Prevention of Estrogen Deficiency–Related Bone Loss With Human Parathyroid Hormone–(1-34)
A Randomized Controlled Trial

Joel S. Finkelstein, MD; Anne Klibanski, MD; Amy L. Arnold, BA;
Thomas L. Toth, MD; Mark D. Hornstein, MD; Robert M. Neer, MD

Context.—Short-term intermittent administration of parathyroid hormone (PTH) prevents bone loss from the spine in women treated with a gonadotropin-releasing hormone (GnRH) analog. However, the effects of a longer period of PTH administration on bone mass in estrogen-deficient women, particularly on the hip and on cortical bone of the total body, are unknown.

Objective.—To determine whether more prolonged PTH administration can prevent estrogen deficiency bone loss from the hip, spine, and total body in young women with endometriosis receiving GnRH analog (nafarelin acetate) therapy.

Design.—Randomized controlled trial.

Setting.—General Clinical Research Center of a tertiary care, university-affiliated hospital.

Patients.—Forty-three women between the ages of 21 and 45 years with symptomatic endometriosis.

Intervention.—Nafarelin alone (200 µg intranasally twice daily) or nafarelin plus human parathyroid hormone–(1-34) (hPTH-[1-34]) (40 µg subcutaneously daily).

Main Outcome Measures.—The primary end points were bone mineral density (BMD) of the anterior-posterior and lateral spine, femoral neck, trochanter, radial shaft, and total body at 12 months of treatment.

Results.—In the women who received nafarelin alone, the mean (SEM) BMDs of the anterior-posterior spine, lateral spine, femoral neck, trochanter, and total body were 4.9% (0.6%) (P < .001), 4.9% (0.8%) (P < .001), 4.7% (1.1%) (P < .001), 4.3% (0.9%) (P < .001), and 2.0% (0.6%) (P = .003) lower than at baseline after 12 months of therapy. In contrast, coadministration of hPTH-(1-34) increased BMD of the anterior-posterior spine by 2.1% (1.1%) (P = .09) and lateral spine by 7.5% (1.9%) (P = .002) and prevented bone loss from the femoral neck, trochanter, and total body, despite severe estrogen deficiency. Radial shaft BMD did not change significantly in either group. Serum bone-specific alkaline phosphatase and osteocalcin concentrations and urinary excretion of hydroxyproline and deoxypyridinoline increased 2-fold to 3-fold during the first 6 to 9 months of therapy in the women who received nafarelin plus hPTH-(1-34) and then declined. Changes in urinary deoxy-
pyridinoline excretion were strongly predictive (r = 0.85) of changes in spinal BMD in the women who received nafarelin plus hPTH-(1-34).

Conclusions.—Parathyroid hormone prevents bone loss from the proximal femur and total body and increases lumbar spinal BMD in young women with GnRH analog–induced estrogen deficiency.

OSTEOPOROSIS affects 20 million people in the United States and leads to approximately 1.3 million fractures in the United States each year.1,2 It has been estimated that 30% of all postmenopausal white women will sustain an osteoporotic fracture.1,2 The annual cost of health care and lost productivity due to osteoporosis has been estimated at $13.8 billion in the United States.3 Currently, there are no methods to reverse osteoporosis completely once it is established. Therefore, it is essential to prevent its development. In the United States, only estrogen, alendronate, and raloxifene have Food and Drug Administration approval for preventing bone loss in women who have recently begun menopause. Only one sixth to one quarter of postmenopausal women receive estrogen replacement therapy, primarily because of concerns about the risk of breast cancer and because cyclic regimens cause menstrual bleeding.4 Because alendronate remains in the skeleton indefinitely, theoretical concerns exist regarding its long-term effects. Although raloxifene is a promising new therapy, it increases the risk of thromboembolic events.5 Therefore, alternative strategies to prevent bone loss due to estrogen deficiency are needed.

