**REVIEW ON THE PHARMACOLOGY OF OSTEOPOROSIS**

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**Abstract:** Osteoporosis is a progressive metabolic disease that affects bone system and represents a major health concern of the 21st century. The biggest consequence is the osteoporotic fractures that contribute with severe health complications such as pain, disability, lower quality of life and even increased rate of mortality.

The purpose of this review is to provide information about prevention and treatment of this silent disease. Non-pharmacological strategy and impact of most important life habits and nutritional supplements used for prevention are accentuated. Different pharmacological treatments are described that can improve the bone mass by reducing osteoclasts activity or by promotion of bone formation through stimulation of osteoblasts activity. The article contains information about mechanism of action of the most used drugs for treatment of osteoporosis. The main goal is the strategy for prevention and therapy that will improve bone mass density and reduce the risk of osteoporotic fragility.

**Keywords:** postmenopausal, osteoporosis, bisphosphonates, food additives

**Introduction**

Osteoporosis is a progressive, metabolic disease which is characterized by reduced bone mass and microstructure deterioration on the bone tissue. World health Organization (WHO) defined osteoporosis as a reduction in bone mineral density (BMD) of a 2.5 standard deviation or more below that of the mean peak BMD of young adults when measured by dual-energy x-ray absorptiometry [1]. Diagnostic criteria of osteoporosis based on BMD measurement expressed as T-score is:

- Normal BMD: Bone density is within 1 SD (+1 or -1) of the young adult men.
- Osteopenia: T-score of between -1 and -2.5
- Osteoporosis: T-score of -2.5 or below
- Severe osteoporosis: T-score -2.5 associated with one or more fractures.

The most common consequence is the risk of bone fractures that can occur even due to insignificant trauma and leads to a decreased quality of life of the osteoporotic patients. It affects millions of people annually and lead to nearly 3.5 million fractures in Europe. Bone fractures may occur in any part of the skeletal system but most often they are localized in vertebral sites, hips and wrist. Depending on the location, osteoporotic fragility may be associated with pain, reduced independence, hospitalisation and increased mortality rate especially in cases when hip and spine are affected. With the extension of lifespan the incidence rate associated with osteoporosis is expected to take large swing [2].

Therefore it is very important for patients to be timely prevented and treated with appropriate medications.
Skeletal system is metabolically active tissue that is constantly remodeled through the process of bone resorption and formation. The basic cells that participate in bone remodeling are osteoclasts and osteoblasts. Through the action of osteoclasts the bone is degraded, process known as bone resorption, following by the action of osteoblasts which synthesize new bone tissue (bone formation). Osteoporosis occurs when bone resorption exceeds the process of bone formation and results with microstructure deterioration and lower bone density [3].

Many factors are involved in the aetiology of the disease. A combination of endocrine, genetic and environmental factors have a major influence. From endocrine factors the most important role have hormones such as estrogen in women and androgen in men, glucocorticoids, thyroid hormones, and the hormones of parathyroid gland - calcitonin and parathormone [3]. Genetic factors have also big influence in regulation of bone mass and in progression of the disease. Life habits, physical activity from the earliest age and the way and the type of nutrition contribute with the quality of the skeletal system.

Osteoporosis can be classified in two basic categories: primary and secondary [3].

The first group is comprised from post-menopausal women and the second type is osteoporosis that occurs among adult population. Postmenopausal women are the most risky group of population that suffers from low bone density. The risk is deeply related with deficiency of oestrogen hormones which play an important role in the maintaining on mineral density. Menopause is a physiological condition related to age that is associated with decline in estrogen levels. After the ovarian function has been discarded the only source of estrogen hormones remains adrenal gland that converted androgens to estrogens in the fatty tissue. Estrogen hormones have a direct simulating activity on osteoblast cells. Decline in oestrogen levels lead to progressive decrease in bone density [4].

Osteoporosis as an age related disease among elderly population also is known as senile osteoporosis and affects both sex equally. Reduced bone mass is associated with reduced gastrointestinal absorption of vitamin D and calcium, and decreased function of osteoblast cells. The occurrence of secondary osteoporosis is most commonly associated with other co-existing medical conditions or as a consequence from the use of a range of drugs. The most common causes of secondary osteoporosis include endocrine disorders (hypogonadism in either sex, hyperthyroidism; hyperparathyroidism; hyperprolactinemia), gastrointestinal (mal-absorption; coeliac disease; bowel disease), rheumatological (rheumatoid arthritis); hematological and respiratory disease. From the list of medications causing secondary osteoporosis are long term use of glucocorticoids, aromatase inhibitors, anticoagulants and gonadotropin releasing agonists [5].

