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Review Article

The Anabolic Effects of Parathyroid Hormone

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Introduction

Several generations ago, the catabolic effects of parathyroid hormone (PTH) on the skeleton gave rise to the description of primary hyperparathyroidism as a disease of 'bones, stones and groans' [1,2]. The skeleton is still universally affected in severe primary hyperparathyroidism. Classical radiographic features include degranulation of the skull (so-called salt and pepper appearance), distal tapering of the clavicles, subperiosteal bone resorption of the phalanges, brown tumors and bone cysts. Both cancellous and cortical elements of the skeleton are affected with the spine (primarily cancellous bone) and the distal radius (primarily cortical bone) showing such catabolic consequences. It is this classic presentation of primary hyperparathyroidism that has given rise to the idea that PTH is bad for bones. In this review we will summarize information from an increasingly compelling set of animal and human data indicating that under certain circumstances, PTH is good for bones.

Primary Hyperparathyroidism: Clues to the Anabolic Potential of PTH

Since the advent of the multichannel autoanalyzer in the early 1970s, primary hyperparathyroidism has presented typically in a milder form, often without clinical manifestations of overt bone disease. In fact, the overwhelming majority of patients with primary hyperparathyroidism, in countries where multichannel biochemical screening is routine, have no evidence radiologically for bone disease. In the series of Silverberg et al. [3], fewer than 2% of patients with primary hyperparathyroidism could be shown to have specific manifestations of hyperparathyroid bone disease by conventional radiographic examination. With this different but now common presentation of primary hyperparathyroidism, namely as an asymptomatic disorder, it has been possible to address a far more subtle but critically important question: do patients with asymptomatic primary hyperparathyroidism have evidence for skeletal involvement? By dual-energy X-ray absorptiometry (DXA), Silverberg et al. [3] have provided evidence for skeletal involvement in a manner that speaks to the dual actions of PTH as an anabolic and catabolic hormone. In the cancellous skeleton, bone mass is relatively well preserved, with only small reductions from age- and sex-specific norms [4]. In the predominantly cortical skeleton, however, it is typical to detect substantial bone loss in the forearm [3,5]. Bone mineral density of the hip region, which contains a more even admixture of cortical and cancellous elements, is intermediate between that of the cancellous and cortical sites.

The patterns of bone loss in postmenopausal women with primary hyperparathyroidism give further proof for the anabolic potential of PTH. Preferential cancellous bone loss might be expected in estrogen-deficient women because this site is the most sensitive to the sex steroids. However, postmenopausal women with primary hyperparathyroidism show the same pattern of bone loss as the entire cohort of patients with primary hyperparathyroidism, in which cancellous bone is relatively well maintained. If postmenopausal women

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with mild primary hyperparathyroidism are generally well protected from lumbar spine bone loss due to estrogen deficiency, the inference is clear: PTH is acting to protect the cancellous skeleton from the potential negative effects of estrogen withdrawal.

Histomorphometric studies of the iliac crest in primary hyperparathyroidism have confirmed that the anabolic effects of PTH predominate in the cancellous skeleton [6–8]. When women with primary hyperparathyroidism are compared with normal age-matched women, cancellous bone volume is the same or greater in the women with primary hyperparathyroidism [8]. Compared to women with postmenopausal osteoporosis, cancellous bone volume is greater in hyperparathyroid subjects. With aging, bone loses its microarchitectural integrity as trabecular struts become thin and disconnected from each other. In primary hyperparathyroidism, cross-sectional data indicate that trabeculae may thin, but they do not break nor does trabecular separation increase [9,10]. Trabecular strut analysis reveals greater than normal trabecular number and plate connectivity in the iliac crest biopsies of patients with primary hyperparathyroidism. The anabolic effect of excess PTH is in marked contrast to the decreased bone remodeling and turnover observed in states of deficient PTH, namely hypoparathyroidism [11].

