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Parathyroid hormone treatment of osteoporosis

TIMOTHY M. MURRAY, MD, FRCPC

Parathyroid hormone (PTH) has historically been known as a bone resorbing hormone mainly because of its negative effects on bone in primary hyperparathyroidism and in secondary hyperparathyroidism associated with chronic renal failure. Currently, PTH is being introduced as a therapy for osteoporosis and is recognized as a bone formation *stimulator*, rather than a bone *resorber*. This seeming paradox is confusing for many physicians. The bone forming properties of PTH were recognized as early as 1932 when Selye observed histological evidence of increased bone formation when parathyroid extract was administered to rats.¹ These data and suggestions from an earlier 1929 paper² went largely unnoticed for 40 years because medical attention was focused on the deleterious effects of PTH associated with hyperparathyroidism; the clinical effects of primary hyperparathyroidism were much more severe in the first half of the last century than we see currently. During that era, before serum calcium tests were widely available, hyperparathyroid bone disease – known as osteitis fibrosa cystica – was observed more frequently and was associated with bone pain, bone cysts, and pathological fractures. However, a seminal paper in 1970 by Kalu et al revived the concept of PTH as a bone-forming substance; they observed impressive and surprising increases in bone mass in rats injected daily with parathyroid extract.³ In the same year, the primary amino sequence of bovine PTH was reported,⁴ followed shortly thereafter by the discovery of the sequence of the human hormone.⁵ Around the same time, a number of experiments demonstrated that all the known effects of PTH could be expressed by a synthetic hormonal fragment of PTH comprised of the aminoterminal 34 amino acids. Since supplies of the native 84 amino acid molecule were limited, the use of the PTH(1-34) fragment became standard and, in 1980, the first clinical trial of the therapeutic use of hPTH(1-34) in osteoporosis was reported.⁶ In this study, significant increases were noted in trabecular bone volume assessed histologically since no standard methodology had been established for clinical measurements of bone mass, nor was there a standard clinical methodology for quantitation of spinal fractures. Availability of PTH as a therapeutic agent would await the discovery of accurate methods for measuring bone by bone densitometry, the development of recombinant technology for peptide synthesis, and the evolution of modern clinical trial methodology.

Dual mechanisms of action

The first step in solving the riddle of how PTH can be both a bone formation stimulator, as well as a bone resorber, was in 1982 with the discovery by Tam et al that the skeletal actions of PTH depend on the mode of administration of the hormone.⁷ Thus, the administration of PTH to rats by continuous infusion is associated with increased bone resorption and dose-related hypercalcemia, as well as a decrease in trabecular bone volume, whereas PTH administration by daily injection results in increased bone formation and trabecular bone volume without an increase in bone resorption or hypercalcemia.⁷

This observation has been repeated in a number of laboratories and in different species^{8,9,10} and, very recently, it was discovered that the two different modes of therapy (continuous vs. intermittent) are associated with different patterns of gene expression. Thus, PTH(1-34) or teriparatide, when given to rats intermittently, has a different pattern of gene expression¹¹ and activates different cytokine pathways.¹² In particular, continuous administration to rats activates the RANK ligand pathway, recognized as the major regulator of bone resorption,¹²⁻¹³



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Table 1: Radiographic evidence of new vertebral fractures			
Variable	Placebo N=448	PTH, 20 µg N=444	PTH, 40 µg N=434
≥1 fractures			
No. of women (%)	64 (14)	22 (5)	19 (4)
R.R. (95% CI) vs. placebo	—	0.35 (0.22-0.55)	0.31 (0.19-0.50)
% reduction in absolute risk	—	9	10
>1 fracture			
No. of women (%)	22 (5)	5 (1)	3 (<1)
R.R. (95% CI) vs. placebo	—	0.23 (0.09-0.60)	0.14 (0.04-0.47)
% reduction in absolute risk	—	4	4
≥1 moderate or severe fractures			
No. of women (%)	42 (9)	4 (<1)	9 (2)
R.R. (95% CI) vs. placebo	—	0.10 (0.04-0.27)	0.22 (0.11-0.45)
% reduction in absolute risk	—	9	7

