

Osteoporosis: How Should It Be Treated?

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ABSTRACT

Osteoporosis develops as a result of imbalance between bone resorption and bone formation. A number of effective and safe therapies for osteoporosis are currently available, most of which are inhibitors of bone resorption. However, because osteoporosis is a complex and heterogeneous disease with different pathogenetic factors, defining the role of the different factors in its development is important in formulating a more selective approach to therapy. This review discusses the advantages and disadvantages of the currently available agents used in the management of osteoporosis.

Key Words: osteoporosis, bone turnover, bone quality, bone density

Osteoporosis, the most common metabolic bone disease in adults, is defined as a skeletal disorder characterized by compromised bone strength predisposing individuals to an increased risk of fracture.¹ During the past two decades, considerable progress has been made in the understanding of the pathogenesis of osteoporosis and its associated complication, fracture(s). It is now clear that osteoporosis is a complex disorder, with different subtypes and different pathogenetic factors. For years, the management of osteoporosis has been mainly focused on the inhibition of bone resorption, with less emphasis on correcting the defect in bone formation. Indeed, most of the available agents for the treatment of osteoporosis are those that inhibit bone resorption (antiresorptive agents). It was over 2 years ago that teriparatide (recombinant human parathyroid hormone 1-34 [hPTH 1-34]), an agent that stimulates bone formation, became available.

In 2003, Nordin cautioned against the indiscriminate use of the available agents for osteoporosis without regard to the patient's metabolic state and recommended a more selective approach to the treatment of osteoporosis.² Such an approach would ensure that the appropriate therapy is

provided to those who would benefit from it and avoid unnecessary treatment of patients who may not need it.

BACKGROUND

Pathogenesis of Osteoporosis

The development of osteoporosis is largely determined by changes in skeletal metabolism and architecture. Bone is a dynamic tissue that continuously remodels throughout life. This process allows the skeleton to increase in size during growth, respond to physical stress, and repair microdamage owing to excessive or accumulated stress or trauma.³ The remodeling process is composed of a series of cellular events that occur on the surface of the bone and is affected by both local and systemic factors. Osteoclasts, osteoblasts, and osteocytes are the three major cells involved in bone remodeling. Osteoclasts, which are multinucleated cells formed by fusion of cells derived from hematopoietic stem cells, are responsible for resorbing bone. Osteoblasts, which are derived from mesenchymal precursors, synthesize and secrete the organic matrix. Osteocytes are mature osteoblasts trapped within calcified bone, interconnected by long dendritic processes. They are believed to provide a communication network to transmit information about mechanical forces that can modify bone formation and bone resorption. The discrete sites of bone remodeling are called bone remodeling units. At the beginning of the remodeling cycle, osteoclasts are recruited at the surface of the bone, and a group of osteoclasts excavates a resorption or erosion cavity. This phase is followed by filling in of erosion cavity with new bone by osteoblasts.

Normally, bone resorption and bone formation are tightly coupled, that is, bone formation equals net bone resorption. The end result of this remodeling process is that the resorbed bone is replaced by an equal amount of new bone tissue; therefore, bone is neither gained nor lost. Thus, the mass of the skeleton remains constant after peak bone mass is achieved in adulthood. After age 30 to 45 years, however, the resorption and formation processes become imbalanced, with resorption exceeding formation.⁴ This imbalance may begin at different ages, varies at different skeletal sites, and becomes exaggerated in women after menopause (Figure 1). The consequence of this imbalance is reduced bone mass, disordered skeletal architecture with development of microperforations

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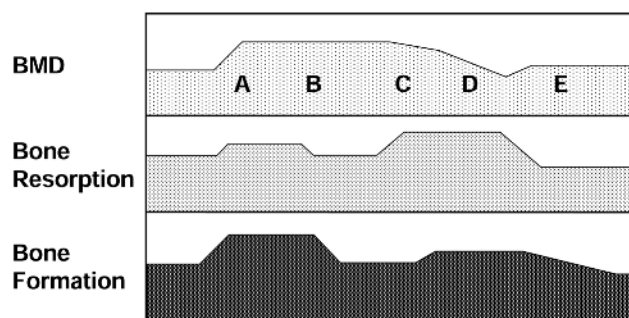


Figure 1 Effect of changes in bone resorption and bone formation on bone mineral density (BMD). At puberty (A), BMD increases because bone formation exceeds bone resorption. BMD remains constant after peak bone mass is achieved in early adulthood (B). After age 30 to 45 years, an imbalance between bone resorption and bone formation develops, with resorption exceeding formation (C). This imbalance becomes exaggerated in women after menopause (D). Administration of an antiresorptive agent allows newly formed bone to fill the resorption cavities and primary and secondary mineralization to take place, thereby improving the BMD (E).

and microfractures, and, hence, increased risk of clinical fractures.

