# Chapter-2

## OSTEOPOROSIS AND CURRENT DEVELOPMENTS

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Chapter-2  Osteoporosis and Current Developments

2.0 INTRODUCTION

Bone is an important connective tissue which plays a vital role in two major functions, i) in providing of mechanical integrity for locomotion and protection ii) in the metabolic pathways associated with mineral homeostasis. Bone also plays additional function as a primary site of hemopoiesis and component of the immune system.¹ There are two important cells which play an important role in maintenance of the bone architecture by mending and rebuilding themselves as 'osteoblasts' that form bone and the 'osteoclasts' that resorb (destroy) bone. The imbalance in the functioning of the cells results in osteoporosis as and when the activity of the bone destroying osteoclast cell outpaces that of bone forming osteoblasts, the bottom line is bone loss.

The term osteoporosis a histological diagnosis "porous bone" entered the medical parlance in France and Germany during the past century. Thus osteoporosis can be defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Osteoporosis and related fractures represent major public health concerns that will only increase in importance as life expectancy increases and the population ages. It has been recognized as a global problem by the World Health Organization (WHO).²

The bone functions to afford the load-bearing material and a repository for mineral. Skeletal architecture provides shape and structure to bone. Osteoporosis is the major medical issues with the increasing incidence of osteoporosis with subsequent morbidity in the todays era. Osteoporosis is a disabling disease characterized by compromised bone strength, and increased probability of patients for towards the risks of fracture. In the United States at least one-quarter of the postmenopausal women’s are affected by osteoporosis and the proportion will rises to 70% in women older than 80 years.³⁻⁵ The osteoporosis reflects the 35% of women population older than 50 years having an osteoporotic fracture which causes a significant communal and monetary burden on society.⁶ The annual first-year direct cost of treating all osteoporotic fractures is estimated at 25 billion and according to literature one person in the Europe maintain an osteoporotic fracture every 30’s.⁷ This disabling disease is not limited to women but the older men can also be affected.⁸ In the future it is premeditated that by 2050, the worldwide occurrence of hip fracture is projected to increase by 310% and 240% in men and women, respectively.⁹ The risk of fracture raised from osteoporosis is around 40%, equivalent to the risk for cardiovascular disease.¹⁰ Therefore the osteoporotic fractures, are the main cause of significant mortality, morbidity, and monetary cost.
The bone loss occurring in both the male and female is a resultant of the natural process of aging. In young adult the rate of bone loss is slow because the remodeling is slow, but it accelerates in postmenopausal women’s due to augmented bone turnover and results in trabecular thinning, disappearance and loss of connectivity, cortical thinning, and increased intracortical porosity leading to fractures.

2.1 Current treatments available

2.1.1 Antiresorptive agents

The current treatments available today are antiresorptive agents including estrogens, selective estrogen receptor modulators (SERMs) such as raloxifene, bisphosphonates (alendronate, risedronate, and ibandronate), and calcitonins all aimed at inhibiting osteoclastic resorption reducing the progression of trabecular thinning, loss of connectivity, cortical thinning, and porosity.

The antiresorptive agents are although successful for the treatment but they lack the ability to replace the lost bone and helps only in reducing the bone loss. The effectiveness of these agents depends on early diagnosis or onset of osteoporotic conditions therefore these agents are ineffective in the fracture condition rise as a consequence of osteoporosis. The examples of the antiresorptive agents are presented in figure 2.1

![Image of antiresorptive agents]

**Figure 2.1. The examples of the antiresorptive agents**

2.1.2 Anabolic Agents

Anabolic agents act by stimulating the formation of new bone and thus provide an additional option for osteoporosis patients. They provide a major advancement in the treatment of osteoporosis and are capable of increasing bone mass to a greater degree than antiresorptive agents with the capacity to improve both the bone quality and strength. Parathyroid hormone PTH (1−34) and PTH (1−84) are the only anabolic agents available for clinical use, which not only increase bone mass but also bone quality and strength by improving microarchitecture and geometry. Recently, PTH (1−84, Preos) has been launched in Europe, including U.K., and is awaiting FDA approval in the U.S. However, PTH is the therapy of last resort and is
recommended for a maximum of only 24 months in the U.S. and in Europe. Major drawbacks associated with PTH are its parenteral route of administration and the risk of developing osteogenic sarcoma. Therefore there is an emergent need of inexpensive skeletal anabolic agents to treat bone deficit conditions such as osteoporosis as well as fractures.

