RESEARCH ARTICLE

A Review of Pharmacotherapy and Treatment in Osteoporosis

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ABSTRACT

Osteoporosis is a common problem that causes bones to become abnormally thin, weakened, and easily broken (fractured). Women are at a higher risk for osteoporosis after menopause due to lower levels of estrogen, a female hormone that helps to maintain bone mass. Fortunately, preventive treatments are available that can help to maintain or increase bone density. Prolonged therapy with and/or high doses of certain medications can increase bone loss. The use of these medications should be monitored by a healthcare provider and decreased or discontinued when possible. For those already affected by osteoporosis, prompt diagnosis of bone loss and assessment of fracture risk are essential because therapies are available that can slow further loss of bone or increase bone density. The aim of all drug treatments is to lower your risk of future fractures and there are a range of effective medications that do just that. Medicines are used to both prevent and treat osteoporosis. Some medicines slow the rate of bone loss or increase bone thickness. Even small amounts of new bone growth can reduce your risk of broken bones. If you take medicine for osteoporosis, you will also need to get enough calcium and vitamin D, eat a healthy diet, and exercise regularly. A large part of treating or reducing the effects of osteoporosis is getting enough calcium and vitamin D. Exercise, which not only improves your bone health, but increases muscle strength, coordination and balance. Safety issues to prevent falls that may result in fractures, such as removing loose rugs around your house. In addition, our orthopedic surgeon may prescribe a medication to slow or stop bone loss, increase bone density, and reduce your risk of fracture which will be discussed in detail in this Review.

INTRODUCTION

Osteoporosis is defined as the structural deterioration of bone due to an imbalance in bone removal (resorption) and replacement Increases in bone resorption lead to low bone mass, increased bone fragility, and ultimately fractures of the hip, spine, and wrist. Osteoporosis is structural failure of the skeleton that causes an increased risk of fracture. Low bone mass and microarchitectural deterioration of bone tissue increase bone fragility, which means that fractures can occur after low-energy traumas. Such fractures are associated with mortality and with significant short- and long-term morbidity. The management of osteoporosis must target *all* aspects of the condition: bone mass should be maximized; fractures should be prevented; and people who have already sustained a fracture should be rehabilitated to minimize associated pain, limitation of activities, and restriction of participation in society. Pharmacological treatments act on bone and have effects on its mass, strength, and turnover. Pharmacological treatments that primarily and effectively reduce bone loss and fracture risk have become available in the last few decades. The role of estrogen for maintenance of bone integrity was recognized early on, and hormone replacement therapy was recommended to prevent osteoporosis. Hormone replacement therapy is non-specific, however, and with evidence of its undesirable side-effects and low compliance rates, the search for more potent and specific treatments with large effects on bone mass resulted in the development of direct anti-resorptive agents, including the bisphosphonates and selective estrogen receptor modulators.

Osteoporosis in India

The population of India is expected to increase to 1,367 million by 2020 and 1,613 million by 2050; of which 9.8% (134 million) and 19.6% (315 million), respectively, will be adults over 60 years.[1] These staggering numbers give some idea of the population at risk for osteoporosis in India in the years to come. Osteoporosis is becoming a serious problem for the public economy and health, because of the increase in elderly population in the near future. Conservative estimates in a study suggest that 20% of women and about 10-15% of men are osteoporotic in India.[2] Another highly conservative estimate by a group of experts suggested that 26 million Indians suffer from osteoporosis, and this number is expected to reach 36 million by 2013.[3]

Nutritional Factors

Despite abundant sunshine, vitamin D deficiency is widespread in India. A recent International Osteoporosis Foundation (IOF) report on the global status of Vitamin D nutrition highlights South Asia, especially India, as one of the most deficient regions. This is due to factors such as skin pigmentation, clothing habits and absence of

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vitamin D fortification.[4] Also in India calcium intakes are also far below western recommendations.[5]

