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Review Article

Orthopaedics Section

Narrative Review on Osteoporosis: A Silent Killer

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ABSTRACT

Osteoporosis is a common condition affecting the elderly population. Most of the time, it is diagnosed only after an individual suffers from a fracture. In addition to the fracture and its complications, the patients and their families must also bear the psychological and financial consequences of the disease. There are multiple risk factors associated with osteoporosis, hence it requires a multimodal approach in management as well. This narrative review aims to provide a comprehensive insight into the classification, prevalence, pathophysiology, signs and symptoms, risk factors, screening tools, management, differential diagnosis, prognosis, complications, and recent advances in osteoporosis.

Keywords: Age related bone loss, Bone mineral density, Male osteoporosis, Postmenopausal osteoporosis

INTRODUCTION

Osteoporosis means porous bones with decreased Bone Mineral Density (BMD), disrupted bone microarchitecture, and altered protein arrangements in the bone. The World Health Organisation (WHO) has defined osteoporosis 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 [1,2].

Definition

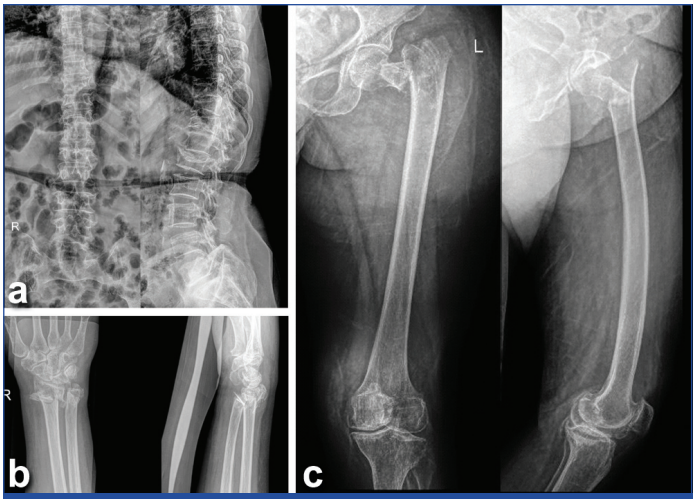
As per BMD classification, a t-score is calculated. A t-score is a statistical test that measures Standard Deviation (SD) from the mean. A t-score of one SD is a normal score and is usually found in young adults (sex-matched 30-year-old). The WHO has a t-score for BMD. The t-score between -1 and -2.5 is known as osteopenia, i.e., low bone mass, and scores below -2.5 as osteoporosis [3]. Osteoporosis is considered a silent menace because it progresses without any significant signs and symptoms until any fractures occur [4]. Normally, the inside of the bone is like a honeycomb with compactly arranged osteocytes. In osteoporosis, the space between the bone cells increases, and the walls of the honeycomb also get thinner, which makes the bone weak and prone to fractures just due to minor fragility fractures, hence making bone density a major determinant of fracture risk [5,6].

An imbalance in the physiological processes of bone resorption and bone remodeling with decreased skeletal mass relates to osteoporosis. The bone mass peaks at about the third decade of life, followed by a period of bone resorption that exceeds bone formation. In histologic specimens, adults with osteoporosis exhibit significantly reduced thickness of trabeculae, smaller osteon size, and enlargement of both Haversian canals and marrow spaces [7,8].

Classification of Osteoporosis

There are mainly two types of osteoporosis:

1. **Primary osteoporosis:** It occurs as a part of the ageing process and according to a decrease in hormone levels in the body. As age progresses, the microstructure of the bones degrades, and BMD decreases, leading to an increased risk of fractures.
2. **Secondary osteoporosis:** It occurs due to secondary causes, including various medications used in the treatment of diseases including hyperparathyroidism, hyperthyroidism, anorexia nervosa, malabsorption syndrome, chronic renal failure, and Cushing syndrome. Conditions leading to long-term immobilisation can also result in secondary osteoporosis. Long-standing secondary amenorrhoea due to non oestrogen hormonal therapy, low body weight, and excessive exercise leading to decreased bone mass can contribute to secondary osteoporosis. Men are reported to have secondary osteoporosis more often than women [Table/Fig-1] [7-9].



