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FACTORS, PREVENTION AND TREATMENT OF OSTEOPOROSIS: A REVIEW

Nirmal Shah*, Kartik Pandya, Dipti Gohil, A K Seth

Department of Pharmacy, Sumandeep Vidyapeeth, Piparia, Vadodara-391760, Gujarat

ABSTRACT

Osteoporosis is the thinning of bone tissue and loss of bone density over time. Osteoporosis is a major and growing public health problem for older women and men in western society. Bone is the major reservoir for the calcium and phosphate and is in constant state of remodeling during stress, many factor effects the bone resorption. Understanding the physiology, pathophysiology and treatment of Osteoporosis will direct the patients about precautions to be taken, to select the correct treatment regimen and to improve the quality of life of the patients. The beneficial effects of treatments can be assessed by the outcome study using quality of life assessment tools.

KEYWORDS: Osteoporosis, Remodeling, DEXA, Bone resorption.

INTRODUCTION

Osteoporosis is a skeletal disease characterized by the low bone mass and microarchitechtural deterioration with resulting increase in bone fragility and therefore susceptibility to fracture. Osteoporosis has recently earned great emphasis in modern society and medicine as it is a “silent disease” researchers estimate that about 1 out of 5 women having the age > 50 years have osteoporosis. About half of all women over the age of 50 years will have a fracture of wrist, the hip or vertebra bones of the spine [1] It has no symptoms and its incident can only be known by an occurrence of a fracture. The age groups above 70 years are most susceptible for the osteoporotic fractures; especially osteoporosis occurs when the body fails to form enough new bone, when too much old bone is reabsorbed by the body, or both. Calcium and phosphate are two minerals that are vital requirement for normal bone development. All the way through youth, our body uses these minerals to construct bones. If enough amount of calcium is not obtained or body does not take up adequate calcium from the diet, bone formation may be deficient. The many reasons of osteoporosis are (1) Short of physical stress on the bones because of immobility, (2) No production of protein matrix due to malnutrition, (3) deficiency of vitamin C that is require for the secretion of intercellular substances by all cells, like osteoid formation by the

osteoblasts, (4) Shortage of estrogen secretion after menopause because it decrease the number and activity of osteoclasts and (5) Cushing's condition, since a huge quantities of glucocorticoids secreted in this condition cause decreased deposition of protein throughout the body and improve catabolism of protein and have the specific effect of reducing osteoblastic activity. Thus, many diseases of deficiency of protein metabolism can cause osteoporosis.[2]

History:

In 1948, Albright and Reifenstein found that primary osteoporosis was composed of two separate entities: one related to menopausal estrogen loss, and the other to aging. Support for this concept has been published by Riggs and associated (1982) who proposed that primary osteoporosis represent two fundamentally different conditions. The disease is divided into two types, primary type I or type II and secondary osteoporosis. Type I osteoporosis is most frequent in women occur after menopause. Primary type II (senile) osteoporosis developed at age 75 years or thereafter in both females and males with a 2:1 ratio. Secondary osteoporosis occurred at any age in equal proportion of men and women. This type of osteoporosis may be result of long-term use of some medications and the presence of susceptible medical troubles or disease conditions.[3]

Incidence:

- In United States, more than 1.5 million fractures may occur every year due to Osteoporosis.
- Every year more than 300,000 hip fractures and 700,000 vertebral fractures are reported in US.
- Osteoporosis cause above 250,000 wrist fractures each year in United States.

Diagnosis:

Dual energy X-ray absorptiometry (DXA, formerly DEXA) is considered as a major technique for the diagnosis of osteoporosis. Osteoporosis is diagnosed when the bone mineral density is less than or equal to 2.5 standard deviations below that of a young adult reference population. This is translated as a T-score. The World Health Organization has established the following diagnostic guidelines:

- T-score -1.0 or greater is "normal"
- T-score between -1.0 and -2.5 is "low bone mass" (or "osteopenia")
- T-score -2.5 or below is osteoporosis [4, 5]

FACTORS LEADING TO OSTEOPOROSIS AND PREVENTION OF OSTEOPOROSIS

Age: In women, Age above 45 years after menopause is most susceptible for bone loss leading to osteoporosis, occurrence of menopause below age 45 is known as premature menopause which leads to osteoporosis.[6]

