

Recent advances in prophylactics and treatment of osteoporosis

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Abstract

Recently, a dramatic increase in the average life expectancy has been noted, regarded as the one of the greatest achievements of the last decades, but in consequence osteoporosis affects millions of people all over the world. Currently osteoporosis is defined as a skeletal disorder characterized by compromised bone strength which leads to an increased risk of fractures. The most commonly used tool to evaluate the 10-year risk of fractures is the fracture risk assessment tool validated in many independent cohorts. Osteoporosis itself has no symptoms, but fractures are common symptoms of osteoporosis which can result in disability and mortality. Hence, osteoporosis is called a silent epidemic as well as a silent killer. The best way to assess patients with osteoporosis is by using the most widely employed techniques – dual-energy X-ray absorptiometry or quantitative computed tomography. There are a lot of precisely documented risk factors of osteoporosis – e.g. cigarette smoking, alcohol use, getting little or no exercise, being small-framed or thin, a diet low in foods containing calcium and vitamin D – and their limitation or elimination is the best way for prophylactics of this dangerous disease. Some other risk factors such as age and sex of patients should not be omitted in the decision making process. In the literature there are numerous therapeutic proposals and different guidelines. In this review we present the recent advances in the prophylactics and treatment of osteoporosis.

Key words: osteoporosis, risk factors, prophylactics, treatment.

Introduction

Osteoporosis is a disease which is characterized by low bone mass resulting in increased risk of bone fractures that occur with low or minimal trauma, such as fractures occurring after falling from a standing position. Osteoporosis occurs most commonly in postmenopausal women [1]. Isolated low bone density and its influence on fractures in young women have no established clinical significance [2]. Bone fragility is an effect of decreased bone mineral density, that alters bone geometry and microarchitecture [3]. According to World Health Organization (WHO) recommendations, osteoporosis should be diagnosed upon results of bone mass density (BMD) measurements compared with the young adult reference population. An analysis of BMD during life span in women revealed that maximum bone density is achieved at the proximal femur in their 20s and at the spine and forearm around the age of 30 [4]. After that time bone loss starts in the perimenopausal period and is related to ovulatory disturbances. Women with a history of premenopausal fracture are in the group of higher risk of fracture during the postmenopausal pe-

riod [5]. The case of association of bone loss with normal pregnancy remains controversial [6]. Nevertheless, lactation has more consistent and profound effects on bone density and is related to the duration of lactation and amenorrhea [7]. Circulating calcitonin, estrogen deficiency and parathyroid hormone-related protein are involved in bone mass loss in breastfeeding women [8]. Pregnancy and lactation-associated osteoporosis (PLO) is a rare condition of no known cause. Some studies suggest a strong genetic component of PLO [9]. Systematic reviews revealed an annual hip fracture rate from less than 100–600 per 100 000 and a vertebral fracture rate from 100–1400 per 100 000 depending on the region. The highest rates of hip fracture occurred in Scandinavia but the highest rates of vertebral fracture occurred in South Korea and in the United States [10]. There is a large number of risk factors responsible for the development of osteoporosis: advanced age, previous fracture, long-term glucocorticoid therapy, inflammatory bowel disease and celiac disease, premature ovarian failure and hypogonadotropic hypogonadism, low body weight, cigarette smoking, excess alcohol in-

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take, long-term GnRH analog treatment due to cancer disease, early oophorectomy due to cancer treatment, race (higher risk in White than others) [11]. Regarding risk factors for osteoporosis, other causes of decreased bone mass should also be considered. Bone fractures can be caused by osteomalacia or malignancy, or decreased levels of estrogens during menopause. Physical abuse should always be taken into account as a cause of fracture. Also chronic kidney diseases should not be omitted as a potential risk factor [12].

