



New anabolic therapies in osteoporosis

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The mainstay of therapy for osteoporosis is anti-resorptive in mechanism. Drugs such as estrogen, raloxifene, the bisphosphonates, and calcitonin all inhibit osteoclast-mediated bone loss and thus reduce bone turnover [1–6]. These anti-resorptive drugs lead to an increase in bone density by permitting bone formation to proceed while bone resorption is inhibited. The net result is to reduce the remodeling space and to prolong the duration of mineralization. The increase in bone density is variable depending on the site and the drug but is generally less than 10% over 3 years [7,8]. These anti-resorptive therapies reduce fracture risk, particularly in the spine, and for alendronate and risedronate at the hip as well.

The concept of an anabolic agent is based upon a therapeutic mechanism entirely different from inhibition of bone resorption. Anabolic agents directly stimulate bone formation. Inherent in this concept is the potential for anabolic agents to increase bone mass to a far greater extent than anti-resorptives. The potential of anabolic agents to improve bone density more substantially than anti-resorptives suggests that they might reduce fracture risk to a greater extent than the anti-resorptives. In this article we review the evidence for various anabolic therapies in osteoporosis, including fluoride, growth hormone (GH), insulin-like growth factor-I (IGF-I), strontium, statins, tibolone, and parathyroid hormone (PTH). Of these, PTH has emerged as the most promising treatment at this time.

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Fluoride

Sodium fluoride was the first anabolic agent to be investigated in postmenopausal osteoporosis. It has been available in Europe for decades but has not been approved in the United States for osteoporosis. Fluoride directly stimulates osteoblasts to form new bone but has little effect on osteoclasts. Early studies of fluoride administration revealed impressive increases in bone mass radiographically and by determination of bone mineral density (BMD). However, randomized, placebo-controlled trials with sodium fluoride at relatively high doses (75 mg daily) were disappointing [9,10]. Despite marked increases in spine BMD, fluoride was not associated with a reduction in vertebral fracture incidence. Of additional concern was a possible increase in nonvertebral fracture risk. Furthermore, severe gastrointestinal side effects and a disturbing lower extremity pain syndrome were reported as common adverse events.

Subsequent clinical trials with a lower dose, slow-release formulation of fluoride have been more encouraging. Increases in bone mass and significant reductions in vertebral fractures were observed [11–13]. With this lower dose formulation, increases in vertebral BMD ranged from 3% to 6% per year [14]. There was no increase in the nonvertebral fracture rate [15] and possibly beneficial effects at cortical skeletal sites were observed [16]. Another formulation of fluoride, monofluorophosphate (MFP), has also yielded promising results when administered in similarly low doses [17–19].

Fluoride has been used in combination with anti-resorptive agents. The rationale for combination therapy is that an anabolic agent like fluoride should stimulate bone formation, whereas the anti-resorptive agent should limit any catabolic effect and contribute its own effect to increase BMD. Therefore, anabolic and anti-resorptive therapy could be more effective than either approach alone. When fluoride was administered with hormone replacement therapy to healthy postmenopausal women for 96 weeks, an increase in spine BMD of 11.8%, which is greater than with either agent alone, was observed [20]. Markers of bone formation increased while markers of bone resorption decreased with the combination of the two agents [20]. Most recently, Ringe et al have reported preliminary results of a pilot study combining fluoride and the bisphosphonate etidronate [21]. Thirty-three men with severe osteoporosis were randomized to cyclic etidronate and MFP, as compared with etidronate or fluoride alone. The combination of etidronate and fluoride resulted in a higher BMD than either agent administered individually. Preliminary results of a larger ongoing study with fluoride and alendronate in 65 men have suggested similarly positive BMD effects at the spine and total hip [21] in the combined treatment arm.

Fluoride, therefore, has the potential to be an efficacious agent in osteoporosis. When administered in a low dosage, either alone or in combination with an anti-resorptive agent, significant gains in BMD result.

Fluoride also has the advantage of being relatively inexpensive. Unfortunately, the limited extent of many of the clinical trials with fluoride in the United States has delayed approval of this product. More data, especially in terms of fracture efficacy, are needed.

GH and IGF-I

The rationale for considering GH and IGF-I as potential anabolic agents is that both are critical for the acquisition and maintenance of bone mass. IGF-I promotes chondrocyte and osteoblast differentiation and growth [22]. It is also a pivotal factor in the coupling of bone turnover because it is stored in the skeletal matrix and released during bone resorption [22]. Two prospective studies have suggested that low levels of IGF-I are linked with a greater risk of spine and hip fractures [23,24].

Most of the studies using GH have been disappointing. Changes in bone mass are minimal [25–27]. The lack of a beneficial effect with GH on bone mass could be due to the concomitant activation of bone resorption along with formation [27] so that a net gain does not occur. Another explanation for a lack of effect could be the relatively short (1-year) duration of many of these studies. Recent evidence has suggested a delayed positive effect of GH on bone. In a double-blind, randomized, placebo-controlled trial, 80 postmenopausal women with osteoporosis on estrogen replacement therapy were administered placebo, GH 1.0 U/d, or 2.5 U/d for 18 months [28]. The women in both GH groups continued on treatment with GH for an additional 18 months. Although there was no difference between the groups after 3 years, at 4 years, the higher dose of GH resulted in a 14% increase in lumbar spine bone mineral content. These results are somewhat surprising and are at odds with most of the published literature on effective osteoporosis therapies in which the major increments in bone mass are invariably confined to the first 3 years of therapy.

IGF-I is theoretically more appealing than GH because it stimulates bone formation more directly and does not demonstrate many of the side effects related to GH, such as diabetes mellitus or carpal tunnel syndrome. When elderly women were administered low doses of rhIGF-I, markers of bone formation were differentially stimulated, with only a minimal increase in bone resorption [29]. Similarly, markers of bone formation increased in a short-term trial of young women with anorexia nervosa who were administered IGF-I [30]. There is also evidence that IGF-I might be more effective if administered together with its major binding protein IGFBP-3 [31]. A major drawback to the development of IGF-I as a therapy for osteoporosis is its widely pervasive effect on many organ systems. Similar to GH, potential serious adverse effects could surface with chronic use of this agent.

Growth hormone and IGF-I require further evaluation as anabolic agents. Longer studies with fracture data are needed. A future direction of investigation might involve co-administration of anti-resorptive agents to

prevent activation of the entire remodeling system. Efforts are also needed to develop formulations and analogues that are more specifically active in the skeleton.

Strontium

Strontium is a divalent cation that chemically resembles calcium and appears to participate in bone mineralization [32]. Anabolic properties include an increase in bone formation and an uncoupling of bone formation from bone resorption. The mechanism seems to be stimulation of osteoblast proliferation and inhibition of osteoclast formation, possibly through regulation of bone cell differentiation [33]. An alternative mechanism might be activation of signaling pathways through a putative cation-sensing receptor (CaSR), which is believed to be specifically expressed in bone cells [34,35]. The CaSR seems to be activated by strontium ranelate in rats and mice, although the degree of activation probably depends on variations in the local calcium concentration [36]. This receptor is believed to be different from the classical membrane-bound calcium receptor described by Brown, Nemeth, et al [137].

In ovariectomized rats, strontium ranelate prevents bone loss by reducing resorption while bone formation remains elevated [37,38]. However, as with fluoride, high doses were found to retard effective bone mineralization [39]. With lower doses, there was no adverse effect on mineralization; rather, there was a salutary effect on trabecular bone [37]. This finding was recently confirmed in adult mice administered strontium ranelate for 104 weeks [40]. Trabecular bone volume increased along with the osteoblastic surface, and concomitant decreases in osteoclast surface and number were observed [40]. Histomorphometric analyses have not revealed any defects in skeletal mineralization at the crystal level in monkeys [41] or rats administered strontium ranelate for as long as 2 years [42].

Clinical trials support the use of strontium ranelate as a treatment for postmenopausal osteoporosis [43–47]. A double-blind, placebo-controlled, dose-finding study in early postmenopausal women showed that 1 g of strontium ranelate administered daily for 2 years prevented the decrease in lumbar spine density that occurred in the placebo group [45]. In a larger study, 160 healthy early postmenopausal women were randomized to placebo or escalating doses of strantium ranelate (125 mg, 500 mg, or 1 g daily) for 2 years. The highest dose of strontium ranelate showed a significantly greater increase of 2.4% in adjusted lumbar BMD than placebo. Increased levels of bone formation were observed, without an effect on markers of bone resorption [48]. Strontium ranelate has not been found to have a negative impact on bone mineralization in human subjects [49].

