RESEARCH ARTICLE

Osteoporosis: A Silent Life-threatening Disease

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Abstract

Osteoporosis is a pervasive multi-factorial chronic disorder characterized by low bone mineral density and increased risk for bone fragility, with a claim for long-term management procedure. Osteoporosis as a disease is a major threat due to our changed lifestyle and aging demographic. It may be viewed as a heterogeneous condition due to various genetic, nutritional, mechanical, endocrine and other lifestyle factors. Although post-menopausal women are the most vulnerable victims, aged men population cannot escape themselves from this disease, as can be diagnosed by Bone Mineral Density (BMD) test. This review work will give insight into how the disease can be controlled by lifestyle changes and usage of some selected pharmaceuticals and nutritional supplements. Hence, assessing the prevalence and awareness of the risk factors associated with the disease may provide the basis of management and future health plans to combat it.

Keywords: BMD, Osteoporosis, Post-menopausal women, Risk factors.

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Introduction

Osteoporosis, demands the second most important position in the global health care arena (2). In 2013, it was found 50 million people in India are either osteoporotic (T-score lower than -2.5) or have low bone mass (T-score between-1.0 and -2.5) (43). Interestingly, studies indicate that osteoporosis and osteopenia or low bone mass may occur at a relatively younger age in Indian population.[44,45] It is characterized by low bone mass with altered micro-architecture of the bone that leads to increased risk of fragility of bones.[4,10] Conventionally, osteoporosis has been classified into primary and secondary type. Primary osteoporosis refers to osteoporotic conditions which are not related to other chronic illnesses and is usually associated with aging and decreased gonadal function, such as decreased level of oestrogen. In contrast, secondary osteoporosis is the type of osteoporosis caused by other health problems. Disuse is one of the many reasons inducing bone loss and resulting in secondary osteoporosis.[12,24] The disuse osteoporosis refers to decrement of bone mass under certain conditions such as decreased mechanical loading, including decreased ground force reaction, muscular contraction. It is also found in microgravity-related bone loss in astronauts after space flights. Disuse osteoporosis is found regionally, mostly in the areas with tremendous decrease in weight bearing like lower limbs. In daily life, bones of lower limbs are subjected to mechanical stimulations provided by static gravity-related weight-bearing, ground reaction forces, and dynamic loading generated by muscle contractions during locomotion. Physical exercise is also essential for increasing or maintaining bone mass and strength.[25] In post-menopausal women, Milliken et al. (26.) have investigated the effect of one-year supervised weight training exercise on their bone mineral density (BMD) level. The study result showed higher BMDs of trochanter and femoral neck in women with weight training exercise than in those lacking exercise. Similarly, Chan et al.[27] have studied the effect of Tai-Chi exercise on the bone quality in post-menopausal women. In fact, there are many effective treatments available for control of primary osteoporosis, but effective treatments for disuse osteoporosis is still to be discovered. This is because of the fact that the aetiology, patho-physiology, and resultant pathology of disuse osteoporosis differ from those of primary osteoporosis.(32)

Osteoporosis as a disease in general is a major threat due to our changed lifestyle and aging demographic.(11). An analogy may be drawn with respect to asymptomatic condition of hypertension, and dyslipidaemia which culminates in stroke or myocardial infarction. Osteoporosis may similarly predispose to multiple fractures in the bones of the body (10). Although the disease prevails in the post-menopausal women population due to their decreased bone mineral density (BMD) resulting from deficiency of female sex hormone, it has found to touch the male population also (2). Thus osteoporosis has always been mislabelled as a women's disease by the public, but it really affects men, too. Usually, young patients if afflicted by the disease, remain undiagnosed until a fracture brings the patient to a doctor. As a major public health problem, it is often associated with the incidence of bone fractures which lead to morbidity specially among older population, culminating in mortality also. It is true for the entire population of the world also. The disease is also associated with a huge financial burden even in the developed countries (10). Indeed it is a multi-factorial disease,

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easily affected by a number of risk factors that influence Bone Mineral density or BMD. (6, 10). Unfortunately this important health hazard though known for a long time, has received a low level of attention in primary health care program in most of the under -developed countries, where specifically most of the women though vulnerable to this disease are almost unaware of the graveness of the disease (1). Naturally, they are also quite in the dark about the remedial measures to be adopted as a part of their lifestyle. The present article aims at reviewing the basic information of the disease, current prevalence and awareness of osteoporosis not only among the women population, but also in the male community in the perspectives for this particular health hazard.