Osteoporosis screening

There can be established a probability of hip fracture and major osteoporotic fractures within 10 years, for untreated patients between the ages of 40 to 90, based on the evaluation of risk factors indicated above and femoral BMD. The so-called fracture risk assessment tool (FRAX) was created at the University of Sheffield in 2008. Since then, FRAX has been validated in approximately 26 independent cohorts including data from large observational studies. Although FRAX is a useful tool for bone fracture prediction it should not be used for monitoring results of the therapy [13]. Bone mineral density in conjunction with established risk factor assessment is then the best tool for osteoporosis screening [14]. Nevertheless, low BMD is a bone fracture prediction factor independently of the technique used for the assessment [15]. Testing all women at 65 or older and those with clinical risk factors is suggested. Bone mass density is measured by dual-energy X-ray absorptiometry (DXA) [16]. Many studies have demonstrated that low DXA is a good diagnostic tool for osteoporotic fracture prediction and is used widely both for screening and for osteoporosis treatment monitoring [17]. Other techniques being practiced in osteoporotic screening are quantitative computed tomography and quantitative heel ultrasound, but they are not recommended for osteoporotic screening because WHO criteria for the diagnosis of osteoporosis are based on BMD measured by DXA [18]. The effectiveness of osteoporosis screening has been evaluated and there was a reduction in hip fractures compared to controls [19]. Results of trials revealed that quality of BMD measurements together with risk factors analysis, appropriate treatment and compliance of patients are responsible for successful osteoporosis screening [20]. A meta-analysis of randomized controlled trials concluded that BMD measurements together with subsequent osteoporosis treatment reduces osteoporotic fractures but no difference in all-cause mortality has been observed [21]. Cost effectiveness of osteoporosis screening is related to the differences in health care costs and varies among the countries [22]. There is a question of how often BMD measurements should be repeated. It is obvious that it would depend on the presence of osteoporosis risk fac-

tors and the results of initial measurements. In short, patients with low bone mass (T-score -2.00 to -2.49) and/or with the presence of risk factors for bone loss ongoing measurements of BMD should be advised every two years. Patients with a T-score of -1.50 to -1.99 should be tested in three to five years and finally patients with a normal or slightly low T-score and with no risk factors should undergo BMD measurements at a 10- to 15-year interval [23]. It is important that osteoporosis screening should be focused on identification of individuals at increased risk of low trauma bone fracture and involve all women at 65 years of age or older and younger women with risk factors present. The basic tool for BMD measurements should be DXA. Patients during therapy of osteoporosis or with clinical factors that can cause accelerated bone loss should undergo BMD evaluation more often. Three- to five-year intervals seem to be effective enough [24]. The bone fracture usually is the first clinical manifestation of osteoporosis and no other symptoms are present. Even painful bones or aches usually are not symptoms of the disease. Pain is quite often a symptom of osteomalacia. The most common symptoms of osteoporosis are bone fractures. Vertebral fractures caused by osteoporosis are usually asymptomatic and diagnosed incidentally on the abdominal or chest radiograph. Other bone fractures including hip fractures in older women are relatively often caused by excessive bone mass loss [25]. Always the evaluation for the risk of osteoporosis should start with the history and a physical examination which could exclude most of the conditions causing osteoporosis. Fragility factors are very important when evaluating the problem. Risk for another fracture in the next year is approximately 19% in women with vertebral fracture. Thus this group of patients requires further evaluation and treatment. In women with a T-score below -2.5 or with risk factors biochemical tests should be recommended (biochemistry profile including calcium, phosphorus, albumin, total protein, liver enzymes, creatinine, vitamin D and complete blood count) [26]. These laboratory tests may exclude other causes of osteoporosis such as renal, liver disease, thyroid or parathyroid or adrenal diseases, hypoestrogenism, and celiac disease [27]. Quite often after the initial blood test patients may require further evaluation in order to exclude or include renal function abnormalities, gastrointestinal disorders, cancer or multiple myelomas or Cushing's syndrome. In contrast, markers of bone turnover have no established role in the care of individual patients although they may be helpful in understanding the mechanism of action of therapeutic agents [28].

Pharmacological treatment of osteoporosis

As osteoporotic fractures cause significant morbidity and mortality this disease constitutes a major public

health problem and after precise osteoporotic screening the proper pharmacological treatment plays the crucial role. Everyone should remember that in clinical practice lifestyle measures should be adopted universally to reduce bone loss both in men and women. These measures include sufficient calcium and vitamin D supply, exercise such as weight-bearing physical activity, quitting smoking and limiting alcohol consumption. These recommendations have a documented beneficial effect on human bones [29–31]. Osteoporosis is typically associated with women, though this disease is an important and frequently overlooked problem in men. Although the risk of hip fracture is lower in men than in women, the risk of death is significantly higher in men. For men with osteoporosis pharmacological treatment is advised and bisphosphonates are the first-line agents for treating this disease, but for men with severe osteoporosis recombinant human parathyroid hormone preparations, such as teriparatide, are an acceptable option. For men with hypogonadism testosterone therapy is considered beneficial [32, 33].

