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Anabolic Agents as New Treatment Strategy in Osteoporosis

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1. Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD), microarchitectural deterioration of bone tissue, and an increase in fracture risk [1]. Several drugs have been developed to treat osteoporosis: most of these are inhibitors of bone resorption. Effective treatment of osteoporosis requires not only resorption inhibitors, but also stimulators of bone formation especially in patients who already have lost a significant degree of bone. Although therapeutic alternatives are available for inhibiting bone resorption, options of bone anabolic agents are much more limited with regard to the bone resorption inhibitors.

Although patients included in randomised controlled trials have osteoporosis defined according to the WHO criteria, i.e. a T score below -2.5 SD and/or prevalent fragility fractures, a large proportion of fractures occurs at T-scores above -2.5 SD and in patients without prior fractures [1]. Therefore, therapies with proven fracture risk reduction efficacy in patients with osteopenia and/or clinical risk factors may contribute to earlier and more effective intervention against fractures.

The past decade has witnessed major advances in the diagnosis and treatment of osteoporosis. It would appear that anabolic drugs challenge prevailing paradigm by stimulating bone formation, therefore enhancing bone turnover. There is a great need to anabolic agents for reverse of osteoporosis. In this review, we summarize current informations about the anabolic agents.

2. Parathormon

Parathyroid hormone (PTH) is released from the parathyroid glands and is an important regulator in the bloodstream's levels of calcium phosphorus. It stimulates both bone formation and resorption [2,3]. Its intermittent low-dose using increases bone formation more than bone resorption, leading to increased bone mass. Intermittent PTH administration increases the number and activity of osteoblasts, enhances the mean wall thickness and trabecular bone volume, and improves bone microarchitecture by establishing trabecular connectivity and increasing cortical thickness [2,4].

Continuous infusions, which result in a persistent elevation of the serum parathyroid hormone concentration, lead to greater bone resorption than do daily injections, which cause only transient increases in the serum parathyroid hormone concentration [5,6]. The anabolic effects of PTH on bone formation are through the medium of PTH receptor-dependent mechanisms. Teriparatide (PTH₁₋₃₄) is the biological active, a recombinant form of PTH [7]. Patients with fractures of postmenopausal osteoporosis administered teriparatide 20 and 40 µg/d in FPT (Fracture Prevention Trial) [8]. After 18 months teriparatide 20 µg/d reduces the risk of spine fracture by %65 and non-spine fracture risk by %53. Over a median of 18 months spine fracture risk reduced by %69 and non-spine fracture risk reduced by %54 with the 40 µg/d regimen [8].

Subbiah et al. reported the second patient to develop osteosarcoma [9]. Although teriparatide reduces osteoporosis related fractures in select patient populations, important contraindications, such as prior radiation exposure, Paget's disease of bone, unexplained elevations of serum alkaline phosphate, open epiphysis should be considered before use.

It has been suggested teriparatide could be useful for treatment of severe and resistant forms of osteoporosis to other medications [10].

In summary, we think that the clinical benefits of parathyroid hormone reflect its ability to stimulate bone formation and thereby increase bone mass and strength. This hormone appears to be effective in preventing fractures in postmenopausal women. However, it should be used attention because of its important contraindications.

3. Strontium ranelate

Strontium ranelate is composed of an organic molecule (ranelic acid) and of two atoms of stable non-radioactive strontium [11]. Strontium naturally present in trace amounts in human body and has close similarities with calcium; act as calcium agonist in most of physiologic process [12].

Strontium is similar to calcium in its absorption in the gastrointestinal track takes place in two ways: passive diffusion and carrier mediated absorption. Both calcium and strontium share the same carrier system, which tends to be greater affinity to calcium. High dietary intake of calcium has been shown to reduce concurrent absorption of strontium [11].

Ingested strontium is distributed in the body in three compartments: plasma extracellular fluid; soft tissue and superficial zone of bone tissue; and bone itself, the greatest portion is the calcified tissues [13]. In bones, total amount of strontium relatively lower than amount of calcium. After its absorption, both strontium and calcium exhibit the same characteristics [12].

The strontium levels in bone vary according to the anatomical site. However, strontium levels at different skeletal sites are strongly correlated [14]. The strontium levels in bone also vary according to the bone structure and higher amounts of strontium are found in cancellous bone than in cortical bone. Strontium is mainly incorporated by exchange on-to the crystal surface. In new bone, only a few strontium atoms may be incorporated into the crystal by ionic substitution of calcium [12, 14]. Bone strontium content is highly correlated with plasma strontium levels. Mechanism of action of strontium ranelate is shown in figure 1.