2.1.3 Growth factors
The complex pathways involved in the bone formation and maintainance are also important targets for therapy as they play essential roles in the complex cascade leading to mature bone formation. The Bone morphogenic Proteins-2 (BMP-2) and platelet-derived growth factor (PDGF) are approved for local bone repair. In general, growth factors have obvious limitations in their ability to act or to be used systemically. These agents are not used in the local indications due to their high cost of manufacturing. Other factors and compounds, with anabolic activity, are being investigated as potential candidates as anabolic agents. However, in general, the larger the molecule, the higher the cost and the more difficult it is to administer. Therefore there is an emergent need of small innovative and more versatile agents as future potential therapies. The use of clinically available small molecular weight systemic agents for local repair of fractures has met with a number of difficulties. A main approach for the finding the new chemical entities should focus the critically important pathways for bone formation.

2.2 Bone Metabolism
The bone is a metabolically active organ which is comprised of mineral and organic components that determine the successful mechanical function of the skeleton. This skeleton is a result of combination of dense, compact, and cancellous (trabecular) bone, reinforced at points of stress. Bone formation is a complex phenomenon but the general steps included are the conscription and imitation of mesenchymal originator of osteoblasts, differentiation into preosteoblasts, osteoblasts, and mature osteoblasts ultimately result in the accumulation and mineralization of the extracellular matrix. Hence the osteoblasts are the primary regulators or targets of the bone formation and therefore the agents regulating the bone formation act by either increasing or decreasing the differentiation function of the osteoblast are the primary targets for therapy.

Different growth factors in the local or systemic circulation are paly an important role in the bone formation. The local regulators of bone formation act directly on the cells of the
osteoblastic lineage. These growth factors (GFs) are polypeptides with important effects on cell function. These GFs although found systemically but most of them are found locally in the specific tissues as a regulator of cell metabolism. These GFs play an important role in the production of new bone during embryogenesis. The expressions of these GFs have their central role in the regulation of the anabolic response in bone. Here is the quick review of some of the GFs.

2.2.1 Bone Anabolic Growth Factors

PTH, 1, 25 dihydroxy vitamin D3 are the main systemic factors for influencing skeletal integrity. The broad range of locally derived growth factors optimistically impact bone development viz. insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), hedgehogs (Shh and Ihh), transforming growth factor-β (TGF-β), PDGF, vascular endothelial growth factor (VEGF), Wnts, and BMPs (Bone Morphogenic Proteins) probably being the most important of these local bone growth factors.

BMPs play an important role in the regulation of both the temporal and spatial aspects of bone formation therefore, BMPs are considered as the most important therapeutic targets where bone loss is indicated. The factors that affect directly or indirectly to the BMPs are also considered as of equal potential. These factors include proteins such as noggin, dan, chordin, follistatin, and cerberus. The SOST gene product, sclerostin (a BMP antagonist) has been shown to exhibit a pattern of expression in trabecular bone only suggesting it as a potential therapeutic target.23-26 All these affect the complex process of bone formation but it is the interaction of all these GFs and their inhibitors that results in the bone formation.

2.2.2 Platelet-Derived Growth Factor (PDGF)

These are the heterodiameric major growth factors of human blood serum and it exist in two isoforms, the PDGF-1 (A) and PDGF-2 (B) homodimers. It can accelerate fracture healing and periodontal bone repair, when applied locally in vivo,27 while when PDGF was administered systemically it increases bone density and strength of the skeleton.28 PDGF in recent times showed improved periodontal regeneration in humans 29-31 and has been approved by the FDA for the treatment of bone loss associated with advanced periodontal disease in combination with the synthetic bone matrix, β-tricalcium phosphate (β-TCP).