These observations suggest that patients with primary hyperparathyroidism should not be at risk for fractures of the axial skeleton where bone mass is relatively well preserved, whereas they might be expected to show an increase in fracture incidence of the appendicular skeleton where bone mass is preferentially reduced. There are few good epidemiologic studies to confirm this expectation [12–14]. Anecdotally, it is noteworthy that vertebral crush fractures are most unusual in primary hyperparathyroidism [15]. Khosla et al. [16] have provided data that both support and conflict with this idea. On the one hand, they confirm an increase in forearm (cortical) fracture incidence in primary hyperparathyroidism. But they also show that vertebral fracture incidence is increased. The latter observation could be due to surveillance bias since these patients may be more likely to have had vertebral spine radiographs after back pain, giving rise to more frequent detection of fractures. The former observation, namely an increase in forearm fracture incidence, is unlikely to be due to surveillance bias since the forearm fracture is a discrete clinical event. These observations are therefore consistent with an increase in fracture incidence at cortical sites in primary hyperparathyroidism.

In primary hyperparathyroidism, therefore, clinical, densitometric, epidemiologic and histomorphometric data suggest that PTH, in a disease process associated with hypercalcemia and elevated concentrations of PTH, helps to protect the cancellous skeleton. If PTH were to be administered in a dosage that does not cause hypercalcemia and also magnifies its anabolic effects, the potential for an efficacious anabolic agent would be realized.

PTH as an Anabolic Therapy for Osteoporosis

All currently approved therapies for osteoporosis in the United States are antiresorptive in mechanism, acting primarily to inhibit osteoclast-mediated bone loss. In this way, estrogen, raloxifene, alendronate, risedronate and calcitonin all reduce bone turnover [17–20], as demonstrated by reduced markers of bone formation and resorption [21,22]. These antiresorptive drugs may be associated with an increase in bone density by reducing the remodeling space and by prolonging the duration of mineralization. The increase is typically less than 10% over 3 years [23,24]. They are generally effective in reducing fracture risk, particularly in the spine, but for alendronate and risedronate at the hip also.

The concept of an anabolic agent is based upon a physiologic process entirely different from inhibition of bone resorption, namely stimulation of bone formation. Inherent in this concept is the potential for an anabolic agent, such as PTH, to increase bone mass to a far greater extent than antiresorptives. The potential of anabolic agents to improve bone density more substantially than antiresorptives, in addition, suggests that they might reduce fracture risk to a greater extent than the antiresorptives.

Mechanisms of PTH's Anabolic Actions

The rationale for considering PTH as an anabolic agent for osteoporosis comes from the clinical observations in primary hyperparathyroidism, reviewed above, and a voluminous animal literature [4] that can be traced remarkably to observations made over 70 years ago [25]. Most human [26,27] and animal [28,29] studies favor the use of low-dose, intermittent PTH administration, as compared with protocols associated with chronically elevated levels, to maximize anabolic and to minimize catabolic potential. It is unclear why continuous PTH secretion elicits a different response in the skeleton from intermittent PTH administration, but the observations have been exploited in recent therapeutic protocols with PTH (see below). A few possible mechanisms to account for these differential effects on cortical and cancellous bone are summarized here.

Since PTH binds to more than one receptor [30–32], it is possible that different receptors mediate the anabolic and catabolic responses [33]. Another idea is that fragments of PTH harbor different activities at bone sites. Yet another hypothesis is that two distinct second messenger systems each directing different responses are activated by PTH [34]. It is noteworthy that PTH acts through dual signaling pathways in bone cells, with the osteoblast being the principal cellular target. In the osteoblast, the type I PTH/PTHRP receptor is coupled to both the adenylyl cyclase activating G protein, Gs, and the phospholipase C-activating Gq protein [35,36]. Native PTH requires the first two amino acids and some part of the 25–34 amino acid domain to activate Gs, but a fragment as small as PTH (28–32) can activate