The main challenge for physicians is that osteoporosis is asymptomatic, and many people are not being diagnosed in time to receive preventive therapy during the early phase of the disease. Osteoporotic patients often present initially with atraumatic fracture(s), and by that time, they would have typically lost 30 to 50% of trabecular bone tissue and 25 to 35% of cortical bone mass.⁵

Bone Mineral Density

Measurements of bone mineral density (BMD) at any skeletal site have value in predicting fracture risk.⁶ In vitro studies have shown that bone mineral content is a major determinant of compressive strength of the bone, accounting for approximately 60 to 80% of bone strength.⁷ Likewise, a number of observational studies have shown that baseline measurement of BMD at multiple skeletal sites can predict different types of osteoporotic fractures in postmenopausal women.^{8,9} In general, a decrease in BMD of about 1 SD doubles the risk of fractures.¹⁰ These observational data have been confirmed by a number of randomized clinical trials showing that antiresorptive agents can significantly increase BMD and decrease vertebral fractures.¹¹ As a consequence, there is a growing belief among practitioners that BMD can be used as the basis for initiating therapy and that changes in BMD can serve as a surrogate for determining the effect of treatment in terms of fracture risk. This is fueled by the now growing trend toward direct patient advertising by drug manufacturers, which appears to have resulted in the public's obsession with "T scores."

Although it is true that low BMD is a major determinant of fracture risk, other factors are also important. This concept is clearly illustrated by the results of studies using

different antiresorptive agents.^{12,13} Although these were not head-to-head studies, available data indicate that although antiresorptive agents vary in their ability to improve BMD, their ability to lower vertebral fracture risk is comparable. Therefore, the reduction in fracture risk is not necessarily proportional to the change in BMD. In addition, it has been shown that when patients are matched for BMD, those who already had a fracture are at higher risk of sustaining another fracture and that the greater the number of prevalent fractures, the greater is that risk.^{14,15} These findings suggest that some patients have skeletons that are more fragile and probably have poorer bone quality than others.

Bone Quality

Bone quality refers to the "totality of features and characteristics that influence the bone's ability to resist fractures."¹⁶ It is influenced by a number of factors, including morphology and architecture,^{17–19} the rate of bone turnover,^{20,21} the degree of mineralization,^{22–25} and damage accumulation,^{26,27} with the last three factors being inter-related. The subsequent discussion focuses on how the available osteoporosis agents approved by the US Food and Drug Administration (FDA) could affect these factors, which could, in turn, affect the biomechanical properties of bone.

ANTIRESORPTIVE AGENTS

It is believed, based on available data, that high turnover can exert multiple adverse effects on bone, including acceleration of bone loss, disruption of trabecular micro-architecture, increased mechanical stress concentration, and decreased mineralization density. All of these changes could potentially reduce bone strength and resistance to fracture.

The observation of increased bone turnover rate during menopause is the basis for the use of antiresorptive agents in the treatment of osteoporosis. Many agents that can slow down bone turnover are now available for the prevention or treatment of osteoporosis, including calcium and vitamin D supplements, estrogen, calcitonin, selective estrogen receptor modulators (SERMs), and bisphosphonates.

The mechanisms by which therapy with antiresorptive agents can decrease fractures are probably multifactorial. First, the slower rate of bone remodeling allows the newly formed bone to be laid down and fill the resorption cavities, therefore partially correcting the imbalance between bone resorption and bone formation. Second, the reduced bone turnover rate allows for primary and secondary mineralization to take place, which results in an increase in the degree of mineralization of newly formed bone.²² The degree of mineralization has been shown to affect the material properties of bone, with low mineralization levels (as seen in osteomalacia) causing

reduced stiffness and strength and hypermineralization likely contributing to reduced fracture toughness.^{23–25} The degree to which bone turnover decreases and mineralization increases varies among different antiresorptive agents. Lastly, administration of antiresorptive agents, especially bisphosphonates, results in the reduction in the size of remodeling space, which could prevent thinning and perforation of trabecular plates. All of these factors are believed to be responsible for the increase in BMD as measured by dual-energy x-ray absorptiometry (DXA) and the decrease in fracture rates during therapy with antiresorptive agents.