2.2.3 Transforming Growth Factor-β
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TGF-β is the local bone growth factor which is promising key factor in bone formation.\textsuperscript{32} The factor is a polypeptide abundantly present in bone matrix and is produced in response to stimuli given by osteoclastic bone resorption. TGF-β is an extremely strong stimulator of osteoblastic bone development. It results in chemotaxis, proliferation, and differentiation in committed osteoblasts. TGF-β mainly restrains the osteoclast development and osteoclast activity.\textsuperscript{33} It is a stored form of protein released as an inert protein by bone tissue which will be released in its active form during resorption intervened by osteoclasts.\textsuperscript{34} The insightful study of the mode of action concerned for the commencement of this pathway is significant as the activation processes may be fundamental for the indulgent role of TGF-β in remodelin of bone. e.g. A single application of human recombinant TGF-β1 to skull defects induced a dose-dependent increase in intramembranous bone formation in rabbits and defects in sheep.\textsuperscript{35-37}

2.2.4 Fibroblast Growth Factors (FGFs)

FGFs are the preliminary receptors which play an important role throughout the evolution. There are 22 FGFs identified and four FGFs receptors FGFRs which have been discovered in humans and mice.\textsuperscript{38} FGFs are important GFs which play a key controller role in several developmental processes concerning cell fate and differentiation. The human and mouse genetic studies supports that the mutations in the FGF results in developmental disorders comprised of dominant skeletal diseases and cancer which indicate the importance of these GFs in the maintainace of skeletal architecture. The overexpression of FGF-2 cause a variety of skeletal malformations including shortening and flattening of long bones and moderate macrocephaly,\textsuperscript{40} while incessant slow administration of a small amount of FGF-2 hasten bone-derived osteogenic cytokine-induced new bone development.\textsuperscript{41} The local and systemic administration of FGF-1 increases new bone formation and bone density, it can also be adminstred in the bone los conditions associated in the estrogen-withdrawal.\textsuperscript{42} The implantation of rhFGF-4 in bone was shown to stimulate bone formation.\textsuperscript{43} It may also be used in surgical angiogenesis as a bone stimulator in necrotic bone with a single injection of FGF-2.\textsuperscript{44} Therefore FGF is an extremely important growth factor in the bone metabolism.

2.2.5 Vascular Endothelial Growth Factors

There are several known vascular endothelial growth factors (VEGFs), the family members currently includes VEGF-A, -B, -C, -D, -E, and placenta growth factor (PIGF). VEGF-A, exist as different isoforms, which emerge to have exceptional biological functions. These proteins bind
specifically to the three structurally related tyrosine kinase receptors denoted as VEGF receptors-1, -2, and -3. The main influence of the VEGF is to stimulate angiogenesis which appears to play a significant role in cancer. The observation provides the basis for the discovery of VEGF inhibitors as potential therapies in cancer treatment. VEGF has been shown to promote bone growth probably by its effects on angiogenesis.

2.2.6 Growth Hormone/Insulin-Like Growth Factors (GH/IGF)

These play an important role in the development of long bone, homeostasis, and disease, while the IGF 1 and IGF 2 showed good systemic and local effects on bone growth and fracture repair by interactions with binding proteins which regulate their effects on bone. These (IGF) have a role in downstream signaling of PTH on bone as mouse osteoblast cultures PTH treatment increased IGF-I mRNA and protein levels, and alkaline phosphatase activity, which was in an adjunct to phosphorylations of IGF-I receptor, insulin receptor substrate 1 (IRS-1), and IRS-2, essential adaptor molecules for the IGF-I signaling. Further results indicate that the PTH bone anabolic action is mediated by the activation of IRS-1 as a downstream signaling of IGF-I.

2.2.7 Bone Morphogenetic Proteins (BMPs)

BMPS are the most important growth factors which accounts for the major proportion of the osteoinductive potential in bone. Over 20 BMPs family members have been identified and characterized. BMPs are members of the TGF-β superfamily. The BMPs are significantly vital as a directive of bone formation, and now draw the major focus for the bone development.

