Review Article

Postmenopausal Osteoporosis – An Indian Perspective

Remya Rajan, Jinson Paul, Nitin Kapoor, Kripa Elizabeth Cherian, Thomas V. Paul
Department of Endocrinology and Metabolism, Christian Medical College, Vellore, Tamil Nadu, India

Abstract

Osteoporosis is the most common metabolic bone disease in humans. It is more common in women and contributes to significant morbidity and mortality. Postmenopausal osteoporosis is due to the withdrawal of the protective effect of estrogen at menopause and increased follicle-stimulating hormone, all contributing to increased bone resorption. Evaluation of osteoporosis involves assessment of risk factors, biochemical evaluation, assessment of bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA), identification of vertebral fractures with vertebral fracture assessment tool, and prediction of fracture risk with various tools. Treatment includes prevention of osteoporosis using lifestyle modification and fall prevention, in addition to pharmacotherapy. Several drugs are licensed to reduce fracture risk namely anti-resorptive agents (such as bisphosphonates and denosumab) and anabolic agents (such as teriparatide). Improved understanding of the cellular basis for osteoporosis has resulted in new drugs targeted to key pathways in the pathogenesis. The response to treatment is monitored using bone turnover markers as well as DXA scan.

Key words: Bisphosphonates, dual-energy X-ray absorptiometry, fragility fracture, postmenopausal osteoporosis

Address for correspondence: Dr. Thomas V. Paul, Department of Endocrinology and Metabolism, Christian Medical College, Vellore - 632 004, Tamil Nadu, India.
E-Mail: thomasvpaul@yahoo.com

Introduction

Osteoporosis being the most common metabolic bone disease in humans, bone health is an important aspect of composite health. According to the 1993 International consensus, osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1]

Overall, osteoporosis is three times more common in women than in men, because women have a lower peak bone mass, which is compounded by the hormonal changes that occur at the time of menopause. It is a silent disease until fractures occur, which causes important secondary health problems and even death. The goal of osteoporosis care is prevention of fractures and ultimately reduction in morbidity and mortality associated with it.

Epidemiology of Osteoporosis

Currently, it is estimated that over 200 million people worldwide suffer from this disease.[2] Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe. In India, the prevalence of osteoporosis in postmenopausal women in various studies varies between 25% and 62%.[3-5] Aging of populations worldwide is responsible for a major increase in the incidence of osteoporosis.[6]

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Patients with a history of vertebral fracture have a 2.3-fold increased risk of future hip fracture (HF) and a 1.4-fold increase in the risk of distal forearm fracture.[7] Twenty percent of women aged above 60 years die within 1 year of sustaining HF.[8] Thus, osteoporosis contributes to significant morbidity and mortality to postmenopausal women.

Factors Determining Bone Strength and Bone Loss

Table 1 lists the various factors leading to low bone mass and strength.[9,10]

Pathogenesis

Skeletal fragility can result from:

a. Failure to produce a skeleton of optimal mass and strength during growth
b. Excessive bone resorption resulting in decreased bone mass and micro-architectural deterioration of the skeleton
c. An inadequate bone formation response to increased resorption during bone remodeling.

Estrogen deficiency was initially proposed to be the sole mechanism by which bone mass decreases in postmenopausal women and elderly men. The pathways involved in this include the differential effects of estrogen on osteoblast/osteoclast apoptosis, inflammatory cytokine-mediated increase in osteoclast, and activity and lack of estrogen-induced suppression of hypoxia-inducible factor 1 alpha protein, leading to osteoclast activation.[11,12] However, recent studies show that increase in follicle-stimulating hormone levels also contributes to the imbalance between bone formation and resorption by messenger RNA expression of genes such as receptor activator of nuclear factor kappa B (RANK), tartrate-resistant acid phosphatase, matrix metalloproteinase-9, and cathepsin K in a dose-dependent manner, thereby increasing osteoclastic activity.[13] Figure 1 depicts the pathogenesis of postmenopausal osteoporosis.[14]

Evaluation for Osteoporosis

Assessment of osteoporosis includes evaluation of risk factors which can adversely impact bone health, biochemical evaluation, radiological imaging, and fracture risk assessment tools. The risk factors that lead to bone loss have been described already.