[Table/Fig-1]: a) Osteoporosis in the dorsal and lumbar spine X-ray showing generalised osteopenia, thinning of the cortex, striated appearance of the vertebral body, codfish vertebral bodies, multiple vertebral collapse with wedge shaped deformity; b) X-ray of wrist showing comminuted distal radius and ulna fracture in the osteoporotic bones. Periarticular osteopenia can be seen in the carpal bones of the hand; c) X-ray of femur with hip joint showing comminuted fracture around the hip in the patient with osteoporosis.

Prevalence

A study done by Gullberg B et al., computed the expected hip fractures for the years 2025 and 2050. The study predicted that by the year 2050, hip fractures would rise to 45%, mainly in Asian countries. Osteoporosis is greatly underdiagnosed and undertreated in Asia, even in the highest-risk patients who have already experienced fractures. This is more prevalent in rural areas of Asian countries, may be due to less accessibility to diagnostic and treatment modalities [10]. The International Osteoporosis Foundation; The Asia-Pacific Regional Audit- Epidemiology, costs, and burden of osteoporosis published in 2013 reported that more

than 300 million Indians are suffering from osteoporosis-related bone fractures without even understanding that this could double the risk of death [11]. By the age of 50, about 50% of Indians have osteopenia, whereas about 10% of the population above the age of 65 is at risk of osteoporotic fracture, and one in every three postmenopausal females is at risk of osteoporotic fracture [12-15].

According to the National Osteoporosis Foundation, people suffer from about 1.5 million fractures annually [12]. A study by Shatrugna V et al., among Indian women aged 30-60 years from a low-income group reported a high prevalence of 52% osteopenia and 29% osteoporosis [16].

Pathophysiology

Primary osteoporosis can be mainly due to age-related factors, including senile osteoporosis, postmenopausal osteoporosis, and idiopathic osteoporosis [17].

1. **Senile osteoporosis:**
    a. Bone marrow mesenchymal stem cells show age-related transformation, leading to the inhibition of osteogenesis, i.e., new bone formation, hence causing excess bone loss.
    b. Changes in the microenvironment of the bone due to age-related osteoblast dysfunction can lead to impairment in the differentiation and functions of the osteoblasts.
    c. Endocrine dysfunctions are very common in the elderly population. Hormonal deficiencies of oestrogen, testosterone, cortisol, parathyroid, and thyroid, which play a major role in bone metabolism and remodeling, can lead to osteoporosis.
    d. Lack of exercise or mobility influences osteoclastic activity, leading to rapid resorption of bone mass.
2. **Postmenopausal osteoporosis:** Caused mainly by oestrogen deficiency.
    a. Inflammation due to oestrogen deficiency is caused by the actions of cytokines (Interleukin-1, Interleukin-17, Interleukin-6, Interleukin-7, Tumour Necrosis Factor-α) on the oestrogen receptors, effectively leading to the inhibition of osteoblasts and promotion of osteoclasts.
    b. Receptor Activator of Nuclear Factor-Kappa-B Ligand (RANKL) is necessary for osteoclast development from myeloid precursors. Oestrogen deficiency affects RANKL, leading to the inhibition of osteoclast differentiation and osteoporosis.
3. **Idiopathic osteoporosis:** Very rare and usually due to genetic mutations.

Signs and Symptoms

Osteoporosis leads to thinning of the cortex, causing fragility of the bones. Hence, fractures can occur in weakened bones even with trivial trauma. Vertebral body fractures are the most common, followed by fractures around the hip and wrist. The maintenance of bone density in our bodies relies on a delicate balance between bone resorption and new bone formation. Total bone mass peaks in an individual around the age of 35. As age increases, this balance is disrupted, leading to increased bone resorption and/or slowed new bone formation, resulting in weakened bones. This imbalance typically begins in a person's late 30's, with accelerated bone resorption in postmenopausal women. This process often goes unnoticed until a fracture occurs. Osteoporosis is more common in females due to several reasons: women generally have less bone mass in comparison to men, they tend to live longer, and their calcium intake is usually less. The rate of bone resorption accelerates in postmenopausal women as oestrogen levels fall. The same occurs when a lady undergoes surgical removal of the ovaries, with or without the uterus [14-16].

