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Osteoporosis: Epidemiology, Pathogenesis, Evaluation and Treatment

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Abstract

Purpose: Osteoporosis is a global health disease. Increasing life span will add to the burden of osteoporosis, especially in postmenopausal women. The lifetime risk of osteoporotic fractures is 30% to 40%. Fractures pose an extensive burden on healthcare resources. Therefore, early diagnosis of osteoporosis is necessary. **Methods:** In this review, we provide a comprehensive approach to the current epidemiology, diagnosis aspects, treatments and fracture management in relation to the osteoporosis. **Results:** In assessing osteoporotic patients, good medical history with identification of clinical risk factors should be done. Along with basic blood investigations, bone mineral density, vertebral imaging, and bone turnover markers can aid the accurate diagnosis of bone loss. Modification of risk factors and dietary interventions are the first step in managing osteoporosis. Multiple options can be tailored to the individual needs in the treatment of osteoporosis. The frequency and duration for which the treatment is continued depend on the individual response to treatment. For fractures, surgical management is necessary whereas pharmacological interventions are needed to prevent further fractures. As osteoporosis often goes unrecognized until one or more fractures occur, it is important to understand the impact of osteoporosis. **Conclusion:** Osteoporosis remains a significant health problem globally that needs immediate attention to improve bone quality and prevent fractures associated with it optimally.

Keywords

Osteoporosis, Bone Loss, Vertebral Fractures, Vitamin D

1. Introduction

Osteoporosis is a global health disease characterized by a reduction in bone mass and disruption in the microarchitecture of bone leading to an increased predisposition for fractures [1]. Osteoporotic fractures account for 0.83% of the global burden of non-communicable diseases. In Europe, osteoporotic fractures are responsible for the loss of more DALYs (daily adjusted life years) than common cancers except for lung cancer [2]. In India, life expectancy is nearly 67 years and is expected to increase to 77 years by 2050. Increased life span will add to the burden of osteoporosis [3]. Around 50 million people in India are either osteoporotic or have lower bone mass, and only 10% - 15% of them are aware of the disease [4]. In women, postmenopausal osteoporosis has been identified as a pervasive health problem globally. The prevalence of osteoporosis in Indian women ranges from 8% to 60% [5] [6] [7] [8] [9]. Osteoporosis increases the risk of fractures, mainly at the hip, wrist, and spine. The lifetime risk of osteoporotic fractures is 30% - 40% in developed countries, equaling nearly to coronary heart disease [10]. Given the global significance of osteoporosis and related fractures, we discussed the current epidemiology, pathophysiology, and management of osteoporosis along with osteoporotic fractures.

2. Epidemiology of Osteoporotic Fractures

Vertebral fractures are the most common cause of osteoporotic fractures worldwide, occurring in around 30% - 50% of patients of age 50 years and older [11]. Women with a previous history of vertebral fractures have a 4-times higher risk of subsequent vertebral fractures and 1.5 to 2 times greater risk of non-vertebral fractures. This risk increases with the number and severity of prior vertebral fractures [12]. Approximately 25% of all women at the age of 75 years show at least one fractured vertebra. This rate increases to 50% at the age of 80 years [13]. Estimates indicate that nearly 30% - 50% of women and 20% - 30% of men will develop vertebral fractures during their lifetime [14]. The overall prevalence of vertebral fractures in India is 17.9% (18.8% in males and 17.1% in females) which is similar to Western populations [15]. Nongkynrih B reported a prevalence of 30.4% in rural postmenopausal women [16].

Hip fractures contribute to 329,000 of total 1.5 million osteoporotic fractures reported annually in the United States. Considered as the most disabling consequences of aging, 10% - 24% of deaths occur within a year of fracture [17]. Globally, the highest rates of hip fractures are reported in the US and North Europe and the lowest in Africa and Latin America. Asian countries have intermediate rates of hip fractures [18]. With increasing life expectancy, the total number of hip fractures will continue to rise and is expected to surpass 6 million by the year 2050 [19].

Distal radius fractures (DRFs) are the commonest type of upper extremity fractures in the elderly population with a higher incidence in women [20]. Over the past 40 years, the incidence of DRFs increased by 17% in the US. In Sweden,

the DRF incidence almost doubled for the older population over 30 years [21] [22]. In the Korean population, the proportion of surgically managed DRFs increased from 32.6% in 2011 to 38.3% in 2015 [23]. These data indicate there is a substantial burden of various osteoporotic fractures across the globe. It contributes to overall health expenditure.

Economic Burden of Osteoporotic Fractures

Fractures pose an extensive burden on healthcare resources. By the year 2025, osteoporosis will account for nearly 3 million fractures and an annual cost of $25.3 billion in the USA [24]. Hip fractures accounting for almost 14% of all fractures can incur 72% of total fracture treatment costs [24]. In the first year of fracture, the average health care cost of $17,000 in the US and $1.1 billion in Canada were attributable to hip fractures in adults > 65 years of age [25] [26]. In the US, >1.5 million osteoporosis vertebral fractures occur every year which are responsible for 500,000 hospitalizations, 800,000 emergency visits, 2.6 million physician visits, and $12 - 18 billion in health care costs [27]. Limited information is available regarding the direct economic burden with cost estimates of different osteoporotic fractures in the Indian population at risk due to scarcity of data.

3. Pathophysiology of Osteoporosis

Bone loss and formation is a continuous process. When the resorption rate exceeds the formation rate (e.g., menopause and advancing age), bone loss occurs. Peak bone mass (PBM) is reached by the end of the third decade, after which the loss of bone starts. Genetic factors, gender, nutrition, health during puberty, endocrine status, and physical activity determine the PBM [28]. Bone remodeling assists in maintaining a healthy skeleton. The older bone is replaced by a new bone to repair the microfractures. The risk of fracture increases when there is an imbalance between the rates of resorption and the formation of bone. Reduced bone formation and disruption of microarchitectural integrity due to various factors (advanced age, menopause, prolonged use of glucocorticoids, etc.) cause the weakening of bone with poor bone quality. Fractures are eminent when the weakened bone is overloaded with daily chores and frequent falls [29].

