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OSTEOPOROSIS – AN OVERVIEW

V. Ashajyothi*, Dr. Rao. S. Pippalla and Dr. D. Satyavati
Vignan Institute of Pharmaceutical Sciences, Department of Pharmacology,
Deshmukhi, Nalgonda, Andhra Pradesh, India.
Email: *ashajyothivadlapudi@gmail.com*

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Abstract:

Osteoporosis is fragility of the bone due to low bone mineral density (BMD) which alters the quality of life (QOL) in patents. 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.

Key words: Osteoporosis, Remodeling, DEXA, Pathophysiology and Treatment.

Introduction:

Osteoporosis is a skeletal disease characterized by the low bone mass and microarchitechtural deterioration with a resulting increase in bone fragility and hence suceptability to fracture.[1] Osteoporosis has recently earned great emphasis in modern society and medicine as it is a “silent disease” it has no symptoms and its occurrence can only be known by an incidence of a fracture. The age groups above 70yr are most susceptible for the osteoporotic fractures, especially women after the menopause the main reason being the lack of estrogen after menopause. Osteoporosis is generally described as primary and secondary osteoporosis. Primary osteoporosis is due to estrogen

loss and aging while secondary osteoporosis is due to the systemic illness or medications such as glucocorticoids or phenytoin.

History:

In 1948, Albright and Reifenstein concluded that primary osteoporosis was composed of two separate entites: 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: Type I osteoporosis, loss of trabecular bone due to estrogen lack in menopause and Type II osteoporosis, loss of cortical and trabecular bone in men and women due to long term remodeling inefficiency, dietary inadequacy and activation of parathyroid axis with age.[2]

Incidence[9]:

- Osteoporosis causes over 1.5 million fractures each year in the USA.
- Osteoporosis causes over 300,000 hip fractures each year in the USA.
- Osteoporosis causes over 700,000 vertebral fractures each year in the USA.
- Osteoporosis causes over 250,000 wrist fractures each year in the USA.
- Osteoporosis accounts for 70% of all fractures for people over 45 in the US.

Diagnosis:

Dual energy X-ray absorptiometry (DXA, formerly DEXA) is considered the gold standard 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: [14, 11]

- 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

Factors leading to Osteoporosis and prevention of Osteoporosis:

Age: Age group above 45yr 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.[3]

Diet and lifestyle: smoking, alcohol, imbalanced diet leads to osteoporosis. Balanced diet consumption rich in Calcium and Vitamin D avoiding smoking and alcohol will help prevention osteoporosis.[4]

Malnutrition: Malnutrition leads to osteoporosis as optimal intake of calcium and Vitamin D are important to attain peak BMD.[3]

Exercise: Regular exercise including weight-bearing and strength training exercises helps prevention of osteoporosis.[4] while excess of physical activity will also lead to 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.

Hormonal disorders:

Menopause (lack of estrogen): Estrogen has great role to play on calcium homeostasis, this is the main reason for occurrence of osteoporosis after the menopause. Reason for increase in bone resorption is an increase in oxidative stress, in this condition as estrogen is a potent antioxidant.

Hypogonadal state: This is a state in which the levels of gonadal hormones are decreased; hormones include Androgens and testosterone in men which cause an increase in oxidative stress.

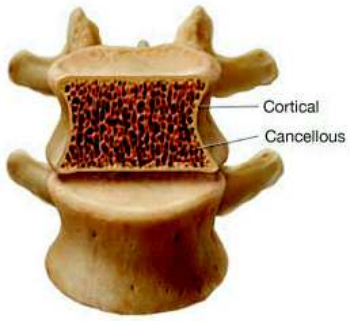
Hyperparathyroidism: This is a state of over production of parathyroid hormone is present which has a negative effect on the BMD.