**Osteoporosis prevention**

Pharmacological treatment plays the main role for osteoporosis and the drug choice strongly depends of the severity of the disease. But before starting with the drugs it is important to make change in some lifestyle habits that have negative impact on the bone health. Leading an active healthy life, good general nutrition, reducing or stop smoking, avoiding alcohol consumption and taking adequate nutritional supplements have a pivotal role in maintaining of the bone health.

Physical activity is a non-pharmacological strategy for prevention of osteoporosis. There are many evidence from trials that asses the positive effect of exercise on BMD especially on proximal femur and lumbar spine [6]. Regular physical activity contribute to better geometry and quality of bones in adulthood and maintains bone strength at older age that lead to decreased risk of osteoporotic fragility.

Smoking is a risk factor for osteoporosis that impacts indirectly the BMD. It decreases intestinal absorption of calcium and leads to low estrogen levels which contribute to lower bone strength [7].

Calcium and vitamin D have an important role in preventing of osteoporotic fragility.
Combined treatment with calcium and vitamin D results in significant reduction on vertebral, non-vertebral, and hip fractures [8]. It is generally recommended daily intake of 1000 mg calcium and 800 IU of vitamin D [9]. Recent studies have shown that prolonged calcium intake leads to deposit of calcium in the blood vessels and increased risk of cardiovascular diseases [10]. Calcium and vitamin D supplements should be considered only in patients with inadequate calcium intake. Dairy products remain the best source of calcium.

**Pharmacological treatment of osteoporosis**

Pharmacological agents used for treatment of osteoporosis are classified on: antiresorptive and anabolic agents. The antiresorptive agents are: bisphosphonates, denosumab, estrogen hormone, selective estrogen receptor modulators, calcitonin, strontium ranelate and calcitriol. These agents realized their pharmacological effect by inhibiting the osteoclast activity providing increased bone density making higher quality of the bones. Anabolic agents as teriparatide and abaloparatide perform their function by stimulating osteoblast activity.

- **Antiresorptive agents**
  - **Bisphosphonates (BP’s)** are the first-line and most widely used antiresorptive medications mainly prescribed for treatment of postmenopausal women, osteoporosis in men and treatment of glucocorticoid-induced osteoporosis. BP’s are classified into two subclasses: nitrogen-containing bisphosphonates which include alendronate, ibandronate, risendronate and zoledronate, and non-nitrogen containing bisphosphonates - etidronate. All BP’s inhibit osteoclasts activity by binding with high affinity to hydroxyapatite crystals in bones but their mechanism of action is different. Nitrogen containing bisphosphonates inhibit the enzyme farnesyl diphosphate synthase that is involved in prenylation of small guanosine triphosphatases signaling proteins. This leads to impaired function of the proteins responsible for different cell process, important for the function of osteoclasts. At higher concentrations they can induce apoptosis of osteoclasts. Non-nitrogen containing bisphosphonates are metabolized into non-hydrolysable analogs of adenosine triphosphate, a non-functional molecule that competes with adenosine triphosphate and initiates apoptosis of osteoclast cells [11].

  Oral bisphosphonates are poorly absorbed and on ideal condition the absorption is less than 1%. They must be taken on an empty stomach with 200 ml of plain water, and the patient should stand upright for at least 30 minutes. Consumption of food, drinks, drugs and nutritional supplementas magnesium, iron or calcium, should be avoided because they reduce the absorption of the BP’s. This type of drugs are contraindicated in hypersensitive patients and in hypocalcaemia. They should be used with caution in patients with chronic kidney disease (glomerular filtration rate < 30-35 ml/min). Oral bisphosphonates are contraindicated in patients with upper gastrointestinal diseases such as dyspepsia, esophagitis and esophageal varices. Some rare adverse effects of BP’s are noticed as for example osteonecrosis of the jaw [12]. In patients with dental disease or other risk factors as poor dental hygiene, invasive dental procedures they should be taken with caution.

  Intravenously administered bisphosphonates might induce an acute-phase reaction in 30-40% of the patients taking their first dose. This acute-phase is characterized with fever, bone and muscle pain lasting for several days. The symptoms of the acute-phase can be reduced and treated with acetaminophen.

