A Comprehensive Review on Osteoporosis

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Abstract:
Osteoporosis is described as a ‘progressive systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture’. Osteoporosis is called a “silent disease” because it progresses without symptoms until a fracture occurs. The fractures caused by osteoporosis have a great impact on public health, as they are often associated to increased morbidity, mortality, reduced quality of life, long hospital stays and high economic cost.

Osteoporosis has been identified as an orthopaedic ‘epidemic’ because of the increased numbers of fractures of the hip and wrist which have been occurring since the 1970s. Because the worldwide incidence and economic burden of osteoporosis are proportionally staggering, the disease can no longer be ignored. About half of all women and one third of all men will sustain a fragility fracture during their lifetime. Increased morbidity and mortality and the high costs associated with the rising incidence of osteoporotic fractures make it imperative to implement prevention strategies by early detection and treatment of osteoporosis. This review focuses on the epidemiology, etiology, clinical features, diagnosis, prevention and treatment of osteoporosis.

Keywords: osteoporosis, postmenopausal, bisphosphonates, Calcium, Vitamin-D

Introduction

The word osteoporosis is derived from the Greek word osteon for bone and poros for porosity indicating that the bone becomes more porous. Osteoporosis is described as a ‘progressive systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture’.1 It is characterized by the net loss of bone, which results in a decrease in total mineralized bone without a decrease in the ratio of bone mineral to the organic matrix. Thus there is a decrease in the overall amount of bone. The size of the osteoid seams is normal, but there is a decrease in the thickness of the cortex and in the number and size of the trabeculae in cancellous bone. The trabecular plates have increased perforations, and there is a decrease in trabecular connectivity. Trabecular connectivity is probably the most important determinant of the tensile strength of bone. Thus ultimately, osteoporosis leads to bone with less tensile strength and significantly more susceptibility to fracture with less force. At some point, the amount of bone available for mechanical support falls below a certain threshold and the patient may sustain a fracture2,3 The condition primarily affects older people, particularly women, and is associated with 80% of fractures in people older than age 60 years. Osteoporosis is called a “silent disease” because it progresses without symptoms until a fracture occurs. The fractures caused by osteoporosis have a great impact on public health, as they are often associated to increased morbidity, mortality, reduced quality of life, long hospital stays and high economic cost.4

Osteoporosis has been identified as an orthopaedic ‘epidemic’ because of the increased numbers of fractures of the hip and wrist which have been occurring since the 1970s. Because the worldwide incidence and economic burden of osteoporosis are proportionally staggering, the disease can no longer be ignored.5 The present review focuses on the epidemiology, etiology, clinical features, prevention and treatment of osteoporosis.

Epidemiology

The most commonly used definition, as defined by the World Health Organization (WHO), is a bone mineral density (BMD) of 2.5 standard deviations (SDs) or more below the young normal mean.1 But this definition only includes postmenopausal women evaluated by the total body dual-energy X-ray absorptiometry (DEXA) scanning technique. Using the WHO definition, a quarter of all postmenopausal white Americans, a total of 26 million people, are osteoporotic. As per Indian scenario is considered 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. 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.6-8 More than one in three of adult women and one in five men will sustain one or more osteoporotic fractures in their lifetime. Common sites of fracture include the vertebral bodies, distal radius, proximal femur and the proximal humerus; distal radius and hip fractures being the commonest. Approximately 50% of patients suffering a hip fracture can no longer live independently and 20% die within 12 months of the fracture.9

Pathophysiology

• The main components of bone are cells, organic matrix and minerals. The osteoblast cell synthesizes bone collagen and other components of matrix. Osteoclasts resorb bone. The skeleton is in dynamic equilibrium by osteoclastic and osteoblastic activity and about 10% of adult skeleton is remodelled every year. The pathogenesis of osteoporosis is complex. In childhood and adolescent period bone formation exceeds resorption, resulting in continued skeletal growth and denser, longer and heavier bones. This process slows down in adulthood, and peak bone mass is attained at about 30 yr of age. After this, resorption begins to exceed formation. Normal bone loss averages 0.7 per cent per year. It gets accelerated at the time of menopause to 2-5 per cent per year in females, which may continue for up to 10 years. Since cancellous bone is much more metabolically active than cortical bone, in periods of accelerated bone loss cancellous bone loss is 3-fold greater.8

