

Novel emerging therapies of Osteoporosis- Review

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Abstract:

Osteoporosis is one of major health problem. It is associated with low bone density and pore formation in the bones. Mainly osteoporosis is caused due to age, sex or deficiency of Estrogen after menopause. Secondary causes may be hyperparathyroidism or intense use of glucocorticoids. Pathophysiology of the disease involves increase in bone resorption by osteoclasts and decreased new bone formation by osteoblasts. Pharmacological treatments to osteoporosis involves bisphosphonates, RANKL inhibitors, SERM. Novel therapies for osteoporosis include cathepsin K inhibitor, sclerostin inhibitors, PTH related peptides. Herbal treatments include use of *Ashwagandha*, *Turmeric*, *Krishna jeera*, *Asthishrunkala*, *pomegranate* etc.

Key words: Menopause, RANKL inhibitors, cathepsin K, herbal treatment.

List of abbreviation:

FPP: farnesyl diphosphate

GGPP: geranylgeranyl diphosphate.

BMD: bone mineral density

SERM: selective Estrogen receptor modulator

RANKL: Receptor activator of nuclear factor kappa- B ligand

PTH: parathyroid hormone.

INTRODUCTION:

Bone is the basic structural unit and provides the major mechanical support for the internal organs. It is the dynamic connective tissue with numerous physiological functions. ⁽¹⁾ Remodelling of the bone is a process of replacement of bone to maintain the strength of the bone. This is a continuous process, which involves replacement of bone tissue with newly formed proteinaceous matrix and mineralization of the matrix to form new bone. ⁽²⁾ Remodelling process involves three process; they are:

- 1) Bone resorption by osteoclasts
- 2) Transition state from resorption to new bone formation
- 3) The new bone formation by osteoblasts.

Disturbance in the dynamic balance in the bone remodelling, that is increased bone resorption and decreased neoformation of bones leads to impairment of bone and causes pores in the bone, this disorder is called **Osteoporosis**, is the major health problem associated with pore formation in bone. ⁽³⁾ Osteoporosis is a silent disease, it is very asymptomatic, as this disease remains undiagnosed until the fracture of hip, spine or wrist is manifested. ⁽⁵⁾ It is also characterised by low bone mass and disruption in the microarchitecture of bone, it is also associated with high risk of fragility and fracture bone. Major cause for osteoporosis is decrease in Estrogen levels in postmenopausal women ⁽⁷⁾ Deficiency of Vitamin D and secondary hyperparathyroidism also contributes to the secondary osteoporosis.

Every one in two women and one in five men over the age 50 are affected by fracture due to osteoporosis. ⁽⁸⁾ Hence osteoporosis is one of the major health disease.

Bisphosphonate derivatives are the major drug of choice for the treatment of osteoporosis (osteoclast induced loss of bone) ⁽¹⁰⁾. These drugs are widely used in medical conditions associated with increased bone resorption, owing to their high affinity for the bone matrix; Bisphosphonates are preferentially incorporated into the sites of active bone remodelling in physiologic conditions

associated with accelerated skeletal turnover. Bisphosphonates inhibit osteoclastic bone resorption by acting on mature osteoclasts by inhibiting their attachment to bone surface ⁽¹¹⁾ as well as the formation of ruffled border ⁽¹²⁾. This article will review on the pathophysiology, etiology, treatment and management of osteoporosis.

Etiology:

Primary osteoporosis:

Osteoporosis caused due to natural reasons such as age, sex, deficiency of sex hormones, declining of Estrogen levels after menopause and hyperparathyroidism which all contributes to the low BMD ⁽¹³⁾.

Secondary osteoporosis:

Osteoporosis occurred due to comorbidity with other diseases such as Cushing's syndrome or deficiency of vitamin D, calcium. Bone loss due to glucocorticoid therapy. Hyperparathyroidism ⁽⁵⁾

Pathophysiology:

Remodelling of bone is a continuous dynamic process in which the bone is continuously resorbed by osteoclasts and new bone is formed by osteoblasts. Impairment in this process leads to pathological condition called as osteoporosis ⁽⁵⁾.