Repeated falls may occur due to age-related factors like impaired eyesight, gait disorders, balance disorders (cerebellar pathology), movement disorders (extrapyramidal tract involvement), dementia (Alzheimer's disease), and sarcopenia (age-related loss of muscle mass). Vertebral body fractures may lead to spine instability, resulting in repeated falls, which can commonly lead to fractures around the hip and wrist joints. Hip fractures require surgical management to prevent complications from prolonged bed rest. Deep vein thrombosis and its complication, pulmonary embolism, are serious complications that can lead to increased mortality. Urinary tract infections, lower respiratory tract infections, malnourishment, protein imbalance, loss of muscle mass, and bedsores are complications that cause higher morbidity in patients with prolonged bed rest following hip fractures. Encouraging the elderly population to walk with support (walking aids), removing obstacles and loose carpets in living rooms, decreasing the height of stairs, and using appropriate footwear may substantially reduce falls [18].

The main issue is the failure to diagnose osteoporosis early, as individuals often do not exhibit specific signs or symptoms. Most of the time, it is diagnosed only after the patient has suffered a fracture or fracture-related complications such as lower limb deformity, chronic backache, reduced height (due to vertebral collapse), or a hunched back (kyphotic deformity). These problems tend to occur after a significant amount of bone calcium has already been lost [19].

Risk Factors for Osteoporosis

Osteoporosis is more common in females, mainly after menopause. Individuals over 65 years old are at an increased risk, as are those with low body weight relative to their height and age. Ethnicity, such as being white or Asian, increases the risk, but African American and Hispanic/Latina women are also at risk, as are those with a history of irregular menstrual cycles or psychiatric illnesses like dementia or anorexia nervosa. Patients with a family history of osteoporosis and fractures are also at a higher risk [20,21]. Patients with a history of long-term use of certain medications, including selective serotonin reuptake inhibitors for treating depression and anxiety, thiazolidinediones [22] glucocorticoids to treat arthritis [23], asthma [24], and lupus [25], antiseizure medicines [26], gonadotropin-releasing hormones for endometriosis [27]; proton pump inhibitors containing aluminum that block calcium absorption [28]; some cancer treatments [29]; too much replacement of thyroid hormone [30]; can also contribute to osteoporosis. Smoking, alcohol consumption, a diet low in dairy products or other sources of calcium and vitamin D, and physical inactivity can also contribute as modifiable risk factors for osteoporosis [31] [Table/Fig-2].

NON MODIFIABLE	MODIFIABLE
• Advanced age • Female gender • White/Asian race • Low peak bone mass • Family history of osteoporosis • Low BMI • Personal history of fracture	• Smoking • Inadequate Calcium intake • Vitamin D deficiency • Low body weight • Estrogen deficiency • Hypogonadism • Chronic glucocorticoid therapy

[Table/Fig-2]: Risk factors of osteoporosis.
BMI: Body mass index

Alarming Signs

The warning signs for osteoporosis include a loss of height after puberty, the development of a slumped or hunched posture, back pain with an unspecified cause, women aged 45 or postmenopausal,

and a history of repeated fractures. Surprisingly, in 50% of cases, the cause of osteoporosis in men is unknown, while the other 50% is due to age-related bone loss, malabsorption, nutritional deficiencies, chronic alcoholism, smoking, testosterone deficiency, pituitary insufficiency, chronic illnesses (such as chronic renal diseases, hepatic insufficiency, GI malabsorption syndrome, chronic inflammatory polyarthritis, chronic debility, or immobilisation), and tumours. Disuse osteoporosis is common in persons with a sedentary lifestyle [30-33].

Screening Tools for Osteoporosis

BMD analysis is widely used for screening osteoporosis. Other simple screening tools available include the Osteoporosis Self-assessment Tool for Asians (OSTA), Osteoporosis Risk Assessment Instrument (ORAI), Simple Calculated Osteoporosis Risk Estimation (SCORE), Age-Bulk-one or Never Oestrogen (ABONE), Male Osteoporosis Risk Estimation Score (MORES), and Fracture Risk Assessment Tool (FRAX). These tools can moderately predict the risk of osteoporosis. Complete laboratory assessments, including renal function tests, thyroid function tests, 25-hydroxyvitamin D, and calcium levels, are also done to confirm osteoporosis. However, Dual-energy X-ray Absorptiometry (DEXA) scanning is considered the "gold standard" for diagnosing osteoporosis. Unfortunately, availability is limited in developing countries like India, especially in primary healthcare settings and rural areas. The rate of fractures increases exponentially with the decrease in DEXA score. X-rays are helpful in identifying osteoporosis only in advanced stages [Table/Fig-3] [34-37].

