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OSTEOPOROSIS: A MAJOR HEALTH PROBLEM

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ABSTRACT

Osteoporosis is an age related and public health problem which is characterized by fragility of bone. It is a chronic progressive metabolic bone disease and clinically manifests skeletal fractures particularly forearm, hip and vertebrae fracture. It is responsible for substantial morbidity and mortality in postmenopausal women. It is seen all group, races, gender and age but more common in women and older people. On the basis of census of 2001 about163 million peoples are over the age of 50; by 2015 expected this figure is increases to 230 million but conservative figures say that 20 percent of women will be osteoporotic, and between 10-15 percent of men. So 25 million peoples are affected by osteoporosis in India. Multiple factors such as hormonal disbalance, environmental factor, dietary sources, menopause, genetic susceptibility and poor knowledge of bone health, these are the some reasons which lead to osteoporosis. The diagnosis of this disease firstly determined by measuring bone mineral density (BMD) using DXA (dual-energy x-ray absorptiometry). Vitamin D, Calcitonin, Estrogen hormone and inhibitors of bone resorption is required for prevention of osteoporosis. In this literature, we describe the introduction of osteoporosis, pathophysiology, risk aspects, examination of osteoporosis, and its prevalence in India.

KEYWORDS: Osteoporosis, Bone tissue, Symptoms, Diagnosis.

INTRODUCTION

Osteoporosis is a disease in which bones become weak and brittle. Bone is a living tissue, everyday bones becomes old and break down and simultaneously forms new bone regularly. The process of bone break down is known as osteoclast and the formation of new bone is called osteoblast. Both the process are coordinate and work together, this complete cycle known as bone remodeling cycle. If any changes in both phases then people suffer from osteoporosis. It is the most important process of bone structure in our body but after the age of 30 years, the reduction of bone mass is an inevitable process. If changes in remodeling cycle, bone become weak cause minor bumps and increased risk of fracture (1). It can be characterized as silent epidemic because in this problem persons do not feel bone weak. It is widespread throughout the world, and the number of patients is continued increasing. It slowly develops over several years and is often diagnosed only when the bone becomes fragile and suddenly causes a fracture (2-3). The Major cause of osteoporosis is morbidity in the elderly population (4). Nearly 10 % of world population suffers from osteoporosis in which approximately 30% are postmenopausal women (2-3).

Different kinds of factors that involved in osteoporosis such as age, treatment, dietary source, menopause, lifestyle and various genetic factors (5). Osteoporosis is a chronic bone disease that is very critical social and medical problem in developed countries (6). According to WHO normal T score of bone mineral density is -1 or higher, in osteopenia -1 to -2.5, in osteoporosis -2.5 or lower. So in osteoporosis bone density is too low to bone become fragile and then breaks. It is measured by a validated technique known as dual-energy x-ray absorptiometry (DXA) (7-8). A low BMD is the major possibility of fracture and BMD test is the best tool for diagnosing osteoporosis (9).

Pathophysiology

Bone tissue: Bone tissue is a hard connective tissue and it is composed of different type of bone cells. It has a honeycomb-like matrix which gives rigidity to bone. This matrix contain inorganic as well as organic component such as salts and collagen. Trabecular (cancellous) and cortical (cortical) are the two characteristic of bone. Trabecular is metabolically active, reason for bone resorption and formation of new bone. It has more surface area which covered the bone cell and found on long bone such as femur. Cortical bone is highly mineralized tissue, found on

peripheral bone region and connect two end of joint. eg- knee joint, hip joint etc.

Bone Cell: Bone is made up of different types of cell – Bone lining cells, Osteoclast, Osteoblast, hematopoietic stem cells, and mesenchymal stem cells.

Bone lining cell: Long slender bone lining cell found on the surface of the bone. When osteoblast can not convert into osteocyte it undergoes into apoptosis or differentiated into bone lining cell so bone lining cell are a major source of pre-osteoblasts (10-12). It also provides sufficient signal to stem cells to hold in an undifferentiated state therefore bone lining cell act as an anchors for hematopoietic stem cells (13). It promotes hematopoietic stem cells in orthoclastic process therefore it plays a key role in bone remodelling (13-13).

