Parathyroid hormone treatment for glucocorticoid-induced osteoporosis

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ABSTRACT
Parathyroid hormone (PTH) was first used in the treatment of osteoporosis in 1929 when Fuller Albright demonstrated an increase in skeletal calcium in rats by injecting parathyroid extracts (1). This was later confirmed by Hans Selye in 1932 (2). The amino acid sequencing of PTH was performed in the early 1970s (3). Subsequently, small clinical studies were initiated to determine if PTH had therapeutic potential to augment bone mass in osteoporotic patients (4). Since then, a lot has been learned about the role of the amino terminal fragments of PTH in the treatment and prevention of osteoporosis in animals and humans. This article reviews the available evidence for the use of PTH fragments in osteoporosis, particularly glucocorticoid-induced osteoporosis (GIOP).

PTH structure and function
PTH is an endocrine hormone secreted by parathyroid glands as an 84-amino acid peptide. Subsequently it is cleaved by endopeptidases into various biologically active fragments containing the amino-terminal 34 residues and inactive fragments consisting of the so-called middle and carboxyl-terminal fragments (5). Most of the circulating PTH consists of the inactive fragments. PTH promotes bone growth by stimulating adenylyl cyclase enzyme in osteoblasts and requires the (1-31) amino acids from the amino-terminal portion for this activity (6). PTH receptors have not been demonstrated on osteoclast cells and in vitro experiments have demonstrated that osteoclast activation requires the presence of osteoblast cells with PTH receptors (7). This PTH-osteoblast interaction may eventually result in changes in the osteoprotegerin (OPG)/osteoprotegerin ligand (OPGL) balance via secondary signaling involving G-proteins, nuclear factor kappa B (NF-kB) and c-jun N-terminal kinase (JNK) (8, 9).

Mechanism of action of PTH
Primary hyperparathyroidism can cause secondary osteoporosis, predominately by stimulating osteoclast activity and increasing bone resorption (10). Tam et al. first suggested that the continuous infusion of bovine PTH (1-84) causes bone resorption in vivo, while intermittent injections of the same hormone is primarily anabolic (11). This has been confirmed in subsequent studies of human PTH (hPTH) (1-34), hPTH (1-84), and PTHrP fragment therapy in both animals and humans. The main pathologic lesion in GIOP is a decrease in bone formation (12). Glucocorticoid (GC) receptors have been demonstrated on osteoblasts (13). GC therapy inhibits osteoblasts by suppressing their replication, inhibiting the development of new osteoblast cells and stimulating osteoblast cell death by apoptosis (14, 15). In vivo animal studies have found that intermittent hPTH (1-34) therapy prevents osteoblast and osteocyte apoptosis and prolongs the lifespan of these cells, resulting in an increase in bone formation (16). Moreover, it increases the activation of lining cells in rats, leading to increased osteoblast number and function (17, 18). GC therapy also markedly inhibits the synthesis of insulin-like growth factor-I (IGF-I) and of IGF binding proteins (IGFBP) in skeletal and non-skeletal cells (19). In osteoblast cell cultures, GC treatment significantly decreases IGF-I mRNA and polypeptide levels by inhibiting IGF-I transcription and decreasing the expression of IGFBP-1,3,4, and 5 (20, 21). IGF-I is among the most abundant growth factors present in the skeletal tissue and has opposite effects to those of GC on bone formation (19). It is a modest mitogen for skeletal cells and increases type I collagen synthesis, the matrix apposition rate and bone formation, while decreasing collagenase expression by skeletal cells (22, 23). GCs
on the other hand decrease collagen synthesis. Therefore, the effect of GC on IGF may have a significant role in GIOP. PTH is a major inducer of IGF-I in skeletal tissues and its selective stimulatory effects on bone formation may be mediated by IGF-I (24, 25).

This is in contrast to the continuously high levels of PTH fragments which appear to stimulate osteoclast activity and bone resorption to a greater extent than bone formation. It is not clear why the different times of exposure to PTH fragments result in different responses of skeletal bone cells. However, recently a cell surface protein belonging to the tumor necrosis factor (TNF) cytokine family known as osteoprotegerin ligand (OPGL) has been identified. It is present on the surface of early osteoblasts and binds to its ligand receptor present on the osteoclast cell surface known as Receptor Activator of Nuclear Factor-kB (RANK). This interaction results in osteoclast maturation and bone resorption. It is regulated by osteoprotegerin (OPG), a soluble decoy glycoprotein from the TNFR family which is synthesized by early osteoblasts, binds to OPGL and prevents its interaction with RANK, thereby suppressing bone resorption (26).

