Review Article

Osteoanabolics

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ABSTRACT

Osteoporosis is characterized by reduced bone mass, impaired bone quality, and a propensity to fracture. An "osteoanabolic" should be referred to any therapy that helps increase bone mass. Bone mass represents 80% of bone mechanical strength. A low bone mass therefore provides the strongest association of future risk of fracture. This review aims to discuss all available and future therapies that attempt to increase bone mass be it organic or inorganic.

Key words: Bone remodeling, osteo-anabolics, osteoporosis, teriparatide

Introduction

The term osteoanabolic should be referred to any therapy that helps increase bone mass. Bone is recognized as a dynamic organ that is in a constant state of remodeling (approximately 10% per year). It takes approximately 7 to 10 years for the entire skeleton to remodel itself. The process of remodeling involves a delicate balance between bone resorption (mediated by osteoclasts) and bone formation (mediated by osteoblasts). Bone, as a tissue comprises of 30% organic substances and 70% inorganic mineral. The organic tissue is made up of predominantly type-1 collagen (90%), proteoglycans noncollagenous proteins (8%), bone cells growth factors and cytokines (2%). The inorganic tissue is made up of insoluble calcium and phosphate salts that precipitate as hydroxyapatite on the organic tissue. This collectively forms the bone mass.[1-3] Therefore, in its literal sense any therapy that might tip the bone remodeling balance in favor of bone formation be it organic or inorganic tissue should be referred to as an osteoanabolic.

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What is osteoporosis?

Osteoporosis was a term coined in the early 1880s in French as a mere description of a pathological state of bone. The term osteoporosis made its way in to the English medical vocabulary only in the twentieth century.[4] It is characterized by reduced bone mass, impaired bone quality, and a propensity to fracture. With the assumption that a healthy premenopausal Caucasian woman around her twenties will have optimal bone mass, standard deviations from this reference point were created to define reduced bone mass and subsequently increased risk of fracture. One standard deviation below (at virtually any skeletal site) increases the risk of subsequent hip fracture by nearly twofold.[5] This standard deviation is expressed as a T-score. It is defined as a difference between measured bone density (BMD) and the expected normal young value (YN) divided by the population standard deviation (SD).[6]

$$\text{T-score} = \frac{\text{BMD - YN}}{\text{SD}}$$

Although far from ideal, it provides the strongest association between reduced bone mass and relative future risk of fracture. It is a quantitative measure of about 80% of the total bone strength. The remaining 20% of bone strength is represented by other qualitative factors such as trabecular connectivity, microarchitecture, etc. In 1994, significance of the T-score was firmly established by a landmark report by the WHO[7] that classified bone health as poor and at increased risk of fracture if it had a T-score 1 SD below normal (T-score –1 and lower). The bone was classified as

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osteopenic (T-score between –1and –2.5) or osteoporotic (T-score less than –2.5) based on the amount of relative bone mass that was reduced. Lower the T-score greater the risk of bone fractures.

Bone mass is currently best measured by dual energy x-ray absorptiometry (DEXA). The precise definition of bone density is mass of bone per unit volume of bone – exclusive of marrow and other non-bone tissue. It is therefore a three-dimensional bone measure. DEXA measures bone mass as a two-dimensional value (mass/surface area, gm/cm^2) and therefore has received criticism as a diagnostic tool, with the belief that it may not be adequately representing true bone mass. The bone mass thus measured seems to be "apparent" and not "true" as it measures marrow and non-bone tissue underestimating the true bone mass value.[6] As DEXA is inversely related to bone surface area, bone with a compact area will be under diagnosed for reduced bone mass and conversely bone with larger surface area will be over diagnosed for low bone mass. The risk of fracture described by DEXA represents a "relative risk" rather than a definitive risk as it compares the bone mass of patient in question with a healthy young Caucasian woman assumed to be in the peak of her health. Although effective in predicting future fracture risk there remains a need to define methods that would state a definitive risk in order to treat the appropriate patient and prevent over or under treatment.