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 divided into cancellous bone (also referred to as trabecular bone) and cortical bone. Cortical bone is the compact shell of the bone and cancellous bone is the inner delicate part, which is

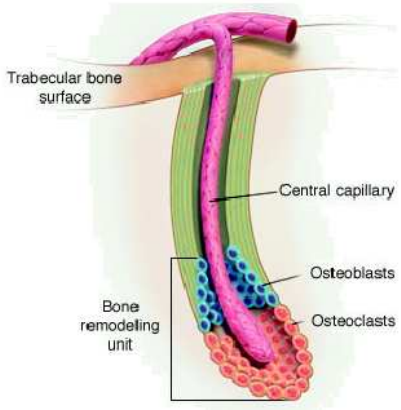
formed by an interconnective latticework of trabeculae. The peripheral skeleton is composed primarily of cortical bone, while the axial skeleton is composed of both cancellous and cortical bone. Surface area of cancellous bone is much greater than that of cortical bone, and is more metabolically active, cancellous bone is more severely affected if bone remodeling occurs during menopause.

Figure-1: Cortical and cancellous bone in vertebra.



After linear growth ceases, 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

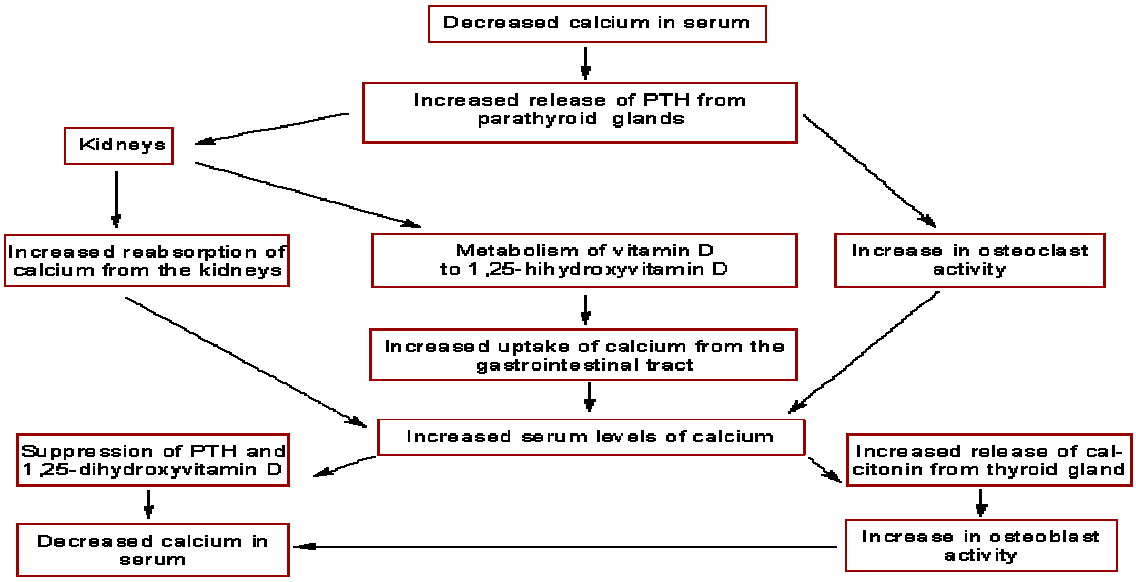


At the cellular level, remodeling can be conceptualized as consisting of approximately 1 million bone remodeling units. These remodeling units are approximately 1-2 mm long and 0.2-0.4 mm wide, and are comprised of a population of osteoclastic cells in front and a group of osteoblastic cells in the rear. 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 process of 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.[6]

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.[7]

Figure-3: Regulation of calcium in the body.



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 mild hyperchloraemic acidosis in states of PTH excess. In bone, PTH receptors are present on osteoblasts, which in turn regulate osteoclast function.[7]

Vitamin D: Vitamin D plays a role in maintenance 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 D_2). 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. [7]

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).[7]

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.[7]

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.[7]

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.[7]