As there is no demonstrable underlying medical cause for osteoporosis in 80% of women and 50% of men who present with fragility fractures, a diagnosis of primary involutional osteoporosis is often made. Riggs and Melton subdivided primary osteoporosis into type I and type II osteoporosis, type I being related to the loss of ovarian function after the menopause and type II being an exaggeration of the normal aging process. A recent study has emphasized the importance of estrogen in bone loss in both men and women and proposed a link between type I and type II osteoporosis. Nowadays, the expression “primary or idiopathic osteoporosis” is more commonly used than “type I or type II osteoporosis.” Despite this, it is important to realize that involutinal osteoporosis is multifactorial and that the roles of each specific fracture are still poorly understood. If there is a cause for osteoporosis such as an endocrine, metabolic, gastrointestinal, renal, or hematologic disorder in addition to certain hereditary diseases and drug treatment, the diagnosis is that of secondary osteoporosis (Table-2).10-12 The higher proportion of secondary osteoporosis in men than in women is usually attributed to alcoholism, malignant disease, long-term corticosteroid treatment, and hypogonadism.

Etiology

Genetic factors: The major genetic component responsible for bone mass may be linked to polymorphism in the gene for vitamin D receptor (VDR).13 Polymorphism of the alleles of the vitamin D receptor gene may account for the major part of the heritable component of bone density in women, possibly mediated in part by impaired calcium absorption from the bowel but this association has not been found in group of men.14 In addition, estrogen receptor a (ERA) gene polymorphisms may also be associated with BMD in women and may influence some determinants of bone metabolism resulting in accelerated age related bone loss.15

Nutritional factors: Calcium and vitamin D nutrition plays an important role in determining bone health. Low vitamin D level and low calcium intake seems to be a major contributing factor to poor bone health and osteoporosis in India. Poor sunlight exposure, skin pigmentation and vitamin D-deficient diet are some obvious causes for this finding. Vitamin D deficiency is highly prevalent in different subgroups of Indian population despite enough sunshine. Majority of Vitamin D deficiency is asymptomatic. In an Indian study, at Vitamin D cut off level of 15ng/ml 66.3% subjects and at cut off level of 20ng/ml 78.3% subjects were Vitamin D deficient.16

Risk factors for osteoporosis and fragility fractures: Risk factors for fragility fractures can be divided into two main types—those related to trauma, such as a tendency to fall, and those related to bone strength, such as BMD, skeletal architecture, and bone size (Table-3). However, several risk factors, such as immobility and aging, may operate through both skeletal and extra skeletal routes.12 Risk factors for osteoporosis specific to men include hypogonadism, thyroid dysfunction, a low body mass index (<19 kg/m2), smoking, high alcohol consumption, long-term corticosteroid therapy (>7.5 mg of prednisolone for >six months), physical inactivity and diseases which predispose to low bone mass and neuromuscular dysfunction. The peak bone mass is as important as the rate of bone loss. Race, genetic factors, diet and exercise all contribute to the peak bone mass, but the most obvious influence is hormonal and the timing of the onset of puberty.14 The risk factors which are important when considering women, are those listed above for men together with specific ones including a maternal history of fractures after minor trauma, or a past history of fragility fractures, loss of height and thoracic kyphosis, an early menopause (<45 years of age) either natural or surgically induced, a late...
regions with minimal soft tissue, usually the distal denser the skeleton, the more photons are absorbed by with which photons pass through skeletal tissue. The relationship between bone mineral content and the ease the technique of photon absorptiometry relies on the technique (SPA) used a single energy radionuclide. The first specific bone scanning method to be developed, the single-photon absorptiometry (SPA) used a single energy radionuclide. The technique of photon absorptiometry relies on the relationship between bone mineral content and the ease with which photons pass through skeletal tissue. The denser the skeleton, the more photons are absorbed by the bone tissue. This method can only be used in regions with minimal soft tissue, usually the distal radius or the calcaneus, because the scan cannot differentiate between absorption in soft tissue and bone.