The available therapies for osteoporosis are presently divided into two groups.

Anti-resorptive agents

Bisphosphonates

Bisphosphonate (alendronate, risedronate, ibandronate and zoledronic acid) preparations are used for both prevention and treatment of osteoporosis. The most frequently prescribed oral bisphosphonate is oral alendronic acid. It is important that this drug is taken correctly. The recommended way of treatment is as follows: in the morning with a glass of water, 45 min before food and remaining upright for about 30–60 min after the dose. This method of treatment allows one to avoid upper gastrointestinal side effects. However, there are patients who are unable to tolerate oral bisphosphonates (malabsorption or dysphagia); then intravenous bisphosphonate-zoledronic acid is a potential alternative. This drug has generally been used annually [30–32, 34].

Denosumab

Denosumab (PROLIA) is a human monoclonal antibody (IgG2), genetically engineered in hamster ovary cells. This antibody has high affinity and specificity for the human receptor activator RANKL, blocking its receptor RANK and in consequence inhibiting osteoclast formation, function and survival, thereby finally decreasing bone resorption. Denosumab is not recommended as initial therapy for most patients with osteoporosis but with exceptions at high risk for fractures. It is advised to administer the drug as a subcutaneous injection once every six months. The results from many clinical trials have shown that the treatment with deno-

sumab leads to increased BMD and finally to reduction in risk of many fractures. In cases when denosumab is discontinued an alternative therapy with bisphosphonates is a good option [30, 35].

Selective estrogen receptor modulators

Selective estrogen receptor modulators (raloxifene, tamoxifen) are used primarily for the prevention and management of breast cancer. At the same time these compounds show an antiresorptive estrogenic effect on the skeleton. Selective estrogen receptor modulators advised in osteoporosis are not without side effects such as thromboembolic events and possibly hot flashes. Selective estrogen receptor modulators are usually chosen for osteoporosis when there is an independent need for breast cancer prophylaxis [30, 36].

Estrogen/progestin therapy

In postmenopausal women estrogens, even with progestins, have a positive effect on BMD but the time to observe favorable action of estrogens is rather long and this therapy should be advised with great caution due to serious side effects such as increased risk of breast cancer, stroke and venous thromboembolism. The main indication for estrogens in postmenopausal women should be the occurrence of persistent hot flashes [30, 37].

Anabolic agents

Parathyroid hormone/parathyroid hormone-related protein analog

Very truly anabolic, bone-forming agents are teriparatide and abaloparatide – recombinant human parathyroid hormone peptide for subcutaneous injection. The possible candidates for anabolic agents are men and postmenopausal women but with severe osteoporosis or those who for various reasons are unable to tolerate bisphosphonates. In contrast to anti-resorptive agents, the above mentioned analogs of parathyroid hormone stimulate bone formation and activate bone remodeling [38–40].

Romozosumab

The humanized romozosumab (EVENTY), which binds sclerostin with high affinity and in consequence leads to an increase in bone density, was approved in 2019 by the US Food and Drug Administration for the United States and later on by the European Medicines Agency for Europe. This drug is intended for women with a history of osteoporotic fractures or multiple risk factors for fracture and also for those who have failed or are intolerant to other osteoporosis therapies. Everyone should remember that this new drug is not without some risk for heart attack, stroke or cardiovascular death [41]. It is very important to select patients for

this therapy carefully. Nevertheless, the safety and efficacy of romosozumab were clearly demonstrated first in two clinical trials involving a total of 11 000 women with postmenopausal osteoporosis [42, 43] and later on confirmed by others [45, 46]. The recommended dose of romosozumab is 210 mg by subcutaneous injection, in two different places, monthly, during one year. Such treatment significantly reduces vertebral and clinical fractures by comparison with placebo and bisphosphonate [44–46].

Conclusions

In many countries a lot of different drugs and preparations are used in the treatment of osteoporosis. The experts of UpToDate, analyzing different publications, which show many conflicting results, present the statement that drugs listed above should be advised in the treatment of osteoporosis and other therapies should not be recommended [30].

Disclosure

The authors report no conflict of interest.

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