Table 1: Factors leading to low bone mass and strength

Bone strength	Genetic make-up
	Nutrition
	Physical activity
	Body weight
Bone loss	Age
	Menopause - estrogen deficiency
	Smoking
	Alcohol
	Late menarche
	Low bone mass - sarcopenia
	Premature ovarian failure

Biochemical evaluation

Biochemical evaluation involves albumin-corrected total serum calcium, phosphate, alkaline phosphatase, creatinine, 25 hydroxyvitamin D (not mandatory), and parathyroid hormone (PTH) (in selected cases). In addition, in selected cases, secondary causes such as Cushing syndrome, primary hyperparathyroidism, and multiple myeloma need to be ruled out.

Bone turnover markers

Bone turnover markers (BTMs) are biochemical markers used in the evaluation as well as monitoring of treatment for osteoporosis. They are reliable and cost-effective in most clinical settings. Bone turnover is balanced with coupling of bone formation and resorption at various rates, leading to continuous remodeling of bone. A study of BTMs provides an insight of the dynamics of bone turnover in many metabolic bone disorders based on the increase or decrease in the bone formation/resorption markers. They are useful in the estimation of fracture risk and monitoring the adherence and response to therapy. However, BTMs are subjected to various preanalytical and analytical variations necessitating strict sample collection and assay methods along with utilizing ethnicity-based reference standards for different populations.[15]

Biochemical markers of bone metabolism are broadly divided into markers of bone formation and markers of resorption. C-terminal telopeptide of type 1 collagen (CTX) and N-terminal pro-peptide of type 1 collagen are the commonly used bone resorption and formation markers, respectively.

In a South Indian study, the authors tried to derive an ethnicity-specific reference range for BTMs and found that BTMs had an inverse correlation with bone mineral density (BMD).[16]

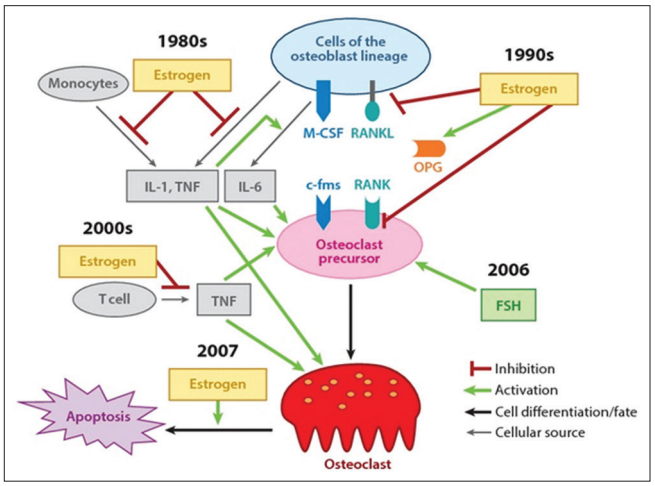

Figure 1: Pathogenesis of postmenopausal osteoporosis with years indicating the time of discovery of new pathogenic mechanisms.

Radiography

Osteopenia is often evident in an X-ray when the patient suffers a low-trauma fracture. However, by the time osteopenia is visible on X-ray, there may be significant bone loss. When a patient presents with back pain, lateral radiograph of the spine may reveal vertebral fractures. Genant grading has been used to categorize the severity of vertebral fractures (mild, moderate, and severe) based on the reduction in height or reduction in projected area of the vertebrae [Figure 2].[16,17]

Dual-energy X-ray absorptiometry scan

BMD assessment by dual-energy X-ray absorptiometry (DXA) scan [Figure 3] is the gold standard for the diagnosis of osteoporosis. It gives an estimate of the quantity of bone present at various sites, and is the standard of measure for osteoporosis. It is a highly accurate X-ray technique used for the measurement of BMD at skeletal sites such as lumbar spine, hip, and wrist. Bone BMD measured by DXA is expressed as g/cm^2. However, by convention, the score then is converted to a T-score and a Z-score.[18]

- T-score: Number of standard deviations above or below BMD of age-matched controls
- Z-score: Number of standard deviations above or below BMD of young normal mean.

According to World Health Organization criteria, osteoporosis is defined as T-score ≤−2.5 [Table 2]. Z-score of ≤−2 is defined as low bone mass or bone mass below the expected range for age (this term is used in women <50 years of age).

DXA technique requires less radiation, is less expensive, and has better reproducibility.