ABSOLUTE INDICATION	• All women 65 years and older and all men 70 years and older should be screened for asymptomatic osteoporosis
RELATIVE INDICATIONS	• Women younger than 65 years old at risk for osteoporosis • Oestrogen deficiency • History of maternal hip fracture before the age of 50 years • Low body mass (less than 127 pounds) • History of amenorrhea more than 1 year before the age of 42 • Current cigarette smoker • Loss of height • Thoracic kyphosis

[Table/Fig-3]: Indications for a DEXA scan.

The WHO recommends DEXA test for assessing BMD. This test can measure calcified tissues, with better specificity than sensitivity compared to other testing modalities for osteoporosis. It takes approximately five minutes of minimal radiation exposure. DEXA provides a t-score and a z-score. The t-score reflects the difference between measured BMD and the mean value of BMD in young adults [37].

Interpretation [3,38]

a. Normal: T score within one standard deviation of the young adult mean.

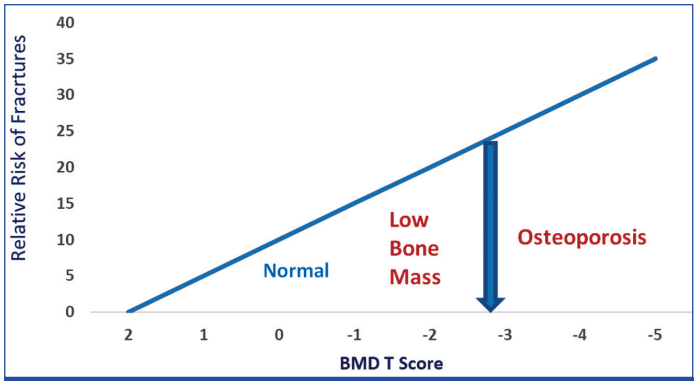
b. Osteopenia: scores between -1 and -2.5.

c. Osteoporosis: scores below -2.5 [Table/Fig-4].

The bottom line is, if an individual is 65 or older or has any risk factors as mentioned above, they should get a bone density test done.

Treatment

Non-pharmacological management of osteoporosis: Lifestyle modification should include weight-bearing and muscle-strengthening exercises. A healthy diet with plenty of calcium and vitamin D is prescribed. Treatment for osteoporosis starts with dietary changes. Calcium supplements and oral vitamin D preparations may be given



[Table/Fig-4]: Bone density and relative risk of fractures.

if oral intake is inadequate. The patients are advised to quit smoking cessation and to restrict alcohol intake [39,40].

The following are dietary recommendations for Bone Health:

1. Calcium: Calcium plays an important role in skeletal mineralisation. More than 99% of the body's calcium is stored in bone as hydroxyapatite. As per the 2020 guidelines from ICMR-NIN, the dietary recommendations for Indian adults are as follows: 1000 mg/day for adult males and females, pregnant women, and 1200 mg/day for lactating women. For infants, 300 mg/day; children aged 1-3 years, 500 mg/day; children aged 4-6 years, 550 mg/day; children aged 7-9 years, 650 mg/day; boys and girls aged 10-12 years, 850 mg/day; boys and girls aged 13-15 years, 1000 mg/day; and boys and girls aged 16-18 years, 1050 mg/day [40]. Other important nutrients include vitamin K, vitamin C, magnesium, zinc, as well as protein to build strong bones [41].
2. Dairy products such as milk, yogurt, and cheese are rich in calcium. Approximately 100 grams of cheese provide 1 gram of calcium, 100 grams of milk provide 100 mg of calcium, and 100 grams of yogurt provide 180 mg of calcium. Fruits like Amla, Guavas, Bananas, Jackfruits, and Chiku, Custard apple are good sources of calcium. Fortified foods can also be important sources of calcium [42-45].
3. Dry beans including Kidney beans, Black-eyed peas, Chickpeas, Black Peas, Turnip greens, radish, Bottle gourd, Foxnut, chestnuts/chestnuts are good sources of calcium. About 100 grams of cereals usually provide around 30 mg of calcium. Vegetables rich in calcium include kale, broccoli, and watercress, providing between 100 and 150 mg per 100 grams [46].
4. Nuts and Seeds including almonds, sesame, and chia can provide between 250 and 600 mg per 100 g of calcium. Peanuts, groundnuts, walnuts, cashew nuts, almonds, and fruit seeds like melon seeds and watermelon seeds are good sources of calcium [47,48].
5. Coconut: Coconut, known as a wonder fruit, due to its rich macro- and micronutrient composition and is a vital mineral for bone strength. Coconut milk provides approximately 38 milligrams of calcium per 100 milliliters, and coconut water contains 27.35 mg/100 mL. It is particularly rich in calcium, phosphorus, and magnesium, essential for bone mineralisation and overall bone health. A review published in the Journal of Food Science and Technology highlighted the role of coconut milk in promoting bone health due to its calcium, phosphorus, and magnesium content, which contribute to bone mineralisation and help prevent bone-related disorders. An animal study in the Journal of Medicinal Food demonstrated that supplementing with coconut milk significantly increased BMD and improved bone strength in rats [42,49,50].
6. Vitamin D: Vitamin D is essential for the absorption of calcium in bones. It is synthesised in the skin with exposure to sunlight. For individuals with Vitamin D deficiency or limited sun exposure,