Aetiology of the Disease

Osteoporosis may be considered as a heterogeneous condition which may express at any age of life and is attributed to various factors, such as advancing age, physical disability, genetic, endocrine, nutritional, metabolic, mechanical factors as well as deficiency of Immune system of the body (4, 10). These may again be categorized as non- modifiable and modifiable factors. Non- modifiable factors include genetic pattern, age, sex, physical structure and modifiable factors are usually body weight, lifestyle factors specially sedentary lifestyle or exposure to microgravity etc. (32).

Genetic Factors

Gene for vitamin D receptor is believed to be a determinant factor for bone mass and difference in VDR gene polymorphism in different races may be responsible for difference in bone mass (7,9). This has been significantly shown in Indian women (8). Moreover, oestrogen receptor α (ER α) gene polymorphism may also be associated with BMD in Indian women (8). Other gene, i.e. collagen type Iα1 gene and Insulin like growth factor I(IGFI) gene, (specially in men have proved their role in earlier studies(2, 15).

Nutritional Factors

Bone health depends much on Calcium and Vitamin D status in the body and thus deficiency of these two factors seems to be the major contributing factors for osteoporosis. Apart from body weight, age and menopausal state, Calcium intake is found to be an important determinant of BMD (10,44). Similarly, low level of serum Vitamin D is associated with low BMD. status (17)

Hormonal and Metabolic Factors

Medical conditions like hypogonadism, thyrotoxicosis, Adrenal cortical disorder like Cushing Syndrome, Chronic Inflammatory conditions, Anorexia nervosa, Renal disease, Chronic liver disorder, malabsorption syndrome, may lead to osteoporosis. (21,32)

Level of Peak Bone Mass Achieved at Puberty

This is usually achieved by proper nutrition and physical exercise (4).

Medications

Use of drugs in the group of Glucocorticoids, Antilipidemics etc may lead to osteoporosis (9). It may be called as secondary osteoporosis.

Osteoporosis due to Disuse of body components

It is in general bone loss or a reduction of bone mass in relation to bone volume, while the ratio of bone mineral to collagen remains unchanged. The loss of trabecular bone is more rapid and dramatic, while the cortical loss continues for a longer period (28). However, during long term bed rest, paralysis, bones of lower limbs are subjected to three categories of mechanical loadings during daily life, namely, static gravity-related weight bearing, ground reaction forces, and dynamic loading generated by muscle contractions during locomotion. Different health problems are associated with absence or decrease in one or more of these mechanical stimulations and may result in bone loss differently in anatomical location, quantity, velocity, and through different mechanisms. (31) Several studies on effects of microgravity on skeleton, i.e reduced weight bearing and ground reactions focused on the impacts on skeletons of astronauts after spaceflights. Collet et al. (29) analyzed the BMD and biochemical parameters of 2 astronauts who stayed one and six months, respectively, in space. However, the impacts of microgravity on human skeletons are highly varied, but in case of astronauts it is to be noted that muscle contractions are not limited or restricted.