The degree of reduction in bone turnover varies between agents, which could be at least in part related to the differences in the mechanisms of action.

Calcium and Vitamin D

A number of studies have previously shown that vitamin D supplementation with adequate calcium intake can help reduce bone loss and prevent fracture.^{28–30} For instance, institutionalized French women given calcium and vitamin D had a significant increase in BMD at the femoral neck and trochanter and had a significantly reduced incidence of hip and nonvertebral fractures compared with those given placebo. In another study, calcium and vitamin D supplementation resulted in a reduced incidence of first osteoporotic nonvertebral fracture in healthy, independently living women.

Estrogen and Raloxifene

Both estrogen and raloxifene presumably decrease bone resorption via the estrogen receptors (ERs) and their binding to the estrogen response element in target deoxyribonucleic acid (DNA), which results in inhibition of the release of cytokines such as interleukins 1 and 6, macrophage colony-stimulating factor, tumor necrosis factor α , and receptor activator of nuclear kappa B ligand from the osteoblasts.^{31–34} These cytokines induce osteoclast differentiation and maturation and are believed to be responsible for increased bone resorption during early menopause. Another mechanism for estrogen action involves protein-protein interaction, whereby receptor-ligand complexes interact with transcription factors. This interaction influences the ability of the transcription factor to influence gene transcription. An example of this mechanism is the ability of the ligated ER complexes to influence the function of activator protein 1 and specific protein 1.^{35,36} Lastly, estrogen can also influence cellular function through more rapid, nonclassic pathways. It has recently become apparent that the rapid effects of sex steroids such as estrogen are mediated by interactions with components of a number of signal transduction pathways, such as adenylyl cyclase, mitogen-activated protein

kinase (MAPK), and phosphatidylinositol 3-kinase. In 2003, Kousteni and colleagues suggested that the rapid activation of MAPK by the nonclassic pathways is responsible for the ability of sex steroids to regulate apoptosis in bone cells.³⁷

Examination of bone biopsy specimens from estrogen- and raloxifene-treated women showed that both bone formation rate and activation frequency were lower than the average for postmenopausal women^{38,39} and that the degree of mineralization of the bone was not statistically different from those given calcium and vitamin D.

A number of small clinical trials have shown that women receiving hormone therapy have 50% less occurrence of vertebral fractures compared with those on placebo.^{40,41} More recently, the Women's Health Initiative study confirmed that hormone therapy can reduce the risk of both hip and symptomatic vertebral fractures by 34% and all other fractures by 24%.^{42,43} However, because of the risks associated with hormone therapy, such as increased risk of cardiovascular disease, stroke, venous thrombosis, and breast cancer, its use for the treatment of osteoporosis may not be appropriate for many. There is no doubt, however, that hormone therapy is very effective in treating the symptoms associated with menopause. Therefore, unless there are contraindications for its use, hormone therapy is still a reasonable option for early postmenopausal women with significant symptoms.

Raloxifene is a SERM that has an estrogenic effect on both bone turnover and BMD. A study of over 7,000 women has shown that raloxifene reduces vertebral fracture risk by 30 to 50%.^{44,45} Its effect on other fractures, however, has not been clearly shown.

Calcitonin

Calcitonin reduces bone resorption by binding to the calcitonin receptor on the osteoclasts. This binding results in the loss of ruffled border; cessation of motility, pseudopodial and margin retraction; and inhibition of secretion of proteolytic enzymes by osteoclasts.⁴⁶

Calcitonin was initially available for intramuscular or subcutaneous administration. Injectable calcitonin has been shown to produce a modest rise in vertebral BMD.⁴⁷ This formulation, however, is associated with considerable side effects, such as nausea, flushing, and diarrhea, and its role in fracture prevention has not been carefully examined in a large-scale, randomized study. The nasal spray formulation was developed to overcome the limitation to therapy and improve patient's compliance. Prevent Recurrence of Osteoporotic Fractures (PROOF), a double-blind, randomized, placebo-controlled study designed to examine the effects of different doses of intranasal calcitonin (100, 200, and 400 IU/d) on fracture risk in postmenopausal women with low BMD and prevalent fractures, showed that 200 IU/d reduced the cumulative relative risk of new morphometric vertebral fractures by

