Review Article

Treatment of Osteoporosis: Current Scenario from a Research Perspective

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ABSTRACT

Osteoporosis is a condition of compromised bone quality and bone density increasing the chances of fracture. In osteoporotic bone, there is a mismatch between bone formation and resorption. The high probability in both women (33.33%) and males (20%) over the age of 50 worldwide to suffer a fracture draws attention to the importance of treatment of osteoporosis. The benefits of using bisphosphonates, the first line of therapy in osteoporosis lasts for 5 years. The other drugs are recommended for a still shorter time. The state of usage of current drugs is discussed. Two drugs Abaloparatide and Romosozumab have been recently approved. There is a better understanding of the means of communication amongst the different players in bone remodeling. These players involved in remodeling, are subjected to local and systemic influences. This increased understanding of physiology led to molecules being investigated which acts on newer targets such as Cathepsin K, $\alpha_v\beta_3$ integrin, chloride channel 7, tryptophan hydroxylase 1, Src, calcium-sensing receptor. Also, a bone anabolic effect for certain drugs belonging to different therapeutic classes such as statins, nitrates, thiazides, beta-blockers has been noted. However, for these drugs, further studies regarding the dose and frequency of drug administration and the effectiveness in the prevention of fractures along with safety profiles are needed. The drugs acting on new targets and new uses of old drugs hold hope to increase our arsenal against osteoporosis and thus preventing the mortality and debility due to fractures.

Key words: Abaloparatide, Romosozumab, Cathepsin K, Chloride channel 7, $\alpha_v\beta_3$ integrin.

INTRODUCTION

'Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality. Bone density is expressed as grams of mineral per area or volume and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (e.g. microfractures) and mineralization'.[1]

Osteoporosis is of two types: primary and secondary osteoporosis. Primary osteoporosis is seen in women due to menopause and in both genders due to advanced age. Secondary osteoporosis is following the intake of drugs or due to diseases. Drugs such as glucocorticoids, histamine and diseases such as hypogonadism, celiac disease cause bone loss.[1]

According to the International Osteoporosis Foundation (IOF), 1 in every 3 women and 1 in every 5 men over 50 years will experience a fracture. 25% of those suffering from hip fractures would die or be bedridden. Osteoporosis results in 8.9 million fractures every year. Thus 1 fracture occurs every 3 sec. Most fractures occur in postmenopausal women. Women above 45 years will spend more days in the hospital due to osteoporotic fracture compared to other

Submission Date: 14-08-2019;
Revision Date: 18-10-2019;
Accepted Date: 03-12-2019

DOI: 10.5530/ijper.54.1.2

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diseases such as diabetes, myocardial infarction and breast cancer. It is forecasted that the number of hip fractures in men in 2025 would be similar to the number in women in 1990.[2]

The combined lifetime risk for hip, forearm and vertebral fractures, coming to clinical attention, is around 40% in women, equivalent to the risk for cardiovascular disease in developed countries. The lifetime risk for hip fractures exceeds 20% in these countries. This is half in the case of men.[3]

Osteoporosis in Asia is not diagnosed, particularly in the rural population as the DEXA machine is expensive and not available. Almost all the Asian countries have an average dietary daily intake of calcium 450mg/day, which is way below the FAO/WHO recommendation of 1000 to 1300 mg/day. Also, Asians have a vitamin D deficiency. It is projected that 50% of all hip fractures would be in Asia by 2050.[2] In a study, there was a prevalence of osteopenia in 50% and osteoporosis in 29% in low-income Indian women aged 30-60 years.[4]

The danger of osteoporosis is fractures which could lead to disability or even death. Forearm, humerus, hip and spine are common fracture sites.[3]

Irrespective of the initial cause, finally there is an imbalance between bone formation and bone resorption.[5] These two processes take place in the Bone Remodelling Cavity. The bone cells are the main players in bone remodeling.

Bone Remodelling

Players involved in bone remodeling

There are two main bone cells–osteoblast and osteoclast. Osteocytes and bone lining cells are formed from osteoblasts. The osteoblast is formed from the Mesenchymal Stem Cells (MSC) and osteoclasts are formed from the Hemopoietic Stem Cells (HSC).