Bone Remodeling

To understand better the concept of osteoanabolic therapy we shall attempt to understand bone biology. The skeletal system is a dynamic organ that is in a constant state of turnover. For the first two decades of life, bone formation (osteoblastogenesis) exceeds bone resorption (osteoclastogenesis) in favor of the bone growth. Thereafter the balance between bone formation and bone resorption is maintained, such that shape, size, structure, and quantity of bone are preserved. The process of remodeling is initiated by osteoblasts (bone forming cells) that secrete various cytokines that help recruit hemopoetic precursor cells to the bone surface to form bone-removing cells (osteoclasts). The main regulatory mechanism involves production of mainly macrophage colony stimulating factor (m-CSF) and RANKL (receptor activator of NF-kappa B ligand) by the osteoblast. RANKL is the main regulatory protein that binds to RANKL receptor on osteoclast and m-CSF acts as a potentiating factor that stimulates the c-fms receptor on the osteoclast.[8,9] The net result is production of various acids, matrix metalloproteinase's (MMP,) and cathepsin-B into the empty space between the bone surface and osteoclast that initiates the process of bone resorption. This process takes approximately 10 to 14 days to complete. The process of bone resorption results in release of cytokines (TGF-beta) growth factors (IGF-1) and collagen components (carboxy and amino-terminal telopeptides of type 1 collagen, hydroxyproline, hydroxypyridinium cross links).[10]

These growth factors and cytokines released during the process of resorption act as internal signals to stimulate osteoblasts and therefore bone formation. This bone forming process takes approximately 3 months to complete [Figure 1]. Osteocytes (entombed osteoblasts in bone osteon) act as important regulatory cells that respond to various biochemical and mechanical stimuli to regulate bone formation. An important signaling pathway identified in the last decade is the WNT/b-catenin pathway. WNT proteins bind to a seven transmembrane domain–spanning grizzled receptor and low-density lipoprotein receptor – related protein 5 and 6. This binding results in release of stabilized beta-catenin into the cytosol that gets translocated to the nucleus to activate osteoclastogenesis. This process is tightly regulated and can be inhibited by osteocyte-generated protein "sclerostin."[11,12] Bone formation results in improved bone quantity (both organic and inorganic) and quality (periosteal apposition, micro architecture, and porosity).

Osteoanabolics

For the sake of simplicity we are going to divide osteoanabolic therapy into:

1. Drugs that Improves bone inorganic tissue
2. Drugs that improve bone organic tissue

Drugs That Improves Bone Inorganic Tissue

Vitamin D and calcium

The first scientific description of a vitamin D deficient

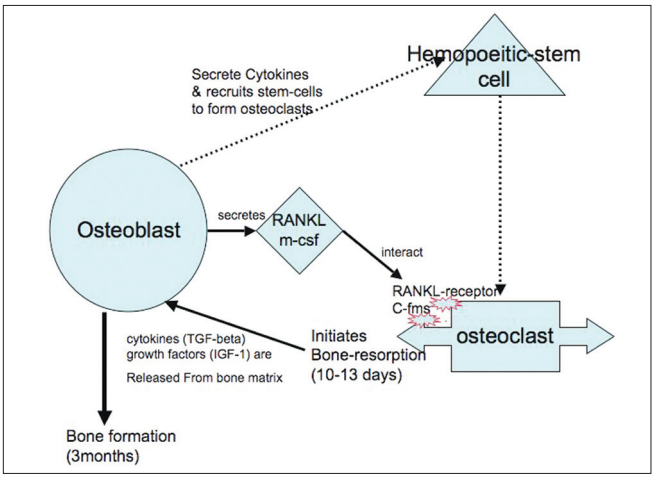

Figure 1: Bone remodelling: m-CSF (macrophage colony stimulating factor) and RANKL (receptor activator of NF-kappaB ligand)

state was described in the seventeenth century by both Dr Daniel Whistler and Professor Francis Glisson. However, it was only in 1923 that Golblatt and Soames described the phenomena of vitamin D like substance being produced following irradiation of skin by sunlight.[13-15]

