Endocrine, *vol. 17, no. 1, 21–27, February 2002* 0969–711X/02/17:21–27/$11.75

Mechanisms of Bone Loss and Gain in Untreated and Treated Osteoporosis

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Introduction

In recent years, there have been significant advances in the management of osteoporosis and a number of options are now available. The emergence of these agents has provided new insights into the mechanisms by which drugs affect bone and, more specifically, their effects on bone mineral density (BMD) and fracture risk. In particular, it has become evident that the relationship between increased BMD and reduced fracture risk is more complex than might be predicted from the known association between age-related bone loss and increased bone fragility, indicating that mechanisms other than an increase in bone mass *per se* contribute to therapeutically induced increases in bone strength. This chapter reviews the changes in bone remodeling and microstructure that accompany bone loss and bone gain in untreated and treated osteoporosis and considers the mechanisms by which antiresorptive and anabolic agents affect both BMD and fracture risk.

Bone Remodeling

Bone remodeling serves to maintain the mechanical integrity of the adult skeleton and also provides a mechanism by which calcium and phosphate ions may be released from or conserved within the skeleton. It consists of the removal, by osteoclasts, of a quantum of bone followed by the formation by osteoblasts within the cavity thus created of osteoid, which is subsequently mineralized. In normal adult bone, the processes of resorption and formation are coupled in both space and time; therefore, bone resorption always precedes formation (coupling), and in the young adult skeleton, the amounts of bone formed and resorbed are quantitatively similar (balance) (Fig. 1). The life span of each remodeling unit in humans is believed to be between 2 and 8 mo, with most of this period occupied by bone formation *(1)*.

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Cellular and Structural Mechanisms of Bone Loss in Osteoporosis

At the tissue and cellular levels, there are two possible mechanisms of bone loss in osteoporosis *(2)* (Fig. 1). Quantitatively the most important is an increase in the activation frequency (also termed high bone turnover) in which the number of remodeling units activated on the bone surface is increased; this results in a greater number of units undergoing bone resorption at any given time and is potentially reversible provided that bone remodeling is coupled and that remodeling balance is maintained. The second mechanism, which often coexists with increased bone turnover, is remodeling imbalance, in which the amount of bone formed within individual remodeling units is less than that resorbed owing either to an increase in resorption, a decrease in formation, or a combination of the two. This form of bone loss is irreversible once the remodeling cycle has been completed, at least in terms of that remodeling unit.

These mechanisms of bone loss can be quantitatively assessed using histomorphometric techniques. The administration of two time-spaced doses of a tetracycline compound prior to bone biopsy enables identification of actively forming bone surfaces and calculation of bone turnover and activation frequency *(3)*. The amounts of bone formed and resorbed within individual bone remodeling units can also be measured; the former is known as the wall thickness *(4)* and is a measure of osteoblast function. The erosion depth and other indices of resorption cavity size can be assessed after computerized or manual reconstruction of the eroded bone surface *(5,6)*.

The alterations in bone remodeling responsible for bone loss determine the accompanying changes in bone architecture, an important determinant of the mechanical strength of bone *(7)*. In cancellous bone, either trabecular thinning or trabecular perforation and erosion may occur; these two processes are, to some extent, interdependent. Trabecular thinning is associated with better preservation of bone architecture than penetration and erosion of trabeculae, the latter having the greater adverse effects on bone strength. Increased activation frequency and increased resorption depth predispose to trabecular penetration and erosion whereas low bone turnover states favor trabecular thinning.