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

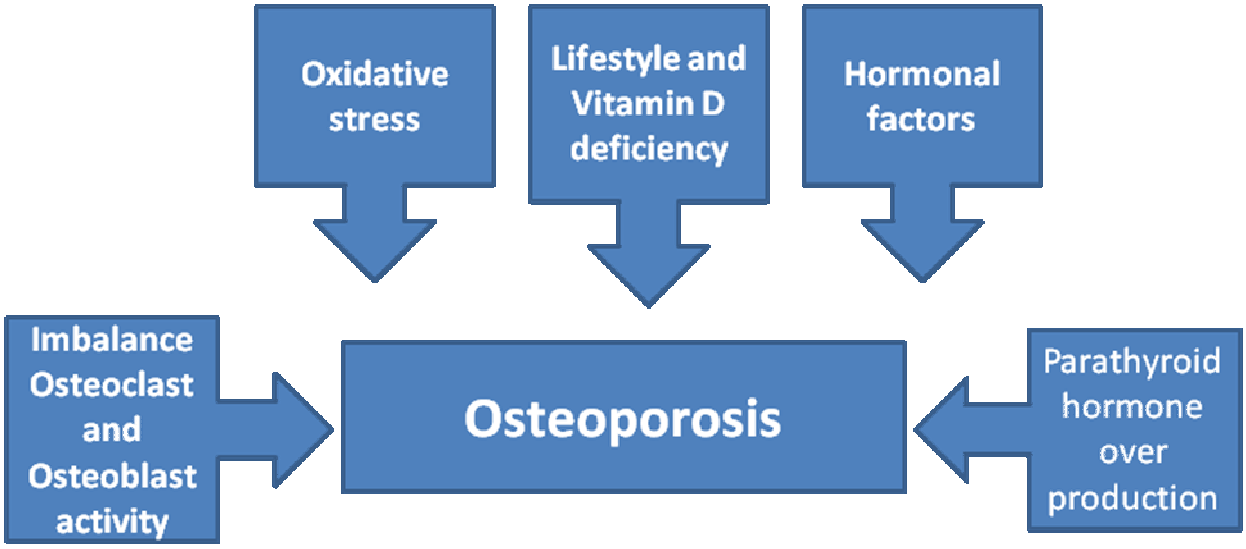
• Parathyroid cells

• 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).[7]

Pathophysiology of Osteoporosis: Progression of the bone mass loss is as aresult of various changes in the body as described in the figure 4.

Figure-4: Pathophysiology of osteoporosis.



Role of non healthy life style play a role as triggering factor for osteoporosis. Chronic heavy drinking (alcohol intake greater than 3 units/day). [10] especially at a younger age, increases risk significantly. Mild vitamin D insufficiency is associated with increased Parathyroid Hormone (PTH) production.[11] PTH increases bone resorption, leading to bone loss. Tobacco smoking inhibits the activity of osteoblasts, and is an independent risk factor for osteoporosis.[10,14] Smoking also results in increased breakdown of exogenous estrogen, lower body weight and earlier menopause, all of which contribute to lower bone mineral density.[11]

A positive association exists between serum 1,25-dihydroxycholecalciferol levels and bone mineral density, while PTH is negatively associated with bone mineral density.[11] The three main mechanisms by which osteoporosis develops are an inadequate *peak bone mass* (the skeleton develops insufficient mass and strength during growth), excessive bone resorption and inadequate formation of new bone during remodeling. Interplay of these three mechanisms underlies the development of fragile bone tissue.[12] Hormonal factors strongly determine 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. [12] In addition to estrogen, calcium metabolism plays a significant role in bone turnover, and deficiency of calcium and vitamin D leads to impaired bone deposition; in addition, the parathyroid glands react to low calcium levels by secreting parathyroid hormone (parathormone, PTH), which increases bone resorption to ensure sufficient calcium in the blood. The role of calcitonin, a hormone generated by the thyroid that increases bone deposition, is less clear and probably not as significant as that of PTH. [12]

The activation of osteoclasts is regulated by various molecular signals, of which RANKL (receptor activator 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 (receptor activator of nuclear factor κB). Osteoprotegerin (OPG) binds RANKL before it has an opportunity to bind to RANK, and hence suppresses its ability to increase bone resorption. RANKL, RANK and OPG are closely related to tumor necrosis factor and its receptors. The role of the *wnt* signalling pathway is recognized but less well understood. Local production of eicosanoids and interleukins is thought to participate in the regulation of bone turnover, and excess or reduced production of these mediators may underlie the development of osteoporosis. [12]

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 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.[6] figures 5 and 6 describes the menopausal and aging osteoporosis mechanisms.