Osteoblasts are columnar to cuboidal in shape having a diameter of 20 to 30 μm. They contain a single nucleus, plentiful endoplasmic reticulum, ribosomes and Golgi apparatus and mitochondria. Their plasma membrane contains an alkaline phosphatase enzyme. The MSC are pluripotent cells and can convert into myocyte, adipocyte, chondrocyte or osteoblast. Whether the cell will commit to forming osteoblast depends on the expression of various transcription factors in response to numerous cell signals. Out of which runx-2 is believed to play a key role. The expression of runx-2 depends on systemic and local factors. One important signaling molecule is Wnt. Wnt binds to its receptor Frizzled which along with its co-receptor activates the canonical Wnt pathway. Osteoblast deposit bone in two steps. They secrete first the various matrix proteins including collagen and non-collagenous proteins such as osteocalcin, osteopontine, bone sialoprotein, osteonectin and proteoglycans such as decorin and biglycan. This is then followed by mineralization of the matrix.[6]

Osteocytes are flat osteoblastic cells trapped in the bone matrix, which do not secrete alkaline phosphatase and do not deposit the bone matrix. The osteocytes are present in the lacunae and are connected to the bone lining cells and osteoblast by the lacunocanalicular system. The osteocytes due to the presence of the lacunocanalicular system act as mechanosensors. Any physical change in external conditions causes fluid present in the canaliculi to change leading to osteocyte response. Osteocytes secrete Fibroblast Growth Factor 23 (FGF 23) which decreases serum phosphate levels by decreasing absorption and increasing excretion of phosphate.[7]

The inactive osteoblasts present on the bone surface form the bone lining cells. These quiescent bone lining cells can take up a large quantity of calcium and give out a large quantity of calcium to the blood. Based on the rate at which the serum calcium homeostasis is maintained, Green and Kleeman *et al.* suggested the quiescent cells are responsible for serum calcium levels, rather than the bone remodeling process.[8] However, others attribute the function of maintaining serum calcium level to the remodeling process.[8,9]

Osteoclasts are 20 to 100μm in diameter. They are multi-nucleated. During resorption, they have a ruffled plasma membrane. Osteoclast originates from the hemopoietic stem cells (HSC). The HSC in the presence of transcription factor PU.1 develops the c-Fms receptor which can bind to Macrophage Colony Stimulating-Factor (m-CSF). Binding of m-CSF to c-Fms leads to the expression of receptor activator of nuclear factor -KB (RANK). Receptor Activator of Nuclear Factor -KB Ligand (RANKL) secreted by osteoblasts-RANK binding leads to the formation of multinucleated osteoclasts. Osteoprotegerin (OPG), a decoy receptor for RANKL prevents the binding of RANKL to RANK. Various cytokines are involved in the activity and determine the life span of osteoclasts. The osteoclast forms a ruffled border and adheres tightly to the bone surface by podosomes (containing actin) thus forming a sealing zone of an actin ring. Osteoclasts attach to an arginine-glycine-aspartate peptide (RGD) of the matrix protein via integrins present on the osteoclast cell membrane, of which $\alpha_v\beta_3$ integrin is the most common. Osteoclasts, then, secrete acid (H^+ via H+ATPase and Cl^- via chloride channel ClC7 channel) and enzymes including Cathepsin K, Matrix Metalloproteinases 9 (MMP-9) and Tartrate-Resistant Acid Phosphatase (TRAP). The acid

and enzymes breakdown the matrix and solubilize the salt. This results in saucer-shaped Howship Lacunae in the trabecular bone and the cutting cone in the cortical bone.

Process of Bone Remodelling

The bone remodeling cycle lasts for 120 days in cortical bone and 200 days in trabecular bones. Bone remodeling can be targeted or non-targeted. Targeted is in response to microcracks where apoptosis of osteocytes triggers the remodeling. Non-targeted bone remodeling is not at any specific site but is triggered by systemic factors such as Parathyroid Hormone (PTH) and is needed for calcium and phosphate homeostasis.[7] Bone Remodelling takes place in the Bone Remodelling Cavity (BRC) (Figure 1). The BRC consists of Basic Multicellular Units (BMU) containing osteocytes, osteoclasts and osteoblasts and nearby blood capillaries. The BMU is covered by a canopy of bone lining cells that are in contact with the quiescent bone lining cells. These quiescent lining cells are in turn in contact with osteocytes via the lacuno canalliculae network.[8]

