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Review Article

REVIEW ON OSTEOPOROSIS

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ABSTRACT

Osteoporosis is characterized by low bone mass with micro architectural deterioration of bone tissue leading to enhance bone fragility, thus increasing the susceptibility to fracture. Osteoporosis is an important public health problem leading to weakness of the skeleton and increased risk of fracture, particularly of the spine, wrist and hip. Osteoporosis and associated fractures are an important cause of mortality and morbidity. Worldwide, lifetime risk for osteoporotic fractures in women is 30-50%. In men risk is 15-30%.

Pharmacological therapies that effectively reduce the number of fractures by improving bone mass are now available widely in markets. At present most drugs available in the markets decrease bone loss by inhibiting bone resorption, but the upcoming therapies may increase bone mass by directly increasing bone mass as is the case of parathyroid hormone. Current treatment alternatives include bisphosphonates, calcitonin, selective estrogen receptor modulators and inhibitors of RANK pathway but sufficient calcium and vitamin D are a prerequisite. To further improve pharmacological interventions and therapeutical choices in this field, improvement of knowledge is very necessary.

Keywords: Osteoporosis, Pharmacological, Parathyroid, Bisphosphonates, RANK pathway

INTRODUCTION

Osteoporosis is a condition that is characterized by low bone mass and micro architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk[1].Osteoporosis is called a "silent" disease because often there are no symptoms until late in the disease process[2].Often the very first symptom of osteoporosis is a broken bone, also called a fracture, which usually happens at the hip, spine or wrist. But the good news is that osteoporosis can be prevented and treated. The prevalence of osteoporosis rises steadily with advancing age and is projected to increase substantially due to the demographic transition occurring worldwide. Osteoporosis is estimated to cause 1.5 million fractures annually in the United States[3]. In Italy, approximately 3.5 million persons are osteoporotic, with over 90.000 fractures yearly in those aged 50 years or older[4].

With increasing longevity of the Indian population, it is now being realized that, as in the West, osteoporotic fractures are a major cause of morbidity and mortality in the elderly. Based on 2001 census, approximately 163 million Indians are above the age of 50; this number is expected to increase to 230 million by 2015[5]. Even conservative estimates suggest that of these, 20 per cent of women and about 10-15 per cent of men would be osteoporotic. The total affected population would, therefore, be around 25 million. If the lower bone density is shown to confer a greater risk of fracture, as is expected, the figure can increase to 50 million[6].

A survey carried out by the Indian Society for Bone and Mineral Research (ISBMR) among orthopaedic surgeons across the country, revealed that in government hospitals about 80%-85% hip fractures are surgically treated whereas in private hospitals almost 100% receive surgical treatment. In government hospitals the direct cost for surgical treatment to the patient is approximately 150 USD (the cost for the pros thesis), whereas in private hospitals the direct cost for surgical treatment is about 2,500-3,000 USD[7].1 out of 8 males and 1 out of 3 females in India suffers from osteoporosis, making India one of the largest affected countries in the world[8].

PATHOPHYSIOLOGY OF BONE LOSS

Bone resorption takes place through the action of osteo-clast cells, which resorbs the bone matrix by secreting hydrochloric acid, which dissolves calcium phosphate, and enzymes such as collagenase and other proteases. After the action of osteoclast cells at the bone resorption site, osteoblast cells synthesize new bone[9,10]. Two stages of mineralization mediated by

osteoblasts then follow, firstly between the collagen fibrils hydroxyapatite crystals get deposited. In this process of mineralization alkaline phosphatase located on the membrane of osteoblast plays very important role. In the second stage deposition of additional minerals occurs on the bone resorption site[9,11-13].

Estrogen is another systemic hormone with direct effects on bone and playing an important role in osteoporosis[14].

DIAGNOSIS

The presence of osteoporosis should be ascertained in all women aged ≥ 65 years (2). Men ≥ 65 years or women aged ≤ 65 years should be screened for the presence of risk factors such as early menopause (≤ 45 years), anorexia, smoking habit or alcohol abuse, chronic use of certain drugs or diseases associated with an increased risk for osteoporosis[15].