† Adapted with permission from Neer RM et al.²⁴ Radiographic fractures were determined according to a semiquantitative rating scale of reduction in vertebral height as mild (20-25%), moderate (26-40%), or severe (>40%), after a mean observation of 21 months since randomization. Numbers of women with new fractures are indicated in parentheses. All values for 20 and 40 µg PTH differed from the placebo group, $p < 0.001$.

while intermittent daily dosing activates the IGF-I pathway in bone.¹² Indeed, the osteogenic action of intermittent PTH(1-34) is not seen in IGF-I knockout mice.¹⁴ PDGF-A is one of the genes preferentially activated with continuous PTH administration. Furthermore, a PDGF-A antagonist has been found to reduce the bone resorption associated with continuous PTH administration.¹⁵ Another important part of the mechanism of the osteogenic effect of PTH is an increase in the lifespan of osteoblasts via a decrease in osteoblast apoptosis.¹⁶ The net effect of these actions of intermittent daily administration of PTH is an increase in the number of active bone-forming osteoblasts.

The fact that PTH-induced stimulation of osteoblastic bone formation results in increased bone mass and strength has been shown extensively in animals.^{17,18} PTH(1-34) has been shown to increase bone mass in ovariectomized rats, rabbits, and monkeys, and to increase bone strength in biomechanical testing.^{18,19} Anabolic effects have also recently been documented in mice with increases in bone volume observed via histology.²⁰

Pivotal clinical trial

Osteoporosis treatment with recombinant human PTH(1-34) (teriparatide) was finally tested in a placebo-controlled randomized clinical trial that was reported in 2001.²¹ In this study, 1637 postmenopausal women with osteoporosis and prevalent vertebral fractures were randomized to placebo or teriparatide 20 µg or 40 µg once daily injection for an average period of 18 months.²¹ The study population had a mean age of 69 years and were, on average, 21 years postmenopausal. On average, they had a lumbar spine t-score of -2.6, and a mean of 2.3 previous vertebral fractures at entry, indicating that the study population had relatively severe osteoporosis. The results of the trial were extremely positive. Over 21 months, the number of women treated with the 20 µg and 40 µg doses of teriparatide had a reduction in new vertebral fractures of 65% and 69%, respectively, (Table 1).

The number of subjects with moderate or severe spinal fractures, as assessed by a semiquantitative grading system, was reduced by 90% and 78%, respectively. Although the study was not powered to analyze hip fractures independently, and hip fractures were not a primary endpoint, the number of women with nonvertebral fragility fractures was reduced by 53% and 54%, respectively. The Kaplan-Meier curves for nonvertebral fractures among both treatment groups began to diverge from that of the placebo group by 8-9 months after institution of therapy. Mean BMD values increased in the lumbar spine by 9.7% and 13.7% with the 20 µg and 40 µg doses, respectively, after 18 months of therapy. This magnitude of increase in BMD had not been seen with previous therapies. At the femoral neck, the respective BMD gains were 2.8% and 5.1%. The BMD values are shown in Table 2. There were also significant reductions in height loss and new or worsening back pain.

With the 20 µg marketed dose, the adverse effects in this study were relatively mild.²¹ Hypercalcemia was dose-related, as was nausea and headache. However, at the 20 µg dose, hypercalcemia was transient and mild (>2.6 mmol/l), occurring once in 11% of patients. When the serum calcium was repeated after several days, only 3% had a second elevated value. It occurred 3 to 6 hours after the dose, and was usually normal at 24 hours after the dose. Monitoring of serum calcium is not required. There was a mean increase in urine calcium, within the normal range, of 0.75 mmol/24h. No hypercalciuria was seen. The creatinine clearance was not abnormal in any subjects. In the 20 µg group, the incidence of nausea and headache was not significantly different from that in the placebo group. The percentage of patients who withdrew because of adverse events was the same in the 20 µg and placebo groups. There was no increased incidence of cardiovascular or other serious illness, and no increase in mortality.²¹ Thus, as revealed in this trial, the side effect profile of teriparatide was quite favourable.

