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Anabolic Therapy for Osteoporosis

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ABSTRACT
All currently available, approved therapies for osteoporosis inhibit bone resorption. By acting at this site in the bone remodeling cycle, estrogens, selective estrogen receptor modulators, calcitonin, and the bisphosphonates all have the capacity to increase bone mineral density and to reduce the risk of new fractures. There can be no doubt that these agents have had an enormous impact on our diagnostic and therapeutic approach to osteoporosis. Despite their great value, the antiresorptives are generally not associated with dramatic increases in bone mass, and their action to reduce fracture risk, although highly significant, is rarely more than 50% of the baseline risk. Another approach is anabolic therapy, in which bone formation is directly stimulated. In this review we will summarize the anabolic agents that have been studied and present a current view of their current standing. Fluoride, GH, insulin-like growth factor I, the statins, and PTH will be reviewed. Although still in development, approaches to combination therapy with antiresorptives and anabolic agents are also promising. (J Clin Endocrinol Metab 86: 957–964, 2001)

THE PAST DECADE has witnessed major advances in the diagnosis and treatment of osteoporosis. Better and wider utilization of bone mass measurement technology combined with a wealth of case-control, cohort, and randomized placebo-controlled trials (RPCTs) have provided the clinician with levels of evidence to support diagnostic and therapeutic interventions to an extent never imagined in the 1980s. In addition, molecular biologists have made great progress in elucidating the intricate symphonic movements and orchestration of the bone-remodeling unit from birth to old age. This information explosion has unleashed several new treatment options for osteoporosis, including designer-like estrogen molecules, calcitonins, and the bisphosphonates. It has also established the current paradigm that the most optimal treatment for preventing fractures in postmenopausal osteoporosis is antiresorptive therapy.

Trailing the development of antiresorptives for osteoporosis is the development of anabolic agents designed to increase bone mineral density (BMD) by stimulating bone formation. Sodium fluoride was a promising anabolic agent for the treatment of postmenopausal osteoporosis, but it was found to increase the risk of nonvertebral fractures despite dramatic increases in BMD (1). It remains to be seen whether a different, lower dose formulation of fluoride will be shown to be efficacious and safe (2, 3). GH has also been the object of interest as an anabolic agent for the skeleton. PTH, long known to have anabolic potential was “rediscovered” about 15 yr ago. The statins, cornerstones of lipid-lowering therapy, have also recently been revisited as potentially important skeletal anabolic agents.

In contrast to drugs that slow bone turnover, secondarily allowing bone formation to exceed bone resorption, PTH and other anabolics directly stimulate bone formation. With several new, albeit small, RPCTs, either just completed or in progress, and with several more studies planned, including a large NIH initiative, PTH has emerged as the leading candidate to be the first anabolic agent approved for the treatment of osteoporosis. In this article we will review the concept of and evidence for various anabolic therapies in osteoporosis.

Low BMD is the most important risk factor for osteoporotic fractures (4, 5). Reduced bone mass results from an imbalance in the bone-remodeling unit (Fig. 1) as a function of enhanced bone resorption without a commensurate increase in bone formation. There is substantial evidence that increased bone turnover due to acute estrogen deficiency, calcium depletion, secondary hyperparathyroidism, glucocorticoids, immunosuppressive therapies, and other medications results in a higher risk of fracture. Although in these settings, BMD falls, it does not completely account for overall fracture risk. The precise reason for this is unclear, but rapid bone loss due to increased bone resorption can lead to skeletal instability, microperforations, and microfractures (6–8). Moreover, inhibition of bone resorption by estrogens, calcitonins, or the bisphosphonates reduces fracture risk by means that are at least partially independent of the increase in bone density (8, 9).

These lines of evidence suggest that sustained high bone turnover may be intrinsically detrimental for maintenance of strength in the adult skeleton. This thesis is supported further by data in African-Americans, who have greater bone mass, lower fracture rates, and slower bone turnover than Caucasians (10). In fact, it is likely that the greatest accretion of bone mass during adolescence occurs when formation is enhanced but resorption is slowed. Finally, as it turns out,
**Fluoride**

