

## Guidelines

# Clinical Practice Guidelines on Postmenopausal Osteoporosis: \*An Executive Summary and Recommendations – Update 2019–2020

Meeta Meeta, C. V. Harinarayan<sup>1</sup>, Raman Marwah<sup>2</sup>, Rakesh Sahay<sup>3</sup>, Sanjay Kalra<sup>4</sup>, Sushrut Babhulkar<sup>5</sup>

Co-Director, Chief Consultant Tanvir Hospital, Hyderabad, Telangana, <sup>1</sup>Professor, Chief Consultant, Fortis Hospitals, Bangalore, <sup>2</sup>Scientific Advisor, Senior Consultant Endocrinology, International Life Sciences, New Delhi, <sup>3</sup>Professor, Osmania Medical College, Hyderabad, Telangana, <sup>4</sup>Consultant Endocrinology, BRIDE, karnal, <sup>5</sup>Consultant, Trauma and Joint Replacement Surgeon, Sushrut Hospital and Post-Graduate Institute of Orthopaedic, Nagpur, India

**Review on Vitamin D:** Michael F. Holick, Professor of Medicine, Physiology and Biophysics and Molecular Medicine. Director, Vitamin D, Skin, and Bone Research Laboratory. Programme Director General Clinical Research Unit. Director, Biologic Effects of Light Research Centre, Director, Bone Healthcare, Boston.

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\*This is a short summary and recommendations from the detailed monogram on clinical practice guidelines on postmenopausal osteoporosis available at the **Indian Menopause Society Website:** [www.indianmenopausesociety.org](http://www.indianmenopausesociety.org).

## INTRODUCTION

Among the several challenges faced by the growing elderly population with increasing longevity in India, postmenopausal osteoporosis (PMO) is emerging as one of the major public health issues. Osteoporosis is an asymptomatic or “silent” disease and generally presents as a fragility fracture. Typical osteoporotic fractures are those of the hip, spine, and wrist. Global data indicate that 20% of women with hip fracture die within 1 year of the fracture and 50% of them never regain their functional independence.<sup>[1]</sup> Vertebral fractures can also have significant mortality and are associated with increased long-term morbidity.<sup>[2]</sup> The World Health Organization (WHO) has identified osteoporosis as an important noncommunicable disease. Osteoporotic fractures impose great financial, medical, and social burden on society. These guidelines are intended to be

used as a resource document by the healthcare providers involved in postmenopausal women’s health at all levels of healthcare with specific reference to India. Although framed for India, it is hoped that these guidelines will be useful for menopause practitioners across the globe.

This is one of the endeavors of the Indian Menopause Society to work toward the slogan, “**Fit @ Forty Strong @ Sixty, and Independent @ Eighty**”.

## BASIC CONCEPTS

### Definitions

1. Osteoporosis: The WHO defines osteoporosis as “a systemic skeletal disease characterized by low bone

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**Address for correspondence:** Dr. Meeta Meeta, Tanvir Hospital, Plot No. 100, Phase-I, Kamalapur Colony, Hyderabad - 500 073, Telangana, India. E-mail: [drmeeta919@gmail.com](mailto:drmeeta919@gmail.com)

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- mass (measured as bone mineral density [BMD]) and micro-architectural deterioration of the bone tissue with a consequent increase in bone fragility and susceptibility to fractures, involving the wrist, spine, hip, pelvis, ribs, or humerus”<sup>[3]</sup>
2. Fragility fracture, the end point of inadequate skeletomuscular health, has been defined by the WHO as “a fracture caused by injury, which would be insufficient to fracture normal bone: the result of reduced compressive and/or torsional strength of bone.” Clinically, a fragility fracture can be defined as one which occurs as a result of minimal trauma, such as a fall from a standing height or less, or no identifiable trauma<sup>[4]</sup>
  3. The most common sites of fragility fracture are the hip, spine, and forearm. The other sites are pelvis, proximal femur, proximal humerus, proximal tibia, and fractures involving three ribs simultaneously<sup>[5]</sup>
  4. Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes, including falls, fractures, physical disability, and mortality. Severe sarcopenia is confirmed by the presence of low muscle quantity or quality and/or low physical performance. Sarcopenia is diagnosed in the presence of low muscle quantity or quality. Low muscle strength indicates the probability of sarcopenia<sup>[6]</sup>
  5. Frailty: Physical frailty is defined as “a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability for developing increased dependency and/or death.”<sup>[7]</sup>
8. The reference range recommended by the International Osteoporosis Foundation, International Society of Clinical Densitometry (ISCD), WHO, and National Osteoporosis Foundation (NOF) for calculating the T-score in the postmenopausal women is the National Health and Nutrition Examination Survey III reference database in Caucasian women aged 20–29 years (Grade C)<sup>[8-11]</sup>
  9. The ISCD diagnostic criteria for osteoporosis in postmenopausal women and in men aged 50 and older is if the T-score of the lumbar spine, total hip, or femoral neck is  $-2.5$  or less. In certain circumstances, the 33% of radius (also called 1/3 radius) may be utilized<sup>[12]</sup>
  10. The Z-score describes the number of SDs by which the BMD in an individual differs from the mean value expected for age and sex. It is mostly used in children, adolescents, and premenopausal women. A Z-score below  $-2$  is regarded as abnormal and should be referred to as “low for age.” A low Z-score in a postmenopausal woman indicates the need to evaluate for secondary osteoporosis.<sup>[12]</sup>

### CRITERIA FOR DIAGNOSIS OF OSTEOPOROSIS

6. The diagnosis of an osteoporosis is by the presence of fragility fracture (clinical or radiological) and/or by BMD (T-score below or equal to  $-2.5$ ) in a postmenopausal woman [Table 1]
  7. The “gold standard” method of BMD testing is by dual X-ray absorptiometry (DXA). Its value is expressed in standard deviation (SD) units from the population mean in young adults (T-score) or from the mean in an age-matched population (Z-score)
11. Osteoporosis is classified as primary (includes type I and type II) and secondary
    - a. Primary osteoporosis is seen in the postmenopausal women in whom there is no specific pathogenetic mechanism other than age
      - i. Type I or PMO affects mainly trabecular bone occurring in the early part of the menopause transition. There is an accelerated bone loss at the rate of 1%–2% per year (range 1%–5% yearly) due to declining estrogen levels and is seen in the first 5–7 years after menopause<sup>[13]</sup>
      - ii. Type II or senile osteoporosis is age related, and bone loss occurs at a rate of 1% per year in both sexes and affects the cortical and trabecular bone.
    - b. Secondary osteoporosis is due to specific causes.<sup>[14]</sup>
  12. Osteoporosis and osteomalacia: Bone is a dynamic tissue with a continuous remodeling, leading to the formation of new bone and resorption of old bone. A mismatch of this process forms the basis for osteoporosis, while defective mineralization of the newly formed osteoid is called osteomalacia.<sup>[15]</sup>