3.1. Difference in Bone Loss at Axial and Appendicular Skeleton

The axial and appendicular skeleton are different entities. Cortical and trabecular bone function as separate compartments, with respect to onset and rate of bone loss. The bone diminution occurring with aging shows quantitative and qualitative differences in both the appendicular and the axial skeleton. Women have little or no bone diminution in the appendicular skeleton until after age 50 years. Bone diminution increases after the age of 51 to 65 years and then decelerates to some extent after the age of 65 years. The midlife acceleration of appendicular bone loss in women can be directly related to postmenopausal estrogen

deficiency [30]. In contrast, bone diminution from the vertebrae begins in young adulthood and continues linearly throughout life. Therefore, in addition to estrogen deficiency, additional factors may contribute to the pathogenesis of osteoporosis in women because about half of vertebral bone loss occurs in the pre-menopausal age [31].

3.2. Risk Factors for Osteoporosis

The non-modifiable risk factors include genetic predisposition, increasing longevity, and ethnicity. Modifiable risk factors are calcium and Vitamin D deficiency resulting from inadequate calcium intake, sociocultural factors responsible for less sunlight exposure, poor fortification of foods with Vitamin D, highly pigmented skin, higher phytates and oxalates (especially in the Indian diet) interfering with the absorption of calcium, early menopause, sedentary lifestyle, less physical activity, lack of awareness about bone health, and previous history of fractures [32].

3.3. Classification of Osteoporosis

Based upon the factors affecting bone metabolism [33]

1) Primary osteoporosis

- Involutional osteoporosis type I (postmenopausal osteoporosis)
- Involutional osteoporosis type II (senile osteoporosis)

2) Secondary osteoporosis

- Low bone mass with microarchitectural alterations in bone leading to fragility fractures due to the presence of an underlying disease and/or medications. Various causes of secondary osteoporosis are summarized in **Table 1** [34] [35].

4. Evaluation of Osteoporosis

Osteoporosis affects women as well as men and it can often go undiagnosed until a patient visits the clinic due to a fracture. Unless proved otherwise, the diagnosis of osteoporosis is always considered secondary.

4.1. History and Physical Examination

A good history of the patient including a history of past medical conditions, long-term drug exposure, dietary history, history of fragility fractures to parents, especially the mother may provide adequate information about the cause of osteoporosis. The clinical risk factors for the assessment of osteoporotic fractures are listed in **Table 2** [36].

Fractures may cause chronic pain, reduced mobility, disability, increasing degree of dependence, and even death. Physical signs such as loss of height (caused by vertebral compression due to fractures), dorsal kyphosis (though not diagnostic criteria for osteoporosis), chest deformity, protuberant abdomen, rib-pelvic overlap suggest evidence of vertebral fractures [37]. Lumbar compression fractures

Table 1. Secondary causes of osteoporosis.

Lifestyle changes	Musculoskeletal and neurological causes	Endocrine disorders	Drugs
Vitamin D deficiency Low calcium intake Frequent falling Inadequate physical activity Smoking, alcohol abuse	Epilepsy Multiple sclerosis Muscular dystrophy Parkinson's disease Spinal cord injury Stroke	Hypercalciuria with or without renal stones Diabetes mellitus Hypogonadal states Hyperprolactinemia Hyperparathyroidism Hyperthyroidism Cushing's syndrome Acromegaly, Central obesity	Excess glucocorticoids Excess thyroid hormones Anticoagulants (heparin) GnRH agonists, Anticonvulsants Aromatase inhibitors, Thiazolidinediones, Opiates, Cyclosporine, Rifampicin, Exchange resins, Methotrexate, Alcohol
Gastrointestinal disorders	**Hematological disorders**	**Rheumatological and autoimmune diseases**	**Others**
Gastrectomy Inflammatorybowel disease Coeliac disease Intestinal bypass surgery Primary biliary cirrhosis Malabsorption Pancreatic insufficiency	Multiple myeloma Hemolytic anemia, hemoglobinopathies Myelo- and lymphoproliferative disorders Skeletal metastases (diffuse or localized) Gaucher's disease	Ankylosing spondylitis Rheumatoid arthritis Systemic lupus erythematosus	AIDS/HIV Chronic obstructive pulmonary disease End-stage renal disease Sarcoidosis Weight loss

Table 2. Risk factors for assessment of osteoporotic fractures.

Low BMD
Advancing age
Prior fragility fracture particularly of hip, wrist, and spine
Family history of osteoporosis or fragility fracture in a first-degree relative
Current smoker
Low body mass index (<19 kg/m^2)
Frequent Falls
Sarcopenia
Dementia

are also responsible for crowding of internal organs causing gastrointestinal complaints such as reduced appetite, early satiety, constipation, abdominal pain. Persistent back pain and positional restrictions are additional complaints [38]. Findings such as impaired ambulation, muscle weakness, impaired balance, reduced vision, orthostatic hypotension are risk factors for falls leading to fractures [37].

4.2. Laboratory Investigation

These include complete blood count, serum creatinine (eGFR), serum calcium,

serum phosphorus, and magnesium, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), thyroid-stimulating hormone (TSH), serum protein electrophoresis, 25-hydroxy Vitamin D (25-OH-D), total testosterone and gonadotropin in younger men, and biochemical turnover markers (BTMs).

Vitamin D levels should be measured after 3 - 4 months of adequate supplementation and need not be repeated if the level is 30 ng/ml or more is achieved [39].

More extensive laboratory evaluation may be required in men with osteoporosis, in cases of unexplained fracture or low BMD and inadequate response to osteoporosis treatment, and clinical suspicion of secondary causes in a patient of osteoporosis. It may include iron and ferritin levels, homocysteine, prolactin, tryptase, urinary histamine, urine protein electrophoresis [35].

Screening Osteoporosis in Women

The Indian Menopause Society (IMS) recommends screening following women for osteoporosis using dual-energy X-ray absorptiometry (DXA) scanning [40].