Sodium fluoride was the first of the true anabolic agents to be used in the treatment of postmenopausal osteoporosis. Radiographic increases in bone mass were impressive in early studies with fluoride when administered to osteopenic individuals. Fluoride, in fact, has been used throughout the world for the treatment of osteoporosis for nearly 4 decades, although in the United States it is not a Food and Drug Administration-approved drug for osteoporosis. One of the reasons for this is the conflicting results of the early RCTs in which the use of fluoride was associated with marked increases in vertebral BMD but no change in vertebral fracture incidence. Moreover, the risk of nonvertebral fractures may have been somewhat higher in the trials using a relatively high daily dosage of sodium fluoride, 75 mg (1, 1a). Side-effects, consisting of upper gastrointestinal symptoms and a lower extremity pain syndrome, were common. The investigation of Meunier et al. was also disappointing when fluoride was used in somewhat lower dosage (1b). Subsequently, Pak and his associates reported on a lower dose, slow release formulation of sodium fluoride in which the pharmacokinetics and serum levels improved the therapeutic/toxicity index. Using this form of fluoride, Pak et al. showed a 50% reduction in vertebral fracture incidence along with impressive increases in bone mass (2, 3, 3a). More recently, Ringe, Register, and their colleagues reported positive results with low dose but a different formulation of fluoride, monofluorophosphate (11, 12, 12a). Despite the potential for this agent, especially when used in lower dosages and more favorable formulations so as to reduce or eliminate gastrointestinal side-effects, consensus about its clinical utility has still not been reached. Reflecting that ambiguity, the U.S. Food and Drug Administration has not approved any fluoride preparation for the prevention or treatment of postmenopausal osteoporosis, and it appears unlikely that position will change in the near future.

**GH**

GH and IGF-I are both critical for the acquisition and maintenance of skeletal mass. Bone is the second richest source of IGF-I in the body, and locally this peptide promotes chondrocyte and osteoblast differentiation and growth (13). IGF-I is also a critical factor in the coupling of bone turnover, as it is stored in the skeletal matrix and is released during bone resorption (13) (see Fig. 1). Several studies have sug-
gested that both serum and skeletal IGF-I levels are related to BMD (14–17). Recently, two prospective studies have provided evidence that low levels of IGF-I are associated with a greater risk of hip and spine fractures (17–19). Hence, there is a strong rationale for considering human GH or IGF-I as potential anabolic agents for the treatment of osteoporosis.

**GH therapy for age-related osteoporosis**

Elderly people have lower GH secretory amplitudes and reduced serum levels of IGF-I and IGF-binding protein-3 (IGFBP-3) than younger adults. Based on these data and others, it has been assumed that skeletal responsiveness to GH in older individuals would be similar to that seen in GHD patients (20–25). The most widely publicized GH trial in the elderly involved 21 men over age 65 yr randomized to receive 0.03 mg/kg recombinant human GH (rhGH) three times per week (as a sc injection) or no treatment. At 6 months, men receiving rhGH exhibited a small 1.6% increase in lumbar BMD, but those changes were not sustained after 1 yr of treatment (26, 27). Holloway et al. conducted a longer, randomized, double blinded, placebo-controlled trial of daily rhGH for 1 yr in 27 healthy elderly women, 8 of whom also were taking a stable dose of estrogen (28). Side-effects prompted a 50% reduction in the original dose of rhGH (from 0.043 mg/kg BW or approximately 0.3 mg rhGH/kg/week to 0.02 mg/kg/day) and led to several drop-outs. There were no changes in BMD at the spine or hip at 6 or 12 months, although markers of bone formation and resorption did increase (28). More recently, Rosen et al. reported a dose-dependent decrease in bone mass after 1 yr of rhGH in frail elderly men and women with low BMD despite striking increases in osteocalcin and serum IGF-I (29).

The absence of a GH effect on BMD in elderly osteoporotic individuals is not surprising, because resorption is coupled to formation, and GH activates the entire remodeling sequence. Indeed, in the same trial of 132 elderly subjects by Rosen et al., urinary N-telopeptide and osteocalcin, markers of bone resorption and formation respectively, both rose to the same extent, suggesting that bone turnover, not just bone formation, was increased by rhGH (29). These *in vivo* observations are consistent with a very recent *in vitro* study using mouse stromal cells, in which IGF-I suppressed the expression of osteoprotegerin, thereby enhancing osteoclast recruitment (Rubin, J., personal communication). On the other hand, 1 yr may be too short a time period to conclude that rhGH does not increase BMD, but the relatively high incidence of side-effects (weight gain, carpal tunnel syndrome, edema, and glucose intolerance) in GH trials, especially in the frail elderly, is particularly troublesome.

