

A BRIEF REVIEW ON THE CURRENT SCENARIO OF OSTEOPOROSIS IN INDIAN WOMEN

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Abstract

The issues of Women's health in India face a plethora of reasons that are deep-rooted and related to gender disparity from consequences of undernourishment, early marriage, multiple pregnancies, poverty, clothing restrictions, restricted outdoor for women, and other socio-contextual causes like inaccessibility to proper health education and care. Among the prevalent health issues affecting women of various age groups in India, osteoporosis is one. Osteoporosis is the depletion of bone mass with the destruction of bone structure leading to fragility and even fractures. The disease symptoms are silent and manifestations appear late, often going to the extent of bone fracture. 'Fragility fractures' occurring even with low mechanical force are the major cause of disability. A developing nation like India has to stress on decreasing the burden through intervening modifiable risks associated at an early stage which includes calcium intake in a regular diet as per ICMR guidelines, sun exposure for vitamin D, lowering body mass index, and performing weight-bearing exercises. Non-modifiable risks like ethnicity, early menopause, aging population, dietary patterns with more phytates, oxalates, ergocalciferol all associated with vegetarianism might not be regulated. Bone mineral density assessment at regular intervals and dietary regulation with calcium and vitamin D supplementation go a long way to combat the problem. But the access to modern instruments like the DEXA scan attributed as an essential device to diagnose the disease is often elusive to the rural population. Once the disease goes beyond the preventable stage the treatment starts. Myriad treatment options available are varying in nature according to the disease condition and cost involvement. The first line of treatment includes bisphosphonates to avoid hip and skeletal bone fracture. Hormone replacement therapy, estrogen agonists, calcitonin, parathyroid hormone, and receptor activator of nuclear factor kappa B ligand inhibitor (Denosumab) are also common treatment protocols for osteoporosis.

Keywords: Osteoporosis, bone mineral density, early menopause, DEXA scan, fragility fractures.

Introduction

In healthy individuals, bone formation dominates for the first three decades of life until peak bone mass is achieved around 30yrs [1]. This bone mass is then maintained for approximately 20 years until resorption begins to outweigh formation and bone mass declines. 'Osteoporosis' (International consensus in 1993) is defined as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [2].

Over 1.3 billion people live in India, with approximately 230 million Indians over 50 years. Most data on the prevalence of osteoporosis among women in India come from studies conducted in small groups spread across the country [3–11]

and estimates from 2015 have suggested that 20% of the 230 million Indian women over the age 50 have osteoporosis [12, 13]. Prevalence of osteoporosis ranges from 8 to 62% in Indian women of different age groups. The awareness of osteoporosis is low in India, with surveys indicating that only 10–15% of Indians are aware of the disease [14]. In India, there were around 26 million osteoporosis cases in 2003, while in 2013, 50 million people were either osteoporotic or had low bone mass. Studies have reported that Asian women have higher predisposition for osteoporosis than their Caucasian counterparts [13]. Osteoporosis is more common in post-menopausal women, due to estrogen deficiency and osteocalcin (OC). The latter is a sensitive bone marker and is significantly elevated during menopause due to the high bone turnover [15]. A retrospective study analysis in India confirms that women from lower socioeconomic strata have higher prevalence of osteoporosis and osteopenia at all bone sites than men. [16]. Life expectancy of Indians at present is 67 years and is expected to rise to 71 years by 2025. 10% of this population is older than 50 years at present. Increasing longevity and greater proportion of Indians over 50 years are likely to rise over the next decade with older women having the burden of the disease [13, 17, 18]. Osteoporotic fractures are a major cause of morbidity and mortality. Estimates suggest that approximately 50 million people in India over the age of 50 have low bone mass with T-scores more negative than -3, with 20% women and 10–15% of men as osteoporotic [5, 19]. Benu et al., have reported 61 million Indians have low bone mass, of which 80% patients are females and 62.2% and 10.9% osteopenic and osteoporotic respectively [20].

