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POSITION PAPER

The Indian Society for Bone and Mineral Research (ISBMR) position statement for the diagnosis and treatment of osteoporosis in adults

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Abstract

Summary The Indian Society for Bone and Mineral Research (ISBMR) has herein drafted clinical practice guidelines for the diagnosis and management of osteoporosis for the people of India. Implementation of the position statement in clinical practice is expected to improve the overall care of patients with osteoporosis in India.

Purpose In India, osteoporosis is a major public health problem. However, in the absence of any robust regional guidelines, the screening, treatment, and follow-up of patients with osteoporosis are lagging behind in the country.

Methods The Indian Society for Bone and Mineral Research (ISBMR), which is a multidisciplinary group of physicians, researchers, dietitians, and epidemiologists and who study bone and related tissues, in their annual meeting, drafted the guidelines for the diagnosis and management of osteoporosis that would be appropriate in a resource constraint setting like India.

Results Diagnosis of osteoporosis can be made in a patient with minimal trauma fracture without the aid of any other diagnostic tools. In others, bone mineral density measured by dual-energy X-ray absorptiometry remains the modality of choice. Data indicates that osteoporotic fractures occur at an earlier age in Indians than in the West; hence, screening for osteoporosis should begin at an earlier age. FRAX can be used for fracture risk estimation; however, it may underestimate the risk of future fractures in our population and still needs validation. Maintaining optimum serum 25-hydroxyvitamin D levels is essential, which, in most cases, would require regular vitamin D supplementation. Pharmacotherapy should be guided by the presence/absence of vertebral/hip fractures or the severity of risk based on clinical factors, although bisphosphonates remain the first choice in most cases. Regular follow-up is essential to ensure adherence and response to therapy.

Conclusions Implementation of the position statement in clinical practice is expected to improve the overall care of patients with osteoporosis in India.

Keywords Osteoporosis · Fracture prevention · Guidelines · ISBMR · India

Introduction

Osteoporosis is a condition characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporosis increases the risk of incident fragility fractures. Fragility fractures are a major health concern that contribute significantly to morbidity and increased mortality. As the population worldwide is aging, a significant increase in the incidence of osteoporosis is expected. Approximately 30% of all postmenopausal women have osteoporosis in the USA and Europe. At least 40% of these women and 15–30% of men will sustain one or more fragility fractures within their remaining lifetime. In other words, 1 in 3 women over age 50 will experience osteoporotic fractures, as will 1 in 5 men over age 50 [1, 2]. Despite marked advances in diagnosis and treatment for osteoporosis, very few patients receive appropriate treatment, even after a fragility fracture [3].

India is home to more than 1.3 billion people, with approximately 230 million Indians over 50 years. Most data

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on the prevalence of osteoporosis among women in India come from studies conducted in small groups spread across the country, and estimates from 2015 have suggested that 20% of the 230 million Indian women over age 50 have osteoporosis [4, 5]. Prevalence of osteoporosis ranging from 8 to 62% in Indian women of different age groups has been reported in several studies [6–14]. The prevalence of osteoporosis in males older than 50 years is also variable, ranging from 8.5 to 24.6% [9, 15, 16]. A 2001 study in expatriate Indians in Singapore showed that the incidence of hip fracture in the Indian population was 361 for women and 128 for men per 1,00,000 population. Extrapolating these observations for the current Indian population as a whole, the number of hip fractures every year would be more than 440,000, with a female to male ratio of about 3:1, with a projected incidence of more than 600,000 in 2020 and over 1 million in 2050.

Urbanization appears to be associated with an increased prevalence of osteoporosis due to lifestyle habits such as sedentary lifestyle, increased indoor living, and lower sun exposure [4]. The awareness of osteoporosis is low in India, with surveys indicating that only 10–15% of Indians are aware of the disease [17]. According to the International Osteoporosis Federation, the availability of dual-energy X-ray absorptiometry instruments (DXA), a key tool for diagnosing osteoporosis, is about 0.26 per million in India, far below the recommended number of 10.6 per million [18]. Moreover, most of the DXA instruments are located in urban areas, and even many large cities in India do not have DXA facilities. Furthermore, the fact remains that the cost of DXA and osteoporosis treatments are largely not covered by insurance. Indians fare poorly compared to the more developed Asian countries like Japan and Korea, where availability of DXA is much higher (20.8 and 24.5 per million, respectively) [19]. Besides, only 20% of patients with osteoporosis are diagnosed and treated in India [20]. Even then, the treatment compliance rate is only around 64% [20].

Apart from the fact that osteoporosis is often asymptomatic (until the patient sustains a fracture), and its treatment is usually life-long and costly, the lack of a definite local consensus guideline makes management of osteoporosis in India even more difficult. The Indian Menopause Society published clinical practice guidelines on postmenopausal osteoporosis in 2013 [21]; however, new guidelines need to be formulated based on recent clinical evidence.