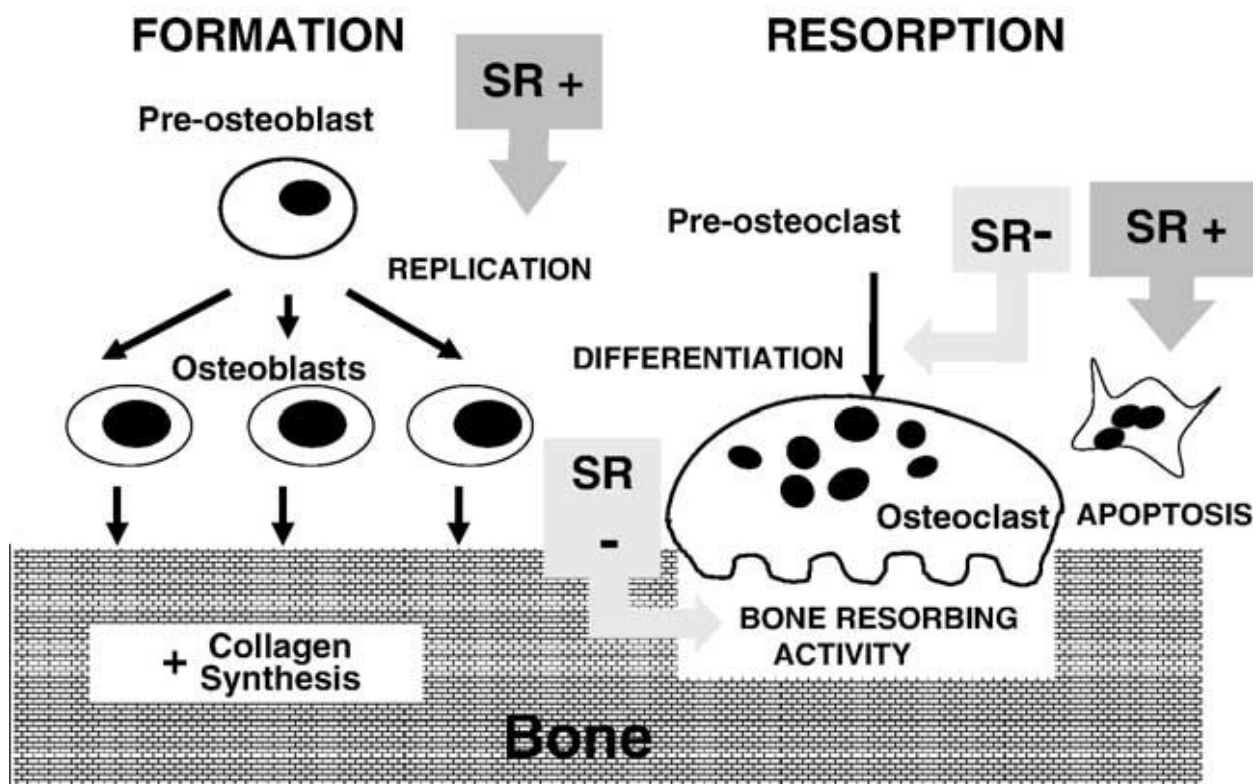


Figure 1. Mechanism of action of strontium ranelate in bone [13]

Strontium ranelate decreases osteoclast differentiation and activity [15]. Also able to increase pre-osteoblast replication, collagen type I synthesis [16]. Therefore strontium ranelate has a dual affect on bone remodeling, being able to stimulate bone formation by osteoblasts, a property shared with bone-forming agents, and to inhibit bone resorption by osteoclasts, as do anti-resorptive agents [17,18].

Strontium ranelate shows affect by binding calcium receptor in bone. Strontium has lower affinity for calcium sensing receptor than calcium[19].

There are higher calcium ion concentrations within the bone microenvironment in case of osteoclastic resorption. Affect of calcium receptor increases in higher extracellular calcium concentrations. Strontium ranelate intake prevents bone loss with non-osteoporotic patients in early post-menopausal period [19].

In the PREVOS study (PREvention Of early postmenopausal bone loss by Strontium ranelate) usage of strontium ranelate 1g/d for period of 2 years resulted in significantly higher increase of femur BMD (bone mineral density). There was a significant increase in the bone formation markers and concurrent increase of bone resorption markers has not been recorded [20].

In the Treatment of Peripheral Osteoporosis (TROPOS) study strontium ranelate increased bone mineral density throughout the study, reaching at 3-yr 8.2% (femoral neck) and 9.8% (total hip). Same study shows %36 decrease in hip fracture risk even in high-risk subgroup over 3-yr period [21].

The Spinal Osteoporosis Therapeutic Intervention (SOTI) study investigated the safety of strontium ranelate and its efficacy against vertebral fractures. In patients used strontium ranelate 2 g/d the risk of vertebral fractures was decreased by 41% over 3-yr [22].

In both studies strontium ranelate was well tolerated. The most common adverse events consisted of nausea and diarrhea was disappeared after third month of treatment [21,22].

Therefore, we suggest that strontium ranelate has been proving antifracture efficacy in patients with osteopenia and/or clinical risk factors and very old elderly. Also, it may contribute to earlier and more effective intervention against fractures because of well- tolerated.

4. Prostaglandins

Prostaglandins act as locally acting hormones, developed as new therapeutic approach. They show the effect and are metabolized in the tissue where they are synthesized. Prostaglandins are synthesized from arachidonic acid, a polyunsaturated fatty acid with 20-carbon chain [23].

Prostaglandins are produced from bone cells by mediated cyclooxygenase. Prostaglandin production is regulated by mechanical stress, cytokines, growth factor and systemic hormones. Furthermore, prostaglandins are able to regulate their own production [24]. Prostaglandins have both inhibitory and stimulatory effects on bone structuring. The most prominent effect of prostaglandin E2 (PGE2) is to stimulate bone resorption and formation [24]. PGE2 exerts its action through the cell surface receptors. Four subtypes of prostaglandin E receptors (EP1, EP2, EP3 and EP4) [25,26] have been identified. PGE2 stimulates bone formation by EP4 receptor mediation [26]. The importance and impact of prostaglandins in bone metabolism is summarized in figure 2