Pharmacogenomics of Osteoporosis

Some drugs used in osteoporosis therapy, bisphosphonates for example, are not subject to metabolism, but many others are metabolized to active components or as part of their elimination pathway. Despite the evidence of genetic effects on the variation in efficacy and safety of pharmacological agents in other diseases, these are still largely untested in the treatment of osteoporosis, but their potential is underlined by their rapid adoption in disciplines such as obesity and hypertension. Nevertheless, recent evidence suggests that genetic factors may mediate the response to drug treatment, and modify the dynamic association between bone turnover markers and bone density. A recent series of studies by Palomba and colleagues suggested that among postmenopausal women who were on alendronate and hormone replacement therapy (HRT) treatments, the *b* allele of the VDR's Bsm-I polymorphisms was associated with a greater increase in BMD than those carriers of the *B* allele. However, interestingly, among patients on RLX the *B* allele carriers were associated with a greater increase in BMD than the *b* allele carriers. As a result of the opposite effects, among those on combined ALN and RLX there was no significant association between VDR polymorphisms and BMD change. These results clearly illustrate the interaction between VDR polymorphisms and various anti-resorptive drug therapies in BMD change. In a study of 21 premenopausal Caucasian women who were homozygous for the VDR genotypes (*BB* or *bb*), it was found that baseline osteocalcin, 1,25-(OH)2D, type I collagen carboxyterminal telopeptide, and inorganic phosphate levels were significantly higher and spinal bone mineral density was significantly lower in the *BB* allelic group. However, after calcitriol administration, similar serum levels of 1,25-(OH)2D were attained in both genotypic groups. The increase in serum osteocalcin levels in the *BB* group was significantly less than that in the *bb* group. The genotype-related baseline difference in osteocalcin levels was not apparent at similar serum 1,25-(OH)2D levels.

Summary of the Available Treatment of Osteoporosis

- Osteoporosis causes bones to become abnormally thin, weakened, and easily broken. This condition can be treated and prevented with diet, exercise, and not smoking.
- Calcium and vitamin D can prevent and treat thinning bones. The main dietary sources of calcium include milk and other dairy products, such as cottage cheese, yogurt, or hard cheese, and green vegetables, such as kale and broccoli. Milk is a primary source of dietary vitamin D, containing approximately 100 IU per cup.
- Calcium and vitamin D can also be taken as a supplement (eg, in a pill). A total of at least 1000 mg of calcium per day (total diet plus supplement) is recommended for premenopausal women and men. Women after menopause should consume 1200 mg calcium per day (total diet plus supplement). Experts also recommend 800 international units (IU) of vitamin D each day for men over 70 years and postmenopausal women, and 600 international units daily for younger men and premenopausal women.
- Exercise can help to prevent and treat thinning bones. Exercise should be done for at least 30 minutes three times per week. Any weight-bearing exercise regimen is appropriate (eg, walking).
- Smoking cigarettes can cause bones to become thinner and weaker. Stopping smoking can reduce this risk.
- Falling can cause fractures in the elderly. Preventing falls can lower the risk of fractures.
- Some medications can cause bone thinning. Such medications include glucocorticoid medications (eg, prednisone), heparin, vitamin A, and certain synthetic retinoids (eg, etretinate), and certain antiepileptic drugs (eg, phenytoin, carbamazepine, primidone, phenobarbital, and valproate). Patients should ask

their healthcare provider about the possibility that these medications should be replaced or the dose lowered.

- There are several medications that help prevent osteoporosis in women after menopause. We think alendronate, risedronate, or raloxifene are the best medications for prevention.
- Alendronate or risedronate are recommended to treat women after menopause who have osteoporosis. Zoledronic acid or raloxifene may be suggested for patients who cannot tolerate oral bisphosphonates, or who have difficulty taking the medication, including an inability to sit upright for 30 to 60 minutes.
- Denosumab improves bone density and reduces fracture in postmenopausal women with osteoporosis. It is another option for patients who are intolerant of or unresponsive to oral and/or intravenous bisphosphonates.
- Parathyroid hormone is another medication that can be used to treat osteoporosis. We recommend this medication for men or postmenopausal women with severe hip or spine osteoporosis.
- Hormone replacement (eg, estrogen, progesterone) is not usually recommended to prevent osteoporosis in women after menopause. Hormone therapy is recommended for young women whose ovaries do not make estrogen normally.
- Testing may be recommended to monitor how the bones respond to osteoporosis treatment. This may include a bone density scan (DXA) or laboratory tests.

