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Osteoporosis: Pathogenesis, Treatment and Opportunities

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Abstract: ***The term "Osteoporosis" is a combination of two words 'osteo' and 'porosis' which means bone and porous respectively, so osteoporosis literally means porous bone. It makes the bone more fragile and easily susceptible to fracture. It may be due to an abnormal increase in bone loss, which results in the loss of normal bone strength. Bone loss increases in women after menopause, due to lower levels of estrogen. On the other hand, men also undergo gradual bone loss with aging, which results into fragile bones. The root cause is the reduction of free testosterone. Osteoporosis may also occur due to a number of diseases (cancer, diabetes), medication (steroids) or treatment. The porosity in this disease may weaken the bone to such a degree, a break may occur with minor stress (fall) and spontaneously. It leads to various types of fractures i.e., vertebral, nonvertebral and hip fractures. In fact, a fracture is typically the first outward sign of the disease, and advanced osteoporosis is potentially very painful and disabling. There is imbalance between the bone cells i.e., osteoclasts and osteoblasts, which effect the bone remodeling process, which plays a major contribution in the development of osteoporosis. The number of women with osteoporosis is increasing in India. Thus, osteoporosis is a major public health problem in Indian women. Different types of drugs are available in the market, but calcium, estrogen, vitamin D and bisphosphonates are the first-line drugs for the treatment of osteoporosis. Some drugs are antiresorptive i.e., bisphosphosphonates, while the others are osteoanabolic by nature i.e., teriparatide. In order to treat vertebral compression fractures (spine fracture), a surgical treatment (noninvasive) is carried out, which is known as vertebroplasty and kyphoplasty.***

Keywords: Osteoporosis, Osteoblasts, Osteoclasts, Bone remodeling, Bisphosphonates

1. Introduction

Osteoporosis is the most common metabolic and systemic disease of bone that affects the entire skeleton, which leads to an increased level of bone fragility and susceptibility to fracture. It is characterized by micro-artectural deterioration of the skeleton and a condition of low bone mass [1, 2]. Osteoporosis or porous bone condition is a silent disease which has no symptoms until a fracture occurs. The World Health Organization (WHO) has defined "Osteoporosis as a condition in which a bone mineral density (BMD) is more than 2.5 standard deviations below the mean of normal, healthy individuals at their peak bone mass" [3]. This term 'osteoporosis' was used by **Jean Lobstein** (French pathologist and surgeon) first time in 1835[4]. There are various types of osteoporosis. These are:

Primary osteoporosis: It is divided into type I (postmenopausal) & type II (senile) osteoporosis [5].

Secondary osteoporosis: It includes age-independent factors i.e, glucocorticoid-induced osteoporosis, moderate or heavy alcohol intake and cigarette smoking.

Idiopathic osteoporosis: It includes dietary factors, diseases, sedentary lifestyle, pregnancy-related and post-partum osteoporosis [6].

About 200 million people suffer from osteoporosis worldwide. Out of them, one-tenth are women of age 60 years, one-fifth of age 70 years, two-fifth of age 80 years and two-third of age 90 years. Moreover, in India, 1 out of every 3 females and 1 out of every 8 males, suffer from osteoporosis. This disease is also among the most common diseases in the United States, and can result in devastating physical, psychological and economic consequences. In Europe, the disability due to osteoporosis is much greater than that caused by cancer (with the exception of lung cancer) and is comparable or greater than a variety of chronic non-communicable diseases, such as rheumatoid arthritis, asthma and cardiovascular diseases [7]. Different types of drugs are used in its treatment like bisphosphonates, strontium ranelate, teriparatide and denosumab.

Bone Cells (Osteoclasts and Osteoblasts):

Bones are living, active tissues that renew themselves via a process called **remodeling**. This remodeling process is initiated by the '**osteoclasts**' which removes the old cells from the bone tissue, deposit them in the bloodstream for their removal and also create small holes in the bone. The cells '**osteoblasts'** fill the holes with the "mortar" of calcium, minerals and collagen. There is an important role of the parathyroid hormone (PTH), as it activates the osteoclasts and osteoblasts and signals the osteoclasts to pull calcium from the bones. The osteoblast cells are stimulated by the calcitonin hormones and deposit calcium into the bones. The osteoblast cells must be able to do their

job effectively. Because the exhausted osteoblasts are one of the primary reasons for bone loss [8,9].