The Indian Society for Bone and Mineral Research (ISBMR), which is a multidisciplinary group of physicians, researchers, dietitians, and epidemiologists and who study bone and related tissues, in their annual meeting, drafted the guidelines for the diagnosis and management of osteoporosis that would be appropriate in a resource constraint setting like India. The position paper has been discussed under the heads, as summarized in Table 1.

Table 1 Summarizing the points that the expert committee have considered while drafting the consensus

Risk factors for osteoporosis
Diagnosis of osteoporosis
Indications for treatment
Pharmacological management of osteoporosis
Follow-up for patients with osteoporosis

Table 2 Summarizing the non-modifiable and modifiable risk factors for primary osteoporosis

Non-modifiable risk factors	Modifiable risk factors
Age	Nutrition
Sex	Calcium intake
Ethnicity	Vitamin D intake
Genetics	Lifestyle factors—smoking, alcohol, exercise
Peak bone mineral density	Use of medications

Risk factors for osteoporosis

Various risk factors that contribute to postmenopausal osteoporosis are broadly classified as non-modifiable or modifiable risk factors and have been summarized in Table 2.

Non-modifiable risk factors include sex, age, ethnicity, and genetics. Women have a smaller body frame size, and in a developing country like India, are more likely to have lower consumption of calcium-rich foods and inadequate sunlight exposure because of cultural or secular reasons. Furthermore, estrogen deficiency resulting from menopause contributes in a significant way to the development of osteoporosis. Although the average age at menarche in Indian girls is ~ 12.5 years, the average age at menopause is 46.2 years which is earlier than that seen in non-Indian women [22], and this is a significant risk factor for the development of osteoporosis in Indian women [13, 23]. Numerous studies have reported increasing prevalence of osteoporosis with advancing age, and this trend has been observed to a great extent among Indian women compared to men [9, 13].

Genetic factors, race, and ethnicity also have a major influence on peak bone mass attainment. Asian Indian women have been shown to have 5–15% lower bone mineral density (BMD) than non-Asian women [24–26]. Also, polymorphisms in the gene for vitamin D receptors in different races have been suggested to contribute to the ethnic differences in BMD [4, 27, 28].

Modifiable risk factors include the following:

1. Nutritional factors: Calcium and vitamin D, the two primary nutrients involved in bone health, play a major role in influencing the risk of osteoporosis.

   a. Calcium: Calcium in the form of hydroxyapatite crystals is deposited in the bone matrix and is responsible for bone hardness. Calcium is obtained from the diet through dairy as well as non-dairy sources. The bioavailability of calcium from dairy sources is much higher than non-dairy sources. Several studies have reported that Indian diets do not meet the recommended dietary allowances of 600 mg/day of calcium for adult women as recommended by the Indian Council of Medical Research [29]. Indian diets are predominantly vegetarian, and the contribution of dairy products to the overall calcium intake is minimal in the lower socioeconomic classes. Furthermore, the unequal distribution of milk and milk products, with boys and men being served larger portions, is another factor that worsens the situation [5]. According to Harinarayan et al., Indian diets have a higher ratio of phytates to calcium, especially among rural Indians [30]. Phytates may hinder calcium absorption from the already calcium-deficient diets. A survey conducted in 2011–2012 in India reported a dietary calcium intake of only 429 mg/day [31].
   b. Vitamin D: Vitamin D is synthesized in the human skin upon exposure to sunlight. Although there is no dearth of sunlight in India, several reports have shown that Indians suffer from vitamin D deficiency [32–34]. Some of the reasons for vitamin D deficiency among Indians may be lower sun exposure due to indoor lifestyle, traditional clothing leading to less skin exposure to sunlight (saris, salwar-kameez, etc.), inadequate dietary intake, poor vitamin D fortification of foods, and darkly pigmented skin and atmospheric pollution [18, 35]. Vitamin D deficiency results in ineffective calcium absorption from the gut, which in turn affects the mineralization of bones. The findings of the Delhi Vertebral Osteoporosis Study (DeVOS) from India suggest that the odds of having osteoporotic fractures in subjects consuming calcium and vitamin D supplements are lower [36].

2. Nutritional status: Poor nutritional status is also a major contributing factor for osteoporosis, especially in India. Bodyweight lower than 60 kg significantly increases the risk of osteoporosis in women [23]. Several pathways link body weight and bone, and both lean and fat masses are determining factors for BMD. Various studies have demonstrated a positive correlation between body mass index (BMI) and BMD [37, 38]. Sarcopenia has also been shown to be associated with low BMD [39].
3. Other lifestyle factors: Urbanization has resulted in a sedentary lifestyle, decreased exposure to sunlight (sometimes from traditional clothing use), and low physical activity, which are detrimental to bone health [18]. Physical exercise, especially weight-bearing exercise, helps to improve and maintain muscle and bone strength and also helps to improve body balance [21]. Lack of exercise is significantly associated with lower BMD in Indian women [38].