**GH therapy for postmenopausal osteoporosis**

It is difficult to judge the potential efficacy of GH in the treatment of postmenopausal osteoporosis because of the paucity of well designed longitudinal studies. Several small trials have looked at the effects of GH-releasing analogs on bone turnover and bone mass. Not unlike rhGH, however, these studies have been small, and the results somewhat conflicting, but in contrast to rhGH, GH-releasing analogs are not associated with significant side-effects. Hence, further trials are likely to be revealing. Finally, combination therapy of rhGH with an antiresorptive agent, calcitonin, has been studied. In a 2-yr randomized trial by Holloway and colleagues, rhGH and nasal calcitonin increased spine BMD by approximately 2% (30). This however, was not different from the results using calcitonin alone. Once again, there were several side-effects that could be attributable to rhGH.

**IGF-I**

Theoretically, there are potential benefits for using rhIGF-I compared with rhGH in the treatment of osteoporosis. These include 1) more direct stimulation of bone formation, 2) bypass of skeletal GH resistance that can be present, and 3) a reduction in GH-induced side-effects such as carpal tunnel and diabetes mellitus. There are, however, even fewer animal and human studies using rhIGF-I than rhGH. Therefore, these advantages have either yet to be fully realized or have not been validated.

**rhIGF-I in the treatment of osteoporosis**

Idiopathic osteoporosis in men is an ill defined syndrome of low BMD and spinal fractures without associated hypogonadism or other definable etiology. By histomorphometry, these men often have low bone turnover, suggesting a possible defect in bone formation. Several groups of investigators have suggested that this syndrome is related to low serum IGF-I levels (31, 32). As the therapeutic options in males with osteoporosis are somewhat limited, and treatment for low bone turnover states, in general, is frustrating, the therapeutic potential for anabolic agents such as IGF-I in this condition should be quite high.

Clinical trials provide evidence that IGF-I acts by increasing the birth rate of remodeling osteons, thereby promoting bone turnover. Yet, it is conceivable that low doses of rhIGF-I (<30 mg/kg/day) may differentially stimulate bone formation. In 1 trial of 16 healthy elderly women, 60 μg/kg/day (high dose) and 15 mg/kg/day (low dose) of rhIGF-I were tested for 28 days (33). The higher dosage of rhIGF-I increased markers of bone resorption and formation; the lower dosage of rhIGF-I increased serum osteocalcin and type I procollagen carboxyl-terminal peptide, but had no effect on total pyridinoline excretion (33). These data would support the concept that low doses of rhIGF-I may directly increase osteoblastic function with only a minimal increase in bone resorption.

Recently, novel approaches to enhancing IGF-I action in bone have been proposed. One strategy is to administer a bone-specific agent, such as PTH, which can stimulate skeletal IGF-I (see below). Another strategy is to administer IGF-I along with an IGFBP. Bagi et al. previously reported that the IGF-I/IGFBP-3 complex could enhance bone mass in the metaphysis and epiphysis of rats (34). One small randomized trial used sc infusions of IGF-I/IGFBP-3 in 24 older women with hip fractures. The rate of bone loss in the contralateral hip was reduced considerably after 6 months (*i.e.* from 6% to 1.5%) in those subjects who were given the complex vs. those receiving saline (35). Accompanying the change in BMD, there was also an increase in grip strength in those who received the active agent. No significant side-effects were reported.
**IGF-I in anorexia nervosa**

Osteopenia frequently accompanies anorexia nervosa (AN). The reduced bone mass in AN is characterized by reduced bone formation. Serum IGF-I levels are reduced by 50% despite a marked increase in the frequency of GH pulsatility. Recently, Soyka and colleagues reported that serum IGF-I concentrations accounted for nearly 70% of the variance in both osteocalcin and bone-specific alkaline phosphatase and that bone resorption indexes were comparable in both AN and age-matched controls (36). Grinspoon et al. administered 100 or 30 µg/kg rhIGF-I or placebo to 23 women with AN and low spine BMD (37). After 6 days, 1 marker of bone formation increased without any change in bone resorption. These data were used to support a much larger, currently ongoing trial of 30 µg/kg rhIGF-I in more than 70 AN patients. Results from that RPCT will help to determine whether this treatment is feasible on a larger scale. Clinical and pharmacological interest in IGF-I has been tempered by the fact that high normal levels of serum IGF-I have been linked to a greater risk of certain malignancies (19). If IGF-I is ultimately to become a useful therapeutic agent, such concerns will have to be carefully addressed and critically evaluated.