Figure-5:

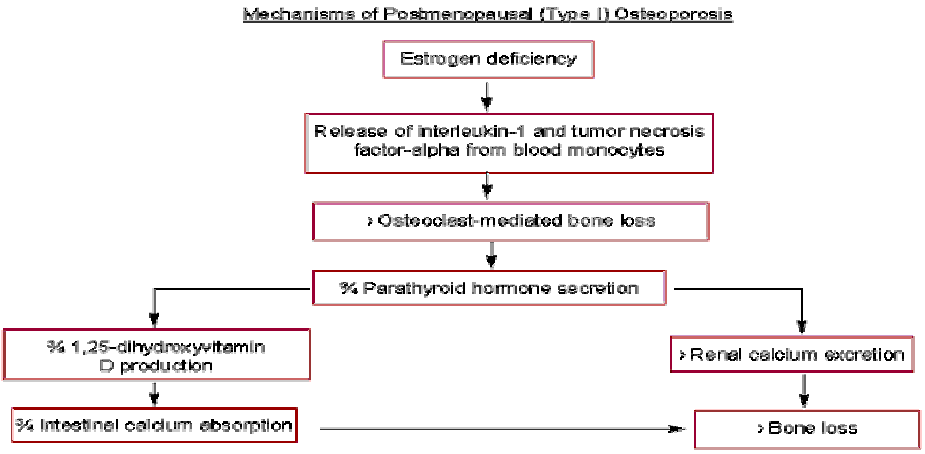
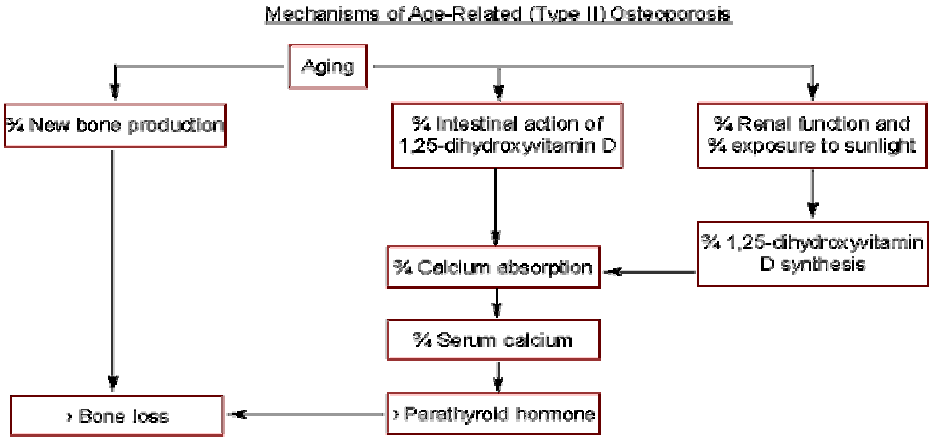


Figure-6:



Treatment of osteoporosis:

Pharmacological intervention:

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

Non- Pharmacological intervention:

1. Hip protectors
2. Verbroplasty
3. Kyphoplasty

Table I Mechanism of Action of Antiosteoporotic drugs[8]

S.No	Category	Drug	Mechanism of Action	Dose
1	HRT	Estrogen (17-β estradiol)	Acts on osteoblasts⇩production of IL-6 and upregulate osteoprotegeun, osteoclast precursor⇩	
		Testosterone	⇧ BMD in hypogonadial men	
		Androgen (Nandrolone decanoate)	⇧ BMD in women	50mg Injection thrice weekly
		PTH ⇧	Axial bone mineral. No⇧effect on cortical bone, with estrogens or sysnthetic androgens axial mineral without cortical bone. PTH also is effective on seconday osteoporosis	