- All postmenopausal women with more than five years of menopause
- Postmenopausal women less than five years of menopause having risk factors (low body mass index, prolonged glucocorticoids use, history of alcohol and smoking, coexisting rheumatoid arthritis and a prior history of fragility fracture)
- Women in menopause transition with secondary causes
- Radiological evidence of osteopenia and presence of vertebral compression fracture
- Women with fragility fractures
- Before initiating pharmacotherapy for osteoporosis

5. Evaluation of Osteoporosis

5.1. Bone Mineral Density (BMD) Measurement

Bone quality and BMD are the two factors that reflect bone strength. While bone quality cannot be measured, BMD can be easily measurable and is able to establish the diagnosis of osteoporosis. Bone mineral density can be measured by dual X-ray absorptiometry (DXA); it is the actual expression of the bone in absolute terms of grams of mineral (primarily, as g/cm^2 of calcium) per square centimeter of the scanned bone. Hip and spine are the common sites used for BMD measurements to confirm the diagnosis of osteoporosis to predict the risk of future fractures. The difference between the patient's BMD and mean BMD of females in the age range of 20 - 29 years (divided by the standard deviation (SD) of the reference population) yields the T-score. The Z-score is calculated by comparing the BMD of a particular age, sex, and ethnicity-matched adult reference population [41]. World Health Organization (WHO) definitions of osteoporosis are represented in **Table 3** [41].

Table 3. WHO classification of osteoporosis based on BMD.

Classification	Bone mineral density by DXA	T-score
Normal	Within 1 SD of the mean level for a young adult reference population	−1.0 and above
Low bone mass (osteopenia)	Between 1 and 2.5 SD below that of the mean level for a young adult reference population	−1.0 and −2.5
Osteoporosis	2.5 or more below that of the mean level for a young adult reference population	At or below −2.5
Severe or established osteoporosis	2.5 or more below that of the mean level for a young adult reference population with fractures	At or below −2.5 with one or more fractures

The preferred sites for BMD measurements are total hip, femoral neck, or total lumbar spine (or a combination of these). If the hip and/or lumbar spine sites cannot be measured or become unusable (e.g., hyperparathyroidism or very obese patients), one-third (33%) of the radius can be used. The WHO definition of osteoporosis based upon the T-scores is applicable only for postmenopausal women and men aged 50 years or more. Z-scoring is used for children, premenopausal women, and men aged less than 50 years [42].

Indications for BMD measurement by various guidelines are shown in **Table 4** [43] [44] [45] [46]. The National Osteoporosis Guideline Group (NOGG) recommends the assessment of fracture risk in postmenopausal women and men above the age of 50 years, using the Fracture Risk Assessment Tool (FRAX). It is recommended that in individuals at intermediate risk, the BMD measurement should be performed using DXA and re-estimation of fracture probability to be done using FRAX [47].

5.2. Important Considerations for BMD Assessment Using DXA

The assessment of BMD by DXA has been the gold standard for the diagnosis of osteoporosis. However, the Study of Osteoporotic Fractures (SOF) concluded that approximately 54% of women with hip fractures had either low bone mass or normal bone density, indicating that BMD assessment by DXA has limitations. DXA can also result in spuriously elevated BMD measurements in patients with a degenerative disease, compression fractures, and/or vascular calcifications [48]. Several factors can significantly affect the BMD measurements at the hip, wrist, and spine, by affecting the bone strength (e.g., increasing age, implants, various bone disorders such as vascular necrosis of femoral head, osteoarthritis, and neurological disorders).

Assessment of bone strength is of utmost importance for prevention as well as treatment of hip fractures. Singh *et al.* [49] classified osteoporosis into six grades based on the visual assessment of rarefaction of trabecular structures by comparing with the femoral neck of intact side on a plain anteroposterior X-ray film.

Table 4. Indications for BMD measurement.

Category	NOF [43]	AACE [44]	OSC [45]	ISCD [46]
Females ≥65 years of age	✓	✓	✓	✓
Females with risk factors	✓ (>50 years)	✓	✓	✓
Men with risk factors	✓ (>50 years)	✓	✓	✓
Men ≥70 years	✓	-	✓ (>65 years)	✓
Monitor	✓	✓	✓	✓

NOF: National Osteoporosis Foundation; AACE: American Association of Clinical Endocrinologists; OSC: Osteoporosis Society of Canada; ISCD: International Society of Clinical Densitometry.

The Singh index is limited by inter-observer variation and the inability to assess the extent of bone mineralization and trabeculae loss in the initial stages of osteoporosis. However, cost-effectiveness and simplicity of method are the advantages.

5.3. Vertebral Fracture Assessment/Vertebral Imaging

Vertebral fracture assessment (VFA) by DXA is a useful tool for imaging the thoracic and lumbar spine to detect vertebral fracture deformities. This method has the advantage of greater patient convenience, a smaller dose of ionizing irradiation, and lower cost when compared with standard radiographs of the spine [50].

Indications of vertebral fracture assessment include [51]

- Women aged ≥70 years or men aged ≥80 years
- History of previous vertebral fracture
- Prospective height loss (difference between the current height and a previously documented height measurement) of ≥2 cm
- Long-term glucocorticoid treatment (glucocorticoid therapy equivalent to ≥5 mg of prednisone or equivalent per day for ≥3 months)
- Non-availability of BMD measurements

Methods for Diagnosis of Vertebral Fractures

- Qualitative visual assessment: this method enables the interpreter to decide whether the vertebra is normal or fractured. However, this method cannot describe the type or severity of the fractures.
- Vertebral quantitative morphometry: the margins of each vertebral body are identified by six points on the upper and lower endplates—one for each corner and one for each of the endplate midpoints. Placement of the six points can be manual or automated. The advantage of this method is that it can be undertaken by relatively inexperienced staff. However, application in practice is subjective and misdiagnosis of vertebral fractures is common [52].

- Semi-quantitative (SQ) assessment: SQ analysis involves either a vertebral height measurement followed by evaluation of such vertebrae by an expert, or an evaluation of spinal X-rays by an experienced interpreter without prior measurement of vertebral height. The most widely used approach is the one recommended by Genant *et al*. [53]. In this approach, the vertebral fractures are graded from 1 (mild) to 3 (severe).

