REVIEW ARTICLE

MEDICAL PROGRESS

Mechanisms of Anabolic Therapies for Osteoporosis

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Osteoporosis, a major worldwide health problem, affects 4 million to 6 million women and 1 million to 2 million men in the United States. Even more people have decreased bone mass, which, in addition to other risk factors, can be a major therapeutic challenge.[1] Fractures, the most important consequence of osteoporosis, are associated with enormous costs and substantial morbidity and mortality. The prevention and treatment of this disease are therefore of paramount importance. Since postmenopausal osteoporosis is characterized by bone resorption that exceeds bone formation, antiresorptive agents can help to restore skeletal balance by reducing bone turnover, primarily at the tissue level.[2,3] By means of this mechanism, antiresorptive agents reduce the incidence of fracture in osteoporosis and thus occupy a central role in the management of this condition.

Another therapeutic approach is anabolic — namely, to enhance bone formation. Anabolic agents differ fundamentally from antiresorptive drugs in their primary mechanism of action. The mechanisms by which anabolic agents stimulate bone formation at the cellular, biochemical, and molecular levels are being actively studied. In this article, we review the mechanisms of polypeptide anabolic agents and strontium ranelate as potential therapeutic options for osteoporosis. Because of space limitations, anabolic steroids and selective androgen-receptor modulators are not considered.

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BONE REMODELING AND MODELING

Bone remodeling is a temporally regulated process resulting in the coordinated resorption and formation of skeletal tissue. This process occurs in microscopical, basic multicellular units (see Glossary) in which the cellular components are osteoclasts and osteoblasts (Fig. 1).[4] Signals that are not yet completely understood attract osteoclasts, multinucleated bone-resorbing cells, to sites that become a bone-remodeling unit. When resorption of bone by osteoclasts in that remodeling unit is completed, a process that takes 3 to 5 weeks, the resorbed surface attracts osteoblasts, mononuclear bone-forming cells that fill the basic multicellular unit with a new matrix. The actions of the osteoblasts and the subsequent completion of the remodeling sequence by mineralization of the matrix take 3 to 5 months.

Osteoclasts are derived from pluripotential hematopoietic cells; osteoblasts are derived from mesenchymal cells that are present in the skeletal microenvironment.[5] Signals that determine the differentiation, function, and death of these cells and their progenitors determine how many units are activated over time, how active and well-balanced the basic multicellular unit is, and whether, at the end of the cycle, bone mass will be gained, lost, or stable. Osteocytes are osteoblasts that have become embedded in lacunae of the calcified bone matrix. With cytoplasmic processes, osteo-

cytes form a large, communicating network that helps to maintain the material and structural properties of bone.[3] Osteocytes, which are considered to be mechanosensors, identify sites for remodeling when the prevailing physical loads are sensed and require adaptation.[6] In this way, osteocytes might help to direct bone remodeling.[3] In adults, bone remodeling is a mechanism for the renewal of bone and the repair of microdamage and microcracks (Fig. 1).

The negative skeletal balance in most postmenopausal women occurs because bone resorption exceeds bone formation. This imbalance may result from an increase in osteoclast number or activity, a decrease in osteoblast number or activity, or a combination of the two. The therapeutic challenge is to redress this imbalance so that the number of osteoblasts becomes equal to that of osteoclasts or so that the osteoblasts become more active than the osteoclasts.

Glossary

Basic multicellular unit (BMU): A microscopical unit in which bone remodeling occurs. A BMU is formed by osteoclasts and osteoblasts.

β-Catenin: An intracellular protein used by Wnt to signal.

BMP-3: An inhibitory bone morphogenetic protein.

Bone modeling: A process driven by bone formation that is not linked to bone resorption. Mechanical forces in the growing skeleton are stimuli.

Bone morphogenetic proteins: Factors that induce maturation of bone-forming cells (osteoblasts).

Bone remodeling: A process in which bone resorption (driven by osteoclasts) is linked to bone formation (driven by osteoblasts).

Dickkopf-1 (Dkk-1): A secreted Wnt antagonist that binds LRP5 and LRP6.

Dual-energy x-ray absorptiometry: A widely used method to measure bone mineral density.

Frizzled: A Wnt receptor.

Insulin-like growth factor: A systemic and local growth factor that enhances osteoblastic function.

Insulin-receptor substrate (IRS): An intracellular molecule used for insulin and IGF-I signaling.

Low-density lipoprotein receptor–related proteins 5 and 6 (LRP5 and LRP6): Wnt coreceptors.

Parathyroid hormone (PTH)–related peptide (PTHrP): An endogenous protein related to PTH that binds to the PTH–PTHrP receptor.

Proteasome: A cellular system in which degradation of proteins takes place.

PTH (1–84): Full-length PTH.

Sclerostin: A secreted Wnt antagonist that binds LRP5 and LRP6.

SOST: A gene encoding sclerostin.

Teriparatide: Human PTH (1–34).

Wnt: The mammalian homologue of *wingless* (a gene in drosophila) that induces differentiation of bone-forming cells.