Deciphering osteoporosis in Indian Context

Osteoporosis increases the risk of fracture at virtually all skeletal sites due to continuous loss of bones [21]. Diagnosing and effectively managing osteoporosis is challenging in the Indian setting due to a lack of state interventions. Bone mineral density (BMD) is measured by dual-energy X-ray absorptiometry (DEXA) bone scanners and are universally accepted as gold standard for bone densitometry. Values obtained through such scans are expressed in units of standard deviation (SD) relating to reference population to eliminate errors of calibration between DEXA instruments [15].

An abrupt fall of BMD takes place in women around the menopausal period. According to World Health Organization (WHO) ‘osteoporosis’ is defined as a loss of BMD with negative BMD T-score with a value of ≤ -2.5 standard deviation (SD) below the peak bone mass of the respective reference population. ‘T’ score of an individual is the number of SD his/her BMD deviates from the mean BMD of 20–29-year-old healthy adult (belonging to the reference population). Two values of BMD T-score threshold units are defined. First defines osteopenia with a BMD T-score ranging from -1.0 up to -2.5 as a measure of lowered bone mass ($-1 \leq T \leq -2.5$) and second is osteoporosis below -2.5 (≤ -2.5). Osteoporosis is classified as primary (type I/ type II), or secondary. Type I is the most common and often referred to as postmenopausal osteoporosis as it is caused by an associated oestrogen deficiency [22, 23]. Type II is also known as senile or age-related osteoporosis and can occur in both men and women with age. Finally, secondary osteoporosis refers to form of the disorder as a consequence of an adverse response to a medication, change in physical activity status, or other underlying disease. “Z” score of an individual is the number of SD his/her BMD deviates from the mean BMD of the same age, gender, and ethnic group reference population [24]. Individuals with a Z-score of -1 will have approximately a 2-fold higher risk of fractures in their remaining life-time than those with an average value for bone mineral for their age. Those with a Z-score of -2.5 will have a greater than 4-fold risk [25].

Examining the WHO definition where reference population is used to compare BMD for calculating osteoporosis or osteopenia a healthy young aged (20-29yrs) subgroup of the diseased population representing normative data is to be

considered. Although attempt to derive for a normative data in India are done in a few studies [6, 26, 27], no reference exists on Indian population from regulating agencies. Controversy exists regarding the matching of reference population for sex and ethnicity [28]. There is still insufficient data to assess the fracture risk using the Indian BMD reference database [6, 26, 27]. According to 2019 International Society for Clinical Densitometry (ISCD) guidelines Caucasian (non-race adjusted) female normative database can be used for women of all ethnic groups to derive T-scores [29]. India's reference population for calculating T-scores are calculated from the NHANES III derived Caucasian female database [30] in the absence of any normative data.

Identification and screening for osteoporosis in Indians

At present, there is no universally accepted policy for screening to identify patients. An affected underprivileged Indian woman without any exposure to a professional clinician will not get diagnosed and thus can be mistreated. It is of vital importance for an underprivileged Indian to visit a clinician at least once in a lifetime to get diagnosed, with prognosis feature and get the most appropriate form of treatment with regard to its cost effectiveness and long-term adherence. Several data reveal that osteoporotic fractures take place at an earlier age in Indians than in the West. Screening should be performed at an earlier age i.e., women younger than 60 years and men aged 50–64 years should go for screening.

Simpler screening tools like age, weight, BMI and clinical risk factors (previous fracture, estrogen therapy, rheumatoid arthritis, and ethnicity) make screening useful in Indian context [31]. In a large cohort of rural postmenopausal women, the SCORE (Simple Calculated Osteoporosis Risk Estimation) screening tool was useful, with good sensitivity and good area under the curve for predicting femoral neck osteoporosis on BMD measurement. A value ≥ 6 was found to have good sensitivity and specificity for estimating risk in the Indian population [32]. Similarly, the risk assessment tools OSTA (osteoporosis self-assessment tool for Asians) and MORES (male osteoporosis risk estimation score) have been validated for use in the Indian population [33]. These tools are rapid, easy to perform, inexpensive, and easily usable making these perfect for the rural Indian setting, but the impact of initiating therapy based on thresholds derived from these tools is not well studied. Serum osteocalcin (OC) levels may be used to assess bone turnover associated with decreased bone mass in women. Serum OC levels are also used extensively to evaluate bone remodelling and metabolic bone disease conditions like osteoporosis [34–36].