   While being a major risk factor for osteoporosis, cigarette smoking is low among Indian women to be a significant risk for osteoporosis [23]. Heavy drinkers have approximately a 1.7-times greater risk for osteoporosis than light drinkers [40]. However, the DeVOS study reported that neither cigarette smoking nor alcohol consumption was common in Indian women and was not significantly associated with prevalent fractures [36].

   Recent data suggest that type 1 (T1D) and type 2 diabetes mellitus (T2D) are significant risk factors for fractures. Bone mineral density tends to be low in patients with T1D, BMD may be normal in patients with T2D, and yet, the fracture risk is increased, reflecting poor bone quality in these patients. It is not known whether better control of diabetes mitigates the increased fracture risk.
4. Medication use: Long-term over-the-counter glucocorticoid use [41] and minimum use of hormone replacement therapy (HRT) in the Indian scenario are a predominant cause of osteoporosis. In addition, use of proton pump inhibitors and anticonvulsants have also been associated with low BMD and osteoporosis [42–44].

Diagnosis of osteoporosis

Clinical

Any adult with a fragility fracture should be suspected of having underlying osteoporosis (primary vs. secondary). In addition, historical height loss of more than 4 cm in postmenopausal women raises the possibility of asymptomatic vertebral fractures [45]. Individuals with persistent back pain may have underlying vertebral fractures as well.

Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry, or DXA, is the most commonly used technique for measuring BMD. Although true density measurement is 3-dimensional, DXA is a two-dimensional measurement and thus calculates areal bone density [46]. We recommend against the use of quantitative

ultrasound (QUS) for screening or initial decision-making regarding treatment of osteoporosis.

Bone mineral density values are calculated in grams per cm^2 (or area of bone density). In order to account for the differences across DXA equipment across different manufacturers, the values are further expressed in standard deviations (SD) units from the mean BMD value of the reference population [47]:

- "T" score of an individual is the number of SD his/her BMD deviates from the mean BMD of 20–29-year-old reference population (usually Caucasian women—see further discussion below).
- "Z" score of an individual is the number of SD his/her BMD deviates from the mean BMD of the same age, gender, and ethnic group reference population.

Whether the reference population should be matched for sex and ethnicity is a matter of debate [48]. Most of the data on fracture/BMD relationship has been derived using young Caucasian women as the reference population. The 2019 International Society for Clinical Densitometry (ISCD) Official Position recommends the use of a uniform Caucasian (non-race adjusted) female normative database for women of all ethnic groups. It also states that manufacturers should continue to use NHANES III data as the reference standard for femoral neck and total hip T-scores [49].

Although normative data on BMD in healthy Indian adults exist [9, 50, 51], at present, there is insufficient data to assess the fracture risk using the Indian BMD reference database. Hence, for all practical purposes and in line with the 2019 ISCD Official Position, the Caucasian female database derived from the NHANES III is used as India's reference population for calculating T-scores [52]. With regard to males, the 2019 ISCD Official Position recommends the use a uniform Caucasian (non-race adjusted) female reference for men of all ethnic groups; nevertheless, most manufacturers continue to use the young male Caucasian database as the reference population.

The purpose of measuring BMD with DXA is to identify individuals at risk of developing future fractures so that preventative strategies can be employed. In addition, changes in BMD measurements over time may be of value in determining response to therapy.

Indications for DXA measurement

The number of available DXA scanners is limited in India, with only 0.26 scanners for 1 million population [18]. This necessitates a judicious use of DXA facilities. Simultaneously, there is a dearth of adequate utilization of DXA by specialties treating individuals at risk for osteoporosis in India [53]. Accordingly, as a trade-off, the following indications from the National Osteoporosis Foundation (NOF) can be adopted for DXA measurement recommendations [54]. Since data indicates that osteoporotic fractures occur at an earlier age in Indians than in the West, we recommend screening at an earlier age [5, 55].