Parathyroid hormone (PTH) is usually thought to cause bone resorption. In some circumstances, however, PTH has a predominantly anabolic effect on the skeleton. Although continuous infusion of PTH decreases bone mass,6,7 daily injection of PTH increases bone formation more than it increases bone resorption,8-10 leading to a net increase in bone mass.6,7,11-15 In animals, intermittent PTH administration prevents castration-induced bone loss16-18 and can completely reverse established osteopenia.19-21 In women with endometriosis who are rendered estrogen deficient by treatment with a long-acting gonadotropin-releasing hormone (GnRH) analog, short-term intermittent administration of human parathyroid hormone–(1-34) (hPTH-[1-34]), prevents spinal bone loss.22 The effects of a longer-term administration of PTH on bone mineral density (BMD), particularly of the femoral neck and total body, are unknown. Because hip fractures are the ma-

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moral source of morbidity in osteoporosis, assessment of the effects of PTH on this site is particularly important. Therefore, to assess the effects of intermittent PTH administration on the hip and total body, we randomly assigned women with endometriosis to treatment either with a GnRH analog alone or a GnRH analog plus hPTH-(1-34) for 12 months.

METHODS

Protocol

Study Population.—Forty-three women between the ages of 21 and 45 years who had symptomatic, laparoscopically proven endometriosis were studied. Twenty-five of these women were continuing in a previous 6-month study and some of their data had been reported previously.22 These women agreed to continue in their randomly assigned study groups for an additional 6 months. The remaining women from the original 6-month study completed their therapy before the study was extended to 12 months. Ovulation was confirmed in the menstrual cycle before entry into the study by a luteal-phase serum progesterone level more than 16 nmol/L (5 ng/dL). All women had normal serum calcium, inorganic phosphate, alkaline phosphatase, bilirubin, creatinine, free thyroxine index, and prolactin concentrations. Women with disorders or taking medications known to affect bone metabolism were excluded.22 Oral contraceptive and danazol use was discontinued for at least 2 months and GnRH analog therapy was discontinued for at least 9 months before entry into the study. The study was approved by the Subcommittee on Human Studies at Massachusetts General Hospital, Boston. All women provided written informed consent.

Study Procedures.—The women were randomly assigned to receive the GnRH analog nafarelin acetate (Synarel, Syntex Laboratories, Inc, Palo Alto, Calif), 200 µg intranasally twice daily, for 12 months (group 1, n = 22) or nafarelin acetate plus hPTH-(1-34), 40 µg (500 U) subcutaneously, for 12 months (group 2, n = 21). The hPTH-(1-34) was synthesized by solid-phase methods (Bachem Inc, Torrance, Calif), and its potency was determined by bioassay.23 If serum estradiol concentrations remained at 147 pmol/L (40 pg/mL) or more or symptoms of endometriosis were not substantially relieved after 3 months, the nafarelin dose was increased by 200 µg/d to 400 µg/d. In group 2, 24-hour urine calcium excretion and serum calcium were measured 2 to 4 weeks after starting hPTH-(1-34) therapy. If urinary calcium excretion was above 8.7 mmol/d (350 mg/24 h), dietary calcium intake was decreased by 50%. If the serum calcium was more than 2.62 mmol/L (10.5 mg/dL), the hPTH-(1-34) dose and/or dietary calcium intake were decreased by 30% to 50%. Serum or urine calcium measurements were repeated to document normality. Four women required reductions in their hPTH-(1-34) dose.

The women were initially admitted to the General Clinical Research Center at Massachusetts General Hospital between days 6 and 10 of their menstrual cycle and were readmitted every 3 months for 1 year. During each admission, the women underwent measurements of radial, spinal, proximal femur, and total body BMD. A fasting second voided urine sample was collected between 8 AM and 10 AM for measurements of hydroxyproline (OHP), deoxypyridinoline (DPD), and creatinine excretion and a fasting blood sample was collected for measurements of serum calcium, inorganic phosphate, cholesterol, phosphatase (BSAP), osteocalcin (OC), PTH, calcidiol, calcitriol, insulin-like growth factor I (IGF-I), and estradiol concentrations. Blood was drawn just prior to the morning hPTH-(1-34) and/or nafarelin dose. In group 2, an additional blood sample was drawn 4 hours after hPTH-(1-34) injection to determine peak serum calcium concentrations. The adverse effects of therapy and self-reported symptom relief were assessed during each visit.