Epidemiology

There is no doubt that Human population of all races and ethnicity is susceptible to osteoporosis. Worldwide, life time risk for osteoporotic fractures in women is 30-50% and 15-30% in men (12.) Based on 2001 census, it was postulated that by 2015, Indian aged population (age above 50 years) would become 230 million from 130 million when 20% of women and 10-15% of men population would be osteoporotic (10). The National Health and Nutrition Examination Survey (NHANES) III data had shown that prevalence of osteoporosis is highest in older White women, followed by Mexican American women and finally by Black women as based on BMD. estimation of femur (8). In current Indian context, it appears from the situation analysis of the elderly in India, most common disability among the aged population is the locomotor disability which may arise due to osteoporosis (5,45). In USA, Osteoporotic fractures are extremely common, with an estimated figure of 1.5 million people suffering from fragility fractures each year.(13) A similar burden of disease was also observed in the UK, with epidemiological studies hypothesizing that one in two women and one in five men aged over 50 years will suffer an osteoporotic fracture in their lifetime.(47). In India, low calcium intake, extensive Vitamin D deficiency, early menopause, increasing longevity, and genetic predisposition, give rise to high prevalence of osteoporosis in women (33).

Pathogenesis of Osteoporosis

Our Bone continually undergoes modelling (during growth) or remodelling (during adult life), and this is brought about by the co-ordinated action of two types of cells, osteoblasts and osteoclasts. Osteoblasts form new bone, whereas osteoclasts are responsible for bone resorption. Both types of cell exert their actions being under hormonal regulation. Osteoporosis, is a condition when bone resorption exceeds bone formation leading to a reduction in bone mass, which again predisposes to fracture. The most important cause of osteoporosis is oestrogen deficiency, resulting in increased bone turnover in which resorption exceeds formation. Corticosteroids can also induce osteoporosis in which trabecular bone is particularly affected. This mainly results from suppression of osteoblastic activity. (46) Pathogenesis of Osteoporosis, unlike other chronic diseases is rather complex. Its prevalence is associated with genetic and other risk factors. An individual's peak bone mass attains a maximum value after sufficient deposition of bone mineral and skeletal growth. The process slows down after adulthood. After that, bone resorption process begins to exceed bone formation. As cancellous bone is metabolically more active than cortical bone, during accelerated bone loss, cancellous bones become three-fold more osteoporotic and the result is evident in the important cancellous bone like vertebrae.[19] Regulation of bone turnover is influenced by hormones, physical activity, nutrition, age and genetic factors.

Osteoporosis is conventionally classified into two main groups, considering the factors which affect bone metabolism: Primary osteoporosis and Secondary osteoporosis.

Primary osteoporosis is again sub-divided into two groups:

- *Involution or Type I Osteoporosis:* It is also known as post-menopausal osteoporosis, mainly caused by the deficiency of female sex hormone oestrogen. Oestrogen mainly affects the trabecular bone. As a result, women are more susceptible to osteoporosis than men, and it is evident by a men/women ratio of 4/5.7.[30]
- *Involution or Type II Osteoporosis:* Also known as senile osteoporosis, and it is related to loss of bone mass during the aging of cortical and trabecular bones.[41,42]

Secondary osteoporosis: is mediated by many factors:

- Different diseases such as Vitamin D deficiency, Vitamin A excess, Thyroid hormone in excess.[21]
- Different medications, especially those used for the treatment of acidity (Aluminum in antacids), anxiety reliever drugs, sedative drugs (Barbiturates,) Anticoagulants (heparin), anticonvulsants, cancer, chemotherapeutic drugs, depomedroxyprogesterone (premenopausal contraception), glucocorticoids (≥5 mg/day prednisone or equivalent for ≥3 months), GnRH (gonadotropin-releasing hormone) agonists, Lithium Cyclosporine A, Tacrolimus, Methotrexate, Parental nutrition, Proton pump inhibitors Selective serotonin reuptake inhibitors, Tamoxifen® (premenopausal use) Thiazolidinediones,
- Lifestyle changes such as, high salt intake, alcohol abuse, low calcium intake, physical immobilization, low physical activity can cause secondary osteoporosis.[40,47]

