Parathyroid Hormone for Treatment of Osteoporosis

Carolyn Crandall, MD

**Background:** Osteoporosis is a common condition associated with multiple deleterious consequences. No therapy entirely abolishes fracture risk.

**Methods:** A MEDLINE database (1966 to the present) search was performed for randomized controlled trials in humans using the keywords osteoporosis and parathyroid hormone (PTH) or parathyroid hormone and fracture. The Cochrane database was searched using the search terms osteoporosis and parathyroid hormone.

**Results:** Parathyroid hormone (usually subcutaneous) dosages varied markedly across the 20 randomized controlled trial studies retrieved. In the range of 50 to 100 µg/d, effects may be dose-related. Results of larger trials (up to 1637 patients) were conflicting as to whether effects were limited to the spine and suggested detrimental effects on radius bone mineral density. Little data analyzed the effects of PTH in older vs younger subjects or directly compared the effects by sex. Increases in spine bone mineral density are induced by PTH in postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, and idiopathic osteoporosis. Parathyroid hormone may protect against gonadotropin-releasing hormone agonist–related bone loss. Effects are less clear at nonspine sites when PTH is used as part of combination or sequential therapies or for treatment of glucocorticoid-induced osteoporosis. Parathyroid hormone decreased the incidence of radiographically detected spinal fractures. The numbers of nonvertebral fractures were too low to be broken down by individual site. Parathyroid hormone injections were difficult for some patients to comply with. Occasionally, PTH-associated hypercalcemia may be dose-dependent, often manifesting early in treatment. An increase in cancer risk from PTH is not reported in humans.

**Conclusions:** Parathyroid hormone decreases vertebral fractures and increases spinal bone density in postmenopausal osteoporosis and glucocorticoid-induced osteoporosis, but at the expense of a decrease in radius bone density. The long-term safety and nonvertebral fracture efficacy are unknown.

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OSTEOPOROSIS IS a common condition. An estimated 17 to 23 million women and 8 to 15 million men older than 50 years in the United States have osteoporosis or low bone density, with consequential elevated fracture risk. Osteoporosis is associated with multiple deleterious consequences, including deformity, pain, loss of ambulation, and death.

To date, all approved osteoporosis treatments are of the antiresorptive class. Antiresorptive agents block resorption of bone, but they do not induce bone formation. They induce a significant decrease in fracture risk, but they do not decrease the risk completely. The increased bone density induced by antiresorptive agents is related to more complete secondary bone mineralization, rather than increased synthesis of new bone. Therefore, interest has intensified surrounding the potential role of bone formation inducers alone or in combination with antiresorptive agents. Several of the bone formation inducers (also called anabolic agents) have been investigated in animal models of osteoporosis, but trial results in humans were initially disappointing. In humans, fluoride treatment unexpectedly increased the risk of fracture, presumably due to abnormal bone quality, despite impressive increases in bone density. Fluoride has not been approved for management of osteoporosis in the United States. More recent efforts have focused on different fluoride dosages and preparations, such as slow-release fluoride preparations, as well as other bone formation inducers, such as parathyroid hormone (PTH).

Preliminary studies of PTH have been overshadowed by concerns about adverse effects at nonspine areas, similar to
thyroid hormone

A MEDLINE database (1966 to the present) keyword search was performed for randomized controlled trials involving PTH and osteoporosis. The Cochrane database was also searched using the search terms osteoporosis and parathyroid hormone. Reference lists of retrieved articles were reviewed for additional pertinent articles.

Table 1. Randomized Controlled Trials of Parathyroid Hormone With Bone Density Outcome*