There are specific sites on the bone surface, where bone undergoes the remodeling process and these sites are known as basic multicellular units (BMU). As it is known to us, the remodeling process is carried out by the osteoclasts (bone resorption cells) and osteoblasts (bone forming cells). Moreover, this process is highly dependent on the delicate balance of the regulatory signalling and the cellular activity. If there is loss of capacity to deactivate osteoclasts or to recruit the active osteoblasts, it results in a net bone loss and to the onset of osteoporosis [9].

Steps of bone remodeling:

1. Stimulation of **osteoclasts (**bone resorption cells**):-** The bone resorption cells secrete the enzymes collagenases and proteinases, which solubilizes the bone matrix and releases calcium into circulation for physiological functions.
2. Once osteoclasts die, **osteoblasts** (bone forming cells) differentiate and lay down new bone matrix at the sites of previous resorption, which is known as osteoid.
3. Once the process bone formation is completed, the osteoblasts are inactivated and differentiated into **osteocytes,** on the surface of the new bone.
4. The new bone is then mineralized with hydroxyapatite (HAP). The complete process of bone mineralization and hardening takes several months [10].

Bone Markers:

1. Serum osteocalcin, bone specific alkaline phosphatase, total alkaline phosphatase and type I procollagen (C-terminal/ N-terminal) - **for bone formation**.
2. Tartrate-resistant acid phosphatase (TRAP), type I collagen cross-linked N- (NTX) and C-telopeptide (CTX) - **for bone resorption** [11].

Increase in the level of alkaline phosphatase (ALP) is the important indicator of the bone formation cells and decrease in tartrate-resistant acid phosphatase (TRAP) is the most important indicator of the bone resorption cells.

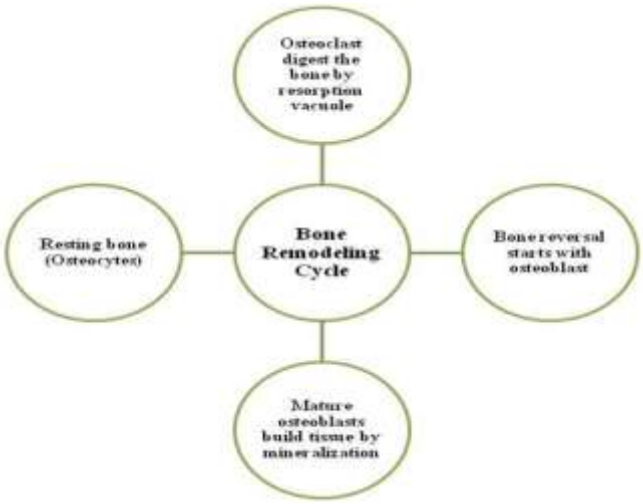

Figure No. 1: The diagrammatic representation of different steps of bone remodeling process

Role of Wingless-type (Wnt) pathway: As shown in the above given figure, it is clear that the bone cells osteoblasts and osteoclasts play a very important role in the bone remodeling process. Moreover, in order to understand this process and to regulate the bone formation properly, it is required to know about the Wnt pathway.

The Wnt pathway recognised as having a major role in the regulation of bone formation. It is a protein signalling pathway for osteoblasts (derived from mesenchymal stem cell). It inhibits differentiation of adipocytes and promotes cell lineages of osteoblast, by controlling its proliferation, maturation, and terminal differentiation. It has Low density Lipoprotein Receptor related Protein (LRP) 5 and 6 as co-receptors to its frizzled receptors. It shows some of the transcription factors, which involves (the bone morphogenetic protein 2 and 7, beta-catenin, Runx2, osterix and nuclear factor of activated T-cells (**NFAT**). When osteoblasts have done their job, then they may become incorporated into the bone matrix as osteocytes (may transform into living cells on the bone surface or may undergo death/apoptosis/necrosis).

Osteoblasts synthesize RANKL (receptor activator of NF-Kappa B ligand) which is necessary for osteoclasts formation and function. But osteoprotegerin (OPG) is its decoy receptor. Ratio of RANKL/OPG is used to predict the induction or suppression of osteoclastogenesis, the decreased ratio represents induction of osteoclastogenesis and vice versa [12, 13]. Moreover, female hormone estrogen may exert its effect on bone by OPG expression in osteoblasts [14].