This process is very important for repair of the fracture and also to maintain the mechanical strength.

Osteoporosis is most common in postmenopausal women. As there is decline of Estrogen levels. In postmenopausal women there is increased remodelling of bone without subsequent bone formation by osteoblasts, which leads to loss of bone mass and osteoporotic fracture. ⁽¹⁴⁾

Osteoblasts found to have several receptors for various factors which are found to have control on bone metabolism. Osteoblasts also influence the function of osteoclasts ⁽¹⁵⁾.

Osteoclasts are formed from the mononuclear precursors in the myeloid lineage of bone marrow stromal cells, which is also involved in formation of macrophages.

Osteoclasts are differentiated by the expression of M-CSF by osteoblastic stromal cells for progenitor cells.

Not only expression of M-CSF, they also require the expression of RANKL by osteoblastic stromal cells. Cytokines also found to influence the bone remodelling process, that is TNF super family, which is called as Receptor activator of nuclear factor- B ligand (RANKL) RANKL is produced by osteoblasts and bind to the RANK receptors on the pre-osteoclasts which causes activation and maturation of osteoclasts, which causes bone resorption⁽¹⁶⁾.

According to recent studies, Cathepsin K is secreted by osteoclasts during bone resorption, which causes the bone matrix degradation; this also contributes to osteoporosis.

Parathyroid hormone (PTH) increases the absorption of calcium via kidneys, bone and intestine and it also increases the osteoclast activation along with this it also activates the vitamin D to form calcitriol, which increases the calcium absorption in intestine.

Estrogen is an important sex hormone which inhibits the bone resorption by binding to the Estrogen specific receptors. They promote osteoclast apoptosis.⁽¹⁷⁾

Treatment:

Pharmacological treatment

Classification of drugs:

Antiresorptive agents

- a) Bisphosphonates
- b) RANKL antibodies
- c) Selective Estrogen receptor modulators (SERM)
- d) Calcitonin

Anabolic agents

- a) PTH analogues

Nutritional supplements

- a) Calcium and vitamin D

Bisphosphonates:

First line of treatment for osteoporosis. These class of drugs include Risedronate, etidronate, clodronate and zoledronic acid.

Bisphosphonates increases the bone mineral density by inhibiting the bone resorption by increasing the apoptosis of osteoclasts.

Bisphosphonates are also associated with number of side effects. They cause gastrointestinal symptoms such as dysphagia and esophagitis. They also cause atypical femoral fractures and osteonecrosis of jaw.⁽¹⁸⁾

Nitrogen containing bisphosphonates: these class of drugs include alendronate, risedronate and zoledronate. These drugs inhibit the metabolic pathways involved in the homeostasis of bone such as bone resorption or new bone formation. Mainly they interfere in mevalonate pathway by inhibiting their metabolites such as FPP and GGPP, which is important for osteoclast function.⁽¹⁹⁾

Non-nitrogen containing bisphosphonates: these class of drugs include clodronate and etidronate. these drugs get inserted into the ATP and they reverse the actions of aminoacyl T-RNA synthetases. Hence the nucleotides get altered and it gets accumulated in the osteoclasts, inhibiting their function they may also cause death of osteoclast cells.^(18, 19)

RANKL antibodies:

These are novel drugs. These include monoclonal antibodies.

Example: Denosumab.

This antibody is highly specific to RANKL and has rapid onset of action. These drugs binds to RANKL and hence it prevents the binding of it to RANK receptor present on the osteoclasts. Hence there is no expression of RANK which leads to inhibition of osteoclasts formation and function.⁽²⁰⁾

SERM:

Example: raloxifene

Raloxifene is a selective Estrogen receptor modulator, it exerts estrogenic effects on bone.