<table>
<thead>
<tr>
<th>Source</th>
<th>Subjects</th>
<th>Regimen†</th>
<th>Calcium† or Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodsman and Fraher, 1990</td>
<td>20 Patients aged 50-78 y, the men having idiopathic osteoporosis and women having postmenopausal osteoporosis, all with symptomatic vertebral fractures</td>
<td>hPTH–(1-38) 400 IU/d SC for 14 d alone or followed by CT 75-100 U/d SC for 56 d, then 30 d treatment-free, randomized, 1 cycle in 1990 report, 2 cycles (total 200 days) in 1991</td>
<td>None mentioned</td>
</tr>
<tr>
<td>Hodsman et al, 1991</td>
<td>40 Women aged 20-44 y with endometriosis</td>
<td>Nafarelin acetate alone (200 µg intranasally bid) or with hPTH–(1-34) 40 µg SC qd for 6 mo, not double-blind†</td>
<td>If dietary urinary calcium excretion was above 350 mg/24h, dietary calcium intake was decreased by 50%. If serum calcium was &gt;10.5 mg/dL, hPTH dosage or dietary calcium intake was decreased by 30%-50%.</td>
</tr>
<tr>
<td>Finkelstein et al, 1994</td>
<td>43 Women aged 21-45 y with symptomatic endometriosis</td>
<td>Nafarelin alone (200 µg intranasally bid) or with hPTH–(1-34) 40 µg SC qd for 12 mo, not double-blind†</td>
<td>Calcium supplement 500 mg elemental calcium per day, no vitamin D supplement.</td>
</tr>
<tr>
<td>Hodsman et al, 1997</td>
<td>30 Women, mean age 67 y, with osteoporosis†</td>
<td>hPTH–(1-34) 50 µg SC for 28 days followed by placebo vs hPTH for 28 days followed by CT 75 U SC qd for 42 days, followed by 20 d treatment-free in cycles, for 2 y, blinding not discussed</td>
<td></td>
</tr>
<tr>
<td>Hodsman et al, 2000</td>
<td>29 Osteoporotic women, mean age 67±7 years, vs 15 untreated osteoporotic controls with severe osteoporosis and multiple vertebral fractures</td>
<td>hPTH–(1-34) 40 µg SC + estrogen or estrogen alone, 12-mo treatment, followed by 12-mo observation in the 2 later studies for total duration of 24 mo, placebo injections were not given</td>
<td>Calcium carbonate 1000 mg/d and vitamin D 800 IU/d as 2 multiple vitamins.</td>
</tr>
<tr>
<td>Lane et al, 2000</td>
<td>51 Postmenopausal women aged 50-82 y with osteoporosis, taking HRT and glucocorticoids†</td>
<td>hPTH–(1-34) 40 µg/d SC + estrogen or estrogen alone, 12-mo treatment, followed by 12-mo observation in the 2 later studies for total duration of 24 mo, placebo injections were not given</td>
<td>Calcium carbonate 1000 mg/d and vitamin D 800 IU/d as 2 multiple vitamins.</td>
</tr>
<tr>
<td>Lane et al, 2000</td>
<td>52 Women aged 58-63 y with osteoporosis taking HRT</td>
<td>hPTH–(1-34) 400 IU/d SC + HRT vs HRT alone for 3 y, followed by 1 y of HRT alone†</td>
<td>Calcium intake maintained at 1500 mg/d total. Vitamin D 400 IU/d.</td>
</tr>
<tr>
<td>Dempster et al, 2001</td>
<td>Subgroup of 6 men and 8 postmenopausal women from the 2001 Cosman et al28 trial, mean age 54 y</td>
<td>hPTH–(1-34) 400 IU/d SC + HRT vs HRT alone for 3 y, followed by 1 y of HRT alone†</td>
<td>Calcium intake maintained at 1500 mg/d total. Vitamin D 400 IU/d.</td>
</tr>
<tr>
<td>Cosman et al, 2001</td>
<td>10 Women with osteoporosis already taking alendronate sodium, aged 59-71 y</td>
<td>hPTH–(1-34) 400 IU/d SC + alendronate vs alendronate continuation alone for 6 wk open assignment</td>
<td>Calcium intake maintained at 1500 mg/d total from diet and supplements. No vitamin D.</td>
</tr>
<tr>
<td>Neer et al, 2001</td>
<td>1637 Postmenopausal women aged 69-70 y with prior vertebral fractures§</td>
<td>hPTH–(1-34) 20 or 40 µg vs placebo SC qd, median duration of treatment 16-17 mo, follow-up 21 mo</td>
<td>Calcium 1000 mg/24 h and vitamin D 400-1200 IU daily supplements. Calcium supplementation to bring total intake to 1500 mg/d, no vitamin D mentioned.</td>
</tr>
<tr>
<td>Lindsay et al, 1997</td>
<td>34 Postmenopausal women with osteoporosis§</td>
<td>hPTH–(1-34) 50, 100, or 200 U SC daily for 48 wk, double-blind</td>
<td>Calcium carbonate 500 mg/d and vitamin D 400 IU/d.</td>
</tr>
<tr>
<td>Fujita et al, 1999</td>
<td>220 Women aged 45-95 y with osteoporosis§</td>
<td>hPTH–(1-84) 50, 75, or 100 µg/d SC for 1 y, followed by alendronate 10 mg/d alone for 1 y (sequential therapy), first year was double-blind, second year open label</td>
<td></td>
</tr>
<tr>
<td>Rittmaster et al, 2000</td>
<td>66 Postmenopausal osteoporotic women aged 50-75 y</td>
<td>hPTH–(1-34) 400 IU vs vehicle SC qd for 18 mo, double-blind</td>
<td>All received calcium to maintain total intake of 1500 mg/d, all took vitamin D 400 IU/d.</td>
</tr>
<tr>
<td>Kurland et al, 2000</td>
<td>23 Men aged 30-68 y with idiopathic osteoporosis§</td>
<td>hPTH–(1-34) 400 IU IV vs vehicle SC qd for 18 mo, double-blind</td>
<td></td>
</tr>
</tbody>
</table>