- Grade 1 (mild) vertebral fracture: ~20% - 25% reduction in vertebral height compared to normal adjacent vertebrae.
- Grade 2 (moderate) vertebral fracture: ~25% - 40% reduction in vertebral height.
- Grade 3 (severe) vertebral fracture: ~>40% reduction in vertebral height.

The approximation symbol (~) is used because of visual assessment of reduction in vertebral height instead of direct measurement. It is a practical and reproducible method for assessing vertebral fractures independent of BMD [53]. However, one should be aware that not all vertebral fractures are due to osteoporosis.

Magnetic Resonance Imaging (MRI) or bone scan should be considered in case the fracture is equivocal or remote. Suspicion of metastatic carcinoma demands biopsy as well as MRI. Finding of lateral or posterior displacement of vertebra on radiographs requires MRI to further assess the diagnosis.

5.4. Biochemical Bone Turnover Markers (BTMs)

Biochemical markers of bone remodeling include resorption and formation markers (**Table 5**) [54]. The advantages of BTMs are that they are non-invasive, can be repeated many times. They are useful in assessing bone dynamics, monitoring response to therapy, and promoting adherence. In combination with BMD, assessment of BTMs improves fracture risk prediction. However, the disadvantages include potentially high biological and analytical variability, the inability to reflect the process of mineralization. Another major disadvantage is that their levels are influenced by the rate of renal clearance, food intake, diurnal variation, storage conditions, assay variations [55].

BTMs play an important role in providing prognostic information on fracture risk that supplements radiographic measures of bone mass, but the utility of BTMs is limited by a large number of preanalytic factors and comorbid clinical conditions that influence BTM levels. Any change in bone physiology causes

Table 5. Biochemical turnover markers.

Resorption markers	Formation markers
Serum C-terminal telopeptide type-I collagen (s-CTX)	Osteocalcin (OC)
Urinary N-telopeptide (NTX)	bone-specific alkaline phosphatise (BSAP)
Deoxypyridinoline (free and total)	N-terminal and C-terminal pro-peptides of type I procollagen (P1NP, P1CP)

rapid alterations in BTM levels, therefore, they can be utilized in assessing the patient's response as well as compliance with therapies for osteoporosis. The preanalytic factors include controllable factors such as seasonal or circadian variation and uncontrollable factors such as the age and sex of the patient. The use of BTMs is not currently recommended as a public health tool to identify patients at increased risk of rapid bone loss due to the lack of prospective RCTs to assess the efficacy and cost-effectiveness of this program [56].

- A hip or vertebral fracture.
- Determination of fractures at the femoral neck, hip, or lumbar spine when the T-score is ≤−2.5.
- Low bone mass with T-score between −1.0 and −2.5 at the femoral neck or lumbar spine, 10-year probability of a hip fracture ≥3, or a 10-year probability of a major osteoporosis-related fracture ≥20%.

6. Management of Osteoporosis

Postmenopausal women and men aged 50 years and above presenting with the following should be considered for treatment [33].

6.1. Modification of Risk Factors

Bone mass begins to increase from childhood, continues till adulthood. Peak bone mass is achieved by the third decade for spine and hip and at 40 years at the radius. After that, bone mass normally declines [57]. Modification of risk factors can lead to improved bone health. Studies have shown a significant association between lower BMD in Indian women and lack of exercise [58]. Physical exercises, especially weight-bearing exercise, helps to improve and maintain muscle and bone strength and also helps to improve body balance [40].

6.1.1. Nonpharmacological Treatment

Less sun exposure, traditional clothing, highly pigmented skin, inadequate dietary intake, and poor fortification of food with Vitamin D led to increased prevalence of Vitamin D deficiency in the Indian population. Thus, the Indian population has impaired calcium absorption from the gut affecting the mineralization of bones [59]. Patients receiving long-term corticosteroid treatment should be given calcium and Vitamin D supplementation. Modification of risk factors such as routine physical exercises, cessation of smoking, moderation of alcohol consumption, can lead to improved bone health thereby significantly reducing the risk of osteoporotic fractures [60].

6.1.2. Universal Recommendations

Therapeutic lifestyle management (balanced diet, adequate physical activity and exposure to sunlight, avoidance of bone depleting agents like tobacco and alcohol, low sodium intake (<5 gm per day), adequate-protein consumption (1 gm/kg body weight per day) and decreased caffeine intake (<3 cups/day)) plays an integral role in the management of osteoporosis.

- The recommended calcium intake should exceed >800 mg/day. Add calcium supplements if the dietary intake of calcium is poor. Drugs such as thyroid medications, corticosteroids, tetracyclines, anticonvulsants, iron interfere with calcium absorption.
- In Vitamin D deficiency, cholecalciferol (Vitamin D3) 60,000 IU/once a week for 8 weeks preferably with milk is recommended. One intramuscular injection of 600,000 IU is given to correct the deficiency (not to be repeated before 3 months and may be given after confirmation of persisting low levels of Vitamin D). Maintenance therapy is advised after correction of Vitamin D deficiency for which cholecalciferol tablet or powder 60,000 IU is given once a month in summer or twice a month in winter. Other options for maintenance therapy are an injection of cholecalciferol 300,000 IU IM, twice a year or 600,000 IU IM once a year [40].

6.2. Pharmacological Management

Majority of the drugs used for prevention and treatment of osteoporosis decrease the bone resorption-antiresorptive agents. These are listed in **Table 6** [60].

6.2.1. Hormone Replacement Therapy for Postmenopausal Osteoporosis

Menopausal hormone therapy (MHT) was widely used for the prevention of symptoms associated with menopause, such as hot flushes, night sweats, and sleep disturbance, with a prevailing view that prevention of cardiovascular diseases and osteoporosis were the additional advantages. As these beneficial results of MHT were based on observational studies, they were challenged by the results from the first of large US Women's Health Initiative (WHI) Hormone Therapy trials. The study reported that though MHT leads to a decreased risk of fractures in women, it was associated with increased risks of cardiovascular and cerebrovascular events, along with increased risks of breast cancer [61]. Subsequent re-analyses of the WHI trials, together with the results from other trials, further suggested that the benefit-risk profile of MHT depends upon the timing of initiation of MHT in relation to the menopause, age of the woman, and the type of MHT regimen (whether with or without progestogen, type of estrogen and

Table 6. Pharmacological approaches in the management of osteoporosis.