Gq [35,36]. Most of the anabolic skeletal actions of PTH are associated with stimulation of the cAMP/protein kinase A pathway with genes such as c-*fos* being activated, but the balance between these two transduction systems in the osteoblast could also be important [35,37]. For example, the PKC system may be active when intermittent use of PTH increases osteoblast activity [38,39]. The activation of adenylyl cyclase is probably important as well, since the anabolic effect of PTH (1–38) is abolished by removal of amino acid residues 1 and 2 [40]. Recently, analysis of gene expression by DNA microarray has demonstrated that the anabolic and catabolic effects of PTH are regulated by both common and unique subsets of genes and pathways [41]. Overall, the activation profile of PTH in bone cells leads to induction of several growth factor genes including those for IGF-1, IGF-II and TGF-beta. In addition, the binding proteins for IGF, IGFBP-1,-4,-5, are induced by PTH as are IGF binding proteases –3 and 5 [35,36,38,39,42–46]. The net effect of PTH on IGF-I production is limited rather exclusively to bone cells.

PTH also links osteoblastic and osteoclastic stimulation by inducing the production of RANKL (receptor activator of nuclear factor-κB ligand), a cytokine that is expressed in committed pre-osteoblastic cells [47] and leads to enhanced osteoclast activity and bone resorption [48,49]. Continuous PTH administration increases RANKL and decreases osteoprotegerin, a decoy receptor which binds RANKL and thereby inhibits its activities at the functional receptor, RANK [50,51]. The interaction between RANKL and RANK on the committed osteoclast cell line is thus facilitated. However, when PTH is administered in an intermittent fashion, the effects differ from those observed with continuous PTH. The alterations in RANKL and osteoprotegerin are only transient [50], or do not occur at all [52], favoring an osteoblast effect in bone. Recently, evidence has emerged that PTH reduces osteoblastic apoptosis, prolonging osteoblast survival and possibly potentiating its differentiated function in collagen synthesis [53]. These observations notwithstanding, the underlying molecular physiology accounting for the true anabolic effect of PTH remains unknown.

Animal Studies of PTH

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 [38,39,42–46,53–55]. Intermittent exposure of PTH for 4–6 weeks in ovariectomized animal models leads to increased cancellous bone thickness (but not trabecular number). Cancellous bone mass and strength are greater, even in the absence of estrogen. Microscopically, bone cell turnover is enhanced, reminiscent of pubertal bone expansion (J. Hock, personal communication). The PTH effect to improve bone mass has been noted in rats, monkeys, dogs and rabbits [46,54–55]. Mechanical strength in the femur and vertebrae also increases with intermittent PTH treatment. A recent study in ovariectomized cynomolgus monkeys has shown that even when PTH administration increases intracortical porosity, it does so in the inner one third of the cortex with no detrimental effect on the mechanical properties of bone [56]. Similarly, when ovariectomized rats were administered PTH for 36 weeks, cortical bone formation was increased, especially at the endocortical surface [57]. PTH has also been administered to animals in combination with different antiresorptive agents. Earlier animal studies employed the rat ovariectomy model, and used estrogen with PTH versus estrogen or PTH alone [43,45,46,53–55]. 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.

Observational Studies of PTH

The earliest human studies of PTH administration were small, uncontrolled observational trials [58–64]. The first clinical trial was conducted in 1976, when Reeve et al. [65] treated 4 osteoporotic women with PTH for 6 months and found an acceleration of bone turnover, with bone formation outweighing resorption. A larger study involved 21 patients (16 women, 5 men) with osteoporotic fractures (some of whom were on other agents, such as vitamin D, estrogen or testosterone) [60]. Radiocalcium kinetic studies showed bone formation and skeletal mass to be increased, correlating with increases in trabecular bone volume by analysis of iliac crest biopsies. However, there was no improvement in overall calcium balance.