**Table 1: Diagnosis of osteoporosis**

Grading	Score
Normal	T-score above (i.e., better than) $-1.0$
Osteopenia or low bone mass	T-score between $-1.0$ and $-2.5$
Osteoporosis	T-score below (i.e., worse than) or equal to $-2.5$
Severe osteoporosis	T-score below $-2.5$ with fragility fracture

### EPIDEMIOLOGY

13. There is a wide prevalence of low dietary calcium in Indians of all age groups, with majority of postmenopausal women consuming  $<400$  mg/day. This extends to all other age groups

(infancy, adulthood, postmenopausal women, pregnancy, and lactation)<sup>[16-20]</sup>

14. Studies on bone mineral health from different parts of India indicate a wide prevalence of Vitamin D deficiency in all age groups, including infancy, adulthood, postmenopausal women, pregnancy, and lactation<sup>[21-31]</sup>

### PEAK BONE MASS

15. Peak bone mass (PBM) is the highest level of bone mass achieved as a result of normal growth and is important as it determines resistance or susceptibility to osteoporosis and fractures. PBM is the result of the interaction of the various factors: genetic, hormonal, racial, nutritional, lifestyle, and physical exercise.<sup>[32-36]</sup> Environmental factors modulate the expression of the genetic potential to achieve PBM<sup>[37,38]</sup>
16. Age, sex, and genetic predisposition are important nonmodifiable risk factors for osteoporosis
17. Although PBM is achieved by 25–30 years, 40%–50% of bone mass is achieved by the age of 18 years. At skeletal maturity, women have 10%–15% lower bone mass than men. Asian Indians have a significant lower PBM than Caucasians.<sup>[39-41]</sup>

### SCREENING AND DIAGNOSIS

18. Osteoporosis is asymptomatic unless a fracture occurs. Fracture risk is defined by BMD (both primary and secondary causes) and clinical risk factors. For treatment purpose, combining BMD with clinical risk factors provides a better estimate of fracture risk. We simply should not treat T-scores but must take a patient's full clinical status into account when we make therapeutic decisions
19. Early diagnosis in the asymptomatic period is essential, and timely management of osteoporosis will prevent the associated morbidity and mortality. Osteoporotic fracture risk screening of large-scale whole population groups is not likely to be cost-effective, so more selective approaches, i.e., targeted screening for disease detection, are advocated. In the absence of a validated population screening tool for PMO in India, a case-finding strategy utilizing clinical risk factors with the addition of DXA as needed is suggested (Grade C)
20. Asymptomatic women: Opportunistic screening for women above 40 years is suggested [Flowchart 1 Refer Appendix 1]
21. Risk assessment factors for fractures are derived by history and clinical examination. It is important to distinguish between those risk factors that lead to reduced bone mass from those that predispose to osteoporotic fractures with a BMD not in the

osteoporotic range. Risk assessment tools such as The Osteoporosis Self-Assessment Tool (OSTA)<sup>[87,88]</sup> for Asians and Simple Calculated Risk Estimation Score (SCORE)<sup>[89]</sup> are simple and cost-effective to screen women at risk for osteoporotic fracture

22. The WHO Fracture Risk Assessment Tool (FRAX) is country specific, and an online tool is available for India (<http://www.shef.ac.uk/FRAX>). FRAX is used to identify patients in the osteopenia group most likely to benefit from treatment. It predicts the 10-year absolute risk for a fracture in an individual, and the cost-effective analysis determines the interventional threshold above which the treatment is cost-effective. FRAX is country specific, and until more Indian data are available on the prevalence of osteoporotic fractures and mortality rates, it may not serve the true purpose for the usage of FRAX in the Indian context (Grade C)
23. Major risk factors defined by the WHO are (Grade A):
- Advancing age is a single most significant risk factor
  - Low body mass index (BMI)
  - Prior history of a fracture
  - Parental history of hip fracture
  - Smoking
  - Alcohol
  - Use of glucocorticoid
  - Rheumatoid arthritis.
24. Environmental factors include nutrition (calcium intake using the quick dietary calculator, protein), physical activity and sunlight exposure, and risk of falling, which are the important modifiable risk factors
25. Secondary osteoporosis: Case finding for secondary osteoporosis is practiced in high-risk disease subgroups, such as chronic glucocorticoid users and patients with rheumatoid arthritis, collagen vascular disease or inflammatory bowel disease, hypogonadism, thyroid dysfunction, type 2 diabetes, and use of aromatase inhibitors in breast cancer survivors (Grade A)
26. Symptomatic women [Flowchart 2 Refer Appendix 2]
27. Women presenting with fragility fracture, complain of severe pain, which is sudden in onset with minimal trauma, or chronic pain localized to the mid-back may radiate to the abdomen. Generalized bone pain indicates osteomalacia or metastasis. A multifactorial fall assessment is recommended. In Vitamin D deficiency, proximal muscle is affected more than the distal, so activities such as using a squatting toilet, climbing stairs, and getting out of low chair can be particularly difficult. Tenderness on the pretibial and sternum can be elicited
28. Physical examination should include recording the

height and weight annually, check for balance and gait, and ask the women to get up from chair without using their arms (get up and go test). The occiput to wall distance in standing position is ideally zero, inability to touch the occiput to wall, while standing implies a thoracic fracture. Inability to insinuate the four fingers of the hand between the lower rib cage and anterior superior iliac crest implies a lumbar fracture. Kyphosis and Dowager's hump are seen in the late stage of osteoporosis (Grade A)

29. Laboratory tests: It is essential to rule out secondary causes.
- a. Essential (Grade A)
    - i. Complete blood picture, ESR
    - ii. Random blood sugar
    - iii. Serum calcium
    - iv. Preferably fasting serum phosphorus
    - v. Serum creatinine
    - vi. Serum albumin
    - vii. Alkaline phosphatase
    - viii. Serum TSH 25 hydroxy vitamin D
    - ix. X-ray of the thoracolumbar spine (lateral view)
    - x. PTH (based on clinical judgment).