Recently, the results of a Phase II, dose-ranging, randomized, placebo-controlled, double-blind trial have corroborated the anabolic potential of

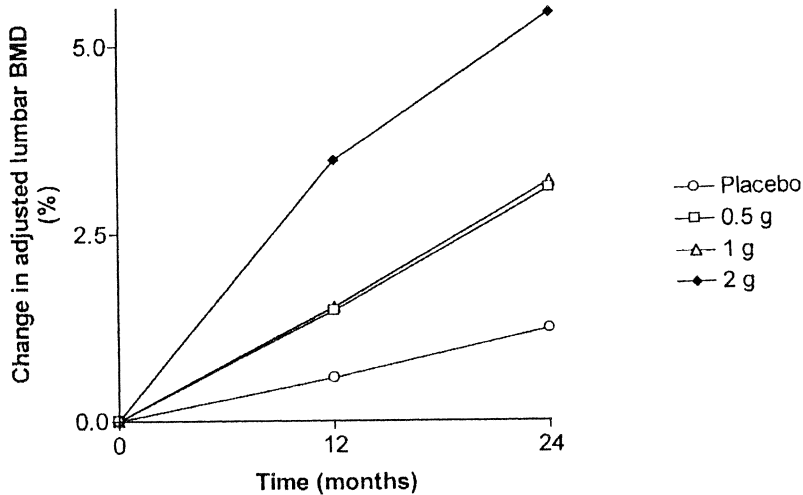


Fig 1. Changes in lumbar BMD in postmenopausal osteoporotic women treated with strontium ranelate for 2 years. Changes are measured by DXA after adjustment for the effect of bone strontium content. (From Meunier PJ, Slosman DO, Delmas PD, et al. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis: a 2-year randomized placebo controlled trial. *J Clin Endocrinol Metab* 2002;87:2060–6; with permission.)

strontium ranelate [50]. A total of 353 osteoporotic women with at least one vertebral fracture were randomized to receive placebo, 0.5 g, 1 g, or 2 g of strontium ranelate daily for 2 years. In the group receiving the highest dose, lumbar BMD increased significantly by 3.0% after adjustment for the presence of strontium in bone (Fig. 1). The rate of increase in BMD was almost the same during the second year of treatment as during the first year, in contrast to anti-resorptive treatments in which most of the gain occurs during the first year [51,52]. New vertebral deformities were also reduced significantly (Relative Risk 0.56) [50]. An increase in the bone formation marker, bone-specific alkaline phosphatase (BSAP), was observed in the group receiving the highest dose of strontium ranelate, along with a reduction in the bone resorption marker, urinary N-telopeptide. Strontium ranelate was well tolerated at all doses. Results of the Phase III clinical trial of 2 g daily of strontium ranelate have also been recently reported [53]. In a double-blind, randomized, placebo-controlled trial, 1649 postmenopausal women with at least one vertebral fracture were administered strontium ranelate daily or placebo for 3 years. A 41% reduction in relative risk of a new vertebral fracture was observed. Lumbar BMD also increased in the treatment group by 11.4% (uncorrected for the presence of strontium in bone), along with increases in BSAP and decreases in serum C-telopeptide [53].

Strontium ranelate thus harbors anabolic properties and is a promising agent to treat postmenopausal osteoporosis. Recent data support its efficacy and safety. By apparently inhibiting resorption as well, strontium ranelate is

probably not best regarded as a purely anabolic agent but instead as a unique drug that has dual activities in bone.

Statins

Recent data, mostly epidemiologic and cross-sectional, have suggested that the use of HMG coenzyme A reductase inhibitors (statins) is associated with a modest increase in BMD and a significant fracture risk reduction [54–59]. An anabolic effect of statins has been implied by several observations. New bone formation was observed when statins were injected into the calvariae of mice [60]. This growth was associated with an increase in bone morphogenic protein-2 (BMP-2), a protein that plays an important role in osteoblast differentiation and bone formation. Statins probably enhance BMP-2 through a reduction in the prenylation of Rho and a subsequent increase in endothelial nitric oxide synthase [61]. The increase in BMP-2 is inhibited by mevalonate, a downstream metabolite of HMG coenzyme A reductase, which is the rate-limiting step in cholesterol production [62–64]. Recently, lovastatin was found to increase cortical bone by single, local administration to the bone marrow cavity of young male rats [65]. In a small clinical trial, 17 hypercholesterolemic subjects who were administered simvastatin 20 mg daily for 4 weeks had a significant increase in the bone formation marker osteocalcin, although other markers, including BSAP, did not change [66].

Other lines of evidence have indicated that the protective skeletal effect of the statins is due to an anti-resorptive mechanism. Statins elicit an anti-osteoclastic effect by interfering with the mevalonate pathway in a step upstream from the site of action of the bisphosphonates [67]. In one study, osteoclast formation and activity were inhibited similarly by either lovastatin or alendronate and were reversed by the administration of mevalonate and geranylgeraniol, respectively [68]. Similarly, *in vitro* studies of statin administration have revealed an inhibition in the development and prenylation of osteoclasts but not osteoblasts [69,70]. Several clinical trials also support an anti-resorptive effect of statins, as shown by decreases in bone resorption markers [71,72]. In a small, randomized trial, 14 postmenopausal healthy women were administered cerivastatin 0.4 mg daily or placebo for 12 weeks. Markers of bone resorption were reduced by 20% in the cerivastatin group, whereas there was no change in the indices of bone formation [73].

Important questions remain unresolved about the beneficial skeletal effects of statins. First, because the bisphosphonates also work on the cholesterol biosynthetic pathway by inhibiting a downstream step, it is unclear how statins could stimulate bone formation when bisphosphonates, working in the same path, inhibit bone resorption. Second, when administered orally, statins do not localize preferentially to bone. They are almost exclusively cleared via first-pass hepatic metabolism, so it is not apparent

how they could affect bone turnover. Third, no randomized, placebo-controlled trials to assess fracture risk reduction with statin administration have been reported. The existing observational trials may be prone to ascertainment bias. Statin users might have fewer fractures because of a higher baseline bone mass [74], possibly associated with a higher BMI. Moreover, fracture risk reduction has not been found uniformly in all statin studies to date [75,76]. Two large-scale, cross-sectional surveys failed to show an association between statin use and fracture risk [77,78]. It is therefore too early to reach any conclusions as to whether statins have anti-fracture potential and, if so, whether they can be classified as anabolic.

Tibolone

Tibolone (Livial, Org OD 14) is a synthetic non-estrogen steroid that by its metabolism has estrogenic, androgenic, and progestogenic properties. Tibolone has no activity before it undergoes metabolic conversion. Tissue-specific conversion of tibolone occurs in different tissues to form the metabolites 3α -hydroxytibolone, 3β -hydroxytibolone, and the $\Delta 4$ -isomer [79]. The properties of tibolone at specific tissue sites relate to the extent to which its metabolites are formed. Several clinical trials have shown that tibolone significantly improves trabecular BMD and reduces bone turnover, especially in women with established osteoporosis [80–86]. Tibolone's actions on bone seem to be mediated by stimulation of the estrogen receptor [80–82,87,88]. This idea is supported by the observation that administration of an anti-estrogen counteracts the protective effects of tibolone in maintaining bone mass in rats after ovariectomy [89]. Because tibolone can be metabolized to isomers that have affinity for androgen and progestin receptors, it is plausible that tibolone may exert an additional anabolic effect on bone.

