

# Parathyroid Hormone(1–84) Treatment of Postmenopausal Women with Low Bone Mass Receiving Hormone Replacement Therapy

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**Abstract** Treatment of postmenopausal osteoporosis (PMO) is based primarily on antiresorptive agents, including hormone replacement therapy (HT). To evaluate whether anabolic therapy together with HT provides additional benefits in the treatment of PMO, we evaluated the effects of parathyroid hormone (PTH) 1–84 in postmenopausal women with low bone mineral density (BMD) who were receiving chronic ( $\geq 6$  months) HT. Subjects were randomized to receive 100  $\mu\text{g}$  PTH(1–84) or placebo injections daily for 24 months ( $n = 90/\text{group}$ ). The primary efficacy outcome was change from baseline in lumbar spine BMD. Secondary end points included changes in hip and distal radius BMD, bone turnover markers, and fracture incidence. The study was terminated early following

recommendations regarding HT for PMO. At 18 months, the mean increase in lumbar spine BMD was 7.9% for PTH(1–84) subjects vs. 1.5% for those receiving HT alone; between-group differences were significant at 6 months and persisted throughout the study. Lumbar spine BMD increased in 94% of women receiving PTH(1–84) compared to 59% for HT alone. Femoral neck BMD and bone turnover markers were significantly higher in PTH(1–84)-treated subjects, but the changes in total hip and distal radius BMD were not significant. PTH(1–84) treatment was generally well-tolerated, with hypercalciuria, hypercalcemia, nausea, vomiting, and dizziness reported more frequently in the HT + PTH(1–84) group. In conclusion, addition of PTH(1–84) to stable HT produced marked increases in lumbar spine BMD and may represent an additional approach to the treatment of PMO women receiving HT.

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Postmenopausal osteoporosis (PMO), in part a consequence of estrogen deficiency, represents a significant health challenge for women. PMO is implicated in 1.5 million fractures annually in the United States alone and incurs an estimated \$12.2 to \$17.9 billion in direct health-care expenditures [1].

Pharmacological therapy for the prevention and treatment of osteoporosis initially focused on a group of agents collectively referred to as “antiresorptive agents,” which included calcitonin, bisphosphonates, and selective estrogen receptor modulators (SERMs), as well as hormone replacement therapy (HT, estrogen alone or in combination

with progestin) [2]. The recent introduction of anabolic therapies has provided a new approach to osteoporosis treatment and prevention. The most extensively studied anabolic agent is the N-terminal human parathyroid hormone (PTH) 1–34 fragment, which is commercially available [3]. More recently, full-length human PTH(1–84) was approved for use in Europe.

Antiresorptive agents appear to act by suppression of both bone resorption and bone formation (i.e., bone remodeling) to a rate consistent with that observed in the premenopausal state. These actions result in a preservation of bone structure, with increased bone mineral density (BMD) and a reduction in fracture incidence [4–6]. In contrast, PTH peptides *increase* the overall bone remodeling rate, with a net stimulation of bone formation. PTH(1–34) treatment increases lumbar spine BMD and reduces the incidence of vertebral and nonvertebral fractures. PTH(1–84) treatment has also been shown to increase lumbar spine BMD and to reduce vertebral fractures [3, 7–9].

It has been suggested that, because of their differences in mechanism of action, a combination of antiresorptive and anabolic therapies might provide additive benefit when compared to monotherapy with either class. However, combination treatment of osteoporotic patients with the bisphosphonate alendronate and either PTH(1–34) or PTH(1–84) attenuated the increase in lumbar spine BMD compared with PTH peptide alone [10, 11]. In contrast, when PTH(1–34) was combined with the SERM raloxifene, there was a tendency for the BMD increase to be larger in the combination group compared with PTH(1–34) alone [12]. PTH(1–34) treatment also caused a substantial increase in lumbar spine BMD in women taking HT, but because no PTH(1–34) monotherapy group was included, whether an additive or synergistic effect occurred is unknown [13, 14]. The reasons underlying these apparent differences in outcomes when PTH peptides were combined with different antiresorptive agents remain unclear. Nevertheless, the promising results of the studies in which PTH(1–34) was combined with HT or raloxifene underscored the importance of further evaluation of combination therapy of PTH(1–84) added to existing HT. We report here the results of the Prevention of Osteoporosis in Women on Estrogen Replacement (POWER) study.