### Dual X-ray absorptiometry

30. It is suggested to conduct central DXA of the spine and hip in all women 5 years beyond the natural age of menopause and in women less than 5 years since menopause with one high clinical risk or more than two clinical risk factors. This suggestion is based on the following: (Grade C)
- a. Early age of natural menopause, i.e., 46.7 years in an Indian women<sup>[42,43]</sup>
  - b. Life expectancy of an Indian woman is 70.3 years (WHO Statistics 2018)
  - c. Accrual of low PBM<sup>[39-41]</sup>
  - d. Early age of presentation of fracture. Accelerated bone loss in the immediate 5 years of menopause<sup>[44-46]</sup>
  - e. Stratification by age shows that the prevalence of low bone mass is more than 40% from the age of 40 years and increases to more than 80% by the age of 65 years.<sup>[47-55]</sup>
31. Indications for DXA (Grade B)
- a. All postmenopausal women more than 5 years of menopause
  - b. Postmenopausal women less than 5 years of menopause with risk factors
  - c. Women in menopause transition with secondary causes
  - d. Radiological evidence of osteopenia and the presence of vertebral compression fracture
  - e. Women with fragility fractures by radiology or DXA

- f. Ideally, before initiating pharmacotherapy for osteoporosis
  - g. Emerging indications are to measure total body fat and lean tissue mass.
32. The lowest BMD score obtained from all the sites is used for diagnosis (Grade A).
33. Screen postmenopausal women for secondary osteoporosis if history or examination shows systemic disease or low Z-scores on DXA (Grade A).
34. To monitor therapy, the interval to the next DXA should depend on the calculated individual risk and would mostly be scheduled between 1 and 5 years later.
35. Peripheral DXA (X-ray based) may be used as a mass screening tool because of its high negative predictive value (Grade C).

### RADIOGRAPHY: QUANTITATIVE ULTRASOUND

36. X-ray abnormality is a feature of advanced bone disease. We recommend X-rays in all the diagnostic protocols for osteoporosis (Grade A). In areas of endemic fluorosis, it is not advisable to follow ultrasound-based bone densitometry for diagnosis of osteoporosis.<sup>[56]</sup>

### BONE TURNOVER MARKERS

37. Bone turnover markers (BTMs) are not a part of the routine tests to be used for clinical diagnosis. They may be used as an initial evaluation. They help identify the fast losers (Grade A). BTMs are also useful to assess compliance and efficacy of therapy and preferably follow the broad guidelines given below (Grade B):
- a. Type of markers
    - i. Bone resorption: Serum C-terminal telopeptide (CTX)
    - ii. Bone formation: Serum procollagen type 1 N-terminal propeptide (PINP), bone-specific alkaline phosphatase.
- Use one marker of bone resorption and one marker of bone formation. More specifically, use markers for bone resorption when on antiresorptives and use bone formation markers when on anabolic agents
- b. Monitoring: Baseline, and for resorption markers at three or six months, for formation markers at six months after treatment has been initiated
  - c. Timing of sample: Morning (before 9 am) after an overnight fast for CTX and anytime for PINP
  - d. Try to use the same laboratory services and same assay or method for monitoring intervals of measurement and compare the difference with the least significance change in terms of percentages or absolute values.



## MANAGEMENT

### Therapeutic lifestyle management

38. Therapeutic lifestyle management is an essential part in the management of osteoporosis. This includes a balanced diet, adequate physical activity and exposure to sunlight, and avoidance of bone-depleting agents such as tobacco, alcohol, caffeine and excessive salt. It is advisable to limit the intake of sodium to 5 g/day (1 tsp), decrease caffeine intake (<3 cups/day), limit alcohol, and avoid use of tobacco (Grade B). The quantity of protein intake should be 0.8–1 g/kg body weight
39. The recommended dietary allowance (RDA) of calcium intake for an adult Indian women is given in Table 2.<sup>[57]</sup> Assess the total calcium intake from dietary sources by using the NOF tool depicted in Table 3.<sup>[58]</sup> If needed, supplements are used to correct the deficient balance. The intake should exceed >800 mg/day (Grade B)
- Encourage dietary intake [Refer Appendix 3]; supplements are added to correct the deficient balance. The risk of cardiovascular events and calculi are not observed with the recommended doses of calcium
  - Limit 500 mg calcium at one time from food and/or supplements. Spread calcium sources throughout the day
  - Dietary calcium restriction is no longer recommended for patients with hypercalciuria
  - The 2016 NOF guideline on the safety and benefit of calcium supplementation stated that calcium intake below the UL (2,000-2,500 mg/d) is not associated with CVD risk in generally healthy adults
  - The data on supplemental calcium intake over and above the RDA is currently controversial. In case where calcium supplementation is medically necessary, patients should be encouraged to take their calcium supplements with a meal and should be monitored for hypercalciuria
  - Absorption of calcium is decreased when taken with foods rich in oxalic acid, phytates and tannins (spinach, fibres, Iron, zinc, spinach, tea, alcohol), vitamin D deficiency, estrogen deficiency, ageing, decreased gastric acid production, and malabsorptive disorders. Thyroid medications, corticosteroids, tetracyclines, and anticonvulsants and calcium should be taken separately
  - 24-h urine calcium is the best method of evaluating adequacy of calcium intake and absorption.

### Vitamin D

40. Vitamin D deficiency can be considered as a National Nutritional Deficiency pandemic. In the background of widespread Vitamin D deficiency in all age groups, it is prudent to adopt the US Endocrine Society 2011 RDA<sup>[59,60]</sup> [Table 4]
- It is preferable to get Vitamin D through sunlight by exposing 15%–30% of body surface area (face, neck, and both arms and forearms) without sunscreen for at least 30 min between 10 am and 3 pm, depending on the season, latitude, altitude, pollution, and skin pigmentation. This is equivalent to consuming 340–490 IU of Vitamin D every day based on the reports that 100 IU of Vitamin D intake will raise serum 25(OH)D by 1 ng/ml
  - Dietary sources are limited; hence, the Government of India has permitted fortification of food which would enable population at large to enhance an intake of RDA of Vitamin D by 30%–50% (200–300 IU). This would be of value if one assumes that the consumption of milk/milk products is 700 ml per day and of oil is 30 ml/day. However, implementing intake from the natural sources has practical limitations. Hence, it is recommended to use Vitamin D as supplements (Grade A)
  - Recommendations for the management of Vitamin D deficiency and maintenance are given below (Grade B):<sup>[61-68]</sup>
    - Cholecalciferol (Vitamin D3) is available in the form of oral tablets (conventional morcellized or nanoemulsion formulations), granules, and oral spray. Dosages of 1000, 2000, and 60,000 IU are available
    - Intramuscular (IM) injections of Vitamin D3

**Table 2: Recommended dietary allowance of calcium**

Group	Calcium (mg)
Adult women	600
Pregnancy	1200
Lactation	1200
Postmenopausal women	800

**Table 3: Quick dietary calcium assessment chart**

Source	Calcium (mg)*	Number of servings	Total calcium (mg)
Diary	300-525/1 glass	x	
source	300/1 katori curds		
Non diary	200-300	x	

Total intake of calcium in mg. \*Approximate estimates. Calculate the total daily dietary intake by entering the sources and the number of servings from diary and nondiary sources before supplementation

**Table 4: US Endocrine Society 2011 recommended dietary allowance 69**

Life stage group	RDA (IU)	Upper limit
Adults (18 years and above)	1500-2000	10,000
Pregnancy and lactation	1500-2000	10,000
Children and adults at risk*	2-3 times the normal requirement for their age	