To overcome this problem, Dual x-ray absorptiometry (DXA) was introduced in 1987 which has become gold standard in BMD measurement. This method uses x-rays as the photon source, avoiding the problems of isotope source decay and replacement. The scan time is reduced to minutes with markedly improved scan image quality and resolution. DXA is currently the most used scanning technique for predicting the risk of fractures, establishing or confirming the diagnosis of osteoporosis, selecting patients for therapy, and monitoring the effectiveness of therapy. It is a relatively cheap, non-invasive, safe and fairly accessible means of diagnosing and monitoring the disease. The BMD readings obtained are either compared with the young adult reference range (T-scores) or with those of an age-matched control group (Z-scores). Since the T-score is a comparison with the 'best ever' BMD it represents an absolute risk of fracture. The Z-score is a comparison within different age ranges and represents a relative risk of fracture. When deciding treatment strategies for osteoporosis, most clinicians currently use the hip scan, or occasionally the spine scan in younger patients, as the gold standard. Newer and smaller DXA equipment that measure the radius or the calcaneus is promising because of lower cost and because the machines are portable.

Other radiological investigations used in the diagnosis of osteoporosis include quantitative ultrasound (QUS) and Quantified computer tomography (QCT). Quantitative ultrasound (QUS) transmits a signal through the bone in the range of 100 kHz up to 2 MHz. It started in 1984 with the introduction of parameter broadband ultrasound attenuation (BUA). This parameter evaluated the attenuation in the bone; this being mainly caused by scattering but also by absorption. Attenuation seems to reflect not only the amount of mineral in the bone but also the bone structure, elasticity, and strength. Bone microstructure and material properties have both been shown to affect QUS parameters, and studies have supported the view that QUS can predict fractures independent of the BMD value estimated by DXA scan but further studies are needed to prove this. Quantified computer tomography (QCT) is a densitometric technique that measures the actual volumetric bone density. The principal advantage of QCT is that the value received is a true volumetric figure for BMD and not a two-dimensional, area-corrected result, as is obtained with DXA. But the disadvantage is, it is expensive and the patient is
exposed to a high level of radiation.12, 17

Assessment of bone metabolism by biochemical bone markers

There are a number of biochemical markers of bone turnover available in most hospital laboratories. They can be broadly divided into those which assess the formation of bone and those which indicate resorption (Table-4).

**Bone Formation**

Bone contains hydroxyapatite crystals, which are present in the matrix, consisting of about 90% type 1 collagen and 10% non-collagenous proteins including osteocalcin, the dominant non-collagenous protein in bone. The basic structure of collagen is a triple helix consisting of two α-1 chains and one α-2 chain with a high content of glycine, proline, and hydroxyproline. Procollagen is formed in the osteoblasts, and after secretion to the extracellular space, the procollagen I extension peptides are split at the amino (N) terminals (P1NP) and carboxyl (C) terminals (P1CP) before final fibril formation. These extension peptides are a marker of bone formation and can be measured in blood. In addition, during bone formation, the bone cells secrete non-collagenous small proteins that become incorporated into the matrix. One of these, osteocalcin (BGP), can be measured in blood as a marker of bone formation. Alkaline phosphatase (ASP) and bone-specific alkaline phosphatase (BSAP), an enzyme involved in the mineralization of bone, are also used as markers of bone formation.12, 23