The major source of vitamin D is sunlight exposure (UV-B), with as little as 5 to 10 min of skin exposure (wavelength 290–315 nm) producing as much as 3000 to 5000 units of vitamin D per day.[16] Food rich in vitamin D include eggs, milk, and fatty fish. Unfortunately, to meet the daily requirements of vitamin D, a very large quantity of the above-mentioned food needs to be consumed, which is very impractical, at least in the third world countries like India where foods are not fortified with vitamin D. Vitamin D supplements are available as D2 (ergocalciferol, plant source) and D3 (cholecalciferol). The efficacy of both vitamin D supplements has long been a subject of debate. Most authors believe that the two are equally efficacious.[17] Emerging evidence might suggest that vitamin D3 might edge over vitamin D2 in efficacy.[18]

In India, vitamin D is generally dealt with at the level of primary health care practitioners, with a limited understanding of vitamin D replacement regimens. Often massive doses of vitamin D are administered parenterally (intramuscular) with doses as high as 1800 000 to 3600 000 units, administered over a 6-week period, risking life-threatening hypercalcemia and hypervitaminosis D. This review is an attempt to help healthcare practitioners provide appropriate vitamin D replacement regimens.

Any patient with musculoskeletal symptoms, such as bone pains, myalgias,generalized weakness, low bone mass, previous fragility fracture, and risk of fall, needs to be evaluated for vitamin D deficiency. Evidence suggests that up to 90% of adults and children with above-mentioned musculoskeletal symptoms have vitamin D deficiency.[19,20]

Optimum vitamin D is considered to be levels greater than 30 ng/mL (to convert to nm mol multiply by 2.49). At these levels parathormone is suppressed to levels thought not to stimulate bone loss. Vitamin D insufficiency is defined as levels between 20–30 ng/mL, deficiency as levels less than or equal to 20 ng/mL and severe deficiency as levels less than 10 ng/mL.[19,21,22]

Optimal replacement regimens include a cumulative dose of ergocalciferol or cholecalciferol totaling no more than 300 000 to 600 000 units over a 3 to 6 month period. Proposed replacement regimens are as follows:

Vitamin D deficiency (< 20 ng/mL)

1. 50 000 units of D2/D3 once every week for 6 to 8 doses. If serum 25 hydroxy vitamin D levels remain subtherapeutic, repeat 50 000 units of D2/D3 once every 1 or 2 weeks for a further six doses till therapeutic values are achieved. This can be followed with a maintenance dose of 50 000 units once a month.[21]
2. Bolus oral dose of 300 000 units repeated after 2 to 3 months as required titrated to serum Vitamin D levels.[18]

Vitamin D insufficiency (20–30 ng/mL)

1. 50 000 units of D2/D3 once every 2 to 4 weeks for six doses. If serum 25 hydroxy vitamin D levels remain subtherapeutic, repeat 50 000 units of D2/D3 once every 2 to 4 weeks for further six doses till therapeutic values are achieved. This can be followed with a maintenance dose of 50 000 units once a month.[23]

Several reports are suggesting that parenteral replacement of vitamin D takes as much as 2 months to achieve therapeutic levels without any major influence on parathormone levels, compared to the oral regimens,[18] questioning their clinical significance.

Rule of thumb for replacement of oral vitamin D supplements

For every 100 units of vitamin D given for 4–6 months, the blood level will increase by approximately 0.5–1 ng/mL. For example if a patient has a vitamin D level of 15 ng/mL, with the aim of reaching 30 ng/mL, one would have to take 1500 units (100 units X {desired Vitamin D (30ng/ml) - exitsting vitamin D (15ng/ml) levels = 1,500} over and above the existing vitamin D dose for 4–6 months in-order to reach the therapeutic target).[23]

Benefits

A meta-analysis was carried out on the efficacy of vitamin D versus calcium supplementation on *risk of falls* in the elderly. The results suggested that "vitamin D" in comparison to calcium and placebo, was far superior in reducing falls in the elderly. Five prospective, randomized controlled clinical studies suggested a 22% reduction in fall rate.[24] In another meta-analysis, use of 700–800 IU/day vitamin D appeared to reduce the risk of *hip* and *nonvertebral fractures* in elderly population. A decreased relative risk of hip fractures by 26% and nonvertebral fractures by 23% compared with calcium alone or placebo was demonstrated. Fracture reduction was not seen when only 400 IU vitamin D3 was used.[25] A meta-analysis of randomized clinical studies in postmenopausal women of the effects of calcium on bone showed that calcium decreased bone loss by about 2% after two years or more,[26] accounting for the rationale of vitamin D and calcium combination therapy for fracture risk reduction.