33% at 5 years. No significant reduction in the vertebral fracture risk was noted with the 100 and 400 IU doses.⁴⁸

Bisphosphonates

Bisphosphonates are agents that suppress osteoclast-mediated bone resorption by binding to the calcium hydroxyapatite through their phosphate group.⁴⁹ Their potency is determined by their side chains. Nitrogen-containing bisphosphonates (such as alendronate and risedronate) can also reduce osteoclast function by inhibiting osteoclast recruitment, impairing osteoclast function, and enhancing osteoclast apoptosis. They are considered the most potent antiresorptive agents available for the treatment of osteoporosis. To date, bisphosphonates appear to be the preferred agent, accounting for 73% of the total prescriptions for osteoporosis treatment written in 1998 to 2003 (51% for alendronate and 22% for risedronate) compared with calcitonin (5%), estrogen (3%), and SERMs (12%).⁵⁰ This is probably because their effect on BMD is greater compared with the other antiresorptive agents (6–10% vs 1.5–2%).^{51,52}

In addition, administration of bisphosphonates results in a more marked reduction in the biochemical markers of bone turnover.^{52,53} At the tissue level, osteoid thickness, volume and surface were all significantly reduced during alendronate therapy. Alendronate has been shown to significantly reduce mineralizing surface and activation frequency (92% and 96% at 2 and 3 years of treatment, respectively).⁵⁴ Administration of risedronate, on the other hand, resulted in a 47% decrease in activation frequency after 3 years of treatment.⁵⁵

A number of studies have shown that administration of bisphosphonates results in a significant reduction in bone turnover, an increase in BMD, and a decrease in vertebral and nonvertebral fractures.^{56–63} However, although bisphosphonates are generally safe and effective, they may carry the potential risk of oversuppressing bone turnover, resulting in impairment of bone quality. In experimental animals, administration of bisphosphonate has been shown to inhibit the normal repair of microdamage arising from marked suppression of bone turnover.^{26,64,65} The resultant accumulation of microdamage has been implicated in the reduction in some of the biomechanical properties of bone. In addition, chronic oversuppression of bone turnover by bisphosphonates such as alendronate may cause “hypermineralized” bone, which may increase the ease of microdamage propagation and make the bone more brittle.⁶⁶

A few reports suggest that severe suppression of bone turnover (SSBT) could have a negative outcome in humans. Whyte and colleagues reported a case of bisphosphonate-induced osteopetrosis in a 12-year-old boy who presented with high BMD and increased susceptibility to spontaneous fractures.⁶⁷ The authors, however, acknowledged that the dose of bisphosphonate given to this pa-

tient was four times the usual dose given to children with osteogenesis imperfecta. More recently, osteonecrosis of the jaw requiring surgical removal of affected tissue was reported in 59 patients who had received intravenous bisphosphonate for malignancy and in 7 patients who took oral bisphosphonate for osteoporosis.⁶⁸ Although the mechanism for its development is yet to be defined, the authors proposed low remodeling and impaired vascularity as possible factors in the development of osteonecrosis.

An earlier study on postmenopausal women maintained on estrogen showed that the addition of bisphosphonate resulted in further reduction in bone turnover.⁶⁹ The spinal fracture rate was higher in the combined estrogen-bisphosphonate group compared with the group on bisphosphonate alone, although it was not statistically significant. In 2001, Ott speculated that chronic alendronate therapy might impair the mechanical strength of bone, noting the apparent increase in the fracture rate with prolonged therapy.⁷⁰ This was, however, challenged by the authors of that report noting that the study was not adequately powered to evaluate meaningful fracture risk reduction.⁷¹ A recent article reported that alendronate given over a period of 10 years was safe and effective.⁷² Although the study was not designed to assess its effectiveness in preventing fractures, the nonvertebral fracture rate appeared to be numerically the same or higher (3 and 4 per 100 subject-years for the 10 and 5 mg groups, respectively) during the late period of alendronate treatment compared with the early period (3 per 100 subject-years) despite higher BMD. These data (although limited) suggest that the higher BMD observed after 10 years of treatment did not offer additional fracture protection.