The first-line assessment includes the determination of erythrocyte sedimentation rate, blood cell count, protein electrophoresis, serum calcium, serum phosphorus, serum alkaline phosphatase, serum creatinine, and 24-hour urinary calcium excretion, in order to exclude possible causes of secondary osteoporosis[15]. Determination of bone turnover markers is not recommended. Dual-energy X-ray absorptiometry (DXA) is presently considered the gold standard imaging technique for the diagnosis of osteoporosis because it shows the best predictive value for fracture risk[15]. An estimate of fracture risk may be obtained with DXA of radium, ulna, spinal column or proximal femur. In persons aged ≥ 65 years DXA should be performed at the proximal femur because osteoarthritis of the column may bias the results. Moreover, Bone Mineral Density (BMD) of the hip is a stronger predictor of future fracture risk than spine BMD. As a general rule, the risk of fracture increases 1.5-3 times each standard deviation of BMD below the reference population (3). Normal BMD is indicated by a T score of 1 to -1, whilst a T score ≥ -2.5 is diagnostic for osteoporosis. T score values between -1 and -2.5 identify a condition known as osteopenia which is associated with low to medium fracture risk, but frequent progression to osteoporosis. The correct identification and management of osteopenic subjects is a high-priority public health issue, if one considers that approximately 35 million Americans suffer from osteopenia[16]. The estimation of absolute risk of fractures and, therefore, therapeutic decision-making should not be based solely on BMD determination; rather, it requires a comprehensive evaluation of the patient, taking into account all of the known risk factors for osteoporotic fractures. In this context, sensitive tools have been developed which are routinely used in clinical practice. Besides its role in the identification of osteoporosis, DXA is also useful to monitor the efficacy of specific treatments. Roughly, 0.5-2% of bone mass is lost every year, whilst anti-osteoporosis therapies allow gaining approximately 1-6% yearly. Since the least significant change of DXA is 2-4%, it is recommended to repeat it not earlier than 1-2 years from the beginning of treatment[15].

TREATMENT OF OSTEOPOROSIS

Calcium and vitamin D

Calcium with or without vitamin D is the first-line therapy for the prevention of bone loss and osteoporotic fractures; even so, the efficacy of its use in fracture prevention is still uncertain. Reports suggest that the reduction of fractures is significantly greater in supplementation trials, where compliances are high and when at least 1,200 mg of calcium and 800 IU of vitamin D are supplemented. Patients with lower vitamin D concentrations and poor calcium intakes tend to benefit more than the patients with adequate calcium and vitamin D[17]. supplementation (500 mg/d) only during pregnancy and lactation. A study comparing the effect of two different doses (500 IU/d and 1,000 IU/d, both groups received calcium carbonate 1,000 mg/d) of oral vitamin D3 (cholecalciferol) on serum 25-hydroxy vitamin D [25(OH)-D] concentrations in healthy postmenopausal Indian women concluded that higher doses of vitamin D (1,000 IU) with calcium carbonate were required for the achievement of optimum serum 25(OH)-D concentrations (>30 ng/mL)[18].

Vitamin D receptors are ubiquitous and are especially abundant in osteoblasts, chondrocytes, hepatocytes, parathyroid cells, and muscle cells[19]. Vitamin D promotes cell proliferation and differentiation by a genomic pathway[20,21]. Vitamin D also acts via a non-genomic mechanism to modulate cell responses to various stimuli[20,21]. The major actions of vitamin D in the context of bone homeostasis include the regulation of calcium metabolism by increasing intestinal absorption and renal reabsorption, and the stimulation of the synthesis of bone proteins such as osteocalcin by osteoblasts[22].

Bisphosphonates

Bisphosphonates are usually the first line of drugs used when pharmacological therapy is instituted. Bisphosphonates are sintetic compounds with anti-resorptive activity [23]. They act on bone through binding to hydroxyapatite and inhibiting osteoclast activation. Bisphosphonates possess high affinity for bone and little effect on other organ systems. Pharmacokinetics of bisphosphonates explain their overall good tolerability. Bisphosphonates have a poor intestinal absorption and therefore show low plasma levels after oral administration[23].

In India, most bisphosphonates, that is, alendronate daily, risedronate weekly, ibandronate monthly, and zoledronic acid yearly are available and commonly used along with calcium and vitamin D supplementation [24,25].Alendronate and risedronate reduce the incidence of fractures of spine and hip by ~40%–50% >3 years in patients with prior vertebral fracture. Risedronate is associated with up to 49% reduction in new vertebral fracture in women with prior vertebral fractures. Ibandronate reduces vertebral fractures by 62%, while zoledronic acid, given by intravenous infusion yearly, reduces the incidence of vertebral fracture by 70%[26].

Hormone replacement therapy

After menopause, due to the lack of estrogens, the rate of bone turnover increases, resulting in accelerated bone loss. Treatment of osteoporotic women with HRT to prevent fractures has been a long-standing controversial issue. Estrogen replacement, alone or in combination with tibolone (a synthetic steroid with estrogenic and androgenic properties), increases bone mass[31]. The Women's Health Initiative trial showed that the incidence of osteoporotic fractures was reduced by 24%, with a 34% risk reduction for hip and vertebral fractures[31]. However, long-term side effects,

in particular the development of breast cancer, risks of cardiovascular events and thromboembolism, limit the use of HRT as a countermeasure to osteoporosis. HRT is indeed no longer recommended for the prevention and treatment of postmenopausal osteoporosis.