**PTH**

PTH is a principal regulator of calcium homeostasis in mammalian systems. PTH responds dynamically to changes in extracellular calcium via a cell surface calcium-sensing receptor. Increases in serum calcium suppress PTH release, whereas falling levels stimulate PTH release. Besides its acute effects on mobilizing skeletal calcium, PTH also stimulates 1α-hydroxylase activity in the kidney, thereby increasing serum 1,25-dihydroxyvitamin D levels. This, in turn, promotes calcium transport in the gastrointestinal tract. PTH also acts on the distal tubule to enhance reabsorption of filtered calcium. In sum, PTH is the center of a homeostatic system that balances calcium intake from the diet with calcium output from the gut and kidney. PTH is a regulator of parathyroid hormone receptor expression in the kidney, thereby increasing renal tubular calcium reabsorption. Furthermore, PTH enhances the transport of calcium in the gastrointestinal tract by stimulating the synthesis of calcitriol, the active form of vitamin D. This leads to increased intestinal absorption of calcium, which is essential for maintaining calcium homeostasis.

**Mechanism of PTH action on bone**

PTH acts through dual signaling pathways in bone cells, with the osteoblast being the principal target. In the osteoblast, the type I PTH/PTH-related peptide receptor is coupled to both the adenylate cyclase activating G protein-coupled protein (Gq) and the phospholipase C-activating G protein (38, 39). PTH requires the first two amino acids and some part of the 25–34 amino acid region to activate Gq, but a fragment as small as 28–32 amino acids can activate Gq (38, 39). Most of the skeletal actions of PTH can be related to cAMP/protein kinase A activation. Although it is likely that the balance of these two systems determines the overall biological effect of PTH, it is well established that PTH activation of adenylyl cyclase is essential for osteoblast function. On the other hand, although cAMP/protein kinase A activates early genes such as c-fos, the protein kinase C system has also been shown to be operative when intermittent use of PTH increases osteoblast activity (40, 41). Overall, the activation profile of PTH in bone cells leads to induction of several growth factor genes, including those for IGF-I, IGF-II, and transforming growth factor-β. In addition, IGFBP-1, -4, and -5 are induced by PTH, as are IGFBP protease-3 and -5 (38–46). The effect of PTH on IGF-I production is limited rather exclusively to bone cells.

Intermittent exposure of PTH for 4–6 weeks in ovariectomized animal models leads to increased cancellous thickness [but not trabecular number (40–48)]. Cancellous bone mass and strength are greater, even in the absence of estrogen. Microscopically, bone cell turnover is enhanced, reminiscent of pubertal bone expansion (Hock, J., personal communication). On a cellular level, PTH enhances the recruitment of osteoblasts from marrow stromal cells and induces the maturation of lining osteoblasts, both of which increase collagen synthesis (38, 43). Expression of skeletal IGF-I, as noted, is markedly enhanced in situ and in vitro by PTH administration (42, 45–46). PTH induces the synthesis of osteoblastic cytokines such as interleukin-6, which, when secreted, target early osteoclasts for recruitment. This process allows for coupling of bone resorption to formation, although in vitro data suggest that bone formation indexes increase consistently more and earlier than bone resorption markers. Thus, the balance favors new bone formation, giving rise to the anabolic properties of intermittent PTH.

Notwithstanding these observations, the underlying molecular physiology accounting for the true anabolic effect of PTH remains unknown. In addition, it is uncertain why intermittent, low dose PTH administration differs so dramatically in its effect on bone cells from chronic sustained PTH treatment in which catabolic effects at cortical sites predominate (41). Recently, evidence has emerged that PTH reduces osteoblastic apoptosis, prolonging osteoblast survival and possibly potentiating its differentiated function in collagen synthesis (47).

The potential for anabolic skeletal actions of PTH is seen in the common disorder of PTH excess, primary hyperparathyroidism. The work of Silverberg and her colleagues have demonstrated that in the mild asymptomatic form of the disease seen today, a particular pattern occurs in terms of bone density (49). The cancellous skeleton of the lumbar spine is relatively well preserved, whereas the cortical skeleton (distal forearm, one third site) is preferentially reduced (49). Histomorphometric studies have confirmed these densitometric studies and shown further that cancellous bone volume and trabecular plate connectivity are actually better than those in age- and sex-matched controls (49–51). These and other observations have supported the idea that PTH could be a useful anabolic therapy for osteoporosis.