Vitamin D supplements with 400 to 600 IU per day or 60,000 International Units once a week are prescribed. Foods such as milk, buttermilk, curds, paneer (cottage cheese), cooked eggs, salmon, and vitamin D-fortified milk are good sources of vitamin D [51-53].

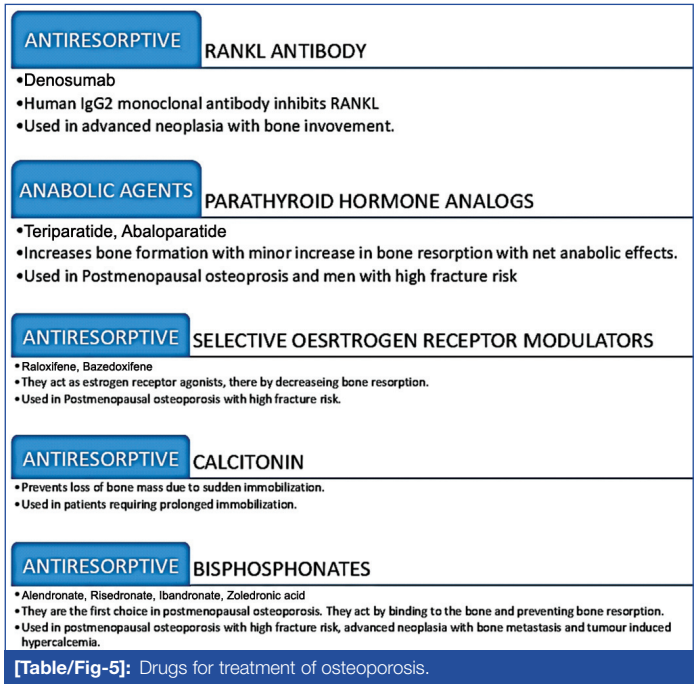
7. Proteins: Dietary protein has a major role in the development and repair of the musculoskeletal system. Proteins break down into essential and non essential amino acids, which are necessary for the synthesis of bone matrix and skeletal muscle proteins. Amino acids also stimulate the gene expression of insulin-like growth factor-1, a hormone that exerts anabolic effects on bone and muscle. Adequate protein consumption is essential for preserving muscle mass and bone health. Non vegetarian sources of protein include lean red meat, chicken, fish, and eggs, which provide first-class and complete protein. Milk and dairy products are also good sources of protein, offering excellent animal protein sources. Vegetarian protein sources include legumes (e.g., lentils, kidney beans), soy products (e.g., tofu), grains, nuts, and seeds, which are considered second-class and incomplete proteins [54-56].
8. Individuals at risk of osteoporosis should stop smoking and limit alcohol consumption [57,58].
9. Additionally, for elderly populations, ensure the home is a safe environment to reduce chances of falls. Use proper lighting at home during the night, place a rubber bath mat in the shower or tub to prevent slips, keep floors free from clutter, remove throw rugs that may cause tripping, and use grab bars in the bath or shower to prevent falls and hence decreases the risk of fractures [59].