Remodeling involves the following steps: Activation, Resorption, Reversal, Formation and Termination. Activation involves the conversion of osteoclast precursors to osteoclast. Resorption by the osteoclasts takes 2 to 4 weeks. This is followed by a reversal, the period where the resorption stops and bone formation begins. New bone is deposited by the osteoblast, this takes 4 to 6 months. Finally, half of the osteoblast undergo apoptosis while remaining get converted to osteocyte or bone lining cell.[9]

In bone remodeling the processes which stop resorption and begin formation are crucial. However, the exact picture is not clear. By staining and using *in-situ* hybridization in cortical decalcified bone sections, Lassen *et al.* observed, the tip of the cutting cone had many osteoclasts, also the middle section had osteoclast interspersed with reversal cells (which are recognized as osteoprogenitor cells) and only osteoblast at the closing cone. They concluded the osteoclasts at the tip is responsible for elongating the tunnel. The osteoclast continues widening the tunnel till certain threshold numbers of osteoprogenitor cells are present and once bone formation starts there are no osteoclasts present. They proposed a similar mechanism in case of cancellous bones as here too there are osteoclasts and reversal cells present and these reversal cells have to be present beyond a threshold for resorption to stop and formation to begin.[11] A number of coupling factors are proposed to play an important role in reversal phase such as factors released from the matrix such as transforming growth factor β (TGFβ), Bone Morphogenic Protein (BMP), Insulin like Growth Factors -I, II (IGF-I, II) as well osteoclasts themselves seem to play a part in reversal.

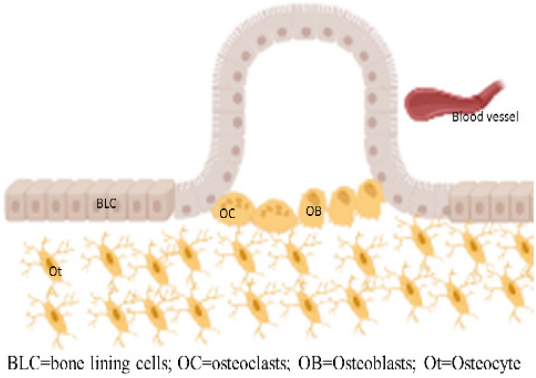
Functions of remodeling

The main functions of remodeling are the repair of microcracks and calcium and phosphate homeostasis. Remodeling takes place at random sites and where there are microcracks. A right balance of bone remodeling is essential. Low bone remodeling would lead to increased strength, however with an accumulation of microcracks. High remodeling, would lead to a decline in the quality of the microarchitecture in bones.[11]

Communication amongst the players

Bone remodeling is a well-orchestrated event; the players communicate with each other and are also influenced by various local and systemic factors (Figure 2).

Apoptosis of the osteocytes leads to the release of RANKL. RANKL interacts with RANK on the pre-osteoclast which gets differentiated into osteoclast which has a ruffled border and is multinucleated. Ephrin B2 is present on the osteoclast cell membrane; whereas



BLC=bone lining cells; OC=osteoclasts; OB=Osteoblasts; Ot=Osteocyte

Figure 1: Bone Remodelling Cavity (BRC).[10]

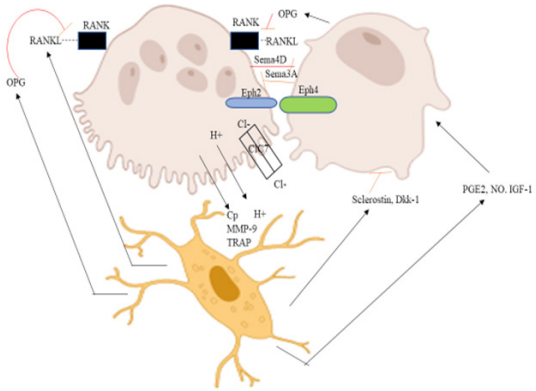


Figure 2: Communication amongst bone cells.[12]

OPG=Osteoprotegerin; RANKL=Receptor Activated Nuclear K B Ligand; Cp=Cathepsin K; MMP9=Matrix Metalloproteinase; TRAP='Tartrate Resistant Acid Phosphatase; Dkk1=Dickkopf 1; PGE_2=Prostaglandin E_2; NO=Nitric Oxide.