PTH

Continuous PTH secretion elicits a catabolic response in the skeleton, as demonstrated by the model of severe primary hyperparathyroidism [90,91]. When PTH is administered in a low-dose, intermittent fashion, its anabolic properties surface. This effect is observed most dramatically in the cancellous skeleton. Possible mechanisms include stimulation of growth factors, especially IGF-1 [92–100], and unique subsets of “bone-forming” genes [101], including gene expression of osteocalcin and tartrate-resistant acid phosphatase [102]. In addition, intermittent PTH seems to prevent osteoblast apoptosis [103] and an increase in receptor activator of NF- κ B ligand (RANKL), an osteoclast-enhancing cytokine [104,105]. Several studies in animals support increases in cancellous bone with PTH

administration [94–100,103,106,107]. Recent animal data also suggest that cortical bone might be similarly enhanced [108,109].

PTH monotherapy in postmenopausal osteoporosis

PTH as a single therapy has been studied in postmenopausal osteoporotic women. One randomized, placebo-controlled trial was a multicenter Phase II dose finding with PTH 1–84 in 217 postmenopausal women with low BMD (T scores <–2.0) [110,111]. After 1 year, women receiving the highest dose (100 µg [400 IU] PTH) demonstrated a nearly 7% increase ($P < 0.001$) in spine BMD with virtually no change in femoral BMD and a slight decrease in total body BMD [110,111]. 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 had transient hypercalcemia.

The largest randomized, placebo-controlled trial tested daily administration of 20 or 40 µg of subcutaneous hPTH 1–34 in 1637 women with postmenopausal osteoporosis (ie, low BMD and fractures) [112]. Median follow-up was 21 months. For the two doses of PTH, spine BMD increased 10% to 14%. Femoral BMD also increased by approximately 3%. Total body BMD increased significantly as well. Most impressive was the reduction in risk for vertebral and nonvertebral fractures in women receiving 20 or 40 µg/d of PTH. Compared with placebo, PTH reduced the risk of one or more new vertebral fractures by 65% and 69%, respectively. New nonvertebral fractures were reduced by 35% and 40%, respectively. Among the women with new vertebral fractures, the mean loss in height was greater in the placebo group (–1.1 cm) than in the 20-µg and 40-µg PTH groups (–0.2 and –0.3 cm, respectively; $P = 0.002$). Back pain was significantly reduced in the PTH group. Nausea and headache occurred infrequently in a dose-dependent manner. Sustained increases in serum calcium above the normal range occurred in 3% of the 20-µg group and in 11% of the 40-µg group. There was no increase in the incidence of hypercalciuria or urolithiasis.

PTH in men with osteoporosis

Idiopathic osteoporosis in men constitutes a group for whom PTH could be suited ideally because this is a disorder of impaired bone formation and low bone turnover [113,114]. The first randomized, controlled trial of PTH in men with idiopathic osteoporosis was carried out by Kurland et al [115]. A total of 23 men, 30 to 68 years old, with idiopathic osteoporosis as defined by z-scores less than –2.0 at the lumbar spine or femoral neck, were randomized to hPTH (1–34) 400 U/d or placebo in a double-blind experimental design for 18 months. The PTH group had an impressive

linear increase in lumbar spine bone density from the beginning to the end of the 18-month trial, culminating in a 13.5% increase of lumbar spine bone density (Fig. 2). Bone turnover markers increased substantially in the men treated with PTH. A baseline pyridinoline cross-link determination and a 3-month osteocalcin level were the best predictors of the skeletal response to

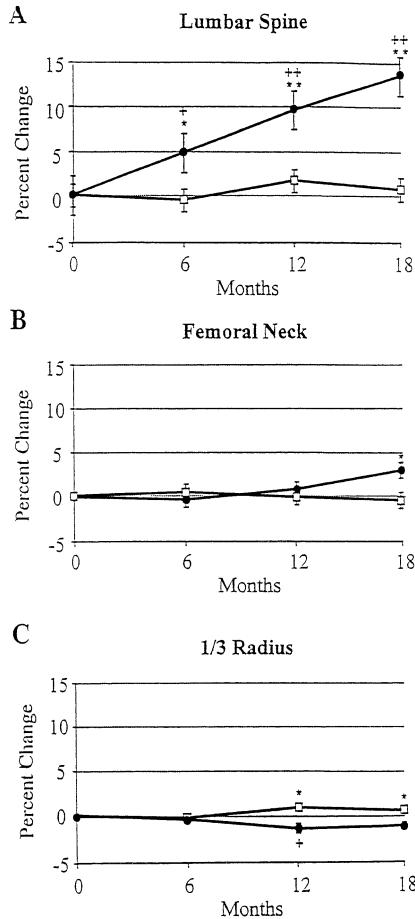


Fig. 2. Changes in bone density after PTH (1–34) treatment in men with idiopathic osteoporosis. Bone density at lumbar spine (A), femoral neck (B), and 1/3 site of the distal radius (C) in men receiving PTH (closed circle) and in control subjects (open square). The data are shown as percent changes from baseline \pm SEM for lumbar spine, FN, and 1/3 radius. * = $P < 0.05$ for repeated measures analysis of between-group comparisons. ** = $P < 0.005$ for repeated measures analysis of between-group comparisons. + = $P < 0.05$ for repeated measures analysis of within-group comparisons between baseline and 6, 12, or 18 months. ++ = $P < 0.005$ for repeated measures analysis of within-group comparisons between baseline and 6, 12, or 18 months. (From Kurland ES, Cosman F, McMahon D, et al. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. *J Clin Endocrinol Metab* 2000;85:3069–76; with permission.)

PTH [116]. When PTH was continued in an open-label design for an additional year, bone density increases were maintained, and bone turnover markers returned to baseline values [117].

The anabolic activity of PTH can perhaps also be understood in kinetic terms by changes in bone formation and bone resorption markers. Studies in which these markers have been tracked after PTH therapy indicate that bone formation markers rise rapidly, sometimes within 1 to 2 weeks. Delayed by perhaps as much as 3 months, bone resorption markers then begin to rise. There is a difference in the kinetics of change over the first 6 to 9 months of therapy with PTH. The difference in these kinetics suggests that bone formation is stimulated earlier than bone resorption. There is an anabolic “window” in the first 9 months of therapy, which is a period that best defines when PTH is maximally anabolic.

Histomorphometric analysis of eight treated men before and after 18 months of PTH made it possible to evaluate more directly the potential anabolic effects of PTH and any possible deleterious effects on the cortical skeleton. Using standard two-dimensional static and dynamic histomorphometry and three-dimensional microcomputed tomographic analysis in tetracycline-labeled samples, it was seen that not only were there quantitative improvements in cancellous bone indices but that there were major improvements in indices of connectivity [119]. Trabecular elements that were separated by short distances seemed to become connected or reconnected because the increase in connectivity density was associated with improvements in trabecular number and thickness. PTH therefore not only helped to remineralize the skeleton but also helped to reverse defects in trabecular microarchitecture. Equally important were the results at the cortical skeleton. Instead of an increase in cortical porosity, impressive increases in bone were apparent on the endocortical surface. The gains seemed to be based on positive bone balance during remodeling; a decrease in the eroded perimeter was consistent with a reduction in resorption at the endocortical surface [119].

A salutary effect at cortical bone was confirmed in other human subjects when postmenopausal osteoporotic women treated with PTH underwent peripheral quantitative computed tomography (pQCT) of the proximal radius [120]. Similar to the primate model, PTH treatment resulted in greater periosteal circumference and cortical area [120]. These differences resulted in greater polar and axial moments of inertia and torsional bone strength index, which are findings that predict increased biomechanical strength. The greater periosteal distribution of cortical bone, reflected in the moments of inertia, may contribute to the reduction in nonvertebral fractures that is not explained by changes in DXA in BMD alone. These observations help to substantiate the densitometric observations at a structural level, suggesting that PTH may be improving the skeleton in ways that are distinctly different from the anti-resorptives and may help to allay concerns that PTH may have adverse effects upon the cortical skeleton. Further studies are needed to confirm these points.

Most recently, results from a larger randomized, controlled trial of PTH in men have confirmed the findings of Kurland et al [115]. A total of 437 men with idiopathic or hypogonadal osteoporosis were randomized to placebo, hPTH (1–34) 20 µg daily, or 40 µg daily for a mean of 11 months [121]. At 12 months, BMD had increased significantly at the lumbar spine in the treatment groups by 6% and 9%, respectively, regardless of gonadal status. An even more important finding was the 50% reduction in vertebral fracture risk observed over an 18-month observational follow-up period after the discontinuation of PTH [122]. Twenty-two percent of the men continued on anti-resorptive treatment after PTH discontinuation, which may have helped to maintain gains caused by PTH.