Inhibitors of Wnt signaling pathway:

Sclerostin, is a protein which is secreted by osteocytes, it binds to co-receptors LRP5/6 and inhibits their association with Wnt pathway, thus acting as an inhibitor of this pathway. Dickkopf1 (DKK1) is another negative regulator of the Wnt signaling pathway that acts by directly binding to LRP5 and LRP6 [12].

Pathogenesis

- Senescence of bone cells
- Lifestyle factors i.e., primary exercise and nutrition
- Loss of vitamin D metabolism with age

Poor vitamin D metabolism leads to a decrease in the absorption of intestinal calcium and, results in the signalling of parathyroid hormone, to withdraw calcium from the bones. Overtime, this continuous removal of calcium from the bones leads to a stage of decreased bone mass and development of osteoporosis [6, 15, 16].

Skeletal fracture can result from:

a) Failure to produce optimal mass and strength during growth.
b) Excessive bone resorption which leads to decreased bone mass.
c) An inadequate formation response to increased resorption during remodeling process.

Moreover, the larger number of unfilled Howship's lacuna (tiny depressions, pits, or irregular grooves in bone that is being resorbed by osteoclasts) and haversian canals (minute tubes which form a network in bone and contain blood vessels) further weaken the bone. Excessive resorption can also result in complete loss of trabecular structures, so that there is no template for bone formation [13, 17].

Central role of estrogen:

Estrogen deficiency plays a major role in the pathogenesis of osteoporosis. In postmenopausal women, whose estrogen levels decline naturally, are at the highest risk for developing this disease. Morphological studies and measurements of certain bone markers have indicated that the process of bone remodeling is accelerated at the menopause.

Moreover, fracture risk is inversely related to estrogen levels in the postmenopausal women. Estrogen is critical for epiphyseal closure in puberty, and is required for the regulation of bone turnover in both sexes. Although androgen play a role, but estrogen has a greater effect than androgen in inhibiting bone resorption in men [13]. Estrogen may also have an important role in the acquisition of peak bone mass in men. Moreover, in older men osteoporosis is closely associated with low level of estrogen than with low androgen. Estrogen treatment decreases the rate of bone remodeling, as well as the amount of bone loss with each remodeling cycle [18, 19].

Animal models and cell culture studies have suggested that, multiple sites are involved for the estrogen action, not only the cells of the BMU, but other marrow cells are also involved in it. Estrogen acts through 2 receptors: estrogen receptor alpha and beta, i.e., ERα and ERβ.

ERα appears to be the primary mediator of estrogen's actions on the skeleton. Osteoblasts do express ERβ, but the actions of ERβ agonists on bone are not much clear. Single nucleotide polymorphisms (SNPs) of ERα may affect the fragility of bone. An orphan nuclear receptor i.e., estrogen receptor-related receptor α (ERRα), having sequence homology to ERα and ERβ is also present in bone cells. Despite its inability to bind estrogens, this receptor may interact with ERα and ERβ or act directly to alter bone cell function. Sex hormone-binding globulin (SHBG) is the major binding protein for sex steroids in plasma, which not only alter the bioavailability of estrogen to hormone responsive tissues, but also affect its entry into cells [20].

Diagnosis of osteoporosis: Computed tomography, x-ray and dual energy x-ray absorptiometry (DXA) images are used in cross-sectional and longitudinal studies in osteoporosis. Fracture Risk Assessment Tool (FRAX), an absolute risk assessment tool, which includes BMD testing based on age and fracture probability by using predetermined assessment thresholds [21, 22].

Animal model: The suitable animal model used for the study of osteoporosis is ovariectomized (OVX) rats or mice; by making use of this model, we can quantify the drug levels in the desired part of the body. The findings will be assessed on the basis of animal weight, morphology of target bone, and histochemical localization of ALP (an osteoblastic marker) and TRAP (an osteoclastic marker). In the target bone sections, the osteoclastic activity will be confirmed by TRAP staining, and the bone formation is assessed by making use of ALP staining. The color intensity of the enzymes TRAP and ALP will be evaluated from the images by the image analysis software, which is developed locally [23].