Results are shown in Tables 1, 2, 3, 4, and 5. The MEDLINE and Cochrane literature searches retrieved 191 references, 20 of which described randomized controlled trials involving PTH and osteoporosis (Table 1). Outcomes of the same trial were sometimes reported in separate articles, and some articles were continuations of results of earlier trials.16-20 The number of subjects per trial ranged from 9 to 1637.20

Treatment duration ranged from 6 weeks22 to 3 years.29 Most studies administered PTH subcutaneously (SC). Two studies18,30 investigated intranasal PTH. Parathyroid hormone has been combined with alendronate sodium, hormone replacement therapy (HRT), calcitriol, or calcitriol (Table 1). Parathyroid hormone has also been compared with placebo and has been studied

METHODS

A MEDLINE database (1966 to the present) keyword search was performed for randomized controlled trials involving PTH and osteoporosis. The Cochrane database was also searched using the search terms osteoporosis and parathyroid hormone. Reference lists of retrieved articles were reviewed for additional pertinent articles.

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Table 1. Randomized Controlled Trials of Parathyroid Hormone With Bone Density Outcome* (cont)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects</th>
<th>Regimen</th>
<th>Calcium or Vitamin D</th>
</tr>
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<tbody>
<tr>
<td>Leder et al,23 2001</td>
<td>11 Men aged 50-80 y with locally advanced node-positive or biochemically recurrent prostate cancer without bone metastases1</td>
<td>hPTH 22.5 mg IV infusion before leuprolide acetate (GnRH agonist) therapy, and again after 6 mo of confirmed GnRH-induced hypoestrogenism</td>
<td>None mentioned.</td>
</tr>
<tr>
<td>Neer et al,24 1993</td>
<td>30 Osteoporotic postmenopausal women2</td>
<td>hPTH(–1-34) 400-500 U/d + calcitriol 0.25 µg/d vs calcium3 for 12 mo</td>
<td>Calcium supplementation 1000-2000 mg/d. None mentioned.</td>
</tr>
<tr>
<td>Rowe et al,25 2001</td>
<td>2 Separate trials. Trial 1: 9 women, Trial 2: 40 women, all with vertebral fractures and primary or postmenopausal osteoporosis4</td>
<td>Trial 1: hPTH(–1-34) 500 U SC qd with HRT5 vs HRT alone for 1 y open study. Trial 2: hPTH(–1-34) 400 U with HRT vs HRT alone randomized for 1 y. HRT continued after hPTH cessation.</td>
<td></td>
</tr>
</tbody>
</table>

*CT indicates salmon calcitonin; hPTH, human parathyroid hormone; HRT, hormone replacement therapy; SC, subcutaneously; bid, twice daily; qd, every day; and GnRH, gonadotropin-releasing hormone.