## Materials and Methods

POWER was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 25 clinical centers in the United Kingdom, Poland, and Denmark and was designed to evaluate the effects of adding PTH(1–84) treatment to women receiving stable HT. The protocol was approved by the institutional review boards of the participating organizations, and

all subjects gave written informed consent. The study was originally planned to evaluate the efficacy and safety of PTH(1–84) after 12 and 24 months of treatment, with a 1-year follow-up study after discontinuation of PTH(1–84) treatment to assess the durability of treatment effects. However, following recommendations by the European Agency for the Evaluation of Medicinal Products (EMA) regarding the lack of support for HT of postmenopausal women with osteoporosis [15], the protocol was modified to terminate participation after treatment for 18 months, although treatment was terminated before 18 months in some subjects. Only three HT alone subjects completed 24 months of treatment. Consequently, “18-month” data represent evaluations conducted between 12 and 18 months and “24-month” data represent measurements between 18 and 24 months.

## Study Population

The women were at least 45 years old; those between ages 45 and 54 had to have been postmenopausal for a minimum of 1 year. Subjects were required to have been on stable HT (no change in dose or formulation) at an appropriate bone-sparing dose for at least 6 months, with a BMD T score  $\leq -2.0$  at the lumbar spine, total hip, or femoral neck. Subjects also needed to be able to self-administer daily PTH(1–84) injections into the thigh or abdomen using a pen injector.

Subjects were excluded if they had a history of endocrine disorders, including hyper- or hypoparathyroidism, five or more vertebral deformities at any site or two or more lumbar vertebral deformities, a history of nephro- or urolithiasis, impaired renal function or renal disorders, recent history (within 5 years) of metabolic bone diseases other than osteoporosis, a history of bone cancer or any cancer within the past 5 years (except basal or squamous cell carcinoma), serum total calcium  $>10.7$  mg/dl (laboratory normal range 8.4–10.6 mg/dl), serum creatinine  $>1.5$  mg/dl, fasting urinary calcium/creatinine ratio  $\geq 1.0$  mmol/mmol, serum total alkaline phosphatase  $>130$  U/l, or body weight  $<40$  kg.

Screening was conducted over a period of up to 2 months at each study site. The screening period included a treatment stabilization period, during which the subjects received supplemental calcium citrate (1,050 mg Ca/day) and vitamin D<sub>3</sub> (800 IU/day).

## Treatments

Subjects were randomized to receive either 100  $\mu$ g recombinant human PTH(1–84) or matching placebo administered by daily subcutaneous injection. All subjects continued on their stable HT regimen throughout the study with supplemental calcium and vitamin D<sub>3</sub>. The calcium supplement was reduced to 700 mg/day during the study because of reports of

hypercalcemia and hypercalciuria in the phase III Treatment of Osteoporosis with Parathyroid Hormone (TOP) study [9]. Subjects were to have fasted overnight and not have injected study drug prior to the collection of blood and urine samples. Should serum ( $>10.7$  mg/dl) or urine calcium ( $>1.0$  mmol/mmol creatinine or  $>360$  mg/day) be elevated, the design of the POWER study included a provision for calcium supplements to be discontinued and, subsequently, for the frequency of the injections (but not the dose) to be reduced in a stepwise manner to every other day, twice a week, and once a week to control the hypercalcemia and/or hypercalciuria.

### Efficacy Evaluations

The primary efficacy variable was percent change from baseline in lumbar spine BMD. Secondary efficacy end points included percent change in hip and distal radius BMD, bone turnover markers, change in height, and incidence of vertebral and clinical fractures.

Dual-energy X-ray absorptiometry (DXA) performed on Lunar (Madison, WI) or Hologic (Waltham, MA) densitometers was used for all BMD measurements. All subjects were to have baseline and postbaseline BMD assessed using the same instrument. All DXA scans were read and BMD was calculated at a central imaging center by trained experts who were blinded to subject treatment. Lumbar spine and hip scans were to be conducted at baseline and at 6, 12, 18, and 24 months and distal radius scans at baseline, 6, 12, and 24 months.