- Women aged 60 and older and men aged 65 and older, regardless of clinical risk factors
- Postmenopausal women younger than 60 years and men aged 50–64 years when there are concerns for osteoporosis based on their clinical risk factor profile
- Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk, such as low body weight, prior low-trauma fracture, or high-risk medication
- Individuals who have had a fragility fracture before the age of 50 years
- Individuals with a condition (e.g., rheumatoid arthritis, diabetes mellitus, malabsorption syndrome) or who are taking medication (e.g., glucocorticoids in a daily dose ≥ 5 mg prednisone or equivalent for ≥ 3 months) associated with low bone mass or bone loss
- Any individual being considered for pharmacologic therapy for osteoporosis

Biochemical investigations

Biochemical investigations should be directed at identifying the underlying cause of osteoporosis. In patients with osteoporosis, prior to initiation of pharmacotherapy, a basic biochemical and hormonal profile that includes serum calcium, phosphorous, total alkaline phosphatase, creatinine, 25-hydroxyvitamin D, and intact parathyroid hormone (iPTH) would be desirable [56]. In patients with secondary osteoporosis, detailed blood investigations should be pursued based on clinical suspicion (Table 3).

Bone turnover markers

Bone turnover markers (BTMs) are dynamic parameters that reflect short-term, acute changes in bone remodeling status that are not measured by BMD and hence, are complementary to BMD measurement. However, BTMs have no role in the diagnosis of osteoporosis. Although BTMs are not routinely used to diagnose osteoporosis, they are increasingly used in the follow-up of patients who are on anti-osteoporotic treatments. Hence, wherever available, patients contemplating anti-osteoporotic therapy can get a baseline BTM level estimated prior to initiation of therapy for subsequent comparison during follow-up [57].

Table 3 Summarizing the biochemical investigations recommended by the expert committee to delineate the underlying cause of osteoporosis

Mandatory tests to be done in all patients with osteoporosis	Specific tests to be done in suspected secondary osteoporosis
Complete blood count	Erythrocyte sedimentation rate and serum electrophoresis for suspected multiple myeloma
Total calcium	IgA tissue-transglutaminase antibody (IgA tTg) in suspected celiac disease
Inorganic phosphate	Serum testosterone (in men) and estradiol (in women) in suspected hypogonadism
Total alkaline phosphatase	Overnight dexamethasone suppression test in suspected Cushing's syndrome
Kidney function test	Fasting blood glucose, post-prandial blood glucose and glycated hemoglobin in a known or suspected case of diabetes mellitus
Liver function test	
25-hydroxyvitamin D	
Intact parathyroid hormone	
TSH	

Indications for treatment

The decision to initiate anti-osteoporotic treatment should be based on clinical screening tools such as fracture risk assessment tool (FRAX) and imaging, including DXA scan or plain radiography. FRAX is an online tool that assesses the 10-year fracture risk of major osteoporotic fractures (wrist, vertebral, hip, and shoulder) based on various risk factors. FRAX thresholds for initiating anti-osteoporotic treatment vary among different ethnicities [58]. The Endocrine Society guidelines broadly recommend treating postmenopausal women at high risk of fractures, especially those with a recent fragility fracture [59]. Nevertheless, the ultimate goal of initiating treatment for management of osteoporosis is to reduce the burden of fragility fractures due to morbidity, mortality, and associated costs. The key indications for initiating therapy for osteoporosis are summarized in Table 4.

Clinical indications for initiating therapy

A clear clinical indication for starting treatment in postmenopausal women presenting with a major osteoporotic fracture (hip, spine, wrist, or humerus) that was found clinically or on imaging. The presence of fracture is a better predictor of future fracture risk than T-score obtained by DXA scan in such patients [60, 61]. There is strong evidence to suggest that individuals presenting with hip or spine fractures if treated appropriately for osteoporosis have significant reductions in future risk of a recurrent fracture.

Based on previously published literature, it is evident that a recent fracture (within the past 2 years) is a good predictor of imminent fracture risk in the near future [62, 63]. This holds true for recent vertebral fractures [64] and non-vertebral fragility fractures such as wrist and humerus fractures [65]. Pharmacological therapies should be started in patients with recent fractures to prevent subsequent fractures, but data on the optimal timing of initiation of therapy after a fracture are sparse. Based on the Horizon trial [61], it is recommended to begin treatment at least 2 weeks after a hip fracture.

Indications of therapy based on bone mineral density

Based on BMD, anti-osteoporotic treatment is indicated in individuals over 50 years of age and with DXA T-score ≤ -2.5 at femoral neck, total hip, and lumbar spine. There is evidence that fracture risk is significantly reduced in these individuals following anti-resorptive or anabolic anti-osteoporotic therapy [66, 67]. Treatment of osteoporosis should be considered if lumbar spine, total hip, or femoral neck BMD T-scores are ≤ -2.5.