Treatment Strategies: Therapy should be chosen on the basis of the type of osteoporosis [24]:

- Antiresorptive drugs, which slow the progressive thinning of bone e.g., hormone replacement therapy (HRT), bisphosphonates (BP), calcitonin, and estrogen agonists.
- Bone forming drugs e.g., teriparatide which helps to rebuild the skeleton, and drugs with a more complex mechanism of action.
- Calcium and vitamin D precursors to ensure adequate intake and to ensure maximum effectiveness of the drug therapy [15].

Drugs used in the treatment of osteoporosis:

1. Bisphosphonates e.g., alendronate, ibandronate, etiodronate, zoledronate and risedronate
2. Teriparatide or Parathyroid Hormone
3. Raloxifene (Selective Estrogen Receptor Modulator, SERM)
4. Calcitonin
5. Strontium Ranelate
6. Hormone Replacement Therapy
7. Calcium and Vitamin D
8. Denosumab

1. Bisphosphonates: They are called bisphosphonates because they have phosphonate groups ($PO(OH)_2$) linked by phosphoether bonds. This arrangement makes BP stable by nature and resistant to the biological degradation. They inhibit the osteoporosis by having antiresorptive action or by slowing bone loss, as they encourages the osteoclasts to undergo apoptosis, or cell death.

They appear to stimulate the proliferation of preosteoblast cells transiently and to increase their differentiation. They may increase the production of antiresorptive protein (osteoprotegerin) by osteoblasts. Drugs of bisphosphonate class are divided into two categories based on their chemical structure, one is the nitrogen containing while the other is non-nitrogen containing bisphosphonates. Nitrogen containing bisphosphonates i.e., alendronate are more potent than the non-nitrogen containing bisphosphonates i.e., etiodronate, by their ability to suppress osteoclast activity (as measured by biochemical markers of bone turnover).

Mechanism of Action: Negative charge on the phosphate group of the bisphosphonate nucleus gave these compounds a high affinity for the surface of bone. BPs act

on bone metabolism by binding and blocking the enzyme farnesyl pyrophosphate synthase (FPPS), in the HMG-CoA (3-hydroxy-3-methylglutaryl-Coenzyme A) reductase pathway (also known as mevalonate pathway). After binding to the mineralized bone surface, BPs are taken up by the osteoclasts during resorption of bone. It causes lipid modification of many proteins which are found in osteoclast i.e., Ras, Rho and Rac (which play a central role in the regulation of core osteoclasts, cellular activity including stress fibre assembly and membrane ruffling. As a result their survival is inhibited by the loss of the protein prenylation. Because of this loss of protein prenylation, osteoclasts become unable to resorb bone, which ultimately lead to osteoclast apoptosis [25]. The BPs also have the ability to inhibit apoptosis in osteocytes, which appears to be mediated through the opening of connexin 3 hemichannels and subsequent activation of extracellular signal-regulated kinases (ERKs).

Different types of BPs with its dosage, uses and marketed products are mentioned in the table given below. Out of them, alendronate and ibandronate are the second generation derivatives of bisphosphonates, which localizes preferentially on bone resorption surfaces by binding to the exposed calcium phosphate bone mineral. Osteoclasts attach to these surfaces by a tight seal enclosing a space into which they secrete acid and dissolve the mineral. During this process, the bisphosphonates are released and can reach local concentration in high micromolecular range [26]. Zoledronic acid which is one of the third generation derivative of bisphosphonates, is the only BP that has been developed exclusively for i.v. but not for oral use, which has led to an attractive once-yearly regimen in the treatment for osteoporosis. It has fastest onset of action among the bisphosphonates on different types of fracture, a rapid effect appears for vertebral fractures and not for reduction of hip and nonvertebral fractures [44,45].

Table No.1: The different drugs of the class bisphosphonates [27].

Drug	Dosage/Frequency	Advantages	Side effects	Marketed Product
Etiodronate	400 mg daily	↑ BMD in lumbar vertebrae	GI tract intolerance, bone, joint and muscle pain, jaw pain, severe diarrhoea, numbness or swelling	Didronel
Ibandronate	2.5 mg daily or 150 mg monthly or 3 mg every 3 months (IV)	↑ BMD spine, trochanter, femur neck	GI tract intolerance, hives, swelling of mouth and throat, flu-like symptoms, osteonecrosis of jaw	Boniva
Alendronate	10 mg daily or 70 mg weekly	↑ BMD in vertebre, femoral neck	GI tract intolerance	Fosamax or Fosamax Plus
Risedronate	5 mg daily or 35 mg weekly or 75 mg monthly or 150 mg monthly	↑ Bone mass	GI tract intolerance	Actonel
Zoledronate	5 mg yearly (IV)	↑ Bone mass	Flu-like symptoms, osteonecrosis of jaw	Reclast, Zomedia