Daily calcium intake, percentage of body fat (using skinfold thickness), body mass index (a measure of weight in kilograms divided by the square of height in meters), and percentage of ideal body weight (using Metropolitan Life Insurance Company tables) were determined by a research dietician. Histories of running, weight lifting, and involvement in aerobic exercises were determined. Running was expressed in terms of miles per week times years of activity and considered “substantial” if 15 miles (24 km) or more.24 Aerobics and weight lifting were expressed in terms of total years exercising at least 3 times per week and considered “regular” if 1 year or more.24 The women were asked to maintain a daily calcium intake of approximately 1200 mg through diet or calcium carbonate supplements.

Compliance was assessed by medication diaries, counting medication vials, and measurements of serum estradiol. Compliance with nafarelin was at least 97% in 42 (98%) of 43 women and at least 99% in 39 women. In group 2, 19 (90%) of 21 women took at least 90% of their hPTH-(1-34) injections and 1 woman took 90% of her injections. Vial counts and estradiol measurements suggested non-compliance with nafarelin and hPTH-(1-34) in 1 woman in group 2.

Four women in group 2 withdrew from the study after 3 months (n = 2) or 6 months (n = 2). Reasons for withdrawal included hot flashes and mild weight gain (n = 1), excessive distance from study site (n = 1), discomfort from injections (n = 1), and depression (n = 1). All data from these women are included and analyzed with their originally assigned group.

Determination of BMD

Bone mineral density of the proximal radius, lumbar spine, proximal femur, and total body was determined by dual-energy x-ray absorptiometry (Hologic QDR-2000, Waltham, Mass).25 Measurements of the nondominant radius were made in the diaphysis at the junction of the proximal two thirds and distal one third; the coefficient of variation of this measurement was 1.5%.25 Lumbar spine BMD was assessed in both the anterior-posterior and lateral projections with the women in a supine position. Lateral spinal BMD estimates trabecular bone mass better than measurements made in the anterior-posterior projection.26 Total body BMD was analyzed without contribution from the head region because the head accounts for most of the variability of this measurement.27 The SDs for anterior-posterior and lateral spine measurements were 0.010 g/cm² and 0.013 g/cm², respectively, and did not vary with BMD. The coefficients of variation for femoral neck, trochanter, and total body BMD measurements were 2.2%, 1.1%, and 1.1%, respectively.28 Follow-up scans were matched to baseline scans to ensure measurement of identical bone regions. Vertebrae with obvious deformities or areas of focal sclerosis were not analyzed, and those with visible overlap from ribs or the pelvis were eliminated from analysis of lateral spine scans.

Assays

Serum PTH-(1-34) and OC were measured with immunoradiometric assays (Nichols Institute, San Juan Capistrano, Calif). The assay for PTH-(1-34) does not detect hPTH-(1-34). Serum calcidiol (Innotest Corp, Stillwater, Minn), calcitriol (Nichols Institute), IGF-I (Nichols Institute), and estradiol29 were determined by radioimmunoassay. Urinary OHP excretion was measured by Smith-Kline Beecham Clinical Laboratories, Van Nuys, Calif, using automated spectrophotometric analysis. Urinary free DPD excretion and serum BSAP were measured with enzyme immunomassays (Pyrilinks D and AllPhase B, Metra Biosystems, Mountain View, Calif). Except for the serum estradiol and urinary OHP determinations, all measurements for each woman were performed in a single assay.

Statistical Analyses

Prior studies have suggested that trabecular and cortical BMD decrease by 6% and 1% to 2%, respectively, during the first
RESULTS

Participant Flow and Follow-up

The number of women screened and their outcomes, including reasons for ineligibility, reasons for nonrandomization, and the flow of women through the trial, are shown in Figure 1.

Clinical and Laboratory Characteristics

The clinical and laboratory characteristics of the women are shown in Tables 1 and 2. In the women treated with nafarelin alone (group 1), 21 women had previously received oral contraceptives for an average of 4 years (+4 years); 6 had received danazol; and 4 had previously received GnRH analog therapy. In the women treated with nafarelin plus hPTH-(1-34) (group 2), 19 women had previously received oral contraceptives for an average of 4 years (+4 years); 6 had received danazol; and 4 had previously received GnRH analog therapy.