\*Obesity, HIV infection, on glucocorticoids, anticonvulsant, antifungal and antiviral therapy. A desirable range is between 30 and 60 ng/mL, although levels up to 100 ng/mL are unlikely to result in Vitamin D toxicity. Except in granuloma disorders, wherein it is advisable to maintain the serum levels of 25(OH) D up to >30 ng/mL. RDA: Recommended dietary allowance

- are available in doses of 300,000 and 600,000 IU per ampoule. Injections of cholecalciferol are cost-effective and may be recommended in cases of malabsorption and also to increase compliance. The disadvantages are painful and erratic blood levels.
- Cholecalciferol is the preferred therapy for correction of deficiency and maintenance.
  - Management of deficiency: Cholecalciferol (Vitamin D3) 60000 IU/orally once a week for 8 weeks preferably with milk is given. One IM injection of 600,000 IU is given to correct the deficiency (not to be repeated before three months and may be given after confirmation of persistent low levels of Vitamin D). This is followed by maintenance therapy
  - Maintenance therapy: Cholecalciferol 60,000 IU once a month in summer or twice a month in winter is preferred. Vitamin D supplements of 2000 IU/day or injection of cholecalciferol 300,000 IU IM twice a year or 600,000 IU IM once a year is given
  - Cholecalciferol, 1000 IU daily, will raise blood levels, on average, by approximately 10 ng/ml
  - Upper acceptable limit: The dose for treatment should not exceed 4000 IU/day and hypercalcemia has been reported when the dose exceeds 10,000 IU/day
  - Vitamin D derivatives: Calcitriol, the active form of Vitamin D, is reserved only for patients with chronic renal and hepatic disease. Alfacalcidol is a synthetic analog of the active Vitamin D metabolite calcitriol (1,25-dihydroxyvitamin-D3), and it is metabolized to calcitriol by its 25-hydroxylation in the liver. It is less potent than calcitriol. The use of Vitamin D derivatives necessitates monitoring of serum and possibly urine calcium. There is the risk of hypercalcemia and hypercalciuria. Adverse effects of prolonged hypercalcemia include impairment of renal function and nephrocalcinosis
  - In postmenopausal women, the intake of Vitamin D should be in addition to sunlight exposure. Vitamin D supplementation ( $\geq 500$ –2000 IU/day) was favorable in the reduction of hip fracture

- and any nonvertebral fracture in persons aged 65 years of age or older
- Vitamin K: For women of postmenopausal age, 180–350  $\mu\text{g/day}$  of Vitamin K2–7 may need to be supplemented along with the recommended intake of calcium, magnesium, Vitamin D, and a balanced diet. Current RDA of Vitamin K2–7 WHO/FAO of 65–80  $\mu\text{g/day}$  is too low and needs to be raised up to at least 100  $\mu\text{g/day}$  throughout life, with larger doses when needed. Both bone and cardiovascular health of women with osteoporosis would benefit from Vitamin K2–7 intake<sup>[69]</sup> (Grade C)
  - Exposure to complex nutrients and food constituents interact to affect bone mass; hence, it is the individual clinician to decide on supplementing Vitamin A, Vitamin B12, and phytoestrogens (Grade B).

### PHYSICAL ACTIVITY/EXERCISE

- Adequate physical activity is needed to maintain bone health. Appropriate resistance, weight-bearing aerobics, and core-stabilizing exercises are needed to maintain bone health (Grade A). Balance exercises are necessary to prevent falls. Brisk walking 4–5 times a week for 30 min is part of maintaining health but on its own would not be sufficient for bone health<sup>[70]</sup>
- Patients with severe osteoporosis should avoid engaging in motions, such as forward flexion exercises, using heavy weights, or even performing side-bending exercises, because pushing, pulling, lifting, and bending exert compressive forces on the spine that may lead to fracture (Grade A)<sup>[71]</sup>
- Prevention of falls: Patients should receive a multifactorial risk assessment and intervention because it is the most consistently effective strategy to prevent falls (Grade A).<sup>[72-74]</sup>

### PHARMACOTHERAPY

- It is good to understand the term prevention and treatment in the context of osteoporosis
  - The term prevention is used to denote the prevention of bone loss in the postmenopausal women with low bone mass (T-score between  $-1$  and  $-2.5$ ) and increased fracture risk

- b. Treatment is defined as reduction in fracture risk in the postmenopausal women with osteoporosis.
47. Indications for pharmacotherapy<sup>[75-82]</sup>
- Fragility fractures (clinical, height loss of >4 cm, kyphosis or morphometric by X-rays, or VFA by DXA) (Grade A)
  - BMD T-scores  $\leq -2.5$  at the femoral neck or spine or wrist by DXA (Grade A)
  - Women with low bone mass by DXA with one major or two other minor risk factors (or) eligible by OSTA for Asians, FRAX, and SCORE (Grade A)
  - In the absence of BMD measurements by DXA, intervention is individualized, based on the clinical risk assessment fracture risk tools such as the SCORE, OSTA, and FRAX (interventional threshold –10-year risk score  $\geq 3\%$  for hip fracture and  $\geq 20\%$  for major osteoporotic fracture), the cost-benefit analysis, and risk-benefit outcome (Grade B).
48. The choice of medication depends on drug-related (risk-benefit), patient profile (age, years since menopause, symptoms, and comorbidities), and environment-related factors (economics and social). Patients should be educated in PMO and its treatment and empowered to take part in shared decision-making to improve adherence. They should be calcium and Vitamin D replete
49. Patients should be monitored initially, every 3–6 months for 2–3 contacts, and then annually for clinical assessment. Assess for side effects and compliance. We suggest that markers of bone resorption and formation may be tested at baseline and after 3–6 months of therapy in certain situations and research settings (Grade C)
50. We suggest that DXA should be performed every 2 years on the same machine to monitor osteoporosis therapy (Grade B)
- Measurement error must be considered when interpreting serial BMD assessments to determine whether the change is real and not simply random fluctuation or artifact. Follow the ISCD guidelines for conducting and interpreting DXA
  - Each center should determine its precision error to estimate the least significant change (i.e., the change in BMD required to have 95% confidence that the change is real). This is a standard of care and has to be meticulously followed by the DXA centers
  - Most osteoporosis therapies do not cause increase in BMD, and the antifracture effect of treatment is only partly explained by the relatively small changes in DXA
  - Stable BMD is consistent with successful treatment.
51. Nonresponders to PMO therapy may be due to poor adherence, poor calcium/Vitamin D health, untreated secondary osteoporosis, concomitant therapy with skeletotropic drugs, inappropriate choice of drugs, or wrong choice of monitoring strategies (Grade C)
52. Duration of therapy has to be individualized depending on the patient's profile, drug used, and response to therapy
53. There is no specific recommendation on combination therapies and sequential therapies these should be planned as per the individual patient's need. Although teriparatide and denosumab combination has been documented with the highest BMD outcomes till date, some guidelines recommend sequential therapies for maintaining BMD gains and long-term protection against fracture. Drug holidays are planned in patients on bisphosphonates, depending on the categorization of risk for fracture
54. There are no head-to-head trials of the various drugs comparing their effects on fracture rates. The details of drug therapy are given in Appendix 4.<sup>[54]</sup>
55. Hormone therapy, alendronate, and risedronate may be considered as initial options for most early postmenopausal women with low or moderate fracture risk. In women who are intolerant of oral bisphosphonates or in whom they are contraindicated, intravenous bisphosphonates or denosumab should be considered (Grade A recommendation)
56. Women with breast cancer risk and with osteoporosis of the spine may be benefitted with raloxifene
57. In older postmenopausal women, injectable agents such as denosumab, zoledronic acid, or teriparatide can be considered as initial therapy for those who have the highest fracture risk, older women who have had multiple vertebral fractures or hip fractures, or those who have very low T-scores, those who have upper gastrointestinal problems, and those might not tolerate or absorb oral medication and patient preference
58. Bisphosphonates are recommended as the first-line drugs for treating postmenopausal women, with proven efficacy in the prevention of vertebral and nonvertebral fractures, including hip fractures (Grade A)