EphrinB4 is present on the osteoblast cell membrane. EphrinB2-EphrinB4 interaction leads to osteoblast formation whereas the reverse interaction inhibits osteoclast formation. Osteoclast secretes Sema4D which inhibits osteoblast; whereas the osteoblasts secrete Sema3A which inhibits osteoclasts. RANKL and OPG are secreted by osteoblast. m-CSF secreted by osteoblast and osteocytes stimulates RANK expression. m-CSF and RANKL lead to osteoclastogenesis by binding to c-Fms receptor and RANK respectively on osteoclast; OPG serves as a decoy receptor thus decreasing RANKL-RANK interaction. BMP, IGF released from the matrix stimulates osteoblast activity. The osteocytes secrete Sclerostin and Dickkopf which inhibits osteoblast formation. Osteocytes also secrete PGE_2, NO and IGF-1 which promotes osteoblastogenesis.[12]

Bone remodeling is a complex process where cells other than the bone cells influence its course. In addition to osteoblasts, the marrow stromal cells and T cells also secrete RANKL.[9] During normal remodeling, B cells secrete more than half the quantity of total OPG thus preventing RANKL-RANK interaction and osteoclast differentiation. Under normal conditions, osteocytes secrete TGF-β, which prevents the formation of osteoclasts.[13]

The effects of bone cells are not restricted to the bone only. Osteocytes secrete Fibroblast Growth Factor (FGF) 23, phosphate regulating endopeptidase homolog, X-linked and Dentin Matrix Protein 1 which regulates phosphate homeostasis.[14] Osteocalcin secreted by osteoblast increases pancreatic insulin secretion. Insulin causes a decrease in OPG which in turn would lead to increase osteoclast formation.[15]

In addition to interaction amongst the bone cells and the release of mediators, other factors trigger resorption/formation. These include inflammatory mediators and mechanical strain. The bone cells respond to local stimuli as well as to systemic stimuli such as estrogen, glucocorticoids, calcitonin, calcitriol, growth hormone, leptin, serotonin, Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), Parathyroid Hormone (PTH).

As osteoporosis is a 'silent disease' where the patient is unaware of the disease until he has a fracture. Therefore, identifying risk factors becomes important. These risk factors are either fixed or modifiable (Table 1).

Table 1: Risk factors for Osteoporosis.[2]

Fixed risk factors	Modifiable risk factors:
Female gender	Smoking
Age	Chronic alcoholism
Genetic makeup	Low Body Mass Index
Ethnicity	Drugs such as: corticosteroids, anxiolytics, neuroleptics, anti-depressants, proton pump inhibitors and other drugs
Hypogonadism in male and females	Low body weight and weight loss
Rheumatoid arthritis	Falls would lead to fractures
	Inadequate nutrition
	Vitamin D deficiency
	Anorexia nervosa
	Sedentary lifestyle

Drugs Approved for use in Osteoporosis

Bisphosphonates

These include non-nitrogen containing bisphosphonates including etidronate, clodronate and tiludronate and nitrogen-containing bisphosphonates including pamidronate, risedronate, alendronate, ibandronate, zoledronate. The non-nitrogenous bisphosphonates are incorporated into ATP which results in osteoclasts apoptosis.[16] The nitrogen-containing bisphosphonates inhibit the farnesyl pyrophosphatase, an enzyme in the mevalonate pathway. This results in inhibition of ruffled border, acid environment and resorption.[15,17] The two main adverse effects with bisphosphonates are atypical femoral fracture and osteonecrosis of the jaw.[18] A summary of three randomized trials showed bisphosphonates did not have any beneficial effect in women with normal bone density and no risk of fracture; whereas it caused harm (atypical fracture, osteonecrosis of the jaw, GI or musculoskeletal disorders) in some patients.[19] In a trial, alendronate was effective in reducing the hip, vertebral and non-vertebral fractures in women with existing spine fractures. Another trial showed, that with no existing fractures there was no significant reduction in non-vertebral and hip fractures; however, this was reduced in a subgroup analysis of women with a T score of -2.5 and lower. Two clinical trials of risedronate, demonstrated risedronate decreased the risk of vertebral, non-vertebral and hip fractures. Ibandronate was shown to decrease the vertebral fractures and had no effect on non-vertebral fractures, however, in a subgroup of women with T score below -3 there was a reduction in non-vertebral fractures. Zoledronic acid given as once a year infusion caused a significant decrease in hip, vertebral and non-vertebral fractures. Zoledronic acid causes flu-like symptoms for up to 3