Clinical Response to Nafarelin Therapy

Serum estradiol concentrations decreased significantly both in group 1 (P<.001) and group 2 (P=.009) (Table 2), reaching postmenopausal values less than 110 pmol/L (30 pg/mL) in 18 (82%) of 22 women in group 1 and 20 (95%) of 21 women in group 2. In group 1, the final daily nafarelin dose was 400 µg in 18 women, 800 µg in 3 women, and 1200 µg in 1 woman. In group 2, the final daily nafarelin dose was 400 µg in 13 women, 600 µg in 1 woman, 800 µg in 5 women, and 1200 µg in 2 women. In group 1, 21 (95%) of 22 women reported at least a 75% decrease in their endometriosis symptoms, 15 of whom reported complete symptomatic relief. In group 2, all 21 women reported at least a 75% decrease in their endometriosis symptoms, 15 of whom reported complete relief.

Bone Mineral Density

In the women who received nafarelin alone (group 1), the mean (SEM) BMDs of the anterior-posterior spine, lateral spine, femoral neck, trochanter, and total body were 4.9% (0.6%) (P<.001), 4.9% (0.8%) (P<.001), 4.7% (1.1%) (P<.001), 4.3% (0.9%) (P<.001), and 2.0% (0.5%) (P=.003), respectively, lower than baseline after 12 months of therapy (Figure 2). In the women who received nafarelin plus hPTH-(1-34) (group 2), anterior-posterior and lateral spine BMD were 2.1% (11%) (P=.09) and 7.5% (1.9%) (P=.002) higher than baseline at the end of therapy. In group 2, BMD of the femoral neck and trochanter decreased slightly during the first 6 months of therapy and then returned to baseline after 1 year (Figure 2). Total body BMD did not change significantly in group 2. At 12 months of therapy, the BMDs of the anterior-posterior spine (P<.001), lateral spine (P<.001), femoral neck (P<.001), and trochanter (P=.04), expressed as a percentage of baseline values, were significantly greater in group 2 than in group 1 (Figure 2). The increase in lateral spine BMD was significantly greater at 6 months than at 12 months of therapy (P=.005). Although total body BMD decreased significantly in group 1 but not in group 2, the difference between the change in total body BMD at 12 months did not achieve statistical significance (P=.08). The BMD of the proximal radius did not change significantly in either group.

Biochemical Values

Serum BSAP, serum OC, urinary OHP, and urinary DPD were significantly higher than baseline at 12 months both in group 1 (P<.001, P=.002, P=.003, and P=.001, respectively) and group 2 (P<.001 for each analyte) (Figure 3). Serum BSAP, serum OC, urinary OHP, and urinary DPD in-
Table 1.—Baseline Clinical and Laboratory Characteristics in Women With Endometriosis Treated With Nafarelin Alone (Group 1) or Nafarelin Plus hPTH-(1-34) (Group 2)†