Table 4 Summarizing the key indications for initiating anti-osteoporotic therapy

- A vertebral fracture (clinically apparent or found on vertebral imaging) or non-vertebral fracture (hip, wrist, and humerus)
- In individuals > 50 years of age with T-score ≤ -2.5 at femoral neck or total hip or lumbar spine measured by DXA
- In individuals with osteopenia (T-score between -1.0 and -2.5 at the femoral neck or lumbar spine) with clinical risk factors or a 10-year probability of a hip fracture $\geq 3.5\%$ or a 10-year probability of a major osteoporosis-related fracture $\geq 10.5\%$ based on the FRAX tool (based on limited data in Indians)
- In individuals with type 2 diabetes mellitus, the intervention threshold should be increased to T-score ≤ -2.0 at femoral neck or total hip or lumbar spine measured by DXA [76]

Among individuals with BMD below the expected range for age (BERA) and low bone mass (T-score between − 1.0 and − 2.5 at the femoral neck or lumbar spine), it is advisable to initiate treatment based on clinical risk factors or on an increased FRAX score. A FRAX score predicting the 10-year probability of a hip fracture ≥ 3%, or a 10-year probability of a major osteoporosis-related fracture ≥ 20%, is indicative of an increased risk of fracture in the future. Derivation of Indian-specific FRAX is based on the fracture risk in individuals living in Singapore and, therefore, may not be fully applicable in the native Indian population. Using the NOF treatment cut-off guidelines of 3% risk for hip fracture and 20% risk for MOF, Indian-specific FRAX may underestimate the fracture risk [68]. Based on studies of Indian patients with hip fractures, these thresholds may be lower, and studies are underway to define these lower treatment thresholds [58, 69]. However, more evidence is needed to support whether treatment initiation based on these criteria truly results in absolute fracture risk reduction. Till conclusive data is available, it is prudent to use white Caucasian database in clinical practice.

Trabecular bone score (TBS), a tool that assesses bone's microarchitecture, has emerged as a valuable modality complementary to BMD [70, 71]. Recently, TBS has revealed significant improvements in bone structure following administration of yearly zoledronic acid in a cohort of Indian patients. A pan-India reference for TBS is underway [72]; however, therapeutic guidelines and thresholds cannot currently be based on TBS [73].

Role of other screening tools

Several other osteoporosis screening tools have been validated in both women and men in the Indian population. These tools are based on simple clinical risk factors and could be easily used in community settings [74]. In a large cohort of rural postmenopausal women, the SCORE (Simple Calculated Osteoporosis Risk Estimation) screening tool was useful, with good sensitivity and good area under the curve for predicting femoral neck osteoporosis on BMD measurement. It uses simple clinical risk factors like age, weight, previous fracture, estrogen therapy, rheumatoid arthritis, and ethnicity. A value ≥ 6 was found to have good sensitivity and specificity for estimating risk in the Indian population [75]. Similarly, the risk assessment tools OSTA (osteoporosis self-assessment tool for Asians) and MORES (male osteoporosis risk estimation score) have been validated for use in the Indian population [76]. These tools are rapid, easy to perform, inexpensive, and easily usable in the rural Indian setting, but the impact of initiating therapy based on thresholds derived from these tools is not well studied.

Pharmacological management of osteoporosis

Fundamentals of osteoporosis management [77]

- Maintain serum 25-hydroxyvitamin D (25[OH] D) ≥ 20 ng/mL in all patients with osteoporosis. However, we feel that a level of 30–40 ng/mL would be ideal.
- Supplement with vitamin D3 if needed; 1000 to 2000 international units (IU) of daily maintenance therapy is typically required to maintain an optimal serum 25(OH)D level in Indians.
- Higher doses of vitamin D may be necessary in the presence of certain factors (e.g., obesity, malabsorption, older individuals)
- Counsel patients to maintain adequate dietary intake of calcium with a total intake (including diet plus supplement, if needed) of at least 1000 mg/day for women ≥ 50 years [3]
- Counsel patients to limit alcohol intake to no more than 2 units per day
- Counsel patients to stop smoking
- Counsel patients to maintain an active lifestyle, including weight-bearing and balance exercises
- Provide counseling on reducing the risk of falls, particularly among older patients

Recommendations for initial first-line therapy for individuals with prevalent vertebral fractures

- Teriparatide is an effective anabolic agent to initiate therapy in these cases, which to be continued for 24 months and followed by antiresorptives.
- Intravenous zoledronic acid or denosumab are also effective options. Since the protocol for discontinuing denosumab is still not firmly established, zoledronic acid is usually preferred as initial therapy for 3–5 years.
- Oral bisphosphonates can be used if the patient wants to avoid injectable therapies.

Recommendations for initial first-line therapy for individuals with prevalent hip fracture

- Intravenous zoledronic acid is the agent of choice in this group—it is recommended that hospitalized/post-surgical patients with hip fracture be given a dose of intravenous zoledronic acid before being discharged from the hospital.
- Denosumab is also an apt and effective choice but is often used after zoledronic acid, for reasons explained above.