Bone modeling, in contrast to bone remodeling, is a process that leads to changes in the size and shape of bone. It is driven by mechanical forces and is predominantly observed in the developing and growing human skeleton. Osteoblasts and osteoclasts are key cellular components of bone modeling, but they are not coupled to each other as they are in bone remodeling. Although bone modeling in the adult human skeleton is not a primary mechanism of skeletal homeostasis, it does contribute to bone mass and strength. As is the case for bone remodeling, the precise molecular mechanisms that initiate bone modeling are not known, but they may play a role in the actions of anabolic therapies for osteoporosis.

SIGNALS THAT REGULATE BONE FORMATION

BONE MORPHOGENETIC PROTEINS, Wnt, AND INSULIN-LIKE GROWTH FACTOR I

Osteoblasts, the cells responsible for bone formation, are rational therapeutic anabolic targets. Signals that determine the replication and differentiation of preosteoblastic cells, which determine the function of osteoblasts and their survival or death, are of critical importance for an anabolic effect. Anabolic agents can increase the number of osteoblast precursors, stimulate the differentiation of these cells into mature osteoblasts, enhance their function or their survival and, as a consequence of any of these effects, lead to a net gain of bone tissue.

Two important signals that induce the differentiation of osteoblastic lineage cells into mature osteoblasts are bone morphogenetic proteins and Wnt, the mammalian homologue of wingless in drosophila.[7,8] Bone morphogenetic proteins and Wnt play a fundamental role in osteoblastogenesis and, ultimately, in the gain of bone mass (Fig. 2).[7-9] Another important regulator of osteoblast function is insulin-like growth factor I (IGF-I).[10] Bone morphogenetic proteins, Wnt, and IGF-I are regulated at the level of their synthesis and their receptors and by specific extracellular and intracellular regulatory proteins.[11,12] Thus, anabolic therapeutic agents might be designed to stimulate the actions of these osteoblastic signals directly or to target their extracellular and intracellular regulators.

Bone morphogenetic proteins are members of the transforming growth factor β superfamily of polypeptides, which includes activins and inhib-

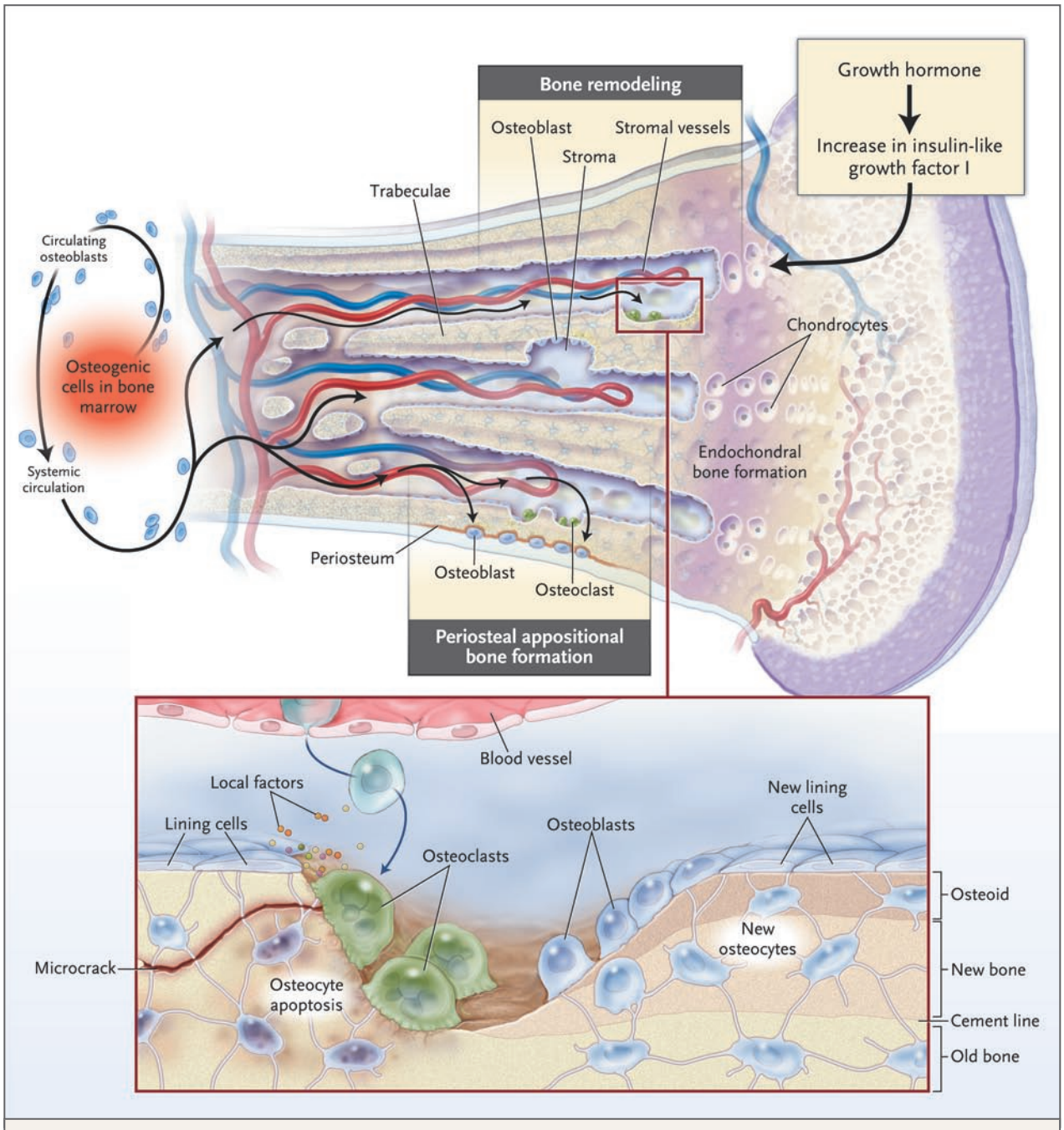

Figure 1. Bone Remodeling in Basic Multicellular Units and Bone Modeling by Osteoblasts and Osteoclasts.