Early this year, our group described nine patients who sustained spontaneous nonspinal fractures while on alendronate therapy, six of whom displayed either delayed or absent fracture healing for 3 months to 2 years during therapy.⁷³ Four of the nine patients were on alendronate for 6 to 8 years, three were on both estrogen and alendronate, and two were also on long-term glucocorticoids. Histomorphometric analysis of the cancellous bone showed markedly suppressed bone formation, with reduced or absent osteoblastic surface in most patients. The osteoclastic surface was low or low normal in eight patients, and the eroded surface was decreased in four patients. Matrix synthesis was markedly diminished with the absence of a double-tetracycline label and an absent or reduced single-tetracycline label in all patients. The same trend was seen in the intracortical and endocortical surfaces.

Our findings suggest that SSBT can potentially develop during long-term alendronate therapy, which could, in turn, result in increased susceptibility to and delayed healing of nonspinal fractures. Although coadministration of estrogen or glucocorticoids appears to be a predisposing factor, this apparent complication may also occur with monotherapy. This report has its limitations. It is anecdotal and uncontrolled; therefore, definite causal relationship

cannot be established. However, our findings, along with the results of animal studies, suggest that excessive suppression of bone turnover may be deleterious to the bone.

ANABOLIC AGENTS

To date, the only FDA-approved anabolic agent is teriparatide, a recombinant hPTH 1-34. It has been shown that administration of teriparatide, which is an anabolic agent, causes an early and rapid rise in the bone formation marker, followed by a more modest increase in bone resorption.⁷⁴ A positive balance in remodeling thus occurs, which results in a substantial increase in bone mass. The idea that parathyroid hormone (PTH) can be used to increase bone mass was first introduced by Bauer and colleagues in 1929.⁷⁵ A number of animal studies have since been published showing the positive effect of PTH on bone mass and bone strength. Studies on postmenopausal women with osteoporosis,⁷⁶ glucocorticoid-induced osteoporosis,⁷⁷ and osteoporotic men^{78,79} have consistently shown that the administration of hPTH 1-34 results in improvement in BMD in both the spine and the hip, and the increase in BMD at the spine, hip, and total body were twice that seen with alendronate 10 mg/d.⁸⁰ In addition, daily administration of teriparatide restores bone microarchitecture.⁸¹

Significant fracture reduction has been demonstrated during hPTH 1-34 therapy. In postmenopausal women, treatment with hPTH 1-34 resulted in a 65% reduction in vertebral fractures after 18 months compared with placebo. For patients with moderate or severe vertebral fractures, the fracture reduction is even greater (90%). In addition, women treated with the 20 µg dose were 35% less likely to develop one or more new nonvertebral fracture(s) compared with the placebo group.⁷⁶ However, it was later found that long-term administration of teriparatide to F44 rats can cause osteosarcoma in a dose-dependent fashion.⁸² Because of these findings, the FDA mandated that the ongoing placebo-controlled trial, which was in its second year of observation, be stopped, and the approval of the drug was limited to 2 years of treatment. This leaves patients and clinicians wondering what to do after the 2 years are up. There are available data that suggest that vertebral fracture protection may persist for at least 18 months after discontinuation of teriparatide.⁸³ The duration of the anti-fracture effect of treatment, however, is not known. Some recommend that patients be switched to a bisphosphonate. A study by Riitmaster and colleagues showed that sequential treatment with PTH and alendronate resulted in an increase in vertebral BMD that is considerably more than has been reported with alendronate alone.⁸⁴

COMBINATION THERAPY

In 1979, Frost introduced the concept of coherence therapy (otherwise known as ADFR) for osteoporosis.^{85,86} The

treatment consists of giving an activator (A) of bone remodeling as a brief pulse followed by a depressor (D) of osteoclast function and then a drug-free period (F) and repeat of the cycle (R). This was based on his and others' observations that continuous treatment with an anti-resorptive agent inadvertently results in suppression of bone formation. The hope was that this treatment scheme would generate a temporary basic multicellular unit population that would evolve coherently and that the use of a drug that depresses bone turnover would decrease the amount of bone resorbed by the coherent osteoclast population. The drug-free period would allow the osteoblasts to form new bone and fill the resorption cavities. An earlier trial using 1 g of phosphate daily for 3 days as an activator followed by etidronate as a depressor resulted in a significant increase in trabecular thickness. Several modifications of the original coherence therapy scheme have since been published, but the results are inconclusive.⁸⁷⁻⁸⁹