To improve calcium absorption [63,64], PTH was used next in combination with 1,25-dihydroxyvitamin D. Slovik and colleagues [63] administered hPTH (1-34) along with oral 1,25-dihydroxyvitamin D to 8 osteoporotic men. In 4 subjects who had vertebral bone density measured by quantitative computed tomography (QCT), there was a remarkable 2-fold increase in bone mineral density when measured by QCT, a technique which exclusively measures cancellous bone, over 1 year. There was no loss of radial bone mass [63]. Other small, early trials have evaluated the effects of intermittent PTH in combination with another agent [66–68], or when administered sequentially [69–73]. Increases in cancellous bone mass occurred when PTH was administered with estrogen [66,74], or in a sequential regimen with calcitonin [71,72]. Cyclical administration of PTH with etidronate, however, did not yield an increase in bone mass [70].

Controlled Clinical Trials

More recently, larger, randomized, placebo-controlled clinical trials have been performed with PTH alone and

in combination with other agents. The principal finding common to all studies in both men and women is a substantial increase in spine bone mineral density (BMD) with PTH. This increase in BMD is greater than the increase commonly observed after 1 year of antiresorptive therapy. By DXA, increases of 7–10% and by QCT increases of 40% are common. The difference between these two densitometric techniques reflects the fact that QCT measures cancellous bone rather exclusively while DXA detects both cortical and cancellous elements in the lumbar spine. Rather consistently, BMD in the forearm either remains the same or declines slightly with treatment. Hip density and total body BMD tend to increase more modestly than the change in vertebral BMD. Bone markers show an uncoupling of bone turnover in favor of formation, as evidenced by an initial increase in formation markers followed by an increase in resorption markers. Over time, bone markers show a trend to return towards baseline despite continued increases in BMD.

PTH in States of Estrogen Deficiency

The potential of PTH to prevent estrogen deprivation-induced bone loss was demonstrated in a trial by Finkelstein et al. [75]. Forty premenopausal women receiving the GnRH agonist, nafarelin, to induce estrogen deficiency for endometriosis, were given PTH or placebo. Those women receiving PTH had an increase of 2.1% in spine BMD after 12 months compared with the calcium-only group, which lost 5% of vertebral bone mass due to estrogen deficiency. Femoral neck bone loss was also prevented in the PTH group, while the calcium only group lost 4.7% at that site over the same time period [75–77].

PTH in Postmenopausal Osteoporosis

PTH as single therapy has also 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) [78,79]. 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 [78,79]. Lower doses of PTH showed lesser changes in 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 largest randomized, placebo-controlled trial to date, by Neer et al. [80], tested daily administration of 20 or 40 μg of subcutaneous hPTH (1–34) in 1637 women with postmenopausal osteoporosis (i.e., low BMD and fractures). Median follow-up was 21 months. For the two doses of PTH, spine BMD increased 10–14%. Femoral BMD also increased, by approximately 3%. Total body BMD increased significantly as well. Most impressive was the reduction in risk for both vertebral and non-vertebral fractures in those women receiving either 20 or 40 μg/day of PTH. Compared with placebo, PTH reduced the risk of one or more new vertebral fractures by 65% and 69%, respectively. New non-vertebral 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

Men with idiopathic osteoporosis constitute a group for whom PTH could be ideally suited in view of the fact that osteoporosis is a disorder of impaired bone formation and low bone turnover [81,82]. The first randomized, controlled trial of PTH in men with idiopathic osteoporosis was carried out by Kurland et al. [83]. Twenty-three men, 30–68 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/day or placebo in a double masked experimental design for 18 months. Ten subjects were randomized to the PTH arm and 13 to the placebo arm. Both groups were well-matched for clinical characteristics, including baseline BMD at all sites, serum and urinary biochemistries and markers of bone turnover. The PTH group had an impressive linear increase in lumbar spine BMD from the beginning to the end of the 18-month trial, culminating in a 13.5% increase of lumbar spine BMD. There was no change in the placebo group (Fig. 1). Femoral neck BMD showed a slower and less dramatic, but nevertheless significant, increase, reaching 3% at 18 months. There was no major change in BMD of the distal radius (1/3 site) in either the treated or control patients. Bone turnover markers increased substantially in the men treated with PTH. The baseline pyridinoline crosslink determination and three 3-month osteocalcin level were the best predictors of the skeletal response to PTH [84]. These results seem to indicate that the higher the baseline bone resorption activity, the greater the effect of PTH. Understood in these terms, perhaps the stimulatory effects of PTH on the skeleton are facilitated by a substantial degree of endogenous bone turnover. This is consistent with the recent histomorphometric observation that PTH treatment directly stimulates bone formation without prior resorption on cancellous and endocortical surfaces [85]. When PTH was continued in an open label design for an