  **Denosumab** is approved for treatment of osteoporotic fragility only in postmenopausal women and men who are at increased risk of fractures with BMD T-score <-3 or below, in patients who are intolerant, contraindicated or unable to comply with the complex instructions for administration of BP’s, or have renal failure [13]. Denosumab is not recommended for use in premenopausal women and pediatric patients younger than 12 years, or as prophylaxis of osteoporosis.
Denosumab is a fully humanized monoclonal antibody (IgG2), produced by recombinant DNA technology. This biological drug binds with high affinity to Receptor Activator of Nuclear factor Kappa β Ligand (RANKL) and inhibits the binding of RANKL to RANK and reduces the differentiation of precursor cells into mature osteoclasts [14].

Before initiating treatment with denosumab patients must be supplemented with adequate doses of calcium and vitamin D and monitored for calcium levels before each dose and two weeks after the initial dose. No dose adjustment is required in elderly people >65 years old and in patients with renal impairment.

The most common reported adverse effects include skin infections (rashes and eczema), musculoskeletal disorders (musculoskeletal pain, pain in extremity), gastrointestinal disorders (constipation and discomfort in abdomen) and urinary tract infection. As a rare adverse effect osteonecrosis of the jaw and atypical femoral fracture has been reported.

It reduce the risk of vertebral, non-vertebral and hip fractures [15]. The effect of the therapy with denosumab is observed one month after initiation the treatment and the beneficial effect lasts only 4-6 months. After stopping the treatment BMD decreased rapidly.

**Hormone replacement therapy**

The occurrence of osteoporosis in postmenopausal women is associated with decreased synthesis and function of estrogen hormones [16]. These hormones act through the estrogen receptors located on the surface of osteoblasts and osteoclasts. Their anabolic effect is manifested by stimulating of osteoblasts on one side and increase of calcitonin level on the other side which leads to suppression of the osteoclasts activity. Estrogen enhances the osteoblastic production of osteoprotegerine that has high ability to bind to the RANKL and block the RANKL/RANK interaction required for activation of osteoclast cells.

Hormone replacement therapy is mainly used for preventing vasomotor symptoms in postmenopausal women. It is not recommended as a first line therapy. Treatment with hormone therapy leads to increased risk of venous thromboembolic disorders, hearth stroke, risk of breast and endometrial cancer [17]. Tibolone is an estrogen-progestin replacement therapy used for prevention and treatment of vasomotor symptoms in postmenopausal women. It has shown beneficial effects on reduction in vertebral and non-vertebral fragility [18].

**Selective estrogen receptor modulators (SERM’s)**

Selective estrogen receptor modulators are non-steroidal synthetic drugs with agonist-antagonist activity in various organ systems of the human body. They act as estrogen agonists in bones and cardiovascular system and as estrogen antagonist at breast and endometrium [19]. SERM’s are mainly used for treatment of postmenopausal osteoporosis with high risk of breast cancer. Raloxifene is the most used SERM’s with high ability to bind to oestrogen receptors and to stimulate bone formation. Raloxifene reduce the risk of vertebral fractures, and has no effect on non-vertebral fractures [20]. The most common adverse effects of raloxifene include hot flashes and venous thromboembolism.

**Calcitonin**

Calcitonin is 32 amino acid polypeptide hormones that is secreted by perifollicular C-cells of thyroid gland, and has a main role in maintaining the calcium homeostasis. The receptors for calcitonin (CT) exist not only in osteoclasts but also in the renal tract epithelium, brain, stomach, ovary, in skeletal muscles and may exert different effects and biological functions. It reduce bone turnover and improve bone density and microarchitecture [21]. The activated CT receptor provides a pain relief on osteoporotic fracture.

Calcitonin for osteoporosis treatment is considered as a second line therapy in patients who are intolerant, or when the first line therapy has failed. It is recommended for treatment of
osteoporosis in women after 5 years of menopause. Calcitonin improves the BMD and reduces the risk of vertebral fractures in postmenopausal women [22].

In 2012, the European Medicines Agency completed a review of the benefits and risks of calcitonin-containing medicines, concluding that there was evidence of a small increased risk of cancer with long-term use of these medicines. The benefit-risk balance remains positive only for the following uses: treatment of Paget’s disease for patients who cannot be treated with alternative treatments; prevention of acute bone loss due to sudden immobilization such as in patients with recent osteoporotic fractures; treatment of hypercalcemia caused by cancer. However the Agency’s Committee for Medicinal products for Human Use (CHMP) recommended that even for these uses, calcitonin treatment should be given for the shortest possible time using the smallest effective dose [23].