1All treatments are oral unless otherwise noted.
2To convert serum calcium from micrograms per deciliter to millimoles per liter, multiply micrograms per deciliter by 0.25.
3Due to substantial nausea and flushing, the 100 U daily used during the first cycle was lowered to 75 U/d for the second cycle.
4Neither subjects nor investigators were blinded to treatment, but readers of bone density tests were blinded.
5Twenty-five of the subjects were continuing the 6-month 1994 trial by the same authors (Finkelstein et al18). The remainder of the patients from the 1994 trial completed their therapy before the trial was extended to 12 months.
6Osteoporosis was based on radiologic evidence of ≥1 vertebral compression fracture.
7Continuation of the 1997 trial by the same authors (Hodsman et al20).
8T score −2.5 at lumbar spine or femoral neck, menopausal ≥3 years, taking hormone replacement therapy for ≥1 year, prednisone 5.0-20 mg/d or its equivalent average daily dose for prior 12 months. Excluded secondary osteoporosis other than rheumatic diseases and glucocorticoid use, and renal or hepatic dysfunction.
9Details of type and dose of hormone replacement not given.
10Continuation of the 2001 study by Lindsay et al29.
11hPTH dosage is equivalent to 25 µg/d, but HRT regimen not specified.
12Nineteen percent of subjects had history of osteoporotic fractures at the spine, hip, forearm, or other site, and all were diagnosed as having osteoporosis, ie, had T score −2.5 at the spine and/or hip. Women were already taking alendronate, 10 mg/d, for at least 4 months at entry. Mean (± SD) age for those in the hPTH plus alendronate group was 69.0 ± 1.8 years; alendronate alone, 64.0 ± 4.8 years.
13Women with <2 moderate fractures had to have hip or lumbar BMD T score of <−1.
14Mean age of hPTH group was 59.3 years, estrogen group, 64.2 years.
15Osteoporosis was defined as T score <−2.5 or atrumatic fractures.
16Conjugated equine estrogen 0.625 mg/d, or transdermal estradiol, 50 µg/d. Women with a uterus also received medroxyprogesterone acetate, 5-10 mg/d, for ≥10 d/mo or 2.5 µg/d continuously. Patients had taken hormone replacement for >1 year before study entry.
17Osteoporosis was defined by a radiographic scoring system. Mean lumbar BMD was 0.694 g/cm².
18Corresponding amounts of the peptide were 15, 30, and 60 µg, respectively.
19Women were at least 5 years postmenopausal with vertebral T score <−2.5.
20Two score <−2.0 or T score <−2.5 at lumbar spine or femoral neck, using male reference database. Seventy-eight percent had sustained fractures of spine, hip, or appendicular skeleton, and 22% had presented with back pain. Hypogonadism was an exclusion criterion, but 2 men in the placebo group were taking stable doses of testosterone replacement by injection.
21All subjects had normal testosterone at baseline and none had received prior androgen deprivation therapy.
22Osteoporosis was not defined in detail. Patients were stratified by age and spinal trabecular bone density.
23Calcium given as carbonate, 1000 to 2000 mg/d. Follow-up duration was at least 12 months, total duration not detailed.
24Study 1: 10 women and 1 man with ≥2 vertebral fractures with primary or postmenopausal osteoporosis, and 1 woman with 1 vertebral fracture and low bone density. Study 2: subject characteristics not described.
25HRT consisted of conjugated equine estrogen, 0.625 mg/d, with norethindrone acetate, 1 mg/d, for days 19-28.

for differing dose effects. The efficacy of PTH has been tested for prevention of gonadotropin-releasing hormone (GnRH)–associated bone loss in both sexes. Mechanisms of the other medications are briefly summarized in Table 3.

Results are discussed in this section according to dosage and duration of therapy, study size, age, sex, baseline disease, anatomical site, histomorphometric effects, bone marker changes, fracture outcome, adverse effects, and compliance. (Single-dose studies are not discussed.)