days. In a few cases, it increases the risk of atrial fibrillation.[18] Combining three Cochrane reviews, it was seen in the case of women with very low bone density or with a prior history of fracture, bisphosphonates prevented vertebral fracture in 1 out of 20 and prevented hip fracture for 1 in 100 women. A small number of women experienced the harmful effects of bisphosphonates.[20]

Denosumab

It is a monoclonal antibody against RANKL thus prevents RANKL-RANK interaction, therefore differentiation to osteoclasts. FREEDOM, the largest randomized trial where Denosumab was compared to a placebo in which women with a T score of -2.5 or lower up to -4.0. were administered Denosumab 60mg *s.c.* or placebo every 6 months for 3 years. The NNT for prevention of new vertebral fracture was 21; non-vertebral fractures were 71 and hip fractures were 230. A meta-analysis of 13 trials found the prevention of non-vertebral fractures in the Denosumab group was non-significant (NNT=121) and a non-statistically significant difference in infection (NNH=167). The long-term safety of Denosumab has not yet been established.[21]

Denosumab decreases the risk of vertebral, non-vertebral and hip fractures in women with a T score of -2.5 to -4. It also causes atypical femoral fracture and osteonecrosis of the jaw.[18] RANKL is a costimulator for activation of T cells. Though there was an increase in infections in the Denosumab group compared to placebo in the FREEDOM trial; there is no clear relation to the time or duration of exposure which would lead to infection.[22]

Teriparatide

Teriparatide (1-34) is an analog of PTH (1-84). PTH increases the serum calcium levels by increasing calcium absorption from the intestine, increase osteoclastic activity and increase the resorption of calcium from renal tubules. Intermittent PTH has a bone formation effect. Teriparatide (PTH 1-34) increases the number of osteoblasts by increasing its formation by increasing the differentiation of pre-osteoblasts to osteoblasts and decreasing their apoptosis.[23] In addition to its effects on the bone, PTH fragment also affects the calcium absorption from intestine and calcium and phosphate reabsorption from the kidneys. The use of Teriparatide is limited to 2 years as its long-term safety is not yet proved.[24] In a 21-month study, involving women with low BMD and vertebral fracture, Teriparatide has been associated with a decrease in vertebral and non-vertebral fractures but not hip fracture. It is approved to be used for 2 years. Stopping Teriparatide would lead to a decrease in BMD and thus increases the risk of fracture.[25] Therefore, Teriparatide should be followed by bisphosphonate to preserve its beneficial effects.

Romosozumab

Sclerostin is produced by osteocytes which inhibits bone formation. Therefore, antibodies to Sclerostin would increase bone formation. Anti-sclerostin treatment in preclinical studies has shown to initiate bone modeling on the inactive trabecular bone surface followed by decrease resorption. Thereafter, there is an attenuation of bone formation and a decrease in resorption. There is a net bone gain. Similar effects were seen on the cortical bone with an increase in bone mass and bone strength. Sclerostin is also produced by chondrocytes and synovial cells. Sclerostin deficit mice develop severe osteoarthritis. The effect of inhibition of sclerostin could have an injurious effect on the cartilages and joints. Wnt pathway is also involved in cell proliferation. The inhibition of this pathway could lead to an increase in osteosarcoma. During Phase III i.e. Fracture Study of Postmenopausal Osteoporosis trials a comparison of Romosozumab, an antibody against sclerostin and placebo for 12 months followed by Denosumab for 12 months in both the groups was made. Compared to the placebo group, there was a relative risk reduction for vertebral fractures by 73% during the first year of treatment. This relative risk was maintained at the end of the second year in the Romosozumab group when both the groups were given Denosumab. The injection site reactions were more for the Romosozumab group compared to the placebo group. Also, two patients developed osteonecrosis of the jaw and one patient had an atypical fracture. There wasn't much difference in the mortality or cardiovascular disease, or adverse effects related to osteoarthritis/back pain/hyperostosis. Anti-bodies to Romosozumab were observed in a few patients who received Romosozumab, however, the efficacy of Romosozumab was seen in spite of them being present. In another fracture endpoint Phase III trial, there were two groups, one was given Romosozumab and the other Alendronate for 12 months, this was followed by both the groups given Alendronate for 12 months. Here too the Romosozumab group had better outcomes compared to the Alendronate group alone. In the ARCH study, there was a preliminary concern about cardiovascular safety. Development of Blosozumab, an anti-sclerostin antibody, was stopped after Phase II, as it caused frequent or severe reactions at the injection site. The risk for non-vertebral fracture in the FRAME study was not significantly lower compares to placebo.[26,27] USFDA has approved Romosozumab on April 9, 2019,