Prevalent vertebral fractures were assessed at screening using lateral and anterior/posterior radiography of the thoracic and lumbar spine (T4–L4). A semiquantitative visual grade was assigned to each fracture using the four-point scale of Genant et al. [16]. Incident vertebral fractures were assessed using lateral radiography at months 12 and 24. Incident clinical fractures were assessed based on a spontaneous report by the subject or on a positive response to a query about new fractures since the previous visit.

Bone formation was evaluated using serum bone-specific alkaline phosphatase (BSAP) by immunoradiometric assay (Tandem R-Ostase; Hybritech, San Diego, CA). Bone resorption was evaluated using urinary N-telopeptide of type 1 collagen (NTX) by enzyme-linked immunosorbent assay (Osteomark; Ostex International, Princeton, NJ) and expressed as a ratio to urine creatinine concentrations. Bone turnover markers were to be assessed at baseline and at 12 and 24 months.

### Safety Evaluations

Safety was assessed based on spontaneous adverse event (AE) reporting and on monitoring of clinical laboratory

measurements, including serum and urinary calcium, vital signs, and electrocardiograms at baseline and at 6, 12, 18, and 24 months, in addition to information derived from unscheduled clinic visits, where appropriate.

### Statistical Methods

Efficacy analyses were conducted primarily on the intention-to-treat (ITT) population, comprising all randomized subjects who received at least one dose of study drug. Last observation carried forward was used for data from subjects who discontinued prior to 18 months. For each time point analysis, only subjects with a baseline and the relevant time point assessment were included.

Between-group comparisons with regard to primary and secondary efficacy variables were based on two-way analysis of variance with linear effects for country and treatment group and on pairwise *t*-tests. Bone turnover markers were not normally distributed, so these data were log-transformed before analysis, and geometric means are reported.

## Results

### Demographics and Baseline Characteristics

A total of 532 postmenopausal women were screened and 187 were randomized. The principal reason for screening failure (76% of subjects) was an insufficiently low BMD at any skeletal site. Seven subjects withdrew prior to receiving study drug. Therefore, the ITT population comprised 180 subjects (90/group). Numbers of subjects from the United Kingdom, Poland, and Denmark were 106 (58.9%), 37 (20.6%), and 37 (20.6%), respectively.

Subject demographics and baseline characteristics are summarized in Table 1. Treatment groups were well matched with regard to age, time since menopause, and physical and bone health parameters; 76% of subjects were  $>55$  years old and 87% were  $>5$  years postmenopausal. The relatively low average age at menopause (46 years) occurred because 20–30% of the subjects had a surgically induced menopause.

### Exposure and Compliance with Treatment

As noted in “Materials and Methods,” the POWER study was discontinued early and, as a result, the duration of treatment varied in each subject. Numbers of women who completed 18 months of treatment were 69 and 55 in the HT alone and HT + PTH(1–84) groups, respectively; 93% of HT alone and 62% of HT + PTH(1–84) subjects completed 18 months on daily study drug (with or without

**Table 1** Baseline demographics, treatment history, and disease status of ITT population

Variable	HT + placebo ( <i>n</i> = 90)	HT + PTH (1–84) ( <i>n</i> = 90)
Age (years)	59.4 ± 6.8	58.1 ± 6.2
Height (cm)	159.9 ± 6.6	159.9 ± 6.7
Weight (kg)	60.4 ± 9.4	61.9 ± 9.2
BMI (kg/m <sup>2</sup> )	23.7 ± 3.7	24.3 ± 3.6
Years postmenopausal	13.1 ± 8.0	12.1 ± 7.1
Hysterectomy, <i>n</i> (%)	17 (18.9)	28 (31.1)
<b>HT</b>		
Combination E and P, <i>n</i> (%)	62 (68.9)	47 (52.2)
Duration of therapy (years)	3.6 ± 2.7	3.4 ± 2.7
Estrogens alone, <i>n</i> (%)	30 (33.3)	37 (41.1)
Duration of therapy (years)	7.0 ± 6.1	5.9 ± 6.9
<b>Prevalent vertebral fractures, <i>n</i> (%)</b>		
0	79 (87.8)	80 (88.9)
1	11 (12.2)	8 (8.9)
>1	0 (0)	2 (2.2)
<b>BMD T scores</b>		
Lumbar spine	−2.27 ± 0.91	−
2.30 ± 0.75		
Total hip	−1.55 ± 0.70	−
1.50 ± 0.70		
Femoral neck	−1.88 ± 0.61	−
1.89 ± 0.61		