**Bone Resorption**

Urinary hydroxyproline (OHP) is widely used to estimate the degradation of bone collagen and as such is a marker of bone resorption. The collagen molecules aggregate to fibrils that are stabilized by covalent cross-links. The pyridinium cross-links comprise pyridinoline (Pyr) and deoxypyridinoline (D-Pyr), which are present in all mature collagen except skin. Because D-Pyr is only present in significant amounts in bone, it is considered to be more bone specific than Pyr. The peptide cross-link fragments at the N terminals (NTx) and C terminals (CTx), in serum are markers of bone resorption. During bone resorption, osteoclasts also secrete tartrate-resistant acid phosphatase isoenzymes (TRACP), and the serum concentration of this enzyme has sometimes been used as a marker of bone resorption. Another collagen degradation product used to estimate bone resorption is C-terminal cross-linking telopeptide of type 1 collagen, which is found in both serum and urine.12, 23 Biochemical markers of skeletal turnover have great advantages of use in both assessing the turnover rate in rapid loosers of bone as well as monitoring of therapy. But however, there is not enough conclusive evidence for an optimum combination of these tests to be defined in an algorithm for predicting fractures.

**Management**

The fundamental management goals for patients who have osteoporosis are prevention and treatment of osteoporosis and management of osteoporotic fractures. Half of all women and one third of all men will sustain a fragility fracture during their lifetime. Increased morbidity and mortality and the high costs associated with the rising incidence of osteoporotic fractures make it imperative to implement prevention strategies in the community.

Non-pharmacological Prevention of Osteoporotic Fractures

1. Nutrition: Normal skeletal health is dependent on a balanced diet with an adequate intake of energy, minerals, vitamins, and proteins. Calcium is the most important nutrient for attaining adequate peak bone mass. The 1994 consensus conference discussing the optimum calcium intake recommended a daily intake of 1200 to 1500 mg for adolescents, 1000 mg for adults up to 65 years of age, and 1500 mg for postmenopausal women not receiving estrogen and for elderly individuals.24 The positive correlation between dietary calcium and BMD has been shown in children, adolescents, and young women, indicating that higher calcium intake results in a higher BMD. Calcium absorption is also dependent on the vitamin D level and serum concentrations of 25-hydroxy vitamin D decline with age. The current recommendation is that the daily intake of vitamin D should be about 400 to 800 IU if exposure to sunlight is low, especially in the elderly, who have decreased ability to activate precursors in the skin, decreased ability to hydroxylate vitamin D in the kidney and liver, reduced dietary intake, and diminished absorption from food. Another problem in frail elderly individuals is achieving an adequate intake of protein, total energy, and a variety of other nutritional components such as phosphorus, magnesium, zinc, copper, iron, fluoride, sodium, and vitamins D, A, C, and K, all of which are required for normal bone health.12

2. Physical Activity: Bone tissue seems to be most adaptive to mechanical load during periods of rapid skeletal change as in the late prepubertal and early pubertal period. Mechanical loading increases BMD and also improves bone structure, geometry, architecture, and possibly material properties such as strength, stiffness, and its energy absorbing capacity. During adulthood physical activity should be regarded
more as bone preserving rather than bone building because most studies show only 1% to 3% increase in BMD with exercise. Nevertheless, the exercise-induced bone-preserving effect in adulthood may be of great importance in maintaining bone strength and preventing age-related fractures because only a small increase in BMD is associated with a significant reduction in the risk of fracture. Brisk walking, climbing up and down stairs, dancing, and calisthenics are the most suitable activities for older people since they are easily available and are inexpensive and safe. Encouragement of an active lifestyle with mild to moderate impact type exercise will undoubtedly contribute to protecting the bone stock. There are many epidemiological studies which support this hypothesis, with sufficient evidence to suggest that all types of insufficient fracture, including those around the hip, can be reduced.12, 25, 26

3. Prevention of falls: Exercise, including balance training, improves balance and decreases the risk of falling. The greatest effect was seen in those who were most compliant with the program. In several recent studies, Tai Chi has been shown to be an effective intervention reducing falls by almost 50%.27 Environmental factors such as rugs, slippery and uneven floor surfaces, poor lighting, electrical cords, foot stools without handrails, slippery top surfaces, and unsuitable footwear are often responsible for fall in elderly, modification of the home environment to eliminate these factors can prevent falls. Because previous falls are an independent risk factor for future falls, it is especially important to evaluate each elderly person who has fallen for any risk factors in the home environment.12 This has been successfully used in the PROFET study (Prevention of Falls in the Elderly Trial), in which intervention decreased the risk of falls by 70% in patients who had presented to emergency departments with fall-related injuries.28 The key elements of such programs of risk reduction are as follows:

- Individual management so that factors relevant to a particular patient are addressed
- Reduction of environmental hazards
- Appropriate reduction of medication
- Education of the individual in behavior strategies
- Education techniques for getting up after falls
- Exercise programs to improve strength, balance, and aerobic capacity

Hip Protectors: More than 90% of hip fractures are related to direct impact on the hip. Energy absorption in the soft tissue surrounding the hip has been shown to protect against hip fractures and as much as 75% of the energy in a fall can be absorbed. Based on these facts, various hip padding systems have been developed. There are a number of different types, including an energy-shunting type (horseshoe) system, a crash helmet type, an energy-absorptive type, and an airbag type, designed to reduce the impact of the skeleton in a fall. Randomized controlled trials, including nursing home residents and those frail elderly living at home, have shown a protective effect of 34% by hip protectors when using pooled data. The most significant problem with this type of prevention strategy appears to be compliance.12

Pharmacological Prevention and treatment of Osteoporosis

1. Calcium and Vitamin D: Calcium suppresses endogenous production of PTH thereby reducing stimulus to bone remodelling. Beneficial effects have been demonstrated in both children and adults especially improving bone density at non-vertebral sites. Reduced Vitamin D activity can cause hypocalcaemia which stimulates parathyroid hormone secretion which mobilizes calcium from bone which is important in genesis of osteoporosis. The active metabolite of Vitamin D; calcitriol directly improves calcium absorption from the gut. Overall calcium and vitamin D together are considered as adjunct to other therapies with proven antifracture efficacy. Furthermore there is evidence that Vitamin D supplementation has beneficial effects on muscle strength and reduces the risk of falls in elderly.29 The recommended daily intake is 1000 to 1500 mg for elemental calcium and 800 IU for vitamin D.

2. Bisphosphonates: Bisphosphonates are stable analogues of pyrophosphates characterized by a phosphorous-carbon-phosphorous bond that strongly binds to the hydroxyapatite crystal with a half-life in bone of several years. The drug inhibits bone resorption by reducing the recruitment and activity of osteoclasts and by increasing their apoptosis.30 Nitrogen-containing bisphosphonates inhibit the mevalonate metabolic pathway, while bisphosphonates that do not contain nitrogen are metabolized in the cell (osteoclast) into cytotoxic analogues of adenosine triphosphate. The plasma half-life of bisphosphonates is very short, but the half-life of bisphosphonates deposited in bone is probably up to 10 years and could be longer.31 Bisphosphonates are absorbed poorly from the gastrointestinal tract, which complicates their oral administration. Oral administration of alendronate and risedronate requires fasting before and immediately after the drug is taken. But intravenous preparations are available now to tackle these problems. If taken intravenously, short-term adverse effects mimicking influenza are commonly seen for a few days, especially after the first injection.12
Etidronate was the first bisphosphonate used for the treatment of low BMD. A dose of 400 mg per day was given for 2 weeks and then repeated every 3 months. The increase in BMD was reported to be about 4% and results showed a reduction of the rate of vertebral fractures after 2 years of treatment.32, 33Alendronate is most efficient at reducing fracture in people at highest risk of fracture that is, women with at least one prevalent vertebral fracture or with a measured bone density that confirms osteoporosis.31 It also reduces steroid-induced bone loss. It is administered as 10mg daily or 70 mg weekly dosage. Risedronate, another oral bisphosphonate given in doses of 5 mg /day or 35 mg/wk, has been shown to increase bone mineral density and reduce the risk of vertebral, non-vertebral, and hip fractures in osteoporotic women.33, 34Ibandronate, one of the newer bisphosphonates made popular by its monthly 150 mg dosing schedule and monthly intravenous 3-mg formulation option, confers similar anti-osteoporotic effects. As with alendronate and risedronate, patients treated with ibandronate have substantial increases in bone mineral density at all sites. In addition, they have decreases in vertebral fracture risk. If compliance is an issue, ibandronate may be a useful option in these patient groups.33, 35Zoledronic acid is available in an intravenous formulation given 5 mg once yearly as an infusion. It has demonstrated efficacy in increasing bone mineral density and reducing fracture risk. Patients being treated with weekly oral alendronate can switch to zoledronic acid if compliance is an issue. This can maintain the beneficial bone effects for twelve months after a single infusion.