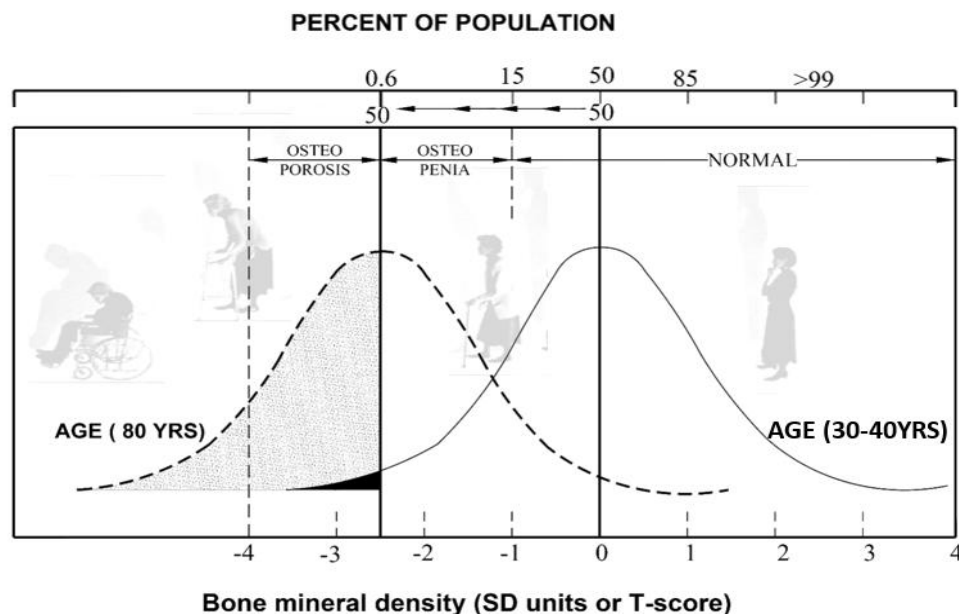


Figure.1. The solid black curve represents the bone mineral densities of young healthy women aged 30-40 years as a BMD score with 15% and 0.6% of population with a T-score of -1 and -2.5 respectively. The hatched line represents a shift of the zero BMD value of 50% normal distribution population for ages up to 80years. The peak for the hatched line representing a normal distribution of 80 years aged women population will be at a BMD of -2.5. Thereby denoting that 50% population at age 80 will have a BMD score of -2.5. [Source: WHO]

Aetiology of Osteoporosis among Indian Women

Reasons attributed for lower bone mineral density (BMD) in Indians include possible genetic differences, nutritional deficiency and smaller skeletal size [34]. Rapidly accumulating data have reported that the genetic factors can explain about 50%- 90% of total BMD variation. A number of bone-related candidate genes, such as the estrogen receptor gene and vitamin D receptor gene, alpha2-HS-glycoprotein and parathyroid hormone, have been investigated for their association with bone phenotypes [37]. Vitamin D and Calcium deficiency, increasing age, low weight, early menopause, poor sunlight exposure, higher intakes of phytate and oxalate in vegetarian diets, poor health infrastructure with scarcity of DEXA scan compounded by lack of national programs for promotion of bone health are the major factors for the meteoric rise of osteoporosis in women [38]. Other factors like socio-economic gender discriminating factors associated with patriarchal family, lower purchasing power to avail quality food, unplanned pregnancies, darkly pigmented skin and atmospheric pollution [39, 40], derogatory influences through religious beliefs are also compounding the burden.

The binding of receptor activator of nuclear factor kappa-B ligand (RANKL) to receptor activator of nuclear factor kappa-B (RANK) responsible for their maturation into osteoclasts (osteoclastogenesis) can be antagonised by osteoprotegerin (OPG), a decoy receptor for RANKL that inhibits osteoclastogenesis. Therefore, whether and how much resorption occurs is determined by the RANKL:OPG ratio [41]. When diseases such as osteoporosis disrupt our bone balance, it is predominantly through an alteration in the RANKL:OPG ratio [42]. Oestrogen deficiency in Type I results in increased RANKL and decreased OPG production that leads to reduction in osteoclast apoptosis [22, 23]. Overexpression of RANKL by immune cells is the primary drive for Type II osteoporosis which include glucocorticoid- and immobilisation-induced osteoporosis as well as inflammation-induced bone loss during periodontitis or rheumatoid arthritis [43].

