

Parathyroid Hormone and Teriparatide for the Treatment of Osteoporosis: A Review of the Evidence and Suggested Guidelines for Its Use

Anthony B. Hodsman, Douglas C. Bauer, David W. Dempster, Larry Dian, David A. Hanley, Steven T. Harris, David L. Kendler, Michael R. McClung, Paul D. Miller, Wojciech P. Olszynski, Eric Orwoll, and Chui Kin Yuen

Department of Medicine (A.B.H.), University of Western Ontario, London, Ontario, Canada N6A 4V2; Department of Medicine, Epidemiology, and Biostatistics, Division of Medicine (D.C.B.), University of California, San Francisco, California 94105-3411; Department of Pathology (D.W.D.), Columbia University, New York, New York 10027-6902; Regional Bone Center (D.D.), Helen Hayes Hospital, West Haverstraw, New York 10993; Division of Geriatric Medicine (L.D.), University of British Columbia, Vancouver, British Columbia, Canada V6T 2B5; Division of Endocrinology and Metabolism, Department of Medicine (D.A.H.), University of Calgary, Calgary, Alberta, Canada T2N 4N1; Department of Medicine (S.T.H.), University of California, San Francisco, California 94117-3619; Department of Medicine and Endocrinology (D.L.K.), Osteoporosis Research Centre, University of British Columbia, Vancouver, British Columbia, Canada V5Z 2N6; Oregon Osteoporosis Center and Department of Medical Education (M.R.M.), Providence Portland Medical Center, Portland, Oregon 97213; Department of Medicine, University of Colorado Medical School, and Colorado Center for Bone Research (P.D.M.), Lakewood, Colorado 80227; Department of Medicine, University of Saskatchewan, and Saskatoon Osteoporosis Centre (W.P.O.), Saskatoon, Saskatchewan, Canada S7K 0H6; Department of Medicine and General Clinical Research Centre (E.O.), Oregon Health & Sciences University, Portland, Oregon 97201-3079; and Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Manitoba, and Manitoba Clinic (C.K.Y.), Winnipeg, Manitoba, Canada R3A 1M3

All therapies currently recommended for the management of osteoporosis act mainly to inhibit bone resorption and reduce bone remodeling. PTH and its analog, teriparatide [recombinant human PTH(1–34)], represent a new class of anabolic therapies for the treatment of severe osteoporosis, having the potential to improve skeletal microarchitecture. Significant reductions in both vertebral and appendicular fracture rates have been demonstrated in the phase III trial of teriparatide, involving elderly women with at least one prevalent vertebral fracture before the onset of therapy. However, there is as yet no evidence that the antifracture efficacy of PTH will be superior to the bisphosphonates, whereas cost-utility estimates suggest that teriparatide is significantly more expensive.

Teriparatide should be considered as treatment for postmenopausal women and men with severe osteoporosis, as well as for patients with established glucocorticoid-induced osteoporosis who require long-term steroid treatment. Teriparatide should also be considered for the management of in-

dividuals at particularly high risk for fractures, including subjects who are younger than age 65 and who have particularly low bone mineral density measurements (T scores \leq 3.5). Teriparatide therapy is not recommended for more than 2 yr, based, in part, on the induction of osteosarcoma in a rat model of carcinogenicity.

Total daily calcium intake from both supplements and dietary sources should be limited to 1500 mg together with adequate vitamin D intake (\leq 1000 U/d). Monitoring of serum calcium may be safely limited to measurement after 1 month of treatment; mild hypercalcemia may be treated by withdrawing dietary calcium supplements, reducing the dosing frequency of PTH, or both. At present, concurrent therapy with antiresorptive therapy, particularly bisphosphonates, should be avoided, although sequential therapy with such agents may consolidate the beneficial effects upon the skeleton after PTH is discontinued. (*Endocrine Reviews* 26: 688–703, 2005)

- I. Introduction
- II. Biological Activity of PTH
- III. Antiresorptive Therapy
 - A. Bisphosphonates
 - B. Other antiresorptive agents
- IV. Anabolic Therapy
 - A. Mechanism of action: anabolic vs. antiresorptive therapy
- V. Clinical Trials with Teriparatide and Intact PTH
 - A. Teriparatide
 - B. Trials with intact PTH
- VI. Side Effects and Precautions
 - A. Hypercalcemia and hypercalciuria
 - B. Osteosarcoma
 - C. Additional precautions
- VII. PTH in Clinical Practice
 - A. Candidates for PTH therapy
 - B. Monitoring
 - C. Duration of therapy
 - D. PTH and cotherapy with antiresorptive agents
- VIII. Summary
- IX. Recommendations

First Published Online March 15, 2005

Abbreviations: BMD, Bone mineral density; C, carboxyl; DXA, dual x-ray absorptiometry; GIOP, glucocorticoid-induced osteoporosis; intact PTH, intact or full sequence PTH(1–84); QCT, quantitative computed tomography.

Endocrine Reviews is published bimonthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

I. Introduction

PTH AND ITS analogs represent a new class of anabolic agents for the treatment of severe osteoporosis, unlike currently licensed therapies to manage osteoporosis, which act primarily to inhibit bone resorption and remodeling. In this paper members of the Western Osteoporosis Alliance have reviewed the clinical literature, published between 1990 and June 2004—the period of active development of the therapeutic use of these agents for the therapy of osteoporosis. In addition to a search of Medline, with particular attention to controlled clinical trials, the important English language bone and specialty journals were hand searched for the most recent publications in the clinical field of PTH therapy. A full historical review of the clinical and experimental evidence was neither appropriate nor necessary to arrive at current consensus. Grades of evidence were assigned according to the published criteria for developing clinical guidelines (1). Randomized clinical trials in which there was an appropriate control group would consistently lead to consensus recommendations of grade A or B. Of the four grades attached to our recommendations, grade D represents consensus expert opinions because there are many areas in which there are no data from randomized controlled clinical trials. Data published in abstract form are identified as such in the reference section, and are included when it seemed necessary to add to the body of information about mechanisms of action or therapeutic response. Table 1 describes the levels of evidence and grades of recommendations with which we have arrived at suggested guidelines for the use of PTH in managing osteoporosis.

II. Biological Activity of PTH

Human PTH is an 84-amino acid peptide that plays a central role in the maintenance of calcium homeostasis in mammals (2). The ambient extracellular calcium level signals an increase in PTH secretion in response to a decrease in calcium concentration via the calcium-sensing receptors on the parathyroid cellular membrane. PTH acts directly to increase renal tubular calcium reabsorption and indirectly to enhance intestinal calcium absorption via its stimulatory action on renal 1- α cholecalciferol hydroxylase (thereby increasing circulating calcitriol). The normal physiological role of PTH on skeletal homeostasis, when secreted endogenously, is more complex but probably serves to regulate bone remodeling rather than overall skeletal mass.

From early structure-function studies of PTH, it has been generally assumed that all of the biological activity of intact PTH (hPTH 1–84) resides in the N-terminal sequence; most clinical studies have used the 34-amino acid peptide hPTH(1–34), now named teriparatide. The first two amino

acids are obligatory for biological activity, and it appears that the bone anabolic properties are fully maintained by the foreshortened fragment hPTH(1–31) or its cyclized lactam. Although the 84-amino acid intact PTH is the natural product of PTH gene transcription and translation, the major immunoreactive circulating PTH species consists of carboxyl (C)-terminal fragments of the hormone. These fragments are secreted by the parathyroid cell, with intracellular cleavage enhanced by elevated extracellular fluid calcium (3). They also arise from cleavage of intact PTH by peripheral (target) tissues (4). N-terminal residues capable of receptor activation do not exist in the circulation under normal physiological conditions; after target tissue receptor binding, amino-terminal fragments may be formed, which are then rapidly degraded. The only known circulating form with biological activity at the PTH/PTHrP receptor is the full-sequence intact PTH(1–84) peptide.

It is possible that C-terminal fragments of intact PTH may have discrete biological properties. Both *in vitro* and *in vivo* studies indicate that the C-terminal part of PTH may have significant biological effects in bone. Evidence is accumulating that a separate receptor for the C terminus of PTH exists. Bringhurst and associates (5) have demonstrated that C-PTH fragments may enhance osteocyte apoptosis, and earlier cell culture studies of osteoblasts have shown that C-terminal fragments containing at least the last 30 or more amino acids of PTH will stimulate production of alkaline phosphatase and other markers of osteoblast activity (6). It is therefore plausible that intact PTH, when used as a therapy for osteoporosis, may have slightly different biological actions compared with teriparatide.

PTH exhibits potent anabolic effects on the skeleton when given exogenously by intermittent injection. This was first reported in humans by Reeve *et al.* (7) in 1980. In this study a small group of patients received teriparatide by daily sc injections for 6–24 months. Paired bone biopsies revealed substantial increases in iliac trabecular bone volume, with evidence of new bone formation and a suggestion that there was a dissociation between bone formation and resorption rates. Numerous historical studies have consistently confirmed improvements in bone tissue after daily injections of PTH analogs (8), but only recently has teriparatide become commercially available. The molecular mechanisms by which PTH analogs result in a partial reconstruction of skeletal architecture in subjects with severe osteoporosis are as yet unclear (2). However, a review of the recent literature supports the observation that architectural improvements do occur within the skeleton after daily PTH injections. This is in contrast to changes in the skeletal architecture observed after therapy with antiresorptive agents, which act mainly by

TABLE 1. Grades of recommendation for clinical practice guidelines (1)

Grade	Criteria
A	One or more randomized controlled trial(s) with adequate power, or metaanalysis ^a
B	Randomized controlled trial(s) not meeting all criteria for grade A ^a
C	Nonrandomized trial(s) or cohort studies, plus consensus
D	Any lower level of evidence supported by consensus (including expert opinion)

^a An appropriate level of evidence was necessary but not sufficient to assign a grade of recommendation; consensus was required in addition.

reducing bone turnover and preserving, rather than improving, skeletal architecture.

III. Antiresorptive Therapy

Most forms of osteoporosis are a consequence of bone loss due to an imbalance in bone remodeling such that bone resorption exceeds bone formation. By decreasing the number, activity, and life span of osteoclasts, several therapeutic agents suppress bone resorption and, indirectly, bone formation. These antiresorptive agents are capable of preserving bone mass, stabilizing bone structure and quality, and reducing fracture rates. Before the availability of PTH, all of our therapies for the prevention and treatment of osteoporosis fell into this category. There is an extensive literature both from well-designed clinical trials and several years of experience with their use in a clinical setting.

A. Bisphosphonates

Bisphosphonates are potent selective inhibitors of osteoclastic bone resorption. Both alendronate and risedronate reduce the incidence of vertebral fractures by 40–50% in women known to have osteoporosis (9–14), with similar reductions in nonvertebral fractures (15). Both agents have been shown specifically to reduce the risk of hip fractures by 40–60% in women with severe osteoporosis (16, 17). Clinical trials involving men and patients with glucocorticoid-induced osteoporosis (GIOP), have shown that bisphosphonates confer similar benefits in improved bone mineral density (BMD) and reduced vertebral fracture risk (18–21).