**PTH as a therapy for postmenopausal and male osteoporosis**

Animal studies with intermittent PTH have demonstrated a significant increase in cancellous bone mass at several sites, with either no change in cortical bone or a slight decline with time (40–48, 52). Mechanical strength in the femur and vertebrae also increases with intermittent PTH treatment. The PTH effect to improve bone mass and strength has been noted in rats, monkeys, dogs, and rabbits (46–48, 52). In contrast, the effects of PTH in mice are more heterogeneous,
The principal finding common to all studies in both men and women is a marked increase in spine BMD with PTH. This increase in BMD is substantially greater than the increase commonly observed after 1 yr of antiresorptive therapy. By dual energy x-ray absorptiometry (DXA), increases of 7–10% annually and by QCT increases of 40% are common. The difference between these two densitometric techniques reflects the measurement of cancellous bone rather exclusively by QCT in contrast to DXA, which detects both cortical and cancellous elements in the lumbar spine. Rather consistently, bone density in the hip and forearm either remains the same or declines slightly with treatment. One of the most interesting studies demonstrating the potential of PTH to prevent postmenopausal bone loss was reported by Finkelstein et al. (55). Thirty premenopausal women receiving the GnRH agonist, naferelin, to induce estrogen deficiency for endometriosis were given PTH or placebo. Those women receiving PTH had a marked increase in spine BMD after 6 months compared with the calcium only group, which lost significant bone mass due to estrogen deficiency (55, 56). This trial confirmed that PTH could indeed prevent estrogen deprivation-induced bone loss. These studies, albeit small, suggest that PTH has strong anabolic properties on cancellous bone, with minimal adverse events.

Three recent RPCTs have helped to substantiate these earlier studies. One trial included 23 males with idiopathic osteoporosis, treated for 18 months with 400 IU rhPTH-(1–34) daily (31). After 18 months there was a 13.5% increase in lumbar BMD, whereas there was no change in the placebo group. Femoral neck BMD increased 3% (P < 0.05) from baseline, whereas no change in the distal radius was noted. Of considerable interest, markers of bone formation during PTH therapy increased more than bone resorption, and these effects on formation were evident earlier than the resorptive changes. A baseline pyridinoline cross-link determination and a 3-month osteocalcin level were the best predictors of the skeletal response to PTH.

The second RPCT was a larger multicenter phase II dose finding with PTH-(1–84) in 207 postmenopausal women with low BMD (t-score, less than −2.0) (57). After 1 yr, women receiving the highest dose, 100 μg (400 IU) PTH, demonstrated a nearly 8% increase (P < 0.0001) in spine BMD, with virtually no change in femoral BMD and a slight decrease in total body BMD (56) (Fig. 2). Lower doses of PTH showed lesser changes in spine BMD, consistent with a dose-dependent effect on trabecular BMD. PTH treatment was not associated with any major adverse events, although nearly 20% of the subjects receiving the highest dose of PTH did have transient hypercalcemia.

The third and largest RPCT to date tested daily administration of 20 or 40 μg human PTH-(1–34), sc, in 1637 women with postmenopausal osteoporosis (i.e., low BMD and fractures) (58). The median follow-up was 21 months, and for the two doses of PTH, spine BMD increased between 12–15%. Femoral BMD also increased approximately 3%. Most impressive, however, was the relative risk reduction for both vertebral and nonvertebral fractures in those women receiving either 20 or 40 μg/day PTH: relative risk for vertebral fracture with 20 μg, 0.35 [95% confidence interval (CI), 0.22–0.55]; with 40 μg, 0.31 (95% CI, 0.19–0.50); and relative risk for nonvertebral fracture, 0.46 (95% CI, 0.25–0.88) for either dose of PTH. Back pain, nausea, and headache were the most common side-effects, and these occurred infrequently and in a dose-dependent manner. Less than 5% of the women had sustained increases in serum calcium above the normal range in any of the treatment groups.

These trials reinforce findings from earlier human trials, confirming that PTH administered intermittently is both safe and efficacious with respect to enhancing BMD. Although concern about cortical bone loss with PTH was an issue in earlier trials, the data from these studies are reassuring and suggest that with adequate calcium and vitamin D, PTH has either no effect or a modest positive action on cortical bone sites.
Combination Therapy

Even when anabolic approaches to osteoporosis are still very much in a developmental stage, efforts to consider combination therapy with antiresorptives and anabolics are being launched. The rationale is clear. The anabolics will stimulate bone turnover with bone formation presumably exceeding bone resorption at least for the initial period of therapy. Concerns about long term use of anabolics as well as a possible advantage of an antiresorptive either during or after a period of anabolic therapy are attractive.