The most common side effects associated with use of zoledronic acid include influenza-like post-infusion symptoms of fever, muscle pain, headache, and bone pain. The majority of symptoms resolve within three days.33, 36The side effects of the oral bisphosphonates are similar and are due to their inherent toxicity to epithelial cells lining the gastrointestinal tract. The result may be gastrointestinal irritation and ulceration. Therefore, it is recommended that patients take the medication first thing in the morning on an empty stomach along with at least two glasses of water and then remain upright for thirty minutes.33Osteonecrosis is another rare but serious complication of bisphophonate therapy.

Hormone Replacement Therapy

Estrogen formulations were approved by the U.S. Food and Drug Administration for use in prevention of osteoporosis, but not for treatment of osteoporosis.33 Estrogen, both with and without progestin, has consistently been shown to not only maintain, but also increase, bone mineral density. Smaller doses of HRT than those often used in early postmenopausal women in the range of 0.5 to 1 mg of oral 17-estradiol, 25 mg of trans-dermal 17-estradiol, or 0.3 mg of conjugated equine estrogens have a similar beneficial skeletal effect. Estrogen influences BMD loss for as long as the drug is given.37When HRT is stopped, bone loss mimics bone loss after the menopause. The downside of HRT is that it has many serious adverse effects including vaginal bleeding, breast tenderness, deep vein thrombosis and pulmonary embolism, stroke, heart disease, gall bladder disease, and an increased risk of breast, endometrial, and ovarian cancer after long-term use. Women who have had a hysterectomy can be given estrogen alone, but in others estrogen and a progestogen should be given cyclically or in a combined continuous regimen to reduce the risk of endometrial cancer.12

Selective Estrogen Receptor Modulator

In contrast to HRT, which has multiple target organs leading to a number of adverse effects, selective estrogen receptor modulators (SERMs) act as estrogen agonists or antagonists depending on the target tissue. Raloxifene acts as an antagonist of estrogen in the breast and the endometrium but acts as an agonist on bone and lipid metabolism. Raloxifene has been shown to prevent post menopausal bone loss, decrease bone turnover to premenopausal levels, and reduce the incidence of fracture.12Raloxifene also lowers the frequency of breast cancer by 70% but increases the incidence of venous thrombosis and pulmonary embolism at a similar rate to HRT. Tibolone is a synthetic steroid that has been used for the prevention of osteoporosis. It acts on estrogen, progesterone, and androgen receptors either directly or indirectly through metabolites and has different effects from different target tissues. Tibolone prevents bone loss in postmenopausal women.33

Calcitonin

Calcitonin is produced by the thyroid C cells. It effectively inhibits bone resorption by decreasing osteoclast formation and activity. Calcitonin acts quickly but its effects are reversible and transient. Despite the increase in bone mineral density the gains are not maintained after discontinuation of treatment. Calcitonin has been approved by the U.S. Food and Drug Administration for treatment of established osteoporosis but not for prevention of postmenopausal osteoporosis. Other than anti-resorptive action calcitonin also has centrally mediated analgesic action which can provide added benefit in patients with
painful vertebral fractures. It is available as both a parenteral injection and nasal spray (200 IU salmon calcitonin). Side effects include nausea, facial flushes, and diarrhea. The intranasal formulation of calcitonin is the most widely prescribed because of its ease of use and superior tolerability.12, 33, 38