A meta-analysis that compared use of vitamin D alone and with combination therapy (vitamin D and calcium) with regards *cardiovascular mortality* reduction, suggested a trend towards benefit with use of vitamin D.[27]

Adverse effects

The women health initiative study (WHI) showed a 17% increased incidence of renal stones in the population receiving calcium (1000 mg) and vitamin D (400 IU) daily.[28] Although the typical Indian diet is calcium poor and protects against the formation of kidney stones, the presence of hypercalciuria (24 h urine calcium) may be monitored particularly in populations on high vitamin D replacement regimens.

Drugs That Improves Bone Organic Tissue

Teriparatide

Teriparatide refers to 1-34 N-terminal active fragment of recombinant parathormone, an osteoanabolic that has revolutionized the treatment of osteoporosis. Recombinant 1–34 parathyroid hormone (rhPTH) (teriparatide) was approved by the Food and Drug Administration (FDA) on November 26, 2002, for the management of postmenopausal osteoporosis and osteoporosis in men.[29]

Teriparatide acts directly on osteoblasts and cells of osteoblast lineage to promote differentiation of preosteoblasts to osteoblasts. It also inhibits osteoblast apoptosis, thereby increasing the total number of active osteoblasts.This inturn leads to increased bone strength, mass and diameter, and bone structural integrity. It triggers the production of several growth factors in bone cells, including insulin-like growth factor-1 (IGF-1) that further contributes to an increase in bone mass. The anabolic effects are pronounced in the trabecular bone and on the endosteal surface of the cortical bone. Preclinical studies performed on rats have shown that cortical bone mass and strength are increased with use of teriparatide. It stimulates renal tubular re-absorption of calcium and excretion of phosphate, and indirectly increases intestinal absorption of calcium via its effects on 1, 25-dihydroxyvitamin D production.[30-34]

Teriparatide is biosynthesized using Escherichia coli as the host. The bioavailability of teriparatide is approximately 95% after subcutaneous administration. Maximum serum levels are achieved after approximately 30 min, and half-life is approximately 75 min.[35]

It is *indicated* for use in postmenopausal women, men with idiopathic or hypogonadal osteoporosis and in men or women with glucocorticoid-induced severe osteoporosis. It can also be used for patients on antiresorptives who fail to achieve the desired bone benefits with persistent T-scores below 3.5 or presence of fragility fractures despite use of antiresorptive therapy for 2 years.[36]

Teriparatide is licensed for use for approximately 18 months and no longer than 24 months.

Its efficacy is seen at both vertebral and nonvertebral sites with increased bone mass formation and fracture risk reduction. Kung AW[37] showed that vertebral bone mineral density values (assessed at the lumbar spine) significantly increased from baseline, to a greater extent with teriparatide 20 ug/mL than with placebo, alendronate[38] or calcitonin.[37] In the fracture prevention trial, bone mineral density was increased by 9% more in recipients of teriparatide.[38]

When used alone, teriparatide results in an increase in BMD at level of spine and hip but not at the radius. When used in patients pretreated with antiresorptives, there results a substantial benefit in bone mass density. Although the bone forming process is not as robust as when teriparatide is used before an anti-resorptive.

When a bisphosphonate (alendronate) is used immediately following use of teriparatide, a further increase of as much as 5% bone mass can be seen at 1 yr and about 8.9% at the end of 2yrs.[39] In a study where teriparatide was used in an alendronate pretreated group, osteoid surface increased by 3.96-9.8% compared to 6.2-11.3% in the teriparatidey-only treated group.[40]

A study that compared the efficacy of zolendronic acid with teriparatide alone, and in combination, in postmenopausal women with osteoporosis found that teriparatide increased spinal bone mineral density more than zoledronic acid and zoledronic acid increased hip bone mineral density more than teriparatide, however combination therapy using zolendronate and teriparatide provided the largest, most rapid increments when both spine and hip sites were considered.[41]