The onset of bisphosphonate action is rapid. Indices of bone resorption were suppressed and occurred within a few weeks of beginning treatment, and the risk of radiological or vertebral fracture was reduced as early as 6–12 months (13, 17, 22). All studies clearly demonstrate improvements in BMD during bisphosphonate therapy. However, histomorphometric studies obtained during the phase III clinical trials show few differences in trabecular bone architecture compared with patients treated with placebo (23, 24). In the absence of improved trabecular microarchitecture, the increments in BMD are most likely due to enhanced secondary mineralization of preformed osteons (25). Suppression of bone resorption allows closure of the existing skeletal remodeling space, further enhancing the increments in BMD compared with placebo treatment. Although the negative balance in the basic multicellular unit is reduced because of shallower resorption cavities during remodeling, there is no consistent evidence that these drugs eliminate the negative bone balance or render it positive, so that the apparent increase in measured bone mass is limited to the reduction of the reversible remodeling space (26).

B. Other antiresorptive agents

Other antiresorptive agents with proven antifracture efficacy include long-term estrogen therapy (27), raloxifene (28), and nasal calcitonin (29). In general, the vertebral fracture risk reduction has been more variable, but is not generally in excess of 40%, whereas neither raloxifene nor nasal calcitonin

has been shown to reduce the risk for appendicular fractures. By comparison with bisphosphonates, the increments in BMD seen with other antiresorptive agents are more modest. All clinical trials evaluating the use of treatment for osteoporosis have included nutritional supplements of calcium and vitamin D to both the placebo and treatment arms. Very low intakes of calcium or impaired calcium absorption due to inadequate vitamin D stores are associated with increased rates of bone loss and increased rates of fracture risk, especially in the elderly who are less able to adapt to low calcium intake because of age-related inefficiencies in vitamin D metabolism (30). The administration of calcium and/or vitamin D to elderly adults deficient in these nutrients slowed bone loss and reduced the risk of vertebral and nonvertebral fractures, including hip fractures (31–34). Thus, effects attributed to antiresorptive agents are in addition to the effects due to calcium and vitamin D alone. Whereas calcium and vitamin D are important aspects of treatments, pharmacological therapy provides more effective protection from fracture; this is probably true for both antiresorptive and anabolic agents.

Thus, clinicians now have an effective group of antiresorptive agents for patients with, or at risk for, osteoporosis. It is against this proven background that the utility of PTH and its analogs must be contrasted.

IV. Anabolic Therapy

A. Mechanism of action: anabolic vs. antiresorptive therapy

The cellular mechanism of action of PTH is fundamentally different from that of antiresorptive agents. The latter can be more aptly termed “antiremodeling agents” because, although their initial action is to inhibit resorption, they also rapidly inhibit formation, which under most circumstances is tightly coupled to resorption. Indeed, inhibition of remodeling is one of the primary mechanisms through which this class of drugs operate. A decrease in the remodeling rate has several effects that are beneficial to bone strength, including: 1) an improvement in bone density through a decrease in the size of the remodeling space; 2) preservation of cancellous bone architecture; 3) a reduction in the number of resorption cavities, which act as mechanical stress concentrators with the potential to trigger mechanical failure; 4) an increase in the amount of bone mineral per unit volume of bone tissue; and 5) a decrease in cortical porosity (25, 35–37).

B. Structural changes in bone after PTH therapy

By contrast, PTH stimulates bone formation through an increase in the bone remodeling rate. Under the influence of exogenous PTH treatment, the amount of bone laid down in each remodeling unit, as assessed by osteon thickness, is increased (38–40). This distinguishes the effects of PTH treatment from other high-remodeling states, such as estrogen deficiency, which are deleterious to bone strength. The combination of an increase in the remodeling rate and in the amount of bone laid down in each remodeling transaction provides a mechanism for ongoing gains in the amount of bone tissue, including an increase in trabecular thickness (38), which is not seen with antiresorptive agents, at least

not at the iliac crest. In addition to stimulation of bone formation through this mechanism, which can be referred to as “remodeling-based formation,” there is also biochemical and histomorphometric evidence that teriparatide is initially able to uncouple formation from resorption, stimulating formation directly without a requirement for prior resorption (41–43). This can be referred to as modeling-based formation. This may occur by activation of lining cells on previously quiescent bone surfaces (44), as well as by osteoblasts engaged in remodeling-based formation migrating outside the borders of the bone remodeling unit to deposit bone on sites that were untouched during the resorptive phase of the cycle (45).

Teriparatide treatment has been shown not only to increase trabecular thickness but also to increase trabecular connectivity as assessed in three dimensions by microcomputed tomography of iliac crest bone biopsies (40, 46). This is shown clearly in Fig. 1. The underlying mechanism is uncertain but could involve the initial thickening of trabeculae followed by intratrabecular tunneling (47); it is in sharp contrast to the mechanism of bisphosphonate action, during which preservation, rather than alteration, of trabecular architecture occurs (24).

Since the landmark study by Reeve *et al.* (7), there have been concerns that at least some of the gains in cancellous bone may be achieved at the expense of cortical bone. Several clinical studies have demonstrated small decreases in areal BMD [measured by dual x-ray absorptiometry (DXA)] at cortical bone sites with both teriparatide (48–52) and intact PTH (53). This is likely due to enhanced intracortical remodeling and is self-limiting. Iliac crest bone biopsies do not show enhanced cortical porosity after 18–36 months of teriparatide treatment (39, 40, 46). Animal data demonstrate increased remodeling in the inner two thirds of the cortex, leading to “trabecularization” of the endocortical envelope. Similar active remodeling is seen along endocortical bone in iliac crest biopsies after teriparatide treatment of postmenopausal women (39). However, expansion of the inner diameter of tubular bone due to this endocortical activity has little effect on calculated bending strength (54–57). The effects are

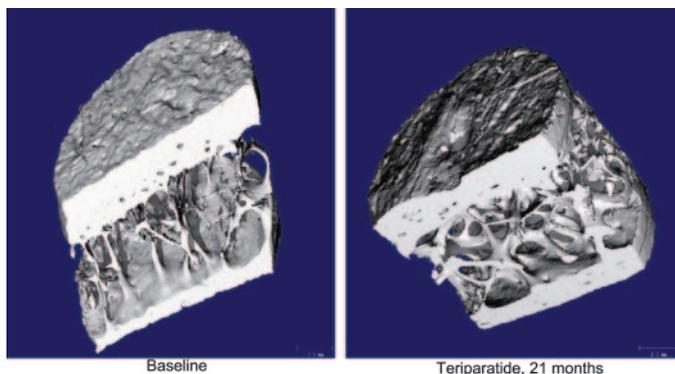


FIG. 1. Reconstructed micro-QCT images of transiliac crest bone biopsies, taken before and after 21 months of teriparatide therapy, 20 $\mu\text{g}/\text{d}$. These images demonstrate increased trabecular thickness and connectivity, together with increased cortical thickness. [Reproduced with permission from Y. Jiang *et al.*: *J Bone Miner Res* 18:1932–1941, 2003 (46) with permission of the American Society for Bone and Mineral Research.]

offset by an increase in both cortical thickness and diameter due to new periosteal bone apposition. Such improvements in cortical bone architecture with teriparatide treatment are now beginning to be documented in humans using a variety of techniques, including histomorphometry (40, 46), peripheral quantitative computed tomography (QCT) (58–61), radiogrammetry (62), and absorptiometric assessment of bone size (63, 64). Thus, Zanchetta *et al.* (59) compared cortical architecture in the distal radius by peripheral QCT, after 18 months of treatment with teriparatide or placebo. During teriparatide therapy, new periosteal apposition occurred, but cortical thickness was unchanged because of concurrent endocortical remodeling. However, the greater radial outer dimension resulted in biomechanically stronger bone as assessed by axial and polar moments of inertia. Similar findings have recently been reported for the femoral neck (61). An increase in the bone formation rate, determined by tetracycline labeling, has been reported on the periosteal surface of iliac cortical bone in patients treated for only 1 month with teriparatide, providing a plausible mechanism for periosteal expansion (43).

That PTH may be able to increase bone size is significant, given that the strength of a cylinder is proportional to the fourth power of its radius. Small increments in bone size therefore may have disproportionately greater effects on bone strength. Bone size increases with age, and this compensates for the age-related loss of bone tissue (65–67). PTH treatment appears to accelerate this natural process. The 20-yr-old belief that intermittent PTH treatment may have deleterious effects on cortical bone therefore appears to be losing ground. With that comes the realization that to assess the effects of PTH treatment in a clinical setting, we need to exercise caution in interpreting BMD changes, particularly areal measurements provided by DXA. Indeed, BMD measurement may give misleading results; a decrease in BMD due to enhanced cortical remodeling may not indicate loss of bone strength if it is accompanied by improvements in cortical, as well as trabecular, architecture. A further reason that areal DXA may underestimate improvement in bone mass lies in the increased volume of relatively undermineralized osteoid, which occurs when bone turnover is increased. This is the opposite of the mechanism seen during bisphosphonate use and has been documented in paired iliac crest biopsies before and after teriparatide use (68). There is therefore a pressing need to explore the utility of other imaging modalities, such as structural analysis by DXA (69), QCT (70, 71), and high-resolution magnetic resonance imaging (72–74) in the noninvasive assessment of the effects of PTH on trabecular and cortical bone. Development of better surrogate measures for bone strength will become increasingly important for assessing the effects of antifracture drugs, both antiresorptive and anabolic, as fracture trials become progressively more difficult to conduct for practical and economic reasons.

In conclusion, PTH represents the first in a new class of bone anabolic agents. It is the first antifracture drug that has been shown to increase osteoblast number and activity, to increase the bone remodeling rate as well as the amount of bone deposited in each remodeling cycle, to increase trabecular thickness and improve trabecular connectivity, to stim-

ulate bone formation without prior resorption, and to increase cortical thickness and bone size.

V. Clinical Trials with Teriparatide and Intact PTH

Table 2 describes the published randomized clinical trials published since 1997. The table describes only those trials that included both a representative sample of “at risk” subjects and a control not receiving PTH. Whereas the table differentiates studies carried out in postmenopausal women, men, postmenopausal women with GIOP, and premenopausal women with acute estrogen deficiency, our brief review of the evidence describes the overall benefits of PTH therapy irrespective of treatment cohorts; treatment effects are quite consistent between studies, and we have highlighted only the inconsistencies.