During growth, chondrocytes mature and direct the formation of new bone trabeculae in the process of endochondral bone formation, and osteoblasts form new bone by periosteal appositional growth. These processes determine the length and width of bones. Bone is remodeled by osteoclasts (bone-resorbing cells) coupled with osteoblasts (bone-forming cells) in basic multicellular units. Bone remodeling is necessary to maintain calcium homeostasis and to renew bone to repair microdamage and microcracks. The shape of bone is determined by the modeling conducted by uncoupled osteoblasts and osteoclasts.

ins.[7] These proteins bind to and activate specific receptors to initiate signal transduction and influence intracellular events leading to osteoblastogenesis (Fig. 3).[13,14] The effects of bone morphogenetic proteins are inhibited by their antagonists, a family of extracellular binding proteins.[11]

The Wnt–β-catenin signaling pathway is central to osteogenesis and bone formation. Wnt and

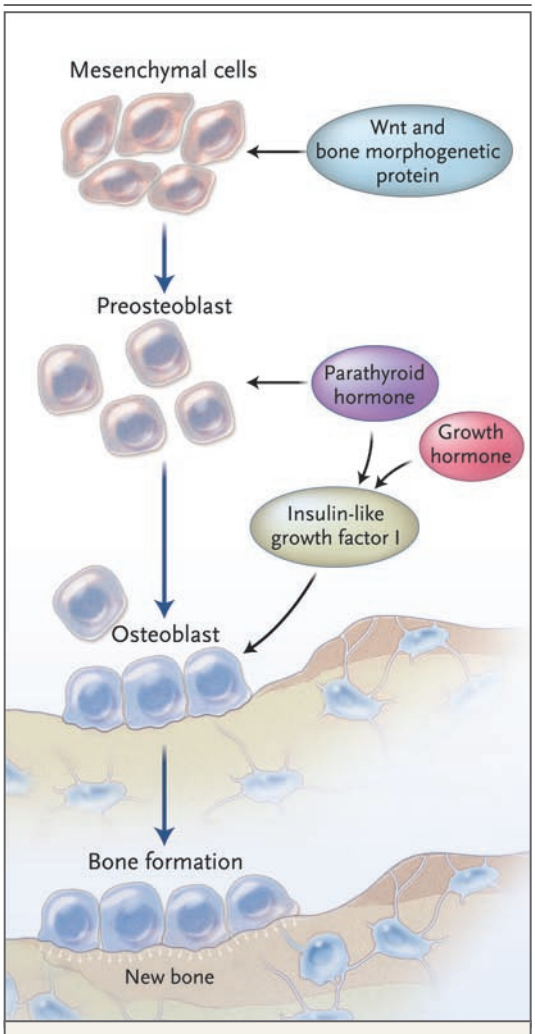

Figure 2. Signals Determining Mesenchymal-Cell Differentiation toward Osteoblasts and Signals Acting on Mature Osteoblasts to Enhance Bone Formation.

Under the influence of Wnt and bone morphogenetic protein, undifferentiated mesenchymal cells differentiate toward cells of the osteoblastic lineage. Parathyroid hormone (PTH) enhances cell replication, and PTH and growth hormone induce the synthesis of insulin-like growth factor I, which enhances osteoblastic bone formation.

bone morphogenetic proteins have similar effects, but they signal through different pathways (Fig. 3 and 4). In skeletal cells, Wnt uses the canonical Wnt–β-catenin signaling pathway.[8] Wnt binds to specific receptors, called frizzled, and to low-density lipoprotein receptor–related proteins 5 and 6 (LRP5 and LRP6). These interactions lead to the stabilization of β-catenin, which translocates to the nucleus and regulates gene expression (Fig. 4). The importance of Wnt–β-catenin signaling in osteogenesis is confirmed by studies of the effects of mutations on this pathway. Activating mutations of Wnt coreceptors result in increased bone mass, whereas inhibition of this pathway leads to reduced bone mass.[15,16]

Secreted Wnt antagonists can block Wnt signaling and actions by binding to Wnt or by interfering with interactions between Wnt and its receptors and coreceptors (Fig. 4). For example, sclerostin and Dickkopf-1 (Dkk-1), both expressed by osteoblasts and osteocytes, prevent Wnt signaling by interacting with Wnt coreceptors.[12,17] When a bone morphogenetic protein or Wnt antagonist is preferentially synthesized in the skeleton, it may become a therapeutic target for inhibition, leading to activation of bone morphogenetic proteins or Wnt. The removal of an antagonist should be specific and targeted to skeletal tissue to prevent unwanted effects at nonskeletal sites.