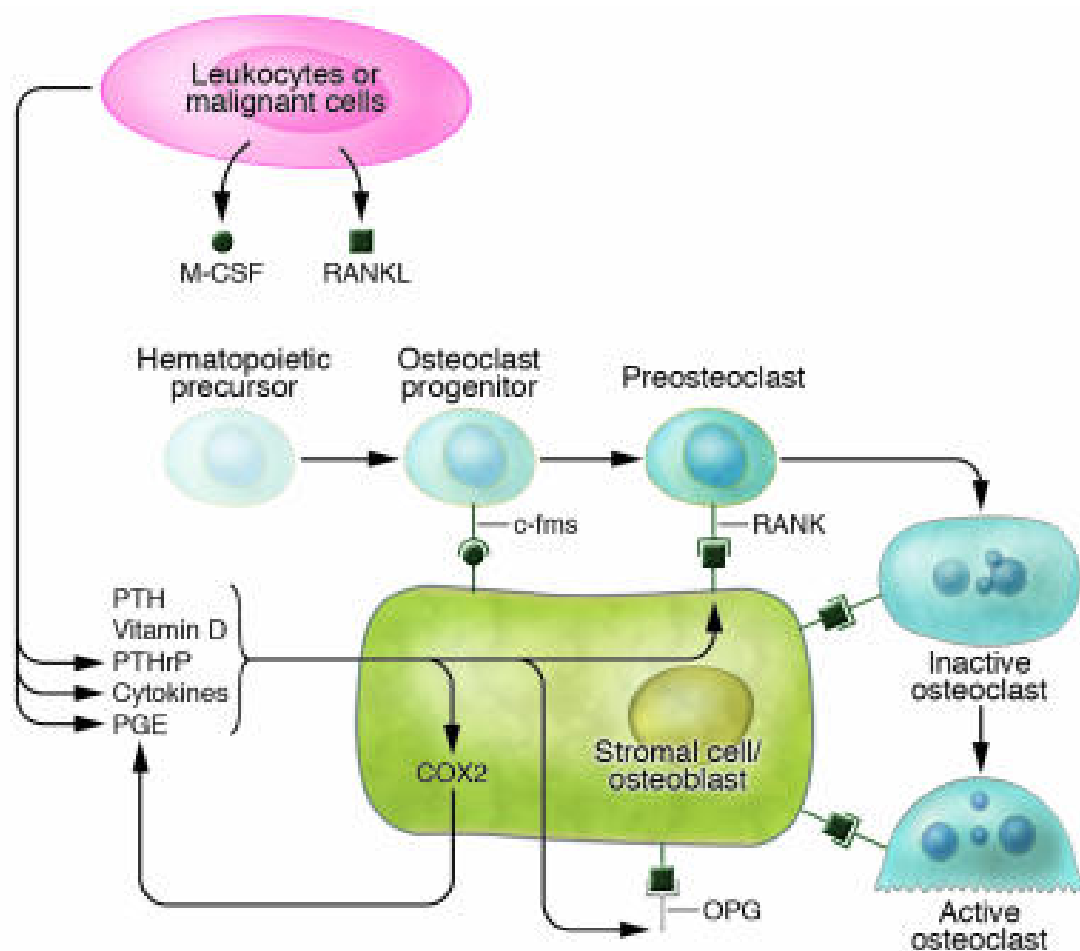


Figure 2. The mechanism of action and place of prostaglandins in bone metabolism [24]

It has been reported in certain studies that prostaglandins have anabolic effect on the bone formation, therefore can be used in osteoporosis treatment [27].

It has been demonstrated that systemic PGE₂ administration stimulates proliferation of osteoblast precursors or differentiation of osteoprogenitor cells in bone marrow and 4.7% increase in bone mass eventually was found in the same study [27]. Increase of total bone surface by means of osteoblast stimulation with PGE₂ administration to rats has been reported [28].

Misoprostol is a methylene analogue of prostaglandin E₁ (PGE₁) has been administered to oophorectomized rats. Misoprostol is being used for treatment of gastric ulcer due to its cytoprotective effect by inhibiting gastric acid and pepsin secretion [23]. Rats receiving misoprostol had significantly reduced oophorectomy related bone loss at site of lumbar spine. Thus, it has been proposed that misoprostol is choice for treatment of post-menopausal osteoporosis prophylaxis [29,30].

Misoprostol 800 µg/d had been administered for 6 months to post-menopausal osteoporotic patients. At the end of the treatment increase by 8.1% in femur bone mineral density, by 5% increase in lumbar spine bone mineral density and by 3.6% increase in Ward's triangle bone

mineral density have been found. It has been reported that misoprostol can be an alternative on treatment of osteoporosis [31].

We think that misoprostol may be an alternative therapy for patients with osteopenia and osteoporosis who are not suitable for hormone replacement therapy.

5. Sesamin

Sesamin is a major lignan compound in sesame seeds. Its activity on bone cell function is unclear. Recently, it has been reported that sesamin has direct effects on osteoblasts by stimulating the expression of essential genes and key enzymes of the bone mineralization process [32,33].

Wanachewin et al suggested that sesamin had the ability to trigger osteoblast differentiation by activation of the p38 and ERK/MAPK (mitogen-activated protein kinase) signaling pathway and possibly indirectly regulate osteoclast development via the expression of OPG and RANKL in osteoblasts [32].

The **MAPK/ERK pathway** is a chain of proteins in the cell that transmits a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. MAPKs play important roles in cellular response to growth factors, cytokines, or environmental stress.

They are classified into four classes: extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinase or stress-activated protein kinase, p38 MAPKs, and ERK5 [34]. ERKs are involved in cell proliferation/transformation and survival. p38 MAPKs are involved in many cellular processes, such as inflammatory responses, osteoblast differentiation, apoptosis [35,36].

We think that sesamin which is a phytochemical agent, may be effective addition to osteoporotic therapy. Future studies are needed.

6. Statins

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Usually, it has been known that they have efficacy and credibility on coronary artery diseases and hyperlipidemia [37,38]. First, Mundy et al showed that statins lead to increase 90 % in the trabecular bone volume by stimulating bone formation invitro and therefore it was started to studies investigating the place of statins for osteoporosis treatment [39]. Hamelin et al suggested that statins decrease the bone destruction by suppressing the formation of the mevalonate that it is an important precursor on the control of osteoclastic activity as bisphosphonates [40].

It was reported that statins have efficacy on the bone metabolism, by increasing bone morphogenetic protein 2 (BMP2) activation stimulated osteoblastic cell proliferation and matu-

ration [41]. Maeda et al showed that hydrophobic statins such as simvastatin, atorvastatin, and cerivastatin stimulated VEGF expression by osteoblasts via reduced protein prenylation and the phosphatidylinositide-3 kinase pathway, promoting osteoblastic differentiation [42].

In 2009 Pault et al revealed a dose-dependent effect and improved fracture healing under local application of simvastatin [43].

Fukui et al reported that the effect of the systemic administration of statins was limited due to its metabolism in the liver and high-dose administration may cause adverse side effects. They locally applied with gelatin hydrogel to fracture sites at a dose similar to that used in clinical settings and shown to induced fracture union in a rat unhealing bone fracture model via its effect on both angiogenesis and osteogenesis [44].

We suggest that the results of studies also point to the need for more information in order to particularly gelatin hydrogel form.

7. Growth hormone and IGF-I

It is known that growth hormone (GH) is important in the regulation of longitudinal bone growth [45]. Several *in vivo* and *in vitro* studies have demonstrated that GH is important in the regulation of both bone formation and bone resorption. In Figure 3 a model for the cellular effects of GH in the regulation of bone remodeling is showed [45].