Parathyroid Hormone

Continuous treatment by parathyroid hormone (PTH) results in increased bone resorption and bone loss. By contrast, intermittent PTH treatment in individuals with osteoporosis stimulates bone formation, increases BMD, and reduces the risk of fractures. Approved by the U.S. Food and Drug Administration in 2002, teriparatide (parathyroid hormone [PTH1-34]) is the only anabolic agent available for the treatment of postmenopausal osteoporosis. Administered 20 micrograms subcutaneously with use of a pen-like device, daily teriparatide injection is the most effective therapy for restoring bone quality. The effects of parathyroid hormone are mediated by enhancement of bone turnover. When administered intermittently, the anabolic effects predominate, increasing bone mass up to 13% over two years of therapy. The anti fracture efficacy of parathyroid hormone is not just by increase in bone mineral density; but it also increases trabecular number as well as trabecular thickness of the bone. Although it has been proven to be efficacious across the spectrum of osteoporosis disease severity, the use of parathyroid hormone has been limited most likely as a result of the combination of high cost, relative inconvenience, and potential adverse reactions associated with use of the drug. The use of teriparatide is contraindicated in patients with active Paget disease of bone, metastatic cancer in the skeleton, or a history of skeletal irradiation, and in children with open epiphyses. Additional adverse reactions associated with teriparatide include nausea, swelling, pain, weakness, erythema around the injection site, and elevation in plasma calcium levels.13, 33, 39, 40

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.41 It has recently been approved for osteoporosis in Europe.42 The recommended dose is 2 g daily. The drug comes in the form of granules to be taken as a suspension in a glass of water. Due to the slow absorption, it should be taken at bedtime, preferably at least 2 hours after eating. Food, milk and medicinal products containing calcium may reduce bioavailability by 60% to 70%, so they should be avoided for at least 2 hours. Side effects include an increased frequency of nausea, diarrhea, and headache in the first few months of treatment, not usually requiring withdrawal of treatment, and an excess of venous thromboembolism.43

Anabolic Steroids

Albright in 1941 first reported the efficacy of androgens in the treatment of osteoporosis. Several anabolic steroids have been tried in humans including Stanozolol and Nandrolone; the former is administered orally and the latter as intra muscular injection.44 As androgen deficiency likely plays an important role in age associated bone loss, androgen replacement might stimulate osteoblasts to produce new bone. Androgens have also been shown to decrease urinary calcium excretion, increase muscle mass. The effects of these steroids on bone mass are essentially consistent with a preferential effect on the cortical bone mass. Stanozolol and nandrolone augment bone mass in postmenopausal women, but at the expense of lowering serum HDL concentrations. Other concerns include the potential for virulization; alteration in blood lipid levels, which might increase risk for heart disease; and increased risk for hypertension. These concerns, along with the risk of hepatotoxicity when androgens are used for more than 3 months, have limited the usefulness of this form of therapy. If the patient is hypogonadal male, the use of testosterone by injection or patch is appropriate to tackle osteoporosis.43

Fluoride

Fluoride is a mineral that is incorporated into the hydroxyapatite crystal of bone. It stimulates osteoblast recruitment and activity and increases BMD in the spine. Though patients receiving sodium fluoride might improve bone mass with a lower dose, confirmation of a benefit from sodium fluoride is lacking, so currently it is not recommended for therapeutic use in osteoporosis.12, 43

Newer Drugs

Denosumab is a human monoclonal antibody against receptor activator of nuclear factor-kB ligand (RANKL). It is a fully human monoclonal antibody that was developed using transgenic mouse technology. Denosumab exerts its action through inhibition of RANK ligand, a key mediator in osteoclast activation. It 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. Denosumab is now awaiting approval for entry into the market.33, 41, 45

Cathepsin-K inhibitors are another group of novel anti-resorptive agents. Cathepsin K is critical for normal osteoclastic bone resorption. The two agents which are under development are balicatib and odanacatib. Clinical trials with these agents have demonstrated increase in hip and lumbar spine BMD, with a significant reduction in bone resorption markers.41, 46

Srr 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. Saracatinib is a novel orally available competitive inhibitor of Src kinase shown to inhibit bone resorption, but is still in trial phase.41, 47