It binds to Estrogen receptor and causes gene transcription by interaction with Estrogen response element and unique DNA target; the raloxifene response element (RRE). It increases the expression of bone matrix proteins such as alkaline phosphatase, osteonectin, osteocalcin and collagen. This causes the proliferation of osteoblasts and decreases the activity of osteoclasts.⁽²¹⁾

PTH analogues:

Example: Teriparatide

Teriparatide is a recombinant human PTH analogue is the anabolic agent. It has same actions as that of PTH, that is it stimulate the new bone formation by stimulating the osteoblast formation and decreasing the apoptosis of osteoblasts.⁽²²⁾

Calcitonin:

It is synthetic peptide which has similar effects of natural calcitonin. It causes inhibition of resorption of bone. It causes the loss of ruffled border of osteoclasts and also decreases the number of osteoclasts. It inhibits the synthesis and release of tartrate resistant acid phosphate (TRAP) an osteoclast acid, by interfering in Na⁺-K⁺-ATPase activity and also carbonic anhydrase hence it decreases the osteoclasts acid secretion.⁽²³⁾

Non- Pharmacological treatments:

It includes many practises such as sufficient intake of calcium and vitamin D, stop smoking, decreasing the consumption of alcohol and caffeine.

By including the adequate amount of calcium and vitamin D in the diet.⁽²⁴⁾

Regular weight bearing exercise, avoid tobacco consumption.

Normally premenopausal women and men should consume 100mg of calcium per day. After menopause, women should consume 1200mg of calcium each day, also consume calcium rich foods such as milk, cottage cheese, yogurt and green vegetables.

Vitamin D mediates the absorption of calcium in the intestine and it also induces the expression of RANK ligand by osteoblasts, hence it also increases the proliferation of osteoclasts. Hence men after 70 years and postmenopausal women should consume 800 international units of vitamin D per day. This reduces loss of bone and decreases the fracture rate.⁽²⁵⁾

Alcohol consumption can induce risk of fracture, hence limit the consumption of alcohol.

Tobacco consumption: smoking tobacco decreases the bone density and it is one of the important determinant, hence the patients should avoid smoking.

Exercise: exercise decrease the risk of fracture by increasing the bone mass in premenopausal women and assists in maintaining the bone density.

But postmenopausal women bearing low bone density should avoid weight bearing exercise and should not exercise vigorously as that increases the risk of fractures.

Prevention of fall: falls play an important role in fractures. Hence osteoporotic patients should take strategies to avoid falls such as checking the vision and hearing etc. patients with high risk of falling should wear protectors for hip and knee joints.^(25, 26)

Novel therapies:

Treatment available for treating osteoporosis has many side effects such as coupling effects.

Current treatment regimen includes Antiresorptive agents that target to decrease bone resorption but these agents also decrease the new bone formation and anabolic agents also increase the bone resorption. Hence there is need of treatment with uncoupling of bone resorption and bone formation⁽²⁷⁾

Recently approved medications:

Denosumab

Combination of Estrogen or SERM

Novel therapies include:

Cathepsin K inhibitors: recent studies have shown that cathepsin K is released by osteoclasts which gets accumulated in the vesicles of lysosome and it is a cysteine protease, it causes degradation of collagen present in the bone hence causes the degradation of the bone. Hence cathepsin K inhibitors increases the BMD and also improves bone strength and it is an efficacious treatment for osteoporosis.^(27, 28)

ONO- 5334, Odanacatib, Relacatib are in phase II clinical trial. These drugs increased the number of osteoclasts but inhibited the resorption function of it and also no effect on the new bone formation by osteoblasts and less active on reducing bone formation markers.⁽²⁹⁾

Odanacatib was withdrawn due to serious cardiovascular side effects seen.⁽³⁰⁾

Anti-sclerostin agents: Sclerostin is released by osteocytes, this antagonizes LRP5/6- mediated canonical wingless signalling (Wnt signalling) within the osteoblast, this inhibits osteoblast activity and increases its apoptosis. Hence inhibiting sclerostin decreases the apoptosis of osteoblasts and preserving the bone formation activity.