A. Teriparatide

1. *Changes in biochemical markers of bone turnover.* PTH is a direct anabolic agent in bone tissue. It induces new bone formation on otherwise quiescent bone surfaces, while also stimulating bone turnover by the classic remodeling cycle involving both osteoclastic resorption and osteoblastic reformation. Not surprisingly, biochemical markers of both bone formation and resorption increase dramatically and can be detected in both blood and urine. Hodsman *et al.* (75) first showed these increments to occur very early on, within 28 d of initiating teriparatide therapy. These findings have been shown in many studies with teriparatide (42, 48, 49, 51, 76–78) and for intact PTH (53). Increments in markers of bone formation (*e.g.*, bone-specific alkaline phosphatase, N-propeptide of type 1 collagen, osteocalcin) and markers of bone resorption (*e.g.*, urinary N-telopeptide, urine deoxy-pyridinoline, serum C-terminal telopeptide) of at least 100% are seen, and, characteristically, bone formation markers increase more rapidly and earlier during the course of therapy than those reflecting bone resorption. This may reflect the direct early anabolic effects of PTH, which is occurring before the bone-remodeling cycle accelerates. Another feature of these bone turnover profiles is a tendency for the increments to peak during the first 12 months of therapy but to gradually decline toward baseline over the next 12–24 months. It is not known whether this represents a form of tachyphylaxis to PTH peptides, resulting in diminishing skeletal response over time.

2. *Reduction in fracture risk.* In the phase III trial of teriparatide, Neer *et al.* (50) demonstrated a significant reduction in both vertebral and nonvertebral fractures, at doses of 20 and 40 $\mu\text{g}/\text{d}$. At the 20- μg dose chosen for the clinical market, the risk of new radiographic vertebral fractures was reduced by 65% compared with placebo over a median treatment period of 19 months (Fig. 2). If the analysis of vertebral fractures was restricted to moderate or severe deformities (>26% reduction in vertebral height), the risk reduction was 90%. Figure 3 shows the incidence of nonvertebral fractures during the study. When all nonvertebral fragility fractures were assessed, women were 53% less likely to fracture (relative risk, 0.47; confidence interval, 0.25–0.88). It is of interest that there

was no clear distinction of fracture risk reduction between the two doses of teriparatide. Moreover, *post hoc* analysis in this cohort demonstrated that the fracture risk reduction was largely independent of age, initial BMD, and prevalent vertebral fractures at baseline (79).

Where fracture incidence data were provided in the other trials, the numbers of treated patients were too small to achieve significance; however, there is a consistent trend to fewer vertebral and nonvertebral fractures in every case (42, 78). Body *et al.* (49) compared teriparatide treatment (40 $\mu\text{g}/\text{d}$) [a dose chosen before the study of Neer *et al.* (50) suggested 20 $\mu\text{g}/\text{d}$ as being the most suitable dose], to standard therapy with alendronate (10 mg/d) over a median of 14 months. There was a significant reduction in nonvertebral fractures compared with treatment with alendronate (4 *vs.* 14%), but some of these may have been traumatic, and the absolute numbers were very small (*e.g.*, toe fractures in the alendronate group are of uncertain significance).

3. *Changes in BMD.* PTH consistently increases BMD (measured by DXA) in predominantly trabecular bone (lumbar spine) and to a lesser degree over a mixed cortical/trabecular site (femoral neck), but has little effect over a mainly cortical site (distal radius) where the measured BMD may actually fall slightly. The effect is dose dependent (50, 51, 53, 80) and, by comparison to alendronate, of significantly greater magnitude (49). Increments in BMD are maximal during the first 18 months of therapy, but the incremental rate may decline beyond this point (49, 76); however, there are studies in which the increments in BMD continue to be linear at or after 18 months duration of therapy (42, 48). Typically, BMD of the lumbar spine increases from 10–14% over 1–3 yr (Table 2). In the phase III teriparatide trial, in which postmenopausal women were treated for a median of 19 months, the mean increment in lumbar spine BMD in the group receiving 20 $\mu\text{g}/\text{d}$ was 9.7%, *vs.* 1.1% for placebo-treated patients (50). *Post hoc* analysis demonstrated that in 96% of individuals there was an increase at least above baseline, and in 72% the increase was at least 5% (81).

In contrast, changes in femoral neck BMD are usually less than 5% over comparable time periods. Changes in BMD over the distal radius have been inconsistent through the historical small trials of PTH, but in the more recent controlled clinical trials, it is apparent that PTH results in a consistent small reduction in radial BMD (in the order of 1–2%) (48–51). The significance of the apparently adverse effect on BMD of the distal radius is controversial. The study by Neer *et al.* (50) was the only trial large enough to begin to evaluate the wrist fracture incidence during teriparatide therapy. Compared with placebo, treated patients had about half the number of wrist fractures. The apparent decrement in radial BMD may be a combination of several effects induced by PTH that occur simultaneously, including increased endocortical remodeling, increased remodeling space within the cortical haversian systems, and an increase in measured area due to periosteal bone apposition as discussed previously in Section IV.B. In general, total body calcium measurements increase (42, 49–51). The increase is small, in the order of 1–2%, although in the study reported by Lindsay *et al.* (42) in which teriparatide was given to

TABLE 2. Controlled trials of PTH therapy

Ref.	Design ^a	Age (yr)	Total enrolled (no. of groups)	Inclusion		Teriparatide (μg/d)	Control	Duration (months)	Primary outcome	Fractures (%) ^b		Δ BMD (%) ^c	
				Vertebral fractures	BMD (T-score)					Vertebral	Nonvertebral	L/S	FN
Postmenopausal women													
Lindsay, 1997 (42)	RT	62	34 (2)	either 1 or both	<2.5	25	Long-term estrogen	36	L/S BMD	6 vs. 29	N/A	13 vs. 0 ^d	2.7 vs. 0 ^{e,f}
Neer, 2001 (50)	RCT	70	1637 (3)	either 2 or <2	<-1.0	20–40	Placebo	21	Fractures	4–5 vs. 14 ^e	3 vs. 5 ^d	10–14 vs. 1 ^e	2.6–3.6 vs. -1 ^f
Body, 2002 (49)	RT	66	146 (2)	<2.5	<2.5	40	Alendronate	14	L/S BMD	N/A	4 vs. 14 ^d	14 vs. 6 ^c	4.5 vs. 2.8 ^{e,g}
Hodsman, 2003 (53)	RCT	65	217 (4)	<2.5	<2.5	50–100 ^h	Placebo	12	L/S BMD	N/A	N/A	3–8 vs. 0 ^e	-0.2–0.5 vs. -0.7 ^g
Black, 2003 (60)	RT	70	238 (3)	<2.5	<2.5	100 ^h	Alendronate	12	BMD	N/A	N/A	6.3 vs. 4.6 vs. 6.1	0.8 vs. 2.0 vs. 1.8 ^g
Men													
Kurland, 2000 (48)	RCT	50	23 (2)	<2.5	<2.5	25	Placebo	18	L/S BMD	N/A	N/A	14 vs. 0 ^f	2.9 vs. 0 ^{d,g}
Orwoll, 2003 (51)	RCT	59	437 (3)	<2.0	<2.0	20–40	Placebo	12	L/S BMD	N/A	N/A	6–9 vs. 0.5 ^e	1.5–2.9 vs. 0.3 ^{d,g}
Finkelstein, 2003 (86)	RT	58	83 (3)	<2.0	<2.0	40	Alendronate	30	L/S BMD	N/A	N/A	18.1 vs. 7.9 ^e vs. 14.8 ^c	9.7 vs. 3.2 ^e vs. 6.2 ^{e,g,i}
GIOP													
Lane, 1998 (78)	RT	63	51 (2)	<2.5	<2.5	25	Long-term estrogen	12	L/S BMD	0 vs. 6	8 vs. 11	11 vs. 1 ^e	1.6 vs. 0.8 ^g
Premenopause													
Finkelstein, 1998 (77)	RT	32	43 (2)			40	Nafarelin	12	L/S BMD	N/A	N/A	2.1 vs. -4.9 ^f	0 vs. -4.5 ^{e,g}

^a RT, Control group received active therapy; RCT, control group received supplements of calcium and vitamin D.

^b Percentage of enrolled patients.

^c Percentage change over baseline. L/S, Lumbar spine; FN, femoral neck.

^d <0.05, Placebo or control vs. PTH.

^e ≤0.01, Placebo or control vs. PTH.

^f Total FN.

^g FN (region of interest).

^h Intact PTH (hPTH 1–84); 100 μg intact PTH = 40 μg teriparatide.

ⁱ PTH vs. alendronate vs. combination.

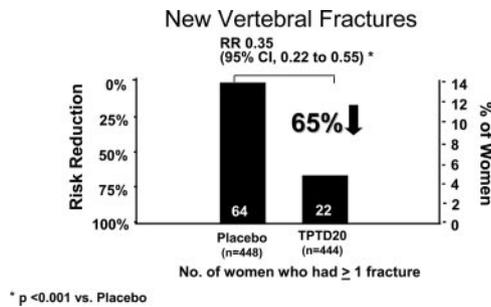


FIG. 2. Reduction in the risk of new morphometric vertebral fractures in postmenopausal women with severe osteoporosis after teriparatide, 20 $\mu\text{g}/\text{d}$, over a median treatment period of 19 months, compared with placebo. [Derived from Ref. 50.]

postmenopausal women on long-term estrogen therapy, the increment in total body calcium was linear and almost 8% over 3 yr.

Therapy with teriparatide has consistently improved lumbar spine and femoral neck BMD in men (48, 51) and in postmenopausal women with GIOP (78). Indeed, changes in BMD and incremental changes in biochemical markers of bone turnover mirror closely those seen in postmenopausal osteoporosis. Finkelstein *et al.* (77) have evaluated the effect of teriparatide in younger women with acute estrogen deficiency after nafarelin therapy. In this study, BMD was maintained during the 12-month treatment period, whereas women treated with nafarelin alone experienced sharp decrements in both lumbar spine and femoral neck BMD measurements (Table 2). These women received a relatively high dose of PTH (40 $\mu\text{g}/\text{d}$), but the specific activity of the peptide was not mentioned. There is no obvious explanation as to why the bone densitometric changes were so much lower than in the other trials utilizing teriparatide.

4. Health outcomes and cost effectiveness. Only one study has evaluated health-related quality of life (82). Using a disease-specific instrument, the Osteoporosis Assessment Questionnaire (OPAQ), Oglesby *et al.* (106) reported on outcomes from the teriparatide phase III randomized controlled trial. Although it could be clearly shown that incident vertebral and nonvertebral fractures were associated with a deteriorating quality of life (compared with those patients who did not fracture), there was no significant difference between the teriparatide-treated patients and those on placebo. Unfortu-

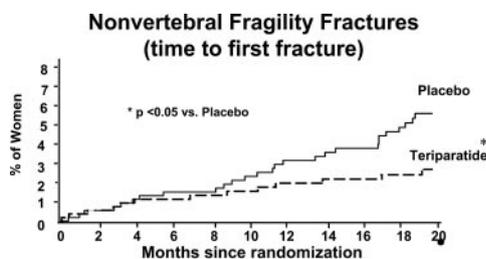


FIG. 3. Cumulative incidence of new nonvertebral fractures, occurring with minimal trauma, in postmenopausal women after teriparatide therapy, 20 $\mu\text{g}/\text{d}$, over a median treatment period of 19 months: relative risk, 0.47 (confidence interval, 0.22–0.88) compared with placebo (Eli Lilly, Canada, Forteo Product Mongraph). [Derived from Ref. 50.]

nately, of more than 1600 patients enrolled in the overall trial, only 365 were assessed with the Osteoporosis Assessment Questionnaire instrument, limiting the statistical power of the analysis. However, in this same fracture prevention trial, the incidence of any back pain (reported as an adverse event), was significantly less in the group receiving 20 $\mu\text{g}/\text{d}$ than in the placebo group (17% vs. 23%; $P < 0.02$) (83). Similarly, patients treated with teriparatide, 40 $\mu\text{g}/\text{d}$, were reported to have significantly less back pain than those receiving alendronate in the small head-to-head trial (6% vs. 19%; $P = 0.012$), but this study did not document vertebral fractures as an outcome (49).