**Calcitriol**

Calcitriol – 1,25-dihydroxyvitamin D is a synthetic, active form of vitamin D prescribed for osteoporosis in postmenopausal women and osteoporosis induced by long-term use of glucocorticoids [24]. Calcitriol, as an active form, realizes the pharmacological effect by binding to vitamin-D receptors expressed in bones, kidneys, parathyroid gland and intestines. As a result of interaction with the receptors it increases calcium serum level by stimulating intestinal calcium absorption, reabsorption in kidney and mobilization of calcium from hydroxyapatite crystals in bones. It stimulates osteoblast cells to produce RANKL a master driver for differentiating osteoclast precursors to mature osteoclast. But the effects of active vitamin D in vivo and in vitro on bone resorption are opposite. In vivo studies have shown that active vitamin D metabolites suppressed RANKL in osteoblasts and prevent failure in bone mineralization [25]. Calcitriol is administered orally and intravenously. The most common adverse effect is hypercalcemia and it is recommended monitoring of serum calcium and phosphorus levels during therapy.

**Strontium ranelate**

Strontium ranelate is an antiresorptive agent used for treatment of severe osteoporosis in men and postmenopausal women who are at high risk of fractures. It is considered as a second line therapy only in patients who are intolerant to others pharmacological agents. Its antiresorptive effect is achieved by inhibition of osteoclast activity and it provides better bone quality and strength [26]. The most common adverse effects are myocardial infarction, cardiovascular disorders, venous thromboembolism, and gastrointestinal discomfort and is not recommended in patients with previous history of the indicated diseases. In 2017 the manufacturer of strontium ranelate, Servier, withdrew it from the market for commercial reasons. Most probably it was withdrawn because of safety concerns. Any benefit of strontium in fracture prevention is outweighed by the risks of cardiovascular events and venous thromboembolism [27].

**• Anabolic agents**

Anabolic agents used for treatment of osteoporosis are considered only in cases when patients have severe osteoporosis with a high risk of fractures, osteoporosis induced by glucocorticoids or intolerability to other antiresorptive drugs [28]. The only approved anabolic agents used for osteoporosis are teriparatide and abaloparatide.

Parathyroid hormone is secreted by parathyroid gland and participate in maintaining of calcium homeostasis. It increases serum calcium via several pathways, by promotion of osteoclast action to release calcium from bones, increasing calcium absorption from intestinal tract and renal reabsorption. Continuous administration of parathyroid hormone leads to increased bone resorption while intermittent use results with increased osteoblast activity and has anabolic effect [29]. It exerts its effect via binding to PTH/PTHrP type 1 receptor exposed on the osteoblast surface [30].
Teriparatide is a recombinant human parathyroid hormone; stimulator of bone remodeling that improves bone density by stimulating osteoblast activity. Abaloparatide is an analogue of parathyroid hormone and currently is approved only in the United States. Both agents are administered by subcutaneous injection. The safety of treatment with teriparatide and abaloparatide is limited to duration of 24 months because it has been demonstrated to induce osteosarcoma among animals in preclinical studies [31].

Discussion

Bone health care should begin in the period of adolescence when bones achieved their peak mass and to continue through life. Leading a healthy life is the basis of prevention from the emergence of this silent disease. Regular physical activity is the first step of non-pharmacological strategy that plays an important role for healthy and strong bones. Good general nutrition abounded with sufficient intake of vegetables and fruits satisfies daily necessary intake of vitamins and minerals. In cases when patients have poor nutrition diet it is recommended additional intake of supplements. Calcium and vitamin D have the most important role for maintaining bone health and different types of medical supplements are available on the pharmaceutical market. Early recognition and timely treatment of the disease is the main key for good therapeutic success. Recognition of risk group patients with family history contributes with the effectiveness of the therapy. The correct assessment of the disease and the proper choice of a drug might improve the bone mass and reduce the possibility of future fractures. Patients with history of osteoporosis and fractures among members of the family, low bone mass index and low body weight should be consulted about the essence of the disease and possible consequenc-es and benefits of adherence to non-pharmacological and pharmacological treatment. Among patients with diagnosed osteoporosis, pharmacological treatment is required to improve bone quality and prevent the risk of fractures. First line choice for treatment of osteoporosis is oral BP’s because of their proven efficacy, safety and low cost. They are one of the most commonly used drugs for osteoporosis treatment. In patients who are intolerant to BP’s or who cannot comply with their complex instruction of use, or have diagnosed severe osteoporosis with high risk of fractures as a second-line therapeutic drugs are considered other antiresorptive or anabolic agents described in this review. They are carefully selected depending on the severity of the disease as well as other co-existing medical conditions for each patient individually.

Conclusion

Routine control of osteoporosis, especially in risk population with family history and postmenopausal women allow early detection of the disease and timely initiation of therapy that would contribute to a low rate of osteoporotic fractures and better quality of life.

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