Table 2: World Health Organization criteria for osteoporosis

WHO criteria for osteoporosis	
Definition	***T*-score**
Normal	≥ −1 SD
Osteopenia	Between −1 and −2.5 SD
Osteoporosis	≤ −2.5 SD

SD: Standard deviation, WHO: World Health Organization

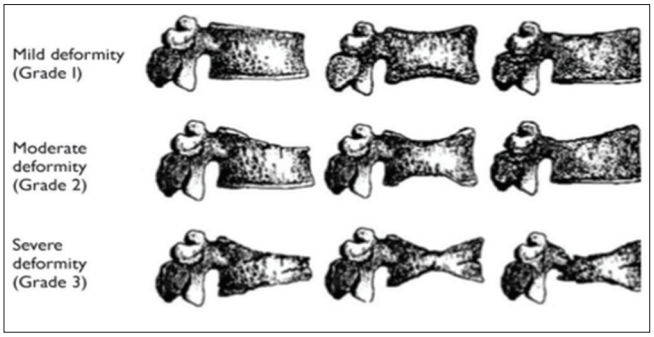

Figure 2: Genant grading-semi-quantitative assessment of vertebrae and classifying them as mild, moderate and severe vertebral fractures according to reduction in height of vertebra.

Limitations of dual-energy X-ray absorptiometry scan

Although BMD is currently the gold standard measure of osteoporosis, many patients with fractures are found to have BMD in the osteopenia/normal range.[18] Thus, a normal BMD cannot rule out the possibility of osteoporotic fracture.[19] In addition, despite BMD being used as a measure of evaluation of treatment efficacy in clinical practice, studies have shown that there is a poor correlation between the increase in BMD with antiresorptive treatment and the extent to which the treatment decreases fracture risk.[20] In India, the number of DXA scanning centers is limited and most of them are located in urban areas.

Vertebral fracture assessment

In patients undergoing DXA for BMD measurement, an additional tool called vertebral fracture assessment (VFA) [Figure 4] helps in imaging the thoracic and lumbar vertebrae to evaluate vertebral fractures.[21] The fractures are categorized into mild, moderate, and severe based on Genant semi-quantitative criteria, by comparing the shape of the vertebrae to the neighboring vertebrae. With 87%–93% sensitivity and 93%–97% specificity for detecting moderate and severe vertebral fractures, VFA compares well with the conventional radiography, at a low radiation dose.[22] In this context, the International Society for Clinical Densitometry has made suggestions regarding possible indications for doing VFA.[23] However, this technology remains underutilized in routine clinical practice till date.

Trabecular Bone Score

The microarchitecture of the bone can be measured by histomorphometric analysis of transiliac crest bone biopsy, quantitative computed tomography (QCT), high-resolution peripheral QCT, high-resolution magnetic resonance imaging, micro-CT, and trabecular Bone Score (TBS). Among the above-said techniques, TBS appears to be a readily clinically available, noninvasive technology that permits efficient and accurate clinical evaluation of skeletal microstructure.[24]

TBS is a textural index that evaluates pixel gray□level variations in the lumbar spine DXA image, providing an indirect index of trabecular micro-architecture. TBS is an

Figure 3: Shows the image of a dual energy X-ray absorptiometry scan in which a patient bone mineral density at femur is being assessed.

indirect physical measurement of bone microarchitecture, but rather, an overall score computed by the projection of the three-dimensional structure onto a two-dimensional (2D) plane. TBS is derived from the experimental variograms of 2D projection images. TBS is calculated as the slope of the log-log transform of the 2D variogram, where the slope characterizes the rate of gray-level amplitude variations [Figure 5]. Currently, certain cutoff points [Table 3] proposed by the manufacturers have been used to define normalcy in TBS.[24]

Fracture risk assessment tool (FRAX)

FRAX is the most widely used fracture risk assessment tool that takes into account nine factors, namely age, BMD, body mass index (BMI), prior fragility fracture, use of oral glucocorticoids, parental history of HF, current smoking, alcohol intake, and rheumatoid arthritis [Figure 6]. It predicts the 10-year probability of HF and major osteoporotic fracture (MOF).[25] A threshold of >20% for MOF and >3% for HF is considered the intervention threshold for initiating for osteoporosis. The main objective of using the FRAX tool is to enable medical professionals to identify those patients who would benefit from pharmacological therapy in reducing fracture risk. However, like any other scientific tool, FRAX has few limitations. It does not encompass all the important factors that may predict fracture risk in a given individual such as physical activity, Vitamin D deficiency, likelihood of fall assessment, BTMs, or the rate of bone loss on sequential BMDs. FRAX also needs validation for deciding thresholds (of MOF and HF) based on ethnicities.[26,27]