Values are means ± SD, unless stated otherwise

BMD, Bone mineral density; BMI, Body mass index; E, Estrogen; HT, Hormone replacement therapy; P, Progestin

supplemental calcium). Of those who remained in the study at month 18, calcium supplementation had been discontinued in 13 of 69 subjects in the HT alone group and in 38 of 55 subjects in the HT + PTH(1–84) group. An elevated (>1.0 mmol/mmol) morning urine calcium-to-creatinine ratio was by far the most frequent reason for a subject having the calcium supplement withdrawn and the frequency of dosing reduced. In the HT alone group at month 18, the numbers of women on every-other-day, twice-a-week, and once-a-week injections of placebo were 1, 1, and 3, respectively. In the HT + PTH(1–84) group, the numbers of women on these dosing frequencies were 14, 5, and 2, respectively.

The median exposure times to study drug were 545 days in the HT alone group and 521 days in the HT + PTH(1–84) group. Subjects were considered compliant if they received >75% of their regimen-defined dosing. Overall compliance, assessed by monitoring of study diaries and inspection of used cartridges at each study visit, was high in each treatment group, with 97% and 96% in the HT

alone and HT + PTH(1–84) groups, respectively, adhering to their dosing regimens at month 18.

## Efficacy

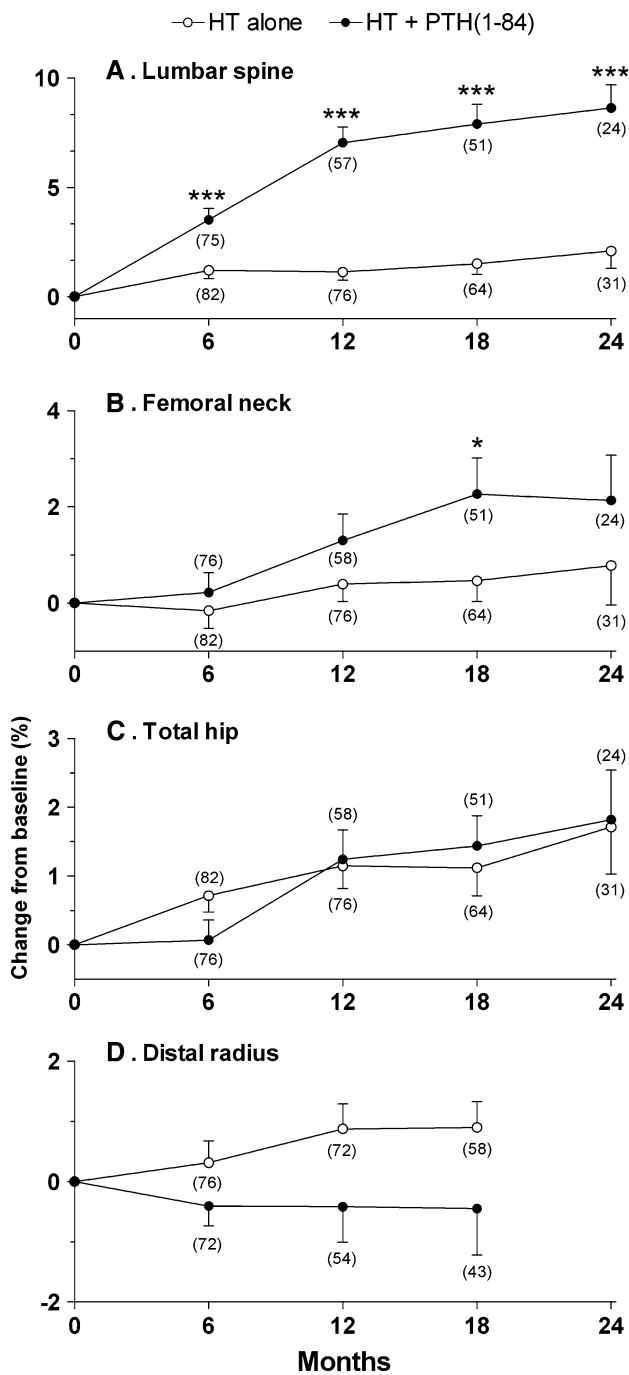
HT alone was associated with a progressive increase in lumbar spine BMD to 2.1% above baseline at 24 months, but HT + PTH(1–84) treatment resulted in an 8.6% increase above baseline (Fig. 1). The between-group difference was highly significant ( $P < 0.001$ ) at the first comparison (6 months) and increased further in magnitude through 24 months. The between-group difference at 18 months was 6.4%. In the HT + PTH(1–84) group, 94% (48/51) of subjects showed an increase over baseline in lumbar spine BMD at 18 months compared to 59% (38/64) for the HT alone group (Fig. 2). In addition, significantly more subjects treated with PTH(1–84) demonstrated a lumbar spine BMD increase of ≥10% than those receiving HT alone (23.5% vs. 4.7%, respectively;  $P = 0.003$ ).