Table 2: Percentage change from baseline in bone mineral density†			
Skeletal Site	Placebo	PTH, 20µg	PTH, 40µg
Lumbar spine	1.1 ± 5.5	9.7 ± 7.4	13.7 ± 9.7
Femoral Neck	-0.7 ± 5.4	2.8 ± 5.7	5.1 ± 6.7
Total Hip	-1.0 ± 4.3	2.6 ± 4.9	3.6 ± 5.4
Radial Shaft	-1.3 ± 3.3	-2.1 ± 4.2	-3.2 ± 4.5

† Adapted with permission from Neer RM et al.²¹ Values are given ± 1 S.D. All values for 20 and 40 µg PTH differed from the placebo group, $p < 0.001$.

It should be noted that in a 2-year toxicity study in rats, a significant incidence of osteosarcomas were noted.²² Furthermore, the increase in sarcoma was dose-related. While this initially caused concern, it was noted that osteosarcomas did not occur in primate studies, nor has there been a significant occurrence of osteosarcomas in human hyperparathyroidism, even in long-term renal dialysis patients where PTH values are often elevated to more than 20 times normal for many years.²³ The occurrences of osteosarcomas in these rats appears to be species-specific; there were also dose-related increases in benign bone tumours and osteoblast hyperplasia in these rats.²² Furthermore, the rats were treated with doses as high as 60 times the therapeutic human dose, and for 80% of the normal rat lifespan. Shorter term treatment in rats was not associated with skeletal toxicity.²⁴ The US FDA approved teriparatide as safe, but have restricted its use to a two-year course of therapy and to patients with closed epiphyses. Under these conditions there should not be safety concerns with teriparatide, except possibly in patients who already have increased risks of bone neoplasia, such as those with Paget's disease of bone, or patients with prevalent hypercalcemia or other neoplastic disease. Nonetheless, as an increased risk of osteosarcoma cannot presently be ruled out, the FDA has mandated a black box package warning concerning osteosarcoma.

Other clinical studies

In other studies, it has been observed that the anabolic effects of teriparatide can be observed as early as 4 weeks, with significant elevation in serum osteocalcin²⁵ and histological evidence of increased osteoblast surfaces and bone formation.²⁶ The use of teriparatide has also been studied in situations other than postmenopausal osteoporosis. In corticosteroid osteoporosis, teriparatide has been shown to increase bone mineral density by 12.6% at the lumbar spine and 5.2% at the femoral neck after 24 months.²⁷ Teriparatide therapy appears to be equally effective in men as in women in increasing BMD,²⁸ but further study is needed to show its effects on fracture incidence.

Combination therapies

PTH therapy has been studied in combination with antiresorptive agents. Teriparatide has been shown to

increase BMD significantly at spine and hip in postmenopausal women on long-term HRT.^{25,29,30} In a relatively small (N=52) study by Cosman et al,³⁰ women on long-term HRT were randomized to 25 µg teriparatide or placebo and treated concurrently with PTH(1-34) and HRT for 3 years. The subjects were then followed for a further year on HRT alone. In this small study, there was not enough power to detect effects on fractures; however, by the end of the trial mean spinal BMD had increased by 14% and femoral neck BMD by 3%. Furthermore, the increase in BMD was maintained during the year after teriparatide was discontinued. Although the numbers were small, vertebral fractures were reduced by teriparatide by 75%-100% in comparison to HRT alone.³⁰

PTH has also been studied in combination with bisphosphonates, both concurrently and sequentially. An early study in ewes suggested that concurrent administration with tiludronate blunted the increase in BMD seen with PTH therapy.³¹ However, a recent study in 93 osteoporotic postmenopausal women found that alendronate, administered concurrently with teriparatide for 30 months, did not blunt the effect of teriparatide on lumbar spine BMD, but resulted in superior changes at total hip and radius, suggesting that concurrent alendronate reduces the minor intracortical resorptive effect of teriparatide.³² More encouraging results were reported in a study by Rittmaster et al³³ who treated 66 postmenopausal osteoporotic women with various doses of PTH(1-84) or a placebo for 1 year. PTH was then discontinued and the subjects treated for a further year with 10 mg alendronate daily. Not only was the PTH-induced increase in bone mineral density maintained on alendronate, but a further substantial increase was also observed.³³ On the basis of current evidence, it appears that teriparatide therapy – currently approved by the FDA for only 2 years of therapy – should be followed by alendronate, rather than accompanied by it. However, the subject of combining antiresorptive agents with bone formation stimulators is complicated. Current studies are small and without fracture data. Considerable further study is necessary to understand how best to combine PTH therapy with antiresorptive agents. Furthermore, the expense of combined concurrent therapy with teriparatide and a potent bisphosphonate will put concurrent combined therapy beyond consideration for most patients.