IGF-I, which is synthesized in the liver and other tissues, including the skeleton, mediates the effects of growth hormone on longitudinal bone growth.[10] IGF-I exerts direct actions in bone and is necessary for skeletal development and the maintenance of bone mass.[10] The physiology of IGF-I is complex, since it acts both as a circulating growth hormone–dependent hormone and as a local skeletal growth factor.[18] IGF-I synthesis in bone cells is primarily dependent on parathyroid hormone (PTH) and is required, in turn, for the anabolic actions of PTH in rodent bone.[19,20] Six IGF-binding proteins can form a complex with IGF-I and modulate the levels of free IGF in plasma and peripheral tissues.[10] IGF-I primarily influences the differentiated function of the osteoblast and prevents osteoblast apoptosis. In vivo, two experimental models confirm the anabolic effect of IGF-I. Overexpression of IGF-I increases the volume of cancellous bone by increasing bone formation.[21] Targeted deletions of the *IGF1* receptor gene or deletions of the insulin–IGF-I signaling molecules, insulin-receptor substrate (IRS) 1 and 2, cause osteopenia due to impaired bone formation.[22,23] These observations confirm the role of IGF-I as a central regulator of bone mass.

PARATHYROID HORMONE

The intermittent administration of low-dose PTH results in anabolic effects on the skeleton. PTH

signals through the PTH-1 receptor, a G protein–coupled protein, which mediates most of the functions of PTH and of its evolutionary relative, PTH-related peptide (PTHrP). Also known as the PTH–PTHrP receptor, it is activated by peptide sequences that include the N-terminal region of either molecule. Other peptide sequences of PTH that do not contain the N-terminal region may serve different functions through another receptor.[24] PTH activates the cyclic AMP–dependent protein kinase A and calcium-dependent protein kinase C signaling pathways to regulate osteoblast function.[25] PTH also activates the MAP kinase and phospholipase A and D pathways. Additional mechanisms of PTH signal propagation and control include the internalization of the PTH receptor, its association with importins, and its nuclear translocation, where it may regulate gene transcription.[26] The exact signaling pathway responsible for the anabolic effect is not known, but the various pathways used by PTH may determine whether it has anabolic or catabolic actions. The Wnt–β-catenin pathway has generated interest because the expression of the Wnt antagonist sclerostin is down-regulated by PTH, and this may partially account for the anabolic actions of PTH.[27]

The anabolic actions of PTH involve direct effects on osteoblast lineage cells and indirect effects through the regulation of selected skeletal growth factors (e.g., IGF-I) and growth factor antagonists, such as sclerostin.[25] PTH has mitogenic properties for osteoblastic cells and decreases osteoblastic apoptosis.[28] As a consequence, it increases the number of bone-forming cells. PTH induces IGF-I synthesis in osteoblasts, and PTH and IGF-I are powerful anabolic agents for cancellous bone. IGF-I neutralization prevents the stimulation of bone matrix by PTH, and the anabolic effect of PTH in vivo is blunted in *IGF1*– and *IRS-1*–null mice.[19,20,29] Although these observations provide support for the role of IGF-I in the anabolic actions of PTH, other factors have been invoked, and the precise mechanisms accounting for the anabolic effects of PTH have not been elucidated.[25] It is unclear why the intermittent administration of low-dose PTH differs in its effect on bone cells from long-term, sustained PTH exposure in which catabolic effects at cortical sites predominate. Knowledge of the molecular mechanisms underlying the actions of PTH is limited, and the intracellular mechanisms determining whether its actions are anabolic or catabolic are poorly understood.

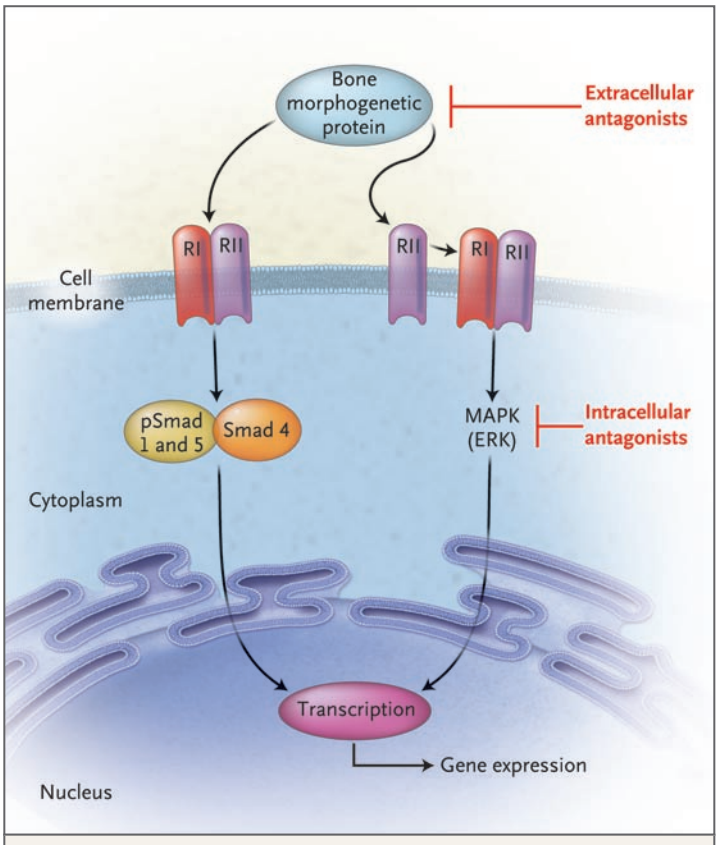

Figure 3. Signaling Pathways Used by Bone Morphometric Proteins in Osteoblasts.

