Introduction

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

Osteoporosis is the most prevalent metabolic bone disease. It is characterized by a deterioration of bone microarchitecture and consequent 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.

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

- Corticosteroids
- Antiepileptics
- Antiretroviral drugs
- Antipsychotics; Lithium
- Unfraccionated heparin
- Warfarin
- Loop diuretics (furosemide)
- Rifampicine
- Serotonin selective re-uptake inhibitors
- Proton pump inhibitors
- Somatostatin analogs
- Thyroid hormones
- Thiazolidinediones
- Medroxyprogesterone acetate (depot)
- Oral retinoids
- Aluminium
- Aromatase inhibitors
- GnRH agonists
- Imunosuppressants (tacrolimus; cyclosporine A)
- Metotrexate
- Cyclophosphamide
- Imatinib
- Tetracyclin
- Colestiramine

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. 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

Their mechanism of action includes primarily the reduction in bone formation, as well as the increase in bone resorption, induction of hypogonadism, increased PTH and a negative calcium balance. 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 %.

According to the American College of Rheumatology, it is important to assess the baseline fracture risk with BMD and FRAX. The treatment with calcium and vitamin D is indicated in low-risk adult patients, while the intermediate and high risk adult patients should add a bisphosphonate, preferably oral. Other second line options are teriparatide and denosumab.

Proton pump inhibitors

Some studies in rats have shown that long-term administration of proton pump inhibitors like omeprazole originates reduced bone density. In humans, 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. Moreover, the use of this drugs seems also to increase the risk of falling, which is a very important issue in the elderly people.
A more recent population-based cohort study in stroke patients using proton-pump inhibitors, showed an increased risk of osteoporosis and of hip and vertebral osteoporotic fractures, also with a pattern of dose-effect. However, the association of these drugs to reduced BMD and mainly to fragility fractures has not been completely clarified.

**Serotonin selective reuptake inhibitors**

The serotoninergic system is known to play a role in bone metabolism, through functional serotoninergic 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. SSRI like citalopram, escitalopram, fluoxetine, paroxetine, sertraline, fluvoxamine, seem to originate bone mass loss and even change bone architecture. 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. 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.

**L-thyroxine**

Despite thyroid hormone (L-thyroxine) being essential for the normal skeletal development and linear growth, its excess in adults, are detrimental for the skeleton because they increase bone resorption, shortening the bone remodeling cycle and causing up to 10% loss of mineralized bone per cycle. Moreover, TSH alone is able to modulate the bone turnover, and when it is suppressed, the bone resorption increases. In thyroid cancer patients on TSH suppressive therapy and with subclinical hyperthyroidism (reduced TSH with normal thyroid hormones), there are conflicting results on BMD reduction especially in men and older populations, but the fracture risk especially hip and vertebral, is increased.

**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 1 summarizes some drug effects on the BMD and fractures.

**Table 1. Effects of drugs on the BMD and fractures**

<table>
<thead>
<tr>
<th>Decrease BMD (lumbar spine/hip)</th>
<th>Increase Fractures (vertebral/non vertebral)</th>
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<tbody>
<tr>
<td>— Corticosteroids</td>
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<tr>
<td>— L-thyroxine</td>
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<td>— Aromatase inhibitors</td>
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<td>— Calcineurin inhibitors</td>
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<tr>
<td>— Selective serotonin reuptake inhibitors</td>
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<td>— Anticonvulsants</td>
<td>— Proton pump inhibitors</td>
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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, 1200 mg and 800–1000 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.

**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

**Trabecular bone score in the diagnosis of osteoporosis**

A major advance in osteoporosis diagnostics is Trabecular Bone Score (TBS), a method to indirectly assess bone structure based on lumbar spine DXA in clinical routine. TBS is a grey-level textural index of bone microarchitecture derived from lumbar spine dual-energy X-ray absorptiometry (DXA) images. It has been accepted by the FDA as a method of osteoporosis diagnosis. Strong correlation between TBS and bone microarchitecture was found. TBS predicts fracture risk independently from BMD, what is particularly important in osteopenic patients. It’s a potential adjustment for FRAX probability. TBS allows for an indirect assessment of the effect of the osteoporotic medications on bone structure.

TBS was assessed from lumbar spine DXA image in Lausanne (D. Hans), blinded from clinical outcome in a group of 16 041 patients of Krakow Medical Centre, including 13 749 women (mean age 61 ± 12 SD). The mean TBS result was 1.263 ± 0.110 SD in women. Mean spine BMD was 0.861 ± 0.16 SD in women. Data regarding prevalent low-energy fractures were available for 1,088 women. In non-fractured group (mean age 67.0 ± 7.6 SD) the mean TBS was 1.241 ± 0.100 SD (partly degraded). In the group with prevalent low energy fractures of any
kind (mean age 70.0 ± 8.2 SD) TBS equaled 1.205 ± 0.100 SD (p < 0.001 after age and BMI adjustment). The mean TBS in the group with prevalent non-spinal fractures was 1.212 ± 0.100 SD and in the group of women with spinal fractures 1.165 ± 0.090 SD (fully degraded) (p < 0.01 after age and BMI adjustment). The highest number of fractures (38.9 %) was in the group with osteoporosis and TBS grade III. In women with normal BMD this was only 2.0 % of fractures. The highest value of ROC curve (0.545) in fracture present prediction occurred for T < −2.5 with TBS > 1.23 operators. OC value for separate TBS and BMB was low (0.6011 and 0.596). TBS and VFA should be incorporated into densitometric measurements in the diagnosis of osteoporosis.