1). Hormone replacement therapy
2). Selective estrogen receptor modulators (SERM): Raloxifene
3). Bisphosphonates: Alendronate, Risedronate, Ibandronate, and Zoledronic acid
4). Human monoclonal antibody against RANKL: Denosumab
5). Strontium ranelate
6). Calcitonin
7). Recombinant parathormone: Teriparatide

RANKL: receptor activator of NF-κB ligand.

progestogen, dose, and route of administration).

The North American Menopause Society guidelines recommend using the lowest possible effective dose of MHT. It allows for an extension of treatment for an individual woman's treatment goals especially when the benefits of menopause symptom relief outweigh the potential risks of MHT. The guidelines also suggest that MHT with the lowest possible dose can be used for further prevention of osteoporotic fracture or preservation of bone mass in women with an established reduction in bone mass when other therapies are not suitable. The lowest effective dose of MHT is determined based upon the dose required for vasomotor symptom relief [62].

DOPS study indicated the start of the MHT early after menopause as the bone resorption is fastest in the first 3 - 4 years after menopause. During this period, the response to treatment can be the highest since alleviating the bone resorption assists in instant filling in of the resorption or remodeling space and increases bone formation thereby resulting in a greater increase in BMD [63]. Numerous randomized controlled trials and observational studies have demonstrated that MHT helps to decrease the risk of CHD and overall mortality in women when started at the time of or soon after menopause. The clinical data support a "window of opportunity hypothesis" stating that MHT is associated with reduced CHD risk and reduced mortality when started in women who are less than 60 years old and/or less than 10 years postmenopausal [64]. For women of age >60 years and >10 years menopausal, osteoporosis preventive strategies such as lifestyle modifications, calcium, and Vitamin D supplementation, and other pharmacological therapies are preferred over MHT [65]. **Table 7** [66] [67] [68] [69] provides a brief summary of studies supporting MHT for bone loss in

Table 7. Menopause Hormone Therapy (MHT) supportive studies.

Authors	Study design	Results
Wells, Tugwell and Shea (2002) [66]	Meta-analysis of 57 preventive and treatment trials including 1000 postmenopausal women	After one year of MHT, increase in BMD at various sites: - Lumbar spine—5.4% - Forearm—3.0% - Femoral neck—2.5% Increase in BMD at various sites After 2 years: - Lumbar spine—6.8% - Forearm—4.5% - Femoral neck—4.1%
Torgerson, Bell-Syer (2001) [67]	Meta-analysis of 22 randomized trials	Significant reduction in hip and wrist fractures compared to non-MHT groups ($p > 0.02$)
Cauley, Robbins and Chen (2003) [68]	HT arm: 16,601 women given either estrogen plus progestin or placebo ET arm: 10,600 women were given either estrogen or placebo	HT arm after 5.6 years: reduced risk of hip fractures by 33% and all fractures by 24% ET arm after 7.1 years: reduced risk of hip fractures by 35% and all fractures by 29%
Cummings, Ettinger, Delmas (2008) [69]	Randomized trial on tibolone, 4538 women were given either tibolone or a placebo	At a median of 34 months, a significant reduction in both vertebral as well as non-vertebral fractures ($p < 0.01$)

postmenopausal women.

6.2.2. Indian Menopausal Society Guidelines Recommendations

- Estrogen progesterone therapy/estrogen therapy (EPT/ET) may be used for prevention and treatment of osteoporosis in the early postmenopausal age group in symptomatic women unless there is a contraindication (Grade A).
- Progestogens should be added to estrogen therapy in women with a uterus to avoid the risk of endometrial hyperplasia. It does not increase the risk of VTE and CVD events (Grade B).
- Pre-MHT workup and an annual follow-up are essential before prescribing MHT. A complete gynecological assessment is mandatory before MHT as well as at regular intervals thereafter. A self-breast examination is advised monthly and clinical breast examination at least annually. Follow-up mammography should be performed every 1 - 3 years if the initial mammogram is normal (Grade C).
- MHT should not be started solely for bone protection after 10 years of menopause. All preparations, including low dose, non-oral routes of estrogen are effective in preserving bone mass. In women with hypertriglyceridemia, obesity, glucose intolerance, history of deep vein thrombosis, and tobacco users, the non-oral route should be preferred (Grade B).
- Extended use of MHT in women with reduced bone mass is an option considering the risk-benefit analysis compared to the other available therapies for osteoporosis (Grade B).
- MHT is indicated as primary therapy to prevent bone loss in women with premature menopause and secondary amenorrhea (Grade C) [40].

6.2.3. Selective Estrogen Receptor Modulators (SERMs)

Selective estrogen receptor modulators (SERMs) are nonsteroidal synthetic drugs with similar effects on bone and the cardiovascular system as estrogen but without any adverse effects on the breast and the endometrium. These are raloxifene, lasofoxifene, and bazedoxifene which are approved for the prevention of postmenopausal osteoporosis. SERMs reduce the risk of vertebral fractures in osteoporotic women, but their efficacy in reducing the risk of nonvertebral or hip fractures is doubtful [70]. Raloxifene hydrochloride in a dose of 60 mg/d is indicated for the prevention and treatment of postmenopausal osteoporosis. In MORE trial on the use of raloxifene, 7705 postmenopausal women with osteoporosis were treated with raloxifene and a placebo for 3 years. The study concluded that raloxifene 60 mg/d decreased the risk of new clinical vertebral fractures by 68% compared to placebo by the end of one year [71]. In a systematic review, Cranney *et al*. reported a 30% to 50% reduction in vertebral fractures among women with postmenopausal osteoporosis with no reduction in the risk of non-vertebral fractures [72].