2.3 BIOLOGICAL FUNCTIONS OF BMPS

Bone morphogenetic proteins (BMPs) have been implicated in a variety of functions. BMPs induce the formation of both cartilage and bone. BMPs also play a role in a number of non-osteogenic developmental processes. Neural induction represents the earliest step in the determination of ectodermal cell fates. In vertebrates, BMPs act as signals of epidermal induction. BMP-2 directs the development of neural crest cells into neuronal phenotypes, while BMP-4 and 7 specifically induce a sympathetic adrenergic phenotype. BMPs give direction to somite development by inhibiting the process of myogenesis. In the limb bud, BMP-2 interacts with the fibroblast growth factor 4 and sonic hedgehog, inhibits limb bud expansion and induces the formation of chondrocyte and osteoblast precursors.
Physiological roles of BMPs and BMP receptor signaling in normal bone formation have been investigated. Injection of BMP-2 locally over the surface of calvariae of mice induces periosteal bone formation on the surface of calvariae without a prior cartilage phase.\textsuperscript{78-79} Over-expression of a dominant-negative truncated BMPR-IB in osteoblast precursor 2T3 cells inhibits osteoblast-specific gene expression and mineralized bone matrix formation.\textsuperscript{80} In the transgenic mice in which expression of a dominant negative truncated BMPR-IB transgene is targeted to the osteoblast lineage using the osteoblast-specific type I collagen promoter, the postnatal bone formation, including bone mineral density, static bone volume and dynamic bone formation rates, is decreased.\textsuperscript{81} These results demonstrate that BMP receptor signaling plays a necessary role in normal postnatal bone formation. The BMP receptor signaling is represented in the figure 2.2.

\textbf{2.3.1 The BMP Pathway and Bone Anabolic Therapies}

\textbf{2.3.2 BMP/SMAD Signaling Pathway}

The bone morphogenetic proteins are very influential promoters of both bone and cartilage and are used in a variety of non-osteogenic developmental processes. These are the multifunctional growth factors belonging to the TGF-β superfamily family. Type I and II BMP receptors and the downstream molecules, SMAD1, 5 and 8 mediate BMP signals. Phosphorylated SMAD1, 5, and 8 form complexes with SMAD4 and translocate to the nucleus where they interact with numerous other important transcription factors such as Runx2/cbfa1 to elicit bone formation.
Figure 2.2. BMP signaling and its regulation. BMP signals are mediated by type I and II BMP receptors and their downstream molecules Smad1, 5 and 8. Phosphorylated Smad1, 5 and 8 proteins form a complex with Smad4 and then are translocated into the nucleus where they interact with other transcription factors, such as Runx2 in osteoblasts. BMP signaling is regulated at different molecular levels: (1) Noggin and other cystine knot-containing BMP antagonists bind with BMP-2, 4 and 7 and block BMP signaling. Over-expression of noggin in mature osteoblasts causes osteoporosis in mice.\(^8^2\) (2) Smad6 binds type I BMP receptor and prevents Smad1, 5 and 8 to be activated.\(^8^3\) Over-expression of Smad6 in chondrocytes causes delays in chondrocyte differentiation and maturation.\(^8^4\) (3) Tob interacts specifically with BMP activated Smad proteins and inhibits BMP signaling. In Tob null mutant mice, BMP signaling is enhanced and bone formation is increased.\(^8^5\) (4) Smurf1 is a Hect domain E3 ubiquitin ligase. It interacts with Smad1 and 5 and mediates the degradation of these Smad proteins.\(^8^6\) (5) Smurf1
also recognizes bone-specific transcription factor Runx2 and mediates Runx2 degradation.\(^{87}\) (6) Smurf1 (Abbreviation) also forms a complex with Smad6, is exported from the nucleus and targeted to the type I BMP receptors for their degradation.\(^{88}\) Over-expression of Smurf1 in osteoblasts inhibits postnatal bone formation in mice.