with a boxed warning regarding the cardiovascular risk for myocardial infarction, stroke and CV death. It is approved for women with a prior history of fracture, or those with multiple risk factors for fracture or who cannot take another osteoporotic therapy or the other therapies are not effective. The drug is effective for 12 doses thereafter its effect wanes.[28]

Estrogen/Selective Estrogen Receptor Modulator (SERM)

Estrogen therapy decreases the risk of hip, vertebral and non-vertebral fractures. However, it is associated with an increased risk of breast and uterine cancer. It is also associated with deep vein thrombosis and thromboembolism. Hence it is not recommended as the first-line therapy in osteoporosis. Raloxifene, a selective estrogen receptor modulator decreases the risk of vertebral fracture but has no effect on hip fracture. It decreases the risk of breast cancer however there is an increased risk of thromboembolism. Newer SERMs approved include Lasofoxifene and Bazedoxifene. These show a decrease in vertebral and non-vertebral fracture risk without having uterine side effects but associated with thromboembolic effects and hot flushes.[29]

Calcitonin

In the year 2012, the European Medical Agency (EMA) has recommended against the prescription of nasal calcitonin for osteoporosis. It asserts the fracture reduction efficacy has not been proved and there is an increased risk of malignancy. Calcitonin in injectable form may be used for minimal time with minimal dose in patients who are immobilized, those with Paget's disease not responding to alternative therapy or those with hypercalcemia due to cancer.[30]

Strontium ranelate

Two Randomised Clinical Trial (RCT), the Spinal Osteoporosis Therapeutic Intervention (SOTI) trial and TReatment of Peripheral OSteoporosis (TROPOS), have established the anti-fracture efficacy of Strontium ranelate for vertebral and non-vertebral (including hip) fractures. EMA in 2012, has raised concerned regarding the cardiac safety of Strontium ranelate due to increased incidence of Myocardial Infarction (MI). EMA has contraindicated its use in patients with uncontrolled hypertension and those who have had ischemic heart disease and/or peripheral arterial disease and/or cerebrovascular disease.[31] This has led to a decrease in the number of patients taking strontium ranelate, due to commercial reasons the manufacturer has stopped its marketing in the UK.[32]

Abaloparatide

Abaloparatide an analog of parathyroid related protein [PTHrP (1-34)] was approved on April 28, 2017, by USFDA. PTH is secreted by the parathyroid glands. PTHrP is secreted by many cells and has a local effect. PTHrP has the same effects on the bone and kidney as PTH. However, it has minuscule if at all, effects on intestinal calcium absorption.[33] Abaloparatide have been approved in patients with high risk for fractures i.e. those with a history of fractures, associated with multiple risk factors or who are unable to use another anti-osteoporotic medicament.[34] It is approved for two years due to uncertainty regarding its safety profile. Abaloparatide binds to the RG conformation of PTHrPR; which results in more anabolic effect. It has been proposed Abaloparatide has greater bone formation effect than Teriparatide and lesser effect on bone resorption; with lesser tendency to cause hypercalcemia.[33]

Calcium and Vitamin D

In the Women's Health Initiative (WHI) study, the group consuming calcium and vitamin D supplement had a higher incidence of kidney stones compared to the placebo group. The recommended standard for calcium is 1000-1500 mg per day and vitamin D is 600-800 IU/day.[18] Out of the many randomized trials only the patients who are frail, elderly and institutionalized benefit from the supplementation of vitamin D along with calcium. The NNT to prevent hip fracture is 42. None of the other groups of patients benefitted. The NNH was 36 for developing kidney stones or renal insufficiency. In non-institutionalized patients, there was increased harm and increased fractures in Vitamin D treated group; calcium supplement has been associated with increased heart attacks.[35]

New Targets Explored

An increased understanding of the physiology of bone remodeling and factors which influence it has led to the exploration of new targets.