At the femoral neck, HT + PTH(1–84) treatment increased BMD at all time points (Fig. 1). The increase was significantly greater than in the HT alone group at 18 months when the mean difference was 1.8% ( $P = 0.024$ ). Total hip BMD increased in both groups, but there were no significant between-group differences at any time point (Fig. 1).

There was a trend toward a decrease in distal radius BMD in the HT + PTH(1–84) group at all time points, while there was a slight increase in BMD in the HT alone group (Fig. 1). However, none of the between-group differences achieved statistical significance. Only one HT + PTH(1–84) and five HT alone subjects had DXA scans performed at the distal radius between 18 and 24 months, so these data were excluded from Figure 1.

Serum BSAP concentrations were below the limit of quantification (2 µg/L) in many subjects at baseline. As a consequence of this and subject discontinuation during the course of the study, the total number of subjects included in this analysis was 22–36 in each treatment group at each time point. The geometric mean percent change from baseline in BSAP levels was significantly greater in the HT + PTH(1–84) group than in the HT alone group at 12 months (98% vs. 18%,  $P < 0.05$ ) and at 24 months (115% vs. 29%,  $P < 0.001$ ). Urinary NTX levels were quantified in most subjects ( $n = 57$ –90/group). The geometric mean percent change from baseline in NTX levels was significantly greater in the HT + PTH(1–84) group than in the HT alone group at 12 months (65% vs. 2%,  $P < 0.001$ ) and at 24 months (69% vs. 24%,  $P < 0.01$ ).

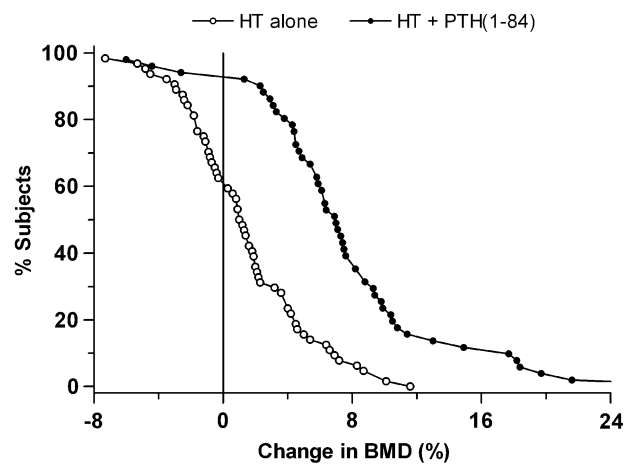
There were no significant changes in height in either treatment group during the study. The mean change in height was +0.06 and +0.09 cm in the HT alone and



**Fig. 1** Change in BMD at (a) lumbar spine, (b) femoral neck, (c) total hip, and (d) distal radius of PMO women receiving stable HT following treatment with placebo (HT alone) or PTH(1-84) for up to 24 months. Results at 18 months are from DXA scans performed between 12 and 18 months, and those at 24 months are from scans between 18 and 24 months. Values are mean ± SE. \* $P < 0.05$ , \*\*\* $P < 0.001$  vs. HT alone. Number of observations at each time point shown in parentheses

HT + PTH(1-84) groups, respectively, at 18 months ( $P = 0.79$ ).

