Drug induced osteoporosis

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Abstract

Background: Osteoporosis, that denotes the bone porosity, is the disease, when the bone mineral density (BMD) is decreased. Bones become porous and fragile, that increase the risk of bone fractures. Bone mass loss develops slowly and progressively. Fractures often develop with no symptoms. According to the WHO criteria, osteoporosis is defined as a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of ≤ -2.5 SD). Bone cell elements are represented with osteoblasts, osteoclasts, osteocytes and lining cells of small quantity. Osteoblasts are the bone forming cells. Their major functions are the bone matrix synthesis and its following mineralisation. Vitamin D and calcium also participate in the process of mineralisation. Osteoclasts are the bone resorption cells. Their main function is the breakdown of old bone and its resorption by lysosomal enzymes. Osteocytes are formed from osteoblasts and promote the maintenance of bone matrix. These cells regulate the activity of modeling and remodeling processes. Osteoporosis represents the result of disbalance of breakdown and synthesis.

Method: 200 million new cases of osteoporosis are diagnosed worldwide and this disease causes 8.9 million fractures each year. It is well known fact for physicians that osteoporosis is associated with age, life style (tobacco, alcohol, caffeine) and postmenopausal state. At the same time epidemiological studies reported that many widely used medications were the reason of decrease of the bone mineral density and increase of the fracture risk.

Results: It is important to know that risk of osteoporosis is increased by the use of glucocorticoids, antidepressants, antiepileptic drugs, aromatase inhibitors, gonadotropin-releasing hormone agonists, androgen deprivation therapy, thiazolidinediones, anti-coagulants, calcineurin inhibitors, medroxyprogesterone acetate and proton pump inhibitors.

Discussion: It must be noted that combination therapy with the above mentioned groups of medications is often used that in turn increases the harmful influence on bone tissue. Physicians must foresee the side effects of these groups and monitor the bone mineral density during their long administration and prevent and treat the drug induced osteoporosis, as indicated.

Keywords: Glucocorticoids, Aromatase inhibitors, Thiazolidinediones, Anticoagulants, Calcineurin inhibitors, Medroxyprogesterone acetate, Proton pump inhibitors.

Introduction

Glucocorticoids that are widely used in medicine for treatment of autoimmune disorders and inflammatory diseases, represent one of the risk factors for development of osteoporosis. The reason of decrease of bone mineral density is the sharp increase of osteoclast quantity and bone resorption, as well as osteoblast inactivation and inhibition of the bone formation process¹,².

GCs change the balance between receptor activator for NF-κB ligand (RANKL) and osteoprotegerin (OPG). RANKL is produced by osteoblasts and osteocytes. It’s a key regulator of bone-resorbing osteoclast activation and survival³. Osteoblasts and osteocytes also produce OPG, which is a decoy receptor for RANKL and thus inhibits RANKL from activating osteoclasts. The balance between RANKL and OPG is a key deciding factor of how much bone resorption is and will be happening (more RANKL = more bone breakdown; more OPG = less bone breakdown). Glucocorticoids tip this balance strongly in favor of RANKL.

Glucocorticoid related bone loss is also caused by decrease of calcium resorbtion, growth hormone suppression and changes in parathyroid pulsatility.

BMD drops 6-12% within the first year of glucocorticoid use, and approximately 3% per year following. Fracture risk escalates up to 75% within the first 3 months⁴.
Some of glucocorticoid group drugs with 7.5 mg daily dose increases 5 times the vertebral and femoral neck fractures risk, while the dose of 10 mg for more than 90 days’ duration increases 17 times vertebral fractures risks. Fracture risk is markedly increased in postmenopausal women and old men, when medication daily dose reaches 20 mg. Additional risk factors are low body mass, tobacco, alcohol and intravenous steroid use. After glucocorticoid withdrawal the fractures risk gradually decrease and return to the pretreatment level in 1-2 years.

There is consensus in the guidelines to recommend a baseline BMD measurement or FRAX (Fracture Risk Assessment Tool) analysis before the initiation of GC. Vitamin D, calcium, renal and hepatic panels are additional studies recommended at baseline and before the decision to prevent or treat GC-induced bone loss.

Bisphosphonates are currently the standard of care for prevention and treatment of GC-induced bone loss15. Denosumab improves the BMD of patients with rheumatoid arthritis receiving oral GCs (average dose ≤ 15 mg/day) and may be considered an alternative therapy for appropriate patients.