Pharmacological Treatment of Osteoporosis [Table/Fig-5]

There are plethoras of pharmacological treatment options that work through Antiresorptive or anabolic mechanisms with the aim of reducing the risk of fractures in patients with osteoporosis [60]. Pharmacological treatments are broadly classified into two categories:

a. Antiresorptive agents like bisphosphonates, oestrogen agonists, oestrogen antagonists, calcitonin, and denosumab act by slowing down the resorption of bones.
b. Anabolic agents like teriparatide act by strengthening bones and stimulating bone synthesis [61].

In women with known osteoporosis, drugs including risedronate, alendronate, zoledronic acid, or denosumab are used to reduce the risk of fractures. Bazedoxifene, a selective oestrogen receptor modulator combined with conjugated oestrogen, has been approved by the FDA for the prevention of osteoporosis but not for treatment. Hormonal therapy is advised for the prevention and treatment of postmenopausal osteoporosis in asymptomatic postmenopausal women [62-64].



[Table/Fig-5]: Drugs for treatment of osteoporosis.

Bisphosphonates are the first-line therapy for osteoporosis in men [65]. The Endocrine Society recommends zoledronic acid for men with a recent hip fracture, risedronate for men at risk for hip fractures, and teriparatide for men at high-risk for fracture [66].

Raloxifene, Ibandronate, and Teriparatide are used if patients are unable to tolerate the above medications. The use of combination therapy with teriparatide and a bisphosphonate or teriparatide and denosumab in patients with severe osteoporosis and hip and vertebral fractures is worth considering [67].

These drugs can also be classified as non nitrogen and nitrogen-containing compounds. The nitrogen-containing compounds inhibit farnesyl pyrophosphate synthase, ultimately inhibiting osteoclast resorption and inducing osteocyte apoptosis.

Commonly used medications include:

- Alendronate, which may reduce the rate of hip, spine, and wrist fractures by 50%.
- Risedronate, which may reduce vertebral and non vertebral fractures by 40% over three years.
- Intravenous zoledronic acid, which reduces the rate of spine fractures by 70% and hip fractures by 40% over three years.
- RANKL inhibitors (denosumab): Denosumab is a monoclonal Ig2 that targets RANKL and inhibits its ability to bind to RANK, resulting in the inhibition of osteoclast activation [68-70].

Differential Diagnosis

Conditions like homocystinuria, hyperparathyroidism, imaging in osteomalacia and renal osteodystrophy, mastocytosis, multiple myeloma, Paget's disease, scurvy, and sickle cell anaemia should be considered for differential diagnosis before starting the treatment of osteoporosis [71].

Prognosis of Osteoporosis

Early detection leads to better outcomes. Chronic bone pain and fractures are the outcomes of untreated osteoporosis. Lifestyle modification in terms of healthy diet and exercise have been proven to be useful in preventing osteoporosis. Special emphasis should be given to postmenopausal women and individuals aged 65 and above [72].

Complications: Hip and spinal column fractures are the most common complications of osteoporosis. Falls are the commonest cause of hip fractures, leading to further disability and an increased risk of mortality. Spinal fractures can also occur, and in the absence of patient falls, compression fractures may lead to back pain and a kyphotic posture [73].

Recent advances: Novel therapies include newer selective oestrogen receptor modulators, Cathepsin-K inhibitors, and antisclerostin antibodies. Gene therapy represents the most recent advancement in the management of osteoporosis. Wingless related integration site (WNT)-modulating gene silencers are being explored as a form of gene therapy for osteoporosis and bone fractures [74,75].

CONCLUSION(S)

Osteoporosis is a common condition affecting the elderly population and is often diagnosed only after a fragility fracture and its complications, osteoporosis also has psychological and financial impacts on individuals. There are multiple known risk factors that contribute to the development of osteoporosis, hence it best managed by an inter-professional team of healthcare workers. Community education is crucial as many people are unaware of the serious consequences

of the disease. Early diagnosis, lifestyle modifications, recognition of risk factors, and their treatment, as well as adherence to prescribed medications, can help reduce high morbidity and mortality rates. Individuals should also be encouraged to quit smoking and refrain from alcohol consumption. Dietitians should educate patients on the importance of a calcium-rich diet and vitamin D supplementation in the prevention and treatment of osteoporosis. Enrolment in an exercise programs, health clubs, and yoga is also recommended. Women over 65 years of age should be encouraged to have a bone density scan for early diagnosis. Finally, the families of elderly individuals play a vital role in preventing frequent falls and, in turn, preventing fragility fractures and their complications.

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