The bone loss conditions like osteoporosis, osteopenia, nonunion fractures, and bone loss from traumatic injury and other bone deficit conditions are exceptionally difficult to treat with the presently accessible agents that only prevent the loss of bone while lacking considerable bone anabolic activity. The bone anabolic agents either locally or systemically will improve the clinical treatment and repair the bone fracture and helps in integrating and stabilizing orthopedic. The implant therapy of different GFs such as BMP-2, FGF and PDGF has the ability to induce the bone repair rates in the animal model improves the bone formation and bone repair. These agents are used as local administration therapy due to their lack of systemic availability, expense and drug stability in such therapies. Because of this, use of these factors is restricted to their local application. The recombinant human growth factors will provide a way for the local application to stimulate bone formation in humans, but this has been unfortunately variable and disquiet have been raised about the disbursement and drug stability. Therefore when considering many growth factors and hormones involved in bone formation, there is an emergent need for the discovery of small molecular weight compounds that can elicit bone anabolic activity. There are many pathways which play an important role in signaling cascades and processes required to be either activated or inhibited to initiate the bone formation. The major signaling cascade that stimulates bone formation is the BMP/SMAD pathway. It has received the utmost attention and a number of compounds have been discovered which can affect this pathway and lead to bone formation.

### 2.3.3 Agents That Act on the BMP Pathway

In view of the stability and other concerns regarding the different GFs, there is an enormous interest in the invention of new small molecular weight anabolic agents. These are the future therapies for the bone loss conditions still a lot of preclinical and developmental studies suggest the possible use of small molecular weight agents as anabolic agents. The compounds or molecules include both the agents, which not only enhance the expression of anabolic growth factors such as BMPs, but also agents that can directly augment the signaling pathways critically involved in the process of bone formation. In the literature a proportion of the agents that have
been reported to have bone anabolic potential, have the ability to affect the BMP pathway either directly or indirectly. Below is a quick review of the reported anabolic agents that affect the BMP pathway.

2.3.4 Statins

Statins are the low molecular weight anabolic agents which increase the BMP-2 transcription. In the initial discovery of these agents as BMP-2 promoters the 2T3 osteoblast cell line transfected with murine BMP-2 promoter was used to discover the extract from natural product which specifically stimulates BMP-2. After characterization of this extract resulted in the identification of lovastatin as a major constituent. After the initial identification of statins as BMP-2 promoters a series of statins including lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, rosvastatin, pitavastatin, and cerivastatin are widely used agents for lowering cholesterol and reducing heart attacks, hyperlipidemia and arteriosclerosis were screened for BMP-2 promoter activity and except pravastatin all stimulates BMP-2 promotion. The experiments of the statins in human and rodent bone cells have been shown to increase the expression of BMP-2 as confirmed by many others. In the in vitro models of bone formation simvastatin elicits a marked increases in osteoblast accumulation and new bone formation over 4–7 days of culture, while pravastatin could not, consistent with its inability to stimulate the BMP-2 expression. Pravastatin cannot enter cells other than hepatocytes, resulting in its reduced pleiotropic effects correlating with its inability to stimulate new bone formation. It has been reported that compactin (mevastatin) at doses of 1–100 µM suppresses osteoclastic bone resorption in vitro by inducing apoptosis of osteoclasts. Studies confirm that the mechanism is through inhibition of the fusion of preosteoclastic cells and the disruption of actin ring in osteoclasts. This effect is because of the inhibition of prenylation of target proteins by prenyl protein transferases, similar to that seen with bisphosphonates. These findings suggest that statins, while able to stimulate osteoblasts are also capable of inhibiting resorbing osteoclasts. However, these in vitro effects occur at markedly different doses where inhibition of osteoclastic activity is between 1–100 µM, while the bone anabolic effects of these agents occur at doses as low as 0.06 µM. Given the hepatoselective nature of these statin drugs and the high doses required, it is unlikely they would be able to inhibit bone resorption in vivo as suggested previously. Structures of few available statins are represented in the figure 2.3.
a. Mechanism of Action.