Antidepressants

Selective serotonin reuptake inhibitors and monoamine oxidase inhibitors are used for treatment of depression, also for generalized anxiety disorder, eating disorders and premenstrual syndrome.

Medications from this group inhibit the dopaminergic production and increase the level of prolactin in blood (hyperprolactinemia)7,8,9,10, which in turn decrease the secretion of sexual hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH) on hypothalamic-pituitary-gonadal axis (HPA). By inhibition of HPA axis hormones the levels of estrogen, progesterone and testosterone are decreased in blood.

Since estrogen and progesterone play very important roles in maintaining healthy bones in women, inhibiting their production by inhibiting that of FSH and LH causes bone loss. Estrogen prevents excessive activation of osteoclasts (the specialized cells that break down old bone), while progesterone activates osteoblasts (the specialized cells involved in building new bone), plus both hormones exert a number of other bone-protective effects. This is why the drop off in the production of estrogen and progesterone that occurs with menopause contributes to bone loss.

Several studies reported increased fracture risk is highest for postmenopausal women and older men.

According to the current recommendations, it is advisable to check the level of prolactin and sexual hormones during treatment with medication from this group. Calcium and vitamin D supplements administration during long term treatment with selective serotonin reuptake inhibitors represents the prevention of BMD decrease. At the same time patients who experience other additional risk factors during the treatment with medications from this group must be checked by dual energy X-ray absorptiometry (DXA) scan and FRAX analysis.

Antiepileptic drugs (AEDs)

The drugs of antiepileptic group are used for the treatment of epilepsy, also severe headache, psychiatric disorders and neuropathies. AEDs accelerate inactivation of vitamin D which decreases calcium uptake, drives secondary hyperparathyroidism and accelerates bone loss10,11. Most studies have concluded that AEDs are associated with a moderate to severe risk of fractures with prolonged use.

It is recommended to check vitamin D in blood once per 6-12 months12 and screen for osteoporosis by DXA scan and FRAX analysis during administration of medications from this group.

It is advisable to administer adequate amount of vitamin D and calcium in all patients during the treatment with antiepileptic drugs and also inclusion of bisphosphonates in treatment schemes of those patients who have high risk of fractures during assessment13.

Aromatase inhibitors (AIs)

Effective adjuvant hormonal therapy implies administration of aromatase inhibitors in postmenopausal women with estrogen receptor positive breast cancer. AIs decrease the estrogen level in blood via blocking the enzyme - aromatase (that can create estrogens from androgens) that is followed by sharp decrease of estrogens and bone mass loss14.

As it was already mentioned estrogens play an important role in female bone homeostasis, in the estrogen deficient state bone resorption is increased.

According to current recommendations DXA monitoring and administration of vitamin D and calcium supplements are advised during the aromatase inhibitor treatment.

Clinical trial evidence indicates that intravenous15,16 and oral bisphosphonates17,18 are effective in maintaining BMD in breast cancer patients receiving hormonal (endocrine) therapy. Denosumab is an alternative prevention and treatment strategy for AI-induced bone loss.

Gonadotropin-releasing hormone agonists (GnRHs) and androgen-deprivation therapy (ADT)

Gonadotropin-releasing hormone agonists are widely used in premenopausal women with breast cancer, also in women with ovarian polycystic syndrome, endometriosis, and in men with prostate cancer. Androgen-deprivation therapy provides a survival benefit to men with invasive or metastatic prostate cancer. The medications of these groups decrease the estradiol and testosterone production by influence on luteinizing hormone and follicle-
stimulating hormone, that in turn causes the decrease of bone mineral density. The studies established that BMD is decreased by 2-5% after 1 year of deprivation therapy, and vertebral and femoral neck fracture risk is increased by 20-50% after 5 years of treatment.20

Current recommendations, in addition to calcium and vitamin D supplementation, include DXA evaluation. Bisphosphonates can prevent and treat ADT-induced bone loss.20

For retaining the bone mineral density bisphosphonates and in particular cases estrogen with gonadotropin releasing hormone agonists therapy are recommended in premenopausal women, and antiandrogens and bisphosphonates are recommended during the androgen deprivation therapy in men.

Selective estrogen receptor modulators, denosumab and additional administration of antiandrogens represent the alternative treatment according to the risk factors.

