its mechanism is still debated. In the period immediately after the transplantation, the patients are particularly prone to fractures: in the liver, heart and lung transplantation, the spine and the ribs fragility fractures are more frequent, while in the kidney transplantation the long bones and feet fractures are the most frequent [45–47].

Other drugs like somatostatin analogs can decrease the vitamin D absorption and insulin-like growth factor 1 levels, while oral retinoids can activate the osteoclasts.

## Conclusions

The mechanisms of action and the effects on BMD and fractures, for some of these medications, have been well defined, while for other drugs more studies are still needed for a better evaluation of their impact on the bone. The table 2 summarizes some drug effects on the BMD and fractures.

**Table 2. Effects of drugs on the BMD and fractures**

<b>Decrease BMD (lumbar spine/hip)</b>	<b>Increase Fractures (vertebral/non-vertebral)</b>
Corticosteroids	Corticosteroids
L-thyroxine	L-thyroxine
Aromatase inhibitors	Aromatase inhibitors
GnRH agonists	GnRH agonists
Thiazolidinediones	Thiazolidinediones
Calcineurin inhibitors	Calcineurin inhibitors
Selective serotonin reuptake inhibitors	Anti-retroviral
Anticonvulsants	Proton pump inhibitors
Heparin	
Anti-retroviral	

In all the patients with such medications, it is very important to monitor the bone mass by DXA and/or with the bone remodeling markers. It is also very important to use the less efficacious dose. The individuals should be also advised to modify the lifestyle to protect bone mass, such as regular exercise, adequate sun exposure, stop smoking,

decrease in alcohol consumption and an adequate calcium and vitamin D ingestion (above 50 years-old in women and 70 years-old in men 1,200 mg and 800–1,000 IU daily, respectively). The intervention strategies to reduce falls should be also encouraged. Sometimes, the anti-resorptive and/or bone-formation anti-osteoporotic agents are also needed (Table 3) [48, 49].

**Table 3. Recommendations for patients on drugs affecting adversely the skeleton**

Evaluate the fracture risk before the prescription Recommend lifestyle changes to promote bone health Choose drugs with less impact on bone	Evaluate periodically the BMD and the fracture risk Re-evaluate periodically the need/dose of such medication	Emphasize periodically the importance of the compliance of the anti-osteoporotic treatment
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### ЯТРОГЕННИЙ ОСТЕОПОРОЗ

**Резюме.** В огляді літератури подано дані про основні кальційрегулюючі гормони та їх роль у регуляції процесів кісткового ремоделювання. На ці процеси впливають також статеві стероїди, гормон росту, інсулін, кортизол, тиреоїдні гормони і різні локальні чинники росту. У зв'язку з цим остеопенія та остеопороз тісно пов'язані з низкою ендокринних захворювань, деякі з них зустрічаються часто (цукровий діабет, тиреотоксикоз), інші — досить рідко (ендогенний гіперкортицизм). Детально розглядається остеопороз, пов'язаний із цукровим діабетом, стероїдний остеопороз, остеопороз при порушеннях функції щитоподібної залози. Підкреслюється, що своєчасна діагностика і адекватне лікування ендокринних захворювань, що супроводжуються зниженням мінеральної щільності кісткової тканини, сприяють уповільненню або припиненню втрат кісткової маси, нормалізації процесів кісткового ремоделювання, дозволяють знизити частоту переломів кісток і поліпшити якість життя пацієнта.

**Ключові слова:** остеопороз, чинники ризику.

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### ЯТРОГЕННИЙ ОСТЕОПОРОЗ

**Резюме.** В обзор литературы представлены данные об основных кальцийрегулирующих гормонах и их роли в регуляции процессов костного ремоделирования. На эти процессы влияют также половые стероиды, гормон роста, инсулин, кортизол, тиреоидные гормоны и различные локальные факторы роста. В связи с этим остеопения и остеопороз тесно связаны с рядом эндокринных заболеваний, некоторые из них встречаются часто (сахарный диабет, тиреотоксикоз), другие — достаточно редко (эндогенный гиперкортицизм). Подробно рассматриваются остеопороз, связанный с диабетом, стероидный остеопороз, остеопороз при нарушениях функции щитовидной железы. Подчеркивается, что своевременная диагностика и адекватное лечение эндокринных заболеваний, сопровождающихся снижением минеральной плотности костной ткани, способствуют замедлению или прекращению потерь костной массы, нормализации процессов костного ремоделирования, позволяют снизить частоту переломов костей и улучшить качество жизни пациента.

**Ключевые слова:** остеопороз, факторы риска.