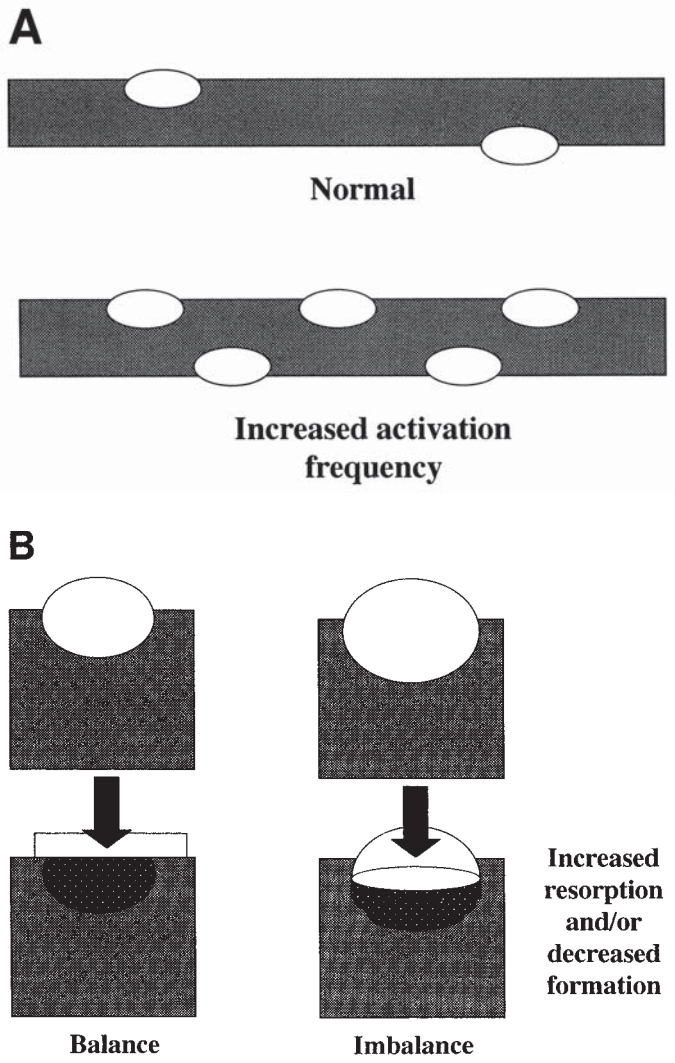

Fig. 1. Mechanisms of cancellous bone loss in osteoporosis. (**A**) Increased activation frequency results in a greater number of unfilled resorption cavities in a given volume of bone at any one point in time. This results in both bone loss and weakening of the trabecular structure and predisposes it to penetration and erosion by osteoclasts. (**B**) A negative remodeling imbalance occurs when the amount of bone formed within individual remodeling units is less than than resorbed. These two mechanisms frequently coexist.

Effects of Therapeutic Agents on Bone Mass and Fracture Risk

General Considerations

Although BMD is a reasonable surrogate for bone strength and fracture risk, it does not capture completely other components of bone quality such as bone geometry, microarchitecture, and the composition of bone matrix and mineral. Thus, some changes in bone geometry (as in hip axis length), collagen crosslinking in bone matrix, and the chemical composition of bone mineral may affect bone strength independent of changes in BMD. In addition, disproportionately large adverse effects on bone strength relative to changes in BMD result from high bone turnover or from increased osteoclastic activity, both of which predispose to trabecular penetration and erosion. Conversely, gains in areal BMD may underestimate the resulting benefits for bone strength in the presence of increased periosteal bone apposition, which increases bone diameter. Finally, some agents may affect fracture risk through effects on postural stability, muscle strength, and other aspects of neuropsychomotor function that are relevant to the risk of falling and the associated protective response *(8,9)*.

Effects of Antiresorptive Agents on Bone Remodeling

The majority of agents currently used in the treatment of osteoporosis act predominantly by inhibiting bone resorption, through effects on osteoclastogenesis and/or osteoclast activity. Changes in bone turnover reflect mainly alterations in osteoclast number, whereas alterations in osteoclast activity are reflected by the depth of erosion in individual remodeling units. A significant reduction in bone turnover in response to antiresorptive agents has been consistently demonstrated in cancellous bone *(10–18)*, with the magnitude of reduction varying between 18% for raloxifene *(18)* and approx 90% for alendronate *(17)*, values for hormone replacement therapy (HRT) being intermediate *(10,15)*. There is also indirect evidence for similar effects in cortical bone, based on studies of suppression of endogenous estrogen in premenopausal women *(19)*. The well-documented stimulatory effects of both estrogen and bisphosphonates on osteoclast apoptosis *(20–22)* are reflected by the demonstration of a reduction in the erosion depth in response to treatment with these agents *(11,13,17,23)*. Supportive evidence was also provided by a study by Eriksen et al. *(24)* in which an increase in erosion depth over 2 yr was reported in untreated postmenopausal women whereas values remained unchanged in women taking HRT.