To a degree, the cost effectiveness of osteoporosis therapy depends on the number of patients who need to be treated to prevent a fracture. Table 3 compares the fracture data between teriparatide and two widely used bisphosphonates, alendronate and risedronate. The data are taken from the randomized clinical trials in which postmenopausal women were enrolled on the basis of having at least one prevalent vertebral fracture; in the four studies cited, the mean age of the study cohorts ranged from 69–71 yr, and treatment duration ranged from 21 months (teriparatide) to 3 yr (alendronate and risedronate). Although there may be other factors influencing future fracture risk, the four study populations should be quite comparable. In the absence of head-to-head studies, this is a pragmatic way to compare effectiveness, because age and the prevalence of fractures, before initiating osteoporosis therapy, greatly influence the number who need to be treated calculation (84). As can be seen, the apparent relative effectiveness of teriparatide and bisphosphonates is quite similar when used in postmenopausal women at higher risk for fragility fractures. The National Institute for Clinical Excellence in the United Kingdom has compared the cost-utility ratio between the bisphosphonates, raloxifene and teriparatide, using a modified individual Markov approach (85). The baseline model examines the cost-utility ratio of bisphosphonates, raloxifene and teriparatide, in postmenopausal women with at least one prevalent vertebral fracture and a T score of less than -2.5 , stratified by ages 50–80 yr. At age 60, the cost-utility ratio (calculated in pounds per Quality of Life Year to prevent one clinical fracture) of teriparatide is nearly 3-fold that of bisphosphonates. It approximates that of the bisphosphonates, alendronate and risedronate, only when the modeled risk is 4-fold higher than that of the baseline model. This increased level of risk would represent women with either 1) two or more fractures, a T score less than -3.0 plus an additional major but nonmodifiable risk factor; or 2) an “extremely” low T score of less than -4.0 (85). The National Institute for Clinical Excellence analysis has the advantage that generally agreed upon quantifiable risks and benefits were applied within a single health care system; the much higher cost-utility ratio for teriparatide as compared with the bisphosphonates is driven by the cost of teriparatide rather than its efficacy.

B. Trials with intact PTH

Intact PTH is undergoing phase III clinical trials. However, in the phase II studies with intact PTH, three doses (50, 75, and 100 $\mu\text{g}/\text{d}$) were evaluated over 12 months (Table 2) (53).

TABLE 3. Comparison of fracture risk reduction between teriparatide (for 19 months) and bisphosphonates (for 36 months) during the clinical trials in postmenopausal women with at least one baseline incident vertebral fracture

	Teriparatide Neer <i>et al.</i> (50)	Alendronate Black <i>et al.</i> (11)	Risedronate Harris <i>et al.</i> (13)	Risedronate Reginster <i>et al.</i> (14)
New vertebral fractures				
Relative risk (95% CI)	0.4 (0.2–0.6)	0.5 (0.4–0.7)	0.6 (0.4–0.8)	0.5 (0.4–0.7)
Placebo incidence rate (%)	14	15	16	29
Absolute risk reduction (%)	9	7	5	11
NNT	11	9	20	10
New nonvertebral fractures				
Relative risk (95% CI)	0.5 (0.3–0.9)	0.8 (0.6–1.0)	0.6 (0.4–0.9)	0.7 (0.4–1.0)
Placebo incidence rate (%)	6	15	8	51
Absolute risk reduction (%)	3	3	3	15
NNT	34	34	43	20

Changes in BMD were dose dependent. At 100 $\mu\text{g}/\text{d}$, the dose currently under evaluation in phase III, the increments in BMD were 7.8% at the lumbar spine, and 0.5% at the femoral neck after 12 months. There was a nonsignificant decrement of 1.5% in whole-body BMC. It is possible that the small changes in femoral neck and whole-body bone mineral measurements reflected transient imbalance between cortical remodeling and bone formation. A subset of these phase II study patients received sequential therapy with alendronate for an additional 12 months and demonstrated very significant increments at both measurement sites (52). As with teriparatide, intact PTH produced similar increments in biochemical markers of bone turnover (53). As yet, there are no data on the antifracture efficacy of intact PTH. Several other PTH analogs have been evaluated in animal models of osteoporosis, but there are no comparable studies in human subjects.

VI. Side Effects and Precautions

Only the study by Neer *et al.* (50) was large enough to consistently search for adverse events in teriparatide-treated patients *vs.* placebo. Circulating antibodies to teriparatide developed in 3% of the women receiving 20 $\mu\text{g}/\text{d}$, but these antibodies had no discernable effects on any of the measured clinical outcomes. Antibody formation was not found after intact PTH therapy (53). During the teriparatide trial, the frequencies of headaches (8%) and nausea (8%) were no greater than in the placebo group. Nine percent reported dizziness and 3% reported leg cramps. These two symptoms were reported by significantly fewer (6% and 1%) of the control patients. They tend to occur within a few hours of injection. The incidence of side effects has been variable from study to study. Although there is not enough published information to comment on side effects associated with intact PTH, they are probably similar. A significant increase in serum uric acid has been found in about 3% of patients after teriparatide therapy (50) and also in patients treated with intact PTH (60), several of whom developed acute gout.

A. Hypercalcemia and hypercalciuria

PTH injections consistently increased serum calcium. Figure 4 shows the pharmacokinetic profile of serum PTH and calcium observed during the phase III teriparatide fracture prevention trial. After injection, serum teriparatide levels

increase to approximately 170 pg/ml within 30 min (an increment of 10-fold over baseline levels, which predominantly reflects measurement by the assay of endogenous intact PTH), rapidly decline with a $t_{1/2}$ of about 1 h, and return to baseline by 4 h. Between 4 and 6 h, the serum calcium peaks, but the level remains within the normal physiological range, with the increment being about 0.2 mmol/liter (0.8 mg/dl). The increased serum calcium is sustained during the day but returns to baseline before the next dose. However, within the pivotal study in postmenopausal women (50) postdose serum calcium was above the upper limit of normal at least once in 11% of patients on teriparatide, 20 $\mu\text{g}/\text{d}$. Repeated serum calcium levels were assessed according to an algorithm, and only if persistently elevated were calcium supplements decreased or discontinued. Ultimately, the dose of teriparatide was reduced by 50% in only 3% of patients, and persistent increments in serum calcium led to withdrawal of active therapy in only one of 541 patients. Similar transient rises in serum calcium have been reported during other controlled trials with teriparatide (51, 86). There is less information for the chosen dose of intact PTH, 100 $\mu\text{g}/\text{d}$, but the incidence of transient hypercalcemia may be higher (53, 60), and 8–10% of patients may develop mild hypercalciuria (60). After teriparatide treatment, there was a small increase in 24-h urinary calcium excretion by a median of 0.75 mmol (30 mg)/d (50). However, the clinical trials with teriparatide excluded patients with hypercalciuria or a history of renal calculi within 5 yr, and the development of hypercalciuria required reduction in daily calcium supplements. Whereas no clinical adverse events were associated with any increments in serum or urine calcium, the most efficient means of identifying the small percentage of patients who require dose reduction has yet to be determined.

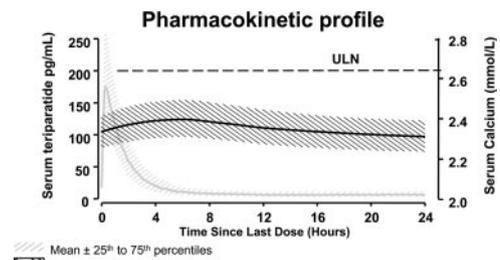


FIG. 4. Pharmacokinetic profile of teriparatide given by sc injection, together with resulting changes in serum calcium (data on file, Eli Lilly, USA, www.fda.gov/ohrms/dockets/ac/01/slides/3761s2_01_lilly).

B. Osteosarcoma

All three of the major teriparatide trials (in postmenopausal women with severe osteoporosis, in men with osteoporosis, and the first head-to-head trial against alendronate) (49–51) were terminated prematurely because of the findings of induced osteosarcoma in an ongoing carcinogenicity study in rats. In this study, Fischer 344 rats were given PTH from infancy through senescence (from 8 wk of age through 2 yr) (87). The administered doses would correspond to approximately 30–4500 $\mu\text{g}/\text{d}$ when given to a 60-kg human subject. Osteosarcoma was found at all dose levels, and, in the lower dose ranges, was first detected after approximately 20 months of therapy (87). It should be pointed out that therapy with teriparatide at these doses causes gross abnormalities in bone tissue in the rat model, with overgrowth of trabecular bone to the point that the marrow space in both the metaphysis and diaphysis is almost completely replaced by bone tissue (88). Osteosarcoma has also been reported in a similar carcinogenicity study with intact PTH. Although there was no difference in the low dose (10 $\mu\text{g}/\text{kg}\cdot\text{d}$) compared with controls, there was a dose-related incidence of osteosarcoma in the mid- (50 μg), and high- (100 μg) dose groups over 2 yr. At the time of writing these results are available only in preliminary form (www.npsp.com/news/releasestxt.php?ReqId=471943).

There is no substantive evidence of clinical osteosarcoma induction in clinical states of high, very prolonged PTH secretion (*e.g.*, renal osteodystrophy). To date there have been four case reports of coincident osteosarcoma in patients with primary hyperparathyroidism, but the cause-and-effect relationship remains unproven (89). In the study of Neer *et al.* (50), no osteosarcomas were found, but the rarity of these cancers in humans makes assessment of the relative risk impossible at present. The relevance of the animal carcinogenicity findings to treating older subjects with severe osteoporosis may be minimal. In adult humans, in whom such exaggerated pharmacological effects in bone do not occur, it is unlikely that the risk of osteosarcoma would be increased by daily treatment with PTH for a relatively small fraction of the normal life span. An independent outside oncology advisory board concluded that the rat carcinogenicity finding is very unlikely to have relevance to humans treated with teriparatide. The approved labeling for teriparatide in the United States limits its use to no more than 2 yr (88).