There were insufficient numbers of vertebral and clinical fractures to permit statistical analysis. Three subjects in



**Fig. 2** Percent change in lumbar spine BMD by subject in PMO women receiving stable HT following treatment with placebo (HT alone) or PTH(1-84) for 18 months. One woman in the HT + PTH(1-84) group who had a BMD increase of 31.7% is omitted from the figure

each treatment group experienced a clinical fracture during the study. In the HT alone group, fractures of a humerus (day 2), rib (day 227), and lumbar vertebra L1 (after a fall on day 402) were reported. The L1 fracture was not confirmed by X-ray at the study site. In the HT + PTH(1-84) group, fractures of a foot (day 195), radius (day 567), and toe (day 630) were reported.

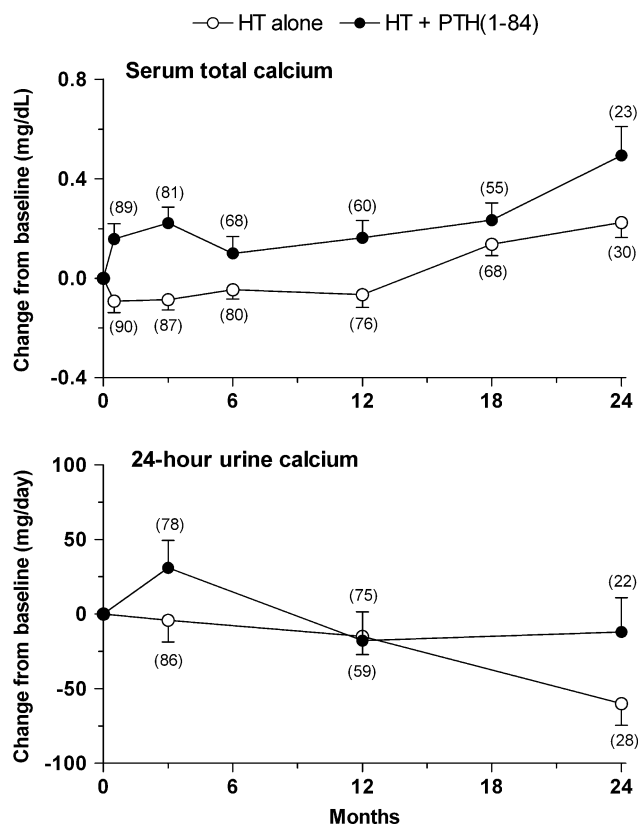
**Safety**

The overall incidence of AEs was similar between the HT + PTH(1-84) (96%) and HT alone groups (93%). Table 2 summarizes AEs reported by >5% of subjects, which were more frequently observed in the HT + PTH(1-84) group than in the HT alone group. The most commonly reported AEs overall were hypercalciuria and hypercalcemia. Ten subjects in the HT alone group and 19 subjects in the HT + PTH(1-84) group discontinued treatment because of AEs. The most common AE leading to discontinuation in the HT alone group was hypercalciuria ( $n = 3$ ), whereas it was nausea in the HT + PTH(1-84) group ( $n = 6$ ). Twelve women in each group withdrew

**Table 2** Adverse events reported by >5% of subjects, with higher incidence in subjects receiving HT + PTH(1-84) than HT alone

Adverse event	HT alone ( $n = 90$ )	HT + PTH(1-84) ( $n = 90$ )
Hypercalciuria	15 (16.7)	39 (43.3)
Hypercalcemia	0	13 (14.4)
Nausea	3 (3.3)	23 (25.6)
Vomiting	4 (4.4)	10 (11.1)
Dizziness	5 (5.6)	9 (10)

Values are  $n$  (%)



**Fig. 3** Change in serum and urine calcium in PMO women receiving stable HT following treatment with placebo (HT alone) or PTH(1–84) for up to 24 months. Values are means  $\pm$  SE. Number of observations at each time point shown in parentheses

consent and meeting an exclusion criterion occurred in five subjects in the HT alone group and in nine subjects in the HT + PTH(1–84) group. Two subjects in the HT + PTH(1–84) group discontinued treatment because of hypercalcemia.