6.2.4. Bisphosphonates

Bisphosphonates (BPs) are widely used in the treatment of osteoporosis, possess

potent inhibitory effects on bone remodeling by inhibiting the osteoclast activity. Alendronate, risedronate, ibandronate, and zoledronic acid are available in India and are used in conjunction with calcium and Vitamin D supplementation. Bisphosphonates given once weekly are preferred because of ease of administration and low risk of gastrointestinal side effects. Oral bisphosphonates, alendronate, and risedronate as well as zoledronic acid have been shown to significantly reduce the risk of vertebral fractures, hip fractures, and non-vertebral fractures [73]. A recent meta-analysis has demonstrated that ibandronate is ineffective in reducing the risk of hip fractures or non-vertebral fractures [74]. **Table 8** summarizes recent evidence on bisphosphonates in reducing fracture risk.

6.2.5. Denosumab

Denosumab is a potent inhibitor of osteoclast-mediated bone resorption having similar characteristics as those of BPs with respect to fracture healing. Denosumab treatment has been shown to decrease the risk of vertebral, non-vertebral, wrist, and hip fractures in postmenopausal women up to 10 years of treatment [80]. Use of denosumab became popular after the results of the large Fracture

Table 8. Efficacy of bisphosphonates in reducing fragility fracture.

Authors	Site of fracture	Study design	Results
Jansen J *et al.* (2011) [75]	Vertebral fractures	Meta-analysis of 8 RCTs	All BPs reduced the risk of fractures with zoledronate providing the greatest reduction of all BPs
Shi L *et al.* (2019) [76]	Vertebral fractures	Meta-analysis involving 11,822 patients with osteoporotic fractures	BPs significantly reduced the risk of new vertebral, and nonvertebral fractures with alendronate being the best intervention for secondary prevention than the other BPs
Climet v *et al.* [77]	Distal radial fractures	RCT	No statistically significant differences in fracture healing rate in alendronate and placebo groups with significantly improved bone mass in the alendronate group
Rosental *et al.* (2009) [78] and Shoji KE (2018) [79]	Distal radial fractures	RCT	No significant differences in fracture healing time, clinical or functional outcomes in conservatively treated DRF patients in BP users and BP naive patients.

Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial in 2009, which showed significant reductions in the incidence of vertebral fractures, as well as reduced nonvertebral and hip fractures, in postmenopausal women treated with denosumab compared with those who were treated with placebo [81]. However, recent evidence shows that patients previously treated with denosumab who discontinue the drug have an increased risk for rebound vertebral fractures, which are often multiple and may occur as soon as eight months after the last injection of the drug due to rapid drops in their bone density and a marked rise in their bone resorption markers [82]. Hence, advice regarding patient compliance and counseling the patient against discontinuation without medical consultation is recommended before starting therapy with denosumab.

6.2.6. Strontium Ranelate

Strontium ranelate is the first antiosteoporotic agent that exhibits a dual mechanism of increasing bone formation and decreasing bone resorption, thus resulting in the creation of new bone. Strontium ranelate is known to be effective in various patient profiles, from early postmenopausal women and osteopenic subjects to elderly women over the age of 80 years in reducing the risk of vertebral as well as non-vertebral fractures [83]. Previous studies in postmenopausal women showed that strontium ranelate reduced the risk of vertebral fractures and lumbar spine osteopenia [84] [85]. It also significantly reduces the risk of vertebral fractures in frail, intermediate, and robust older patients [86].

6.2.7. Calcitonin

Calcitonin suppresses the osteoclast activity by acting on the osteoclast calcitonin receptor but is a weaker antiresorptive agent than other therapies [87]. Supplementation with calcium and Vitamin D is necessary while starting calcitonin. Calcitonin has high patient compliance as the drug is administered as a single daily intranasal spray. Intranasal application is associated with a rare risk of rhinitis, epistaxis, and allergic reactions. Calcitonin is used in osteoporotic women who are at least five years menopausal and in whom alternative therapies are not suitable. Calcitonin preparations are approved by USFDA for Paget's disease, hypercalcemia, and osteoporosis in women who are at least five years menopausal [88]. In Europe, the EMA (European Medicines Agency) has removed osteoporosis indication for calcitonin due to increased risk of carcinomas. Calcitonin is not indicated for the prevention of postmenopausal osteoporosis and is not potent to prevent bone loss in early postmenopausal women [89].

6.2.8. Teriparatide

Teriparatide, recombinant human parathyroid hormone [1]-[34] (20 μg/day), stimulates new bone formation by virtue of increased stimulation of osteoblastic than osteoclastic activity. It improves both trabecular and cortical bone structures. It is approved for the treatment of postmenopausal osteoporosis, treatment of osteoporosis in men, and for the treatment of osteoporosis associated

with glucocorticoid therapy in men and women at risk of fracture [90] [91]. In the first phase III clinical trial, after treatment for a median of 21 months, Neer *et al*. reported increased BMD at the lumbar spine by 9% and 13% with 20 μg and 40 μg respectively. Compared to placebo, both doses significantly reduced new vertebral fractures and fragility fractures at nonvertebral sites such as the hip and wrist [92]. A summary of recent evidence on the efficacy of teriparatide in reducing fracture risk is shown in **Table 9**. **Table 10** provides the dosing regimen and adverse effects of antiresorptive agents.

6.2.9. Drugs in Pipeline

Romosozumab: it is a monoclonal antibody that blocks sclerostin which is a potent inhibitor of bone formation. Blocking of sclerostin further leads to osteoblast stimulation and bone formation. Cosman *et al*. (2016) in their FRAME phase III trial, demonstrated a significant reduction in the risk of new vertebral fractures by 73% after romosozumab and subsequent denosumab treatment, compared to placebo and subsequent denosumab treatment. The study however failed to show a reduction in non-vertebral fracture risk [97]. Subsequent treatment with alendronate or denosumab following romosozumab demonstrated beneficial results on fracture risk compared to subsequent treatment with placebo as reported in the ARCH Phase III trial [98] and the FRAME Extension study [99]. The efficacy of romosozumab in osteoporotic male patients was shown in

Table 9. Efficacy of teriparatide in reducing fracture risk.