Initiation of GC therapy results in an increase in RANKL expression and a decrease in OPG synthesis (27). Based on these observations, we hypothesize that the intermittent daily injection of hPTH (1-34) results in a favorable OPG/OPGL ratio permitting bone formation and decreased bone resorption. However, with persistent hPTH exposure, OPGL levels may increase, resulting in osteoclast differentiation and bone resorption (28).

**Animal studies**

A number of animal studies have demonstrated that PTH fragments are anabolic agents to the bone (30-43). Lane et al. treated ovariectomized osteopenic rats with daily injections of hPTH (1-34) for 4 weeks (20 injections) at various doses (37). Using three-dimensional (3D) high resolution x-ray morphometry methods (XTM), the hPTH (1-34) treated animals showed a nearly 40% increase in trabecular bone mass from baseline value (p < 0.05) and it was equal to the control sham-operated animals. However, the increase in bone mass was due to the thickening of existing trabeculae and no new trabeculae were formed by this treatment. Interestingly, other investigators have reported that the trabecular bone mass gained after treatment with hPTH (1-34) and hPTH (1-84) is of good quality and tensile strength (38-43). Also, there is emerging data to suggest that hPTH (1-34) therapy may accelerate fracture healing (44, 45).

**Human studies**

The encouraging results with the use of PTH fragments in animal models of osteoporosis led to an interest in their use in clinical studies involving humans. In addition, several studies demonstrated that trabecular bone mass and structure was preserved in patients with mild primary hyperparathyroidism (46-51), even among postmenopausal women expected to have an accelerated trabecular bone loss due to estrogen deficiency (50, 52, 53). Histomorphometric studies in these patients showed an increase in the indices of trabecular bone connectivity despite high bone turnover, with an increase in trabecular wall width and an active formation period consistent with an "anabolic" action of PTH on trabecular bone (48-54).

Initial observational studies using PTH fragments to treat osteoporosis in humans demonstrated a positive effect in increasing bone mass (55-58). This was followed by several uncontrolled clinical trials. Reeve et al. studied 21 men and women with involutional osteoporosis treated with hPTH (1-34) 400-500 U for 6-24 months. There was a significant increase in bone formation and skeletal mass with a marked increase in bone accretion, cancellous bone volume and osteoid surface on iliac crest biopsies. However, there was no improvement in calcium retention (59). Slovik et al. studied 8 men (mean age 50 years) with idioptic osteoporosis confirmed by iliac crest biopsy and characterized by ≥1 vertebral fracture and low bone density, who were treated with the daily subcutaneous injection of 400-500 U of hPTH (1-34) plus oral calcium (15-30 mmol) and 0.25 micrograms of 1,25(OH)2 D3 daily for one year. Trabecular vertebral bone density increased significantly in all the patients tested (198% increase from baseline, p < 0.001) with an improvement in calcium retention (60). Neer et al. studied osteoporotic women treated with a similar combination of hPTH (1-34) and active vitamin D (calcitriol) and found a 32% increase in vertebral bone mass by quantitative computerized tomography (QCT) (12% increase by dual photon absorptiometry) (61).

In another study, Reeve et al. recruited 12 patients with vertebral fracture osteoporosis and treated them with hPTH (1-34) injections for one year combined with antiresorptive agents (estrogens, n=9, nandrolone, n=3). There was a significant increase in indices of whole body bone formation (p < 0.005) and an increase in trabecular bone volume (62). Finkelstein et al. conducted the only placebo-controlled, randomized clinical trial using hPTH (1-34) to prevent bone loss. Forty pre-menopausal women starting nafarelin (gonadotropin releasing hormone analogue) for the treatment of endometriosis were studied for 6 months. Half of them were treated with hPTH (1-34) 40 micrograms daily and the other half served as a control (63). At the end of the study, patients receiving hPTH (1-34) + nafarelin had increased spinal bone mineral density (BMD) in the lateral projection by 3.4% (p = 0.01) while the control group lost spinal BMD by 3.5% in the same projection (p < 0.001). Radial bone mineral density did not change in either group, while the femoral neck BMD decreased slightly and similarly in both groups. The same group conducted a longer (12-month) randomized, placebo-controlled trial of 43 women similarly divided between nafarelin only and nafarelin plus PTH groups (64). While the nafarelin only group lost bone mass (4.9% AP spine, 4.7% femoral neck, 4.3% trochanter and 2.0% total body) at one year, the active PTH treatment group gained bone mass at the AP spine by 2.1% and had no bone loss from the femoral neck, trochanter and total body despite severe estrogen deficiency.