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 22)</th>
<th>Group 2 (n = 21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31 ± 7</td>
<td>32 ± 7</td>
<td>.74</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167 ± 6</td>
<td>164 ± 5</td>
<td>.04</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.2 ± 13.0</td>
<td>65.7 ± 11.6</td>
<td>.36</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.7 ± 4.4</td>
<td>24.3 ± 3.9</td>
<td>.76</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>31.8 ± 5.4</td>
<td>32.0 ± 5.8</td>
<td>.93</td>
</tr>
<tr>
<td>Calcium intake, mg/d</td>
<td>1064 ± 497</td>
<td>1056 ± 689</td>
<td>.96</td>
</tr>
<tr>
<td>Alcohol intake, g/d</td>
<td>6 ± 10</td>
<td>4 ± 6</td>
<td>.55</td>
</tr>
<tr>
<td>Cigarette use†</td>
<td>7 (32)</td>
<td>7 (33)</td>
<td>.92</td>
</tr>
<tr>
<td>Substantial running†</td>
<td>5 (23)</td>
<td>4 (19)</td>
<td>.77</td>
</tr>
<tr>
<td>Regular aerobics†</td>
<td>4 (16)</td>
<td>8 (38)</td>
<td>.26</td>
</tr>
<tr>
<td>Regular weight lifting†</td>
<td>5 (23)</td>
<td>8 (38)</td>
<td>.44</td>
</tr>
<tr>
<td>Anterior-posterior spine BMD, g/cm²</td>
<td>1.125 ± 0.098</td>
<td>1.075 ± 0.093</td>
<td>.08</td>
</tr>
<tr>
<td>Lateral spine BMD, g/cm²</td>
<td>0.852 ± 0.121</td>
<td>0.833 ± 0.078</td>
<td>.39</td>
</tr>
<tr>
<td>Femoral neck BMD, g/cm²</td>
<td>0.976 ± 0.145</td>
<td>0.939 ± 0.101</td>
<td>.32</td>
</tr>
<tr>
<td>Trochanter BMD, g/cm²</td>
<td>0.772 ± 0.109</td>
<td>0.759 ± 0.073</td>
<td>.66</td>
</tr>
<tr>
<td>One-third radius BMD, g/cm²</td>
<td>0.688 ± 0.032</td>
<td>0.683 ± 0.049</td>
<td>.69</td>
</tr>
<tr>
<td>Total body BMD, g/cm²</td>
<td>1.033 ± 0.076</td>
<td>0.992 ± 0.058</td>
<td>.06</td>
</tr>
<tr>
<td>BSAP, U/L</td>
<td>10.1 ± 3.6</td>
<td>8.6 ± 2.8</td>
<td>.15</td>
</tr>
<tr>
<td>Osteocalcin, µg/L</td>
<td>5.7 ± 1.6</td>
<td>6.1 ± 2.4</td>
<td>.63</td>
</tr>
<tr>
<td>Urinary OHP, creatinine</td>
<td>0.024 ± 0.006</td>
<td>0.024 ± 0.009</td>
<td>.78</td>
</tr>
<tr>
<td>Urinary DPD, mmol/L: creatinine, mmol/L</td>
<td>4.7 ± 1.6</td>
<td>4.3 ± 1.9</td>
<td>.43</td>
</tr>
<tr>
<td>Parathyroid hormone, ng/L</td>
<td>28 ± 11</td>
<td>31 ± 16</td>
<td>.46</td>
</tr>
<tr>
<td>Calcidiol, nmol/L</td>
<td>82 ± 30</td>
<td>77 ± 52</td>
<td>.66</td>
</tr>
<tr>
<td>Calcitriol, pmol/L</td>
<td>91 ± 30</td>
<td>89 ± 30</td>
<td>.81</td>
</tr>
<tr>
<td>IGF-I, µg/L</td>
<td>310 ± 98</td>
<td>272 ± 88</td>
<td>.20</td>
</tr>
</tbody>
</table>

†Plus-minus values are mean ± SD. hPTH indicates human parathyroid hormone; BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; OHP, hydroxyproline; DPD, deoxypyridinolone; and IGF-I, insulin-like growth factor I.

‡Values indicate the number of women participating, with percentage in parentheses.

Table 2.—Serum Chemistries and Hormone Values in Women With Endometriosis Receiving Nafarelin Alone (Group 1) or Nafarelin Plus hPTH-(1-34) (Group 2)‡