C. Additional precautions

In view of the carcinogenicity studies in animals, certain warnings have been issued to avoid the use of teriparatide and, presumably, other PTH peptides in patients who might be at increased risk for osteosarcoma, *i.e.*, patients with Paget's disease, prior skeletal irradiation, unexplained increases in serum bone-specific alkaline phosphatase, and adolescents in whom the epiphyses have not yet closed. In addition to bone and kidney, many normal tissues express the PTH/PTHrP receptor, including those of epithelial and endothelial origin, and the receptor has been found in some solid tumors, including breast and clear-cell renal cancer. This raises the theoretical possibility of nonosseous cancer

induction during PTH therapy. The use of PTH in patients with a recent history of cancer has not been explored because clinical trials routinely exclude such patients. In the phase III teriparatide trial, nonosseous cancers developed in 40 women, with a higher incidence in the placebo group (4%) than in the 20- $\mu\text{g}/\text{d}$ (2%) and 40- $\mu\text{g}/\text{d}$ (2%) groups, and this apparent difference in cancer incidence was significant in the 20- μg treatment group ($P = 0.02$) (50). There is therefore little current evidence to warrant concern that PTH therapy is attached to a significant risk of inducing either bone or nonosseous cancer, but it may be prudent not to recommend it in patients with a history of cancer within the past 5 yr.

PTH should be avoided in patients with a history of nephrolithiasis and/or gout, unless careful monitoring of serum and urine calcium or uric acid is maintained. Before PTH therapy is initiated, nutritional vitamin D status should be evaluated with serum 25-OH vitamin D levels. Vitamin D deficiency (serum levels < 40 nmol/liter) (90) and insufficiency (< 80 nmol/liter) (91) are relatively common. This is particularly relevant for patients with very low T scores, of less than -3.5 , in whom nutritional osteomalacia should be clearly excluded before PTH therapy is begun. Obviously, PTH should not be considered if other metabolic bone disease, including primary hyperparathyroidism or renal osteodystrophy, is suspected, although a theoretical case might be made for treating "osteoporotic" fractures in dialysis patients with adynamic bone disease and severe functional hypoparathyroidism.

VII. PTH in Clinical Practice

A. Candidates for PTH therapy

To date, almost all clinical trials of PTH have been carried out in postmenopausal women with osteoporosis, using teriparatide. Therefore our recommendations apply mainly to postmenopausal women, although men with osteoporosis should also be considered. The following three groups of patients should be considered candidates for therapy with teriparatide. At present there are insufficient data to comment on intact PTH, which has yet to receive regulatory approval.

1. *Patients with preexisting osteoporotic fractures.* The best evidence to date supporting the therapeutic efficacy of teriparatide to reduce the risk of both vertebral and nonvertebral fractures comes from the study by Neer *et al.* (50), which tested teriparatide in postmenopausal women, over 65 yr of age, who also had prevalent vertebral fractures before therapy. However, in this trial, the risk for developing new vertebral fractures was largely independent of initial lumbar spine BMD and was seen in patients with T scores between -2.1 and -3.3 (79). Moreover, in this study, the risk for new vertebral fractures was reduced similarly, irrespective of the number of prevalent fractures before the onset of therapy. These data are in contrast to the antifracture efficacy of bisphosphonates, where the fracture risk reduction is clearly dependent on the number of prevalent fractures as well as the reduction in BMD present before therapy is started (17, 79, 92). Thus, PTH therapy is likely to be most effective in

patients with preexisting “fragility” fractures irrespective of whether measured BMD falls below the cut-off point definition of osteoporosis (*i.e.*, a T score of ≤ -2.5). Because the increment in BMD in response to teriparatide is very similar for men to that seen in women (51), the antifracture efficacy of PTH will likely be similar for men and women.

2. Patients with very low bone density. The rapidity with which increments in BMD are seen in response to teriparatide may make this a preferred therapy in individuals at particularly high risk for incident fractures. Because fracture risk increases exponentially, doubling with each integer decrease in BMD T score, such high-risk individuals may be arbitrarily defined with T scores of -3.5 or below even in the absence of fractures. In the absence of a head-to-head comparative trial comparing antifracture efficacy, whether teriparatide or bisphosphonate therapy should be the preferred initial therapeutic choice in patients meeting the World Health Organization’s definition of “severe osteoporosis” (a T score of -2.5 plus vertebral fractures) cannot be defined. In a short trial comparing teriparatide with alendronate, the increments in BMD at both the lumbar spine and femoral neck were significantly earlier and of greater magnitude for teriparatide (49). On the other hand, there is no evidence that teriparatide is superior to bisphosphonates in its antifracture efficacy (Table 3), and therefore its much higher cost may not justify its use as a first-line therapy.

3. Patients with an unsatisfactory response to antiresorptive therapy. There may be reasons to select teriparatide in patients previously treated with a potent antiresorptive agent, recognizing that bisphosphonates may blunt or delay the anabolic response to PTH. Intolerance to the local upper gastrointestinal irritation by bisphosphonates would be a clear indication. An incident fragility fracture during bisphosphonate treatment is not an indication of treatment failure of itself: no treatment reduces the risk of fracture to zero. However, an incident fracture in the face of continuing and significant reduction in BMD despite 2 yr of apparently compliant therapy would be evidence of an unsatisfactory response to the bisphosphonate. In such cases it would be important to exclude secondary causes of osteoporosis, including vitamin D deficiency, other endocrine conditions, or unrecognized intestinal malabsorption syndromes. At present there is no evidence that patients with an unsatisfactory response to bisphosphonates will have a more favorable outcome to PTH, particularly if future studies confirm that some or all bisphosphonates blunt the anabolic action of PTH (see below).

4. Patients who should not be treated. Most studies with either teriparatide or intact PTH have involved postmenopausal women or men over the age of 50. There is no clinical reason for an age restriction, but younger men and women with a low BMD as their sole abnormality should probably not be treated, as prevalent fragility fractures are unusual in individuals under the age of 50, and the clinical significance of low T scores in this age group is unclear. Safety in pregnancy has not been determined, and PTH should not be prescribed to women in their reproductive years. Although the risk of osteosarcoma is not considered to be significant for humans,

the manufacturer recommends that teriparatide not be used in situations where the risk of developing osteosarcoma might be increased, particularly in adolescents with open epiphyses (in whom the incidence of osteosarcoma is much higher than in older individuals) and in older patients with Paget’s disease or previously treated with external ionizing radiation.

B. Monitoring

The clinical trials with teriparatide and intact PTH have included algorithms for dose adjustment in response to hypercalcemia. However, the recent Food and Drug Administration approval of teriparatide does not include recommendations for monitoring serum calcium because persistent hypercalcemia requiring dose reduction was uncommon ($\sim 3\%$ of patients taking $20 \mu\text{g}/\text{d}$), and the hypercalcemia that was occasionally seen was mild. Although nausea and vomiting were reported as significant, but occasional, adverse reactions to teriparatide, there was no correlation between these symptoms and the rare incidence of hypercalcemia (data on file, Eli Lilly, Indianapolis, IN). Nonetheless, many physicians may feel it prudent to monitor fasting predose serum calcium after 1 month of stable daily teriparatide injections. If persisting hypercalcemia is found, decreasing calcium supplements to ensure a total daily calcium intake of no more than 1000 mg would be the first action. If hypercalcemia persists, the frequency of injections can be reduced to alternate days. Significant hypercalciuria, renal calculus formation, or nephrocalcinosis has not surfaced as a clinical problem in patients receiving teriparatide.

Consistent increments in serum uric acid have been reported with teriparatide and intact PTH, but the utility of monitoring serum uric acid in the absence of a history of gout is unclear.

The frequency of BMD measurement should not be any different from other osteoporosis therapies; the small but expected decrease in peripheral cortical measurement sites (*e.g.*, the distal radius) occurs during the first year of treatment (as discussed above), but is not associated with an increased risk for wrist fracture (50). Increments in biochemical markers of bone turnover are consistently seen beginning within the first 1–3 months of teriparatide and intact PTH treatment, but there is no indication that these measurements provide any guidance to therapeutic decisions.

C. Duration of therapy

At present, teriparatide therapy is approved for 2-yr duration. This is largely because longer term data are not available from randomized, placebo-controlled studies. Furthermore, the prevalence of osteosarcoma in rats was dependent on dose and duration of treatment (87).

D. PTH and cotherapy with antiresorptive agents

The development of PTH as a therapy for osteoporosis raises many questions concerning how it should be used in concert with other treatments. The pivotal studies that demonstrated the effectiveness of PTH in increasing BMD and reducing fracture risk were conducted as placebo-controlled

trials involving participants not receiving other treatments immediately before or during PTH treatment. Hence, there are few data that directly inform a variety of clinical situations that routinely arise when treatment recommendations for patients with osteoporosis are being formulated. Key questions that must be addressed by targeted research include whether PTH therapy can be effectively used in patients who are already being treated with antiresorptive drugs, whether PTH should be administered in combination with other treatments, and what therapeutic approach should be adopted at the conclusion of treatment with PTH. This final question is particularly pertinent for a treatment that, for various reasons, is likely to be seen as a short-term approach to produce a rapid and significant improvement in bone mass. Moreover, the drug is currently given by daily injection and is considerably more expensive than antiresorptive therapy, and there remain some concerns about long-term safety.

1. The influence of previous or concomitant antiresorptive therapy. Although the anabolic effects of PTH might be accentuated if osteoclastic bone resorption is suppressed, there is also concern that the decrease in overall remodeling rates induced by antiresorptive agents might impair the ability of PTH to stimulate osteoblastic activity and new bone formation. Some (93, 94), but not all (95, 96), studies in animals suggest that pretreatment with calcitonin, clodronate, risedronate, or estrogen does not materially blunt the bone-forming effects of PTH.

a. Estrogen and raloxifene. Trials in postmenopausal women who had been on previous long-term estrogen replacement, and continued during teriparatide therapy, revealed that the expected response to PTH occurred nonetheless, as reflected by increases in markers of bone remodeling and bone density (42, 97, 98). When teriparatide was added to established estrogen therapy, the observed increments in spinal BMD (~13%) and in the hip (2.7–4.4%) over 3 yr were certainly consistent with those found in the randomized controlled trials (42, 97). Similarly, postmenopausal women receiving both estrogen and glucocorticoids responded well to PTH treatment (78). Ettinger *et al.* (100) reported similar findings in postmenopausal women who had been treated for at least 12 months with raloxifene before teriparatide was substituted, namely that increments in biochemical markers of bone formation and BMD were similar to those expected from historical controls, suggesting that raloxifene does not blunt the anabolic effects of PTH.

b. Bisphosphonates. There is increasing evidence from some (86, 100), but not all (101, 102), studies that prior therapy with the potent bisphosphonate, alendronate, may indeed blunt the effectiveness of PTH by mitigating the expected increments in both bone turnover and bone density. On the one hand, Cosman *et al.* (101, 102) have consistently reported in preliminary findings that women with postmenopausal osteoporosis, who had been previously treated with alendronate for well over 1 yr, responded with the expected changes in BMD and biochemical markers of bone turnover when treated with teriparatide. However, their findings were compared with historical controls and were not internally controlled.