At baseline, mean ( $\pm$  SE) serum total calcium was  $9.49 \pm 0.04$  ( $n = 90$ ) and  $9.56 \pm 0.05$  mg/dl ( $n = 90$ ) and mean urine calcium was  $221 \pm 13$  ( $n = 86$ ) and  $230 \pm 15$  mg/24 h ( $n = 79$ ) in the HT alone and HT + PTH(1–84) groups, respectively. The changes from baseline in serum and urinary calcium during the study are shown in Figure 3. There was a small ( $\sim 0.2$  mg/dl) increase in serum calcium by month 3 in the HT + PTH(1–84) group, whereas calcium levels tended to decrease in the HT alone group. A between-group difference of  $\sim 0.1$ – $0.2$  mg/dl in serum calcium was maintained through most of the study. Urine calcium excretion decreased by 60 mg/day across the study in the HT alone group. A small transient increase occurred in the HT + PTH(1–84) group, but calcium excretion was maintained at or below baseline levels from 12 to 24 months.

A total of 18 serious AEs were reported by 12 subjects (HRT + PTH[1–84], four subjects; HT alone, eight

subjects). Three subjects in the HT alone group experienced more than one serious AE. Two subjects (one in each group) discontinued treatment because of a serious AE.

## Discussion

This study demonstrated that treatment of postmenopausal women receiving long-term stable HT with PTH(1–84) significantly increased lumbar spine BMD at all time points when compared to women receiving long-term stable HT with placebo injections. The increase in lumbar spine BMD in the HT + PTH group at 18 months was 7.9%. This compares favorably with a phase III study, where a 6.4% increase occurred and was associated with an approximately 60% decrease in the incidence of vertebral fractures [9]. HT + PTH(1–84) treatment was also associated with a significant increase in femoral neck BMD at 18 months. When compared with HT alone, there were no significant effects of HT + PTH(1–84) treatment at total hip or distal radius. Few fractures occurred, and there were no changes in height in either group. The increases in BSAP and NTX are consistent with the known effects of PTH(1–84) to increase bone turnover [3, 9].

Subjects on stable HT alone experienced no marked changes in any efficacy parameter, although tendencies for increases in BMD were observed at some skeletal sites. The reason for this increase in BMD in the HT alone group is unclear. One possible explanation is that the high levels of calcium and vitamin D supplementation may have reversed a mild secondary hyperparathyroidism. However, as neither serum PTH nor 25-hydroxyvitamin D levels were measured in this study, this possibility remains speculative. Alternatively, since subjects had to have been on HT for only 6 months at randomization, all the beneficial effects of HT on the skeleton may not have manifested in all subjects when treatment was started.

Although terminated early following recommendations by the EMEA, the results of this study were consistent with a previous study using PTH(1–34) in women on stable HT [14]. However, the  $\sim 8\%$  increase in lumbar spine BMD in this study was lower than the  $\sim 13\%$  increase observed by Cosman et al. [14]. This apparent difference in efficacy outcome may be partially attributable to the longer treatment period (3 years) in the study of Cosman et al. as well as to the numerous other differences in design of the two studies. However, a similar difference between PTH(1–84) and PTH(1–34) has also been observed in other studies in postmenopausal women not receiving HT. Despite the apparent differences in BMD gain, the vertebral antifracture efficacy of the two peptides was similar [8, 9].

When compared to studies of PTH peptides in combination with the bisphosphonate alendronate, the results of

studies of PTH peptides together with HT show some striking differences. PTH(1–34) treatment of osteoporotic men who previously received alendronate for 6 months, which was continued throughout the study, was associated with a marked blunting of the increase in lumbar spine BMD measured by DXA compared with PTH(1–34) alone [10]. Similarly, when PTH(1–34) was given to osteoporotic women previously treated with alendronate for 18–36 months, there was also a delayed and smaller increase in BMD, even though alendronate was discontinued when PTH(1–34) treatment was initiated [17]. In contrast, when combination PTH(1–84) and alendronate was initiated in treatment-naïve patients, there was only a small, nonsignificant blunting of the increase in lumbar spine BMD when measured by DXA relative to PTH(1–84) alone. However, a substantial blunting of the increase in lumbar spine trabecular BMD measured by quantitative computed tomography was observed [11].