## MENOPAUSAL HORMONE THERAPY

59. Estrogen progesterone therapy/estrogen therapy (EPT/ET) may be used for low bone mass and treatment of osteoporosis in the early postmenopause with vasomotor symptomatic unless there is a contraindication. (Grade A)<sup>[83-85]</sup>
60. Pre-menopausal hormone therapy (MHT) workup and an annual follow-up are essential when prescribing MHT. The dose and duration of MHT should be

individualized, and a risk–benefit assessment was carried out annually. A full gynecological assessment is mandatory before starting MHT and at regular intervals thereafter. Self-breast examination is advised monthly and clinical breast examination at least annually. A mammogram where available should be carried out 1–3 yearly, if the initial mammogram is normal (Grade C)

61. All preparations including low-dose, nonoral routes of estrogen are effective in preserving bone mass. In women with hypertriglyceridemia, obesity, glucose intolerance, history of deep vein thrombosis, and tobacco users, nonoral route should be preferred (Grade B)
62. MHT should not be started solely for bone protection after 10 years of menopause. Extended use of MHT in women with reduced bone mass is an option after considering the risk–benefit analysis compared to the other available therapies for osteoporosis (Grade B)
63. MHT is indicated as primary therapy to prevent bone loss in women with premature menopause and secondary amenorrhea (Grade C)
64. Progestogens should be added to estrogen therapy in women with uterus (Grade A)
65. If MHT is given to women below the age of 60 or within 10 years of menopause, the risks are rare. Tables 7 elaborates the risks and benefits in terms that can be used during counseling for easy and understandable communication [Table 5]
  - a. Harms: Based on WHI, the number of excess events on MHT versus placebo per 10,000 women per year of MHT. Use between the age group of 50 and 59 years (Grade A) [Table 6]<sup>[83]</sup>

**Table 5: Council for International Organisations of Medical Sciences definitions are as follows which can be easily communicated to the lay person**

Term	<i>n</i>	Colloquial
Very common	1/1 to 1/10	A person in family
Common	1/10 to 1/100	A person in street
Uncommon	1/100 to 1/1000	A person in village
Rare	1/1000 to 1/10000	A person in a small town
Very rare	Less than 1/10000	A person in a large town

RCOG Clinical Governance Advice<sup>[82,83]</sup>

b. Benefits of hormone therapy are presented in Table 7 (Grade A).

66. Tibolone may be preferable to MHT in symptomatic menopausal women with mammographically dense breast tissue (Grade A). It can be used as an add-back therapy with GnRH analogs for vasomotor symptoms and to maintain BMD (Grade B). Tibolone should be used with caution in women over 60 years and should not be used in those who have strong risk factors for stroke, in breast cancer survivors (Grade A)
67. Selective estrogen receptor modulators (SERMs, e.g., raloxifene at 60 mg daily) has been shown to be beneficial in reducing new vertebral fracture risk by 69% in the postmenopausal women with osteoporosis and 47% in the postmenopausal women with osteopenia over 3 years simultaneous reduction by 76% in the risk of invasive breast cancer (Grade A)
68. Raloxifene can be used as therapy for the prevention and treatment of osteoporosis, especially for women with an increased risk of breast cancer. It has shown to reduce the risk of invasive breast cancer by 76% (Grade A)
69. Raloxifene and estrogen are associated with a similar increased risk of venous thromboembolism (VTE) (Grade A). However, no cases of VTE were reported among young healthy postmenopausal Asian women while on therapy
70. Bazedoxifene (BZA) is an SERM that has been purposely synthesized to specifically improve skeletal and lipid parameters, while benefiting or having no effect on hot flushes. Conjugated estrogens/bazedoxifene (CE/BZA) is the first FDA-approved medication that combines conjugated estrogens with an estrogen agonist/antagonist, BZA, and is an option for vasomotor symptoms as well as for the prevention of osteoporosis. The combination of CE/BZA has been labeled the tissue-selective estrogen complex, yet to be launched in India.

## TERIPARATIDE

71. Teriparatide is reserved for treating women at high risk for fracture, including those with very low BMD and with a previous vertebral fracture. 20 mcg/day subcutaneously (SC) is given for 18 months. Serum calcium and serum uric acid are monitored at 1, 6,

**Table 6: Based on WHI, Number of excess events on HT versus placebo per 10,000 women per year of HT use between the age group of 50-59 years**

Disease	Estrogen	WHO/CIOMS definition of risk	Estrogen + progesterone	WHO/CIOMS definition of risk
Venous thromboembolism	4	Rare	11	Rare
Stroke	1	Rare	4	Rare
Breast cancer			5	Rare
Cardiovascular disease			5	Rare



**Table 7: Based on WHI: number of less events on ET and EPT versus placebo per 10,000 women per year of HT use between the age group of 50 years and 59 years**

Disease	Number of less events with ET
Heart Disease	12
Breast Cancer	8
Disease	Number of less events with E / EPT
Overall Mortality	10
Fractures	5
Colorectal cancer	6

and 12 months

72. A recommendation can be made for the treatment with antiresorptive therapy (bisphosphonates) following discontinuation of teriparatide (Grade A)
73. Adverse effects are headache, hypercalcemia, hypercalciuria, renal adverse effects, nausea, rhinitis, and arthralgia. It is contraindicated in hypocalcemia and hypersensitivity.

### CALCITONIN

74. Calcitonin is approved for PMO treatment but not for prevention. It helps in relieving pain in vertebral fractures in short-term period only.