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**Endocrine osteoporosis**

Osteoporosis most often develops from an inadequate peak bone mass, postmenopausal-related bone loss, age-related changes in bone and mineral metabolism; nevertheless, some diseases and drugs may induce low bone mass. Secondary osteoporosis usually manifests itself at much earlier ages, and may even occur in children and young people, depending on its etiology. Another important aspect is that fractures are often repeated and arise in unusual places. It affects about 25 % of children with diseases interfering with the intake and absorption of nutrients (calcium and vitamin D). When such diseases are not diagnosed, empirical medications are even ineffective or suboptimal. Secondary osteoporosis may contribute for 20 to 30 % of osteoporosis after menopause and 50 % or more of cases in men. The prevalence of non-diagnosed generators to bone loss in women with low bone mass or fractures is unknown.

Most of the secondary osteoporosis are associated with endocrine dysfunction. Hypercortisolism (exogenous and endogenous), vitamin D deficiency, type 1 and type 2 diabetes mellitus, hyperthyroidism (endogenous and exogenous), hypogonadism (female and male: exogenous and endogenous) and hyperparathyroidism are the main endocrine causes of bone loss and fractures.

Excessive cortisol in blood (exogenous by glucocorticoid therapy which is by far the most frequent cause of endocrine osteoporosis) may reduce the bone formation and by several other mechanisms may induce osteoporosis and provoke bone fractures. TSH, T4 and T3 may have influence in the bone tissue by acting in the osteoclast and osteoblast cells. Estrogen and androgen hormones deficiencies may also contribute to bone loss and osteoporotic fractures.

Type 1 (T1DM) and 2 diabetes mellitus (T2DM) patients have an increased risk of fragility fractures, but the BMD underestimates this risk in individuals with T2DM; however, bone quality assessed by trabecular bone score (TBS) is decreased as compared to non-diabetic people. Medications (thiazolidinediones, canagliflozin a SGLT2 inhibitor), microarchitecture and macroarchitecture abnormalities may reduce resistance to mechanical stress and bone fractures. By the other hand, hypoglycaemia (induced by insulin or sulfonamide), peripheral neuropathy, orthostatic hypotension, visual impairment, foot ulcers or amputation and vitamin D deficiency may also increase the risk of falling.

Excess of parathyroid hormone may lead to increased bone resorption with hypercalcemia, osteoporosis and fragility bone fractures.

Vitamin D deficiency may lead to osteomalacia — the ratio of mineral to matrix is decreased (ie there is too much matrix relative to the amount of bone) — and an increased number of falls, above all in the elderly, exposing those persons to osteoporotic fractures.

Until the current date, here are no evidence-based guidelines for the clinical and laboratory evaluations of osteoporosis. In young people, certain endocrine diseases that cause osteoporosis may be identified through medical history by the presence certain clinical symptoms and signs at the physical examination:

- hirsutism, wine colored cutaneous marks, in Cushing’s disease or syndrome;
- weight loss and diarrhea in hyperthyroidism;
- renal lithiasis, in primary hyperparathyroidism.

Some endocrine diseases are related to osteoporotic fractures of the hip, such as: corticosteroid therapy, L-thyroxine therapy, hyperthyroidism, hypogonadism, chronic alcohol abuse (may originate several endocrine dysfunctions), which are highly associated with increased morbidity and precocious mortality.

However some medications, such as corticosteroids (the most prevalent etiology of endocrine and secondary osteoporosis), gliazones, serotonin reuptake inhibitors and second generation antipsychotics, antiepileptics, levothyroxine, aromatase inhibitors, GnRH analogs are also contributors to endocrine osteoporosis.

Nevertheless the etiology of osteoporosis may remain hidden unless additional diagnostic testing is performed. The “routine” blood tests are fundamental in the laboratory evaluation of osteoporosis, but depending on the specific clinical context, the following laboratory tests may be requested:

- calcium, phosphorus and calciuria, PTHi and vitamin D;
- TSH, free T4 and free T3;
- total and free testosterone, estradiol, FSH, LH, SHBG;
- 24 h urinary cortisol, blood or salivary cortisol, Screen dexamethasone 1 mg at midnight test;
- HbA1C in diabetes mellitus.

So, individuals with suspicion of or with endocrine osteoporosis should be submitted to a densitometry in order to evaluate the fracture risk and also, in some cases, to diagnose osteoporosis precociously.

Etiological treatment usually increases bone mineral density, thus reducing the osteoporotic fracture risk. In cases of severe osteoporosis and empirical medication in order to diminish the fracture risk may be necessary.