Inhibition of Cathepsin K

The osteoclasts bind to the matrix and create a sealing zone where they release acid and enzymes such as Cathepsin K. Cathepsin K acts on type 1 collagen, osteopontin and osteonectin, the bone matrix-forming proteins. Cathepsin K is found in osteoclasts, heart, lungs and liver. Inhibiting Cathepsin K would lead to decrease resorption. Therefore, inhibitors of Cathepsin K were explored. Balicatib's clinical trials were stopped as it caused skin adverse effects, which was ascribed to its non-specific Cathepsin inhibition i.e. B and L in addition

to K.[36] In September 2016, Merck and Co. discontinued the development of Cathepsin K inhibitor Odanacatib. Odanacatib, though it decreased the fracture incidence; increased cardiovascular events and stroke.[37]

$\alpha_v\beta_3$ antagonism

$\alpha_v\beta_3$ is the most abundant integrin found on the osteoclast cell membrane. This integrin is responsible for the attachment of osteoclast to the RGD sequence of bone matrix protein. L-000845704, a $\alpha_v\beta_3$ integrin antagonist, increased BMD of lumbar spine and hip in postmenopausal women in a phase 2 trial.[38]

Chloride Channel-7 (ClC-7) inhibitors

Mice lacking CLC-7 do not have any active osteoclast, therefore no bone loss. However, bone formation continues. ClC-7 is specific to osteoclasts, ovaries, Purkinje cells and appendix. NS3736 (1-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea), a chloride channel inhibitor, prevented bone loss in OVx rats.[39] Inhibiting ClC-7 affects only resorption, without affecting bone formation thus providing an exciting target as here the coupling mechanism does not seem to hold.[40]

Glucagon-like peptide 2 (GLP2) molecules

A diurnal cycle of bone remodeling takes place with maximum resorption at night. Food intake results in the release of GLP2 which indirectly decreases the secretion of PTH. In two randomized controlled trials, the administration of GLP-2 at night to post-menopausal women prevents the resorption at night, without changing the bone formation rate. There were no serious adverse events and a modest decrease in the hip BMD.[14] Further studies are warranted.

Src inhibitors

Src, a non-receptor tyrosine kinase, plays a role in adding a phosphate group to tyrosine residues on proteins from ATP. Src is important for the formation of the ruffled border and bone resorption. Src inhibitor Saracatinib, decreased bone resorption in phase I trials.[41]

Calcilytics

These inhibit the calcium-sensing receptor on the parathyroid gland, thus causing the release of PTH. This was expected to have an effect like Teriparatide. Ronacaleret, a calcilytic, though effective in animals, was not effective in human trials.[42]

Inhibition of Tryptophan Hydroxylase1 (TPH1)

TPH1 is present in the GIT and pineal. TPH is the rate-limiting enzyme for the synthesis of serotonin. Peripheral serotonin decreases bone formation by acting on the osteoblast.[43] Inhibition of TPH1 in rodents led to a cure of osteoporosis in ovariectomized rodent models.[44] Attacking on newer targets would pave the way for better molecules. Molecules acting on these new targets provide hope for the discovery of an ideal anti-osteoporotic drug and thus saving patients from the painful consequences of fractures.