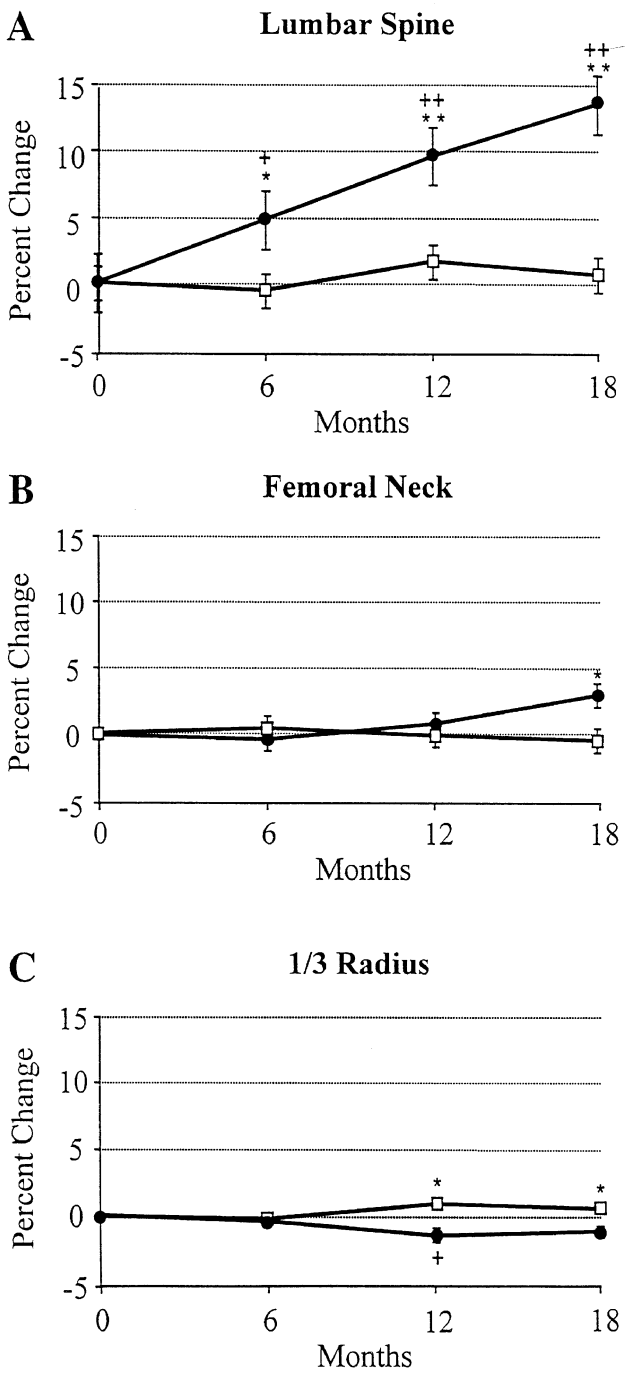

Fig. 1. Changes in bone density after PTH (1–34) treatment in men with idiopathic osteoporosis. Bone density at the lumbar spine (**A**), femoral neck (**B**) and 1/3 site of the distal radius (**C**) in men receiving PTH (*filled circles*) and in controls (*open squares*). The data are shown as percent changes from baseline ± SEM for lumbar spine, femoral neck 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. (Reprinted with permission from Kurland et al. [83].)

additional year, BMD increases were maintained, while bone turnover markers returned to baseline values [86].