Diet and lifestyle: Smoking, consumption of alcohol, imbalanced diet may result in osteoporosis. Consumption of balanced diet with sufficient amount of Calcium and Vitamin D avoiding smoking and alcohol will help in avoidance osteoporosis.[7]

Malnutrition: Malnutrition may have major influence for osteoporosis because proper intake of calcium and Vitamin D are vital to attain good bone mass density.[6]

Exercise: Regular exercise including weight-bearing and strength training exercises may helpful for avoidance of osteoporosis. But sometime, heavy and overloaded exercise or physical activity may also responsible for osteoporosis.

Injury: Immobilization causes bone loss, prolonged immobilization of the fracture limb cast will lead to localized osteoporosis. Fractures of vertebrae, rib, hip and wrist are the areas that are affected due to loss of bone mass.[7]

Hormonal disorders: Lack of estrogen has important role to play on calcium homeostasis, this is the key reason for incidence of osteoporosis after the menopause.[7]

Hyperparathyroidism: This is a state of over production of parathyroid hormone that may have negative impact on the bone mass density.

BONE PHYSIOLOGY

Bone physiology is mainly dependent on the two major processes Bone remodeling and Regulation of calcium in the body.

Bone remodeling: Bone architecture is categorized into Trabecular bone and cortical bone. Cortical bone is the compact shell of the bone and Trabecular bone is the inner delicate part, which is formed by an interconnective work of trabeculae. The peripheral skeleton is composed primarily of cortical bone, while the axial skeleton is composed of both cancellous and cortical bone. Surface area of cancellous bone is much larger than that of cortical bone, and is more metabolically active, cancellous bone is more severely affected if bone remodeling occurs during menopause.[8]

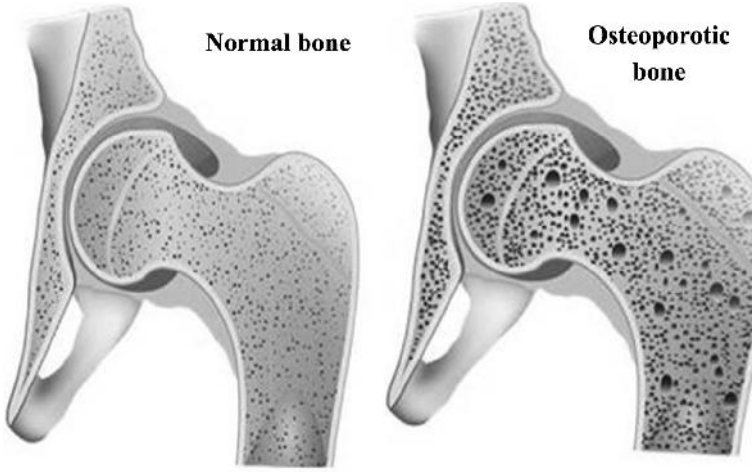

Figure 1: Bone fragility in osteoporosis

Once linear growth of bone stops, bone constantly undergoes remodeling with repeated cycles of bone resorption followed by deposition of new bone. In healthy individuals, bone resorption followed by bone formation is sequential without overall loss of bone. Bone is a major reservoir for calcium in various physiologic and pathologic situations, bone mass may be sacrificed to satisfy intra- and extracellular calcium needs. Osteoporosis is mainly caused due to aberrations in bone remodeling leading to bone fragility. Prevention and treatment of osteoporosis involves manipulation of the remodeling cycle and number of remodeling sites.