Risk Factors for Osteoporosis in India

Studies have suggested that polymorphism in the gene of vitamin D receptor (VDR) genetically linked to bone mass [44]. Since VDR gene may be a determinant of bone mass, differences in VDR gene polymorphism in different races could account for differences in bone mass and low bone density specifically in women due to impaired calcium absorption from the bowel [45]. A recent study by Mitra et al [46] also revealed that bone metabolism is influenced by VDR gene polymorphisms resulting in BMD in postmenopausal Indian women. Another study done by Vupputuri et al [47] reported that parathyroid hormone levels and VDR gene polymorphisms variation is related to hip, spine and forearm BMD in vitamin D deficient urban Asian Indians. Accelerated age-related bone loss may also be associated with estrogen receptor α (ER α) gene polymorphisms in Indian women [48].

The average age at menarche in Indian girls is ~ 12.5 years; late menarches though seldom in Indian scenarios, predispose an individual for the disease. Again, the average age at menopause is 46.2 years which is earlier than that seen in non-Indian women [49]. Estrogen deficiency due to early menopause becomes a contributing risk factor for Osteoporosis. Numerous studies reveal that Indian women are more vulnerable to osteoporosis with advancing age compared to men [6, 10]. Asian Indian women have 5–15% lower BMD than non-asian women [16, 38, 50]. Studies show peak bone mass attainment is related to Genetic factors, race, and ethnicity. Indian diets fail to meet recommended dietary allowances of 600 mg/day of calcium (as per ICMR guideline) [51] with a minimal contribution of dairy products to the overall calcium intake especially in lower socioeconomic classes make the situation graver. Cultural, traditional clothing (purdah, burqa, saris, salwar kameez) and secular reasons compel Indian women to be less exposed to sunlight, thus depriving them of vitamin D which in turn is responsible for loss of bone mass. Vitamin D deficiency results in ineffective calcium absorption from the gut, which in turn affects the mineralization of bones. Lack of exercise in Indian women is significantly associated with lower BMD [52]. Long-term over-the-counter glucocorticoid use in a daily dose ≥ 5 mg prednisone or equivalent for ≥ 3 months [53] and minimum use of hormone replacement therapy (HRT) in postmenopausal Indian women are significant contributors to osteoporosis. In addition, the use of proton pump inhibitors and other antacids and anticonvulsants are linked to low BMD and osteoporosis [54–56]. Other causes include impaired phosphate transport or the chronic use of some drugs such as aluminium salts, high doses of fluoride, or etidronate.

Intervention

The individuals who require interventions are the women with a vertebral and non-vertebral fracture (hip, wrist, and humerus), individuals >50 years of age with T-score ≤ -2.5 at the femoral neck or total hip or lumbar spine measured by DEXA, individuals with osteopenia (T-score between -1.0 and -2.5 at the femoral neck or lumbar spine) with clinical risk factors or a 10-year probability of a hip fracture $\geq 3.5\%$ or a 10-year probability of a major osteoporosis-related fracture $\geq 10.5\%$. These calculations are based on Fracture risk assessment (FRAX) tool (with limited data in Indians) [57]. In individuals with type-2 diabetes mellitus, the intervention threshold should be increased to T-score ≤ -2.0 at the femoral neck or total hip or lumbar spine measured by DEXA [57].

Biochemical investigations should be directed at identifying the underlying cause of osteoporosis. Before starting pharmacotherapy, a basic biochemical and hormonal profile that includes serum calcium, phosphorous, total alkaline phosphatase, creatinine, 25-hydroxyvitamin D, and intact parathyroid hormone (iPTH) is beneficial [58] in patients with osteoporosis. Based on clinical suspicion detailed blood investigations should be continued in patients with secondary osteoporosis.