<table>
<thead>
<tr>
<th>Serum Measurement</th>
<th>Baseline</th>
<th>6 mo</th>
<th>12 mo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol, pmol/L</td>
<td>Group 1</td>
<td>341 ± 250</td>
<td>158 ± 110</td>
<td>114 ± 37</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>411 ± 327</td>
<td>106 ± 59</td>
<td>106 ± 40</td>
</tr>
<tr>
<td>Parathyroid hormone, ng/L</td>
<td>Group 1</td>
<td>28 ± 11</td>
<td>27 ± 12</td>
<td>27 ± 14</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>31 ± 16</td>
<td>13 ± 7</td>
<td>24 ± 17</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>Group 1</td>
<td>2.25 ± 0.12</td>
<td>2.35 ± 0.10</td>
<td>2.35 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>2.27 ± 0.12</td>
<td>2.37 ± 0.17</td>
<td>2.37 ± 0.17</td>
</tr>
<tr>
<td>Phosphate, mmol/L</td>
<td>Group 1</td>
<td>1.16 ± 0.19</td>
<td>1.23 ± 0.26</td>
<td>1.26 ± 0.16</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>1.23 ± 0.10</td>
<td>1.23 ± 0.16</td>
<td>1.29 ± 0.13</td>
</tr>
<tr>
<td>Calcidiol, nmol/L</td>
<td>Group 1</td>
<td>82 ± 30</td>
<td>82 ± 50</td>
<td>85 ± 50</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>77 ± 52</td>
<td>62 ± 30‡</td>
<td>67 ± 45‡</td>
</tr>
<tr>
<td>Calcitriol, pmol/L</td>
<td>Group 1</td>
<td>91 ± 29</td>
<td>82 ± 29</td>
<td>91 ± 31</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>89 ± 29</td>
<td>82 ± 34</td>
<td>96 ± 34</td>
</tr>
<tr>
<td>IGF-I, µg/L</td>
<td>Group 1</td>
<td>310 ± 98</td>
<td>287 ± 80</td>
<td>254 ± 77</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>272 ± 88‡</td>
<td>192 ± 69‡</td>
<td>206 ± 46‡</td>
</tr>
</tbody>
</table>

†Plus-minus values are mean ± SD. hPTH indicates human parathyroid hormone; IGF-I, insulin-like growth factor I.
‡To convert serum estradiol, calcitriol, and parathyroid hormone values to picograms per milliliter divide by 3.671, 2.4, and 1.0, respectively.
§To convert serum calcium and inorganic phosphate values to milligrams per deciliter, divide by 0.2495 and 0.3229, respectively.
¶To convert serum calcidiol values to nanograms per milliliter divide by 2.496.
%P values are for paired comparisons between values at baseline and 12 months.
*P = .01 vs group 1.
**P = .11 vs group 1.
††P = .02 vs group 1.
‡‡P = .20 vs group 1.
§§P = .03 vs group 1.

Serum PTH levels were significantly lower in group 2 than in group 1 (P = .001, P < .001, P < .001, P = .014, respectively). In group 2, all 4 markers peaked at 6 to 9 months of therapy and then began to decline (Figure 3).

Serum calcium and inorganic phosphate levels were significantly higher than baseline at 12 months in group 1 (P = .007 for calcium and P = .009 for inorganic phosphate) but did not change significantly in group 2 (Table 2). Mean serum calcium and inorganic phosphate levels remained within the normal range in both groups (Table 2). Baseline serum calcidiol levels were normal in both groups and 39 (91%) of 45 women had levels greater than 37 nmol/L (15 ng/mL). § Serum calcitriol concentrations did not change significantly in either group (Table 2). Serum IGF-I concentrations were significantly lower than baseline at 12 months in group 1 (P = .002) and group 2 (P = .001) and were significantly lower in group 2 than group 1 at 6 months (P < .001) and 12 months (P = .003) (Table 2). Mean total (SEM) serum cholesterol concentrations were 10% (3%) above baseline in group 1 (P = .001) and 13% (3%) above baseline in group 2 (P = .001) at 12 months. Serum low-density lipoprotein concentrations were 10% (4%) above baseline in group 1 (P = .02) and 18% (4%) above baseline in group 2 (P = .005) at 12 months. Serum high-density lipoprotein concentrations were 7% (18%) above baseline in group 1 (P = .06) and 9% (22%) above baseline in group 2 (P = .10) at 12 months. There were no differences in total serum, low-density lipoprotein, or high-density lipoprotein cholesterol levels between groups after 6 or 12 months of therapy.