Osteoclast: Osteoclast is a special type of cell that originate from monocyte/macrophage hematopoietic lineage after that create and adhere to the bone matrix, it secretes the acid and lytic enzymes that kill it in a specific, extracellular alcove (14). The differentiation of osteoclast precursor cells is critically dependent on the existence of NF- κB ligand-receptor activator. NF-κB ligand-receptor activator is a member of the TNF family and expressed on osteoclast by bone-forming osteoblasts. T and B lymphocytes are activated by Receptor activator of nuclear factor κ B (RANK). RANK stimulates Receptor activator of nuclear factor kappa-B ligand (RANKL) which involves proliferation and activation of osteoclast that enhanced bone resorption (15). Osteoprotegerin (OPG) is a inveigle receptor of RANKL and prevents bone resorption (16). In early menopause or in estrogen deficiency, high level of RANKL induced bone resorption and cause rapid bone loss (17).

Osteoblast: It is a bone-forming cell, obtained from mesenchymal stem cells. The mature osteoblast secretes matrix which provides minerals to the bone. The amount of bone synthesis is determined by life span of osteoblast. These procedures are induced by vitamin D and intermittent parathyroid hormone (PTH) pulses. In bone resorption on the site of lacunae osteoblast produces non-collagenous proteins such as osteonectin, osteopontin, and osteocalcin and extracellular matrix contain type I collagen. Vitamin D, calcium, and phosphate helping in matrix mineralization. Finally, osteoblast is died by the process of apoptosis and embedded as osteocytes in the bone matrix. On the presence of PTH the calcium-sensing receptor (CaSR) has maintain serum calcium that level within a limited physiological range (18). Still it is not fully understood that CaSR is express or not in osteoblasts or osteoclasts but its effect on osteoporosis drug have been seen (19).

Osteocyte: Osteocytes is found in mineralized matrix. It is morphological similar to neural cells and formed by differentiated osteoblasts. It forms a sensory network by dendric processes and communicates in mechanical stress. Osteocytes secrete sclerostin that inhibits the Wnt signaling pathway and reduced osteoblast differentiation (20). Osteocyte also produces some factors which control phosphate which have a key function in bone mineralization.

Mesenchymal and Hematopoietic stem cell: Bone marrow contains a special type of cell known as Mesenchymal stem cell. It is involved in repairing and remodeling of bone (21-23). Mesenchymal stem cell has the ability to act as feeder layers for the growth of hematopoietic stem cells (21-23) and give rise different type of cell such as osteoblasts, myocytes, adipocytes, chondrocytes (24). According recent studies said transplantation is the best treatment of osteoporosis due to high osteogenic differentiation capacity of mesenchymal cell which performs bone repair and regeneration. The hematopoietic stem cell produces IL-17 that induces osteoclast differentiation (25-26). It also produces RANKL that contributes to bone resorption and bone remodelling (27). If hematopoietic stem cell increases it may cause osteoporosis and many other bone diseases (25).

Bone Remodeling: Bone remodeling is a procedure in which changes in bone structure and micro damages are repaired. At the cellular level, the bone cells communicate and linked with each other. In bone remodeling process, bone-resorbing osteoclasts remove minerals and digest old bone, and bone-forming osteoblasts mineralize and form new bone, both are arranged in temporary anatomical conformation are called "Basic Multicellular Units" (BMUs). BMUs are a canopy of a cell to make a compartment for bone remodelling (28). Its canopy compartment facilitates osteoclast for resorption and osteoblast for bone formation and provides marginal changes in bone volume in remodelling (29).

After the activation of BMU, start the bone resorption process. Reversal cells follow the osteoclast and cover the newly bone surface. It initiates the deposition of replace bone and then osteoblasts occupy the end portion of BMU and secret unmineralize bone matrix called osteoid. Osteoid become mineralized and developed new bone tissue. The bone remodeling is a sequential process which described below:

Before the activation phase, the bone lining cells are covered by bone surface and preosteoblasts, intercalated with osteomas. B cell produces OPG that suppress osteoclast process and after that activation phase is start.