These trials reinforce findings from earlier human trials and confirm that PTH administered intermittently is 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 more recent studies are reassuring and suggest that with adequate calcium and vitamin D, PTH has no effect or a modest positive action on cortical bone sites.

PTH in combination with another agent

PTH and estrogen

Combined therapy with PTH and estrogen was studied in a 3-year randomized, controlled trial of 52 postmenopausal osteoporotic women who were on hormone replacement therapy [123,124]. The group receiving PTH had significant increases in bone density: 13% at the spine (the greatest increase occurring during the first year of treatment), 4.4% at the hip, and 3.7% in the total body (Fig. 3). There was no evidence of cortical bone loss. PTH significantly reduced the percentage of women who had a vertebral fracture, based on a reduction in loss of vertebral height. Bone formation markers (osteocalcin) rose before bone resorption markers (N-telopeptide) during the first 6 months, followed by a return of both indices to baseline values within 2.5 years of initiation of treatment.

Iliac crest bone biopsy analysis of eight of the women treated with estrogen and PTH was performed [119]. Similar to the histomorphometric findings in the men treated with PTH, quantitative improvements in cancellous bone indices along with major improvements in indices of connectivity were found [119] (Fig. 4). At the cortical skeleton, the increases were even more impressive in the women, reaching statistical significance. The greater increase in cortical width in the women could be attributed to the longer duration of PTH treatment (36 months versus 18 months in the men) and perhaps to the additive effects of estrogen and PTH.

In another study, 74 postmenopausal women were randomized to receive 400 IU of PTH (1–34) or placebo while remaining on stable doses of conjugated equine estrogens [125]. There was a nearly 30% increase in spine

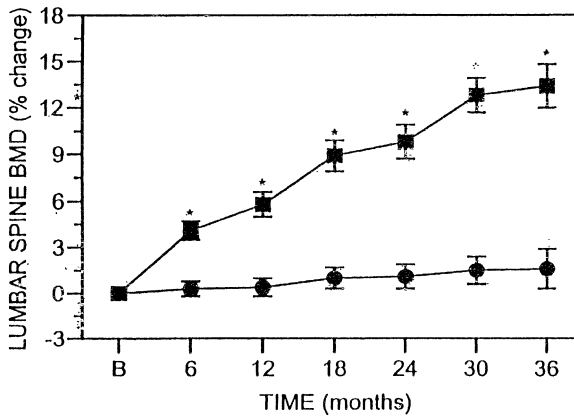


Fig. 3. The effect of PTH in women being treated with estrogen. Changes in lumbar spine bone mass when estrogen was given with (*closed squares*) or without (*closed circles*) PTH over 3 years to postmenopausal osteoporotic women. (From Cosman F, Nieves J, Woelfert L, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. *J Bone Miner Res* 2001;16: 925–31; with permission.)

BMD and an 11% increase in femoral BMD as measured by DXA among women receiving combination therapy compared with women on estrogen alone. The increase in vertebral BMD was even greater—close to 80%—when measured by QCT of the vertebrae.

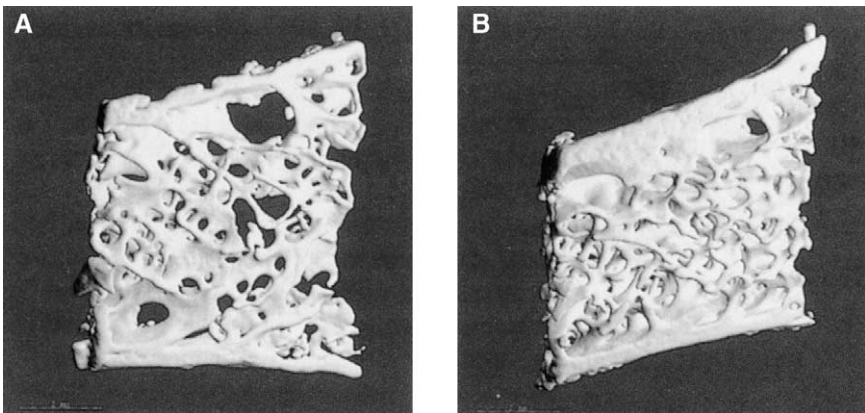


Fig. 4. Bone structure by scanning electron microscopy of bone biopsies before (A) and after (B) PTH treatment in one patient. Note the marked improvement in trabecular architecture and increase in cortical thickness after PTH treatment. (From Dempster DW, Cosman F, Kurland ES, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res* 2001;16:1846–53; with permission.)

PTH in glucocorticoid-induced osteoporosis

Glucocorticoid-induced osteoporosis is characterized by prolonged suppression of bone formation and transient increases in bone resorption. With a secondary increase in PTH considered by many no longer to be a major pathophysiologic component of glucocorticoid-induced osteoporosis, the use of PTH in combination with an anti-resorptive to treat glucocorticoid-induced osteoporosis is attractive. Lane et al conducted a 12-month, randomized, controlled trial of 51 postmenopausal women on hormone replacement therapy and glucocorticoids (>5 mg/d prednisone) who were randomized to hPTH (1–34) for 1 year or not (placebo injections were not used). In the PTH group, vertebral bone density increased 35% by QCT and 11% by DXA. The total hip bone density increased by 2% in the PTH group, whereas there was no difference in forearm BMD between groups. Bone markers showed an increase of bone formation in the first 3 months, whereas resorption peaked at 6 months [126]. This pattern is similar to that seen in an earlier study of PTH and estrogen [123] and is consistent with the recent histomorphometric observation that PTH treatment directly stimulates bone formation without previous resorption at cancellous and endocortical surfaces [127].

PTH and alendronate

The rationale for combination therapy with a bisphosphonate, as with alendronate, is to decrease the enlarged remodeling space created by PTH exposure and thus consolidate further gains in bone density and to prevent any decline. A randomized, controlled trial was performed to assess the effects of PTH followed by alendronate [111]. Sixty-six women with postmenopausal osteoporosis were treated for 1 year with placebo or varying doses of hPTH, followed by 1 year of alendronate for all subjects. After the year of alendronate treatment, those who had received the highest dose of PTH had spinal bone density increases of up to 14.6%. On the other hand, 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. It is unclear, however, how much of the bone density improvement occurred solely as a result of a continued anabolic effect after PTH withdrawal because there was no placebo group that did not receive alendronate. It is also not known whether 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 [128].

Withdrawal of parathyroid hormone

A powerful anabolic agent like parathyroid hormone might be expected to lead to certain consequences after therapy is withdrawn. Although there is concern that parathyroid hormone withdrawal without any subsequent therapy (ie, anti-resorptive) could lead to bone loss, another expectation might be that there could be even further increases in bone mass. First, reflections on surgical cure of primary hyperparathyroidism, a paradigm of parathyroid hormone withdrawal, are noteworthy. Parathyroidectomy for primary hyperparathyroidism leads to increases in lumbar spine and femoral neck bone density that can exceed 10% [129,130]. The increased bone density in the setting of parathyroidectomy may occur because of the postoperative remineralization that occurs in the enlarged bone remodeling space created by excess PTH [131]. Similarly, in patients treated with PTH, there is evidence that the new bone matrix is not fully mineralized because of the high rate of bone turnover [132]. A greater than normal amount of matrix is found at lower mineralization densities because of the higher amounts of newly formed bone that have not had time to undergo complete secondary mineralization. This provides an explanation for the observation that apparent bone density, as measured by DXA, increases after parathyroidectomy [129]. As the bone turnover rate is decreased, more time is available for secondary mineralization, resulting in an increase in apparent bone density. The technology of quantitative backscattered electron imaging will shed light on transformations at the level of bone mineralization [133].

The data are sparse in therapeutic regimens. Estrogenized postmenopausal women treated with PTH did not lose bone density 1 year after the PTH was withdrawn [124]. During this post-treatment year, their estrogen replacement continued, suggesting that the maintenance of BMD could have been due to the anti-resorptive effects of estrogen. Women on glucocorticoids and hormone replacement therapy treated with PTH had a maintenance in lumbar spine BMD and a 2% increase in total hip BMD 1 year after PTH was discontinued [134]. The withdrawal of PTH with the continued presence of an anti-resorptive seems to permit maintenance of the gains achieved by PTH therapy [129,131].