Hodsman et al. studied 30 postmenopausal women with osteoporosis (mean age 67 years) treated every 3 months with a 28-day cycle of hPTH (1-34) (800 U) injections for 2 years. Sixteen patients also received sequential calcitonin im-
mediated after hPTH (1-34) and 14 patients received placebo. After two years, lumbar spine BMD in the hPTH (1-34) only group increased by 10.2%, compared to a 7.9% increase in the hPTH (1-34) + calcitonin group (p < 0.001). The BMD at the femoral neck changed by +2.4% and -1.8% respectively (not significant). The vertebral fracture incidence was 4.5/100 patient-year in the hPTH (1-34) only group compared to 23/100 patient-year in the hPTH plus calcitonin group (p = 0.078) (65). Lindsay et al. conducted a 3-year randomized controlled trial using hPTH (1-34) 400 U per day in postmenopausal women with osteoporosis taking hormone replacement therapy and compared them to a matched group of women taking HRT only. Parathyroid hormone fragment (1-34) therapy at 25 microgram/day resulted in a significant increase in BMD, averaging 13% at the spine (p < 0.001), 2.7% at the hip (p = 0.05) and 8% in the total body-bone mineral (p = 0.002) without any loss of BMD at any skeletal site (66). Significantly fewer fractures were seen in the PTH treatment group (p < 0.05) and 8% in the total body-bone mineral (p < 0.001) without any loss of BMD at any skeletal site (66). Significantly fewer fractures were seen in the PTH treatment group (p < 0.04) using the 15% vertebral height reduction criteria. The successful and safe use of PTH fragments in postmenopausal and involutional osteoporosis led to the use of these agents in GIOP. GIOP is a disease of decreased bone formation characterized by thinning of the trabecular plates. Since treatment with amino-terminal PTH fragments in animal models of osteoporosis increased bone formation and thickness in the existing trabeculae, it seemed logical to test whether the same treatment could override the suppressive effects of GC on bone formation and increased bone mass. Lane et al. performed a randomized controlled clinical trial in postmenopausal women on chronic GCs and hormone replacement therapy (67), specifically 51 postmenopausal (≥ 3 years) osteoporotic women on chronic GC (average 8.5 mg prednisone/day), who were also on HRT for >1 year. All subjects received calcium (total 1500 mg/d) and vitamin D (800 IU/d) supplementation, and 23 women received hPTH (1-34) 40 micrograms/day for 1 year. Subjects were carefully monitored for calcium metabolism, biochemical markers of bone turnover and bone densitometry by DXA and QCT at frequent intervals. All subjects tolerated the therapy well. At the 4-week visit, serum osteocalcin, a marker of osteoblast activity, had increased to nearly 150% over the baseline level. Deoxypyridinoline cross-links, a urinary marker of bone resorption, also increased at 4 weeks but did not reach the level of osteocalcin until 6 months, showing an uncoupling of bone turnover in favor of formation. BMD of the lumbar spine increased in the hPTH (1-34) treated group by nearly 6% at 6 months and by 11% after 12 months by DXA scan. QCT of the lumbar spine, a measure of trabecular bone volume, increased nearly 35% after 12 months of hPTH (1-34) therapy. There was no significant change in BMD in the control group. These subjects were followed for an additional year off the hPTH (1-34) therapy with similar outcome measures (68). Interestingly, it took 9 months after the cessation of hPTH (1-34) therapy for biochemical bone markers to return to baseline. In addition, at the end of the second year of observation, the bone mass of the hip increased nearly 5% over the baseline levels. Therefore, treatment of postmenopausal women on chronic GCs and HRT resulted in a dramatic increase in lumbar spine and hip bone mass. This treatment was safe and there were no significant adverse effects.

Conclusion

Intermittent injections of the amino-terminal fragments of human parathyroid hormone have an anabolic action on trabecular bone which is quite potent and, when used for up to 3 years in duration, it appeared to be quite safe. GC use is associated with a significant reduction in bone formation leading to rapid bone loss and fractures. hPTH (1-34) therapy dramatically increased bone mass in osteoporotic post-menopausal women on GC and hormone replacement therapy. It is our hope that in the near future, we will have this anabolic bone building agent to reduce osteoporotic fractures risk in our GC-treated patients.

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