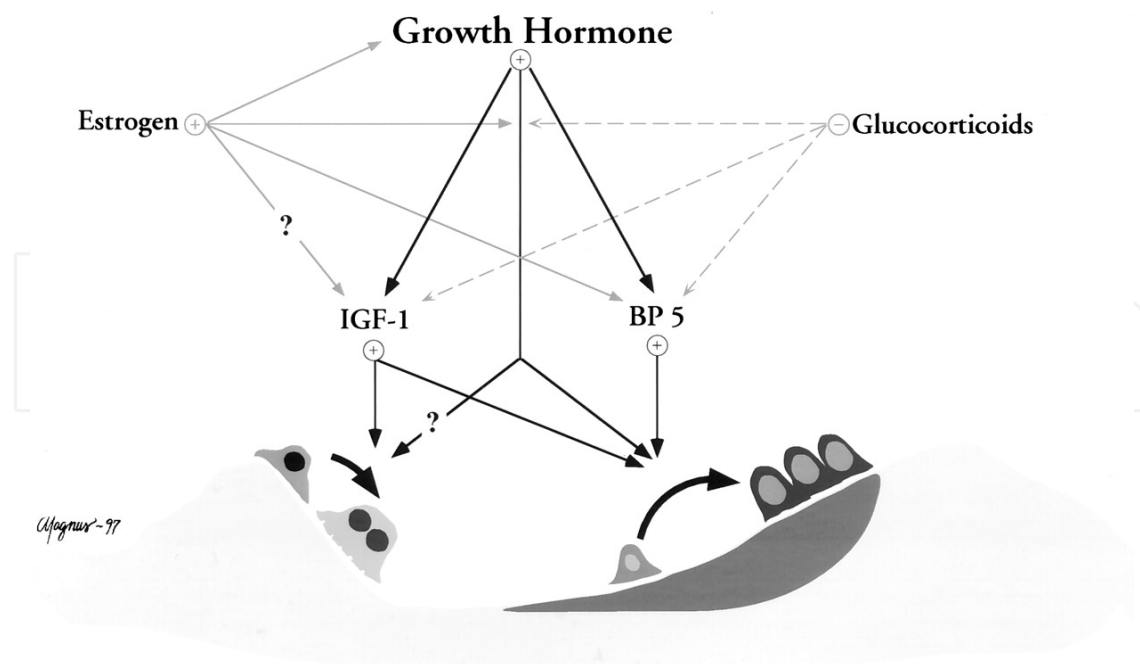


Figure 3. The mechanism of action at the cellular level for GH in regulation of bone remodeling. The left part of the figure represents osteoclast-mediated bone resorption. The right part represents osteoblast-mediated bone formation. ? indicates that both stimulatory and inhibitory effects have been shown [45]

GH increases bone formation in two ways [46]:

1. via a direct interaction with GHRs on osteoblasts
2. via an induction of endocrine and autocrine/paracrine IGF-I (Insulin like Growth Factor-1).

rhGH (recombinant human Growth Hormone) increases bone turnover in normal subjects and improves bone mineral metabolism in postmenopausal females [45]. GH treatment also results in increased bone resorption. It is still unknown whether osteoclasts express functional GHRs, but recent in vitro studies indicate that GH regulates osteoclast formation in bone marrow cultures [45, 46]. Possible modulations of the GH/IGF (Insulin like Growth Factor) axis by glucocorticoids and estrogens are also included in Fig. 3 [45].

Bone is the second richest source of IGF-I in the body. Locally this peptide promotes osteoblast differentiation and growth [48]. Recently, studies show that low levels of IGF-I are associated with a greater risk of hip and spine fractures [49–51]. Hence, there is a strong opinion for considering human GH or IGF-I as potential anabolic agents for the treatment of osteoporosis. There are potential advantages for using rhIGF-I (recombinant human Insulin like Growth Factor-1) compared with rhGH in the treatment of osteoporosis. These include

1. more direct stimulation of bone formation,
2. bypass of skeletal GH resistance that can be present, and
3. a reduction in GH-induced side-effects such as carpal tunnel and diabetes mellitus. [47]

It was reported that low doses of rhIGF-I may directly increase osteoblastic function with only a minimal increase in bone resorption [52]. In 2008, it was suggested a potential role for IGF-1 in the early identification of women at risk for low bone mass and osteoporosis. They suggested measuring the serum level of IGF-1 in women around 40 years old. When its value is 1.5 SD below the peak, BMD measurement by DXA could be considered [53]

There are limited number studies using rhIGF-I than rhGH. Therefore, these advantages have not been validated yet.

8. Sodium fluoride

Sodium fluoride is the first anabolic agent to be used in the treatment of postmenopausal osteoporosis. Side-effects, consisting of upper gastrointestinal symptoms and a lower extremity pain syndrome, are common.

Using slow release formulation of sodium fluoride, it was showed a 50% reduction in vertebral fracture incidence with impressive increases in bone mass [54–56]. More recently, it has been suggested that a different formulation of fluoride, monofluorophosphate when is used in lower dosages and more favorable formulations, gastrointestinal side-effects are reduced [57–59]. However, consensus about its clinical utility has still not been reached.

9. Other potential agents for anabolic treatment of osteoporosis

Bortezomib: There are multiple potential alternative agents for increasing bone formation. A potential treatment is to target the osteoblast proteasome. It was reported that the proteasome inhibitor bortezomib (Bzb) had bone forming effects in patients with multiple myeloma [60]. The mechanism for Bzb's effects on osteoblastic differentiation has not been clearly defined.

It was showed that Bzb with lenalidomide or thalidomide may increase bone formation by stimulating osteoblast activity and inhibiting osteoclastic bone destruction, respectively Figure 4.