Nevertheless, it is possible for withdrawal of PTH to be associated with a reduction in bone mass if an anti-resorptive is not present. If this is the case, the rationale for using an anti-resorptive agent after a course of parathyroid hormone therapy would be evident. Preliminary data from Kurland et al support the concept that anti-resorptive therapy may be necessary to maintain gains due to PTH after its withdrawal [118]. Men who immediately began a bisphosphonate after PTH therapy had further increases of 3% in lumbar spine BMD, whereas those who did not take additional treatment lost as much as 6% of lumbar spine bone density over 2 years of follow-up. The results of further clinical trials to address these points are awaited [128].

Concerns about PTH

There are concerns about the use of PTH as an anabolic agent in osteoporosis. Along with the increase in cancellous bone mass, there is the fear of cortical bone loss, or a “cortical steal” phenomenon [135]. If cortical bone is lost, sites enriched in cortical bone could be placed in jeopardy for fracture. However, histomorphometric analysis of eight osteoporotic men treated with PTH for 18 months and eight osteoporotic women treated with PTH and estrogen therapy for 18 months demonstrated an anabolic effect in cortical bone. Cortical width was maintained in the men and was significantly increased in the women. There was no increase in cortical porosity. A distinct anabolic effect on cortical bone was observed at the endosteal surface, with significant increases in the width of bone packets. This was accompanied by a significant decrease in eroded perimeter on this surface in both groups. The positive effect of increased endocortical wall width and cortical thickness may have been enhanced by a reduction in resorption on that surface due to a marked decrease in eroded perimeter. Anabolic action may have additionally occurred at the subperiosteal surface, but it was not possible to assess the wall width of newly formed bone units there. A recent study in ovariectomized cynomolgus monkeys has shown that even when PTH administration increased intracortical porosity, there was no detrimental effect on the mechanical properties of bone [108]. The increased cortical porosity did not translate into decreased strength because it occurred in the inner one third of the bone where the mechanical effect was small and was offset by increases in cortical area and cortical thickness [108]. The consequent increase in cross-sectional diameter would be expected to increase bone strength.

This effect was recently confirmed in human subjects. Postmenopausal women treated with PTH underwent pQCT of the proximal radius to assess specific changes in cortical bone density that were undetectable by DXA [120]. Similar to the primate model, PTH treatment resulted in greater periosteal circumference and cortical area [120]. Recent data in PTH-treated mice suggest that the anabolic actions of PTH can occur at the long bones, possibly because they constitute areas of greater mechanical stress in mice [102]. These observations provide evidence that PTH is anabolic for cortical bone. Furthermore, fracture data from the study of Neer et al [112] indicate a substantial reduction in fractures of the nonvertebral skeleton. This would be unlikely if PTH were exerting a catabolic effect on cortical bone.

Long-term studies (18 to 24 months) with high-dose hPTH (1–34) administered to 6-week-old Fisher 344 rats have demonstrated an increased risk of osteogenic sarcoma. This effect, which is dose dependent, seems to be related to duration of use and is consistent with lifetime exposure in a growing rodent to an anabolic agent that increases osteoblast proliferation. There is uncertainty, however, about whether this toxicity study in a rodent model has relevance to human physiology. All primate studies 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 or from any of the 1- to 3-year clinical trials performed in over 2500 patients. Osteogenic sarcoma has also never been reported in parathyroid cancer, a disorder in which patients can survive for years with markedly elevated levels of PTH. Although further safety data are needed, it is reasonable to assume that PTH is safe in humans who are most likely to benefit (ie, postmenopausal women and men with clinical fractures and low BMD). The benefits of PTH are also likely to extend to individuals with established osteoporosis before fractures occur.

Summary

Anabolic agents represent an important new advance in the therapy of osteoporosis. Their potential might be substantially greater than the anti-resorptives. Because the anti-resorptives and anabolic agents work by completely distinct mechanisms of action, it is possible that the combination of agents could be significantly more potent than either agent alone. Recent evidence suggests that a plateau in BMD might occur after prolonged exposure to PTH [118]. Anti-resorptive therapy during or after anabolic therapy might prevent this skeletal adaptation. Protocols to consider anabolic agents as intermittent recycling therapy would be of interest.

Of all the anabolics, PTH is the most promising. However, there are unanswered questions about PTH. More studies are needed to document an anabolic effect on cortical bone. More large-scale studies are needed to further determine the reduction in nonvertebral fractures with PTH, especially at the hip. In the future, PTH is likely to be modified for easier and more targeted delivery. Oral or transdermal delivery systems may become available. Recently, Gowen et al have described an oral calcilytic molecule that antagonizes the parathyroid cell calcium receptor, thus stimulating the endogenous release of PTH [136]. This approach could represent a novel endogenous delivery system for intermittent PTH administration. Rising expectations that anabolic therapies for osteoporosis will soon play a major role in treating this disease are likely to fuel further studies and the development of even more novel approaches to therapy.

References

- [1] Lindsay R, Cosman F. The pharmacology of estrogens in osteoporosis. In: Bilezikian JP, Raisz LG, Rodan GA, editors. *Principles of bone biology*. San Diego: Academic Press; 1996. p. 1063–8.
- [2] Fleisch H. Bisphosphonates: mechanisms of action and clinical use. In: Bilezikian JP, Raisz LG, Rodan GA, editors. *Principles of bone biology*. San Diego: Academic Press; 1996. p. 1037–52.

- [3] Azria M, Avioli L. Calcitonin. In: Bilezikian JP, Raisz LG, Rodan GA, editors. *Principles of bone biology*. San Diego: Academic Press; 1996. p. 1083–98.
- [4] Fogelman I, Ribot C, Smith R, et al. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. *J Clin Endocrinol Metab* 2000;85:1895–900.
- [5] Rosen CJ, Chesnut CH III, Mallinak NJ. The predictive value of biochemical markers of bone turnover for bone mineral density in early postmenopausal women treated with hormone replacement or calcium supplementation. *J Clin Endocrinol Metab* 1997;82:1904–10.
- [6] Greenspan SL, Parker RA, Ferguson L, et al. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. *J Bone Miner Res* 1998;13:1431–8.
- [7] The Writing Group for the PEPI. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. *JAMA* 1996;276:1389–96.
- [8] Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 1995;333:1437–43.
- [9] Riggs BL, Hodgson SF, O’Fallon WM, et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med* 1990;322:802–9.
- [10] Kleerekoper M, Peterson EL, Nelson DA, et al. A randomized trial of sodium fluoride as a treatment for postmenopausal osteoporosis. *Osteoporos Int* 1991;1:155–61.
- [11] Pak CY, Sakhaee K, Zerwekh JE. Safe and effective treatment of osteoporosis with intermittent slow release sodium fluoride: augmentation of vertebral bone mass and inhibition of fractures. *J Clin Endocrinol Metab* 1989;68:150–9.
- [12] Pak CY, Sakhaee K, Adams-Huet B, et al. Treatment of postmenopausal osteoporosis with slow-release sodium fluoride: final report of a randomized controlled trial. *Ann Intern Med* 1995;123:401–8.
- [13] Pak CY, Zerwekh JE, Antich PP, et al. Slow-release sodium fluoride in osteoporosis. *J Bone Miner Res* 1996;11:561–4.
- [14] Riggs BL, O’Fallon WM, Lane A, et al. Clinical trial of fluoride therapy in postmenopausal osteoporotic women: extended observations and additional analysis. *J Bone Miner Res* 1994;9:265–75.
- [15] Ringe JD. What is proven about hip fracture and fluoride treatment? *Osteologie* 1998;7:151–6.
- [16] Peiche P, Zamani O, Kupman W. Antiosteoporotic therapy with monofluorophosphate and calcium increases cortical and trabecular bone density. *Osteologie* 1995;4:87–98.
- [17] Ringe JD, Kipshoven C, Coster A, et al. Therapy of established postmenopausal osteoporosis with monofluorophosphate plus calcium: dose-related effects on bone density and fracture rate. *Osteoporos Int* 1999;9:171–8.
- [18] Reginster JY, Meurmans L, Zegels B, et al. The effect of sodium monofluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis: a randomized, controlled trial. *Ann Intern Med* 1998;129:1–8.
- [19] Ringe JD, Dorst A, Kipshoven C, et al. Avoidance of vertebral fractures in men with idiopathic osteoporosis by a three year therapy with calcium and low-dose intermittent monofluorophosphate. *Osteoporos Int* 1998;8:47–52.
- [20] Alexandersen P, Riis BJ, Christiansen C. Monofluorophosphate combined with hormone replacement therapy induces a synergistic effect on bone mass by dissociating bone formation and resorption in postmenopausal women: a randomized study. *J Clin Endocrinol Metab* 1999;84:3013–20.
- [21] Ringe JD, Rovati LC. Treatment of osteoporosis in men with fluoride alone or in combination with bisphosphonates. *Calcif Tissue Int* 2001;69:252–5.