In the study that assessed the efficacy of teriparatide in combination with raloxifene, it was seen that use of teriparatide consistently increased markers of bone formation (PINP {procollagen type I N-terminal propeptide}) that was comparable in both teriparatide-only versus teriparatide-raloxifene group, however markers of bone resorption (CTX {carboxy-terminal collagen crosslinks}) was 60% lower in the teriparatide-raloxifene group compared to teriparatide only group tipping the

balance in favour of bone formation in the teriparatide-raloxifene group.[42]

In another study the addition of raloxifene after 12 months of teriparatide was associated with significantly greater decreases in markers of bone formation and bone resorption than those seen after teriparatide therapy ceased. At 3 months after randomization to raloxifene or placebo (no further treatment), CTX levels in both treatment groups had decreased significantly and to a greater extent with raloxifene than placebo reflecting suppression of bone turnover by raloxifene.[43]

In women taking hormone replacement therapy, use of teriparatide as add-on therapy resulted in increase of lumbar spine bone mineral density by 14.0%, compared to only 3% in women on hormone replacement therapy alone.[44]

Teriparatide can be used effectively in patients with cured primary hyperparathyroidism (undergone parathyroidectomy) but still at residual risk of fracture particularly at the spine. An increase of up to 7.1% in bone mineral density can be seen with use of 18 months of teriparatide in these patients. Teriparatide should therefore be considered as a viable alternative for the treatment of these patients as it may help in the prevention of fractures and their complications.[45]

When teriparatide therapy is interrupted it results in approximately 3.7% bone loss per (39) year that it stays interrupted.

In bisphosphonate-related subtrochanteric fracture, use of teriparatide augmented the healing process with 6 months of use.[46]

In patients with glucocorticoid-induced osteoporosis, teriparatide 20 μg/day over 18 months was more effective in increasing lumbar spine BMD than alendronate.

Adverse effects

Teriparatide injections are usually well tolerated. Transient redness at the injection site, headache, and nausea occur (<10%). Hot flushes, nausea, vomiting, muscle spasms, was seen more commonly with teriparatide in the raloxifene study.[42] Mild, early, transient hypercalcemia can occur, but severe hypercalcemia is rare as suggested earlier. Increases in urinary calcium (by 30 μg per day) and serum uric acid concentrations (13%) are seen but do not appear to have clinical consequences (gout, arthralgia, or urolithiasis). Teriparatide should not be used for patients at increased risk for bone tumors (osteosarcoma) based on animal experiments. The FDA has a black box warning about osteosarcoma in rodents treated with teriparatide and the manufacturer warns against using teriparatide in the following settings: Paget's disease or unexplained elevations of alkaline phosphatase, open epiphyses in children or young adults, bone metastases, prior radiation therapy involving the skeleton, metabolic bone disease other than osteoporosis, and hypercalcemia, pregnant women, children, lactating women.

A study of teriparatide on the effects of calcium were studied and it was seen that following teriparatide 20 mcg/day therapy, serum calcium levels increased from approximately 2 h postdose, reaching peak levels at 4-6 h postdose (median increase 0.4 mg/dL [0.1 mmol/L]). Serum calcium reach baseline levels at 16-24 h after each dose.[32] After 12 months treatment with teriparatide in >98% of postmenopausal women or men with primary or hypogonadal osteoporosis had peak serum calcium levels <11 mg/dL (2.76 mmol/L). Median peak serum levels were 9.68 mg/dL (2.42 mmol/L) in postmenopausal women with osteoporosis and 9.44 mg/dL (2.35 mmol/L) in men with primary or hypogonadal osteoporosis.[33] Sustained hypercalcaemia (calcium levels >11 mg/dL [2.76 mmol/L]) was not observed in the studies.[29,33]

Transdermal preparations of parathormone are under investigation.[47]

Strontium ranelate

Strontium ranelate is a divalent strontium salt comprised of two molecules of stable strontium and one molecule of ranelic acid. It is capable of increasing bone formation and reducing bone resorption, thereby uncoupling and rebalancing bone turnover in favor of bone formation. *In vitro* studies suggest that osteoblasts play a key role in the mechanism of action of strontium ranelate by mediating both its bone-forming and antiresorptive actions, at least partly, via the activation of the calcium-sensing receptor (CaSR), strontium, like calcium, acts as an agonist at the CaSR, promoting the replication, differentiation and survival of rodent or human primary osteoblasts.[48-51]