Relationship Between Changes in Bone Turnover and Changes in BMD

There were significant associations between the change in BSAP and lateral spine BMD (r = 0.64; P = .01), urinary OHP excretion and lateral spine BMD (r = 0.57; P = .03), urinary DPD excretion and anterior-posterior spine BMD (r = 0.65; P = .006), and urinary DPD excretion and lateral spine BMD (r = 0.85; P < .001). Serum OC was not significantly associated with changes in spinal BMD. There were no significant associations between changes in any of the biochemical markers of bone turnover and changes in femoral neck BMD or total body BMD.

Adverse Effects

As expected, vasomotor flushes occurred in almost all patients. More than half of the women reported headaches at some time during therapy, although most stated that their headaches were no different.
vents spinal bone loss in women rendered severely estrogen deficient for 1 year. Previously, we had demonstrated that intermittent PTH administration prevents bone loss from the proximal femur and total body in young women whose hPTH-(1-34) dose was decreased, although only 1 woman reported that these symptoms affected her routine activities. One third of the women in each group gained more than 5 kg and 12% of women lost more than 5 kg. Mean changes in body weight were similar in both groups. Two women complained of mild discomfort from the hPTH-(1-34) injections and 2 women developed mild erythema at the injection site. Serum calcium levels were mildly elevated in 17% of samples collected 4 hours after hPTH-(1-34) injection (range, 2.64-2.79 mmol/L [10.6-11.2 mg/dL]) but were normal in 99% of samples collected 24 hours after hPTH-(1-34) injection with 1 value of 2.67 mmol/L (10.7 mg/dL). In the 4 women whose hPTH-(1-34) dose was decreased, serum calcium levels normalized (Table 3).

**COMMENT**

In this study, we have demonstrated for the first time that once-daily PTH administration prevents bone loss from the proximal femur and total body in young women rendered severely estrogen deficient for 1 year. Previously, we had demonstrated that intermittent PTH administration prevents spinal bone loss in women rendered estrogen deficient for 6 months. In that study, however, BMD of the femoral neck decreased slightly both in the women who received nafarelin alone and the women who received nafarelin plus hPTH-(1-34). The current data demonstrate that after more prolonged use, PTH also prevents bone loss from the proximal femur. The BMD of the femoral neck and greater trochanter returned to baseline in women treated with nafarelin plus hPTH-(1-34) for 12 months, whereas bone loss continued at these sites in the women treated with nafarelin alone. Because hip fractures are a major source of morbidity and mortality in osteoporosis, the ability of PTH to prevent bone loss at this site is particularly important.

Although the catabolic effects of PTH on the skeleton are well known, the ability of PTH to increase bone mass is less appreciated. Multiple studies have demonstrated that intermittent PTH administration increases trabecular bone mass in animals and humans. The present study now demonstrates that PTH-induced increases in lateral spine BMD are even greater after 12 months than were observed after 6 months of PTH administration. In fact, the increases in spinal BMD in these women may lower their long-term risk of osteoporotic fractures, since multiple studies have demonstrated that differences in BMD of this magnitude are associated with large reductions in fracture risk.

The effects of intermittent PTH administration on cortical bone mass are less clear. In animals, intermittent PTH administration increases cortical bone mass. However, PTH appeared to accelerate cortical bone loss from the radius in elderly women with postmenopausal osteoporosis. Cortical BMD also decreased in osteoporotic patients treated with hPTH-(1-34) plus calcitonin, although the lack of an untreated control group limited the ability to determine if the decrease in cortical bone mass was due to PTH or other factors such as estrogen deficiency. Intermittent PTH administration increases spinal and total body BMD in osteoporotic women taking estrogen. In our patients, all of whom started with normal BMD, cortical BMD of the radius did not decrease in either group. Therefore, we could not determine whether PTH can prevent bone loss at this site. Clearly, however, PTH did not accelerate cortical bone loss. Parathyroid hormone also appeared to prevent a decrease in total body BMD as total body BMD decreased significantly in the women treated with nafarelin alone but not in the women...
treated with nafarelin plus hPTH-(1-34), though the difference between groups at 12 months was of borderline statistical significance. Because most of the skeleton in humans is composed of cortical bone, these data suggest that PTH prevents both cortical and trabecular bone loss in estrogen-deficient women.