A unique effect on bone quality

Teriparatide treatment has unique effects on bone in ovariectomized animals and in patients with osteoporosis. The increased osteoblast activity results not only in increased bone mass, but also has important effects on bone quality and structure that are not shared by antiresorptive drugs currently in clinical use for osteoporosis therapy. The differences in bone effects between hPTH(1-34) and antiresorptive drugs are summarized in Table 3.

Some earlier studies of PTH therapy in humans suggested that while PTH treatment increased the bone density of cancellous bone in spine and hip, it might have

Table 3: Biological effects of antiresorptive agents and teriparatide on bone

Parameter	Antiresorptive agents	Teriparatide
Bone remodeling	Decrease	Increase
Mechanism of increase in BMD	Increased secondary mineralization of static older bone units	Formation of new bone structures in trabecular and cortical bone
Trabecular architecture	Maintains existing structure and prevents further deterioration	Increases trabecular number, increases plate-like trabeculae. Formation of trabecular bone on quiescent bone surfaces
Cortical bone	Reduces cortical resorption	Increases cortical width and outer diameter, thickened endocortical bone, increased vertebral area
Biological half-life	Long for bisphosphonates	Short
Hypermineralized bone	Increased with long-term bisphosphonates	Not increased

adverse effects on cortical bone, with bone loss at the radius. While some decrease in BMD has been seen at the mid-radial site, particularly in trials of shorter duration, it no longer seems likely that this compromises bone strength. Recent studies of cortical bone in animals and humans strongly indicate that while there may be endosteal tunneling in cortical bone with PTH therapy, it is a transient phenomenon and that these effects are more than offset by increases in cortical thickness, periosteal diameter, and bone size.³⁴ Parfitt has suggested that the increase in the diameter of long bones through periosteal expansion that is observed with PTH therapy results from a process of renewed modeling.³⁵ One interesting example is a recent study in women with corticosteroid osteoporosis that demonstrated that teriparatide results in an increase in mean vertebral area.³⁶ These positive structural effects on cortical bone result in a net increase in bone strength.

It is a long-held belief that it is impossible to create new trabecular bone at sites where bone surfaces are inactive. However, very recent studies have indicated that this is not the case. A study from Denmark studied the effect of teriparatide in an aged rat model where, by 2 years of age, cancellous bone has disappeared from the distal femur. After treatment with teriparatide in these rats, the marrow cavity of the distal femur was consistently filled with a network of trabecular bone with increased biomechanical properties.³⁷

Summary and conclusions

Teriparatide is the first safe and effective drug of the new class of bone formation stimulators. It was recently given regulatory approval by the FDA in the USA and is currently in clinical use in that country, and it is hoped that it will soon be available for use

in Canada. Although not yet approved in Canada, teriparatide has been favourably rated in an evidence-based review of osteoporosis therapy by the Osteoporosis Society of Canada in their recent treatment guidelines.³⁸ Teriparatide is a potent anabolic therapy that results in significant reductions in vertebral and non-vertebral fractures via a unique mechanism of action. While treatment with PTH(1-34) has been reviewed above, current trials are examining the clinical effects of hPTH(1-84), and PTHrP analogs.³⁹ Other candidates for bone formation stimulators include strontium ranelate.⁴⁰ However, the focus is currently on teriparatide as an effective anabolic therapy for the treatment of osteoporosis. This addition to the treatment menu for osteoporosis will not be introduced as a generally indicated osteoporosis therapy. The FDA has approved its use for patients with severe osteoporosis or patients with a very high fracture risk. The drug is administered by daily SC injection using a simple pen; patients will need initial education and support regarding injection technique. The bisphosphonates and raloxifene will continue to be first line drugs for osteoporosis therapy. On the other hand, the advantages of this potent anabolic agent are clear for patients with severe osteoporosis, or those who are refractory to treatment with bisphosphonates.