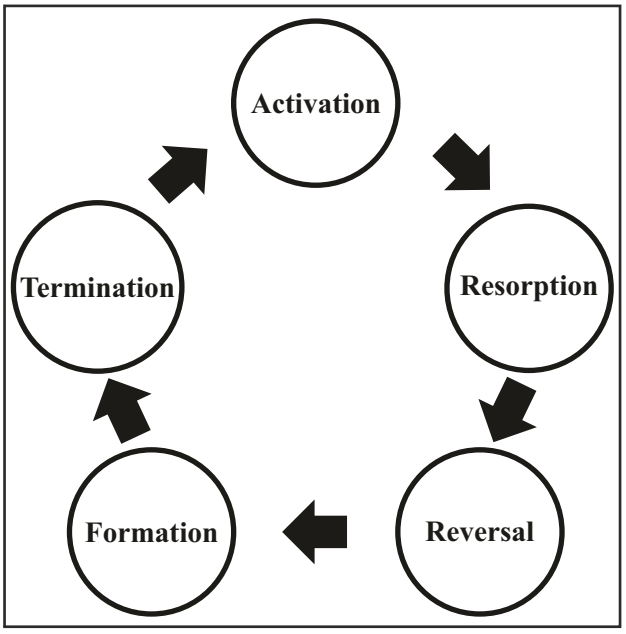

Fig 1: Sequential Process of Bone Remodeling

Activation phase: In this phase firstly, the bone cell detect the initial signal for remodeling. These signals can lead to different forms such as direct mechanical bone stress, leads to structural distruction or hormonal activity (e.g. estrogen or PTH) on bone cells which reaction changes of homeostasis. In basal condition osteocyte secretes transforming growth factor β (TGF-β), which inhibit bone resorption process or osteoclastogenesis but on the other hand mechanical strain is going on in osteocyte and convert the physical energy change in the form of biological signals that start bone remodeling, osteocyte apoptosis, bone matrix or limb immobilization damage and then results increase in osteoclastogenesis (30-32).

On the other hand, Parathyroid glands secretes PTH (parathyroid hormone), it generate endocrine remodeling stimulus to maintain serum calcium homeostasis. G-protein-coupled receptor is a seven-transmembrane protein which is present on osteoblast and activated by PTH (33). PTH and G-protein-coupled receptor activate protein kinase A, protein kinase C, and calcium intracellular signaling pathways (34). These pathways induce osteoclast differentiation, stimulation and enhance bone resorption.

Resorption Phase: PTH plays a key role in enrollment of osteoclast precursors and modulation of osteoblast expression of the main osteoclastogenesis cytokines, CSF-1, RANKL, and OPG (35). If CSF-1 and RANKL production increase it take part in promote osteoclast promotion. It also increases proliferation and survival of osteoclast precursors that directly induce bone resorption. It reduce expression of OPG which does not inhibit osteoclast process (35-36). RANKL is coordinating with osteoclast precursors to promote resorption activity (37). Unmineralized osteoid are degrade by Matrix metalloproteinases (MMPs). RGD adhesion sites are found within the mineralized bone which promote osteoclast attachment and involve bone resorption (38).

Reversal Phase: After the resorption phase, the undigested demineralize collagen matrix covered Howship lacunae (39). A mononuclear cell removes remnants of collagen, produce of osteoblast-mediated bone and prepare bone surface. Based on the functional perspective, osteomacs and mesenchymal bone-lining cells both perform together and promote reversal cells. Osteomacs remove matrix debris (40) and mesenchymal bone-lining cells accumulate the collagenous matrix that produce osteopontin lines inside Howship lacunae (39) so the reversal cells produce signals which are responsible for bone formation from bone resorption within BMU.

Formation Phase: In the bone matrix coupling molecule is stored and correlates this transition but the formation of bone on the location of bone resorption always controversial. On the site of bone resorption, TGF-β, Insulin-like growth factors I and II and every other factors produce signal for the recruitment of mesenchymal stem cells (41). Other studies say osteoclasts produced coupling factor(s) (42). Mechanisms of Some factors are described here-Sphingosine 1-phosphate released by osteoclasts induces recruitment of osteoblast precursors and facilitates mature osteoblast survival (42-43). EphB4 receptors are exhibit on osteoblasts, it induces osteogenic differentiation through forwarding signals albeit osteoclasts express the ligand ephrin-B2. By preventing osteoclastogenic c-Fos/NFATc1 cascade, ephrin-B2 into osteoclast precursors inhibits bone resorption through reverse signalling (44). This signaling complex produce a special opportunity for bone remodeling by activating bone synthesis and inhibit bone resorption simultaneously. PTH can produce bone production signals through osteocytes. In resting phase osteocytes exhibit sclerostin (45) which bind low-density lipoprotein receptor-related protein-5/6, preventing Wnt signaling (46) and enhance bone formation process.