There is evidence that estrogens and bisphosphonates inhibit the apoptosis of osteoblasts, indicating the potential for increased bone formation at the cellular level. However, the majority of studies have not been sufficiently long term to demonstrate an increase in wall thickness although an increase has been reported in women treated for 24 mo with alendronate *(17)*. In addition, in iliac crest biopsies obtained from women treated long-term with high-dose estradiol therapy, values for wall thickness were significantly greater than in normal premenopausal women *(25)*, indicating an anabolic effect.

Effects of Antiresorptive Agents on Bone Mineralization

Overall, the evidence indicates that antiresorptive agents act predominantly by suppression of bone turnover although relatively subtle effects on remodeling balance may also contribute. These effects on bone turnover are reflected in alterations in the degree of mineralization of bone, which is itself a determinant of bone strength. Mineralization occurs in two phases: a primary deposition of mineral at actively forming surfaces of bone followed by a secondary phase in

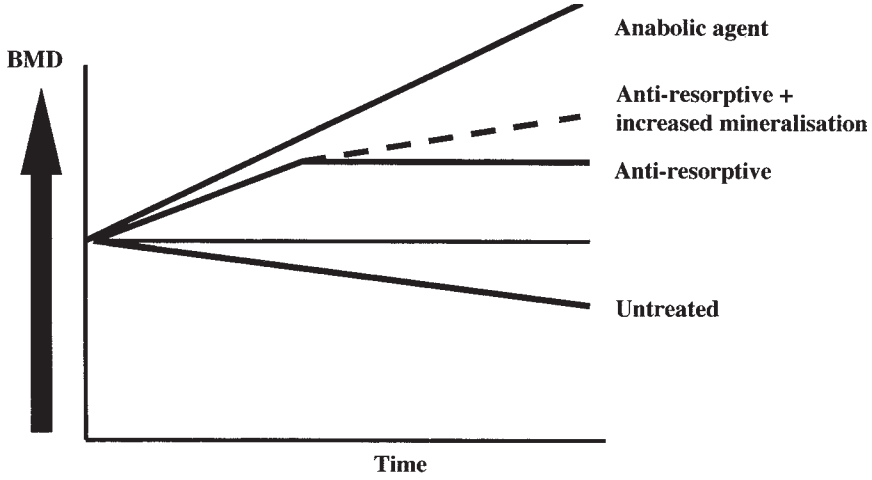

Fig. 2. Pattern of changes in BMD in response to antiresorptive and anabolic agents.

which there is a slow and progressive increase in mineralization. With greater degrees of suppression of bone turnover, there is an increase in the average lifetime of the bone structural unit, leading to an increase in the duration of the secondary mineralization phase and hence an increase in the mean degree of mineralization of bone *(26,27)*. This is believed to be responsible for the sustained increase in BMD that is seen with agents such as alendronate, in comparison to weaker antiresorptives that produce a transient increase in BMD, attributable to filling in of existing resorption cavities, followed by a plateau as a new steady state is achieved. These different patterns of change in BMD and that seen with anabolic therapy are shown in Fig. 2.

The relationship between bone mineralization and bone strength is complex; adverse effects are seen at both extremes of mineralization *(28)*. While high turnover states compromise bone strength by reducing the amount of bone, causing focal weaknesses in trabeculae and preventing complete mineralization of bone structural units, marked suppression of remodeling may also reduce bone strength as a result of failure to repair microdamage and replace old or dead osteocytes. In a study of dogs treated with high doses of bisphosphonates, increased accumulation of microdamage and reduced bone toughness were reported, although vertebral strength was increased; in that study the reduction in activation frequency was between 76 and 90%, similar to that seen in postmenopausal women treated with the more potent bisphosphonates *(29,30)*. At present, there is no direct evidence that adverse effects on bone strength are seen in women treated with bisphosphonates, but longer-term studies are required to establish whether reductions in fracture risk are maintained after 5 yr or more of treatment.

Effects of Antiresorptive Agents on Bone Structure

There are few reported histomorphometric data on the effects of antiresorptive therapy on cancellous or cortical bone structure. In a prospective study of postmenopausal women treated with HRT *(31)*, no change in cancellous bone structure, assessed by strut analysis, marrow star volume, and trabecular bone pattern factor, was demonstrated over the 2-yr treatment period. This finding indicates that HRT is able to preserve existing bone structure but provides no evidence that reversal of previous architectural damage can occur. This is in accordance with the evidence that antiresorptive therapy preserves and/or increases BMD mainly through effects on activation frequency and, in the case of some agents, bone mineralization.