Statins are generally known as the HMG-CoA inhibitors. These are acting on the rate-limiting step in the mevalonate pathway affecting the totaling of downstream metabolites mevalonate, farnesyl pyrophosphate, or geranylgeranyl pyrophosphate which inhibit statin-stimulated bone formation. Prenylation plays an important role in the activity of important intracellular molecules including GTPases, such as Rho, Rac, Rab, and Rap. Which have a major role in cellular proliferation and differentiation hence any perturbation of their activity influences cellular activity. The process of bone formation is mainly affected by the inhibition of prenylation by these drugs. As geranylgeranyl pyrophosphate reverses these effects, inhibition of prenylation appears to play a major role in the stimulation of bone formation by this class of drug. Perhaps this observation supports the role of the statins or effects of statins on BMP-2 but the most important finding of this study is that statins themselves would be effective drugs for bone loss conditions, but these findings focus attention on the mevalonate pathway and its relationship to BMP-2 expression and bone formation. This could lead to the identification of other potential molecular targets for drug discovery as well as other therapeutic approaches to enhance bone formation and produce the ideal anabolic agent for osteoporosis.

2.3.5. Proteasome Inhibitors

Proteasomal activity in osteoblasts plays a pivotal role in regulating the intracellular levels of molecules important for many of the critical signaling pathways. The proteosomes plays an important role in the regular lifecycles and degradation for maintaining cellular homeostasis. The proteosomes are the main multicatalytic enzymes meant for protein degradation hence they are working as garbage disposals for removing the damaged or misfold proteins from the cells and the proteins involved in the cell cycle and cell growth regulation and differentiation. Proteosomes play an important role in maintaining the cell cycle regulators, signaling molecule,
tumor suppressors, transcription factors and in preservation and recycling of over 80% of the cellular proteins.

The cAMP pathway through proteolytic degradation of Cbfa1/Runx2 involving an ubiquitin/proteasome-dependent mechanism suppresses the osteoblast function.\(^95\) The inhibition of proteosomal activity consequently results in the elevation of the levels of cbfa1/Runx2 which prolongs the anti-apoptotic effect of PTH.\(^96\) These agents generally enhance the ATF4 amassing in cells which is an important in the regulation of bone cell activity and resulted in the activation of an osteocalcin promoter.\(^97\) The other factors such as Smurf1, an E3 ligase responsible in targeting Cbfa1 and other important transcription factors. It also supports the function of the proteasome in bone cells and has emerged to be an imperative regulatory factor in osteoblast differentiation and a probable molecular target for identification of bone anabolic agents \(^98\) and confirmed where Smurf1 induces Runx2 degradation in a SMAD6-dependent manner.\(^99\) Smurf1 also broadly intermingle with MEKK2, a vital arbitrator of BMP signaling, and promotes the ubiquitination and yield of MEKK2 which negatively regulates osteoblast commotion and rejoinder to BMP through controlling MEKK2 degradation.\(^100\) The proteosomal pathway indeed has the intricate hedgehog signaling mechanism of the Gli family of transcription factors where the activity of Gli2 and Gli3 are synchronized by the proteasome which subsequently resulted in to the increased expression of BMP-2 and results in bone formation.\(^101\) Bone morphogenetic protein is a powerful stimulator of bone formation. It acts through its receptors BMPR-I and -II and through the downstream effector molecules known as SMADs. Structures of some proteosome inhibitors were represented in the figure 2.4

Figure 2.4. Structures of some protesome inhibitors.
2.3.6 Flavonoids

Flavonoids are widely available in various plants and show broad spectrum of activities ranging from anticancer and antibacterial activities to effects on bone. This is the biggest factors in limiting the flavonoids as a drug or as pharmaceutical agents for the treatment of bone deficit conditions. The effects of the flavonoids on bone were firstly reported in 1984, with the example of catergen which showed an improvement in bone quality. After that many flavonoids were tested for their effects on bones. Iprifalvone a synthetic flavonoid has been shown to have effects on bone cells in vitro.