There are three sclerostin inhibitors developed, they are Romosozumab, Blosozumab and BPS804.⁽³¹⁾

PTH related peptide: Parathyroid hormone has an anabolic effect on bone. But its daily administration increases the resorption of bone and it also inhibits its anabolic effect. So the synthetic PTH peptides should be such that it should be administered at longer intervals and it should be efficacious and safe. Abaloparatide, a new PTH analogue in phase II has better effect than that of teriparatide, a marketed PTH peptide.⁽³²⁾

Dickkopf- 1 antagonists: Dickkopf- 1 (Dkk- 1) is the endogenous negative regulator of Wnt signalling. Wnt signalling is an important mechanism which stimulates the production of osteoblasts by increasing the proliferation and differentiation of pluripotent mesenchymal stem cells to osteoblasts. Specifically, Wnt signalling increases the progression of Osterix 1 expressing cells to bone producing osteoblasts simultaneously this signalling also prevents apoptosis of osteocytes (mature osteoblasts). In addition to osteoblast differentiation, this also decreases osteoclast differentiation by promoting the generation and secretion of osteoprotegerin, a naturally occurring inhibitor of RANKL.⁽³³⁾ Dkk- 1 inhibitors have positive actions such as preserving the actions of osteoblasts and its levels are found high in the serum of postmenopausal women.

Several Dkk- 1 antagonists have been investigated, and NCT01293487 showed safe and efficacious use in phase I study.⁽³⁴⁾

Activin A antagonists: Activin A is an TGF- β signalling ligand, which is present at higher concentrations on bone and it also plays a role in regulation of bone metabolism.⁽³⁶⁾ Recent studies have showed that activin promotes the formation of osteoclasts and it also inhibits the osteoblast mediated mineralization in bone matrix. Hence the inhibition of activin ligand can help in treating osteoporosis.⁽³⁵⁾

β -arrestin agonists: β -arrestin is a molecule has anabolic effect by increasing the bone formation by osteoblasts by signalling the PTH- β arr receptor. Hence the agonists to this receptor can increase the bone formation and they also uncouple with bone resorption. But these agents are not bone- specific molecules. Hence these molecules are not yet being the used for the treatment.⁽³⁷⁾

Herbal treatments:

Reviewing of several texts have showed that almost 11 drugs have been used for treating and management of osteoporosis in texts of Ayurveda.⁽³⁸⁾ They are as following:

Ashwagandha:

Botanical name: *Withania somnifera*.

Ashwagandha contains active constituents such as steroidal lactones, withanolides, withaferin and alkaloids such as cuscohygrine, anahygrine, tropine, pesudotropine and anaferine.⁽³⁹⁾

Root extract of *Withania* contains Withanolides, this has Estrogen like effects on bones for treating osteoporosis. This effect was proved by administering 65mg/kg of Ashwagandha extract to ovariectomized rats and the results showed that Ashwagandha extract increased the ash weight, ash calcium, ash phosphorous and ash magnesium in tibia and femur bones.⁽⁴⁰⁾

Asthishrunkala:

Botanical name: *Cissus quadrangularis*.