A number of animal and human studies have used a combination of PTH with several different antiresorptive agents. Earlier animal studies employed the rat ovariectomy model, and used estrogen with PTH vs. estrogen or PTH alone (43, 45–48, 52). More recently, animal studies with a bisphosphonate and PTH have also been undertaken with similar results, i.e. an enhancement in cancellous bone mass, connectivity, and strength, with modest increases in cortical bone sites as a result of the antiresorptive component. Two uncontrolled trials with hPTH-(1–34) and calcitonin also demonstrated that PTH plus calcitonin had a significant effect not only on cancellous BMD (i.e. vertebral bone density), but also on mixed cortical and cancellous sites, such as the femoral neck (59). More recently, Lindsay et al. performed a 3-yr, randomized, placebo-controlled of PTH-(1–34) in 60 women already receiving estrogen therapy (60). Seventeen women received PTH plus estrogen for 3 yr, and 17 women remained on estrogen alone. At the end of the trial, vertebral BMD increased 13% in the PTH group, femoral BMD increased 2.7%, and total body BMD was 0.8% higher than baseline. These results were markedly different from those in estrogen-treated controls, whose bone density did not change at any site. In addition, the number of vertebral fractures appeared to be fewer among those receiving PTH plus estrogen compared with those receiving estrogen alone.

In a more recent study by Roe et al., 74 postmenopausal women were randomized to receive either 400 IU PTH-(1–34) or placebo while remaining on stable doses of conjugated equine estrogens (61). There was a nearly 30% increase in spine BMD as well as an 11% increase in femoral BMD as measured by DXA among women receiving combination therapy compared with those taking estrogen alone. The increase in vertebral BMD was even greater, close to 80%, when measured by QCT of the vertebrae. Taken together, these data make two important points: 1) PTH plus estrogen has a greater effect on bone mass than either alone; and 2) the beneficial effects of combination therapy are found in both the spine and the femur, the two most vulnerable areas for subsequent fractures.

There are virtually no data in humans on the use of PTH plus bisphosphonates, either given together or sequentially. However, in one open label study after the 1-yr, multicenter PTH trial described above, 60 women, some taking PTH and some taking placebo, who completed 1 yr in the trial, were then given 10 mg alendronate daily for an additional year (57). Those receiving the highest dose of PTH followed by alendronate demonstrated a 14.3% increase in spine BMD after 2 yr and a 3.4% increase in femoral neck (see Fig. 2). On the other hand, those women receiving placebo showed a second year increase in spine BMD of 7%, consistent with the effects of alendronate alone. In fact, the slope of change during the second year in spine BMD did not differ between groups, even though during the first year the treatment effects differed dramatically. Hence, PTH did not hinder the subsequent alendronate response in the second year; in fact, the response was additive. What is not known, however, is whether treatment with PTH and a bisphosphonate used simultaneously is better, worse, or no different than sequential therapy. A randomized trial sponsored by the NIH is currently underway to test that hypothesis.

Combination therapy with PTH for glucocorticoid-induced osteoporosis

Glucocorticoid-induced osteoporosis (GIO) is the most common cause of drug-related osteoporosis. It is associated with rapid bone loss, fractures, and increased morbidity. Although bone formation is markedly impaired, there is also an increase in bone resorption. Several of the bisphosphonates have been shown to preserve BMD and reduce the risk of subsequent fracture in patients with GIO (62, 63). However, the bisphosphonates do not directly counteract the reduced bone formation characteristic of GIO. Hence, the use of PTH in combination with an antiresorptive agent to treat GIO is attractive. The seminal study in this regard comes from Lane et al., who conducted a randomized, 12-month, placebo-controlled trial with hPTH-(1–34) in 51 women with chronic inflammatory diseases (e.g. rheumatoid arthritis) taking chronic glucocorticoids (>5 mg/day prednisone) who were already being treated with hormone replacement therapy (64–66). Women receiving PTH plus estrogen experienced an 11% increase in spine BMD by DXA compared with a 1.7% increase in those remaining on estrogen alone. There were no differences in hip or forearm BMD between groups, but by QCT of the spine, the increase in BMD was even greater (35%) in those women receiving PTH. Markers of bone turnover were increased by 3 months in the PTH treatment arm to nearly 150% of baseline, whereas resorption markers also were enhanced, but to a much lesser degree (64–66). Overall, the treatment was well tolerated. During the second year of the protocol, although PTH had been discontinued, a further increase in lumbar spine BMD of 15% was observed (64). These data establish that 1) GIO can be managed with combinations of PTH and estrogen; 2) despite the presence of an antiresorptive agent, PTH markedly induces bone formation; and 3) the actions of PTH on the skeleton persisted for at least 1 yr after treatment was discontinued (66).