Many of the flavonoids have different roles on bone metabolism in animals and humans. Quercetin has prominent property on bone cells preventing bone loss as well as having marked bone-building properties. The flavonoids like naringerin can act to inhibit HMG-Co reductase and can augment in the confined new bone development and thus being used as a bone graft material. The flavonoids sometimes be termed as phytoestrogen as most of them have the bone formation ability through an estrogen-like activity. Although the majority of the flavonoids inhibit the bone resorption but recent studies support their role as stimulators of new bone formation and therefore they can be considered bone anabolic agents. E.g. BMP-2 promoter activity of Robustone from the Derris robusta plant caused a dose dependent increase in BMP-2 promoter activity in osteoblastic cells.

Many flavonoids influence bone metabolism and most restrain osteoclastic resorption and thus decrease bone loss. But the literature reveals a reported above the possible role of these flavonoids in BMP expression and signaling pathway stimulation to enhance bone formation. Therefore, some flavonoids do affect the BMP pathway and are potential anabolic agents. They do have the clinically relevant as potential to be bone anabolic agents. Although, it is unclear if these agents, mostly from dietary intake, would reach sufficient serum concentrations to elicit a systemic bone anabolic response but it may not preclude their use for local administration for fracture and bone defect repair. Structures of some flavonoids are shown in Figure 2.5.
2.3.7 Antagonists of Sclerostin

The sclerostin is capable of inhibiting the BMP-2 and acts as a negative regulator of bone formation. The amino acid sequence of their antagonist is similar with the DAN family of secreted glycoproteins that share the ability to provoke BMP activity. It is having the ability to bind and antagonize the activities of BMPs but it is unable to antagonize the BMP mediated responses. Sclerostin acts through a different and unique because of its unique expression pattern and function in reducing the bone formation.\(^\text{111}\) it has been suggested that blocking the activity of this factor would increase the anabolic activity leading to enhanced bone formation.\(^\text{112}\) The sclerostin antibodies developed and used had shown a marked increases in bone mass and bone formation.\(^\text{113}\) This is an alternative approach where the bone deficit conditions are particularly correlated with disorders which are resultant of the sites where the sclerostin is expressed. It is consequently uncertain if this would be true at fracture sites or other sites of bone formation.

2.3.8 Prostaglandin Agonists

Prostaglandin (PG) plays significant role in bone metabolism particularly in bone resoroption and hence PGE-2 PG cause the bone resorption but it could also stimulate bone formation.\(^\text{116-117}\) This observation leads basic in the discovery of its tissue-specific pharmacological activity through four different G-protein-coupled receptor subtypes, EP1–4.\(^\text{118-119}\) The EP-2, 4 and FP receptors are have play an important role in mediating the anabolic effects on bone. Literature also supports the role of EP4 receptor in stimulation of resorption (and possibly formation), while activity of the FP receptor produces new trabeculae.\(^\text{120}\) This observation led to the basis of synthsing the EP4 receptor selective prostaglandin E2 agonists which enhance bone formation\(^\text{121}\) and can supplement BMP-induced bone formation.\(^\text{122}\) These agents have been further explored in preclinical studies for their ability to enhance fracture healing.\(^\text{123}\) Although the detailed mechanism of action of these agents as BMP pathway signaling agents is yet to be studied nevertheless these agents do appear to enhance the effects of BMP on bone tissues.\(^\text{124}\)
2.3.9 Parathyroid Hormone (PTH)

PTH is the effective preclinical hormone and effective anabolic agent which is being developed and marketed under the name of Preos for the treatment of osteoporosis. Although unlike PTH-peptide it has not yet been approved. Preos established important fracture risk diminution in postmenopausal women with osteoporosis, with a major incidences of hypercalcemia with Preos compared to placebo.\(^ {125}\) The PTH as a peptide has its own limitation as it can be only given by the injection like the PTH-peptide (Teriparatide) and is very expensive which limits its use for the treatment of osteoporosis and bone diseases. Therefore the PTH-peptide remains the solitary agent with considerable bone anabolic activity. While PTH has been shown to interact with BMP to increase osteoblastogenesis and decrease adipogenesis, other studies show that PTHrP and PTH inhibited BMP induced osteogenesis.\(^ {126}\) PTH has been shown to reduce sclerostin, a very potent inhibitor of the BMP signaling pathway, which is one of the mechanisms of action of PTH.\(^ {127}\)
References