Histomorphometric analysis of 8 of the treated men before and after 18 months of PTH made it possible to evaluate more directly the potential anabolic effects of PTH, as well as 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 could be seen that not only were there quantitative improvements in cancellous bone indices but there were major improvements in indices of connectivity [87]. Trabecular elements that were separated by short distances seemed to become connected or reconnected, since the increase in connectivity density was associated with improvements in trabecular number and thickness. PTH therefore not only remineralized the skeleton but also helped to reverse the 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 appeared 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. 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 anitresorptives, and help to allay concerns that PTH may have adverse effects upon the cortical skeleton. Further studies will be needed to confirm these points.

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 more recent 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.

PTH in Combination with Another Agent

PTH has been studied in controlled trials in conjunction with antiresorptive agents. The rationale for combination therapy is that PTH should stimulate bone formation, while the antiresorptive agent should limit any catabolic effect as well as contribute its own effect to increase bone mineral density. In concept, therefore, anabolic and antiresorptive therapy should be more effective than either approach alone. Theoretically, however, the presence of an antiresorptive could prevent PTH from stimulating bone formation. This concern receives some support from the observations of Kurland et al. [83] in which the baseline level of bone turnover was correlated positively with the eventual effect of PTH. This suggests that parathyroid hormone might be more effective in

stimulating bone formation when bone turnover is active than when it is suppressed.

PTH and Estrogen

Combined therapy with PTH and estrogen was studied in a 3-year randomized controlled trial by Lindsay and colleagues [88,89] of 52 postmenopausal osteoporotic women who were on hormone replacement therapy. 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. 2). There was no evidence of cortical bone loss. PTH significantly reduced the percent 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 8 of the women treated with estrogen and PTH was performed [90]. 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 [90] (Fig. 3). 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 vs 18 months in the men) and perhaps to the additive effects of estrogen and PTH.

In another study by Roe et al. [91], 74 postmenopausal women were randomized to receive either 400 IU of PTH (1–34) or placebo while remaining on stable doses of conjugated equine estrogens. 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 on estrogen alone. The increase in vertebral BMD was even greater, close to 80%, when measured by QCT of the vertebrae.

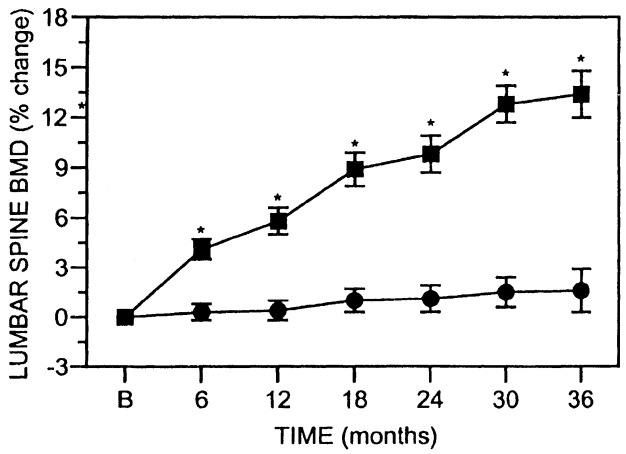

Fig. 2. The effect of PTH in women being treated with estrogen. Changes in lumbar spine bone mass when estrogen was given with (*filled squares*) or without (*filled circles*) PTH over 3 years to postmenopausal osteoporotic women. (Reprinted with permission from Cosman, F. et al. [89].)