On the other hand, there are two randomized controlled studies (Table 2) that show that alendronate (either started shortly before or concurrently) significantly modifies the expected outcomes of PTH therapy over 1–2.5 yr (60, 86). Both studies, one in postmenopausal women treated with intact PTH, 100 $\mu\text{g}/\text{d}$ (60), and one in men treated with teriparatide, 40 $\mu\text{g}/\text{d}$ (86), showed that the hypothesized synergy between the two drugs did not occur. If anything, the anabolic effect of PTH appeared to be blunted, particularly the increments in biochemical markers of bone metabolism. There was no additive effect on BMD gains for a combination of intact PTH and alendronate, whereas this bisphosphonate actually reduced the BMD gains observed with teriparatide alone. As expected, patients treated with alendronate alone showed smaller increments than either teriparatide alone or the combination. Somewhat in support of these observations, Ettinger *et al.* (100) found that when teriparatide, 20 $\mu\text{g}/\text{d}$, was substituted for alendronate therapy (previously given for at least 1 yr to postmenopausal women with osteoporosis), the expected increments in biochemical markers of bone formation and BMD were delayed for 6 months; in this study, subsequent changes in these outcomes appeared to improve as expected. No clinical information currently exists regarding interactions between other bisphosphonates and PTH. Given that many patients with severe osteoporosis may already be receiving antiresorptive therapy, this issue has important implications for planning optimal therapy with PTH, particularly if potent bisphosphonates prevent or delay the anabolic response.

2. Antiresorptive therapy after PTH. After cessation of teriparatide therapy, BMD tends to fall (103). Although some antifracture efficacy of PTH has been shown to persist for some time after the cessation of therapy (103), it may be desirable to retain the new bone formed during the treatment period. Some animal studies suggest that estrogen treatment can sustain higher levels of bone mass after PTH therapy is discontinued. However, in the study of Roe *et al.* (104) in which a 29% improvement in spine BMD, measured by DXA, was seen after 2 yr of treatment with PTH and estrogen, continuing estrogen after the PTH was stopped did not totally prevent bone loss, and a 4% decline in lumbar BMD was seen in the subsequent year. These trends have been observed in other studies (97, 105). Two studies have explored the benefit of alendronate after PTH is stopped. In one study in postmenopausal osteoporotic women, Rittmaster *et al.* (52) found that alendronate given sequentially for 1 yr after intact PTH therapy led to an overall increase of 14.6% at the spine together with significant increments in the femoral neck and total body calcium. The typical improvement normally seen with alendronate was added to the prior improvement produced by intact PTH. Bone turnover declined but still remained above that of the original placebo (no PTH) group (52). In a study of the effect of alendronate for 2 yr after PTH treatment in osteoporotic men, the findings were similar; those on no antiresorptive therapy after stopping PTH eventually began to lose bone (99). A different approach has been the use of intermittent PTH used cyclically with an antiresorptive. Calcitonin has been studied in this manner, but the combined cyclical therapy was not found to be superior to

cyclical PTH alone (76). The final answer to the best combination or sequence of PTH and an antiresorptive medication awaits larger trials and, particularly, fracture data.

VIII. Summary

Teriparatide [hPTH(1–34)] is the first agent in a unique class of anabolic therapies acting on the skeleton. Current evidence supports the concept that teriparatide significantly reduces fracture risk (Table 2), by improving bone microarchitecture as well as enhancing overall bone mass. The intact hormone hPTH(1–84) may have similar potential, pending completion of ongoing phase III trials of fracture efficacy. PTH should be considered as an alternative therapy to existing antiresorptive agents for the prevention of fractures in patients with severe osteoporosis. Teriparatide appears to be superior to antiresorptive therapy (alendronate) in improving BMD at the lumbar spine. However, there are as yet no direct comparisons of the antifracture efficacy between these two classes of agents. A historical comparison of antifracture efficacy between teriparatide, on the one hand, and two bisphosphonates (alendronate and risedronate), on the other, does not suggest superior antifracture efficacy for teriparatide (Table 3).

There is now evidence that prior therapy with a potent bisphosphonate (alendronate) may blunt the anabolic action of teriparatide, although the mechanism for this is not known. The same is not true for postmenopausal women chronically treated with estrogen or raloxifene. Nonetheless, there is no evidence to support a need for concurrent therapy with an antiresorptive agent during treatment with PTH, other than providing appropriate supplemental calcium and vitamin D to ensure adequate availability of calcium to mineralize newly formed bone matrix.

IX. Recommendations

1. Teriparatide should be considered as a treatment for postmenopausal women with severe osteoporosis (grade A) (50). The World Health Organization's definition of severe osteoporosis includes a prevalent fragility fracture in the presence of a T score less than -2.5 . However, the evidence to date supports a clinically significant reduction in fracture risk in postmenopausal women with prevalent fractures that is independent of BMD. This benefit was seen with T scores as high as -2 (79).

2. Teriparatide should be considered for men with severe osteoporosis (grade B) (48, 51). Teriparatide results in increments in BMD (as measured by DXA) when given to men with osteoporosis over relatively short periods of up to 18 months. These increments are similar to those observed in postmenopausal women with severe osteoporosis. However, there are no data for the efficacy of teriparatide therapy to reduce fractures in men.

3. Teriparatide should be considered for patients with established GIOP who require long-term steroid treatment (grade B) (78). Teriparatide increased BMD in postmeno-

pausal women with GIOP and who were also receiving long-term estrogen therapy (grade B). There is no evidence that concurrent estrogen therapy is required for the anabolic action of teriparatide (grade D). Teriparatide should also be effective in men with GIOP (grade D), but there are no antifracture efficacy data for men or women with GIOP.

4. Teriparatide may be considered for the management of individuals at particularly high risk for fractures, including subjects who are younger than age 65 yr and who have particularly low BMD measurements (T scores < 3.5) (grade D). There is as yet no head-to-head trial, comparing the antifracture efficacy of PTH with antiresorptive agents. This recommendation is based on the biologically plausible mechanism that PTH produces a rapid improvement in skeletal architecture, whereas antiresorptive agents do not. Thus, patients at very high risk of fracture may benefit in the long term from initiating treatment with PTH. The gradient of risk may be even higher in the face of other major risk factors such as low body mass index, glucocorticoid use, or gastrointestinal disease leading to malabsorption.

5. Therapy with alendronate should be discontinued when treatment with teriparatide is initiated (grade A) (60, 86). Controlled clinical trials suggest that alendronate may blunt the expected anabolic effects, if started before, or concurrently, with PTH. At present there is no indication that the interactions between alendronate and PTH are specific to this drug or represent a class effect that will be seen with other bisphosphonates. There is no evidence for any clinical advantages to adding an antiresorptive agent to PTH, and no studies have approached such an interaction with respect to fracture rates. To date there is no evidence that continuing either estrogen or raloxifene during PTH therapy confers either clinical advantage or disadvantage.

6. Therapy with an antiresorptive agent after cessation of teriparatide is recommended to further enhance increments in BMD measurements (grade C) (52). There is as yet no evidence that this approach will further reduce fracture risk (grade D).

7. Therapy with teriparatide is not recommended beyond 2 yr (grade D). In part this recommendation is based on the current limitations of the experience with this agent and the lack of longer term data. Moreover, the induction of osteosarcoma in the rat model was dependent on both dose and duration of therapy.

8. Total daily calcium intake from both supplement and dietary sources should be limited to 1500 mg, together with adequate vitamin D intake (≤ 1000 U/d) (grade D).

9. Routine serum calcium monitoring may not be required for safety monitoring (grade D). However, after the first month of therapy, it may be prudent to measure the "trough" serum calcium, just before the daily teriparatide injection. In the small percentage of individuals with increased serum calcium during PTH therapy, adjustment of dietary calcium supplements or reduced teriparatide dosing frequency will usually be sufficient.

10. Routine measurements of biochemical markers of bone turnover are not recommended to monitor the response to treatment over a 2-yr cycle with teriparatide (grade D).

Acknowledgments

We thank Elke Henneberg for her editorial support and assistance with the preparation of this manuscript.

Address all correspondence and requests for reprints to: Anthony B. Hodsman, Professor of Medicine, University of Western Ontario, % St. Joseph's Health Care, Room 2F-15, 268, Grosvenor Street, London, Ontario N6A 4V2, Canada. E-mail: anthony.hodsman@sjhc.london.on.ca