### DENOSUMAB

75. It is a monoclonal antibody approved recently in India, specifically targets RANKL, and is approved for postmenopausal women with osteoporosis at high risk of fracture
76. It increases both trabecular and cortical bone strength; reduces vertebral, nonvertebral, and hip fracture risk; and increases BMD more than bisphosphonates, thereby providing benefits over 10 years therapy without any drug holiday
77. 60 mg is given SC once in 6 months which has good patient convenience, well tolerated even in patients with creatinine clearance <30 ml/min where bisphosphonates and teriparatide are contraindicated
78. Denosumab is cost-effective. When the antiresorptive drugs are discontinued, there is rebound bone resorption over variable time frames, leading to the risk of multiple vertebral fractures, which is also seen with denosumab discontinuation. Thus, Swiss association guidelines have mandated the sequential administration of alendronate or zoledronic acid for 2 years; starting it at 6 months from the last dose of denosumab. Follow-on therapy of alendronate or zoledronic acid helps maintain the continuous BMD gained while on denosumab and prevents the increased risk of multiple vertebral fractures on discontinuation of denosumab.

## SURGICAL MANAGEMENT

### 79. Vertebral fractures

- Vertebral compression fractures are common but are often silent consequences of osteoporosis
  - All vertebral compression fractures without neurological deficit should be treated conservatively for 3 weeks as majority get better during this period
  - In a recent Cochrane review, the role of percutaneous vertebroplasty and kyphoplasty in the management of those vertebral compression fractures that do not respond to nonoperative treatment has been questioned<sup>[86]</sup>
    - Occult hip fractures are not uncommon. In intracapsular fractures, internal fixation could be considered, if the fracture can be reduced anatomically (Grade B)
    - Hemiarthroplasty should be considered to eliminate thigh pain secondary to loosening and is ideal for elderly patients with limited life expectancy (Grade A)
    - Total hip replacement should be considered when internal fixation is inappropriate or contraindicated in physiologically younger patients for improved quality of life (Grade B).
80. All patients who suffer from fracture should be subjected to BMD after surgery where possible and appropriate treatment for osteoporosis initiated (Grade A)
81. Postfracture fixation – patient-specific osteoporosis-related medical management is used to avoid subsequent fractures (Grade A)
82. Postoperatively, start appropriate pharmacological therapy for osteoporosis. Drugs such as teriparatide which facilitates osteoblastic bone formation can be started (Grade A). Antiresorptives such as denosumab, when started before or after 6 weeks of postfracture, did not affect fracture healing as it is fracture neutral and does not accumulate at the fracture rims; denosumab can also be given along with teriparatide; bisphosphonates are started 4–6 weeks later (Grade B). All need to be calcium and Vitamin D replete
83. Anabolic steroids may be used in very old frail women with sarcopenia for 6 months.

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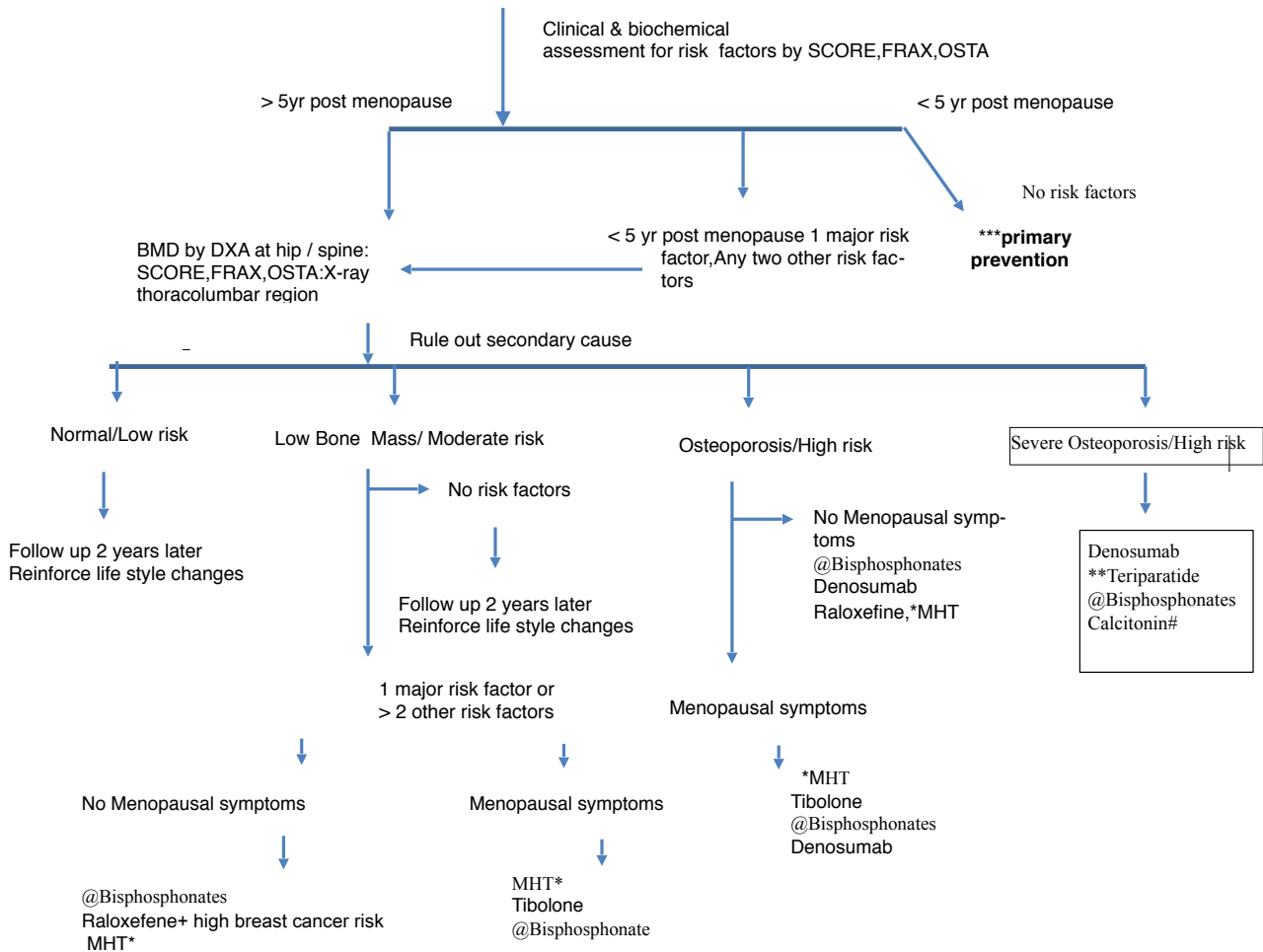
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## APPENDIX 1

### FLOWCHART 1: ALGORITHM FOR ASSESSING AND MANAGING BONE HEALTH

#### Asymptomatic Post Menopausal Woman



@Bisphosphonates  
 - Drug holiday after 3yrs for IV,5 years for oral ( at low risk )  
 - Consider continuation after a drug holiday  
 -  
 Raloxefine -effective on vertebral fractures