Current Therapies for Osteoporosis and their Clinical Implications

In general, pharmacological agents either decrease bone resorption to produce secondary gains in bone mass or are anabolic and produce direct increases in bone mass. Ideally, such drugs also should increase bone strength and bone quality. As the turnover of bone is slow, the time between starting treatment and assessing its effect on bone mass or fracture takes several years. Because this makes it difficult to show the effect of treatments on the dichotomous and uncommon key outcome of fracture, the continuous variable bone mass is often used as a surrogate measure. An increasing number of randomized controlled trials of several anti-osteoporotic drugs have fracture as an endpoint, however, and show reductions in the incidence of fractures within 1–3 years. In addition to estrogen, drugs with specific anti-resorptive actions are available for the treatment of osteoporosis, including bisphosphonates, calcitonin, and selective estrogen receptor modulators. Furthermore, calcium and vitamin D act on bone by decreasing resorption, while calcium also is regarded as an essential building block for bone.

Calcium and Vitamin D

Calcium and vitamin D in combination is the accepted baseline treatment for osteoporosis and also is used as a preventive measure, particularly for frail elderly patients. After three years of treatment with calcium (1200 mg) and vitamin D (20 μg (800 IU)), the incidence of new hip and nonvertebral fractures in elderly patients was lower than in patients who did not receive such treatment and a significant benefit was seen after 18 months. [6] Vitamin D therapy may have additional benefits for very elderly patients, because it increases muscle strength and thus may reduce the number of falls and possibly of fractures. [7, 8]

Bisphosphonates

The most commonly prescribed drugs are bisphosphonates which are used to treat osteoporosis in the US and many other countries including India. Alendronate, a once daily oral medication, was the first bisphosphonate to be approved for treatment of osteoporosis in the US in 1995. Since that time, newer bisphosphonates with less frequent dosing intervals have been introduced, partially in an attempt to improve compliance. Risedronate is an oral medication

that can be administered daily, weekly, or monthly at varying doses. Zoledronic acid is the newer medication which is administered once yearly by intravenous transfusion.[9] Bisphosphonates bind to hydroxyapatite crystals and thus have a very high affinity for bone. Bisphosphonates are released from the bone matrix upon exposure to acid and enzymes secreted by an active osteoclast.[10,11] Out of all bisphosphonates, zoledronic acid has the highest affinity for binding to the bone mineral matrix followed by pamidronate > alendronate > ibandronate > risedronate > etidronate > clodronate. Bisphosphonates with higher affinity like zoledronic acid bind avidly to the bone surface, but spread through bone slowly whereas lower affinity agents like clodronate distribute more widely through the bone, but they have shorter time of residence when the treatment is stopped. Suppression of bone resorption occurs within approximately three months of initiation of oral bisphosphonate therapy regardless of dosing frequency, but it is more rapid after intravenous administration. After three years of treatment, bisphosphonates have shown to increase BMD of the hip by 3%-6% and at the spine by 5%-8%. In women with osteoporosis zoledronic acid, alendronate and risedronate also reduced nonvertebral fractures by 25%-40%, including hip fractures by 40%-60%.[11]

Some Important Adverse events Associated with Bisphosphonates Therapy

Orally administered bisphosphonates may cause irritation in the esophagus. It is recommended to swallow oral bisphosphonates with full glass of plain water on arising in the morning, remaining upright for at least 30 minutes after swallowing the tablet and discontinuing the drug promptly if esophageal symptoms develop. Rapid intravenous administration of parenteral bisphosphonates may cause renal toxicity. For patients with creatinine clearance less than 30-35 mL/min, use of parenteral bisphosphonates is not recommended. [12]

Examples of Bisphosphonates

Nitrogen-containing bisphosphonates
• Alendronate
• Risedronate
• Ibandronate
• Zolendronate

Non-nitrogen-containing bisphosphonates
• Etidronate
• Tiludronate
• Clodronate

Calcitonin

Calcitonin acts as an endogenous inhibitor of bone resorption by decreasing osteoclast formation. It is available for delivery as a subcutaneous injection or nasal spray; both formulations are developed from salmon calcitonin, which is about 10 times more potent than naturally produced human calcitonin. Several studies have shown positive effects on bone mineral density in postmenopausal women, but the effect on fractures has been less well documented. In a recent report, new vertebral fractures were reduced by 33% in postmenopausal women after salmon calcitonin was given at a dose of 200 IU daily, despite the effect on lumbar bone mineral density being small. [13] This was interpreted as a quality effect on bone trabeculae beyond the effect on bone mineral density. As a desirable additional effect, calcitonin has been noted to reduce the pain of clinical vertebral fractures. [14]