Amongst a wide range of drugs available in the treatment of osteoporosis, bisphosphonates are known as first-line drugs, on account of their reasonable efficacy, while cost benefits also matter to a sizable extent [28]. Drugs of this class are commercially available as oral tablets and/or i.v. infusion viz., ibandronate (Boniva®), alendronate (Fosamax®), risedronate (Actonel™) and zoledronate (Zometa®). However, these often lead to adverse side-effects, which include severe gastrointestinal (GI) disturbances, inflammation, pain and osteonecrosis of jaw. It also sometimes leads to transient post-infusion influenza-like illness, arrhythmia, serious atrial fibrillation, mild transient hypocalcemia and renal failure.

The major challenge of a vast majority of drugs of this class, is patient non-compliance and intolerance, while their bioavailability is also considerably sub-optimal. The poor GI absorption and decreased bioavailability demand more number of molecules (i.e., high dose) to be administered, which eventually leads to multiple side-effects involving GI tract, and beyond. These observations call for research to bring novelty in terms of enhanced absorption, reduced dosage and bio-acceptable interactions with the absorbing GI mucosal membrane. This can be worked out either by chemical modification or by modifying the surface characteristics of the molecules, without tampering its original chemistry.

The latter is more feasible, less time-consuming and economically viable option, which attracts the interest and attention of the formulation scientists. The present time is quite conducive and encouraging, as it provides the advancements in the field of drug delivery coupled with the relevant development in engineering and technology to support research and development in this domain.

Risedronate (RSD)

RSD is a FDA-approved third generation bisphosphonate, which is an antiresorptive agent, for the treatment of osteoporosis, available in the market as oral tablet dosage forms. It has considered to possess strong affinity for bone, prolonged stay period, high potency in blocking the bone dissolution, and versatile usage, i.e., in the treatment of Postmenopausal Osteoporosis (PMO), Male Osteoporosis (MO), Glucocorticoid-induced Osteoporosis (GIOP) and Paget's Disease (resulting in enlarged and mis-shaped bones). However, the patients show poor compliance to its regimen due to GI irritation or ulceration with its oral administration, while permeation remains the challenge [29-31]. Moreover, all the marketed products are based on age-old formulation approaches (empirical practices), made up of conventional materials like crospovidone, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide and titanium

dioxide (www.fda.gov.), which have no capacity to overcome the bio-hurdles present therein.

2. Mechanism of Action

RSD is a bone resorption inhibitor. It has good affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent, as it is an inhibitor of farnesyl pyrophosphate synthase (FPPS) enzyme in osteoclasts. FPPS is a key enzyme in the mevalonate pathway, which generates isoprenoid lipids utilized for the post-translational modification of small GTP- binding proteins that are essential for osteoclast function, which results in downstream inhibition of osteoclast activity and reduced bone resorption and turnover [(32).]

Pharmacokinetics

The pharmacokinetics of RSD is not influenced by age or gender. Though the drug inherently is reported to be well-absorbed, but, the hindrances occur due to the varied complex interactions in GI environment majorly, on account of bivalent ions like calcium or other polyvalent cations. It has low plasma protein binding (~ 24%), with no evidence of systemic metabolism. It is excreted unchanged primarily via the kidney. Insignificant amounts (<0.1% of intravenous dose) of drug are excreted in the bile in rats. It has a short biological/elimination half life (~ 1.5 hours) and faster clearance rate (122 mL/min) [(33,34)].

Adverse effects and Contraindications

The GI disturbance (irritation and ulceration) is the major adverse effect**.** There is no reported drug interaction with the orally administered drug. The drug is contraindicated in individuals with a history of renal disease i.e., creatinine clearance less than 30 mL/min [(34,35)].