Bone Anabolic Effect of Drugs Currently used for other Indications

Statins

MSC is a pluripotent stem cell, which may differentiate into either osteoblast, myocyte, adipocyte, chondrocyte; depending on the differentiating factors present. Adipose tissue secretes leptin which has a direct effect on the bone cells and central effects.[45] A meta-analysis of various trials and cohort studies reveal that statins increase the BMD and decrease fracture risk with greater benefit in male patients rather than female patients.[46]

Nitrates

The exact mechanism by which Nitric Oxide (NO) acts is not known. It is suggested nitrates would cause local vasodilation which in turn would have an effect on osteocytes similar to mechanical loading or it could have a direct effect on osteoblasts and osteoclasts. In a randomized clinical trial, the nitro-glycerine ointment was administered for 2 years to 243 post-menopausal women with T score at lumbar spine between 0 to -2; there was an increase in BMD at the hip, spine, femoral neck. Nitrates are unique in which they have a more positive effect on cortical bone rather than trabecular bone.[47] Analysing data of WHI trial, postmenopausal women who took nitrates when needed were shown to have an increase in BMD and decrease the risk of total and arm/wrist fractures.[48]

Thiazide Diuretics

Thiazide diuretics decrease the excretion of calcium. This may be the reason for the increase in the hip BMD of patients taking Hydrochlorothiazide for 3 years compared to those taking placebo.[49]

Beta-blockers

Sympathetic activation is associated with a decrease in bone formation and an increase in bone resorption. A meta-analysis of various trials associates Beta 1 selective blockers with a decreased risk of fracture.[50]

CONCLUSION

The currently approved drugs are recommended for a short duration of time, as there is no additional benefit

seen with continuous use or the safety profile is not yet established. The latest two additions - Abaloparatide and Romosozumab, are approved for those with a history fracture or multiple risk factors or unable to take existing drugs or due to the failure of existing drugs. More drugs are needed to add to the existing lot. With a greater understanding of the physiology of bone remodeling, molecules can be evaluated on newer targets. Further study would reveal whether molecules acting on these newer targets would be effective. There also is a possibility of finding a new use for existing drugs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

BMP: Bone Morphogenic Protein; **BMU:** Basic Multicellular Units; **BRC:** Bone Remodelling Cavity; **ClC-7:** Chloride Channel-7; **FGF 23:** Fibroblast Growth Factor 23; **FSH:** Follicle-stimulating hormone; **GLP2:** Glucagon-like peptide 2; **HSC:** Haemopoietic stem cells, **IGF-I, II:** Insulin like Growth Factors -I, II; **IOF:** International Osteoporosis Foundation. **LH:** Luteinizing hormone; **m-CSF:** Macrophage Colony Stimulating-Factor; **MMP-9:** Matrix Metalloproteinases 9; **MSC:** Mesenchymal stem cells; **NNH:** Number needed to harm; **NNT:** Number needed to treat; **NO:** Nitric Oxide; **OPG:** Osteoprotegerin; **PTH:** Parathyroid Hormone; **PTHrP (1-34):** Parathyroid related protein; **RANK:** Receptor activator of nuclear factor – KB; **RANKL:** Receptor activator of nuclear factor -KB Ligand; **RCT:** Randomised Clinical Trial; **RGD:** Arginine-glycine-aspartate peptide; **SERM:** Selective Estrogen Receptor Modulator; **TGFβ:** Transforming growth factor β; **TPH1:** Tryptophan Hydroxylase1; **TRAP:** Tartrate-Resistant Acid Phosphatase; **WHI:** Women's Health Initiative.

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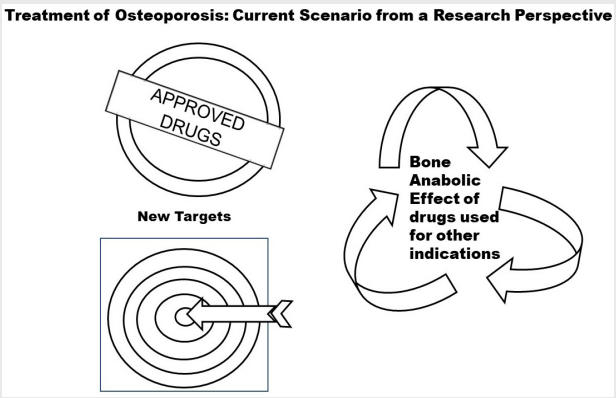
PICTORIAL ABSTRACT



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Cite this article: Pherwani PU, Sathaye S. Treatment of Osteoporosis: Current Scenario from a Research Perspective. Indian J of Pharmaceutical Education and Research. 2020;54(1):8-16.