More recently, studies aimed at concomitant suppression of bone resorption and stimulation of bone formation with alendronate and human PTH showed that the combination of two agents had no clear additive effect.^{90,91}

Strontium is a bone-seeking element that appears to induce uncoupling of bone remodeling, stimulate bone formation, and reduce bone resorption. In theory, this would be an ideal drug for osteoporosis treatment. In postmenopausal women, a significant increase in BMD (14.4% and 8.3% for the lumbar spine and femoral neck, respectively) was noted after 3 years of treatment.⁹² The impressive increase in bone density, however, is most likely an overestimation. Strontium has a higher atomic number than calcium and could lead to an artificial increase in BMD (measured by DXA) when incorporated into the bone.⁹³ Nonetheless, administration of strontium for 1 year in postmenopausal women resulted in a 49% reduction in vertebral fractures and a 41% reduction during the 3-year study period.⁹² In addition, a recently published study (Treatment of Peripheral Osteoporosis [TROPOS] Study) showed that strontium ranelate significantly reduced the risk of all nonvertebral fractures and, in a high-risk subgroup, hip fractures over a 3-year study period.⁹⁴ Based on the published data, it appears that strontium has the potential to be an important therapeutic agent in the management of osteoporosis. The long-term effect of strontium on bone is still not known.

RECOMMENDATIONS AND FUTURE DIRECTIONS

This review does not diminish the role of the available medications in the treatment of osteoporosis but rather cautions physicians on their indiscriminate use. Although it is true that the FDA-approved medications have been proven effective in clinical trials, to assume that those findings can totally be applied in clinical practice would be naive. Patients enrolled in clinical trials are carefully screened for confounding conditions, which is not the

case in the “real world.” Like any other chronic illnesses, management should be individualized. The decision to use more active agents should be made only after careful evaluation of the patient’s metabolic status and should not be based mainly on BMD results. This would allow physicians to adopt a more selective therapy. For instance, for a patient who has increased bone turnover because of poor intestinal absorption or inadequate intake of calcium, the rational approach would be to provide adequate amounts of vitamin D and calcium rather than use the more expensive agents. On the other hand, a patient who is losing bone due to increased urinary calcium loss would likely benefit more from an agent that enhances tubular reabsorption of calcium, such as thiazide.

Although the FDA-approved antiresorptive drugs are still the main agents to consider, further studies should be done to determine the safe duration of treatment (especially with bisphosphonates) and the degree of bone turnover suppression that needs to be achieved during therapy. Unfortunately, the clinical use of markers of bone turnover has been limited by the inherent analytic and biologic variability of the assays. Based on the previous studies showing the residual effect of alendronate on bone mass and markers of bone turnover,^{95,96} a finding that was not seen with estrogen withdrawal,^{97,98} it is reasonable to consider a “drug holiday” after a few years of alendronate therapy. Ott suggested that, based on available data, bisphosphonates should be stopped after 5 years, and those patients who remain at high risk of fractures be considered for intermittent PTH therapy.⁹⁹ Although the effect of a ‘drug holiday’ on fracture risk has not been systematically examined, the data from the FIT Long-term Extension suggest persistent fracture protection (morphometric spinal and nonvertebral fractures) in patients who were switched from alendronate to placebo.¹⁰⁰ The incidence of clinical spinal fractures, however, was significantly lower in those who continued to take alendronate. Additional studies are needed to address this issue.

Anabolic agents have the potential to increase BMD and decrease fracture risk more than what can be achieved by antiresorptive agents. In addition, they have the potential to correct the defect in bone formation. However, the availability of such agents is still limited, with only one drug approved by the FDA to date, an agent that can be used only for 2 years. Because of this limitation, we may never know the long-term effects of teriparatide on bone.

Ideally, osteoporosis should be treated by correcting the abnormalities of both bone formation and bone resorption. How we can achieve it obviously needs additional studies, probably a modification of Frost’s ADFR concept using teriparatide followed by an antiresorptive drug^{85,86} or perhaps with the use of an agent that can uncouple bone resorption and bone formation, such as strontium ranelate.

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