Selective estrogen receptor modulators (SERMs)

SERMs are synthetic molecules that bind to the estrogen receptor thereby acting as estrogen agonists on bone and liver and as antagonists on breast and genitor-urinary tract. Raloxifene at the dose of 60 to 120 mg daily increases BMD by 2 to 3% at the lumbar spine and femoral neck[32,33]. Based on data from the MORE study, raloxifene reduces the incidence of vertebral fractures by 40 to 50%, with no effect on non-vertebral fractures[34]. Raloxifene also reduces the risk of estrogen receptor-positive breast cancer, whilst the impact on cardiovascular risk is controversial[35-38].

Calcitonin

Calcitonin reduces the occurrence of vertebral fractures by ~30% in women with prior vertebral fractures, but it has not been shown to reduce the risk of nonvertebral fractures[26]. Since it is administered as a single-daily intranasal spray, compliance is likely to be higher. Supplementation with calcium and vitamin D is mandatory with calcitonin. Though calcitonin is also an antiresorptive agent, it is believed to have weaker action than the other agents[39].

Parathyroid Hormone

Intermittent parathyroid hormone (PTH) is a bone anabolic therapy and increases BMD by restoring trabecular microarchitecture. It is also believed to reduce fracture risk to a greater extent than the antiresorptive therapies[40].

In osteoporotic women with prevalent vertebral fractures, rhPTH decreases the incidence of new vertebral fractures by 65% and non-vertebral fractures by 53%[41]. The best candidates for teriparatide and rhPTH(1-84) treatment are patients with pre-existing osteoporotic fractures, patients with very low BMD and those with unsatisfactory response to antiresorptive therapy. The effects of the combination therapy with rhPTH(1-84) and alendronate on BMD are controversial, with some authors reporting no synergy[42], while others found an additive effect[43]. However, according to guidelines, the combined treatment with recombinant PTH and bisphosphonates should not exceed 24 months (74). The safety profile of teriparatide is overall good. A transient increase in serum calcium levels and calcium renal excretion without clinical manifestation has been reported. Absolute contraindications to teriparatide include primary hyperparathyroidism, Paget's disease of bone, previous radiation therapy of the skeleton and primary or metastatic bone cancer[44].

Receptor activator of nuclear factor-kappaB ligand inhibitor (Denosumab)

Denosumab is a human monoclonal antibody; it binds to receptor activator of nuclear factor-kappaB ligand (RANKL), a transmembrane or soluble protein essential for the formation and function of osteoclasts, which are the cells responsible for bone resorption. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone. By this mechanism, denosumab reduces bone resorption and increases BMD. It is available as 60 mg/mL in prefilled syringes and approved for osteoporosis in postmenopausal women (60 mg sc twice yearly).

Denosumab is a human monoclonal antibody that blocks the interaction of receptor activator of nuclear factor kB ligand (RANKL) with receptor activator of nuclear factor kB (RANK), whereby inhibiting bone resorption strongly and rapidly (51). Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

In postmenopausal women with low BMD, denosumab administered subcutaneously 60 mg every 6 months increased BMD by 1 to 7% depending on the skeletal site[45]. The increases in BMD are higher than those obtained with the more potent bisphosphonates[45]. In postmenopausal osteoporotic women, denosumab decreased the risk of vertebral and non-spine fractures by 70% and 20%, respectively[46]. Denosumab slowed bone turnover also in older men receiving androgen-deprivation therapy for prostate cancer, increasing BMD by 4 to 7% as well as decreasing the incidence of vertebral fractures by 60% and the incidence of multiple fractures by 70%[47].

CONCLUSION

In conclusion, bone health can be optimized by creating an environment to achieve peak bone mass during adolescence, maintenance of healthy bone throughout the life cycle, and prevention of bone loss postmenopausally. Medical community is called to promote an adequate awareness on the subject and put in place large-scale screening and diagnostic procedures in order to identify people with osteoporosis or at risk of developing the condition. This would allow the early correction of risk factors for osteoporosis.Increasing longevity and risk factors, such as low calcium intakes, vitamin D deficiency, sex inequality, early menopause, genetic predisposition, lack of diagnostic facilities, and poor knowledge of bone health, have contributed toward the high prevalence of osteoporosis and fractures. Calcium, vitamin D, and bisphosphonates are the commonest first-line therapies used. The use of other drugs, such as HRT, estrogen agonists, calcitonin, PTH, and denosumab, are decided as per the affordability and availability of treatment options. Major gaps still remain in the diagnosis and management of osteoporosis, thus highlighting the need for more structured research in this area.

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