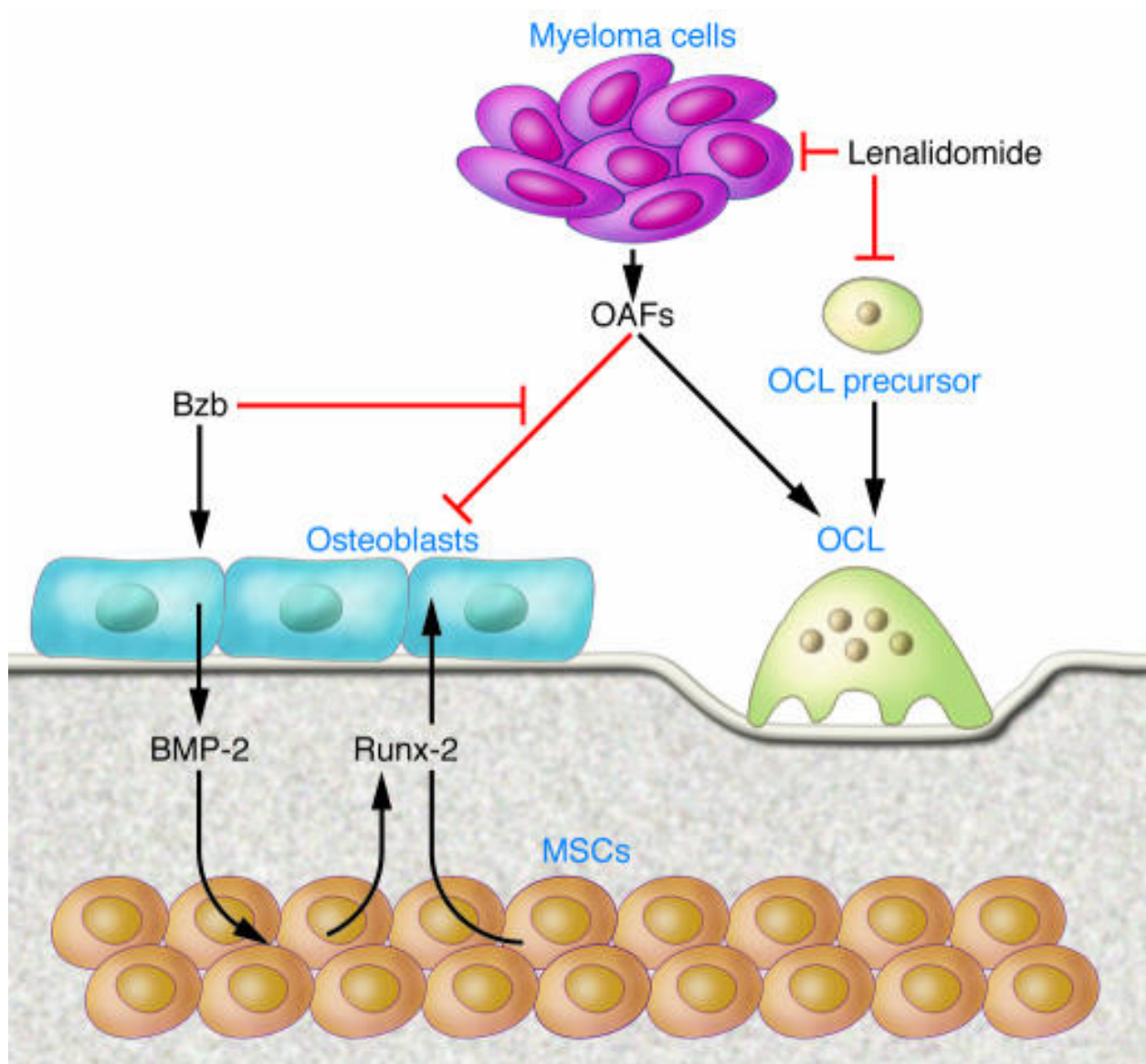


Figure 4. Bzb's action on bone formation in the patients with multiple myeloma [60]

Oxytocin: An other approach is oxytocin (OT) that increases osteoblastic bone formation. It has been reported that OT may regulate maternal skeletal homeostasis during pregnancy and lactation. The fetal skeleton is unlikely to be mineralized effectively in the absence of calcium mobilized from the maternal skeleton [61]. It has been suggested that elevated OT levels during pregnancy and lactation not only enhance bone resorption by increasing the number of osteoclasts to make maternal calcium existing to the fetus, but also prevent unrestricted bone removal by inhibiting the activity of mature osteoclasts. Therefore, it was reported that recombinant OT or its analogs because of its skeletal anabolic action, might have potential utility in therapy for human osteoporosis [61].

Beta-blocker: Wiens et al found that beta-blocker use was associated with a significant decrease in fracture risk [62]. However, in 2008, Reid determined that there was no any evidence to support the hypothesis that beta,-blockers reduce fracture numbers [63]. In 2012, Yang et al reported that beta-blockers are associated with reduced risk of fracture in older adults, but the effect size is likely to be modes [64]t. In summary, there was no an adequate evidence to support using beta-blockers in the treatment of osteoporosis.

Lithium: The mean (+/-SD) bone density in lithium treated patients was reported that 4.5% higher at the spine (P<0.05), 5.3% higher at the femoral neck (P<0.05) and 7.5% higher at the trochanter (P<0.05). In addition, lithium treated patients had lower serum total ALP (P<0.005), lower serum osteocalcin (P<0.005) and lower serum CTX (P<0.05) but the totalcalcium, PTH and urinary calcium excretion did not differ significantly between patients and controls. In conclusion, it was suggested that therapy with lithium carbonate may preserve or enhance bone mass [65].

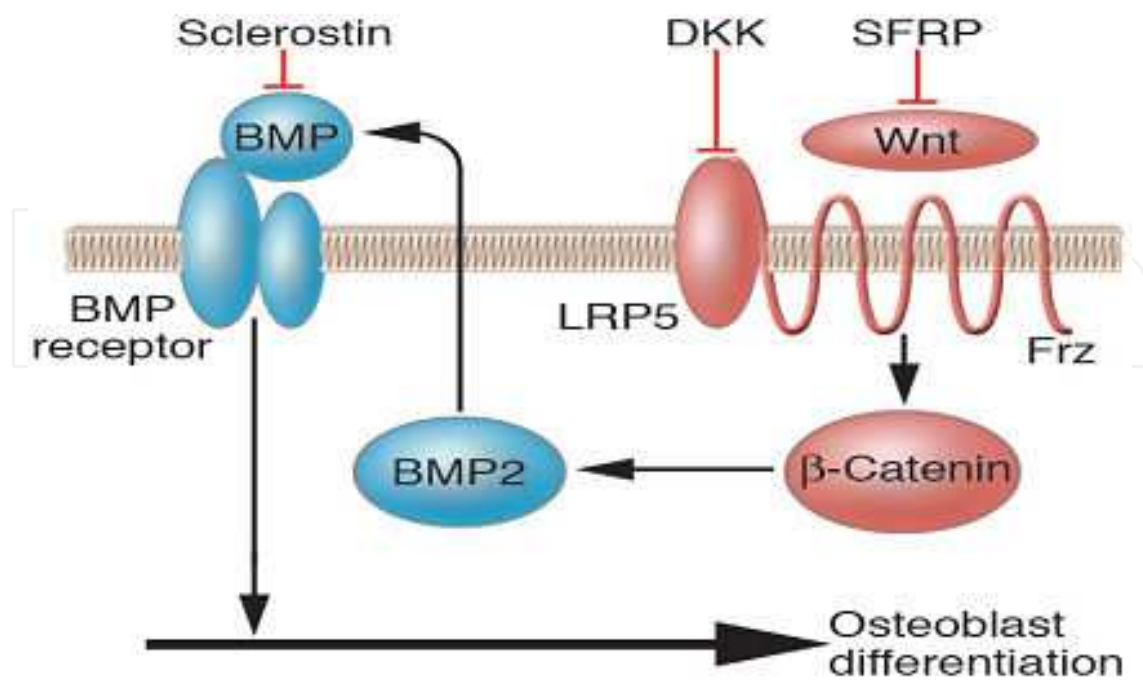


Figure 5. Modulation of Wnt signaling by sclerostin [73]