\*\*\* Primary Prevention for all --Nutrition ,Lifestyle Modification,Adequate Vitamin D and Calcium, Exccercise, Avoid bone depleting agents  
 Denosumab-long term,On discontinuation add Bisphosphonates

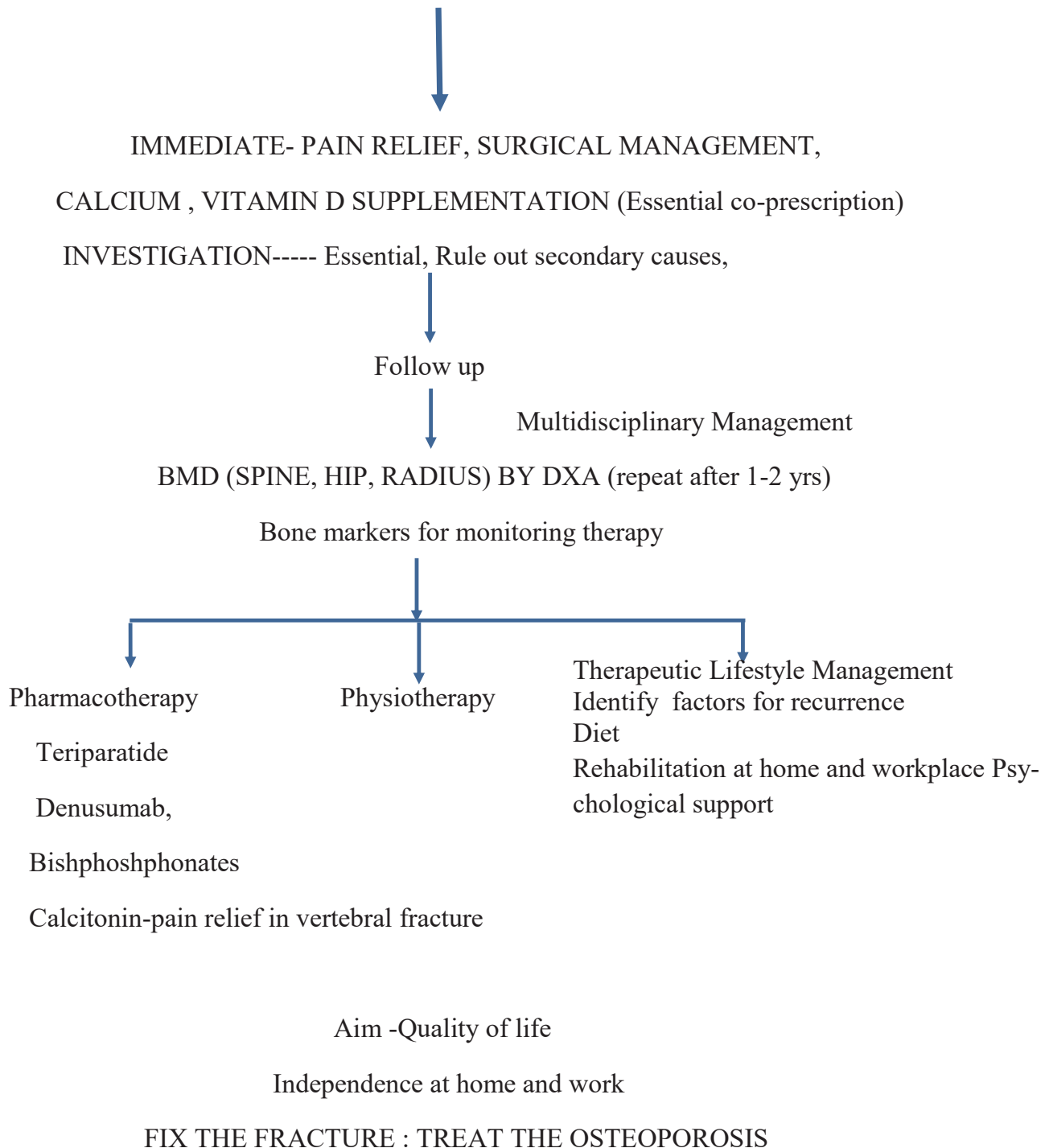
\*\* Teriparatide – can be used upto 2 years  
 Calcitonin#  
 Analgesic ,short term for three months in vertebral fractures  
 .5yrs postmenopause

\*Hormone therapy  
 To be used within 10 yrs of menopause  
 - Pre initiation workup  
 - Review annually  
 - Individualize therapy

SCORE,Simple Calculated Osteoporosis Risk Estimation)FRAX,Fracture Risk Assessment Tool  
 OSTA-The Osteoporosis Self-Assessment Tool for Asians

**APPENDIX 2**  
**FLOWCHART 2**

**POSTMENOPAUSAL WOMAN- WITH FRAGILITY FRACTURE**



### APPENDIX 3

**TABLE 4 : INDIAN FOODS WITH CALCIUM RICH CONTENT**

S.NO	DIATERY PRODUCT	SERVING	CALCIUM(mg)
1	MILK/CURD(BUFFALO)	1 GLASS(250ML)	520
2	MILK/CURD(COW)	1 GLASS(250ML)	300
3	MILK/CURD(LOW FAT)	1 GLASS(250ML)	300
4	KHOA	100GMS	600
5	PANEER	100GMS	320
6	CHEESE SLICE	20 GMS	160
7	RAGI	100 GMS	360
8	HORSE GRAM WHOLE/RAJMA	100 gms	280
9	SOYABEAN	100 gms	240
10	MOTH BEAN/BENGAL GRAM (WHOLE)	100 gms	200
12	RED/GREE/BLACK GRAM/CHICKPEAS	100 gms (WHOLE)	100-120
14	DRUM STICK LEAVES	100 gms	300
15	RADISH LEAVES/METHI LEAVES	100 gms	270
16	MINT/PARSLEY	100 gms	200
17	OKRA(BHINDI)	100 gas	85
18	CABBAGE	100 gms	60
19	DRIED FIGS	5 whole	95
20	ALMONDS	1 handful 25 gms	60
21	SESMAE SEEDS(til)	15 gms, 1 Tablespoon	90
22	CUMIN	6 gms 0.4 Tablespoon	60
23	ORANGE	1 medium size	50
24	FISH ROHU	25 gms	160

T. Longvah, R. Ananthan, K. Bhaskarachary and K. Venkaiah, Indian Food Composition Tables, 2017 by National Institute of Nutrition, Indian Council of Medical Research