Dietary Supplementation and Pharmacological Management of Osteoporosis

All patients with osteoporosis should maintain serum 25-hydroxyvitamin D at ≥ 20 ng/mL with an ideal level of 30–40 ng/mL by supplementing vitamin D3 when required. The maintenance therapy of Indians typically requires a 1000 to 2000 international units (IU) of D3. Obesity, malabsorption and older ages may require even higher doses of vitamin D. Dietary intake of calcium (including diet plus supplement, if needed) in doses necessary to maintain at least 1000 mg/day for women ≥ 50 years. Maintaining an active lifestyle with weight-bearing and balance exercises are essential. Counselling for fall prevention, use of low-heeled shoes with rubber soles for more solid footing, using hand rails whenever necessary for support and installing grab bars on the bathroom's walls all decreases risk of injury and fractures to the aged fragile bones.

International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommend using serum type I collagen C-telopeptide (CTx) and serum procollagen type I N-propeptide (PINP) as bone turnover markers BTMs for quick short-term monitoring of osteoporosis. A consensus statement on the use of BTMs treatment in the Asia-Pacific region has recently been published, and in the absence of data from India, an analogy can be drawn from the aforementioned guideline [60].

Challenges

Only 20% of patients with osteoporosis are diagnosed and treated in India [61]. Even then, the treatment compliance rate is only around 64% [61]. There is still considerable confusion among clinical community with regard to diagnosis criterion and protocol of treatment for osteoporosis considering lack of Indian reference data. No insurance policies cover osteoporosis as debilitation/ disability. There is a need for increased involvement of medical and government regulatory bodies. Awareness campaigns about bone health, treatment interventions and use of postmenopausal hormone replacement therapy (HRT) are much lower in proportion than in western countries. There are 0.26 dual-energy X-ray absorptiometry instruments (DEXA) instruments per million in India which is far below the recommended number of 10.6 per million [39]. Absence of accepted policies for Indian women to identify patients with osteoporosis results in identification errors and secludes the possibility of early intervention only leading to fragility fractures pain as diagnostic criteria. Due to a lack of state interventions, a very few data exist to identify the vulnerable women communities. Maintaining optimum serum 25-hydroxyvitamin D levels is essential, which in most cases would require regular vitamin D supplementation. Regular follow-up is essential and adherence to treatment should be ensured.

Observations

National Institute of Nutrition (NIN) established sun exposure guidelines for Indians to be 20 minutes of direct sunlight at solar noon in summer with 10% of body surface area exposed as an adequate exposure for cutaneous synthesis of vitamin D3. These recommendations can be followed in almost all regions of the country except for the hilly regions and North-eastern India and Srinagar. For other seasons the time of exposure is higher up to a maximum of 45 minutes a day in the cloud-covered rainy season. Exposure is associated with lowered RDA for calcium and Vitamin D. UV- B rays are particularly beneficial and UV-B maximizes between 11am and 3pm [73]. Vitamin D requirement varies with Calcium intake with higher calcium intakes decreasing the requirement of the vitamin. Vitamin D2 (ergocalciferols)

prevalent in vegetarian diets competes with the more active form of the Vitamin i.e., Vitamin D3 and thereby reduces the biological efficacy of D3 by competing to bind the Vitamin D binding protein.