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators, such as raloxifene, block conformational changes of the estrogen receptor. In postmenopausal women treated with raloxifene, the incidence of vertebral fractures was reduced by 30% over three years, but no effect was seen on the incidence of non-vertebral Fractures. [15] In addition, other beneficial effects have been seen: a significant (72%) decrease in new cases of breast cancer [16] and a significant reduction in the incidence of

cardiovascular events in women who had increased cardiovascular risk. [17]

Estrogen Replacement Therapy

Treatment of women with osteoporosis with estrogen replacement therapy to prevent fracture has been controversial. Large studies to evaluate the effect on the incidence of fracture, particularly in the elderly, have been lacking, and the indication for its efficacy relies on observational studies. The Women's Health Initiative trial on estrogen replacement therapy was the first large-scale, randomized, controlled study of healthy women aged 50–79 years. [18] The incidence of osteoporotic fractures — a secondary endpoint of the study — was reduced by 24%, and the risk reduction for hip and vertebral fractures was 34%. Long-term side-effects, particularly development of breast cancer, and the long-term absence of benefits for cardiovascular events limit their use. The primary reason for using estrogen replacement therapy therefore is to eliminate climacteric symptoms in women soon after menopause: the bone-sparing effect should be regarded as an added benefit, and the treatment rarely should exceed five years.

Tibolone

Tibolone is a synthetic steroid with estrogenic, androgenic, and gestagenic properties, which exerts its effect by binding to the estrogen receptor. Tibolone relieves climacteric symptoms without causing menstrual bleeding and with less breast tenderness than is caused by hormone replacement therapy. After two years of treatment with tibolone in early postmenopausal women, the bone density response was similar to that after estrogen replacement therapy [19, 20], while in a head-to-head trial, tibolone induced a dose dependent increase in bone mineral density of the lumbar spine, although this increase was smaller than with conventional continuous hormone replacement therapy. [21] The change in bone mineral density in the hip was similar but did not reach significance.[21] No data are available on fracture prevention, so from an evidence-based perspective, tibolone cannot be recommended for the treatment of osteoporosis.

Parathyroid Hormone

The only anabolic agent currently approved for treatment of osteoporosis is PTH analog. It is available in the form of human recombinant PTH peptide 1−34 (teriparatide), a fragment of PTH that has a similar affinity for PTH receptor-1. Normally in response to low serum calcium, PTH is secreted from parathyroid glands, and acts to increase the concentration of calcium in serum by mobilizing calcium from bone. Pharmacologically, when PTH is administered intermittently at low doses, it has been shown to have predominantly anabolic effects on osteoblasts. PTH initiates bone formation first and only later promotes bone formation, which is indicated by bone turnover markers.[22] In clinical studies, treatment with teriparatide increased BMD in the lumbar column and femur and also reduced the incidences of vertebral fractures and non-vertebral fractures.[23, 24] The long term safety and efficacy of PTH have not been evaluated beyond 2 years, so it cannot be prescribed for more than 2 years. [22]

Strontium Ranelate

Strontium ranelate, a novel orally active agent, has been developed for the treatment of osteoporosis. It consists of two atoms of strontium and an organic moiety ranelic acid. Strontium ranelate acts by both stimulating bone formation and decreasing bone resorption. In vitro, strontium ranelate has been shown to increase osteoblastic activity, including increasing collagen synthesis and modulating the OPG/RANKL system in favour of OPG, as well as decrease bone resorption by decreasing osteoclast differentiation and resorbing activity, and increasing osteoclast apoptosis. Since 2004 strontium ranelate has been approved for the treatment of osteoporosis in European countries.[25] In a summary of the results of four clinical trials of strontium ranelate, three for treatment of osteoporosis [27,28,29,30 and 31] and one for prevention[30], 2 g/day of strontium ranelate resulted in increased BMD at all sites, a 37% reduction in

vertebral fractures and a 14% reduction in non-vertebral fractures over three years.[26] More recently, a five-year follow-up of one of the treatment trials demonstrated a 43% reduction in hip fractures and 24% reduction in vertebral fractures.[31]