After bone morphogenetic protein binds to its predimerized type I and II receptors (RI and RII), Smad 1 and 5 proteins are phosphorylated (pSmad), associate with Smad 4, and translocate to the nucleus to regulate transcription. Another pathway used by bone morphogenetic protein involves binding to its type II receptor, an intrinsic kinase that activates the type I receptor; the newly dimerized receptor complex activates the mitogen-activated protein kinase (MAPK) extracellular regulated kinase (ERK) pathway to regulate transcription. Extracellular antagonists bind bone morphogenetic protein and prevent signal transduction.

CLINICAL RELEVANCE OF ANABOLIC SIGNALING MOLECULES

PARATHYROID HORMONE

The effects of teriparatide [PTH (1–34)] on bone metabolism have been studied in postmenopausal women and in men with advanced osteoporosis.[30] In a study of postmenopausal women, teriparatide administered as a 20-μg daily subcutaneous injection increased vertebral bone mineral density (BMD), measured by means of dual-energy x-ray absorptiometry, by 8 to 9% and femoral BMD by about 3% over a 21-month period. There was an associated 65% reduction in the incidence of fracture at vertebral sites and a 54% reduction in the

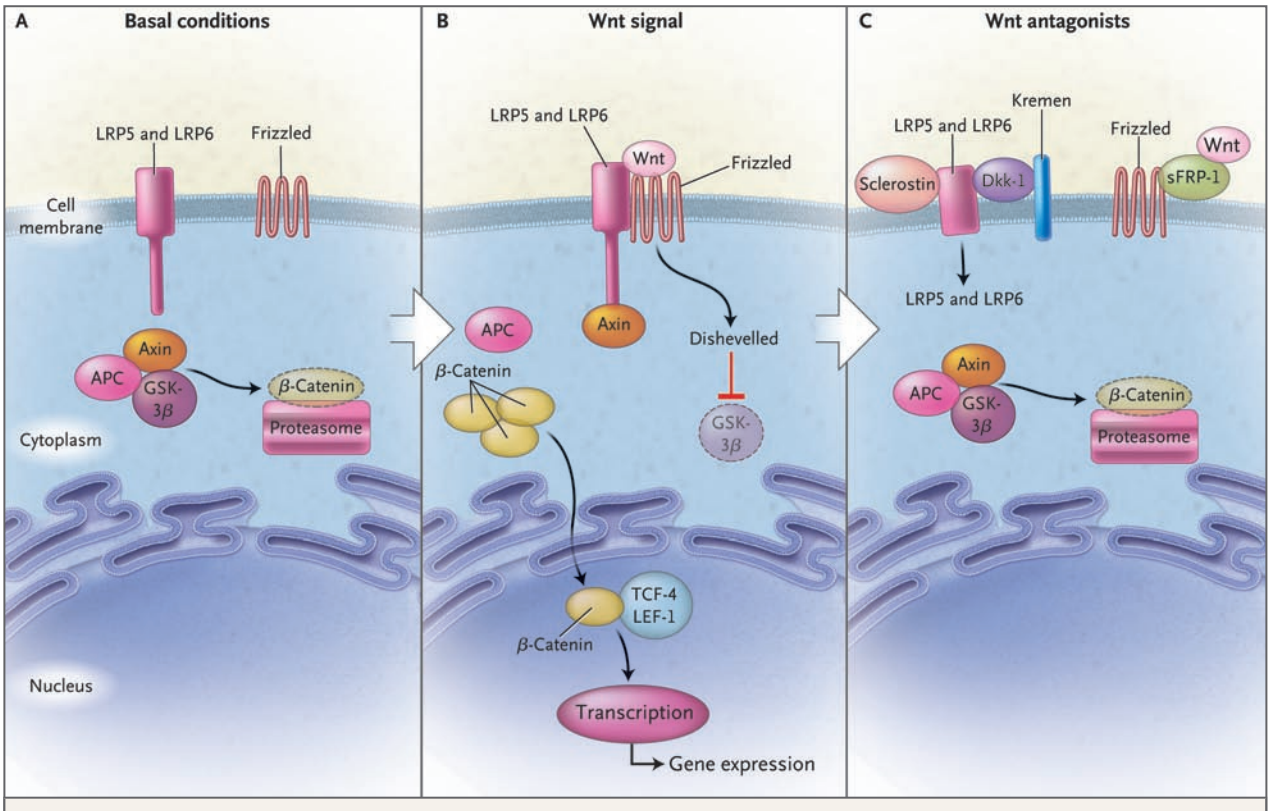

Figure 4. The Canonical Wnt–β-Catenin Signaling Pathway Used in Osteoblasts.