Anti-sclerostin monoclonal antibody: Sclerostin is a protein encoded by the SOST gene in osteocytes. It inhibits osteoblastic bone formation [66,67]. The binding of Wnt proteins to the LRP5/6-Frizzled co-receptor on the cell membrane of osteoblasts leads to stabilization of intracellular beta-catenin and regulation of gene transcription that promotes osteoblastic bone formation. Sclerostin is a modulator of osteoblast function. It antagonizes Wnt signaling and inhibits osteoblastic bone formation [68]. Recent studies reported that anti-sclerostin therapy enhances fracture healing and bone repair.[69-71]. AMG 785 is a humanized sclerostin monoclonal antibody, was first studied in humans. It enhances Wnt signaling and increase osteoblastic bone formation [72]. Figure 5

Treatment with AMG 785 has been well tolerated. In postmenopausal women with low bone mineral density (BMD) after 12 months of AMG 785 administration, increase in BMD is determined. Although there is no evidence that AMG 785 increases the risk of osteosarcoma, new studies are needed to modify this risk.

10. Conclusion

Aging is associated with impaired bone formation which is a principal pathogenetic cause mediating bone fragility in osteoporosis. Ideally, patients at high risk of fracture should be identified early and treated by a combination of lifestyle changes, correction of secondary causes of osteoporosis, and specific treatments to improve bone density and decrease fracture risk. By now, there were a limited number of therapeutic agent for activating bone formation and increasing bone mass and strength. More effective and better tolerated therapies will become available soon. We think that new treatments will be able to contribute to increase the currently low treatment rate of even severe osteoporosis by allowing approaches aimed at minimising fracture risk at the individual patient level.

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References

- [1] World Health Organisation. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organisation Technical Report Series. Geneva: WHO, 1994.
- [2] Hock JM, Gera I. Effects of Continuous and Intermittent Administration and Inhibition of Resorption on The Anabolic Response of Bone to Parathyroid Hormone. *J Bone Miner Res* 1992;7:65–72.
- [3] Schlüter KD. PTH and PTHrP: Similar Structures but Different Functions. *News Physiol Sci*. 1999;14:243-49.
- [4] Marie PJ, Kassem M. Osteoblasts in Osteoporosis: Past, Emerging, and Future Anabolic Targets. *Eur J Endocrinol*. 2011;165 (1):1-10.
- [5] Tam CS, Heersche JN, Murray TM, Parsons JA. Parathyroid Hormone Stimulates The Bone Apposition Rate Independently of Its Resorptive Action: Differential Effects of Intermittent and Continuous Administration. *Endocrinology* 1982;110:506-12.
- [6] Uzawa T, Hori M, Ejiri S, Ozawa H. Comparison of The Effects of Intermittent and Continuous Administration of Human Parathyroid Hormone (1-34) on Rat Bone. *Bone* 1995;16:477-484.
- [7] Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of Parathyroid Hormone (1-34) on Fractures and Bone Mineral Density in Postmenopausal Women with Osteoporosis. *N Engl J Med* 2001;344:1434-1441.
- [8] Geusens P, Reid D. Newer drug treatments: their effects on fracture prevention. *Best Practice and Clinical Rheumatology* 2005;19(6):983-9.
- [9] Subbiah V, Madsen VS, Raymond AK, Benjamin RS & Ludwig JA. Of Mice and Men: Divergent Risks of Teriparatide-Induced Osteosarcoma. *Osteoporosis International* 2010;21: 1041–1045.
- [10] Manuele S, Sorbello N, Puglisi N, Grasso S, La Malfa L, Durbino G, et al. The teriparatide in the treatment of severe senile osteoporosis. *Arch Gerontol Geriatr* 2007;1:249-58.
- [11] Reginster JY, Deroisy R, Jupsin I. Strontium ranelate: a new paradigm in the treatment of osteoporosis. *Drugs of Today* 2003;39(2):89-101.
- [12] Nielsen SP. The biological role of strontium. *Bone* 2004;35:583-8.
- [13] Marie PJ, Ammann P, Boivin G, Rey C. Mechanisms of action and therapeutic potential of strontium in bone. *Carcified Tissue International* 2001;69:121-9.
- [14] Dahl SG, Allain P, Marie PJ, Mauras Y, Boivin G, Ammann P, et al. Incorporation and distribution of strontium in bone. *Bone* 2001;28:446-53.