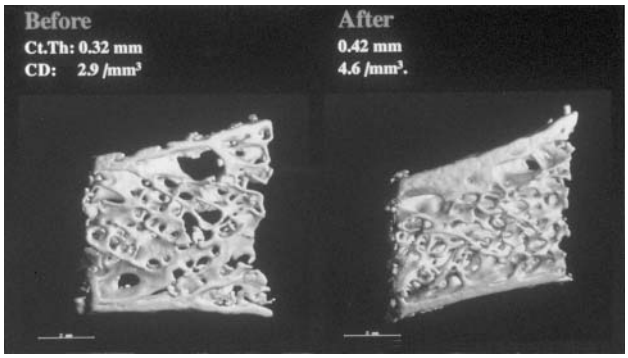

Fig. 3. Bone structure by scanning electron microscopy of bone biopsies before and after PTH treatment in two patients. Note the marked improvement in trabecular architecture and increase in cortical thickness following PTH treatment. (Reprinted with permission from Dempster et al. [90].

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 antiresorptive to treat glucocorticoid-induced osteoporosis is attractive. Lane et al. [92] conducted a 12-month, randomized, controlled trial of 51 postmenopausal women on hormone replacement therapy and glucocorticoids (>5 mg/day prednisone), who were randomized to hPTH (1–34) for 1 year or not (placebo injections were not used). In the PTH group, vertebral BMD increased 35% by QCT and 11% by DXA. The total hip bone density increased by 2% in the PTH group, while there was no difference in forearm BMD between groups. Bone markers showed an increase of bone formation in the first 3 months, while resorption peaked at 6 months [92]. This pattern is similar to that seen in an earlier study of PTH and estrogen [88] and is consistent with the recent histomorphometric observation that PTH treatment directly stimulates bone formation without prior resorption, at cancellous and endocortical surfaces [85].

PTH and Calcitonin

PTH was studied in a randomized trial with calcitonin [93], in addition to earlier, smaller trials [26,71–73]. Similar to the rationale for other antiresorptive agents, it was hoped that calcitonin use would limit the resorption induced by PTH and thus augment the overall anabolic

effect. The study patients were 30 postmenopausal osteoporotic women who were all given cyclical high-dose hPTH (1–34); half were given calcitonin. At the end of 2 years, however, the difference between the two groups was not significant. Calcitonin combined with PTH did not prove to have an additive effect [93], possibly because calcitonin is a relatively weak antiresorptive agent.

PTH and Alendronate

The rationale for combination therapy with a bisphosphonate, such as alendronate, is to decrease the enlarged remodeling space created by PTH exposure and thus consolidate further gains in bone density as well as to prevent any decline. One small study seemed to indicate that PTH can *de novo* stimulate bone formation even in the presence of a bisphosphonate [94]. More recently, a randomized controlled trial was performed to assess the effects of PTH followed by alendronate [79]. Sixty-six women with postmenopausal osteoporosis were treated for 1 year with either 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 impressive spinal bone density increases of up to 14.6%. There was a trend toward increased hip bone density that was not statistically significant. 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. It is unclear, however, how much of the bone density improvement occurred solely as a result of a continued anabolic effect after PTH withdrawal, since there was no placebo group which did not receive alendronate. What is not known, additionally, is whether PTH and a bisphosphonate used simultaneously is better, worse or no different from sequential therapy. A randomized trial sponsored by the US National Institutes of Health is currently under way to test that hypothesis [95].

Withdrawal of PTH

A powerful anabolic agent such as PTH might be expected to lead to certain consequences after therapy is withdrawn. Although there is concern that PTH withdrawal without any subsequent therapy (i.e., antiresorptive) could lead to bone loss, expectations suggest, on the other hand, that there could be even further increases in bone mass. First, reflections on surgical cure of primary hyperparathyroidism, a paradigm of PTH withdrawal, are noteworthy. Parathyroidectomy for primary hyperparathyroidism will lead to increases in lumbar spine and femoral neck bone density that can exceed 10% [96,97]. 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 [98].