- While teriparatide can be used in this situation, there is limited data available in the prevention of hip fracture [78].

Recommendations for initial first-line therapy for high-risk individuals without prevalent fractures

- Bisphosphonates are generally agents of choice for those at high risk for fracture. While either weekly oral (alendronate, risedronate) or annual intravenous agents are effective, concerns about compliance and ease of once a year administration has made zoledronic acid the preferred drug for most patients. Both options should be discussed with the patient (weekly oral vs. annual intravenous) and treatment chosen accordingly. Denosumab can be used as a first choice too if the patient reacts to or wants to avoid bisphosphonates. Teriparatide can be considered for some with very low BMD (T score < -3.5) and high risk of vertebral fracture.
- The risk of rebound fractures is increased if subsequent doses of denosumab are not administered in time.

Recommendations for initial first-line therapies for low and moderate risk cases for vertebral, non-vertebral, and hip fractures

- Approved agents with efficacy to reduce hip, non-vertebral, and spine fractures include alendronate, risedronate, zoledronic acid, and denosumab, and these are appropriate as initial therapy for most patients at risk of fracture. Often, oral bisphosphonates are preferred in low and moderate risk cases.

Recommendations for the management of osteoporosis in chronic kidney disease patients and those on haemodialysis

- Management of patients with osteoporosis and chronic kidney disease (CKD) is difficult as bisphosphonates are contraindicated in stage 4 and 5 kidney disease (eGFR below 30 to 35 mL/min). Denosumab is not cleared by the kidney and therefore can be used in these patients. However, the risk of hypocalcemia is high with this agent, especially in patients in stage 5 disease. Optimal calcium intake and vitamin D status should be assured before starting denosumab.
- A major concern with antiresorptive therapy in patients with CKD is dynamic bone disease and selected patients should undergo undecalcified iliac bone biopsy if facilities are available, to guide correct decision-making for the management of osteoporosis.

Recommendations for the use of Hormone Replacement Therapy (HRT) in the management of osteoporosis [79]

- Although effective in increasing bone mass and prevent fractures, HRT is not recommended for managing osteoporosis due to high risk of side effects such cardiac events and breast cancer (although breast cancer risk is not increased with estrogens alone). Hormone Replacment Therapy can be used when there is an additional indication to use estrogens such as uncontrollable menopausal symptoms. In select cases (within the first 10 years after menopause in women without contraindications), HRT can be used for prevention of postmenopausal osteoporosis.
- Testosterone therapy may be added in androgen-deficient men (testosterone level less than 200 ng/dL on more than one determination) if accompanied by signs or symptoms of androgen deficiency (e.g., low libido, unexplained chronic fatigue, loss of body hair, hot flushes) or "organic" hypogonadism (due to hypothalamic, pituitary, or specific testicular disorder). If testosterone treatment does not alleviate symptoms of androgen deficiency after 3–6 months, it should be discontinued, and other therapies considered. It should be noted that anti-resorptive and anabolic drug therapies are equally effective for osteoporosis in men as well.

Recommendations for the use of intranasal calcitonin in the management of osteoporosis [59]?

- Intranasal calcitonin can be used for temporary bone pain relief.
- However, calcitonin's effectiveness in prevention of osteoporotic fractures is very limited and should therefore be prescribed only in women who cannot tolerate bisphosphonates, denosumab, teriparatide, or raloxifene or for whom these therapies are not considered appropriate.

Recommendations for the use of combination therapies in the management of osteoporosis [79]

- Combination therapy can be considered in patients with very high or imminent fracture risk [80]. The use of teriparatide and denosumab has been shown to result in a great increase in BMD as against either agent alone. However, fracture prevention data are not yet available.

Recommendations for the use of sequential therapies in the management of osteoporosis [79]

- Treatment with teriparatide should always be followed by antiresorptive agents to prevent bone density decline

and loss of fracture efficacy. Either bisphosphonates or denosumab can be used in this setting.
- In patients unresponsive to anti-resorptive therapy alone, treatment can be followed by a combination of teriparatide and anti-resporptives [81].
- Treatment with denosumab, if it has to be discontinued, should be followed by bisphosphonate, either zoledronate [82] or alendronate [83] in patients with adequate renal function. Delay in denosumab therapy or lack of an alternate therapy 6 months after last denosumab dose is associated with a rebound increase in fractures.