References

- Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, Yale JF, Zinman B, Lillie D 1998 Clinical practice guidelines for the management of diabetes in Canada. Canadian Diabetes Association. *Can Med Assoc J* 159(Suppl 8):S1–S29
- Rosen CJ, Bilezikian JP 2001 Anabolic therapy for osteoporosis. *J Clin Endocrinol Metab* 86:957–964
- Watson PH, Hanley DA 1993 Parathyroid hormone: regulation of synthesis and secretion. *Clin Invest Med* 16:58–77
- Segre GV, D'Amour P, Potts JT 1976 Metabolism of radioiodinated bovine parathyroid hormone in the rat. *Endocrinology* 99:1645–1652
- Divieti P, Inomata N, Singh R, Juppner H, Bringham FR 2001 Receptors for the carboxyl-terminal region of PTH (1–84) are highly expressed in osteocytic cells. *Endocrinology* 142:916–925
- Sutherland MK, Rao LG, Wylie JN, Gupta A, Ly H, Sodek J, Murray TM 1994 Carboxyl-terminal parathyroid hormone peptide (53–84) elevates alkaline phosphatase and osteocalcin mRNA levels in SaOS-2 cells. *J Bone Miner Res* 9:453–458
- Reeve J, Meunier PJ, Parsons JA, Bernat M, Bijvoet OL, Courpron P, Edouard C, Klenerman L, Neer RM, Renier JC, Slovick D, Vismans FJ, Potts Jr JT 1980 Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial. *Br Med J* 280:1340–1344
- Hodsman AB, Hanley DA, Watson PH, Fraher LJ 2002 Pharmacologic mechanisms of therapeutics: parathyroid hormone. In: Bilezikian JB, Raisz LG, Rodan GA, eds. *Principles of bone biology*. San Diego: Academic Press; 1305–1324
- Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH 1990 Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 322:1265–1271
- Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, Licata AA, Ross P, Woodson GC, Yanover MJ 1990 Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 323:73–79
- Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE 1996 Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 348:1535–1541
- Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Bogt T, Wallace R, Yates AJ, LaCrois AZ 1998 Effect of alendronate on risk fracture in women with low bone density but without vertebral fractures. Results from the Fracture Intervention Trial. *JAMA* 280:2077–2082
- Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut 3rd CH, Brown J, Eriksen EF, Hoseney MS, Axelrod DW, Miller PD 1999 Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *JAMA* 282:1344–1352
- Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R 2000 Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int* 11:83–91
- Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C 2002 Meta-analysis of therapies for postmenopausal osteoporosis. IX. Summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocr Rev* 23:517–523
- Black DM, Thompson ED, Bauer DC, Ensrud K, Musliner T, Hochberg MC, Nevitt MC, Suryawanshi S, Cummings SR; Fracture Intervention Trial 2000 Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. *J Clin Endocrinol Metab* 85:4118–4124
- McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY; Hip Intervention Program Study Group 2001 Effect of risedronate on hip fracture risk in elderly women. *N Engl J Med* 344:333–340
- Ringe JD, Orwoll E, Daifotis A, Lombardi A 2002 Treatment of male osteoporosis: recent advances with alendronate. *Osteoporos Int* 13:95–199
- Adachi JD, Roux C, Pitt PI, Cooper C, Moniz C, Dequeker J, Ioannidis G, Cawley MI, Jenkins EA, Walker-Bone KE, Pack S, Stephenson GF, Laan RF, Brown J, Geusens P 2000 A pooled data analysis on the use of intermittent cyclical etidronate therapy for the prevention and treatment of corticosteroid induced bone loss. *J Rheumatol* 27:2424–2431
- Adachi JD, Saag KG, Delmas PD, Lierman UA, Emkey RD, Seeman E, Lane NE, Kaufman JM, Poubelle PE, Hawkins F, Correa-Rotter R, Menkes CJ, Rodriguez-Portales JA, Schnitzer TJ, Block JA, Wing J, McIlwain HH, Westhovens R, Brown J, Melo-Gomes JA, Gruber BL, Yanover MJ, Leite MO, Siminowski KG, Nevitt MC, Sharp JT, Malice MP, Dumortier T, Czachur M, Carofano W, Daifotis A 2001 Two year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. *Arthritis Rheum* 44:201–211
- Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, Doherty SM, Maricic M, Rosen C, Brown J, Barton I, Chines AA 2000 Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int* 67:277–285
- Watts NB, Adami S, Chesnut CH 2001 Risedronate reduces the risk of clinical vertebral fractures in just 6 months. *J Bone Miner Res* 16(Suppl 1):S407
- Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ 1997 Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodelling in patients with osteoporosis. *J Clin Invest* 100:1475–1480
- Dufresne TE, Chmielewski PA, Manhart MD, Johnson TD, Borah B 2003 Risedronate preserves bone architecture in early postmenopausal women in 1 year as measured by three-dimensional micro-computed tomography. *Calcif Tissue Int* 73:423–432
- Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ 2000 Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. *Bone* 27:687–694
- Seeman E 2003 Bone quality. *Osteoporos Int* 14:S3–S7
- Rossouw JE, Anderson GL, Prentice RL, LaCrois AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators 2002 Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 288:321–333
- Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Gluer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR 1999 Reduction of vertebral fracture risk in post menopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. *JAMA* 282:637–645
- Chesnut 3rd CH, Silverman S, Andriano K, Genant H, Gimona A, Harris S, Kiel D, LeBoff M, Maricic M, Miller P, Moniz C, Peacock M, Richardson P, Watts N, Baylink D 2000 A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med* 109:267–276

30. **Lips P** 2001 Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 22:477–501
31. **Chapuy MC, Arlot ME, Delmas PD, Meunier PJ** 1994 Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *Br Med J* 308:1081–1082
32. **Dawson-Hughes B, Harris SS, Krall EA, Dallal GE** 1997 Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 337:670–676
33. **Recker RR, Davies KM, Dowd RM, Heaney RP** 1999 The effect of low-dose estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. *Ann Intern Med* 130:897–904
34. **Trivedi DP, Doll R, Khaw KT** 2003 Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: a randomized double-blind controlled trial. *Br Med J* 326:469–475
35. **Parfitt AM** 1991 Use of bisphosphonates in the prevention of bone loss and fractures. *Am J Med* 91(Suppl 5B):S42–S46
36. **Roschger P, Rinnerthaler S, Yates J, Rodan GA, Fratzi P, Klaushofer K** 2003 Alendronate increases the degree and uniformity of mineralization in cancellous bone and decreases the porosity in cortical bone of osteoporotic women. *Bone* 29:185–191
37. **Hernandez C, Beaupre GS, Marcus R, Carter DR** 2001 A theoretical analysis of the contributions of remodelling space, mineralization, and bone balance to changes in bone mineral density during alendronate treatment. *Bone* 29:511–516
38. **Bradbeer JN, Arlot ME, Meunier PJ, Reeve J** 1992 Treatment of osteoporosis with parathyroid peptide (hPTH 1034) and oestrogen: increase in volumetric density of iliac cancellous bone may depend on reduced trabecular spacing as well as increased thickness of packets of newly formed bone. *Clin Endocrinol (Oxf)* 37:282–289
39. **Hodsman AB, Kisiel M, Adachi JD, Fraher LJ, Watson PH** 2000 Histomorphometric evidence for increased bone turnover and cortical thickness without increased cortical porosity after 2 years of cyclical hPTH (1–34) therapy in women with severe osteoporosis. *Bone* 27:311–318
40. **Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, Shane E, Plavetic K, Muller R, Bilezikian J, Lindsay R** 2001 Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res* 16:1846–1853
41. **Hodsman AB, Steer BM** 1993 Early histomorphometric changes in response to parathyroid hormone therapy in osteoporosis: evidence for novo bone formation on quiescent cancellous surfaces. *Bone* 14:523–527
42. **Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, Dempster D, Cosman F** 1997 Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet* 350:550–555
43. **Dempster DW, Zhou H, Cosman F** 2001 PTH treatment directly stimulates bone formation in cancellous and cortical bone in humans. *J Bone Miner Res* 16(Suppl 1):S179 (Abstract)
44. **Leaffer D, Sweeney M, Kellerman LA, Avnur Z, Krstenansky JL, Vickery BH, Caulfield JP** 1995 Modulation of osteogenic cell ultrastructure by RS-23581, an analog of human parathyroid hormone (PTH)-related peptide-(1–34), and bovine PTH-(1–34). *Endocrinology* 136:3624–3631
45. **Pagitt AM** 2002 Parathyroid hormone and periosteal expansion. *J Bone Miner Res* 17:1741–1743
46. **Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Ericson EF** 2003 Recombinant human parathyroid hormone (1–34) [teriparatide] improves both cortical and cancellous bone structure. *J Bone Miner Res* 18:1932–1941
47. **Jerome CP, Burr DB, VanBibber T, Hock JM, Brommage R** 2001 Treatment with human parathyroid hormone (1–34) for 18 months increases cancellous bone volume and improves trabecular architecture in ovariectomized cynomolgus monkeys (*Macaca fascicularis*). *Bone* 28:150–159
48. **Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP** 2000 Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. *J Clin Endocrinol Metab* 85:3069–3076
49. **Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, Dore RK, Correa-Rotter R, Papaioannou A, Cumming DC, Hodsman AB** 2002 A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1–34)] with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 87:4528–4535
50. **Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH** 2001 Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 344:1434–1441
51. **Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman JM, Clancy AD, Gaich GA** 2003 The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 18:9–17
52. **Rittmaster RS, Bolognese M, Ettinger MP, Hanley DA, Hodsman AB, Kessler DL, Rosen CJ** 2000 Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab* 85:2129–2134
53. **Hodsman AB, Hanley DA, Ettinger MP, Bolognese MA, Fox J, Metcalfe AJ, Lindsay R** 2003 Safety and efficacy of human parathyroid hormone (1–84) in increasing bone mineral density in postmenopausal osteoporosis. *J Clin Endocrinol Metab* 88:5212–5220
54. **Mashiba T, Burr DB, Turner CH, Sato M, Cain RL, Hock JM** 2001 Effects of human parathyroid hormone (1–34) LY333334, on bone mass, remodelling, and mechanical properties of cortical bone during the first remodelling cycle in rabbits. *Bone* 28:538–547
55. **Burr DB, Hirano T, Turner CH, Hotchkiss C, Brommage R, Hock JM** 2001 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* 16:157–165
56. **Hirano T, Burr DB, Cain RL, Hock JM** 2000 Changes in geometry and cortical porosity in adult, ovary-intact rabbits after 5 months treatment with LY333334. *Calcif Tissue Int* 66:456–460
57. **Hirano T, Burr DB, Turner CH, Sato M, Cain RL, Hock JM** 1999 Anabolic effects of human biosynthetic parathyroid hormone fragment (1–34), LY333334, on remodelling and mechanical properties of cortical bone in rabbits. *J Bone Miner Res* 14:536–545
58. **Cann CE, Roe EB, Sanchez SD, Arnaud CD** 1999 PTH effects in the femur: envelope-specific responses by 3D-QCT in postmenopausal women. *J Bone Miner Res* 14(Suppl 1):S137 (Abstract)
59. **Zanchetta JR, Bogado CE, Ferretti JL, Wang O, Wilson MG, Sato M, Gaich GA, Dalsky GP, Myers SL** 2003 Effects of teriparatide [recombinant human parathyroid hormone (1–34)] on cortical bone in postmenopausal women with osteoporosis. *J Bone Miner Res* 18:539–543
60. **Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, Garnero P, Bouxsein ML, Bilezikian JP, Rosen CJ; PaTH Study Investigators** 2003 The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med* 349:1207–1215
61. **Semanick LM, Uusi-Rasi K, Zanchetta JR, Bogado CE, Eriksen EF, Sato M, Beck TJ** 2003 Teriparatide [rhPTH (1–34)] treatment improves the structure of the proximal femur in women with osteoporosis. *J Bone Miner Res* 18(Suppl 1):S40 (Abstract)
62. **Hyldstrup L, Jorgensen JT, Gaich G** 2001 Assessment of effects of LY333334 [recombinant human parathyroid hormone (1–34)] on cortical bone using digital x-ray radiogrammetry. *Bone* 28(Suppl 1):S97 (Abstract)
63. **Lindsay R, Cosman F, Nieves J, Woelfert L** 2000 Does treatment with parathyroid hormone increase vertebral size? *Osteoporos Int* 11 (Suppl 2):S206 (Abstract)
64. **Uusi-Rasi K, Beck TJ, Oreskovic TL, Sato M, Bogado CE, Zanchetta JR** 2002 Teriparatide [rhPTH(34)] improves the structural geometry of the hip. *J Bone Miner Res* 17(Suppl 1):S208 (Abstract)
65. **Gam SM** 1970 The earlier gain and later loss of cortical bone. Springfield, IL: Charles C. Thomas
66. **Duan Y, Seeman E, Turner CH** 2001 The biomechanical basis of vertebral body fragility in men and women. *J Bone Miner Res* 16:2276–2283