Timothy M. Murray, MD, FRCPC, is Professor of Medicine, University of Toronto and a physician at the Osteoporosis Centre, St. Michael's Hospital, Toronto. He is a Consultant to Eli Lilly, Inc., NPS Pharmaceuticals, and Procter & Gamble, Ltd. He has received research grants from both Eli Lilly and NPS Pharmaceuticals.

References

- Selye H. On the stimulation of new bone formation with parathyroid extract and irradiated ergosterol. *Endocrinology* 1932;16:547-58.
- Bauer W, Aub, JC, Albright F. Studies of calcium and phosphorus metabolism. V. A study of the bone trabeculae as a readily available reserve supply of calcium. *J Exp Med* 1929;49:145-61.
- Kalu DN, Pennock J, Doyle FH, Foster GV. Effect of parathyroid hormone on metaphyseal bone in the rat. *J Endocrinol* 1970 Sep;48(1):1363-66.
- Niall HD, Keutmann H, Sauer R, et al. The amino acid sequence of bovine parathyroid hormone I. Hoppe-Seylers Zeitschrift fur *Physiologische Chemie* 1970;351(12):1586-8.
- Jacobs JW, Kemper B, Niall HD, et al. Structural analysis of human parathyroid hormone by a new microsequencing approach. *Nature* 1974;249(453):155-7.
- Reeve J, Meunier PJ, Parsons JA, et al. Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial. *Br Med J* 1980;28:1340-44.
- Tam CS, Heersche JNM, Murray TM, Parsons JA. Parathyroid hormone stimulates the bone apposition rate independently of its resorptive action: differential effects of intermittent and continuous administration. *Endocrinology* 1982;110:506-12.
- Podbesek R, Edouard C, Meunier PJ. Effects of two treatment regimes with synthetic human parathyroid hormone fragment on bone formation and the tissue balance of trabecular bone in greyhounds. *Endocrinology* 1983;112:1000-06.
- Dobnig H, Turner RT. The effects of programmed administration of human parathyroid hormone fragment (1-34) on bone histomorphometry and serum chemistry in rats. *Endocrinology* 1997; 138(11):4607-12.
- Morley P, Whitfield JF, Willick GE, et al. Prolonged low-dose infusion of human parathyroid hormone does not increase femoral cancellous bone volume in ovariectomized rats. *Eur J Endocrinol* 1999;141:70-74.
- Onyia JE, Gelbert I, 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. *J Bone Min Res* 1991;16(Suppl 1):S227.
- Locklin RM, Riggs BL. Mechanisms of biphasic anabolic and catabolic effects of parathyroid hormone (PTH) on bone cells [Abstract OR41]. Paper presented at: International Bone and Mineral Society, 2001; Madrid.
- 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 Sep;142(9): 4047-54.
- Bikle DD, Sakata T, Leary C, et al. Insulin-like growth factor I is required for the anabolic actions of parathyroid hormone on mouse bone. *J Bone Min Res* 2002;17(9):1570-8.
- Lotinun S, Sibonga JD, Turner RT. Differential effects of intermittent and continuous administration of parathyroid hormone on bone histomorphometry and gene expression. *Endocrine* 2002;17(1):29-36.
- Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. *J Clin Invest* 1999;104(4):439-46.
- Dempster DW, Cosman F, Parisien M, Shen V. Anabolic actions of parathyroid hormone on bone [review]. *Endocrine Reviews* 1993;14:690-709.
- Rubin MR, Cosman F, Lindsay R, Bilezikian JP. The anabolic effects of parathyroid hormone. *Osteoporosis Int* 2002;13:267-77.
- Hirano T, Burr D, Turner C, Sato M, Hock RCJ. Anabolic effects of human biosynthetic parathyroid hormone fragment (1-34) on remodeling and mechanical properties of cortical bone in rabbits. *J Bone Min Res* 1999;14:536-45.
- Iida-Klein A, Zhou H, Lu SS, et al. Anabolic action of parathyroid hormone is skeletal site-specific at the tissue and cellular level in mice. *J Bone Min Res* 2002;17(5):808-16.
- 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.
- Vahle JL, Sato M, Long GG, et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. *Toxicologic Pathology* 2002;30(3):312-21.
- Tashjian AH Jr, Chabner BA. Commentary on clinical safety of recombinant human parathyroid hormone 1-34 in the treatment of osteoporosis in men and postmenopausal women. *J Bone Min Res* 2002;17(7):1151-61.
- Sato M, Ma YL, Hock JM, et al. Skeletal efficacy with parathyroid hormone in rats was not entirely beneficial with long term treatment. *J Pharm Exp Therapeutics* 2002;302(1):304-13.
- 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(9077):550-5.
- Hodsman AB, Kiesel M, Adachi JD, Fraher LJ, Watson PH. Histomorphometric evidence for increased bone turnover without change in cortical thickness or porosity after 2 years of cyclical hPTH(1-34) therapy in women with severe osteoporosis. *Bone* 2000;27(2):311-18.
- Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. 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 Min Res* 2000;15(5):944-51.
- Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. *J Clin Endocrinol Metab* 2000;85(9):3069-76.
- Roe EB, Sanchez S, del Puerto GA, 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. Paper presented at: American Society of Bone and Mineral Research, St. Louis, MO. 1999:Abstract 1019.
- 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 Min Res* 2001;16(5):925-31.
- Delmas PD, Vergnaud P, Arlot ME, Pastoureaux P, Meunier PJ, Nilsson MH. The anabolic effect of human PTH (1-34) on bone formation is blunted when bone resorption is inhibited by the bisphosphonate tiludronate—is activated resorption a prerequisite for the in vivo effect of PTH on formation in a remodeling system? *Bone* 1995;16(6):603-10.
- Neer R, Hayes A, Rao A, Finkelstein J. Effects of parathyroid hormone, alendronate, or both on bone density in osteoporotic postmenopausal women. *J Bone Min Res* 2002;17(Suppl 1): S135.
- Rittmaster RS, Bolognese M, Ettinger MP, Hanley DA, Hodsman AB, Kendler DL, et al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocr Metab* 2000;85:2129-34.
- 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 Min Res* 2001;16(10):1846-53.
- Parfitt AM. Parathyroid hormone and periosteal bone expansion. *J Bone Min Res* 2002;17(10):1741-3.
- Rehman Q, Lang TF, Arnaud CD, Modin GW, Lane NE. Daily treatment with parathyroid hormone is associated with an increase in vertebral cross-sectional area in postmenopausal women with glucocorticoid osteoporosis. *Osteoporosis Int* 2003; 14(1):77-81.
- Oxlund H, Dalstra M, Ejersted C, Andreassen TT. Parathyroid hormone induces formation of new cancellous bone with substantial mechanical strength at a site where it had disappeared in old rats. *Eur J Endocrinol* 2002;146:431-38.
- Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *Can Med Assn J* 2002;167(10 suppl):S1-34.
- Horwitz MJ, Tedesco MB, Gundberg C, Garcia-Ocana A, AF S. Short-term high-dose parathyroid hormone-related protein as a skeletal anabolic agent for the treatment of postmenopausal osteoporosis. *J Clin Endocr Metab* 2003;88(2):569-75.
- 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 Endocr Metab* 2002;87(5):2060-6.