Table 3: Trabecular bone score cutoff points

TBS score (no units)	Bone status
>1.350	Normal
1.200 and 1.350	Partially degraded bone
≤1.200	Degraded bone

TBS: Trabecular Bone Score

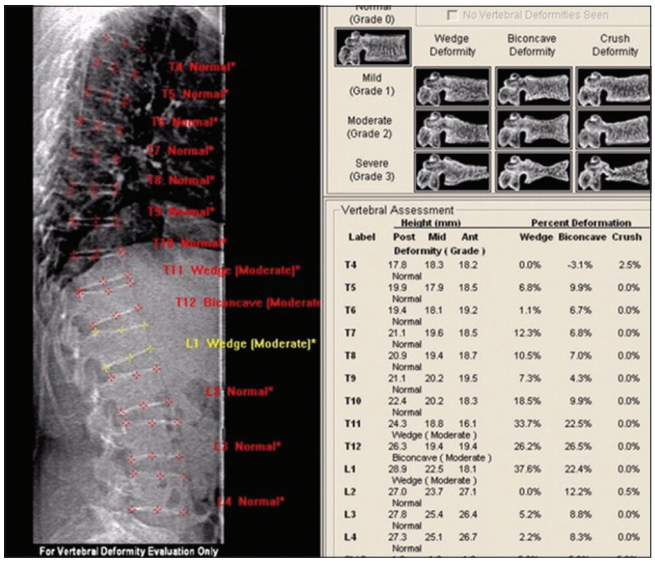

Figure 4: Example of a vertebral fracture assessment study. Left panel: Spine image with markers placed on vertebral edges. Upper right panel shows Genant classification. Lower right panel shows a table with measurements and percentage deformity for each vertebrae.

Whom to Screen for Osteoporosis?

The following patients need to be screened for osteoporosis by DXA based on the recommendation by the Indian Menopause Society (IMS):[28]

- All postmenopausal women more than 5 years of menopause
- Postmenopausal women <5 years of menopause with risk factors (low BMI, glucocorticoid use, alcohol, smoking, rheumatoid arthritis, prior history of fragility fracture, and parental history of HF)
- Women in menopause transition with secondary causes
- Radiological evidence of osteopenia and presence of vertebral compression fracture
- Women with fragility fractures
- Ideally before initiating pharmacotherapy for osteoporosis.

Whom to Treat for Osteoporosis?

According to the IMS, treatment of osteoporosis is indicated in the following situations:[28]

- Presenting with fragility fractures
- Diagnosis of osteoporosis based on DXA, i.e., Tscore ≤-2.5 at hip or spine
- With secondary causes and highrisk fractures
- In the absence of BMD measurements by DXA, for treating postmenopausal women, intervention is individualized, understanding and considering the cost benefit and risk benefit outcomes of the intervention.

Osteoporosis and Diabetes Mellitus

Both type 2 diabetes mellitus (T2DM) and osteoporosis are negatively affected by aging and lifestyle changes and often

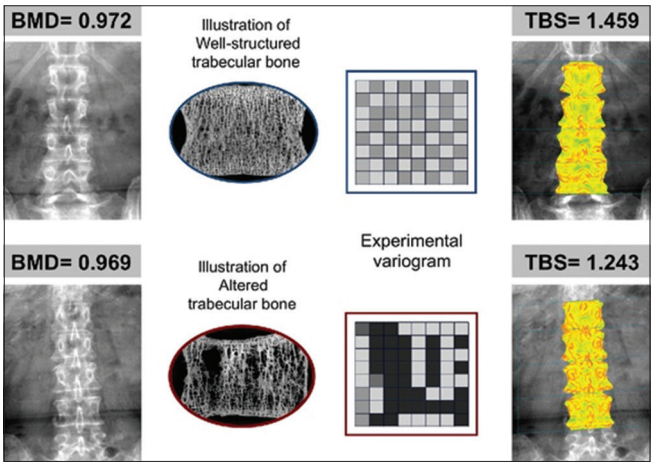

Figure 5: The trabecular bone score principle is based on the fact that numerous, connected and less sparse trabeculae translate into a high trabecular bone score value, whereas a low trabecular number and connectivity and high trabecular separation translate into a low trabecular bone score.