Termination Phase: After the replacement in same amount of resorbed bone the bone remodelling cycle has been terminates. The termination signal(s) tell the remodeling machine has been stop by termination signal(s) while the function of osteocytes is emerging. The initiation of osteoblast bone formation is likely to return towards the termination of remodeling cycle, it

is possible when the expression of sclerostin is loss. The mature osteoblast undergoes apoptosis, Switch to bone-lined appearance or become trapped in mineralized matrix and converts in osteocytes. Finally, bone surface environment is renewed and control for the adjacent bone remodeling cycle.

Prevalence of osteoporosis in India: Osteoporosis is an unexpressed metabolic bone disorder that is widespread in India that accelerates to loss of bone mass. This fracture is more common in Indian adult men and women. According to the studies revealed that the incidence of osteoporosis is greater in women than men in India. In India estimate that approx 230 million people predicted to be above the 50 years of age in 2015.According to the reports approxmitely 20% women are osteoporotic (47). Osteoporosis is most common manifestation in vertebra, hip and lumbar spine fracture (48). Delhi Vertebral Osteoporosis Study (DeVOS) reported that the prevalence of 17.1% of vertebral fractures out of 415 females subjects (age >50 years) are enlisted in the research (48). 159/100,000 rates of hip fracture in women above 50 years of age is reported in North India at the district of Rohtak (49). The incidence of 34.3/100,000 has been reported for hip, spine, and wrist because of low injury fractures (50).

Types of osteoporosis:

Primary osteoporosis: The primary osteoporosis is origin with aging and accelerates after menopause. The primary osteoporosis is two types:

Primary Type 1 osteoporosis: Estrogen is a sex hormone but recently seen that the hormone regulates and promotes osteoclast activity and osteoblast activity which responsible for bone health. At age about 45 to 55 menstrual cycle stop and production of estrogen become low then the women suffer from Type 1 osteoporosis. Men also suffer from this type of osteoporosis when testosterone slows down at age about 45 to 50 but it is more common in postmenopausal women . So this osteoporosis is called postmenopausal Osteoporosis.

Primary Type 2 osteoporosis: A long term of calcium deficiency cause primary type 2 osteoporosis, also called senile osteoporosis. Mostly senile osteoporosis is seen in both men and women nearly 70 years of age. Calcium and Vitamin D level are low from the body of elderly people, the rate of bone turnover become low, result hip fracture so it is called Low turnover osteoporosis.

Secondary osteoporosis: Prevalence of secondary osteoporosis is severe in men than women (Up to 30% of women and 50% to 80% of men). It can be occur at any age of men and women. The risk factor of secondary osteoporosis is current dietary, Lifestyle, Vitamin D deficiency, hormonal level, and medicals treatment. Steroid is a major group of drug and mostly use in the form of glucocorticoid or glucocorticosteroid which is used in inflammatory, autoimmune diseases and many other diseases like asthma, heart disease, allergic, bone disease. Excess use of Glucocorticosteroid inhibit bone formation become the major reason of osteoporosis. Secondary osteoporosis developed due to the frequent use of medicine and enhances the risk of fracture in spine and hip.

Idiopathic osteoporosis: If osteoporosis occurs in children or young adults, osteoporosis is considered as idiopathic osteoporosis. It is uncommon disease and no such factor induces it because children's have sufficient amount vitamin and hormone levels. So no explanation of weak bones that's why it is a rare type of osteoporosis.

Causes: Bones are alive and constantly growing throughout our life. Some bone cells are dissolve and new bone cells are formed this process is known as bone remodeling but if any changes in bone dissolving and bone developing process people suffer from osteoporosis. Some factors are given below:

- **Age:** Age reduces the bone mass so with growing age of people has developed osteoporosis. Especially in older age loss of calcium and other minerals effect in the bone to become fragile, loss of bone density and results are likely broken bone.
- **Family history:** In some research studies found genetic factors determining how bones are strong and weak. So genes are transfer from generation to generation, if your parents or sibling suffer from osteoporosis then you could be at greater risk.
- **Use of certain medicine for Long-time and high doses:** Long time medication is responsible for osteoporosis. Certain medicine - Glucosteroid is commonly used in various diseases like autoimmune diseases, inflammatory diseases, some immunosuppressant agents, anticoagulants, some anticancer, if these medicine used for long-duration it can impact on bone strength.
- **Heavy drinking and smoking:** The chemical found in cigarettes make it more difficult to use calcium in the body and impact of hormone level. Excess drinking of alcohol can lower your calcium supply and increase the risk of osteoporosis.
- **Long period of inactivity and lack of exercise:**

Moving body maintain the amount of mineral and thickness of bone. When person exercise (walking, going up, housework, weight-bearing exercise) muscles pull against the bone which causes minerals deposit in the bones and bones become strong. Thus the loss of activity and lack of exercise are the major reason of osteoporosis.