Diagnosis

Osteoporosis is a silent disease since it does not show any symptom until a fracture occurs. Hence, the bones become so weak that sudden strain, bump or fall causes vertebrae to collapse or cause a hip fracture. If vertebrae collapse, it initially exhibits back pain, followed by loss of height, spinal deformities such as kyphosis or stooped posture, Major signs of osteoporosis are sloping shoulders, the curve in the back, loss of height, back pain, hunched posture, protruding abdomen etc.[22] Osteoporosis affects all bones of the body. However, breakage is common in the hip, wrist and spine.[23] The gold standard for diagnosing osteoporosis is by measuring BMD using DEXA (Dual Energy X ray Absorptiometry) at different indicative sites such as lumbar spine, femoral neck and total hip. Using the guidelines of WHO, osteoporosis is believed to be present if t-score of BMD is at least more than 2.5 SD below the peak bone mass of reference standard for young white women(2,18). The most important question here arises regarding the appropriateness of Western standard in the case of Indian population, since B.M.D.at all the sites seems to be 5–15% lower than the Caucasians.[3] A few years ago, the International Society for Clinical Densitometry (ISCD) recommended using ethnic- or race-adjusted Z-scores: Z-scores of -2.0 or lower are defined as "low bone mineral density for chronological age" or "below the expected range for age" and those above -2.0 are defined as "within the expected range for age".[33] The bone mineral density can be easily measured, the degree of the bone tissue deterioration cannot be measured in clinical settings, except the biochemical markers of bone tissue.[34] Bone remodeling (or turnover) occurs throughout our life to repair small or minimum fatigue damage and microfractures in the bone and maintain mineral homeostasis. Biochemical markers of bone remodeling include some resorption markers, namely serum C-terminal telopeptide type-I collagen (s-CTX) and urinary N-telopeptide (NTX), and formation markers, such as serum procollagen type-I N-terminal propeptide (s-PINP) may provide information on fracture risk independent of BMD and predict the rapidity of bone loss in untreated patients. Following studies are also necessary to rule out secondary osteoporo:[40] Complete blood count (CBC), Serum creatinine, calcium, phosphorus, and magnesium, Alanine aminotransferase (ALT), aspartat aminotransferase (AST), and alkaline phosphatase (AP) Thyroid-stimulating hormone (TSH) and free T4, Vitamin D (V-D) (25 (OH) D, Parathyroid hormone (PTH), Total testosterone and gonadotropin in younger men.

Remedial Measures for Prevention and Treatment of Osteoporosis

Osteoporosis is a preventable and treatable disease, but because of a lack of warning signals, people are not aware

or nor being diagnosed in time to receive effective therapy during the early phase of this disease.[36,37] So universal recommendations for all patients are:

- An adequate intake of calcium and Vitamin-D, through natural/artificial sources[16]
- Life-long regular weight-bearing and muscle-strengthening exercises.[12,20]
- Treatment of risk factors for falling[36]
- Cessation of tobacco use and excess alcohol intake

On top of that, it is to be remembered that low serum calcium levels promote bone resorption, and calcium requirements increase among older persons; thus, the older population is particularly susceptible to calcium deficiency. Moreover, all calcium preparations are absorbed adequately if taken along with food, particularly in the absence of gastric acid secretion. For optimal absorption, the amount of calcium should not exceed 500–600 mg per dose. A few foods are rich in oxalate, and they prevent the absorption of calcium by binding with it. On the contrary excess intake over and above 1200–1500 mg/day may increase the risk of developing kidney stones, cardiovascular diseases, and strokes. Calcium absorption is assisted by Vitamin D. Chief dietary sources of V-D include V-D–fortified milk, juices and cereals, saltwater fish, and liver. Supplementation with V D2 (ergocalciferol) or V-D3 (cholecalciferol) may be used. Many older patients are at a high risk for V-D deficiency,[9] which include the following: patients with malabsorption issues (e.g., celiac disease) or other intestinal diseases (e.g., inflammatory bowel disease, gastric bypass surgery); gastric acidity; some anticonvulsive drugs); or glucocorticoids, which decrease calcium absorption; housebound and chronically ill patients; persons with limited sun exposure; individuals with very dark skin; and obese individuals. Therefore, Serum 25 (OH) D levels should be measured in patients at the risk of V-D deficiency. V-D supplements should be recommended in amounts sufficient to bring the serum 25 (OH) D level to approximately 30 ng/mL (75 nmol/L).