2.1.2.1. Challenges

The patient-compliance to current formulations is inadequate due to complications of its oral intake regimen and GI inflammatory reactions. Some of the main challenges with this drug molecule are enlisted below:

- Oral bioavailability is less than 1 % (0.63% in fasting)
- Adverse effects such as ulcers, esophagitis, gastritis, renal failure, osteonecrosis and musculoskeletal pain
- The presence of Ca^{2+} or other divalent cations in the GI tract or intestinal lumen hampers its absorption, by forming nonabsorbable complexes with the metal ions
- It cannot be given to the patient at bedtime or within 2 hours of food or fluid (except water)
- Patients should not lie down for at least 30 minutes after taking the medication
- Absorption is reduced by food, especially by products containing calcium or other polyvalent cations.

2. Teriparatide and Parathyroid Hormone: It is a 34-amino acid polypeptide of the 84 amino acids native parathyroid hormone molecule; it is produced by recombinant DNA technique. It is the only skeletal osteoanabolic agent, which is approved by US Food and Drug Administration (FDA). But, the teriparatide treatment has limited by FDA to 24 months lifetime, because it can lead to the formation of osteosarcoma. It is given to the patient once a day by subcutaneous injection. But teriparatide treatment alone is more expensive and produced a smaller increase in Quality-adjusted life-year (QALYs) than alendronate. So, combination of teriparatide with other agents i.e., estrogen, alendronate, zoledronate and denosumab increases BMD substantially [(27, 36)].

3. Raloxifene (SERM): It is the only marketed SERM which has approved for treatment and prevention of postmenopausal osteoporosis. It prevents bone loss and is indicated for the prevention and treatment of vertebral fractures in postmenopausal women. Post hoc analysis showed a significant reduction of nonvertebral fractures. **Bazedoxifene** in combination with conjugated estrogens is recently approved by the FDA as 'antiosteoporotic drug' [(10, 36)].

4. Calcitonin: Calcitonin (hormone) act as a antiresorptive agent, which reduces the occurrence of vertebral fractures in women but has not been shown to reduce the risk of nonvertebral fractures. Supplementation with calcium and vitamin D is mandatory with calcitonin [(6)].

5. Strontium Ranelate: Marketed and registered for the treatment of postmenopausal osteoporosis. It has dual mechanism of action: it has an antiresorptive action and anabolic action (stimulates osteoblasts to increase bone mass).

Dose:-2 gm sachet once daily by mouth. Strontium ranelate is not given to the patient with a history of thrombophlebitis [(37)].

6. Hormone Replacement Therapy (HRT): After menopause, due to the lack of hormone i.e., estrogen, rate of bone turnover increases, which results in accelerated bone loss. Indian guidelines advise that therapy with estrogen may be used for prevention and treatment of osteoporosis in the early postmenopausal period in women who are symptomatic. Thus, therapy with estrogen or estrogen and progesterone is believed to prevent osteoporotic fractures and increase lumbar spine and femoral neck BMD [(6)]. Due to the reduction of free testosterone in men, they may develop gradual bone loss and testosterone replacement is one of the way to treat this condition [(27)].

7. Calcium and vitamin D: In order to treat osteoporosis, adequate calcium and vitamin D supplementation is required. The National Osteoporosis Foundation recommends elemental calcium dietary intake of 1200 mg per day for postmenopausal women. The recommended intake for vitamin D is 800–1000 IU per day with a target 25-hydroxy vitamin D level of at least 30 ng/ml [(38)].

Table No. 2: The comparison of different FDA approved medications and indications.

Drug	PMO		GIO (Men and Women)		MO
	Prevention	Treatment	Prevention	Treatment	
Estrogen	√				
Alendronate PO	√	√		√	√
Risedronate PO	√	√	√	√	√
Risedronate Delayed Release PO		√			
Ibandronate PO	√	√			
Ibandronate IV		√			
Zoledronate IV	√	√	√	√	√
Calcitonin IN		√			
Raloxifene PO	√	√			
Denosumab SC		√			√
Teriparatide SC		√		√	√

PMO: Postmenopausal osteoporosis, **GIO**: Glucorticoid Induced Osteoporosis, or **MO**: Male osteoporosis, **PO**: Peroral, **IV**: Intravenous, **IN**: Intranasal, **SC**: Subcutaneous.

As it is known to us, there are different types of drugs available for the treatment of osteoporosis. The above given table contains FDA approved drugs with their respective uses in PMO, GIO & MO respectively.