		Calcitrol	A powerful inhibitor of osteoclast resorption Suppresses parathyroid function High doses ⇧BMD	Nasal spray 200 Units/ Day
		Progestrin (Norethisterone acetate)	Act synergistically with estrogen and ⇧BMD	
2	ANTIRESORPTIVE AGENTS	Alendronate (Fosamax)	⇧BMD (both in men and women) ⇩vertebral fracture riskused both for prevention and treatment	Prevention-5mg/ day Treatment-10mg/ Day
		Risedronate (Actonel)	⇧ BMD and⇩vertebral fracture risk.	
3	SERM'S	Raloxifene	Estrogen agonist with no effect on uterus antiestrogen on breast.	5mg/ Day
4	VITAMIN D		⇧ Intestinal absorption of Ca+2 and BMD ⇩Bone remodeling	
5	BONE FORMING AGENTS	Fluoride	Some fluorides⇧bone volume due to⇧in osteoblastic activity. Fracture rick is⇩at dose	75mg/Day 30-50mg/Day
6	MISCELLANEOUS	Thiazide Diuretics	⇩ Urinary Ca+2 excretion in hypercalciurea ⇩Bone loss	25mg once or twice daily
		Calcium	Dietray suppliment	500-600mg

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]

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 are contemplated in an individual patient.[16]

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. In severe cases, particularly in the presence of fractures, bisphosphonates can be remarkably effective. In some cases, such as idiopathic juvenile osteoporosis, the rule is spontaneous resolution, and the advisability of an aggressive drug therapy is discussed.[17]

Many women seek advice about bone health at the time of the menopause. A variety of therapeutic interventions is available for the prevention of osteoporotic fractures in postmenopausal women. Hormone replacement therapy (HRT) is a second-line option in most, although it has a place in the management of perimenopausal women with menopausal symptoms who are at risk from fracture and in other postmenopausal women who express a preference for HRT over other options, after being fully informed about known risks and benefits.[18]

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.[19]

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.

References:

1. S. R. Cummings, L.T.Melton. Lancet, 2002, 359, pp 1761-67.
2. A.G.Gillman, J.G.Hardman, L.E. Limbird, The Pharmacology Basis of Therapeutics, 10th Edition, Mc Graw Hill, 2001, pp1736- 39.
3. D. Crosbie D.M. Reid, Surgery, 2006, 24:11, 386-387.
4. www.osteoporosis.org.au.osteoporosisaustralia- Medication and treatment of osteoporosis, pp 1-4.
5. http://www.wrongdiagnosis.com/o/osteoporosis/stats.htm
6. http://stg.centrax.com/ama/osteo/part4/module03/pdf/osteo_mgmt_03.pdf, American medical association, 2004.
7. J.Horner, Surgery, 24:6, pp 215-219.
8. A.G.Gillman, J.G.Hardman, L.E. Limbird, The Pharmacology Basis of Therapeutics, 10th Edition, Mc Graw Hill, 2001, pp1737- 39.
9. American medical association, Report 2004.
10. Poole KE, Compston JE (December 2006). *BMJ* **333** (7581): 1251–6.
11. WHO Scientific Group on the Prevention and Management of Osteoporosis (2000 : Geneva, Switzerland) (2003).
12. Raisz L (2005). *J Clin Invest* **115** (12): 3318–25.
13. Wong PK, Christie JJ, Wark JD (2007). *Clin. Sci.* **113** (5): 233–41.
14. WHO (1994). "Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group". *World Health Organization technical report series* **843**: 1–129.
15. S.E. Papapoulos, Best Practice & Research Clinical Rheumatology, 2005, Vol. 19, No. 6, pp. 965–973.
16. P. Sambrook, Best Practice & Research Clinical Rheumatology, 2005, Vol. 19, No. 6, pp. 975–981.
17. M. L. Bianchi, Best Practice & Research Clinical Rheumatology, 2005, Vol. 19, No. 6, pp. 991–1005.

18. J. Compston Best Practice & Research Clinical Rheumatology, 2005,Vol. 19, No. 6, pp. 1007–1019.

19. Nancy E. Lane* Best Practice & Research Clinical Rheumatology, 2005, Vol. 19, No. 6, pp. 1021–1037.

Corresponding Auhtor*:

V. Ashajyothi*
Email: *ashajyothivadlapudi@gmail.com*