The Statins as Anabolic Agents

One of the most exciting developments in the past year has been the discovery that HMG coenzyme A reductase inhibitors (i.e. the statins) might have an anabolic action on bone, thereby potentially reducing the risk of fractures with long-term therapy. Mundy and colleagues made the seminal observation that this class of lipid-lowering drugs induced bone morphogenic protein-2, and that when lovastatin or simvastatin was injected into the calvariae of mice, there was a significant increase in new bone formation (67). In addition, they demonstrated that oral statins could prevent ovariec- tomy-induced bone loss in rats. These lines of evidence spurred clinical investigators to reexamine datasets from observational and cohort trials to assess the effect of short-
and long-term statin use on fracture risk. Subsequently, several observational studies have suggested that the use of statins is associated with a modest increase in BMD and a significant fracture risk reduction on the order of 40–50% for all clinical fractures (68–71).

Despite these observations, several aspects of this story remain unclear. First, there are no randomized, placebo-controlled trials of the statins to assess the validity of fracture risk reduction. As noted with estrogens, observational studies may be particularly prone to ascertainment bias and may lead to conclusions that are not completely justified. Second, these agents when administered orally are almost totally cleared by first pass through the liver. Hence, it is unclear how this class of drugs reaches the bone and how it affects bone turnover. Third, the statins inhibit HMG Coenzyme A reductase, a rate-limiting step in cholesterol biosynthesis. The bisphosphonates block bone resorption also by working on the cholesterol biosynthetic pathway, in this case by inhibiting a step further down that path (i.e., farnesyl-pyrophosphate synthase). Yet, it is still unclear how the statins could stimulate bone formation while the bisphosphonates, working in the same pathway, inhibit bone resorption. Moreover, there is no mechanism to explain the effects of this class of agents on bone morphogenic protein-2 gene expression. In summary, this is an exciting area of future development, which could offer great potential for patients and physicians. Just as importantly, this class of drugs is certain to open up new research opportunities as investigators begin to unravel the effects of statins on bone and the mechanisms responsible for enhanced bone formation.

### The Future of Anabolic Agents for the Treatment of Osteoporosis

The therapies discussed in this article share the property of stimulating bone formation, but the cumulative evidence from RPCTs favors PTH treatment as the most promising anabolic agent. Issues of safety remain a major concern for regulatory agencies for all of the anabolics under investigation at this time. rhGH and/or IGF-I increase bone formation, but the long-term risk of increasing serum IGF-I, especially with respect to neoplastic transformation, has not been determined (19). In contrast, PTH is relatively bone specific and therefore may be safer with respect to nonskeletal cell proliferation. However, long-term studies (18–24 months) with hPTH-(1–34) administered to 6-week-old Fisher 344 rats have demonstrated an increased risk of osteogenic sarcoma. This effect, which may or may not be dose dependent, does appear to be related to the duration of use and would be consistent with lifetime exposure in a growing animal to an anabolic agent that increases osteoblast proliferation. Shorter term studies (6–12 months) in other strains of rats and all primate studies to date have failed to find an association between intermittent administration of PTH and osteogenic sarcoma. Moreover, there have been no cases of osteogenic sarcoma in patients with primary, secondary, or tertiary hyperparathyroidism from several large patient cohorts. Although further safety data are needed, it is reasonable to assume that PTH is safe in humans for short-term administration to those most likely to benefit, i.e. postmenopausal women and some men with clinical fractures and low BMD.

Other questions about PTH that remain to be answered include the following. 1) How long should patients receive PTH? Recent evidence would suggest that there is a indeterminate period after PTH is discontinued in which bone mass continues to increase or, at a minimum, is maintained (72). Such expectations are supported by studies of bone mass in primary hyperparathyroidism after successful parathyroid surgery (73).

### References