Cissus quadrangularis contains iridoid 6-O-[2,3-dimethoxy]-trans-cinnamoyl catalpol⁽¹⁾ and 6-O-methoxy-benzoyl catalpol. These active principles are called as phytoestrogen rich compounds and considered to have Estrogen like actions.⁽⁴¹⁾ these also contains steroids

such as ketosteroids, sitosterol, alpa amayrin, alpa ampyrone and tetracyclic triterpenoids. ⁽⁴²⁾ ketosteroid is an anabolic steroid it acts as an antagonist to glucocorticoid receptor and increases bone health. It also increases the regeneration of fibroblasts, chondroblasts and osteoblasts which increases the mineralization and new formation of bone. ⁽⁴³⁾

Extract of *Cissus quadrangularis* was administered to the ovariectomized C57BL/6 mice for eleven weeks. Then distal femoral metaphysis, femoral diaphysis, and proximal tibia were subjected to estimation of bone mineral density and the results showed that *Cissus quadrangularis* effectively decreased the bone loss in femur and tibia. ⁽⁴⁴⁾

It is also investigated that the extract of *Cissus quadrangularis* has property of stimulating the growth of fetal bone during intra uterine developmental period, this evidences that *Cissus quadrangularis* has effect on bone. ⁽⁴⁵⁾

Pomegranate:

Botanical name: *Punica granatum*.

Pomegranate contains steroidal Estrogen, estrone along with non-steroidal phytoestrogens such as Comesten, coumestrol and isoflavones such as genistein and daidzein. This showed agonist as well as antagonist behaviour to Estrogen, this shows that according to the hormonal imbalance pomegranate extract have different effects. ⁽⁴⁶⁾

Genistein has stimulatory effects on calcification of bones and it is proved in-vitro. ^(47, 48) the anabolic effects of isoflavones on metabolism of bone is reported in cell cultures. ⁽⁴⁹⁾

Ovariectomized mice were treated with pomegranate juice, peel and totum. After ten weeks of treatment it showed that pomegranate effected the BMD of femur and it also increased the function of osteoblasts and decreased the activity and the expression of osteoclasts when compared to the control groups. ⁽⁵⁰⁾

Guduchi:

Botanical name: *Tinospora cordifolia*.

Guduchi contains alkaloids, terpenoids, lignans, steroids. ⁽⁵¹⁾ It is identifying that 20- OH- β - ecdysone is an active principle which has bone protective effects ⁽⁵²⁾ and it is also reported that this constituent increases the osteogenic proliferation of stem cells and helps in treating osteoporosis. ⁽⁵³⁾

Two in-vitro osteoporotic models such as human osteoblast like cell MG-63 and primary osteoblast cells isolated from femur of rats were taken and these were treated with the alcoholic extract of *Tinospora cordifolia*. Then assays for cell growth and viability, cell differentiation into osteoblasts were evaluated and it showed that the Guduchi promoted the osteogenic differentiation to osteoblasts and it also increased the mineralization of bone matrix. ⁽⁵⁴⁾

Turmeric:

Botanical name: *curcuma longa*

Turmeric contains active principles such as curcuminoids importantly curcumin, demethoxycurcumin and bisdemethoxycurcumin ⁽⁵⁵⁾

Clinical trial was conducted regarding the treatment of turmeric for osteoporosis among 100 patients. The results showed that the curcumin increased the BMD in femoral neck and hip. curcumin present in turmeric suppressed the number of osteoclast progenitors. Hence it inhibits the osteoclastogenesis by inhibiting the cytokines such as NF-kappa B. ⁽⁵⁶⁾

Krishna jeeraka:

Botanical name: *Nigella sativa*.

Nigella sativa extract was orally administered to ovariectomised rats for 12 weeks. Then the results showed that *Nigella sativa* extract treated rats showed increase in bone thickness. ⁽⁵⁷⁾

CONCLUSION:

Osteoporosis is a one of the worldwide disease causing more than 8.9 million fractures per year. Bisphosphonates remain as the first line treatment for osteoporosis. But there is always continuous research is ongoing to get novel medications to the market. Investigations carried out in pathophysiology and their new interventions have found way for the novel drugs and new signalling pathways within bone cells. The cathepsin K inhibitors, PTH related peptides have showed promising osteoporotic actions for the future use. Herbal remedies for treating osteoporosis include turmeric, pomegranate, Krishna jeera, Guduchi etc.

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