- [22] Donahue L, Rosen CJ. IGFs and bone: the osteoporosis connection revisited. *Proc Soc Exp Biol Med* 1998;219:1–7.
- [23] Sugimoto T, Nishiyama K, Kuribayashi F, et al. Serum levels of insulin-like growth factor (IGF) I, IGF-binding protein (IGFBP)-2, and IGFBP-3 in osteoporotic patients with and without spinal fractures. *J Bone Miner Res* 1997;12:1272–9.
- [24] Bauer DC, Rosen CJ, Cauley J, et al. Low serum IGF-1 but not IGFBP-3 predicts hip and spine fracture: the study of osteoporotic fracture. *J Bone Miner Res* 1998;23:S561.
- [25] Rudman D, Feller AG, Nagraj HS, et al. Effects of human growth hormone in men over 60 years old. *N Engl J Med* 1990;323:1–6.
- [26] Holloway L, Butterfield G, Hintz RL, et al. Effects of recombinant human growth hormone on metabolic indices, body composition, and bone turnover in healthy elderly women. *J Clin Endocrinol Metab* 1994;79:470–9.
- [27] Rosen CJ, Friez J, MacLean D, et al. The RIGHT study: a randomized placebo controlled trial of recombinant human growth hormone in frail elderly: dose response effects on bone mass and bone turnover. *J Bone Miner Res* 1999;14:S208.
- [28] Landin-Wilhelmsen KLL, Nilsson A. Growth hormone increases bone mineral content in postmenopausal osteoporosis. *J Bone Miner Res* 2001;16(Suppl 1):F404.
- [29] Ghiron LJ, Thompson JL, Holloway L, et al. Effects of recombinant insulin-like growth factor-I and growth hormone on bone turnover in elderly women. *J Bone Miner Res* 1995;10:1844–52.
- [30] Grinspoon S, Baum H, Lee K, et al. Effects of short-term recombinant human insulin-like growth factor I administration on bone turnover in osteopenic women with anorexia nervosa. *J Clin Endocrinol Metab* 1996;81:3864–70.
- [31] Geusens P, Bouillon R, Broos P. Musculoskeletal effects of rhIGF-I/IGFBP-3 in hip fracture patients: results from a double-blind, placebo controlled phase II study. *Bone* 1998;23:S157.
- [32] Johnson AR, Armstrong WD, Singer L. The incorporation and removal of large amounts of strontium by physiologic mechanisms in mineralized tissues. *Calcif Tissue Res* 1968;2:242–52.
- [33] Li L, Kruszewski FH, Punnonen K, et al. Strontium induces murine keratinocyte differentiation in vitro in the presence of serum and calcium. *J Cell Physiol* 1993;154:643–53.
- [34] Quarles LD. Cation sensing receptors in bone: a novel paradigm for regulating bone remodeling? *J Bone Miner Res* 1997;12:1971–4.
- [35] Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. *Physiol Rev* 2001;81:239–97.
- [36] Coulombe J, Faure H, Robin B, et al. Activation of the rat and mouse cation-sensing receptor by strontium ranelate and its modulation by extracellular calcium. *Osteoporos Int* 2002;13(Suppl 1):S25.
- [37] Arlot ME, Roux JP, Boivin G. Effects of strontium salt (S 12911) in both tibial metaphysis and epiphyses in normal growing rats. *J Bone Miner Res* 1995;10(Suppl 1):M415.
- [38] Marie PJ, Hott M, Modrowski D, et al. An uncoupling agent containing strontium prevents bone loss by depressing bone resorption and maintaining bone formation in estrogen-deficient rats. *J Bone Miner Res* 1993;8:607–15.
- [39] Morohashi T, Sano T, Yamada S. Effects of strontium on calcium metabolism in rats: I. A distinction between the pharmacological and toxic doses. *Jpn J Pharmacol* 1994;64:155–62.
- [40] Delannoy P, Bazot D, Robin B, et al. A 104-week treatment with strontium ranelate increases vertebral bone mass without deleterious effects in mice. *Osteoporos Int* 2002;13(Suppl 1):S26.
- [41] Boivin G, Farlay D, Panczer G, et al. Long-term strontium ranelate administration in monkeys: effects on mineral crystals and on the degree of mineralization of bone. *J Bone Miner Res* 2001;16(Suppl 1):SA401.

- [42] Ammann P, Shen V, Robin B, et al. Long-term exposure to strontium ranelate dose-dependently increases bone strength in intact male and female rats. *Osteoporos Int* 2002;13(Suppl 1):S24.
- [43] Meunier PJ, Slosman DO, Delmas PD, et al. The strontium salt S-12911: a new candidate for the treatment of osteoporosis. *Osteoporos Int* 1996;6(Suppl 1):241.
- [44] Meunier PJ, Slosman DO, Delmas PD, et al. Strontium ranelate as a treatment of vertebral osteoporosis. *J Bone Miner Res* 1997;12(Suppl 1):129.
- [45] Reginster JY, Roux C, Tsouderos Y, et al. Role of strontium ranelate in prevention of early postmenopausal bone loss: a double-blind, prospective, randomised, placebo-controlled study. *Arthritis Rheum* 1998;41(Suppl):580.
- [46] Reginster JY, Roux C, Juspin I, et al. Strontium ranelate for the prevention of bone loss of early postmenopause. *Osteoporos Int* 1998;8(Suppl 3):12.
- [47] Reginster JY, Roux C, Juspin I, et al. Safety of strontium ranelate in prevention of postmenopausal bone loss- a double-blind, prospective, placebo-controlled study. *J Bone Miner Res* 1999;14(Suppl):S129.
- [48] Reginster JY, Deroisy R, Tsouderos Y, et al. Prevention of early postmenopausal bone loss by strontium ranelate: a randomized two-year double-blind placebo-controlled trial. *J Bone Miner Res* 2001;16(Suppl 1):F400.
- [49] Boivin G, Schenker E, Tupinon-Mathieu I. Uptake and distribution of strontium in human bone evolution of the degree of mineralisation after strontium ranelate administration. *J Bone Miner Res* 1999;14(Suppl 1):284.
- [50] Meunier PJ, Slosman DO, Delmas PD, et al. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis: a 2-year randomized placebo controlled trial. *J Clin Endocrinol Metab* 2002;87:2060–6.
- [51] Cranney A, Guyatt G, Krolicki N, et al. A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis. *Osteoporos Int* 2001;12:140–51.
- [52] Lees B, Stevenson JC. The prevention of osteoporosis using sequential low-dose hormone replacement therapy with estradiol-17 beta and dydrogesterone. *Osteoporos Int* 2001; 12:251–8.
- [53] Meunier PJ, Roux C, Ortolani S, et al. Strontium ranelate reduces the vertebral fracture risk in women with postmenopausal osteoporosis. *Osteoporos Int* 2002;13(Suppl 1):45.
- [54] Chung YS, Lee MD, Lee SK, et al. HMG-CoA reductase inhibitors increase BMD in type 2 diabetes mellitus patients. *J Clin Endocrinol Metab* 2000;85:1137–42.
- [55] Edwards CJ, Hart DJ, Spector TD. Oral statins and increased bone-mineral density in postmenopausal women. *Lancet* 2000;355:2218–9.
- [56] Chan KA, Andrade SE, Boles M, et al. Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. *Lancet* 2000;355:2185–8.
- [57] Meier CR, Schlienger RG, Kraenzlin ME, et al. HMG-CoA reductase inhibitors and the risk of fractures. *JAMA* 2000;283:3205–10.
- [58] Wang PS, Solomon DH, Mogun H, et al. HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA* 2000;283:3211–6.
- [59] Pasco JA, Kotowicz MA, Henry MJ, et al. Statin use, bone mineral density, and fracture risk: Geelong Osteoporosis Study. *Arch Intern Med* 2002;162:537–40.
- [60] Mundy G, Garrett R, Harris S, et al. Stimulation of bone formation in vitro and in rodents by statins. *Science* 1999;286:1946–9.
- [61] Garrett IR, Gutierrez G, Chen D. Statins stimulate bone formation by enhancing eNOS expression. *J Bone Miner Res* 2001;16(Suppl 1):1018.
- [62] Coxon FP, Benford HL, Russell RG, et al. Protein synthesis is required for caspase activation and induction of apoptosis by bisphosphonate drugs. *Mol Pharmacol* 1998; 54:631–8.
- [63] Sugiyama M, Kodama T, Konishi K, et al. Compactin and simvastatin, but not pravastatin, induce bone morphogenetic protein-2 in human osteosarcoma cells. *Biochem Biophys Res Commun* 2000;271:688–92.