The mechanism whereby intermittent PTH administration increases bone mass is unclear. Receptors for PTH are located on cells of osteoblast lineage and administration of hPTH-(1-34) increases osteoblast number and osteoid formation in vitro. It appears that the anabolic action of PTH on the skeleton is mediated by the local production of growth factors in bone. Local release of IGF-I, a protein that stimulates collagen synthesis in cultured rat calvariae, is stimulated by PTH. Parathyroid hormone also stimulates type I collagen synthesis in bone cultures and this effect is blocked by antibodies to IGF-I. Thus, PTH may exert its anabolic action on osteoblasts via an autocrine or paracrine effect to increase production of IGF-I. Serum IGF-I levels decreased during PTH administration in our subjects. Although serum IGF-I levels may not reflect local IGF-I production, this result was surprising and requires further study.

All approved therapies for osteoporosis in the United States, including estrogen, calcitonin, raloxifene, and bisphosphonates, primarily act by decreasing bone resorption, with a secondary decrease in bone formation. In contrast, PTH primarily increases bone formation with an associated increase in bone resorption, as was indicated by the marked increases in bone turnover markers in our patients. Because BMD increased, it appears that PTH stimulates bone formation more than it stimulates bone resorption in these women. Interestingly, our data also suggest that PTH-mediated increases in bone turnover begin to decline after 6 to 9 months of daily administration. Similar changes in bone turnover have been reported recently in osteoporotic women treated with PTH and estrogen. We have observed similar results in animals undergoing long-term treatment with PTH. It is unclear whether this decline in bone turnover will be associated with a waning of the anabolic action of PTH on bone when PTH therapy is continued for longer periods. If so, optimization of PTH as a therapy for osteoporosis may require adjustments of dosage or pattern of delivery.

There are some potential limitations of our study. Because not all eligible women were enrolled in the study, it is unclear whether the results can be applied to all women with endometriosis receiving GnRH analog therapy. The lack of blinding could affect end points that are subjective in nature, such as the prevalence of adverse effects. Finally, prevention of total body bone loss was of borderline significance and needs further study.

The ability of PTH to prevent GnRH analog–induced bone loss has important clinical implications. Although GnRH analogs are effective therapies for conditions like endometriosis and uterine leiomyomas, long-term GnRH analog therapy is limited by bone loss. Unfortunately, these conditions recur when GnRH analog therapy is discontinued so that prolonged therapy is needed. Many different regimens have been used to prevent GnRH analog–induced bone loss. In women with endometriosis, addition of high-dose medroxyprogesterone acetate may prevent bone loss but blunts the benefits of GnRH analog therapy on symptoms. Combining norethisterone or norethindrone with a GnRH analog does not compromise the efficacy of the latter but reduces high-density lipoprotein cholesterol.
levels and has variable effects on bone loss. Similarly, combinations of GnRH analogs with estrogen-containing regimens may have increased efficacy for bone loss. Furthermore, these regimens may mitigate the benefits of GnRH analog therapy in patients with estrogen-sensitive disorders.47 Because PTH and GnRH analogs may allow long-term use of GnRH analogs in patients with benign gynecologic conditions. Moreover, because PTH prevents bone loss in young women with GnRH analog-induced bone loss, it should prevent bone loss in women entering the natural menopause.

This work was supported by National Institutes of Health grants RO1-HL-42049 and RO1-HL-11384. We are grateful to Syntax Laboratories, Inc, Palo Alto, Calif, for freely supplying nafarelin acetate (Synarel) and to Metra Biosystems, Mountain View, Calif, for freely supplying kits for measurements of BSAP and DPD.

We also wish to thank Elizabeth Schafer and the nursing staff of the General Clinical Research Center for their meticulous performance of the study protocol and dedicated care of the patients; Ellen Anderson, RD, and Jane Hubbard, RD, for obtaining the dietary histories and body fat measurements; Robbin Cleary and Sarah Zhang for performing the BMD measurements; Gregory Neubeck, BD, for statistical analyses; and Isaac Schiff, MD, Veronica Ravnikar, MD, Najmose Niki, MD, Raja Sayegh, MD, and Keith Issaean, MD, for patient referrals.

References


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