Authors (year)	Site of fractures	Study design	Results
Fatima M (2020) [93]	Vertebral fractures	Systemic review and meta-analysis	Significantly improved bone density and reduced risk of vertebral fractures
Yangyang Ma, *et al*. (2020) [94]	Vertebral fractures	Prospective cohort study	Comparable results in terms of pain relief, quality of life, and cost-effectiveness when compared with vertebroplasty
Kindler *et al*. [95]	Vertebral fractures	Double-blind randomized study	Significant reduction in the risk of vertebral fractures compared to risedronate
Diez-Perez A *et al*. (2019) [96]	Hip and wrist fractures	Systematic review and meta-analysis involving 23 RCTs	Teriparatide reduced the risk of hip fractures by 56% with no significant reduction in the risk of wrist fractures compared to placebo

Table 10. Dosing regimen and adverse effects of antiresorptive agents.

Drug name	Dosing regimen	Adverse effects
Alendronate	10 mg/day or 70 mg per week orally	Gastrointestinal discomfort and acute influenza-like illness, acute phase reactions, ONJ, atypical fracture of the femoral head
Risedronate	5 mg/day or 35 mg per week orally	
Ibandronate	2.5 mg/day or 150 mg per month orally	
Zoledronate	5 mg yearly IV	
Denosumab	60 mg SC once in six months	Serious infections, dermatitis, rashes, eczema and ONJ, atypical fracture of the femoral head
Raloxifene	60 mg daily orally	Skin rash, hot flushes, abdominal pain
Teriparatide	20 mcg daily SC	Hypercalcemia and hypercalciuria
Strontium ranelate	2 mg daily orally	Thromboembolism, skin rash

the BRIDGE trial in which after 12 months, a significantly increased BMD was observed in patients receiving romosozumab compared to those receiving placebo [100]. It has been recommended that the treatment with Romosozumab has to be followed by the antiresorptive agent to preserve the bone mass and reduce the fracture risk [101].

Abaloparatide: it is a parathyroid hormone-related protein analog having a comparable mechanism of action as that of teriparatide with a high bone formation-to-resorption ratio. The ACTIVE double blind randomized clinical trial by Miller *et al*. (2016) in 2463 postmenopausal women with osteoporosis showed that abaloparatide significantly reduced the incidence of new vertebral and non-vertebral fractures when compared with placebo [102]. Abalaoparatide has also shown faster and more robust increases in the BMD at the total hip, femoral neck, and lumbar spine compared to teriparatide. Abaloparatide is well tolerated with a mild adverse effect profile, including dizziness, headache, nausea, and palpitations with a lower incidence of hypercalcemia than teriparatide. An anti-resorptive treatment has to be started after stopping abaloparatide to maintain the reduced fracture risk [103].

6.2.10. Pharmacological Treatment Strategies

Romosozumab: it is a monoclonal antibody that blocks sclerostin which is a potent inhibitor of bone formation. Blocking of sclerostin further leads to osteoblast stimulation and bone formation. Cosman *et al*. (2016) in their FRAME phase III trial, demonstrated a significant reduction in the risk of new vertebral fractures by 73% after romosozumab and subsequent denosumab treatment, com-

pared to placebo and subsequent denosumab.

6.2.11. Single Drug

Bisphosphonates have been widely used for the treatment of osteoporosis for more than 50 years. These are used as single-drug therapy for the management of postmenopausal osteoporosis and glucocorticoid-induced osteoporosis. However, no approved single-drug therapy is capable of restoring the skeletal integrity in the majority of patients and long-term use of these drugs is controversial. Hence, combination or sequential drug therapy is adapted for many patients.

6.2.12. Combination/Sequential Therapy

In the DATA study by Tsai *et al*., women with postmenopausal osteoporosis were divided in a 1:1:1 ratio to receive 20 μg teriparatide daily, 60 mg denosumab every 6 months, or both. BMD was measured at 0, 3, 6, and 12 months. The study demonstrated that therapy with combined teriparatide and denosumab significantly increased the lumbar spine BMD, femoral neck BMD, and total-hip BMD compared with teriparatide and denosumab alone. The combination also increased BMD more than that has been reported with approved therapies [104]. The DATA SWITCH study, an extension of DATA study, in which 94 postmenopausal osteoporotic women were randomly assigned to receive 24 months of teriparatide (20 mg daily), denosumab (60 mg every 6 months), or both drugs. The study concluded that the BMD continued to increase in postmenopausal women who switched from teriparatide to denosumab. However, transient or progressive bone loss occurred in women who switched from denosumab to teriparatide treatment. These findings may help the physicians to select the initial and subsequent therapies for the management of postmenopausal osteoporosis [105].

6.2.13. Monitoring and Follow-Up

The postmenopausal women who are on anti-osteoporotic treatment should be monitored for the potential adverse effects of the drugs. The frequency and duration for which the treatment is continued depend upon the individual response to treatment. It is recommended that evaluation of bone tumor markers to be performed (if available) once in every 3 - 6 months, BMD by DXA once in every 1 - 2 years, and X-ray spine and hip—if clinically indicated. Drug holidays may be required for patients who are on antiresorptive therapy, except for those with severe osteoporosis and in whom the bone turnover is suppressed.

6.3. Surgical Management of Osteoporotic Fractures

6.3.1. Vertebral Fractures

Most vertebral fractures respond well to non-operative treatment. However, about one-third of vertebral fractures become chronically painful and 10% need hospital admission. However, the number of patients who need surgical treatment remains obscure. Mechanical pain, claudication/sciatica, severe deformity are the indications of surgery for vertebral fractures. The various types of surgeries

include vertebroplasty, kyphoplasty or lordoplasty and open surgical intervention with decompression and instrumentation.

Vertebroplasty is indicated when conservative management fails. Several prospective case series have been published and confirm rapid and lasting pain relief in 80% - 90% of patients. In fresh fractures, pain improvement is seen in 93% of patients [106]. But also, in older lesions, the treatment can be effective in as many as 80% of patients [107]. Risk of adjacent fractures, cement leakage into the spinal canal, infection, fat embolism are the potential complications of vertebroplasty.