- [64] Maeda T, Matsunuma A, Kawane T, et al. Simvastatin promotes osteoblast differentiation and mineralization in MC3T3–E1 cells. *Biochem Biophys Res Commun* 2001;280: 874–7.
- [65] Crawford DT, Qi H, Chidsey-Frink KL, et al. Statin increases cortical bone in young male rats by single local administration but fails to restore bone in ovariectomized rats by daily systemic administration. *J Bone Miner Res* 2001;16(Suppl 1):SA410.
- [66] Chan MH, Mak TW, Chiu RW, et al. Simvastatin increases serum osteocalcin concentration in patients treated for hypercholesterolaemia. *J Clin Endocrinol Metab* 2001;86:4556–9.
- [67] Luckman SP, Hughes DE, Coxon FP, et al. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res* 1998;13:581–9.
- [68] Fisher JE, Rogers MJ, Halasy JM, et al. Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation in vitro. *Proc Natl Acad Sci USA* 1999;96:133–8.
- [69] Baumann AP, Grasser W, Petras S, et al. Inhibition of osteoclast formation by statins. *J Bone Miner Res* 2001;16(Suppl 1):M309.
- [70] Frith JC, Armour KJ, Feyen JHM, et al. Statins inhibit protein prenylation in osteoclasts in vivo. *J Bone Miner Res* 2001;16(Suppl 1):M313.
- [71] Rejnmark L, Buus NH, Vestergaard P, et al. Decreased bone turnover in postmenopausal women treated with statins: a cross-sectional study. *J Bone Miner Res* 2001;16(Suppl 1): SA411.
- [72] Salbach P, Kreuzer J, Seibel MJH. Short-term administration with atorvastatin does not change bone turnover in patients with hypercholesterolemia: a randomized controlled study. *J Bone Miner Res* 2001;16(Suppl 1):SA409.
- [73] Cosman F, Nieves J, Zion M, et al. Effects of short-term cerivastatin on bone turnover. *J Bone Miner Res* 2001;16(Suppl 1):SA415.
- [74] Braga V, Gatti D, Rossini M, et al. Association between lipid profile and bone mass in healthy men. *J Bone Miner Res* 2001;16(Suppl 1):F307.
- [75] Solomon DH, Finkelstein JS, Wang PS, et al. Statin lipid-lowering drugs and bone density. *J Bone Miner Res* 2001;16(Suppl 1):SA399.
- [76] Reid IR, Hague W, Emberson J, et al. Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomized controlled trial: long-term intervention with pravastatin in ischaemic disease. *Lancet* 2001;357:509–12.
- [77] van Staa TP, Wegman S, de Vries F, et al. Use of statins and risk of fractures. *JAMA* 2001;285:1850–5.
- [78] LaCroix AZ, Cauley J, Jackson R, et al. Does statin use reduce risk of fracture in postmenopausal women? Results from the Women's Health Initiative Observational Study (WHI-OS). *J Bone Miner Res* 2000;15(Suppl 1):1066.
- [79] Kloosterboer HJ, Sands R. Intracrinology: the secret of the tissue-specificity of tibolone. *J Brit Menopause Soc* 2000;6(Suppl 2):23–7.
- [80] Berning B, Kuijk CV, Kuiper JW, et al. Effects of two doses of tibolone on trabecular and cortical bone loss in early postmenopausal women: a two-year randomized, placebo-controlled study. *Bone* 1996;19:395–9.
- [81] Bjarnason NH, Bjarnason K, Haarbo J, et al. Tibolone: prevention of bone loss in late postmenopausal women. *J Clin Endocrinol Metab* 1996;81:2419–22.
- [82] Bjarnason NH, Bjarnason K, Hassager C, et al. The response in spinal bone mass to tibolone treatment is related to bone turnover in elderly women. *Bone* 1997;20: 151–5.
- [83] Lindsay R, Hart DM, Kraszewski A. Prospective double-blind trial of synthetic steroid (Org OD 14) for preventing postmenopausal osteoporosis. *Br Med J* 1980;280: 1207–9.

- [84] Geusens P, Dequeker J, Gielen J, et al. Non-linear increase in vertebral density induced by a synthetic steroid (Org OD 14) in women with established osteoporosis. *Maturitas* 1991; 13:155–62.
- [85] Gallagher JC, Baylink DJ, Freeman R, et al. Prevention of bone loss with tibolone in postmenopausal women: results of two randomized, double-blind, placebo-controlled, dose-finding studies. *J Clin Endocrinol Metab* 2001;86:4717–26.
- [86] Netelenbos JC, Siregar-Emck MT, Schot LP, et al. Short-term effects of Org OD 14 and 17 beta-oestradiol on bone and lipid metabolism in early post-menopausal women. *Maturitas* 1991;13:137–49.
- [87] Kloosterboer HJ. Tibolone: a steroid with a tissue-specific mode of action. *J Steroid Biochem Mol Biol* 2001;76:231–8.
- [88] Gambacciani M, Ciaponi M. Postmenopausal osteoporosis management. *Curr Opin Obstet Gynecol* 2000;12:189–97.
- [89] Ederveen AGH, Kloosterboer HJ. The protective effect of tibolone on ovariectomy-induced bone loss is blocked by an anti-estrogen. Presented at The First Amsterdam Menopause Symposium. Amsterdam, The Netherlands, 1998.
- [90] Albright F, Aub JC, Bauer W. Hyperparathyroidism: a common and polymorphic condition as illustrated by seventeen proven cases from one clinic. *JAMA* 1934;102:1276–87.
- [91] Albright F, Reifenstein EC. The parathyroid glands and metabolic bone disease. Baltimore: Williams & Wilkins; 1948.
- [92] Kronenberg HM. PTH: mechanism of action. In: Favus M, editor. *Primer on metabolic bone diseases*. Philadelphia: Lippincott Williams & Wilkins; 1996. p. 68–70.
- [93] Morley P, Whitfield JF, Willick GE. Anabolic effects of PTH on bone. *Trends Endocrinol Metab* 1997;8:225–31.
- [94] Abou-Samra AB, Jueppner H, Westerberg D, et al. Parathyroid hormone causes translocation of protein kinase-C from cytosol to membranes in rat osteosarcoma cells. *Endocrinology* 1989;124:1107–13.
- [95] Goltzman D. Interactions of PTH and PTHrP with the PTH/PTHrP receptor and with downstream signaling pathways: exceptions that provide the rules [editorial]. *J Bone Miner Res* 1999;14:173–7.
- [96] Canalis E, Centrella M, Burch W, et al. Insulin-like growth factor I mediates selective anabolic effects of parathyroid hormone in bone cultures. *J Clin Invest* 1989;83:60–5.
- [97] Hock JM, Gera I, Fonseca J, et al. Human parathyroid hormone-(1–34) increases bone mass in ovariectomized and orchidectomized rats. *Endocrinology* 1988;122:2899–904.
- [98] Hodsmann AB, Fraher LJ, Watson PH. Parathyroid hormone. In: Rosen CJ, Glowacki J, Bilezikian JP, editors. *The aging skeleton*. San Diego: Academic Press; 1999. p. 563–78.
- [99] Linkhart TA, Mohan S. Parathyroid hormone stimulates release of insulin-like growth factor-I (IGF-I) and IGF-II from neonatal mouse calvaria in organ culture. *Endocrinology* 1989;125:1484–91.
- [100] Watson PH, Lazowski DA, Han V, et al. PTH restores bone mass and enhances osteoblast IGF-1 gene expression in ovariectomized rats. *Bone* 1995;16:1–9.
- [101] Onyia JE, Gelbert L, Zhang M, et al. Analysis of gene expression by DNA microarray reveals novel clues to the mechanism of the catabolic and anabolic actions of PTH in bone. Presented at the 23rd Annual Meeting of the ASBMR. 2001.
- [102] Iida-Klein A, Zhou H, Lu SS, et al. Anabolic action of parathyroid hormone is skeletal site specific at the tissue and cellular levels in mice. *J Bone Miner Res* 2001;16(Suppl 1): F482.
- [103] Jilka RL, Weinstein RS, Bellido T, et al. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. *J Clin Invest* 1999;104:439–46.
- [104] Ma YL, Cain RL, Halladay DL, et al. Catabolic effects of continuous human PTH (1–38) in vivo is associated with sustained stimulation of RANKL and inhibition of osteoprotegerin and gene-associated bone formation. *Endocrinology* 2001;142: 4047–54.