Denosumab (Inhibitors of Rank Signaling)

Denosumab is a fully human monoclonal antibody that was developed using transgenic mouse technology. Denosumab binds with high affinity to RANK ligand which prevents the interaction of RANK ligand with its receptor, RANK, which is present on the surface of osteoclasts and their precursors. Denosumab thus inhibits osteoclast activity, thereby decreasing bone resorption in trabecular and cortical bone [32, 33 and 34]. In a randomized, double-blind, placebo-controlled trial, treatment with denosumab significantly reduced the risk of vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis. Denosumab effectiveness in reducing the risk of vertebral fractures was regardless of BMD baseline, bone turnover baseline rate and baseline history of fracture.[32,33,34 and 35] For the treatment of postmenopausal women with osteoporosis or who are at high risk of osteoporosis, denosumab was granted marketing authorization by the European commission in May 2010.[33] Denosumab was also approved by US FDA in June 2010.[32]

Drugs Under Clinical Development

Cathepsin K

Cathepsin K is critical for normal osteoclastic bone resorption. The two agents which are under development are balicatib (AAE581) and odanacatib (MK-0822). Clinical trials with these agents have demonstrated increase in hip and lumbar spine BMD, with a significant reduction in bone resorption markers. [36] A newer highly potent cathepsin K inhibitor named relacatib is presently being studied in experimental animals. [37]

SRC Kinase Inhibitors

Src kinase is a non-receptor tyrosine kinase and a member of the Src family of protein kinases which plays an important role in activity and survival of osteoclast cells. [38] Osteopetrosis was caused in mouse due to Src inactivation; therefore it clearly indicated that Src is an important requirement for Osteoclastic bone resoption.[39] In *Src* null mutants, osteoclasts fail to form a ruffled border and do not resorb bone. Saracatinib is a novel orally available competitive inhibitor of Src kinase shown to inhibit bone resorption *in vitro*. In a randomized, double-blind, placebo-controlled, multiple-ascending-dose phase I trial treatment with saracatinib inhibited osteoclast mediated bone resorption in healthy men without any significant adverse effects. The results of this study show that saracatinib has the potential to become an agent for the treatment of osteoporosis. [40]

Emerging Therapies

The Wnt/β-catenin pathway regulates gene transcription of proteins important for osteoblast function.[41] Study of the pathway has led to further discovery of inhibitors of Wnt signalling secreted by osteocytes. These include sclerostin and dickkopf1 protein (DKK1), both of which block binding of Wnt toLRP5 (lipoprotein receptor-like protein 5), thereby inhibiting osteoblast stimulation. [42 and 43] Monoclonal antibodies designed to block the inhibiting action of both sclerostin and DKK1 are being considered for clinical trials based on promising results in animal models.[44,45 and 46] Because both of these molecules appear to be secreted only by bone, it is hoped that they will have fewer systemic adverse effects. Therapies targeted at other molecules in the pathway, for example a small molecule inhibitor of GSK3β,[47] the enzyme which causes degradation of β-catenin in the absence of Wnt signaling, are considered less desirable targets due to their action in many tissues in addition to bone.[48]

Conclusion

In our conclusion, if osteoporosis is diagnosed and treated early, osteoporotic fractures may be prevented. Newer bisphosphonates like Zoledronic acid with long dosing intervals, newer SERMs with little non-skeletal adverse effects, Strontium ranelate and Denosumab have been introduced to overcome previous shortcomings. Advancement in cellular and molecular level of bone recycling has revealed some newer targets for the therapy of osteoporosis. Several of the new agents are well-advanced in clinical studies, including, cathepsin K inhibitors and Src Kinase Inhibitors. There is a chance that one of these agents may reach the clinic. The other candidate drugs under pharmacological development are likely to emerge for evaluation in clinical studies in the next few years. Of these, drugs targeting the Wnt-β catenin signaling are likely to be prominent. These agents may also be useful in combination with existing antiresorptive agents, further expanding therapeutic options.

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