- **Hormonal level in the body:** Hormone balancing the activity of body but many hormones can affect the process of bone turnover. Changing of hormonal level produce many bone diseases like osteoporosis in the body most likely of estrogen and testosterone. At age of 45 females become menopause because low level of estrogen and at elderly age in men lack of testosterone hormone, so in research studies found lack of sex hormone responsible for osteoporosis. Many other hormones like parathyroid hormone maintain calcium level stimulates resorption and formation of bone, calcitriol stimulates absorb the calcium in the intestine, calcitonin can inactivate osteoclast and promote bone formation so imbalance hormone level causes osteoporosis in people.
- **Current dietary:** Current dietary can also affect your bones. People who eat salty food, caffeine, soft drink, fast food and food item which deficient calcium and vitamin D then most likely to suffer osteoporosis.

Symptoms: In early stages, no symptoms are seen in the loss of bone mass but after a long time some signs are seen like back pain caused by collapsed vertebra, loss of height, wrist, hip, back or other bone fractured easily are seen in osteoporosis.

Osteoporosis in men and women: Due to increasing age both men and women bone density becomes low which cause bone fragile and people suffer from osteoporosis. According to the study 9·1 million women and 2·8 million men are suffering from osteoporosis in India.

Diagnosis of Osteoporosis: The diagnosis criteria of osteoporosis is depend on BMD (bone mineral density) established by WHO. The BMD elucidate by T score in terms of SDs number. This varies to the value of mean peak in adult healthy people of similar sex (51). According to WHO criteria, the mean below to -2.5 SDs it is a condition for diagnosis of osteoporosis in young adult women (52). If the T-score more than -1.0 SDs but less than -2.5 SDs is the condition of osteopenia (52). The osteoporosis is diagnosis by central dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) which is depend on Bone Mineral Density. This is a non-invasive procedure that generates precise outcomes.

Methods of Evaluation:

Patient's Profile and physical examination: For correct diagnosis of osteoporosis history and physical examination of patient are essential because low BMD are also found in hyperparathyroidism, osteomalacia and other metabolic bone diseases so patient history (previously medication, family, lifestyle, diet) are major factors that involved in the risk of fracture (53). Usually, no specific symptoms are seen but on the basis of a physical diagnosis may identify kyphosis, a extend abdomen, loss of height and weak vision activity, which is a risk aspect of collapsing (54). Low BMD, hepatic enlargement, jaundice also may be indicative of osteoporosis (53, 55).

Evaluation of BMD by DXA and QCT: BMD is the best tool for the detection of osteoporosis. Several methods are used to evaluate BMD such as DXA and QCT but on the basis of WHO guidelines osteoporosis is diagnosed by DXA.

DXA: Dual-energy X-ray absorptiometry is a usual procedure used to evaluating bone minerals content at any site of the body in which the central part is the lumbar spine, peripheral part and proximal femur as well as forearm (51, 56-57). In this method, different energies of two beams pass from the position of patient body (58). In DXA BMD is record as a T-score. This test is less effective in estimating the likelihood of proximal fracture than the hip and spinal fractures. Low BMD acquired by peripheral technique which is not appropriate for examination or treatment but it is important for further analysis. Under treatment condition the sites of peripheral sites are slightly less than the sites of central to display arise in BMD (58).

QCT: Quantitative computed tomography is applied to evaluate the BMD of lumbar spine and the site of peripheral. QCT has more accuracy and efficacy to predict the spine fracture is comparison to DXA but 3 dimensional, true volumetric and areal BMD is obtain by DXA. It is very sensitive to identify the changes of skeletal with time and can be implementing to monitor the disorder. So this technique is used to determine BMD and diagnose osteoporosis (51).

CONCLUSION

Osteoporosis is a common worldwide public health problem which induces the fractures over 8.9 million in every year (59). Extension of mortality rate, reduce life quality and permanent disability is the result of these fracture. In adolescence, generating an environment to attain the peak of bone mass can improve bone health and prevent the loss of bone at older age in men and in postmenopausal women. By analysis and effective treatment of osteoporosis also

can reduce the fractures. Still persist lots of research in the diagnosis of osteoporosis. So this review will give us better understanding of pathogenesis of osteoporosis. It will improve the knowledge of development of osteoporosis which helps in therapeutic approach.

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