Panel A shows that under basal conditions, β-catenin is phosphorylated by glycogen synthase kinase 3β (GSK-3β), axin, and adenomatous polyposis coli (APC) tumor-suppressor protein and degraded in the proteasome. Panel B shows that after Wnt binding to its receptor (frizzled) and coreceptors (low-density lipoprotein receptor–related proteins 5 and 6 [LRP5 and LRP6]), dishevelled, an intracellular protein, is induced to degrade GSK-3β. In addition, the cytoplasmic tails of LRP5 and LRP6 bind and anchor axin. These two events lead to the stabilization of β-catenin and its translocation to the nucleus, where it binds to T-cell factor 4 (TCF-4) or lymphoid enhancer binding factor 1 (LEF-1) to regulate transcription. Panel C shows that the extracellular Wnt antagonists prevent Wnt signaling. Dickkopf-1 (Dkk-1) in association with Kremen and sclerostin bind LRP5 and LRP6. Soluble frizzled-related protein 1 (sFRP-1) binds Wnt and prevents its interaction with frizzled.

fracture incidence at nonvertebral sites. As with antiresorptive agents, increments in BMD, at least as measured by dual-energy x-ray absorptiometry, explain only in part the efficacy of PTH in preventing fractures in women with osteoporosis.[31] When changes in true volumetric density are assessed in grams per cubic centimeter by means of quantitative computed tomography, the increase in BMD as a result of PTH therapy is much greater.[32] Teriparatide is available throughout most of the world, but full-length PTH (1–84) is available only in Europe.

Teriparatide is approved in the United States for the treatment of osteoporosis in postmenopausal women and in men who are at high risk for fracture. The definition of high risk could be a T score on dual-energy x-ray absorptiometry that is very low (i.e., less than −3.0), with or without other risk factors such as a previous fragility fracture or a strong family history of osteoporosis. In many countries in Europe, teriparatide cannot be administered unless a patient has received a previous, unsuccessful course of bisphosphonate therapy and has had a previous osteoporotic fracture. These restrictive indications are due, in part, to the fact that teriparatide is expensive and is administered by daily subcutaneous injection. The recommended duration of teriparatide therapy (2 years in the United States and 18 months in Europe) is relatively short because its safety and efficacy were not evaluated after 2 years in clinical trials.

Adverse events with teriparatide include mild hypercalcemia, which has been reported in 1 to 3%

of patients treated.[30,33] Hypercalcemia is generally corrected by reducing calcium or vitamin D supplementation. If these measures fail, a dosage adjustment of teriparatide from daily to every-other-day administration is usually effective. A higher incidence of hypercalcemia and hypercalciuria has been reported with full-length PTH (1–84).[34] Although it is not specifically recommended, many practitioners check the serum calcium concentration 1 month after initiating therapy. The serum uric acid concentration may rise, but gout does not appear to be a clinical concern. Other uncommon side effects include dizziness, nausea, and leg cramps.

Teriparatide is contraindicated in children and in persons with hypercalcemia, active Paget's disease of bone, skeletal metastases or skeletal malignant conditions, or a history of irradiation to the skeleton. Some of these contraindications are related to concerns about the development of osteosarcoma. The disorder develops in rodents exposed to prolonged, high-dose teriparatide or PTH (1–84).[35,36] For this reason, teriparatide labeling in the United States carries a black-box warning. A case of osteosarcoma in a woman who had received teriparatide for 1 year was reported recently.[37] That single case, reported after more than 300,000 exposures to teriparatide, has been interpreted as being consistent with epidemiologic expectations with respect to cases of osteosarcoma in the general population. Thus, the relationship of the reported osteosarcoma in rodents to the same condition in patients is uncertain.[37]

Many patients who are candidates for anabolic therapy with teriparatide or with PTH (1–84) have been treated previously with bisphosphonates or raloxifene. It appears that antiresorptive agents that cause a modest decrease in bone turnover do not substantially influence the densitometric response to PTH, whereas more potent inhibitors of bone turnover such as alendronate may substantially influence the initial response to teriparatide.[32,38,39] Because of the possibility of a sluggish response to teriparatide after alendronate therapy, some practitioners advocate a 6-month hiatus between discontinuation of treatment with alendronate and initiation of teriparatide therapy. Others suggest that teriparatide therapy be initiated immediately after the bisphosphonate has been withdrawn because of concerns about the lack of therapy for any period in a patient with severe osteoporosis.

Although the concomitant use of PTH with an antiresorptive agent may be considered to be a potentially attractive option because of their different mechanisms of action, initial studies with alendronate and teriparatide or PTH (1–84) have not shown an obvious benefit of combining the two drugs as compared with administering either agent alone.[32,40] However, the combination of raloxifene and teriparatide was associated with greater improvement in hip BMD than was teriparatide alone in a 6-month trial.[41]

Discontinuation of PTH leads to a rapid decline in BMD.[42] Consequently, it is advisable to administer an antiresorptive agent such as a bisphosphonate after treatment with teriparatide in order to maintain the densitometric gains achieved with PTH.[42] It is not known how long the antiresorptive agent should be used after the course of PTH therapy, but many experts recommend the continuation of long-term antiresorptive therapy for its own therapeutic benefits as well as for maintenance of the therapeutic gains achieved with PTH.