Follow-up for patients with osteoporosis

Treatment of osteoporosis with either anti-resorptive or osteoanabolic therapy reduces the risk of incident fractures along with a subsequent reduction in morbidity and mortality. In a study assessing treatment algorithms in patients with osteoporosis in India, most clinicians preferred bisphosphonates as the first line of therapy [84]. However, in another study that aimed explicitly to evaluate the treatment adherence and compliance of postmenopausal osteoporotic women for different regimens of bisphosphonates in Indian postmenopausal women, the authors found that an adherence rate of 56% was found with the monthly regimens, 36% for weekly regimens, and 32% for daily regimens [85]. Herein lies the paramount importance of continuous monitoring and vigilant follow-up.

Frequency of follow-up

There exists no consensus regarding the frequency of follow-up for patients on anti-osteoporotic therapy. The first follow-up can be planned after 3 months following initiation of therapy. Thereafter, patients can be followed up at 3–6 monthly intervals for 2–3 subsequent contacts followed by annual visits [21]. This promotes adequate adherence to the treatment regime and reinforcement of fall prevention practices.

Clinical follow-up

History

At each visit, a brief history with an emphasis on assessing new incident fractures, new-onset/worsening of kyphosis/scoliosis, new-onset or worsening of back pain, and perceptible height loss should be elicited. A history of falls is a predictor of future falls and hence should be specifically queried. Patients should also be asked about the possible side effects of anti-osteoporotic therapy, notably, thigh and jaw pain. At each and every visit, the need for continuation of treatment and regular follow-ups should be reinforced and family members/caregivers should be actively involved in decision-making.

Physical evaluation

A short physical examination focusing on the patient's height should be undertaken. Other characteristics to assess include spinal tenderness, kyphosis, decreased spacing between lower ribs and pelvis, and oral hygiene. Patients on anti-resorptive therapy with poor dentition may be referred to a dental physician for a detailed oral evaluation.

Biochemical evaluation

Although no consensus exists, we recommend estimating serum 25-hydroxyvitamin D at 6-month intervals for the initial 2–3 visits, and thereafter annually, to ensure vitamin D sufficiency while on treatment and target a serum 25-hydroxyvitamin D of at least 20 ng/ml.

Therapy with teriparatide is occasionally associated with hypercalcemia [67]. Serum calcium can be measured at least 12 h after administering the first injection of teriparatide because serum calcium levels can be transiently elevated within 6 h of injection. If a patient develops hypercalcemia, oral calcium intake should be reduced by 50% and serum calcium repeated. If a patient develops persistent hypercalcemia, calcium supplementation should be stopped, although discontinuation of teriparatide is rarely needed. An assessment for other causes of hypercalcemia (e.g., hyperparathyroidism, malignancy, sarcoidosis, or hydrochlorothiazide) should be undertaken simultaneously [86, 87].

Radiology

A new radiograph of the spine may be ordered at annual follow-up for all patients, particularly for patients complaining of new-onset or worsening back-pain/kyphosis to rule out any incident vertebral fractures. In addition, patients on bisphosphonate therapy complaining of thigh pain should undergo a radiograph of the upper femur to rule out cortical beaking, the precursor of atypical femoral fracture [88]. Similarly, patients on anti-resorptive therapy with suspected osteonecrosis of the jaw should undergo a computed tomography of the jaw to rule out the same.

Bone mineral density

Treatments for osteoporosis increase BMD, but only modestly. Evidence to support the use of BMD to monitor the treatment response is weak, but suggests that BMD can be used for this purpose [89]. The latest Endocrine Society guidelines suggest monitoring of BMD by DXA at the spine

and hip every 1–3 years to assess treatment response [59]. In the Indian scenario, repeating DXA every 1–2 years is recommended. It has been suggested that serial BMD measurements in treated patients may identify individuals who do not adhere to treatment or have a secondary cause for bone loss. An increase in BMD above the least significant change (LSC) with treatment is good and is associated with a greater reduction in fracture risk than a stable BMD [90]. Usually, changes in lumbar spine BMD are more robust, while those at the hip are less dramatic, irrespective of the treatment modality used [91]. A stable BMD on treatment is also an acceptable endpoint; however, a loss of BMD beyond the LSC (usually 5% in the lumbar spine, 4% in the total hip, and 5% in the femoral neck) over 2 years suggests treatment failure. In addition, having two or more fractures, especially vertebral fractures, while on therapy also constitutes treatment failure [92]. In such a case, low compliance, improper dosing, vitamin D deficiency, celiac disease, multiple myeloma, concurrent glucocorticoid use, and endocrinopathies (e.g., primary hyperparathyroidism, Cushing's syndrome, thyrotoxicosis, and unrecognized hypophosphatemic states) should all be considered [59, 93, 94].

Assessing changes in BMD on serial follow-up measurements requires careful attention to detail. Using the same scanner and a well-trained technologist who is aware of the pitfalls of bone densitometry can mitigate these problems. The provider responsible for reporting the results also needs to be aware of assay limitations. Degenerative changes in the spine or a new fracture in the region of interest may falsely give the impression of BMD gain.