**EFFECT BY DOSAGE, SCHEDULE, AND DURATION OF THERAPY**

Dosages of PTH ranged markedly across trials. They were variously reported in micrograms or units per day in the different articles. Furthermore, because of different combinations across trials and different comparison groups, conclusions regarding dose effects are difficult. Three trials,30,31,32 directly compared different dosages of PTH with each other. The first30 of the 3 compared 50, 100, and 200 µg/wk SC for 48 weeks. Corresponding amounts of the peptide were 15, 30, and 50 µg, respectively. Increases in lumbar bone mineral density (BMD) were dose-related (range, 0.6%-8.1%), but there were no changes at the femoral neck with any PTH dosage. The second trial31 compared 50, 75, or 100 µg/d SC for 1 year, followed by alendronate alone for 1 year. Although all dosages increased spine and femoral neck BMD compared with placebo, specific dose-effect analysis was not presented. Increases in bone density ranged from 4.3% to 9.2% at the lumbar spine. Although there was no change at the femoral neck with PTH compared with placebo, the group treated with PTH followed by alendronate had better femoral neck bone density than the group treated with placebo followed by alendronate. The third trial32 compared 20 or 40 µg/d SC with placebo for 16 to 17 months. Both dosages increased spine and hip (total hip, femoral neck, and trochanter) BMD compared with placebo, but dose-effect analysis per se was not provided. Bone density increases with 20-µg dosing were 9.7%, 2.6%, 2.8%, and 3.5% at the lumbar spine, total hip, femoral neck, and femoral trochanter, respectively. Cor-


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responding values for the 40-µg/d dosage were 13.7%, 3.6%, 5.1%, and 4.4%. Both dosages were associated with decreases in radius BMD (~2.1% and ~3.2% for 20- and 40-µg/d dosages, respectively) compared with placebo (Table 2).

Therefore, on the basis of the little existing data, it is possible that dose-related effects exist throughout the dosage range of 50 to 100 µg/d SC. More dose-effect information is needed.

Because almost all trials used human PTH–(1–34) (hPTH–[1–34]), conclusions about any relative advantage of hPTH–(1–38) or hPTH–(1–84) are not possible. The 2 trials (described in 3 articles) that did not involve hPTH–(1–34) were small and involved postmenopausal osteoporosis16,17,31 or idiopathic osteoporosis.16,17

All trials except 2 involved administration by the SC route. The first exception was 1 trial (2 articles18,19) testing intranasal PTH. The trial was designed with the goal of preventing bone loss induced by GnRH agonist therapy. Therefore, the intranasal route of PTH has not been tested in the context of glucocorticoid-induced osteoporosis or postmenopausal osteoporosis, nor has it been tested in men. The trial found that intranasal PTH for 12 months increased lumbar BMD 2.1% and protected against femoral neck and trochanter bone loss. Neither nafarelin acetate nor PTH plus nafarelin affected radius BMD.

Therefore, although a few studies support the intranasal administration of PTH to prevent bone loss in women receiving specific endometriosis therapies, most data available refer to the SC route.

Study duration varied substantially across trials, ranging from 6 weeks20 to 3 years29, the longest trial involving SC administration was 3 years (Table 1). The more recent trials had access to more advanced bone density