Effects of Anabolic Agents on Bone Remodeling and Structure

Anabolic skeletal agents are defined by their ability to stimulate bone formation in excess of any stimulatory effects on bone resorption, resulting in a sustained increase in BMD throughout the duration of therapy. Fluoride salts were the first true anabolic agents to be used in osteoporosis, but inconsistent data on their antifracture efficacy in the spine and concerns about adverse effects on cortical bone and fracture risk at nonvertebral sites have significantly limited their use *(32)*. Other anabolic agents include growth hormone (GH), and insulin-like growth factor-1 (at least when used in GH-deficient children and adults), and parathyroid hormone (PTH); strontium and the statins are also currently being evaluated for their potential to produce anabolic effects on bone. The question of whether anabolic agents have greater antifracture efficacy than antiresorptives remains to be answered and, in this respect, the mechanisms by which anabolic effects are achieved are highly relevant.

The basic mechanisms by which anabolic effects in cancellous bones may be achieved are illustrated in Fig. 3. A positive remodeling balance resulting from an increase in bone formation at the level of the remodeling unit will produce anabolic effects; if combined with an increase in activation frequency, this has the potential to produce relatively large increases in bone mass. *De novo* bone formation,

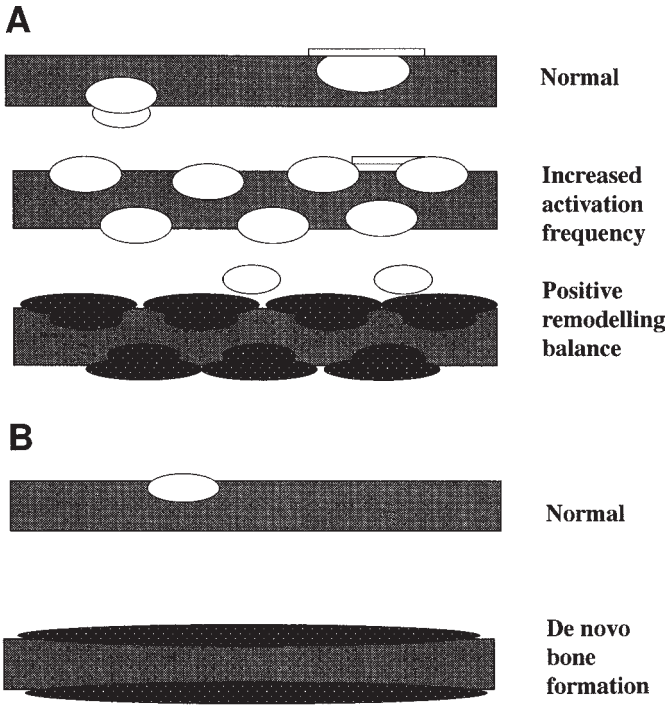

Fig. 3. Mechanisms of cancellous bone gain in response to anabolic agents. A positive remodeling balance will result in increased cancellous bone volume and trabecular thickening, whether or not activation frequency is increased. (**A**) Combination of positive remodeling balance and increased activation frequency (**B**) *De novo* bone formation on quiescent bone surfaces represents another mechanism of bone gain.

in which new bone is formed either on quiescent bone surfaces in the absence of prior resorption or in the marrow cavity without a preexisting template of bone, will also increase bone mass and has the potential to increase the connectivity of cancellous bone.

Potential mechanisms for anabolic effects on cortical bone are illustrated in Fig. 4. An increase in cortical width may result from increased formation at either the endosteal or periosteal surface; however, only the latter will increase the external diameter of bone, an important and independent determinant of bone strength. Effects on cortical porosity may also occur, with respect to the number, size, and distribution of canals.

PTH Peptides

The recent demonstration of antifracture efficacy of recombinant human PTH peptide 1–34 at both vertebral and nonvertebral sites *(33)* has stimulated renewed interest in the role of anabolic agents in the management of osteoporosis. Although reports of the anabolic skeletal effects of PTH date back for several decades, the mechanisms by which these are achieved remain only partially defined. Furthermore, it was initially believed that intermittent administration of PTH was required to achieve anabolic effects, whereas continuous administration led to bone loss. However, it is now well documented that exposure to increased endogenous secretion of PTH in primary hyperparathyroidism is associated with anabolic effects in cancellous bone *(34)*. In addition, preservation of cancellous bone mass by continuous administration of PTH has recently been demonstrated in ovariectomized rats (OVX) *(35)*. It is therefore possible that dose, rather than mode of administration, may determine the skeletal response.