67. Duan Y, Turner CH, Kim BT, Seeman E 2001 Sexual dimorphism in vertebral fragility is more the result of gender differences in age-related bone gain than bone loss. *J Bone Miner Res* 6:2267–2275
68. Misof BM, Roschger P, Cosman F, Kurland ES, Tesch W, Messmer P, Dempster DW, Nieves J, Shane E, Fratzl P, Klaushofer K, Bilezikian J, Lindsay R 2003 Effects of intermittent parathyroid hormone administration on bone mineralization density in iliac crest biopsies from patients with osteoporosis: a paired study before and after treatment. *J Clin Endocrinol Metab* 88:1150–1156
69. Beck TJ, Stone KL, Oreskovic TL, Hochberg MC, Nevitt MC, Genant HK, Cummings SR 2001 Effects of current and discontinued estrogen replacement therapy on hip structural geometry: the study of osteoporotic fractures. *J Bone Miner Res* 16:2103–2110
70. Lochmuller EM, Lill CA, Kuhn V, Schneider E, Eckstein F 2002 Radius bone strength in bending, compression and falling and its correlation with clinical densitometry at multiple sites. *J Bone Miner Res* 17:1629–1638
71. Pistoia W, VanRietbergen B, Lochmuller EM, Lill CA, Eckstein F, Rueggsegger P 2002 Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. *Bone* 30:842–848
72. VanRietbergen B, Majumdar S, Newitt D, MacDonald B 2002 High-resolution MRI and micro-FE for the evaluation of changes in bone mechanical properties during longitudinal clinical trials: application to calcaneal bone in postmenopausal women after one year of idoxifene treatment. *Clin Biomech* 17:81–88
73. Wehrli FW, Hilaire L, Fernandez-Seara M, Gomberg BR, Song HK, Zemel B, Loh L, Snyder PJ 2002 Quantitative magnetic resonance imaging in the calcaneus and femur of women with varying degrees of osteopenia and vertebral deformity status. *J Bone Miner Res* 17:2265–2273
74. Wehrli FW, Saha PK, Gomberg BR, Song HK, Snyder PJ, Benito M, Wright A, Weening R 2002 Role of magnetic resonance for assessing structure and function of trabecular bone. *Top Magn Reson Imaging* 13:335–355
75. Hodsman AB, Fraher LJ, Ostbye T, Adachi JD, Steer BM 1993 An evaluation of several biochemical markers for bone formation and resorption in a protocol utilizing cyclical parathyroid hormone and calcitonin therapy for osteoporosis. *J Clin Invest* 91:1138–1148
76. Hodsman AB, Fraher LJ, Watson PH, Ostbye T, Stitt LW, Adachi JD, Taves DH, Drost D 1997 A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 82:620–628
77. Finkelstein JS, Klibanski A, Arnold AL, Toth TL, Hornstein MD, Neer RM 1998 Prevention of estrogen deficiency-related bone loss with human parathyroid hormone (1–34): a randomized controlled trial. *JAMA* 280:1067–1073
78. Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD 1998 Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. *J Clin Invest* 102:1627–1633
79. Marcus R, Wang O, Sattershite J, Mitlak B 2003 The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. *J Bone Miner Res* 18:18–23
80. Fujita T, Inoue T, Morii H, Morita r, Norimatsu H, Orimo H, Takahashi HE, Yamamoto K, Fukunaga M 1999 Effect of an intermittent weekly dose of human parathyroid hormone (1–34) on osteoporosis: a randomized double-masked prospective study using three dose levels. *Osteoporos Int* 296–306
81. Eli Lilly 2004 Product monograph: Forteo. Toronto, Ontario, Canada: Eli Lilly
82. Morrissey JJ, Cohn DV 1979 Regulation of secretion of parathormone and secretory protein I from separate intracellular pools by calcium dibutyryl, cyclic AMP and (1)-isoproterenol. *J Cell Biol* 83:93–102
83. Genant HK, Scheele WH, Sie L, Krege JH 2003 Teriparatide reduces the incidence of new or worsening back pain in women with osteoporosis. *J Bone Miner Res* 18(Suppl 2):M376 (Abstract)
84. Hodsman AB, Hanley DA, Josse R 2002 Do bisphosphonates reduce the risk of osteoporotic fractures? An evaluation of the evidence to date. *Can Med Assoc J* 166:1426–1430
85. National Institute for Clinical Excellence, Final Appraisal 2004 The clinical effectiveness and cost effectiveness of technologies for the secondary prevention of osteoporotic fractures in postmenopausal women. www.nice.org.uk
86. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM 2003 The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 349:1216–1226
87. Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, Westmore MS, Linda Y, Nold JB 2002 Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1–34) for two years and relevance to human safety. *Toxicol Pathol* 30:312–321
88. Tashjian AH, Chabner BA 2002 Commentary on clinical safety of recombinant human parathyroid hormone (1–34) in the treatment of osteoporosis in men and postmenopausal women. *J Bone Miner Res* 17:1151–1161
89. Betancourt M, Wurfel KL, Raymond AK, Yasko AW, Lee J, Vassilopoulos-Sellin R 2003 Osteosarcoma of bone in a patient with primary hyperparathyroidism: a case report. *J Bone Miner Res* 18:163–166
90. Need AG, Horowitz M, Morris HA, Nordin BC 2000 Vitamin D status: effects on parathyroid hormone and 1,25-dihydroxyvitamin D in postmenopausal women. *Am J Clin Nutr* 71:1577–1581
91. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, Meunier PJ 1997 prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int* 7:439–443
92. Ensrud KE, Black DM, Palermo L, Bauer DC, Barrett-Conner E, Quandt SA, Thompson DE, Karpt DB 1997 Treatment with alendronate prevents fractures in women at high risk. *Arch Intern Med* 157:2617–2624
93. Mosekilde L, Danielsen CC, Gasser J 1994 The effect on vertebral bone mass and strength of long term treatment with antiresorptive agents (estrogen and calcitonin), human parathyroid hormone (1–38), and combination therapy, assessed in aged ovariectomized rats. *Endocrinology* 134:2126–2134
94. Hock JM, Hummert JR, Boyce R, Fonseca J, Raisz LG 1989 Resorption is not essential for the stimulation of bone growth by hPTH (1–34) in rats in vivo. *J Bone Miner Res* 4:449–458
95. Cheng PT, Chan C, Muller K 1995 Cyclical treatment of osteopenic ovariectomized adult rats with PTH (1–34) and pamidronate. *J Bone Miner Res* 10:119–126
96. Delmas PD, Vergnaud P, Arlot ME, Pastoureau P, Meunier PJ, Nilsson MHL 1995 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 remodelling system? *Bone* 16:603–610
97. Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, Lindsay R 2001 Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. *J Bone Miner Res* 16:925–931
98. Reeve J, Bradbeer JN, Arlot M, Davies UM, Green JR, Hampton L, Edouard C, Hesp R, Hulme P, Ashby JP 1991 hPTH (1–34) treatment of osteoporosis with added hormone replacement therapy: biochemical, kinetic and histological responses. *Osteoporos Int* 1:162–170
99. Kurland ES, Heller SL, Cosman F, Diamond B, Lindsay R, Bilezikian JP 2001 The post-PTH experience in men with idiopathic osteoporosis: bisphosphonates versus non-pharmacologic therapy. *J Bone Miner Res* 16(Suppl 1):F363 (Abstract)
100. Ettinger B, San Martin JA, Crans GG, Pavo I 2004 Differential effects of teriparatide after treatment with ralozifene or alendronate. *J Bone Miner Res* 19:745–751
101. Cosman F, Nieves J, Woelfert L, Shen V, Lindsay R 1998 Alendronate does not block the anabolic effect of PTH in postmenopausal osteoporotic women. *J Bone Miner Res* 13:1051–1055
102. Cosman F, Nieves JW, Luckey MM, Zion M, Woelfert L, Lindsay R 2003 Daily versus cyclic PTH combined with alendronate versus alendronate alone for treatment of osteoporosis. *J Bone Miner Res* 18 (Suppl 2):S32 (Abstract)

103. Lindsay R, Scheele WH, Clancy AD, Mitlak BH 2001 Incident vertebral fractures during an 18-month observation period following discontinuation of LY333334 [recombinant human parathyroid hormone (1–34), rhPTH (1–34)] use in postmenopausal women with osteoporosis. *J Bone Miner Res* 16 (Suppl 1):1105 (Abstract)
104. Roe EB, Sanchez SD, Cann CE, del Puerto GA, Pierini E, Arnaud CD 2000 PTH-induced increases in bone density are preserved with estrogen: results from a follow-up year in postmenopausal osteoporosis. *J Bone Miner Res* 15(Suppl 1):S193 (Abstract)
105. Lane Ne, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD 2000 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* 15:944–951
106. Oglesby AK, Minshall ME, Shen W, Xie S, Silverman SL 2003 The impact of incident vertebral and non-vertebral fragility fractures on Health-Related Quality of Life in established postmenopausal osteoporosis: results from the teriparatide randomized, placebo-controlled trial in postmenopausal women. *J Rheumatol* 30:1579–1583

Erratum

The May 2005 article “Selective Progesterone Receptor Modulator Development and Use in the Treatment of Leiomyomata and Endometriosis” by K. Chwalisz, M. C. Perez, D. DeManno, C. Winkel, G. Schubert, and W. Elger (*Endocrine Reviews* 26:423–438, 2005) contained the following errors:

On page 425, the second sentence in the paragraph subtitled “A. SPRM definition” should read as follows: Accordingly, SPRMs represent a class of PR ligands that exerts clinically relevant tissue-selective progesterone agonist, antagonist, partial, or mixed agonist/antagonist effects on various progesterone target tissues in an *in vivo* situation depending on the biological action studied.

On page 425, in the *Leiomyoma* row in Table 1, the downward arrow in the *Progestins* column should be removed and placed in the *SPRM* column. The corrected table appears below.

TABLE 1. Comparison of major pharmacodynamic effects of progestins, PAs, and SPRMs based on studies in humans and animals

Pharmacodynamic effects	Progestins	PAs	SPRMs
Ovary			
Ovulation	↓	↓	(↓) ^{a,b}
Estrogen secretion	↓	Maintained	Maintained
Progesterone secretion	↓	↓	↓ or → ^{a,b}
Eutopic endometrium			
Endometrial bleeding	Irregular (breakthrough bleeding and spotting)	Amenorrhea (via anovulation)	Amenorrhea (via an endometrial effect)
Endometrial morphology	Secretory or atrophy ^c	Weakly to strongly proliferative ^d	Nonphysiological secretory effect/atrophy ^b
Endometrial vessels	Fragile	Robust	Robust Thick-walled vessels common ^b
Pregnant uterus			
Myometrium (contractility)	↓	↑ ↑	No or marginal effects
Cervix	No effect	↑ ↑ ^e	→
Leiomyoma	↑	↓	↓ ^b
Breast proliferation	↑	Unknown	↓

↓, Inhibition; (↓), partial inhibition; ↑, stimulation; →, no effect.

^a Variable effects, depending on dose and duration of treatment.

^b Human studies with asoprisnil.

^c Depending on the duration of treatment.

^d Depending on compound, dose, and duration of treatment.

^e Cervical ripening.