Table 2. Bone Mineral Density Response to Parathyroid Hormone*

<table>
<thead>
<tr>
<th>Source</th>
<th>Lumbar (%)</th>
<th>Total Hip (%)</th>
<th>Femoral Neck (%)</th>
<th>Trochanter (%)</th>
<th>1/3† Radius (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodsman et al,17 1991</td>
<td>↑13% with PTH alone vs baseline (P&lt;.01)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↓ by 11% vs baseline (P&lt;.05) with PTH alone vs no change with PTH followed by CT, but no difference in change between groups, used absorptiometry</td>
</tr>
<tr>
<td>Finkelstein et al,18 1998, Cosman et al,19 1998§</td>
<td>↑2.1% P&lt;.001 vs baseline</td>
<td>-</td>
<td>↓slightly during first 6 mo, then returned to baseline after 1 y, P&lt;.001 nafarelin acetate+PTH vs nafarelin</td>
<td>↓slightly during first 6 mo, then returned to baseline after 1 y, P = .04 nafarelin+PTH vs nafarelin</td>
<td>-</td>
</tr>
<tr>
<td>Hodsman et al,18 1997</td>
<td>↑10.2% with PTH vs 7.8% with PTH+CT, no significant difference between groups</td>
<td>-</td>
<td>No significant difference compared with baseline or between groups with PTH or PTH+CT</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lane et al,22 1998</td>
<td>↑in PTH+estrogen group 9.8% vs estrogen group (no change), P&lt;.001</td>
<td>No significant difference in change between PTH+estrogen and estrogen alone</td>
<td>No significant difference in change between PTH+estrogen and estrogen alone</td>
<td>No significant difference in change between PTH+estrogen and estrogen alone</td>
<td>-</td>
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<tr>
<td>Lane et al,20 2000</td>
<td>12 mo after cessation of PTH ↑ was 11.9% with estrogen+PTH vs estrogen alone, P&lt;.001 between groups</td>
<td>3.4% ↑ with PTH+estrogen vs estrogen alone, P&lt;.01, 12 mo after cessation of PTH</td>
<td>Nonsignificant ↑ vs baseline with PTH+estrogen, no significant difference between groups 12 mo after cessation of PTH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cosman et al,24 2001</td>
<td>↑13.4±1.4% with PTH+HRT, vs no significant change with HRT†</td>
<td>4.4±1.0% with PTH+HRT, vs no significant change with HRT</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neer et al,25 2001</td>
<td>↑9.7±7.4% with 20 µg and 13.7±9.7% with 40 µg, P&lt;.001 vs placebo for both</td>
<td>↑2.6±4.9% with 20 µg and 3.6±5.4% with 40 µg, P&lt;.001 vs placebo for both</td>
<td>↑2.8±5.7% with 20 µg and 5.1±6.7% with 40 µg, P&lt;.001 vs placebo for both</td>
<td>↑3.5±6.8% with 20 µg and 4.4±7.5% with 40 µg, P&lt;.001 vs placebo for both</td>
<td>2.1±4.2% with 20 µg (P=.09 vs placebo) and 3.2±4.5% with 40 µg (P=.001) vs placebo</td>
</tr>
<tr>
<td>Lindsay et al,26 1997</td>
<td>↑13% with PTH+estrogen, P&lt;.02 PTH+estrogen vs estrogen alone</td>
<td>↑2.7% with PTH+estrogen, P&lt;.001 PTH+estrogen vs estrogen alone</td>
<td>↑2.6% with PTH+estrogen, P = 0.11 PTH+estrogen vs estrogen alone</td>
<td>↑ by 1% with PTH+estrogen vs estrogen alone</td>
<td>-</td>
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</tbody>
</table>

(continued)
measurement technology, such as dual-energy x-ray absorptiometry, and measured a greater number of sites than did the older studies (Table 2). Correspondingly, results are sometimes expressed in the context of different bone density measurement techniques.

First, the longer (1-year and 3-year) trials will be described. A 1-year trial reported a greater increase in spine (11.9% higher) and total hip (3.4% higher) BMD 12 months after treatment with PTH plus estrogen compared with estrogen alone. However, changes were not significant with PTH plus estrogen or estrogen alone at the femoral neck, trochanter, or radius. The estrogen preparation and dosage were not specified. One 18-month trial revealed increases in lumbar (13.5% higher; \(P < .001\)) and femoral neck (2.9% higher; \(P < .05\)) BMD in subjects receiving PTH vs untreated control subjects (Table 2). However, total hip BMD did not change with PTH treatment, and radius BMD decreased insignificantly with PTH, compared with an increase in the untreated controls \(P < .05\) between groups. (The possible decrease in radius BMD emphasizes the importance of inclusion of control groups in trials of osteoporosis therapies.) In the other 18-month trial, lumbar BMD increased (range, 4.3%-9.2%, depending on the dosage) with 1 year of PTH administration compared with placebo, but did not change in the following year of alendronate administration. Increases were less marked at the femoral neck (Table 2). Subjects received PTH or placebo for 1 year, followed by a second year of open-label alendronate, 10 mg/d.

The single 3-year study, which compared PTH plus HRT with PTH alone, showed that combination therapy with PTH plus HRT induced higher increases in spine and total hip BMD (13% and 2.7%, respectively) compared with HRT alone. Differences between groups were less marked.