Glucocorticoid-induced osteoporosis is a condition for which PTH might be particularly effective, because impaired bone formation is a primary pathogenetic feature.[43] The results of a trial comparing teriparatide with alendronate, over an 18-month period, in patients with glucocorticoid-induced osteoporosis showed greater increases in vertebral BMD and a greater reduction in new vertebral fractures with teriparatide than with alendronate.[44]

The anabolic actions of PTH may be considered with regard to its stimulatory effects on bone resorption. Both the anabolic and resorptive actions can be considered in the context of the anabolic window, a period of time during which PTH affects bone formation to a greater extent than it stimulates bone resorption (Fig. 5).[45] Evidence providing support for this concept comes from the kinetics of change in bone-turnover markers with PTH. Bone-formation markers increase before bone-resorption markers. During this period, PTH is thought to be maximally anabolic. Histomorphometric analysis of bone-biopsy specimens from humans and from ovariectomized rhesus monkeys has shown the anabolic effects of PTH.[46-48] Increases were seen in the trabecular bone volume, connectivity, bone microarchitecture, and biomechanical properties of bone. PTH appears to increase bone volume by increas-

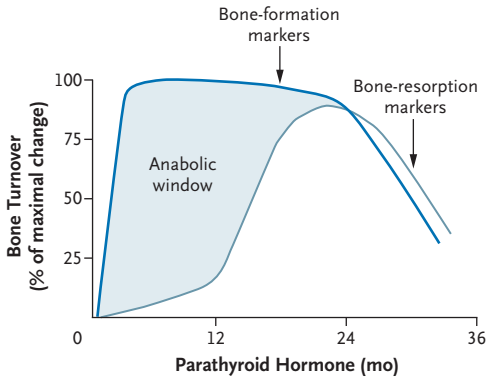

Figure 5. The Anabolic Window.

Parathyroid hormone (PTH) stimulates the processes associated with bone formation before there is a subsequent stimulation of the processes associated with bone resorption. The "window" between the effects of PTH on these actions is variable, but it is thought to represent the period when PTH is maximally anabolic for bone. Data are from Rubin and Bilezikian.[45]

ing the number of bone trabeculae, possibly after the division of thickened trabeculae.[46] In rodent models, PTH increases bone formation to a greater extent at periosteal than at endocortical sites, suggesting a potential effect on bone modeling that can strengthen bone by increasing the periosteal circumference.[49] In humans, the anabolic effects of PTH on cortical bone do not appear to be as pronounced as the effects on cancellous bone.[46,47] Although morphometric observations confirm the anabolic effect of PTH on bone, the specific underlying cellular and molecular mechanisms leading to an anabolic response remain to be eludicated.

Other delivery systems for PTH besides subcutaneous administration, such as oral, transdermal, and nasal administration, are of interest.[50-52] Although they are more convenient than subcutaneous injection, these different routes of administration must first be shown to have pharmacokinetic profiles that are consistent with the pulsatility characteristics required for the anabolic effects of PTH, and they must be shown to be efficacious. Another approach would be to stimulate endogenous PTH secretion by means of an agent that interferes with the calcium-sensing receptor on the parathyroid cell. When the signal generated by the calcium receptor is blocked, PTH secretion is stimulated. Oral calcilytic agents stimulate endogenous PTH secretion in rodents, and they are being studied for their effects in humans.[53] A truncated variant of PTH (PTH 1–34) that maintain the N-terminal region of the intact peptide is also of interest.[54]

PTHrP is currently being studied for its potential anabolic effects in humans. Initial studies in postmenopausal women with osteoporosis suggested that PTHrP at a daily dose of approximately 400 μg for 3 months increases vertebral BMD by 4.7%.[55] Serum osteocalcin was increased, but serum calcium and biochemical markers of bone resorption were not affected. Larger and longer trials are required to assess the anabolic potential of PTHrP.

STRONTIUM RANELATE

Strontium ranelate, like calcium, becomes incorporated into the crystal structure of bone. The dual anabolic and antiresorptive actions of strontium ranelate have been reported, particularly in in vitro models.[56,57] Bone-biopsy specimens from patients treated with strontium ranelate show a reduction in bone resorption but no evidence of increased bone formation.[58] Increases in bone-remodeling markers are small. Vertebral BMD, however, is increased, in part because strontium introduces a densitometric artifact as it becomes incorporated into the bone mineral itself. In a prospective clinical trial, treatment with strontium ranelate, at a dose of 2 g given daily for 3 years, was associated with a 40% reduction in new vertebral fractures in postmenopausal women with osteoporosis.[58] Another study showed a modest but significant reduction in nonvertebral fractures but not in hip fractures.[59,60] A reduction in hip fractures was observed only in a subsequent analysis of a high-risk subgroup of patients older than 74 years of age with hip BMD T scores below –3.5. Strontium ranelate is approved in Europe, but it is not approved in the United States for the treatment of postmenopausal osteoporosis. It is administered orally and has few side effects, although it has been associated with a slight increase in venous thrombosis of the legs.