Kyphoplasty is the procedure of restoration of the vertebral body height and correction of the kyphotic deformity to realign the spine. However, its usefulness is doubtful considering the complexity and the cost of the procedure. Its indications are restricted to selected cases where height loss is associated with spinal stenosis [108]. Lordoplasty is an effective alternative to kyphoplasty.

Combined anterior-posterior procedures are commonly recommended in patients with kyphotic deformities with neurologic dysfunction secondary to osteoporosis. However, it has been found that combined anterior-posterior surgery is associated with significant morbidity in elderly patients. The posterior closing wedge osteotomy procedure though is technically challenging, results in better surgical outcomes in terms lesser mean operative time and lesser blood loss compared to combined anterior-posterior surgery and is a better alternative to the combined procedure [109].

6.3.2. Hip Fractures

Hip fractures are broadly classified based upon their relationship with the hip capsule as extracapsular and intracapsular. This classification enables the facilitation of communication between orthopedic surgeons regarding the diagnosis and treatment of hip fractures. Accordingly, the sliding screw devices or cephalomedullary systems dominate the fixation of extracapsular fractures whereas intracapsular fractures are treated with screw/plate fixation or arthroplasty. The surgical treatment of hip fractures are associated with significant morbidity and mortality which can be reduced or prevented by optimization of the patient's clinical condition, meticulous preoperative evaluation, appropriate anesthetic, and surgical management along with proper postoperative care of the patient. [110]. Age, sex of the patient, and associated co-morbid conditions are the predictors of the outcome of hip fractures. Return to pre-injury level of function has been reported in 40% - 48% of patients by various studies in the literature [111] [112] [113]. Multidisciplinary care plays a very important role in increasing the percentage of patients returning to the pre-injury level of function. Studies have demonstrated a significant increase in physical activity and mobilization in postoperative elderly patients following appropriate postoperative care and rehabilitation [114].

6.3.3. Wrist Fractures

Various conservative and surgical treatments have been recommended for the

management of DRFs, which include cast immobilization, pin-in-plaster, percutaneous pining, locked volar plating, open reduction and internal fixation, external fixation. However, the evidence supporting the efficacy of one surgical technique over the other is not sufficient as uniformly good results have not been achieved with any one procedure and therefore the definitive management of DRFs remains controversial. As a result of the lack of data regarding the clinical effectiveness of these procedures, the healthcare team should take into consideration the cost of the procedure as the major determinant of the type of operation performed [115].

6.3.4. Technical Challenges in Fracture Fixation of Osteoporotic Bone

Osteoporotic fractures pose a greater risk of failure at the implant-bone interface before the healing is achieved. This is due to the impaired ability of osteoporotic bone to hold screws or support implants and also due to the crushing of cancellous bone with subsequent voids after fracture reduction. Augmentation of pedicle screws with bone cement, such as polymethylmethacrylate or calcium-based cement is a useful alternative to enhance chances of fixation in osteoporotic fractures and improve the healing rates.

Osteoporotic bone faces lots of challenges with the conventional fixation methods due to its inability to resist the pull-out of screws or other fixation devices, thereby resulting in potential loss of fracture reduction and subsequent alignment. Therefore, the functional outcomes in osteoporotic patients have been shown to be worse than those in non-osteoporotic patients [116].

7. Bridging the Gap in the Screening and Management of Osteoporosis

Osteoporosis often goes unrecognized until one or more fractures occur. Though the importance of diagnosis of osteoporosis is well recognized by orthopedic surgeons, the gap in the management of osteoporosis in both primary as well as tertiary settings is acknowledged by them, accepting imperfect post-fracture osteoporosis care. In a survey conducted at Virginia Tech Carilion School of Medicine, many surveyed Orthopaedic Surgeons were unfamiliar with the approaches in the treatment of osteoporosis and most said that they were uncomfortable prescribing medications for osteoporosis. Based on these findings, the Department of Orthopaedic Surgery at Virginia Tech Carilion School of Medicine used a fracture liaison service (FLS) model instead of a protocol-based approach to improve osteoporosis recognition and management. Professional bodies including the International Osteoporosis Foundation (IOF), American Orthopaedic Association (AOA), and American Society of Bone Mineral Research (ASBMR), strongly support the FLS model as the preferred approach to secondary prevention of osteoporotic fractures. In the FLS model, orthopedic surgeons refer patients with suspected fragility fractures to a fracture liaison service, where a nurse practitioner formally evaluates them for osteoporosis and initiates treatment as indicated. This method helps to alleviate the burden of orthopedic surgeons to

manage the osteoporotic patients under the protocol. Challenges such as logistical and institutional barriers need for hiring dedicated personnel, limited resources due to small private clinics, and independent practitioners affect the feasibility of setting up an FLS model in certain settings [117].

8. Conclusions

Osteoporosis is a silent disease unless it is complicated by osteoporotic fractures which impair patients' quality of life, cause disabilities, and increase mortality with the tremendous burden on patients as well as the nation's health care economy. Diagnosis and management of osteoporosis are possible with available effective therapies which can decrease the risk of fractures. It is advised to initiate Calcium & Vitamin D3 supplementation in middle-aged women with deficiencies. Postmenopausal women should undergo BMD testing by DXA for early detection of osteoporotic changes. Based upon the opinion of an endocrinologist or gynecologist, HRT/SERMs can be initiated. For treatment naïve patients, bisphosphonates are the first choice of monotherapy which can be continued for two years. After two years, the same drugs can be continued based on the patient's response or can be swapped to denosumab which is a monoclonal antibody. Bisphosphonates need treatment holiday at 4 years while denosumab can be continued for 10 years. Severe cases of osteoporosis can be managed with teriparatide which can be continued for two years.

Reduction in the treatment gap in osteoporosis is the need of the hour as the majority of osteoporotic fractures remain under-recognized and under-treated. This is mainly due to the reluctance of several orthopedic surgeons in prescribing pharmacotherapy for osteoporosis despite the advances in fracture risk prediction and the availability of cost-effective therapies to reduce the risk of fractures. This gap can be fulfilled by a continuing process of sensitization and education of the orthopedic community on the one hand and employing resources like fracture liaison service on the other.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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