Table.1. APPROVED PHARMACOLOGICAL INTERVENTIONS FOR OSTEOPOROSIS IN INDIA

Name	Use
<i>Calcium and vitamin D supplementation [25]</i>	First-line therapy for the prevention of bone loss and osteoporotic fractures, it is a major non-HRT intervention used in osteoporosis, decrease the rate of bone loss and also prevent osteoporotic fractures
<i>Bisphosphonates [potent antiresorptive agents] [63,64]</i>	
<i>Alendronate</i>	
<i>Risedronate</i>	All these effectively reduce the risk of vertebral, non-vertebral, and hip fractures,
<i>Zoledronic acid</i>	Ibandronate also reduces spine fracture risk
<i>Ibandronate</i>	
<i>Hormone replacement therapy [65]</i>	
<i>Oestrogen</i>	
<i>Estradiol</i>	Prevents bone loss in postmenopausal women and reduces the risk of vertebral and hip fractures
<i>Estropipate</i>	
<i>Conjugated oestrogen</i>	
<i>RANK ligand inhibitor [fully human monoclonal antibody] [66]</i>	
<i>Denosumab biosimilar [Receptor activator of nuclear factor kappaB ligand inhibitor]</i>	Inhibit Osteoclast formation, function, survival, thereby decreasing bone resorption which leads to increase in bone mass and strength in both cortical and trabecular bone and also reduces the risk of vertebral, non-vertebral and hip fractures
<i>Bone anabolic therapy [13]</i>	
<i>Parathyroid hormone</i>	Increases BMD by restoring trabecular microarchitecture, reduces fracture risk to a greater extent than the antiresorptive therapies
<i>Selective oestrogen receptor modulators [67-69]</i>	
<i>Raloxifene [estrogen agonist and antagonist]</i>	A weak antiresorptive agent known to reduce the risk of vertebral fractures
<i>Bazedoxifene</i>	Combination of conjugated oestrogen and bazedoxifene is approved in the USA for prevention of postmenopausal osteoporosis
<i>Tamoxifen</i>	Use in treatment for prevention of breast cancer, can maintain bone loss in postmenopausal women
<i>Parathyroid hormone receptor agonist [70-71]</i>	
<i>Teriparatide</i>	Reduced the risk of vertebral and non-vertebral fracture
<i>Abaloparatide [a synthetic analogue of PTHrP]</i>	Skeletal effects similar to teriparatide
<i>Calcitonins [an inhibitor of bone resorption]</i>	Acute management of vertebral fracture, particularly where bed rest or other forms of immobilization are required
<i>Oestrogen Derivatives and Receptor Agonists [25]</i>	
<i>Tibolone [synthetic analogue of the gonadal steroids with combined oestrogenic, progestogenic and mild androgenic properties]</i>	Prevents oestrogen deficiency bone loss, is effective in controlling hot flushes and sweats
<i>Potential new treatments [72]</i>	
<i>Romsozumab [a humanised antibody]</i>	Binds sclerostin and activates bone formation and inhibits bone resorption

Easier screening strategies like loss of height may be estimated from the history or from the difference between measured height and arm span since these measurements are usually nearly the same. Anthropometric camp may help in this regard considering the cost effectiveness of the procedure. Activities in areas open to sky like roof tops or east west openings through balcony and terraces in buildings to percolate sunlight indoors with sun path diagrams considered in implementation of sanctioning rules by authorities might be considered. In absence of DEXA scan, a simple bodyweight or a BMI with predictive density scanners like Calcaneal quantitative ultrasound (QUS) may be used as an inexpensive screening measure. Despite low body weight in Indian women lean body mass contribution towards BMI is found to be low with higher fat percentages contributing to BMI. Dietary and bone health counselling may act as precautionary measure bridging the gaps between osteoporosis and lowered bone density. Higher intakes of Calcium through conventional dietary sources of inexpensive oily fish in coastal belts, fortified milk, low phytate and oxalate containing vegetables, jaggery derived from coconut and sago palm, nerringi, cauliflower greens, amaranth, fetid cassia (*Chakunda.B*), curry leaves, cumin, cereal sources like ragi, bengal gram, horse gram, rajma and soyabean sources like figs, sesame seeds are always beneficial and go a long way in the prevention of disease [74].