GROWTH HORMONE AND IGF-I

In patients with growth hormone deficiency, replacement of growth hormone increases bone mass. Results from a cross-sectional study indicate that patients with growth hormone deficiency who are receiving growth hormone-replacement therapy have a reduced risk of vertebral fractures as compared with untreated patients.[61] Although

the beneficial effects of growth hormone on the skeleton appear to be clear in patients with growth hormone deficiency, this is not the case in the absence of growth hormone deficiency.[62] Growth hormone increases BMD in patients with postmenopausal osteoporosis, but the effects are inconsistent, and well-designed longitudinal studies showing a reduction in the risk of fracture in this condition with growth hormone have not been reported. As compared with young adults, older persons have lower serum levels of growth hormone and of IGF-I, but growth hormone has not been shown to increase bone mass.[63] The use of growth hormone in osteoporosis also is likely to be limited by side effects such as weight gain, carpal tunnel syndrome, glucose intolerance, and edema.[64]

Serum levels of IGF-I correlate with BMD, and the administration of IGF-I in healthy persons or patients affected by growth hormone deficiency or IGF-I deficiency causes a skeletal anabolic response and an increase in bone remodeling.[65,66] Recombinant human IGF-I is available for the treatment of short stature caused by IGF deficiency that is due to mutations of the *GH* receptor or the *IGF1* gene. Studies of the effects of IGF-I on bone turnover in humans have been limited. At high doses, IGF-I increases biochemical markers of bone remodeling, whereas at low doses, it increases exclusively markers of bone formation, without an effect on bone resorption.[62,65] IGF-I has been studied in patients with anorexia nervosa, a disorder associated with low serum IGF-I levels.[65] In such patients, the administration of IGF-I at doses that normalize serum IGF-I, in combination with estrogen-replacement therapy, increases BMD.[67] Notwithstanding these results, the long-term efficacy and safety of IGF-I for the treatment of osteoporosis, including the osteoporosis associated with anorexia nervosa, remain to be determined. Potential side effects and the lack of tissue specificity are concerns with respect to the long-term administration of IGF-I.

SCLEROSTIN ANTAGONISM

Sclerostin inhibits osteoblastogenesis and bone formation in vitro and in vivo. Mutations in *SOST*, the gene that encodes sclerostin, eliminate the expression of sclerostin; this causes skeletal dysplasias characterized by increased bone mass (sclerosteosis and van Buchem's syndrome).[68-70] Sclerosteosis is characterized by hyperostosis, syndactyly, facial palsy, deafness, and the absence of nails,[70,71] whereas van Buchem's syndrome is characterized by hyperostosis, a protruding chin, a high forehead, and facial-nerve palsy.[68,69] Patients with sclerosteosis, as well as heterozygous carriers, have increased BMD.[72] It follows from these genetic deletion syndromes that the antagonism of sclerostin might be associated with anabolic effects on bone. Monoclonal antibodies against sclerostin, for example, prevent its binding to Wnt coreceptors, enhancing Wnt signaling and increasing bone mass in rodents and nonhuman primates.[73] These observations, if confirmed by definitive studies in patients, might have clinical applicability. However, it is possible that enhancement of Wnt signaling through the inhibition of a Wnt antagonist will have unwanted effects in nonskeletal tissues. This possibility could potentially be minimized by blocking sclerostin in specific skeletal cells.

OTHER CANDIDATE MOLECULES FOR ANABOLIC THERAPY

ANTAGONISTS OF Dkk-1

Gain-of-function mutations of *LRP5* and *LRP6* that lead to impaired binding of Dkk-1 to this Wnt coreceptor are associated with increased bone mass.[15] This clinical observation and data from rodent models of Dkk-1 misexpression established its function as an inhibitor of Wnt signaling and bone formation and led to the development and testing of Dkk-1 antibodies. Dkk-1 neutralization increased BMD, trabecular bone volume, and bone formation in rodents, suggesting that Dkk-1 inhibitors might have potential as an anabolic approach in the treatment of osteoporosis, particularly if they are targeted specifically to bone.[74]

SOLUBLE ACTIVIN RECEPTORS

Activin enhances osteoclastogenesis, and its effects on bone formation are controversial.[75,76] Activin receptors bind activin and bone morphogenetic protein 3, an inhibitor of bone formation.[77] A soluble activin receptor II, which binds activin and possibly bone morphogenetic protein 3, decreases bone resorption and enhances bone formation in rodents.[78] However, the exact mechanisms involved in the anabolic response are not clear.

THE OSTEOBLAST PROTEASOME AND ITS INHIBITORS

As a major structure for intracellular protein degradation, the proteasome could be targeted for anabolic-drug development. Inhibitors of proteolytic processing systems might unmask or enhance ana-

bolic pathways.[79,80] The use of proteasome inhibitors will depend on their skeletal specificity and their safety profile, since such inhibitors can induce cellular toxic effects and the intracellular accumulation of misfolded proteins.[79]

CONCLUSIONS

During the past decade, we have witnessed major developments in the diagnosis and management of osteoporosis. Important progress in our understanding of the cellular events that regulate bone modeling and remodeling has occurred. Antiresorptive agents have been the most prominent therapeutic advances, but we are now on the verge of seeing a new class of agents, the so-called anabolics. Anabolic agents have the potential to rebuild skeletal losses by stimulating the processes and mechanisms associated with bone formation. PTH is the only prototypical anabolic agent available at this time. However, other agents may be developed, based on a new understanding of anabolic pathways and intermediate molecules such as bone morphogenetic proteins, Wnt, and IGF-I and their regulatory molecules. Although the systemic administration of anabolic agents constitutes a promising therapeutic approach, the modification of anabolic signals specifically within bone may become another new avenue for the treatment of osteoporosis.

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