In therapeutic regimens, the data are sparse. In the study of Finkelstein and Arnold [77], when estrogen-deficient young women with endometriosis on GnRH therapy were followed for a post-treatment year after PTH was withdrawn, they continued to maintain bone density. During this post-treatment year, their estrogen status returned to normal, suggesting that the maintenance of BMD could have been due to return of estrogen sufficiency. Similarly, estrogenized postmenopausal women treated with PTH did not lose bone density 1 year after the PTH was withdrawn [89]. Women on glucocorticoids and hormone replacement therapy treated with PTH maintained their lumbar spine BMD and had a 2% increase in total hip BMD 1 year after PTH was discontinued [99]. The withdrawal of PTH, but with the continued presence of an antiresorptive, seems to permit maintenance of the gains achieved by PTH therapy [96,98].

Nevertheless, it is possible for withdrawal of PTH to be associated with a reduction in bone mass if an antiresorptive is not present. If this concern proves to be the case, the rationale for utilizing an antiresorptive agent after a course of PTH therapy would be evident. Preliminary data from Kurland et al. [100] support the concept that antiresorptive therapy may be necessary to maintain gains due to PTH after its withdrawal. Men who immediately began treatment with a bisphosphonate after PTH therapy had further increases of 3% in lumbar spine BMD, while 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 [95].

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 [101]. If cortical bone is lost, sites enriched in cortical bone could be placed in jeopardy for fracture. However, preliminary histomorphometric analysis of osteoporotic men and women treated with PTH did not reveal a loss of cortical bone or an increase in cortical porosity [90]. In fact, a distinct anabolic effect on cortical bone was observed at the endosteal surface, with significant increases in the width of bone packets and reduced endocortical resorption. 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 [56]. 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 [56]. The consequent increase in cross-sectional diameter would be expected to increase bone strength. This effect was recently confirmed in human subjects, when postmenopausal women treated with PTH underwent peripheral quantitative computed tomography (pQCT) of the proximal radius to assess specific changes in cortical bone density, undetectable by DXA [102]. Similar to the primate model, PTH treatment resulted in greater periosteal circumference and cortical area, findings predictive of increased biomechanical strength [102]. These observations provide evidence that PTH is anabolic for cortical bone. Furthermore, fracture data from the study of Neer et al. [80] clearly indicate a substantial reduction in fractures of the non-vertebral skeleton. This would be unlikely if PTH were exerting a catabolic effect on cortical bone.

Long-term studies (18–24 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, appears to be related to duration of use, and would be consistent with lifetime exposure in a growing rodent to an anabolic agent which increases osteoblast proliferation. There is great uncertainty, however, about whether this toxicity study in a rodent model has relevance to human physiology. 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 or from any of the 1–3 year clinical trials performed so far 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 in those most likely to benefit, i.e., postmenopausal women and men with clinical fractures and low BMD. The benefits of PTH are likely also to extend to individuals with established osteoporosis before fractures occur.

Conclusions

PTH represents an important new advance in the therapy of osteoporosis. As an anabolic agent, its potential might be substantially greater than the antiresorptives. Clear evidence in human trials now documents the ability of PTH to stimulate cancellous bone formation and to reduce fractures. Since the antiresorptives and PTH clearly work by completely distinct mechanisms of action, it is possible that the combination of agents could be significantly more potent than either agent alone. There are other 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 more clearly the reduction in non-vertebral fractures with PTH, especially at the hip. More information is required to determine the possible need for antiresorptive therapy after PTH. Protocols to consider PTH as an intermittent recycling therapy would be of interest. 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. [103] have described an oral calcilytic molecule that antagonizes the parathyroid cell calcium receptor, thus stimulating the endogenous release of PTH. This approach could represent a novel endogenous delivery system for intermittent PTH administration. Ultimately, when the anabolic and catabolic mechanisms of PTH can be clearly distinguished both mechanistically and in molecular terms, it may be possible to develop PTH analogs that are more purely anabolic.

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