both coexist. Assessment of bone quantity based on BMD underestimates the risk of fracture in patients with T2DM as BMD may be falsely high in people with diabetes.[29] Hence, assessment of bone micro-architecture by TBS may be a better measure of bone health in T2DM.[30,31] In addition, one should be cautious in using oral antidiabetic drugs such as pioglitazone and canagliflozin in elderly women due to the potential increase in the risk of fracture associated with these drugs.[32,33]

Management of Osteoporosis

Lifestyle modification

Dietary calcium

Calcium helps in maintaining the strength and structure of bones. Calcium is available in most of the dairy products. The recommended daily allowance of calcium is 1000–1500 mg. Many Indian studies have shown that our dietary calcium intake is well below the recommended amount. In a cross-sectional study from South India, 74.5% of the postmenopausal women were consuming less than the recommended daily allowance of calcium.[34]

Physical activity

Reduced physical activity is a major risk factor for the development of osteoporosis and fractures.[35] Moderately increased physical activity, which is done regularly for long-term periods, helps in improving the mechanical competence of the skeletal system considerably.

Fall prevention

Elderly people are more prone to fall because of poor eye sight, loss of coordination, and development of neuropathy. They should be aware of the fall preventive measures such as, using hand rails for going up and down the steps, avoid walking in slippery surfaces, and using a walking stick if needed.

Calcium and cholecalciferol

Calcium and Vitamin D supplements are considered a first-line treatment in osteoporosis. Various calcium preparations are available in our country. Calcium carbonate needs acid for its absorption. In patients who are taking drugs which reduce gastric acid secretion, it is advised to give calcium citrate maleate. Vitamin D supplementation in the form of cholecalciferol is considered one of the early treatments in osteoporosis. Vitamin D deficiency is prevalent in 70% of the general population in our country.[36] Cholecalciferol 60,000 U once in every 1–2 months is recommended in all postmenopausal women with or without osteoporosis. Active Vitamin D (calcitriol) is not indicated in the usual management of osteoporosis unless patients have renal dysfunction.

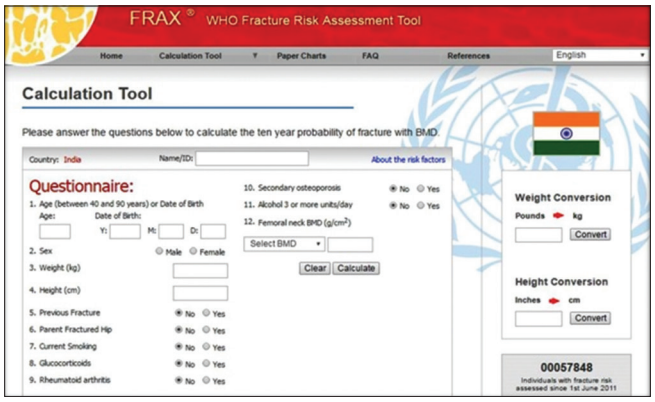

Figure 6: The image shows the web-based FRAX tool.

Pharmacotherapy

Drugs used for the treatment of osteoporosis are widely divided into antiresorptive and anabolic agents.

Antiresorptive agents

The classification of anti-osteoporotic drugs is shown in Figure 7.

Bisphosphonates

Bisphosphonates are the most widely used drugs in the treatment of osteoporosis. Various bisphosphonates are listed below:[37]

1. Zoledronic acid 4 mg intravenous (IV) once a year
2. Alendronate 70 mg weekly
3. Ibandronate 150 mg monthly
4. Risedronate 35 mg weekly.

In a study by Sooragonda *et al*. from South India, it was found that yearly administration of zoledronic acid for 2 years showed significant improvement in BMD at lumbar spine and preserved BMD at the neck of femur.[38]

Contraindications for bisphosphonates

- Chronic kidney disease (estimated glomerular filtration rate <35 ml/min)
- Suppressed bone turnover beta cross-Laps (CTX) <200 pg/ml
- Severe allergic reaction to previous bisphosphonate therapy.

Side effects of bisphosphonates[37]

Acute side effects

- Gastrointestinal toxicity, related to oral bisphosphonates
- Acute-phase reaction – Fever, chills, and body pain, related to IV bisphosphonate
- Atrial fibrillation
- Electrolyte imbalance – Hypocalcemia, hypomagnesemia, hypokalemia, and hypophosphatemia.