8. Denosumab: It is a human monoclonal antibody, which is very potent antiresorptive drug and blocks RANKL specifically. It is quiet efficacious in reducing the risk of vertebral, hip and nonvertebral fracture. Moreover, it fully inhibits teriparatide-induced bone resorption at approved doses. Significantly greater treatment adherence is observed for subcutaneous administration, of denosumab every 6 months than for oral alendronate once weekly [39, 40].

Adverse effects of antiosteoporotic drugs [41,43]:

1. **Bisphosphonates**: Gastrointestinal Effects i.e., abdominal disturbances, Barrett's esophagus, Esophageal cancer, Musculoskeletal pain, Acute-phase reaction, Atrial fibrillation, Atypical subtrochanteric fractures, Osteonecrosis of the jaw, Hypersensitivity reactions.
2. **Denosumab**: Infections, Osteonecrosis of the jaw, Cancer.
3. **Raloxifene**: Hot flushes and Leg cramps, Venous thromboembolism, Cardiovascular events and Stroke.
4. **Strontium Ranelate**: Venous thromboembolism, Hypersensitivity.
5. **Teriparatide or Parathyroid hormone:** Nervous system disease, Osteosarcoma.

Vertebroplasty and Kyphoplasty (Surgical treatment): Whenever we study osteoporosis induced fracture, then we come to know an invasive surgery i.e., vertebroplasty and kyphoplasty. It is used to treat a vertebral compression fractures (VCFs) in the spinal column, which are a common result of osteoporosis. Physician inject a cement mixture into the fractured bone, in vertebroplasty. On the other hand, a balloon is inserted into the fractured bone to create a space, and then is filled with cement in kyphoplasty [5].

The goals of this surgery:

- To reduce pain in the patient from the fracture.
- To stabilize the vertebra.
- To restore the vertebra back to its normal height.

New agents for the treatment of osteoporosis: With the evolving understanding of human bone biology, there is development of new approaches, for the treatment of osteoporosis. They are the inhibitors of cathepsin K and sclerostin. Cathepsin K, a cysteine protease expressed by osteoclasts, which mediates bone resorption through its effects on collagen matrix degradation. As already explained, sclerostin is an osteocyte-secreted Wnt signaling antagonist, which suppresses bone formation via its effects on osteoblast differentiation, activity, and survival [25]. Some of New agents for the osteoporosis are:

'anti-resorptive'- Odanacatib, 'anabolics'- teriparatide analogues (abaloparatide), 'monoclonal antibody to sclerostin'- romosozumab [42].

Challenges with the drugs of osteoporosis:

Different drugs have different challenges e.g., alendronate drug is hydrophilic by nature and is not able to permeate the lipid barriers of the body. Moreover, the drugs of the BP group are ready to form complexes with the metal ions, as a result the active entity is not able to reach the site of action. Moreover, these drugs highly irritate the gastrointestinal tract by oral route and if given directly by intravenous routes, then they cause osteonecrosis of the jaw. In case of teriparatide treatment, trabecular thickness and trabecular connectivity increases, but there is no effect on cortical thickness, which is also required for the bone formation. Moreover, it induces bone resorption, for which we need denosumab in order to inhibit teriparatide-induced bone resorption at approved doses. Raloxifene (SERM) is specific to vertebral fracture only, it is not effective for the nonvertebral fractures. Calcium and vitamin D supplements are required to treat the disease along with the other drugs, if the patients having less calcium intake through diet.

3. Conclusion

In the understanding of the bone disease osteoporosis, substantial progress has been made in the past several years, which also includes modification in its management or treatment. The guidelines for the prevention and treatment of osteoporosis have revised and now, it include criteria for commencing medical treatment in addition to, continued diligence in early diagnosis and implementation of treatment. In Indian women, low calcium intakes, vitamin D deficiency, difference in both sexes, early menopause, lack of diagnostic facilities, and poor knowledge for bone health, have been contributed towards the high prevalence of osteoporosis based fractures. Bone health can be achieved by creating an environment which includes peak bone mass during adolescence, prevention of bone loss after menopause and maintenance of healthy bone throughout the life cycle. A new medication or treatment for osteoporosis is required for the body, which helps to rebuild bone and potentially strengthen the skeleton against osteoporosis based fractures. Though, different drugs are available for the treatment of osteoporosis, but they are devoid of adverse effects, so there is a need to investigate for a safer drug treatment.

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