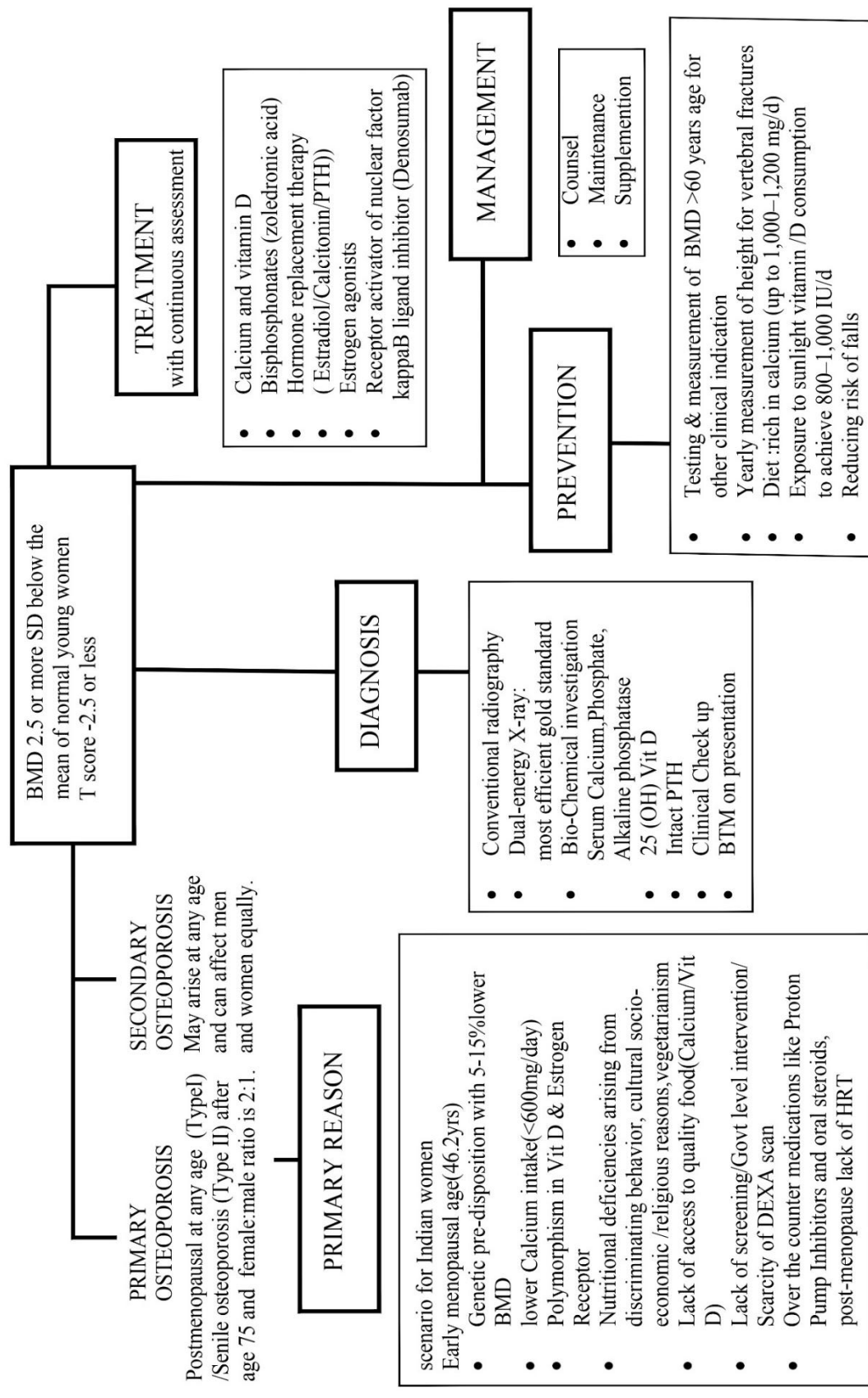
It is known that endogenous hormonal factors play a part in the aetiology of the disease all through life. A healthy lifestyle with healthy foods, a visit to women's health clinic, physical exercise, especially weight-bearing exercise, improves muscle and bone strength [62]. Prevention of risk factors through education and awareness programme would go a long way towards better nutrition, lowering the usage of sun-protecting lotions and increasing outdoor physical activities.

Conclusion

It appears that Indian women have poor bone health. Peak bone mass achieved is low during puberty and this continues throughout the individual's life predisposing them to osteoporosis in later years. As a public health measure, it is important to encourage children to drink milk and play in the sun. Bone health can be optimized through creating an environment to achieve peak bone mass during adolescence, maintaining a healthy bone throughout life and adopt strategies of prevention for postmenopausal bone loss.

OSTEOPOROSIS

Depletion of bone mass with the destruction of bone structure leading to fragility and even fractures. 'Fragility fractures' are major cause of disability imposing huge social and financial burden



Osteoporosis in Indian Women : At a glance

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