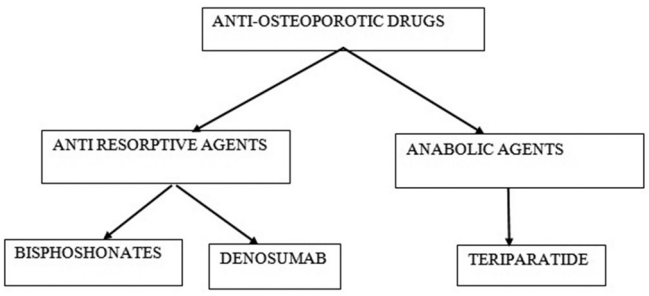

Figure 7: Classification of anti-osteoporotic drugs.

Related to long-term therapy

- Excessive suppression of bone remodeling leading to increased bone fragility
- Atypical fractures – Low-energy subtrochanteric femoral fractures. These are often preceded by prodromal thigh pain
- Osteonecrosis of the jaw.

Denosumab[37]

Denosumab is another potent antiresorptive agent which acts by inhibiting RANK ligand, thus preventing proliferation and maturation of pro-osteoclasts. It is given as subcutaneous injections once in every 6 months. This drug can be used even in patients with chronic kidney disease Stage 3 or above. Skin rash or eczema, hypocalcemia, and oversuppression of bone turnover are some of the side effects of denosumab therapy.

Estrogen replacement and selective estrogen receptor remodulators[39]

Because of the roles estrogen receptor α and estrogen receptor β play in osteoclast apoptosis, the use of estrogen replacement is effective for the prevention of osteoporosis in postmenopausal women. Studies show that treatment with hormone replacement therapy increases bone density at the lumbar spine and reduced BTMs at 2 years' treatment. Because of a potentially increased risk for venous thromboembolic disorders, breast cancer, cardiac events, stroke, and endometrial cancer, estrogen replacement is not recommended as the first-line preventive treatment for osteoporosis.

Selective estrogen receptor remodulators (SERMs) are nonsteroidal synthetic drugs with similar effects on bone and the cardiovascular system as estrogen, but without any of the adverse events on the breast and endometrium. The most frequently used SERMs for the prevention of osteoporosis in postmenopausal women are raloxifene, lasofoxifene, and bazedoxifene. SERMs reduce vertebral fractures in osteoporotic women, but there is no statistically significant data demonstrating that they decrease the risk of nonvertebral or HFs compared to placebo.

Calcitonin[39]

Calcitonin acts by inhibiting bone resorption by increasing osteoblast activity. To date, data on the effect of calcitonin on BMD of other skeletal sites are conflicting, as shown in recent studies. Hence, it is not recommended for the treatment of osteoporosis.

Anabolic agent[37]

Teriparatide

Teriparatide is a recombinant human PTH (1–34) which is administered as subcutaneous injections daily (20 μg/day). The total duration of treatment ranges from 18 to 24 months. Cost is a major concern in PTH therapy. As teriparatide increases both bone formation and resorption, it is advised to give bisphosphonates after completing the course of PTH therapy.

Indications for teriparatide

- Multiple vertebral fractures (clinical or radiographic)
- Very low BMD (T-score <−3)
- Suboptimal response to antiresorptive therapy (incident fractures or active bone loss during therapy).

Newer drugs in anti-osteoporotic therapy[40]

- Abaloparatide
- Romosozumab.

Using anabolic and antiresorptive agents in combination or in succession improves bone density and bone strength more than either agent alone due to their synergistic action. This is called combination/sequential therapy and is useful in selected cases.

Monitoring and Follow-up

Those who are on anti-osteoporotic treatment should be monitored for side effects of the drugs. It is very important to decide the frequency and duration of the treatment for each patient according to their response to therapy. BTMs (if available) can be monitored once in every 3–6 months, BMD by DXA once in every 1–2 years, and X-ray spine and hip – if clinically indicated. It is important to screen for atypical femur fracture in any patient on bisphosphonate therapy who presents with thigh pain.

Drug holiday – in patients who are on antiresorptive therapy, it is advisable to withhold treatment if the bone turnover is suppressed.

Conclusion

Osteoporosis is a major cause of morbidity and mortality in older people due to the increased risk of fractures. Despite the advancement in the field of fracture risk assessment and the availability of a range of pharmacological options to reduce fracture risk, many high-risk individuals do not receive adequate investigation and treatment. Strategies to improve bone health include lifestyle modification and fall prevention, in addition to pharmacotherapy. Improved understanding of the cellular basis for osteoporosis has resulted in new drugs targeted to key pathways, which are under development.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Ethical statement

We certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check.

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