Bone turnover markers

Bone turnover markers (BTMs) reflect the underlying bone turnover status. BTMs are dynamic parameters that can reflect short-term/acute changes in bone that are often missed by BMD. Hence, BTMs reflect the therapeutic responses to anti-osteoporosis therapies much earlier than BMD, and therefore can be used in clinical practice, especially to monitor compliance and adherence to treatment [57]. The absolute values or the degree of change from baseline for BTMs can be used; considering the ethnic variations in BTMs and the pre-analytical variables involved in their measurement, using the degree of change rather than absolute values is more reasonable. Of the commercially available BTM clinical tests, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommend using serum type I collagen C-telopeptide (CTx) and serum procollagen type I N-propeptide (PINP). A consensus statement on the use of BTMs for short-term monitoring of osteoporosis treatment in the Asia–Pacific region has recently been published, and in the absence of robust data from India, an analogy can be drawn from the aforementioned guideline [95]. CTx and/or PINP can be used to evaluate patient adherence and drug responses to anti-resorptive agents, with measurements suggested at baseline, 3, 6, and 12 months after starting treatment. Similarly, PINP can be used to evaluate patient adherence and drug responses to anabolic agents, with measurements at baseline, 1 to 3 months, 6 months, and 12 months after starting anabolic treatment. A decrease in CTx by at least 30% or by at least 100 ng/L from the pre-treatment value is expected in a patient on anti-resorptive therapy [92, 96]. For PINP, a threshold of > 20% or > 10 µg/L from baseline is considered to be significant [92, 97, 98]. The above cut-offs, however, do not apply for combination and sequential therapies with anti-osteoporotic medications.

Drug holiday

The concept of a "drug holiday" has been proposed to potentially reduce the incidence of the rare adverse events associated with long-term anti-resorptive therapy [99]. However, the recommendation for drug holidays is still a matter of debate [100], especially since there is a dearth of data from India. However, the Endocrine Society guidelines 2020 do recommend a drug holiday in selected groups of patients [59]. In patients on bisphosphonate therapy, fracture risk needs to be evaluated after 3–5 years (3 years for intravenous, 5 years for oral therapy). Patients with high-risk (defined as prior spine or hip fracture, or a BMD T-score at the hip or spine of − 2.5 or below, or 10-year hip fracture risk ≥ 3%, or risk of major osteoporotic fracture risk ≥ 20%) or very high risk of fracture (defined as multiple spine fractures and a BMD T-score at the hip or spine of − 2.5 or below) are not deemed eligible for drug holiday.

On the contrary, patients qualifying as having low risk (defined as no prior hip or spine fractures, a BMD T-score at the hip and spine both above − 1.0, and 10-year hip fracture risk < 3% and 10-year risk of major osteoporotic fractures < 20%) or moderate risk (defined as no prior hip or spine fractures, a BMD T-score at the hip and spine both above − 2.5, or 10-year hip fracture risk < 3% or risk of major osteoporotic fractures < 20%) of fracture can be considered for drug holiday; however, fracture risk needs to be evaluated regularly at 2–4 year intervals, with therapy being reinstituted if the patient falls into the high-risk category. In patients on denosumab therapy, fracture risk needs to be evaluated in 5–10 years. A drug holiday can be considered in low-moderate risk patients following a course of bisphosphonate with fracture risk being revaluated every 1–3 year. There is no consensus on using BTMs to assess the need for drug holiday [95].

Osteoporosis education—fall prevention

Fall prevention is an integral part of comprehensive osteoporosis care, and physicians following up patients with osteoporosis should educate patients about fall prevention. Important points that need to be reiterated at each visit include use of low-heeled shoes with rubber soles for more solid footing, avoiding walking on slippery floors/sidewalks, using hand rails while walking up or downstairs, keeping rooms, bathrooms, and stairs well lit, securing in-room carpets, and installing grab bars on the bathrooms walls.

Conclusions

Osteoporosis is a major public problem in India. However, diagnosing and effectively managing osteoporosis is challenging in the Indian setting. Since data indicates that osteoporotic fractures occur at an earlier age in Indians than in the West, screening for osteoporosis should begin at an earlier age. Maintaining optimum serum 25-hydroxy-vitamin D levels is essential, which, in most cases, would require regular vitamin D supplementation. Pharmacotherapy should be guided by the presence/absence of vertebral/hip fractures or the severity of risk based on clinical factors, although bisphosphonates remain the first choice in most cases. Regular follow-up is essential to ensure adherence and response to therapy.

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Compliance with ethical standards

Ethics approval Being a position statement, ethical committee approval was not required.

Consent to participate Not applicable.

Conflicts of interest None.

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