Although no direct comparisons of HT + PTH peptide vs. PTH peptide alone have been performed, a controlled 6-month study in postmenopausal osteoporotic women by Deal et al. [12] provided evidence that the combination of PTH(1–34) and the SERM raloxifene in treatment-naïve subjects resulted in a greater BMD increase than PTH(1–34) alone. They showed that lumbar spine BMD increased by 6.2% in the combination group vs. 5.2% in the PTH(1–34) alone group. While the difference was not statistically significant at the lumbar spine, a significantly greater increase in total hip BMD was observed with combination treatment. The mechanism responsible for the greater increase in BMD in the combination group appeared to be that raloxifene did not suppress bone formation (serum procollagen type I amino-terminal propeptide) but did significantly reduce the magnitude of the increase in resorption (serum  $\beta$ -cross-linked C-terminal telopeptide) [12]. This clearly contrasts with the results with combination PTH peptide and alendronate, where a marked suppression of both bone formation and resorption compared to PTH peptide alone was observed [11]. Collectively, these results suggest that the PTH peptide-induced increases in bone turnover and perhaps bone formation itself may be impaired when combined with bisphosphonates, as has been suggested in studies in rats by Gasser et al. [18].

As noted above, there was a significantly greater increase in total hip BMD in women who received raloxifene and PTH(1–34) than PTH(1–34) alone [12]. When comparing across studies with PTH(1–84), there was also a slightly larger BMD increase at 18 months in the POWER study than in the TOP study at total hip (1.4% vs. 1.0%) and femoral neck (2.3% vs. 1.8%) and a smaller decrease at distal radius (–0.5% vs. –4.4%). This suggests that existing stable HT may partially protect sites rich in

cortical bone during PTH(1–84) treatment. Although such an interpretation is also limited by the small study population and relatively younger age, one possible explanation for the difference in observed treatment effects is the ability of HT to limit the magnitude of haversian remodeling, especially at the distal radius where the difference between PTH(1–84) monotherapy and HT + PTH(1–84) appeared to be most pronounced.

PTH(1–84) treatment was associated with a mean increase in serum total calcium levels of 0.1–0.2 mg/dl. This was slightly less than the  $\sim$ 0.3 mg/dl increase observed in PTH(1–84)-treated subjects in a phase III study (unpublished results) and by Deal et al. [12] in women receiving PTH(1–34) alone. Although the design of their study differed substantially, Cosman et al. [14] noted that there were no changes in serum calcium or incidence of hypercalcemia in their study of HT + PTH(1–34); but no data or normal ranges were provided, and they did not report urinary calcium data. This omission is important because an elevated morning urine calcium-to-creatinine ratio was the most common reason that subjects in the POWER study had their calcium supplements withdrawn and the frequency of dosing reduced.

PTH(1–84) treatment was generally well tolerated in this study, with hypercalciuria, nausea, hypercalcemia, vomiting, and dizziness as the most common AEs, which were more frequently reported by subjects in the HT + PTH(1–84) group than in the HT alone group. Of note, the incidence of hypercalcemia in this study was lower than that reported with PTH(1–84) monotherapy [9]. This may be attributable, among other possibilities, to the recognized hypocalcemic effects of estrogen, which may relate to the suppression of bone turnover [19]. A lower incidence of hypercalcemia was also observed in the Parathyroid Hormone and Alendronate for Osteoporosis (PaTH) study [12], possibly because the acute increase in serum calcium following PTH injection was reduced in subjects receiving concomitant alendronate [20].

In conclusion, the addition of PTH(1–84) to stable long-term HT produced a statistically significant increase in lumbar spine BMD relative to HT alone. Despite the recent precautions with regard to HT for prevention and treatment of osteoporosis, many women continue to receive HT for control of acute menopausal symptoms. The use of PTH(1–84) in such women may provide an additional approach to osteoporosis risk reduction in women already receiving HT.

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