Effects of PTH Peptide on Bone Remodeling in Cancellous Bone

Evidence that PTH increases activation frequency has been reported in rats *(35,36)*, sheep *(37)*, and postmenopausal women *(38,39)* in remodeling species, this is accompanied by an increase in wall thickness, leading to a positive remodeling balance *(39)*. These changes, illustrated in Fig. 3A, indicate an increase in both osteoblast number and activity, a contention supported by the known effects of PTH in stimulating recruitment of osteoblast precursors, inducing maturation of lining osteoblasts *(40)*, and inhibiting apoptosis of osteoblasts *(41)*.

Hodsman et al. *(39,42)* have provided histomorphometric evidence for *de novo* bone formation in postmenopausal women treated with PTH peptide. In their studies, biopsies taken only 28 d after initiation of PTH showed an increase in the surface extent of double tetracycline labeling. This finding would be consistent with new bone formation on quiescent bone surfaces, as demonstrated in animal models *(43,44)*. However, it is also possible that prior resorption had occurred, particularly if the time course of this phase of remodeling was accelerated by PTH therapy.

Effects of PTH on Architecture of Cancellous Bone

The potential for anabolic agents such as PTH peptides to restore previously disrupted bone architecture has stimulated much interest, but there are currently few studies that have addressed this issue. Shen et al. *(45)* reported recovery of connectivity in cancellous bone of OVX rats treated with either estrogen and PTH or PTH alone, and in another study *(46)*, administration of PTH to OVX rats restored or maintained cancellous bone connectivity. However, Lane et al. *(47)* were unable to demonstrate any increase in connectivity in osteopenic rats treated with intermittent PTH peptide; in their study, the increase in cancellous bone volume could be accounted for by an increase in trabecular thickness. Similar findings were reported by Meng et al. *(36)*, who found that administration of PTH was associated with an increase in trabecular thickness but not trabecular number. In the only study to date in humans, Dempster et al. *(48)* have recently reported an increase in the connectivity density of cancellous bone in osteoporotic patients treated with intermittent PTH.

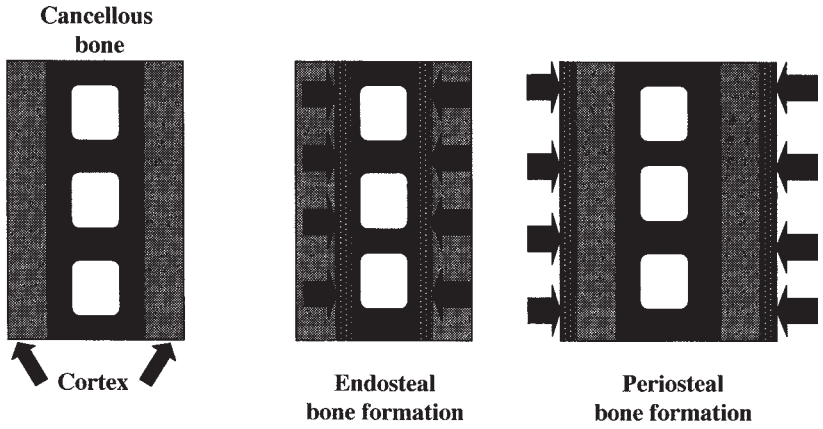

Fig. 4. Potential effects of anabolic agents on cortical width and bone size. Endosteal new bone formation increases cortical width but not bone diameter, whereas periosteal new bone formation increases both cortical width and bone diameter.

The effects of PTH on cancellous bone structure thus remain to be clearly defined. It is possible that the ability to restore architecture may depend on the extent of preexisting bone loss and architectural disruption; the dose and duration of therapy may also be relevant in this respect. Thus, although very high doses of PTH can stimulate *de novo* bone formation in the marrow cavity *(49)*, it is likely that the lower doses used therapeutically in humans are associated predominantly with bone formation on existing bone surfaces.