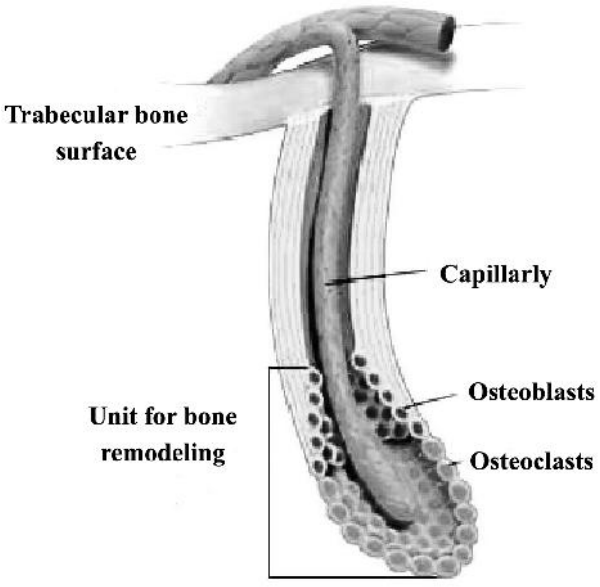

Figure 2: Bone Remodeling Units

At the cellular level, remodeling can be conceptualized as consisting of approximately 1 million bone remodeling units. These remodeling units are approximately 1-2 mm long and 0.2-0.4 mm wide, and are comprised of a population of osteoclastic cells in front and a group of osteoblastic cells in the rear. Osteoclasts are multi nucleated cells derived from monocyte/ macrophage lineage with ruffled border. Osteoblasts are derived from multipotent mesenchymal stem cells synthesize new bone. These remodeling units are also composed of a central vascular capillary, a nerve supply and associated connective tissue. During the bone resorption, osteoclasts adhere to the bone and subsequently remove it by acidification and proteolytic digestion. As the remodeling unit advances, osteoclasts leave the resorption site and osteoblasts move in to cover the excavated area and begin the new bone formation by secreting osteoid which is eventually mineralized into new bone. Osteoblasts synthesize new bone by first laying new protein matix. The lifespan of an individual bone remodeling is 6 to 9 months. Type I collagen is secreted in the form of a precursor, which contains peptide extensions at both the amino-terminal and carboxyl ends of the molecule. Each collagen molecules become interconnected by the formation of pyridinoline cross-links which provide extra strength. Osteoblasts also secrete other proteins that are incorporated into the bone matrix, including osteocalcin and osteonectin. Two stages of mineralization are mediated by osteoblasts. They are essential to the process of mineralization which involves the deposition of hydroxyapatite. Osteoblasts are thought to regulate the local concentrations of calcium and phosphate in such a way to promote the formation of hydroxyapatite. First, hydroxyapatite crystals are deposited between the collagen fibrils. Alkaline phosphatase located on the membrane of osteoblasts is thought to play a role in this mineralization. The second stage occurs over the course of several months as additional mineral is added to the resorption cavity.[8, 9]

Regulation of Calcium in the body: Extracellular calcium is regulated by the effects of interdependent hormonal mechanisms that regulate fluxes of calcium between the extra-cellular fluid and bone, kidney and intestine

Parathyroid Hormone (PTH): Parathyroid hormone is the main regulator of calcium, which is an 84 aminoacid single chain polypeptide .Secretion of PTH is mainly regulated by the concentration of ionized calcium in extracellular fluid, which is detected by calcium-sensing receptors on the parathyroid cells. These receptors are cell surface G protein-coupled receptor detects changes in ionized calcium of only a few percent. Low concentration of ionized calcium stimulates secretion of PTH and high concentrations inhibit it, restoring normocalcaemia. PTH binds to cell surface receptors in target tissues, activating adenylate cyclase and phospholipase C.

In the kidneys, PTH increases distal tubular reabsorption of calcium, inhibits proximal tubular reabsorption of phosphate and increases the activity of 1α-hydroxylase enzyme in the proximal tubular cells, increasing synthesis of 1,25(OH)2D. It decreases the proximal tubular reabsorption of bicarbonate, leading to a leading to a mild hyperchloraemic acidosis in states of PTH excess. In bone,PTH receptors are present on osteoblasts, which in turn regulate osteoclast function.[10]

Vitamin D: Vitamin D plays a vital role in maintenance of normal calcium in serum. Vitamin D is synthesized in the skin by the action of ultraviolet light on 7-dehydrocholesterol to produce cholecalciferol (vitamin D3). Vitamin D is also present in a variety of foods in the form of cholecalciferol or ergocalciferol (Vitamin D2). The calciferols are virtually without biological activity unless they have been hydroxylated:

• 25-hydroxylation in the liver to form 25-hydroxyvitamin D (25(OH)D), which is the principal circulating metabolite.