Abstracts of Interest

Teriparatide (rhPTH(1-34) Improves the Structural Geometry of the Hip

UUSI-RASI K, BECK TJ, ORESKOVIC TL, ET AL. VARIOUS CENTRES, USA, BUENOS AIRES, ARGENTINA.

Postmenopausal women administered teriparatide (rhPTH (1-34) showed increased BMD with lower fracture rates, suggesting that bone strength properties were improved. We used the hip structure analysis (HSA) program to clarify possible effects of teriparatide on the hip structural geometry. This program measures BMD and geometric properties within narrow regions across the femoral neck, intertrochanter and femoral shaft from images acquired by DXA. Subjects were participants in a multi-center placebo-controlled clinical trial of teriparatide (Lilly). Data for this pilot study were obtained from the Buenos Aires cohort of patients and included 84 postmenopausal women (mean age 67.6 ± 6.4 years) randomized into those receiving daily injections of placebo (n=26), 20 (n=32) or 40µg (n=26) teriparatide, respectively. Hip DXA scans (Lunar-GE, Madison WI) were performed at baseline and repeated on average at 20.1 months. General linear models were used to assess the effects of teriparatide treatment on bone structure using baseline values as covariates. Adjusted % mean differences (95% CI) from baseline at termination are listed for treatment groups in the table with significant differences (p<0.05) noted with asterisks.