The drug is effective in reducing the risk of fractures, including both vertebral and nonvertebral fractures, in patients with postmenopausal osteoporosis. Significant improvements in cortical thickness (+18%), trabecular number (+14%), structure model index (−22%), and trabecular separation (−16%), as assessed by microcomputed tomography, were observed in biopsies from 41 women who received strontium ranelate 2 g/day versus placebo in various studies.[52-54]

It is administered in an oral dose of 2 g/day. The half-life of strontium is about 60 h. Approximately half of a dose of strontium is excreted via the kidneys, whereas the remainder is eliminated by gastrointestinal secretion and by slow release from bone tissues.

The efficacy data comes from two large, randomized, double-blind, placebo-controlled, multicentre, phase III trials, known as spinal osteoporosis therapeutic intervention (SOTI) and treatment of peripheral osteoporosis (TROPOS) that were carried out. Patients received double-blind treatment with strontium ranelate or placebo for 5 years in the TROPOS trial and for 4 years in the SOTI trial.

Oral strontium ranelate was shown to be effective in reducing the risk of vertebral fractures in patients with postmenopausal osteoporosis. The relative risk (RR) of developing a new vertebral fracture was significantly reduced by 41% and 39% with strontium ranelate compared with placebo after 3 years of therapy in the SOTI and TROPOS trials. The risk of a new vertebral fracture remained significantly reduced with strontium ranelate relative to placebo at later time points, with RR reductions of 33% after 4 years and 24% after 5 years of therapy.[54-56]

Adverse effects

The most common adverse events are nausea and diarrhea. Rare adverse effects include increase in musculoskeletal creatine kinase activity >3 times the upper limit of normal, (strontium ranelate 1.4% *vs.* placebo 0.6%), headache, disturbances in consciousness (strontium ranelate 2.6% *vs.* placebo 2.1%), memory loss (strontium ranelate 2.5% *vs.* placebo 2.0%) and seizures ((strontium ranelate 0.4% *vs.* placebo 0.1%). Over 5 years of treatment, strontium ranelate was also associated with an increased risk of venous thrombo-embolism (including pulmonary embolism) relative to placebo, although the overall annual incidence of this event was low 0.7%. Strontium ranelate is not recommended for use in patients with severe renal impairment (CL_{CR} <30 mL/min) and caution is advised in patients who are at increased risk of developing venous thromboembolism

Drugs acting via WNT signaling pathway

WNT proteins are a family of secreted proteins that regulate many aspects of cell growth, differentiation, function, and death. Of the pathways activated by WNTs, it is signaling through the canonical (i.e., WNT/[beta]-catenin) pathway that increases bone mass through a number of mechanisms including renewal of stem cells, stimulation of preosteoblast replication, induction of osteoclastogenesis, and inhibition of osteoblast and osteocyte apoptosis. It has been shown that WNT can also regulate bone morphogenesis via [beta]-catenin-independent (non-canonical) mechanisms during vertebrate development[57,58] [Figure 2].

WNT/beta-catenin represents a new recognized molecular pathway in the process of bone formation. Bone formation seems to be initiated by binding of the WNT protein to a 7-transmembrane domain-spanning frizzled receptor and low-density lipoprotein receptor-related protein 5 and 6 (LRP5/6) co-receptor. A variety of extracellular regulatory proteins take part in this WNT/frizzled receptor/LPR 5/6 interaction, for example, secreted frizzled receptor related protein, Dickkopf, sclerostin, WNT-inhibitory protein. This then sets off a cascade of intracellular secondary proteins such as disheveled, axin, glucogen synthase kinase 3-binding protein, casein kinase-1, adenomatosis polyposis coli, and Frat-1 that proceed to stabilize and translocate beta-catenin (stable) to the nucleus. Beta catenin can be dephosphorylated and rendered unstable/inactive by intracellular glycogen synthase kinsae 3 enzyme and subsequently degraded by a proteolytic system (ubiquitin proteasome). For the signals of bone formation to proceed, beta-catenin needs to be stabilized (phosphorylated) and interact with the nuclear receptors. This process is regulated by various proteins [Figure 1].