• Further hydroxylation of a small proportion in the cells of the proximal renal tubules produces 1,25 (OH) 2D, the principal active metabolite of vitamin D.

The circulating 25(OH) D is metabolized in the liver into inactive metabolites and are excreted into the bile. Renal 1α hydroxylation is closely regulated. Vitamin D is increased by low phosphate in serum and 1,25 (OH) 2D concentrations, and high concentrations of PTH. 1,25(OH)2 D acts principally on the intestine, where it stimulates the synthesis of the calcium-binding protein calmodulin, which mediate calcium absorption in the intestine. It also has a negative feedback effect on the hydroxylation of 25(OH)D in the kidney. [11, 12]

Intake and absorption of calcium: Absorption is passive and active, the latter being regulated by calcitriol, and is reduced by phosphate, oxalate (found in green vegetables), and phytate (found in unrefined cereals).

Renal handling of calcium: Ten percent of calcium reabsorption occurs in the distal nephron and is subject to regulation by PTH. Volume expansion and loop diuretics decrease tubular reabsorption of calcium, whereas hypovolaemia and thiazide diuretics have the opposite effect.

Calcium and bone: There is an active exchange of calcium between bone and extracellular fluid. This can occur as a result of bone remodeling or by a process of mineral exchange between bone and the extracellular fluid,without local changes in bone matrix. The latter is important for the everyday regulation of Ca2+, but the precise mechanisms controlling this are not known.

Other hormones: Many hormones influence the metabolism of calcium and bone, including oestrogen,testosterone, glucocorticoids, growth hormone, thyroid hormones and PTH-related peptide. PTH-related peptide is a 141-amino acid peptide that shares amino terminal homology

with PTH and can bind to the PTH receptor. It is expressed widely in tissues, usually acts locally in an autocrine fashion, and appears excluded from the circulation. It mimics the actions of PTH, causing hypercalcaemia, phosphaturia and increased synthesis of 1,25(OH)2D

The calcium-sensing receptor: They act as the body's 'calciostat'. The principal ligand of calcium-sensing receptor is ionized calcium (Ca2+). Calc**i**um-sensing receptors are found on:

• Parathyroid cells

• Thyroidal C cells (where they mediate the Ca2+ regulation of calcitonin secretion)

• Renal tubule (where they directly regulate tubular reabsorption of Ca2+ and modulate vasopressin-stimulated reabsorption of water).

PATHOPHYSIOLOGY OF OSTEOPOROSIS

Progression of the bone mass loss is due to many changes in the body. Role of non healthy life style play a role as triggering factor for osteoporosis. Chronic heavy drinking in younger age > 3 units/day, increases risk significantly. Mild vitamin D insufficiency is associated with increased Parathyroid Hormone (PTH) production. PTH increases bone resorption, leading to bone loss. Tobacco smoking inhibits the activity of osteoblasts, and is an independent risk factor for osteoporosis. Smoking also results in increased breakdown of exogenous estrogen, lower body weight and earlier menopause, all of which contribute to lower bone mineral density. The three main mechanisms responsible for osteoporosis development are an inadequate peak bone mass, excessive bone resorption and inadequate formation of new bone during remodeling. Interplay of these three mechanisms leads to the development of fragile bone tissue. Hormonal factors strongly deciding the rate of bone resorption; lack of estrogen (e.g. as a result of menopause) increases bone resorption as well as decreasing the deposition of new bone that normally takes place in weight-bearing bones. The amount of estrogen needed to suppress this process is lower than that normally needed to stimulate the uterus and breast gland. The α-form of the estrogen receptor appears to be the most important in regulating bone turnover. The activation of osteoclasts is harmonized by various molecular signals, of which RANKL (Receptor Sctivator for Nuclear Factor κB Ligand) is one of best studied. This molecule is produced by osteoblasts and other cells (e.g. lymphocytes), and stimulates RANK. Osteoprotegerin (OPG) binds RANKL before it has an opportunity to bind to RANK, and hence suppresses its ability to increase bone resorption.[13, 14]

Changes during menopause:

During the accelerated period of bone loss immediately after menopause, cancellous bone loss increases 3-fold, while rates of cortical bone loss are also slower. The vertebrae are rich in

cancellous bone; vertebral fractures are relatively common in the early postmenopausal years, with hip fractures tending to occur in later years. Bone strength is related to bone mass i.e. BMD and other factors, such as remodeling frequency (bone turnover), bone size and area, bone microarchitecture and degree of mineralization.[15]

TREATMENT OF OSTEOPOROSIS

Pharmacological intervention[11]

1. Hormone replacement therapy (HRT): Estrogen, Androgens, Parathyroid Hormone (PTH), Calcitrol
2. Antiresorptive agents: Bisphosphonates- Etidronate, Alendronate and Risedronate.
3. Selective estrogen receptor modulators: Raloxifene [16,17]
4. Bone- Forming agents: Fluoride
5. Vitamin D and Analogs: Vitamin D, 1α-hydroxycholecalciferol (Vit Dmetabolite)
6. Miscellaneous: Thiazide Diuretics.

Non- Pharmacological intervention[11]

1. Hip protectors
2. Verbroplasty
3. Kyphopl

A variety of therapeutic interventions is available for the prevention of osteoporotic fractures in postmenopausal women.

Hormone replacement therapy

Hormonal replacement therapy (HRT) had in the past been widely used in the prevention and treatment of postmenopausal osteoporosis. [18] The repletion of endogenous estrogen with the above therapy effectively prevents postmenopausal bone loss and reduces the risk of fragility fractures. While the benefit of HRT on the prevention and treatment of postmenopausal osteoporosis and related fracture has been demonstrated, its effects on the health of other estrogen sensitive tissues such as the uterus and breast must be carefully considered. In many circumstances, estrogen induces proliferation of the uterine and breast tissues. In addition, postmenopausal women are at a higher risk for coronary heart disease (CHD) and breast cancer than their premenopausal counterparts, and the effects of HT may modify these risks.[18,19]

Antiresorptive agents

Bisphosphonates are very effective treatments of postmenopausal osteoporosis. They suppress bone turnover,increase bone mineral density (BMD), and maintain or improve structural and material properties of bone, thereby decreasing the risk of fractures.[15]

Selective estrogen receptor modulators (Raloxifene)

Raloxifene be used mainly in postmenopausal women with milder osteoporosis as a preventive measure or for treatment in those with predominantly spinal osteoporosis. Since the effects of raloxifene on bone mineral density and bone turnover may reverse soon after cessation, it is recommended that

raloxifene be used as long-term therapy for 5–10 years. Because of its quicker offset, use of raloxifene may have advantages over potent bisphosphonates if use of anabolic agents is contemplated in an individual patient

Vitamin D and Analogs

The basis of therapy is the correct daily intake of calcium and the use of vitamin D (or active metabolites). In case of long term treatment with corticosteroids in children, restraining the long-term use of corticosteroids to the minimum effective dose and shorter duration is essential.

Secondary osteoporosis is common among patients being evaluated for osteoporosis. All men and premenopausal women with unexplained bone loss or a history of a fragility fracture should undergo a work-up for secondary osteoporosis. Also, postmenopausal women with risk factors for secondary osteoporosis should be carefully evaluated. The evaluation should include a thorough history, physical examination, bone mineral density testing, and laboratory testing. While there is no consensus for a cost-effective laboratory evaluation, some recommendations include: 25-hydroxyvitamin D, parathyroid hormone (PTH), serum and urine calcium, phosphate, creatinine, liver function tests, a complete blood count, testosterone in men, and thyroid-stimulating hormone.[15]

QUALITY OF LIFE AND OSTEOPOROSIS

Quality of life (QOL) study is an outcome research study in which the effect of the antiosteoporotic drugs can be assessed based on scores obtained from the questionnaire; such questionnaire are the known as QOL assessment tools. Many such questionnaires are designed to assess the QOL of the osteoporosis patents. SF-36, ADL Hannover ADL scope, QUALIOST-QOL Questionnaire in Osteoporosis and QUALIFO 41- QOL Questionnaire of European Foundation of Osteoporosis are few of such QOL assessment tools.[20]

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