- [15] Baron R, Tsouderos Y. In vitro effects of S12911-2 on osteoclast function and bone marrow macrophage differentiation. *European Journal of Pharmacology* 2002;450:11-7.
- [16] Reginster JY, Lecart MP, Deroisy R, Lousberg C. Strontium ranelate: a new paradigm in the treatment of osteoporosis. *Expert Opin Investig Drugs* 2004;13(7):857-64.
- [17] Marie PJ. Strontium ranelate: a physiological approach for optimizing bone formation and resorption. *Bone* 2006;38:10-4.
- [18] Ammann P, Shen V, Robin B, Mauras Y, Bonjour J-P, Rizzoli R. Strontium ranelate improves bone resistance by increasing bone mass and improving architecture in intact female rats. *Journal of Bone and Mineral Research* 2004;19(12):2012-20.
- [19] Coulombe J, Faure H, Robin B, Ruat M. In vitro effects of strontium ranelate on the extracellular calcium-sensing receptor. *BBRC* 2004;323:1184-90.
- [20] Reginster JY, Deroisy R, Dougados M, Jupsin I, Colette J, Roux C. Prevention or early postmenopausal bone loss by strontium ranelate: The randomized, two-year, double-masked, dose-ranging, placebo-controlled PREVOS trial. *Osteoporos Int* 2002;13:925-31.
- [21] Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (tropos) study. *The Journal of Clinical Endocrinology and metabolism* 2005;90(5):2816-22.
- [22] Meunier JM, Roos C, Seeman E, Ortolani S, Budurski J, Spencer T, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *The New England Journal of Medicine* 2004;350:459-68.
- [23] Mycek MJ, Harvey R, Champe P (Çeviri: Ş. Oktay). *Farmakoloji*. İstanbul: Nobel Tıp Kitabevleri Ltd. Şti.; 1998:419-20.
- [24] Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *The Journal of Clinical Investigation* 2005;115(12):3318-25.
- [25] Watkins BA, Li Y, Seifert MF. Lipids as modulators of bone remodelling. *Current Opinion in Clinical Nutrition and Metabolic Care* 2001;4:105-10.
- [26] Yoshida K, Oida H, Kobayashi T, Maruyama T, Tanaka M, Katayama T, et al. Stimulation of bone formation and prevention of bone loss by prostaglandin EP4 receptor activation. *PNAS* 2002;99(7):4580-5.
- [27] Weinreb M, Suponitzky I, Keila S. Systemic administration of an anabolic dose of PGE2 in young rats increases the osteogenic capacity of bone marrow. *Bone* 1997;20(6):521-6.
- [28] Yao W, Jee SSW, Zhou H, Lu J, Cui L, Setterberg R, et al. Anabolic effect of prostaglandin E2 on cortical bone of aged male rats comes mainly from modeling dependent bone gain. *Bone* 1999;25(6):697-702.

- [29] Sonmez AS, Birincioglu M, Özer MK, Kutlu R, Chuong CJ. Effects of misoprostol on bone loss in ovariectomized rats. *Prostaglandins and other Lipid Mediators* 1999;57:113-8.
- [30] Ahmet-Camcioglu N, Okman-Kilic T, Durmus-Altun G, Ekuklu G, Kucuk M. Effects of strontium ranelate, raloxifene and misoprostol on bone mineral density in ovariectomized rats. *Eur J Obstet Gynecol Reprod Biol.* 2009;147(2):192-4.
- [31] Yasar L, Sönmez AS, Utku N, Özcan J, Çebi Z, Savan K, et al. Effect of misoprostol on bone mineral density in women with postmenopausal osteoporosis. *Prostaglandins and Other Lipid Mediators* 2006;79:199-205.
- [32] Wanachewin O, Boonmaleerat K, Pothacharoen P, Reutrakul V, Kongtawelert P. Sesamin Stimulates Osteoblast Differentiation Through p38 and ERK1/2 MAPK Signaling Pathways. *BMC Complement Altern Med* 2012;12(1):71
- [33] Boulbaroud S, Mesfioui A, Arfaoui A, Ouichou A, El-Hessni A. Preventive effects of flaxseed and sesame oil on bone loss in ovariectomized rats. *Pak J Biol Sci* 2008;11(13):1696–1701.
- [34] Chang L, Karin M. Mammalian MAP kinase signalling cascades. *Nature* 2001;410:37–40.
- [35] Suzanne M, Irie K, Glise B, Agnes F, Mori E, Matsumoto K, Noselli S. The Drosophila p38 MAPK pathway is required during oogenesis for egg asymmetric development. *Genes Dev* 1999;13:1464–1474.
- [36] Hu Y, Chan E, Wang SX, Li B. Activation of p38 mitogen-activated protein kinase is required for osteoblast differentiation. *Endocrinology.* 2003;144(5):2068-74.
- [37] LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999; 282 (24): 2340-6.
- [38] Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998; 339 (19): 1349-57.
- [39] Mundy G, Garrett R, Harris S, et al. Stimulation of bone formation in vitro and in rodents by statins. *Science* 1999; 286 (5446): 1946-9.
- [40] Hamelin BA, Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. *Trends Pharmacol Sci* 1998; 19: 26-37.
- [41] Bauer DC. HMG CoA reductase inhibitors and the skeleton: a comprehensive review. *Osteoporos Int* 2003; 14 (4): 273-82.
- [42] Maeda T, Kawane T, Horiuchi N. Statins Augment Vascular Endothelial Growth Factor Expression in Osteoblastic Cells via Inhibition of Protein Prenylation. *Endocrinology* 2003;144(2):681–692 doi: 10.1210/en.2002-220682.

- [43] Pauly S, Luttsch F, Morawski M, Haas NP, Schmidmaier G, Wildemann B. Simvastatin locally applied from a biodegradable coating of osteosynthetic implants improves fracture healing comparable to BMP-2 application. *Bone*. 2009;45:505–511. doi: 10.1016/j.bone.2009.05.010.
- [44] Fukui T, Ii M, Shoji T, Matsumoto T, Mifune Y, Kawakami Y, Akimaru H, Kawamoto A, Kuroda T, Saito T, Tabata Y, Kuroda R, Kurosaka M, Asahara T. Therapeutic effect of local administration of low-dose simvastatin-conjugated gelatin hydrogel for fracture healing. *J Bone Miner Res*. 2012 May;27(5):1118-31. doi: 10.1002/jbmr.1558.
- [45] Ohlsson C, Bengtsson BA, Isaksson OGP, Andreassen TT, Słotweg M. Growth Hormone and Bone. *Endocrine Reviews* 1998; 19: (1) 55-79.
- [46] Ransjö M, Lerner U, Ohlsson C. Growth hormone inhibits formation of osteoclast-like cells in mouse bone marrow cultures. *J Bone Miner Res* 1996;11 [Suppl]:T394
- [47] Rosen CJ, Bilezikian JP. Clinical Review 123: Hot Topic Anabolic Therapy for Osteoporosis *J Clin Endocrinol Metab* 2001;86: 957–964.
- [48] Donahue LR, Rosen CJ. IGFs and bone. The osteoporosis connection revisited. *Proc Soc Exp Biol Med*. 1998;219:1–7.
- [49] Sugimoto T, Nishiyama K, Kuribayashi F, Chihara K. Serum levels of IGF-I, IGFBP-2, and IGFBP-3 in osteoporotic patients with and without spine fractures. *J Bone Miner Res*. 1997;12:1272–1279.
- [50] Bauer DC, Rosen C, Cauley J, Cummings SR. Low serum IGF-I but not IGFBP-3 predicts hip and spine fracture: the study of osteoporotic fracture. *J Bone Miner Res*. 1998;23:S561.
- [51] Rosen CJ, Pollak MF. IGF-I and aging: a new perspective for a new century. *Trends Endocrinol Metab*. 1999;10:136 –142.
- [52] Ghiron L, Thompson J, Holloway L, Butterfield GE, Hoffman A, Marcus R. Effects of rhGH and IGF-I on bone turnover in elderly women. *J Bone Miner Res*. 1995;10:1844 –1852.
- [53] Liu JM, Zhao HY, Ning G, Chen Y, Zhang LZ, Sun LH, Zhao YJ, Xu MY, Chen JL. IGF-1 as an early marker for low bone mass or osteoporosis in premenopausal and postmenopausal women. *J Bone Miner Metab* (2008) 26:159–164
- [54] Pak CYC, Sakhaee K, Zerwekh JE, Parcel C, Peterson R, Johnson K. Safe and effective treatment of osteoporosis with intermittent slow release NaF: augmentation of vertebral bone mass and inhibition of fractures. *J Clin Endocrinol Metab*. 1989; 68:150 –159.
- [55] Pak CYC, Sakhaee K, Adams Huet B, Piziak V, Petersen RD, Poindexter JR. Treatment of postmenopausal osteoporosis with slow-release NaF. *Ann Intern Med*. 1995;123:401– 408.
- [56] Pak CYC, Zerwekh JE, Antich PP, Bell NH, Singer FR. Slow-release sodium fluoride in osteoporosis. *J Bone Miner Res*. 1996;5:561–564.