Effects of PTH on Cortical Bone

Although some early studies in women treated with PTH peptides suggested that the administration of PTH might have adverse effects on cortical bone, similar to those seen in primary hyperparathyroidism *(50)*, these fears have been, to some extent, allayed in later studies of postmenopausal women with osteoporosis treated with intermittent PTH. Lindsay et al. *(51)* reported small increases in BMD in the femoral neck and total body in women maintained on HRT and treated with PTH. Neer et al. *(33)* reported significant and dose-dependent increases in total BMD and BMD in the proximal femur, although radial shaft BMD decreased by 2 to 3%. To date, there are no detailed histomorphometric studies of cortical bone in patients treated with PTH peptides, but Dempster et al. *(48)* have reported an increase in cortical thickness of iliac crest bone in postmenopausal women treated with combined estrogen and PTH and in men treated with PTH alone.

Studies in animals generally support a lack of adverse effects on cortical bone. Intermittent administration of human PTH peptide increases cortical width in estrogen-deficient rats, mainly as a result of increased endosteal bone formation *(52)*. Continuous administration of PTH was also shown to increase cortical remodeling in the estrogen-deficient rat, with increases in cortical porosity, canal number, mineral apposition rate, and bone formation rate, although cortical width did not change significantly *(35)*. Increased remodeling activity was also seen in rats treated with estrogen and PTH, and in this group, there was also a significant increase in cortical width. More importantly, PTH has been shown to increase bone strength in rats at several skeletal sites including the vertebrae and femoral neck *(36,53,54)*, and Zhou et al. *(35)* reported improved biomechanical properties of femoral midshaft cortical bone in animals treated with continuous PTH and estrogen.

Studies in larger animals, in which the osteonal structure of cortical bone is similar to that found in humans, also support the contention that the biomechanical strength of cortical bone is not compromised by the administration of PTH. In monkeys and rabbits, the increase in cortical width resulting from appositional bone formation offsets the increase in porosity and osteonal remodeling that occurs predominantly in endocortical bone, and biomechanical characteristics remain stable *(55)*.

Potential Adverse Skeletal Effects of PTH

In mature female rats, small quantities of woven bone were reported in the marrow cavity following the administration of high doses of PTH *(49)*. Zhou et al. *(35)* reported significant amounts of peritrabecular fibrosis and woven bone formation in rats treated with continuous PTH and estrogen. However, these changes have not been seen in postmenopausal women treated with PTH peptides *(39)*, nor is there any evidence that this treatment impairs bone mineralization.

Sodium Fluoride

The effects of sodium fluoride on bone remodeling have been studied in both cortical and cancellous bone in postmenopausal women undergoing treatment. In a prospective study of 24 postmenopausal women with osteoporosis, biopsies were obtained before and 5 yr after treatment with sodium fluoride (40–60 mg/d), calcium, phosphate, and

vitamin D_2 *(56)*. Over the treatment period, there was a significant increase in cancellous bone volume, associated with an increase in wall width and positive remodeling balance. In cortical bone, an increase in activation frequency was demonstrated at 6 mo after the initiation of treatment, but no change in remodeling balance was detected after 5 yr of treatment, nor was there any change in cortical width or porosity *(57)*. From the limited data available in humans, it therefore seems likely that the anabolic skeletal effects of fluoride are mediated mainly via an increase in wall width and trabecular width.

Although small amounts of woven bone have been reported in biopsies from treated patients *(58)*, the main concerns are the development of a mineralization defect with long-term treatment *(56,57,59)* and abnormalities of the newly formed bone matrix *(60)*. These changes may contribute to the reduction in bone strength demonstrated in iliac cancellous bone biopsies obtained after 5 yr of treatment with sodium fluoride *(61)* and to the failure consistently to demonstrate a significant reduction in vertebral fracture risk despite large increases in BMD.

Conclusion

Histomorphometric studies have made an important contribution to our understanding of how pharmacologic interventions affect BMD and bone strength in patients with osteoporosis. For antiresorptive agents, the therapeutic effect is mediated predominantly by suppression of bone turnover; in the case of more potent antiresorptive agents, changes in secondary mineralization also occur that affect BMD and, potentially, bone strength. The mechanisms by which anabolic agents increase BMD and reduce fracture risk include *de novo* bone formation and induction of a positive remodeling balance. The relationship between BMD and bone strength is influenced by different factors in the case of antiresorptive and anabolic agents, and the relative antifracture efficacy of the two approaches at both vertebral and nonvertebral sites requires further study.

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