Other Drugs

Several other drugs have been used in the treatment of osteoporosis. Vitamin K has been suggested as a treatment for osteoporosis, and it has been reported that a low intake of vitamin K is associated with an increased risk of hip fracture. Growth hormone is another drug used in the treatment of osteoporosis because it theoretically could increase muscle strength and BMD. However, there is no proof that it prevents bone loss and reduces fracture risk in postmenopausal women. Ipriflavone, a synthetic compound belonging to the family of isoflavones, may prevent bone loss, but it does not seem to reduce the incidence of fractures in osteoporotic women. Finally, Statins have been shown to increase BMD in animal studies but further information is required about their effects in humans before it can be recommended for the prevention of fragility fractures.12

Management of osteoporotic fractures

If an old osteoporotic patient sustains a fracture, there are several important age-related factors to consider when planning treatment. The functional demands in the elderly are low but long-term immobilization in bed must be avoided. Thus, it is probably even more important in the elderly to achieve stable fracture fixation that will reduce pain and facilitate mobilization. Reduced bone mass, increased bone brittleness, and structural changes such as medullary expansion must be taken into account in the osteoporotic patient when deciding on the type of surgical method to be used. The major problem in osteoporotic fracture treatment is fixation of the device to the bone because bone failure is much more common than implant breakage. Internal fixation devices such as sliding nail plates, intramedullary nails, and tension band constructs that permit skeletal loading and minimize stress at the implant-bone interface should be used. Some osteoporotic fractures are also associated with bone loss. If this occurs, it is important to achieve bone contact between the two main fragments even if this results in shortening of the extremity to achieve bony union.

Several types of fragility fractures can be mobilized in a sling, cast, or brace. Immobilization in casts can lead to joint stiffness. Furthermore, a cast does not control fracture shortening, which is often seen in osteoporotic bone, and if the subcutaneous tissue is very mobile, as it often is in the elderly, cast fixation will not provide adequate fracture fixation. External fixators can be used, but the main problem with external fixation in osteoporotic bone is the same as for screw fixation—namely, loss of fixation. Loosening of the device is often followed by pin tract infection and local bone resorption, sometimes leading to a secondary fracture at the pin site. The introduction of hydroxyapatite-coated pins has reduced this complication because fixation is improved compared with when using titanium-coated and standard pins. Another method used to improve internal fixation and to avoid bone resorption is to anchor the pins or screws with polymethylmethacrylate bone cement. This can be inserted into the bone and allowed to harden before drilling, or it can be inserted into the screw holes just before the screws are inserted. If this method is used, it is important that the cement does not penetrate the fracture so as to interfere with fracture healing.

Intramedullary nailing is a popular treatment for osteoporotic long-bone fractures. It is biomechanically more favorable and permits early weight bearing. With the introduction of interlocking nails, it is also possible to nail fractures that are close to the metaphyseal regions in long bones. The fixation can be improved by the use of several interlocking screws in different directions or by augmentation of the screws with bone cement. It is also important to realize that because osteoporosis causes the diameter of the intramedullary canal to increase; larger-diameter nails must often be used in older patients. Even if osteoporosis does not impair fracture healing, the diminished bone mass will reduce the amount of callus formation and increase the time taken to restore adequate bone strength. Therefore, autogenous cancellous bone graft is often recommended to enhance fracture healing. However, in patients with
osteoarthritis, the amount of cancellous bone available for grafting is reduced, often necessitating the use of allografts or biodegradable synthetic products such as calcium phosphate cement that fill defects in osteoporotic bone.

Introduction of locked plating has improved the quality of fixation of osteoporotic fractures. It provides better fixation than conventional plates and also reduce stress at implant bone interface. Joint replacement surgery is a good option after displaced femoral neck fractures because the stability provided by the implant permits immediate weight bearing and mobilization.

The treatment of osteoporotic vertebral compression fractures has usually been non-operative, with the amount of disability directly relating to the number of fractured vertebrae. However, within the past few years, vertebroplasty and kyphoplasty have been introduced as new treatment modalities which allow immediate pain relief and weight bearing; thus reducing the co-morbidities.

along with the other standard measures. More research needs to be conducted to develop a separate questionnaire for Indian and or Asian population.

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