- [57] Ringe JD, Kipshoven C, Coster A, Umbach R. Therapy of established postmenopausal osteoporosis with monofluorophosphate plus calcium: dose related effects on bone density and fracture rate. *Osteop Int.* 1999; 9:171–178.
- [58] Reginster JY, Meurmans L, Zegels B, et al. The effect of sodium monfluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis. A randomized controlled trial. *Ann Intern Med.* 1998;129:1–8.
- [59] Ringe JD, dorst A, Kipshoven C, Rovati LC, Setnikar I. Avoidance of vertebral fractures in men with idiopathic osteoporosis by a three-year therapy with calcium and low-dose intermittent monofluorophosphate. *Osteop Int.* 1998;8:47–52.
- [60] Shimazaki C, Uchida R, Nakano S, Namura K, Fuchida SI, Okano A, Okamoto M and Inaba T. High serum bone-specific alkaline phosphatase level after bortezomib-combined therapy in refractory multiple myeloma: possible role of bortezomib on osteoblast differentiation. *Leukemia* 2005;19, 1102–1103.
- [61] Tamma R, Colaianni G, Zhu LL, DiBenedetto A, Greco G, Montemurro G, Patano N, Strippoli M, Vergari R, Mancini L, Colucci S, Grano M, Faccio R, Liu X, Li J, Usmani S, Bachar M, Bab I, Nishimori K, Young LJ, Buettner C, Iqbal J, Sun L, Zaidi M, Zallone A. Oxytocin is an anabolic bone hormone. *Proc Natl Acad Sci U S A.* 2009;106(17):7149-54
- [62] Wiens M, Etminan M, Gill SS, Takkouche B. Effects of anti-hypertensive drug treatments on fracture outcomes: a meta-analysis of observational studies. *J Intern Med* 2006;260:350-62
- [63] Reid IR. Effects of beta-blockers on fracture risk. *J Musculoskelet Neuronal Interact.* 2008 Apr-Jun;8(2):105-10. Review.
- [64] Yang S, Nguyen ND, Eisman JA, Nguyen TV. Association between beta-blockers and fracture risk: A Bayesian meta-analysis. *Bone.* 2012;51(5):969-974.
- [65] Zamani A, Omrani GR, Nasah MM. Lithium's effect on bone mineral density. *Bone.* 2009 Feb;44(2):331-4
- [66] Poole KE, van Bezooijen RL, Loveridge N, Hamersma H, Papapoulos SE, Lowik CW, Reeve J. Sclerostin is a delayed secreted product of osteocytes that inhibits bone formation. *FASEB J* 2005;19(13):1842-1844.
- [67] van Bezooijen RL, Roelen BA, Visser A, van der Wee-Pals L, de Wilt E, Karperien M, Hamersma H, Papapoulos SE, ten Dijke P, Löwik CW. Sclerostin is an osteocyte-expressed negative regulator of bone formation, but not a classical BMP antagonist. *J Exp Med* 2004;199(6):805-814.
- [68] Lewiecki EM. Sclerostin: a novel target for intervention in the treatment of osteoporosis. *Discov Med.* 2011;12(65):263-73. Review.
- [69] Li X, Ominsky MS, Niu QT, Sun N, Daugherty B, D'Agostin D, Kurahara C, Gao Y, Cao J, Gong J, Asuncion F, Barrero M, Warmington K, Dwyer D, Stolina M, Morony

- S, Sarosi I, Kostenuik PJ, Lacey DL, Simonet WS, et al. Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength. *J Bone Miner Res* 2008; 23(6):860-869.
- [70] Li X, Ominsky MS, Warmington KS, Morony S, Gong J, Cao J, Gao Y, Shalhoub V, Tipton B, Haldankar R, Chen Q, Winters A, Boone T, Geng Z, Niu QT, Ke HZ, Kostenuik PJ, Simonet WS, Lacey DL, Paszty C. Sclerostin antibody treatment increases bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis. *J Bone Miner Res* 2009b;24(4):578-588.
- [71] Ominsky MS, Vlasseros F, Jolette J, Smith SY, Stouch B, Doellgast G, Gong J, Gao Y, Cao J, Graham K, Tipton B, Cai J, Deshpande R, Zhou L, Hale MD, Lightwood DJ, Henry AJ, Popplewell AG, Moore AR, Robinson MK, Lacey DL, Simonet WS, Paszty C. Two doses of sclerostin antibody in cynomolgus monkeys increases bone formation, bone mineral density, and bone strength. *J Bone Miner Res*.2010;25(5):948-59.
- [72] Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. *J Bone Miner Res* 2011;26(1):19-26.
- [73] Lawrence G. Raisz. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J Clin Invest* .2005;115(12):3318-25.
- [74] Amgen and UCB. Amgen and UCB announce positive phase 2 results of AMG 785/CDP7851 in patients with postmenopausal osteoporosis (PMO). http://www.amgen.com/media_pr_detail.jsp?releaseID=1553039. (accessed 1 Jun 2011).