### Appendix 4: DRUG CHART

Drug	Dosage	Route	Position in therapy	Vertebral*	Hip*	Non-vertebral*	Precautions
Alendronate	5/10 mg daily 35/70 mg weekly 150 mg monthly	Oral	1 <sup>st</sup> line	Yes, 50%	Yes, 51-56%	Yes, 49%	Hypocalcemia, Vitamin D status, should not be used in patients with eGFR below 30 ml/min, pregnancy, lactation, pediatric, ONJ, AFF
Risedronate	5 mg daily 35 mg weekly 150 mg monthly	Oral	1 <sup>st</sup> line	Yes, 41-49%	Yes, 30%	Yes, 36%	Hypocalcemia, Vitamin D status, should not be used in patients with eGFR below 30 ml/min, pregnancy, lactation, pediatric, ONJ, AFF
Zoledronate	5 mg	IV	1 <sup>st</sup> line	Yes, 70%	Yes, 41%	Yes, 25%	Hypocalcemia, Vitamin D status, should not be used in patients with eGFR below 30 ml/min, pregnancy, lactation, pediatric, ONJ, AFF
Teriparatide	20 mcg	SC	For severe osteoporosis	Yes, 65%	Insufficient data	Yes, 53%	Hypocalcemia, Vitamin D status, Hypersensitivity, local tissue damage, pregnancy, lactation, pediatric,
Denosumab	60 mg	SC	1 <sup>st</sup> line	Yes, 68%	Yes, 40%	Yes, 20%	Hypocalcemia, Vitamin D status, pregnancy, lactation, pediatric,
MHT	Various regimes	Various regimes	1 <sup>st</sup> line with menopausal symptoms (<10 years menopause)	Yes, 30-70%	Yes, 40%	Yes, 27%	Blood clots, Cancer (such as breast, uterine, or endometrial), Heart or liver disease, Heart attack, Known or suspected pregnancy, Stroke
Raloxifene	60 mg	Oral	At risk of breast cancer, without Vasomotor symptoms, <10 years menopause	Yes, 40%	No	No	With a low risk of DVT and for whom bisphosphonates or denosumab are not appropriate, or with a high risk of breast cancer
Tibolone	2.5 mg	Oral	1 <sup>st</sup> line <10 years menopause	Yes, 50%	Yes, 26%	Yes, 26%	To stop tibolone a few weeks before any operation to reduce the risk of a blood clot, drug interaction with warfarin
Calcitonin	200 IU	Nasal spray	2 <sup>nd</sup> line	Yes, 21%	No	No	Serious hypersensitivity reactions, including fatal anaphylaxis, reported; consider skin testing prior to treatment

Drug	Advantages	Disadvantages	Contraindications	Adverse effects
Alendronate	Most commonly used drug	Inconvenient administration - Stay upright for 30 min on intake, drink lots of water, no food before taking the drug, drug holiday may be needed after 3-5 years	Hypocalcemia, Hypersensitivity, Compromised renal function, Upper GI disease - Abnormalities of the esophagus which delay esophageal emptying such as stricture of achalasia, patients at increased risk of aspiration	Dyspepsia, esophagitis abdominal pain, musculoskeletal pain
Risedronate		Inconvenient administration - Stay upright for 30 min on intake, drink lots of water, no food before taking the drug, drug holiday may be needed after 3-5 years	Hypocalcemia, hypersensitivity, compromised renal function, Upper GI disease - Abnormalities of the esophagus which delay esophageal emptying such as stricture of achalasia, patients at increased risk of aspiration	Rash, abdominal pain, dyspepsia, diarrhea, arthralgia
Zoledronate	1 <sup>st</sup> line drug,	anaphylaxis, including fatal events,	Hypocalcemia, hypersensitivity, compromised renal function	Acute reaction (flu such as symptoms, fever, myalgia) may occur within 3 days of infusion, hypotension, fatigue, eye inflammation, more nausea, vomiting, abdominal pain

*Contd...*



**Appendix 4: Contd...**

<b>Drug</b>	<b>Advantages</b>	<b>Disadvantages</b>	<b>Contraindications</b>	<b>Adverse effects</b>
Teriparatide	Potent bone forming activity, Large increase in spine BMD over 2 years	Reserved line drug, 2 years usage, daily injections required,	Hypocalcemia, hypersensitivity	Headache, hypercalcemia (high-quality); hypercalciuria, renal adverse effects, nausea, rhinitis, arthralgia
Denosumab	1 <sup>st</sup> line drug, Rise of BMD reported over 10 years at spine, hip and nonvertebral sites, can be used in patients in eGFR 15-30 ml/min	Loss of effect and drop in BMD after discontinuation (should be continued on bisphosphonates)	Hypocalcemia, Hypersensitivity	Dermatitis, rash, mild bone/muscle pain, UTIs
MHT	Less musculoskeletal symptoms of aches and pains and possibly sarcopenia (or muscle wasting)	breast cancer VTE, stroke, potentiation of preexisting breast cancer, increased risk of gall stones, depression, headache, premenstrual syndrome, breast tenderness, skin irritation, weight gain, menstrual bleeding	Active endometrial and gynecological hormone- dependent cancers Active breast cancer, Undiagnosed, abnormal vaginal bleeding Moderate and high risk for breast cancer Established CVD and at severe increased risk of CVD, Previous personal or family history of venous thromboembolism Systematic lupus erythematous, Diabetes with end organ disease Severe active liver disease with impaired or abnormal liver function x Previous personal or family history of venous thromboembolism x Known or suspected pregnancy	Bloating, Breast swelling or tenderness, Headaches, Mood changes, Nausea, Vaginal bleeding
Raloxifene	benefit of a reduced incidence of invasive estrogen receptor-positive breast cancer both during treatment and for at least 5 years after completion	Daily oral administration	Pregnancy, lactation, Active history of thromboembolic disorders	Venous thromboembolism, stroke
Tibolone	Increases BMD, decreases cholesterol and triglycerides similar to conventional MHT	Reduction of HDL levels and its high cost	Pregnancy and lactation, breast cancer, estrogen-dependent malignant tumors (e.g., endometrial cancer) Undiagnosed genital bleeding, Untreated endometrial hyperplasia, venous thromboembolism (deep venous thrombosis pulmonary embolism, thrombophilic disorders, arterial thromboembolic disease (e.g., angina, myocardial infarction, stroke or TIA), Acute liver disease, or a history of liver disease, Hypersensitivity to the active substance(s), Porphyria	May increase stroke rates in women over 60 years of age, Weight gain, Unscheduled bleeding
Calcitonin	Ease of administration	Circulating antibodies to calcitonin-salmon may develop, and may cause loss of response to treatment	Hypersensitivity to calcitonin-salmon	Rhinitis, epistaxis, and allergic reactions

\*% reduction in fracture in individual pivotal studies only and not in head-head studies. eGFR: Estimated glomerular filtration rate, HDL: High-density lipoprotein, BMD: Bone mineral density, DVT: Deep vein thrombosis, GI: Gastrointestinal, MHT: Menopause hormone therapy, TIA: Transient ischaemic attack, ONJ: Osteonecrosis of the jaw