While not all points reached significance, BMD, cross-sectional area (CSA), and section modulus (Z) an index of bending strength, were higher in 20 or 40 mg groups. Reduction in buckling ratio (BR), an index of cortical instability, may be particularly important since fracture cases in other studies have high BRs and the ability to reduce this parameter may help to explain teriparatide efficacy in reducing non-vertebral fractures. Results of this pilot study are encouraging and should be verified with a larger sample size to further clarify the structural effects of teriparatide treatment.

Percent Mean Difference (95% Confidence Interval) from Placebo Controls

Variable	Narrow Neck		Shaft	
	20 ug	40 ug	20 ug	40 ug
BMD	6.4 (1.1 to 12.0)*	12.5 (6.7 to 18.6)*	8.9 (3.1 to 15.0)*	3.1 (-2.5 to 8.9)
CSA	3.3 (-2.5 to 9.3)	13.4 (6.9 to 20.4)*	7.9 (2.7 to 13.3)*	3.7 (-1.3 to 9.0)
Z	0 (-7.4 to 7.9)	14.8 (6.1 to 24.4)*	6.9 (0.3 to 13.9)*	4.2 (-2.3 to 11.1)
Avg. Cortex	6.8 (1.3 to 12.6)*	12.7 (6.7 to 19.1)*	10.0 (3.4 to 17.1)*	3.3 (-3.0 to 10.0)
BR	-9.1 (-13.8 to -4.3)*	-10.3 (-15.1 to -5.3)*	-10.2 (-17.4 to -2.4)*	-2.6 (-10.4 to 5.9)

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Effects of Parathyroid Hormone, Alendronate, or Both on Bone Density in Osteoporotic Postmenopausal Women.

NEER R, HAYES A, RAO A, FINKELSTEIN J. BOSTON, MA.

Once-daily parathyroid hormone (PTH) administration increases bone formation and bone mineral density (BMD) and reduces vertebral and non-vertebral fractures in osteoporotic postmenopausal women, but does not eliminate fragility fractures. Because PTH also increases bone resorption, combining it with an anti-resorptive agent may enhance its effectiveness. To test this hypothesis, we randomly assigned 93 such women whose lumbar spine and/or femoral neck BMD T-score was ≤ minus 2.0 to receive alendronate 10 mg orally daily (ALN, n=31), PTH 40 ug sc daily (PTH, n=31), or BOTH (n=31) for 30 months. PTH treatment started at month 6. All women had normal serum PTH, 25-OH D, and TSH levels at entry. None had other disorders that (or took medications that) affect bone metabolism or BMD. Calcium intake was maintained at 500-1500 mg/day and serum 25-OH vitamin D was maintained >15 ng/mL. BMD of the posterior-anterior lumbar spine, proximal femur, radius diaphysis, and total body (without head region) were measured every 6 months by DXA (Hologic 4500A). To date, 53 women (n=19, 19, and 15 receiving ALN, PTH, or BOTH, respectively) have completed at least 12 months of therapy. Mean (±SD) percent changes in BMD and serum alkaline phosphatase to month 12 are:

Group	Vertebrae	Total Hip	Radius Diaphysis	Total Body	Alk P'tase
ALN	4.7 ± 3.3	0.9 ± 5.3	2.2 ± 2.9	2.1 ± 2.8	-18 ± 15
PTH	7.5 ± 5.0	0.1 ± 7.5	-2.2 ± 3.1 *	0.5 ± 4.1	96 ± 61 **
BOTH	7.3 ± 2.3	3.6 ± 6.2	0.1 ± 3.0	2.5 ± 2.9	6 ± 25

* p < 0.05 vs. ALN ** p < 0.01 vs. ALN

Adding ALN reduced the PTH-induced increase in serum alkaline phosphatase, reduced the incidence of PTH-induced mild, transient, hypercalcemia, and did not alter PTH's effects on vertebral BMD (substantially trabecular bone). The superior changes in total hip, radius diaphysis, and total body BMD suggest that ALN prevents PTH-induced losses of cortical bone mineral. Co-administration of PTH+ALN illuminates bone resorption-formation interactions; prolonged co-administration is likely to improve the treatment of postmenopausal osteoporosis.

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