1. Sclerostin - secreted by osteocyte (entombed osteoblast in bone matrix) that inhibit WNT.
2. WNT inhibitory factor - Inhibits WNT.
3. Secreted frizzled related protein.
4. Glycogen synthase kinase 3 (phosphorylates and inactivates beta-catenin).
5. Proteolytic system - ubiquitin proteasome (degrades beta-catenin).
6. Histone deacetylases (inactivates nuclear signals required for osteoblastogenesis following beta-catenin/nuclear interaction).

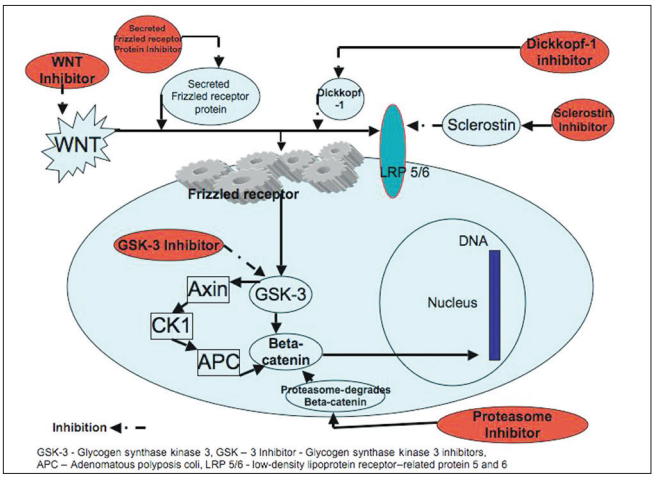

Figure 2: Possible future therapeutic targets for drugs acting via WNT signaling pathway[59]

All of the above could serve as potential targets for inhibition; thus, bone formation (sclerostin inhibitor, secreted frizzled related protein inhibitors, Dickkopf inhibitors, glycogen synthase kinase 3 inhibitors, proteasome inhibitors, and histone deacetylase inhibitors)

Sclerostin was originally thought to be an antagonist of bone morphogenetic proteins (BMPs), however, in subsequent experiments it was demonstrated that sclerostin could not antagonize all BMP responses, and had a mechanism of action distinct from that described for classical BMP antagonists. Sclerostin was shown to inhibit bone formation by blocking WNT signaling in osteoblasts. Sclerostin binds to LRP5 and antagonizes WNT signaling in a noncompetitive manner.[59,60]

Other investigational therapies

1. *(PTH-βarr), an arrestin pathway-selective agonist for the parathormone (PTH) type-1 receptor (PTH-1) R* - although the conventional PTH-1 receptor agonist teriparatide, PTH[1-34] is effective in the treatment of osteoporosis; its utility is limited by its bone-resorptive effects and propensity to promote hypercalcemia/hypercalcuria. In contrast,[7-34] (PTH-βarr), an arrestin pathway-selective agonist for the PTH[1] receptor, induces anabolic bone formation independent of classic G protein-coupled signaling mechanisms. Unlike PTH,[1-34] PTH-βarr appears to "uncouple" the anabolic effects of PTH(1) receptor without affecting catabolic and calcitropic effects of PTH.[61]
2. *Growth hormone therapy - in vitro* studies show that GH and its intermediary substance {insulin-like growth factor (IGF)-1} affect osteoblastic production of skeletal collagen, and noncollagen proteins. *In vivo* infusions of IGF-1 have shown to increase cortical and trabecular bone, via increased osteoblastic activity and decreased osteoclastic activity.[62]
3. *Tissue growth factors* and *bone morphogenetic proteins*.[63]
4. *Parathormone-related peptide therapies*.[64]
5. *Neuropeptide Y (NPY)* is emerging as an important regulator of bone remodeling. Central NPY over expression has shown to decrease osteoblastic activity, while on the other hand specific NYP-receptor1 deletion has shown to enhance bone mass (trabecular and cortical). These effects seem to be dependant mostly on the NPYR1 receptor with regulatory input from NYPR2 and 4 and the leptin system. Central NYP inhibition via NYP-receptor 1 (antagonists) might represent an exciting future therapeutic option.[65,66]

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