Treatment with Pharmacological Agents

Pharmacological interventions are often required especially for persons with a high risk of osteoporotic fractures**.** The main objectives of this therapy in osteoporotic patients are to improve their quality of life. It is mediated by preventing fractures by improving bone strength and reducing the risk of falling and injury. Most of the current therapies in the prevention of osteoporosis and fractures are designed to arrest bone resorption and increase bone mass and these are known as antiresorptive agents. Some important agents in this group are: oestrogen; Bisphosphonates (BPs) such as alendronate, risedronate, ibandronate, and zoledronic acid; other drugs are Selective Estrogen Receptor Modulators (SERM)-such as Raloxifene; another one is Human Monoclonal Antibody against receptor activator of NF-κB ligand (RANKL): Denosumab; and Strontium Ranelate (SR). Of all these drugs Bisphosphonates are the most widely used drugs for treating osteoporosis. Bisphosphonates are a group of drugs that work by slowing bone loss. They reduce the risk of hip and spine fractures. Bone renewal is a slow process, but an increase in bone density can be measured over five years of treatment in many people. Alendronate is used to prevent and treat post-menopausal, glucocorticoid-induced, and male osteoporosis cases. Zoledronic acid is used to prevent and treat post-menopausal osteoporosis and osteoporosis in men and glucocorticoid-induced osteoporosis.). Ibandronate is another BP used for the prevention and treatment of post-menopausal osteoporosis, which has proven efficacy in reducing the risk of spinal fractures of post-menopausal women who have osteoporosis, but it is not proven in reduction of s non-vertebral or hip fractures except for higher-risk subgroup. Ibandronate has been studied in trials of up to 3 years and its efficacy and safety beyond 3 years is unknown.[43,47]

Biphosphonates are the main drug of choice for the usual case of reducing the risk of mild to moderate fractures in vertebrae or non-vertebral regions, while for severe osteoporosis use of teriparatide is the answer.[38,39,47] Teriparatide (recombinant human PTH 1–34) with all its adverse effects has been selected as a drug of choice specially for post-menopausal women with a high risk of fracture, and those who have failed or are intolerant to previous osteoporosis therapies. It is also used to increase bone mass in men with idiopathic or hypogonadal osteoporosis. Denosumab (human monoclonal antibody against RANKL) as a new drug is considered as a drug of choice for the treatment of post-menopausal women at a high risk of fracture and also for patients having a history of osteoporotic fractures, or patients who have failed or are intolerant to other available osteoporosis therapies. Pharmaceutical vitamin D (D3) or its precursor alfacalcidol are approved drugs for treatment of osteoporosis but not for prevention for which Cholecalsciferol is more effective.[38] Researchers in this field opine that the lifestyle of an individual is to be modified. We must create general public awareness in this regard. This awareness program must convey a few important points to the susceptible persons, such as a brief idea about B.M.D., importance of regular exercise, consumption of Calcium and Vitamin D rich foods, building up of strong bones at childhood, frequent exposure to Sun light, and special awareness programs are also to be made for post-menopausal women. Apart from these, avoidance of high salt diet, coffee, and alcohol consumption and cigarette smoking, indulgence in regular physical (weight-bearing and muscle-strengthening) exercise, and a balanced diet with adequate calcium and Vitamin intake.[35] Another cheap but useful therapy recommended is daily skin exposure to sunshine for at least 15 minutes.[37] It is also important to motivate our children to drink milk and to enjoy playing under the sun. People with sleep- apnoea are victims of osteoporosis, since oxygen depletion can weaken bones.[36]

Conclusion

Osteoporosis is a common household name. We are also aware of its grave consequences. In fact, osteoporosis causes many people to suffer from a fracture. Every year, we consider 20th October as world osteoporosis day. The severity of the disease increases with the increase in the aging population throughout the world. Understanding the reasons behind the multi-factorial nature of bone health, preventive care towards control and mitigation of the problems underlying the disease must be given due importance and this can only be achieved with the adoption of a changed lifestyle, dietary habit, appropriate low-cost medicines and genuine, constructive awareness about this debilitating disease.

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