Thiazolidinediones (TZDs)

Type 2 diabetes mellitus patients are widely prescribed drugs called thiazolidinediones, which increase insulin sensitivity via activation of peroxisome proliferator–activated receptor (PPAR)-γ receptors. Numerous studies have demonstrated that activation of PPAR-γ in mesenchymal stem cells (the precursor cells that live in bone marrow and can become either osteoblasts, which build new bone, or adipocytes, which store fat) causes them to become fat cells instead of osteoblasts.

TZDs may act on bone remodeling by increasing adiposity of bone marrow, decreasing aromatase activity, and promoting osteoclast differentiation, leading to increased bone resorption. Thus, TZDs reduce bone formation and increase bone resorption, increasing osteoporosis and fracture risk.21,22

Before starting TZDs, patients should be evaluated for fracture risk by FRAX analysis or DXA scan. In case of high fracture risk, it is necessary to withdraw the thiazolidinedione treatment and in case of established osteoporosis administration of this group must be avoided.

It must be noted that currently there is no convincing strategy to decrease the thiazolidinediones caused fractures’ risk.

Anticoagulants

Heparin is widely used for venous thrombosis prevention and treatment. There are several types of heparin, including unfractioned heparin and low molecular weight heparin. Low molecular weight heparins, appear to be the least harmful to bone.23

Although short-term use is not associated with reductions in BMD or increased fractures, long-term use leads to reductions in BMD and increased fractures.

Vitamin K-dependent posttranslational modification of glutamate to gamma-carboxyglutamate is a biochemical feature of the vertebrate blood-clotting cascade. This conversion activates clotting factors and bone proteins, including osteocalcin, a widely accepted marker of osteoblastic activity. Vitamin K antagonists, such as warfarin, inhibit this process.24

Part of the studies indicate that warfarin has negative influence on BMD, but the second part of studies oppose this fact.

At this time, data are inconclusive as to the impact of warfarin on bone. Calcium and vitamin D supplement administrations are used for prevention and treatment.

Calcineurin Inhibitors

Calcineurin Inhibitors are used in transplantology, often in combination with glucocorticoids for suppression of immune system during organ transplantation to avoid rejection of transplanted organ.

These drugs markedly increase bone resorption via two mechanisms: they disrupt vitamin D metabolism and therefore calcium absorption, and cause secondary hyperparathyroidism.

Secondary hyperparathyroidism occurs as a protective response when calcium levels drop too low in the bloodstream, which they do when vitamin D is deficient or its metabolism is disrupted. In response, parathyroid hormone is secreted to trigger calcium release from bone, so calcium can be restored to its required levels in the bloodstream. When parathyroid levels are continuously elevated, calcium gets continuously withdrawn from bone.25,26

Guidelines from the National Kidney Foundation support BMD evaluation with DXA prior to transplantation and 1 and 2 years post transplantation. If the T score is -2.0, in addition to calcium and vitamin D supplementation, bisphosphonates are indicated.27

Depot medroxyprogesterone acetate (DMPA)

Depot medroxyprogesterone acetate with intramuscular and subcutaneous administration once per 3 months is widely used in women for contraceptive purposes. This group inhibits the gonadotropin secretion and impedes the ovulation and decrease the estrogen production which leads to BMD decrease.28

Bone tissue decrease intensity is more pronounced during 2 years after starting the treatment.

All patients who use long acting medroxyprogesterone acetate must be checked for vitamin D level in blood and administer calcium and vitamin D supplements. Many scientific studies confirmed that low dose estrogen in combination with DMPA prevents the decrease of BMD in premenopausal women.29

Proton pump inhibitors (PPIs)

Proton pump inhibitors reduce the production of acid by blocking the enzyme in the wall of the stomach that
produces acid. These drugs are used in the treatment of esophageal, duodenal and stomach ulcers, gastroesophageal reflux disease, as part of Helicobacter pylori eradication therapy, gastrinomas and other conditions that cause hypersecretion of acid including Zollinger–Ellison syndrome. Some evidence indicates that acid suppression may reduce calcium absorption and thereby lead to an increase in the risk of fracture, though this is controversial.\textsuperscript{30,31} It was reported, that long-term PPI therapy, particularly at high doses, is associated with and increased risk of hip fractures.\textsuperscript{32}

Patients on PPIs should also be on calcium and vitamin D supplementation.

References