- [105] Locklin RM, Khosla S, Riggs BL. Mechanisms of biphasic anabolic and catabolic effects of parathyroid hormone (PTH) on bone cells. *Bone* 2001;28:s80.
- [106] Baumann BD, Wronski TJ. Response of cortical bone to antiresorptive agents and parathyroid hormone in aged ovariectomized rats. *Bone* 1995;16:247–53.
- [107] Cheng PT, Chan C, Muller K. Cyclical treatment of osteopenic ovariectomized adult rats with PTH (1–34) and pamidronate. *J Bone Miner Res* 1995;10:119–26.
- [108] Burr DB, Hirano T, Turner CH, et al. Intermittently administered human parathyroid hormone (1–34) treatment increases intracortical bone turnover and porosity without reducing bone strength in the humerus of ovariectomized cynomolgus monkeys. *J Bone Miner Res* 2001;16:157–65.
- [109] Kneissel M, Boyde A, Gasser JA. Bone tissue and its mineralization in aged estrogen-depleted rats after long-term intermittent treatment with parathyroid hormone (PTH) analog SDZ PTS 893 or human PTH (1–34). *Bone* 2001;28:237–50.
- [110] Lindsay R, Hodsman AB, Genant HK, et al. A randomized controlled multi-center study of 1–84hPTH for treatment of postmenopausal osteoporosis [abstract]. *Bone* 1998;23(Suppl 1):S175.
- [111] Rittmaster RS, Bolognese M, Ettinger MP, et al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab* 2000;85:2129–34.
- [112] Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434–41.
- [113] Kurland ES, Rosen CJ, Cosman F, et al. Insulin-like growth factor-I in men with idiopathic osteoporosis. *J Clin Endocrinol Metab* 1997;82:2799–805.
- [114] Johansson AG, Eriksen EF, Lindh E, et al. Reduced serum levels of the growth hormone-dependent insulin-like growth factor binding protein and a negative bone balance at the level of individual remodeling units in idiopathic osteoporosis in men. *J Clin Endocrinol Metab* 1997;82:2795–8.
- [115] Kurland ES, Cosman F, McMahon D, et al. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. *J Clin Endocrinol Metab* 2000;85:3069–76.
- [116] Kurland E, Cosman F, McMahon DJ, et al. Changes in bone markers predict bone accrual in osteoporotic men treated with parathyroid hormone [abstract]. *Bone* 1998;23(Suppl 5):S158.
- [117] Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effect on bone mineral density and bone markers. *J Clin Endocrinol Metab* 2000;85(9):3069–76.
- [118] Kurland ES, Heller SL, Cosman F. The post-PTH experience in men with idiopathic osteoporosis: bisphosphonates vs. non-pharmacologic therapy. *J Bone Miner Res* 2001; 16(Suppl 1):F363.
- [119] Dempster DW, Cosman F, Kurland ES, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res* 2001;16:1846–53.
- [120] Zanchetta JR, Bogado C, Ferretti JL, et al. Effects of LY333334 [recombinant parathyroid hormone (1–34)] on cortical bone strength indices as assessed by peripheral quantitative computed tomography [abstract]. Presented at the 1st Joint Meeting of the International Bone and Mineral Society and the European Society for Calcified Tissue. Madrid 2001:OR66.
- [121] Orwoll E, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 2003;18(1):9–17.
- [122] Orwoll E, Scheele WH, Clancy AD, et al. Recombinant human parathyroid hormone (1–34) therapy reduces the incidence of moderate/severe vertebral fractures in men with low bone density. *J Bone Miner Res* 2001;16(Suppl 1):1104.

- [123] Lindsay R, Nieves J, Formica C, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet* 1997;350:550–5.
- [124] Cosman F, Nieves J, Woelfert L, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. *J Bone Miner Res* 2001;16:925–31.
- [125] Roe E, Sanchez S, del Puerto G, et al. Parathyroid hormone 1–34 (hPTH 1–34) and estrogen produce dramatic bone density increases in postmenopausal osteoporosis: results from a placebo-controlled randomized trial. *J Bone Miner Res* 1999;14(Suppl 1):S137.
- [126] Lane NE, Sanchez S, Modin GW, et al. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis: results of a randomized controlled clinical trial. *J Clin Invest* 1998;102:1627–33.
- [127] Dempster D, Zhou H, Cosman F, et al. PTH treatment directly stimulates bone formation in cancellous and cortical bone in humans. *J Bone Miner Res* 2001;16(Suppl 1):1171.
- [128] Black DM, Rosen CJ, Greenspan SL, et al. PTH and bisphosphonates in the treatment of osteoporosis: design of the PTH and alendronate (PaTH) trial. *J Bone Miner Res* 2001;16(Suppl 1):SA365.
- [129] Silverberg SJ, Shane E, Jacobs TP, et al. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. [published erratum appears in *N Engl J Med* 2000;342:144]. *N Engl J Med* 1999;341:1249–55.
- [130] Nakaoka D, Sugimoto T, Kobayashi T, et al. Prediction of bone mass change after parathyroidectomy in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2000;85:1901–7.
- [131] Christiansen P, Steiniche T, Mosekilde L, et al. Primary hyperparathyroidism: changes in trabecular bone remodeling following surgical treatment—evaluated by histomorphometric methods. *Bone* 1990;11:75–9.
- [132] Roschger P, Grabner BM, Messer P, et al. Influence of intermittent PTH treatment on mineral distribution in the human ilium: a paired biopsy study before and after treatment. *J Bone Miner Res* 2001;16(Suppl 1):S179.
- [133] Boivin GY, Chavassieux PM, Santora AC, et al. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. *Bone* 2000;27:687–94.
- [134] Lane NE, Sanchez S, Modin GW, et al. Bone mass continues to increase at the hip after parathyroid hormone treatment is discontinued in glucocorticoid-induced osteoporosis: results of a randomized controlled clinical trial. *J Bone Miner Res* 2000;15:944–51.
- [135] Horwitz M, Stewart A, Greenspan SL. Sequential parathyroid hormone/alendronate therapy for osteoporosis—robbing Peter to pay Paul? [editorial]. *J Clin Endocrinol Metab* 2000;85:2127–8.
- [136] Gowen M, Stroup GB, Dodds RA, et al. Antagonizing the parathyroid calcium receptor stimulates parathyroid hormone secretion and bone formation in osteopenic rats. *J Clin Invest* 2000;105:1595–604.
- [137] Garrett JE, Capuano IV, Hammerland LG, Huag BC, Brown EM, Hebert SC, et al. Molecular cloning and functional expression of human parathyroid calcium receptor cDNAs. *J Bio Chem* 1995;270(21):12919–25.