<table>
<thead>
<tr>
<th>Source</th>
<th>Lumbar</th>
<th>Total Hip</th>
<th>Femoral Neck</th>
<th>Trochanter</th>
<th>1/3† Radius</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujita et al, 1999</td>
<td>↑ 6.0%, 3.6%, and 8.1% with 50, 100, and 200 U, respectively, (P &lt; .05) for each of 100 U vs 50 U, 200 U vs 50 U, 200 U vs 100 U</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Rittmaster et al, 2000</td>
<td>During PTH alone for 1 y ↑ of 1.3%, 4.3%, 6.9%, or 9.2% with placebo, 50, 75, or 100 µg, respectively, no significant further change during the second year (alendronate sodium only). Over 2 years, ↑ in PTH-alendronate vs placebo-alendronate (P = .003), (P &lt; .001), and (P = .08) for 100-, 75-, and 50-µg groups vs placebo</td>
<td>...</td>
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</tr>
<tr>
<td>Kurland et al, 2000</td>
<td>↑ 13.5±3% vs no change in untreated controls, (P &lt; .001) between groups</td>
<td>No significant change in either PTH or untreated control group</td>
<td>↑ 2.9±1.5%, (P &lt; .05) between groups</td>
<td>...</td>
<td>Nonsignificant ↓ with PTH vs increase in untreated controls, (P &lt; .05) between groups</td>
</tr>
<tr>
<td>Neer et al, 1993</td>
<td>↑ 12% by DPA with PTH, no change with calcium‡</td>
<td>...</td>
<td>...</td>
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<td>...</td>
</tr>
<tr>
<td>Reeve et al, 2001</td>
<td>↑ more with PHT + HRT (12.2%) than with HRT alone (4.8%), (P = .03)</td>
<td>No significant difference between ↑ with PTH+HRT (1.5%) vs HRT alone (−0.2%), (P = .70)</td>
<td>No significant difference between ↑ with PTH+HRT (2.0%) vs HRT alone (2.4%), (P = .86)</td>
<td>By pQCT, ↑ at distal radius 1 y after treatment was 4.8% for PTH+HRT vs 1.9% for HRT alone, (P = .70)</td>
<td></td>
</tr>
</tbody>
</table>

*PTH indicates parathyroid hormone; HRT, hormone replacement therapy; CT, salmon calcitonin; DPA, dual-photon absorptiometry; and pQCT, peripheral quantitative computed tomography.
†Bone mineral density by dual x-ray absorptiometry (DEXA), unless otherwise noted.
‡The earlier trial by the same authors is not included because the 1998 trial is the continuation.
§The possible decrease in radius BMD emphasizes the importance of inclusion of control groups in trials of osteoporosis therapies.

Inhibitors of bone resorption
Alendronate sodium
Calcitonin
Estrogen replacement therapy
Mechanisms incompletely understood and necessary for optimal intestinal calcium absorption
Calcitriol
Gonadotropin releasing hormone agonists (GnRH agonists) inducing hypogonadism
Nafarelin acetate
Leuprolide acetate
Nafarelin acetate

Table 3. Mechanisms of Action of Medications Included in Osteoporosis Trials of Parathyroid Hormone

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Table 4. Effect of Parathyroid Hormone Administration on Fractures*

<table>
<thead>
<tr>
<th>Source</th>
<th>Fracture Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodsman et al,</td>
<td>No hip or other appendicular fracture. Vertebral fracture incidence no different</td>
</tr>
<tr>
<td>20, 1997</td>
<td>between PTH + CT and PTH alone. Very low incidence of radiographically detected</td>
</tr>
<tr>
<td></td>
<td>vertebral fracture rates over 2 y. Fewer fractures with PTH group vs PTH + CT</td>
</tr>
<tr>
<td></td>
<td>group, but small sample size yielded no difference between groups (P = .08). No</td>
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<tr>
<td></td>
<td>nonsynipal fractures.</td>
</tr>
<tr>
<td>Lane et al, 22</td>
<td>No patient in PTH group and 1 patient in estrogen-only group had new vertebral</td>
</tr>
<tr>
<td>1998</td>
<td>fractures. Nonvertebral fractures occurred in 2 patients in each group.</td>
</tr>
<tr>
<td>Cosman et al, 26</td>
<td>During 3 y, radiographically detected vertebral fractures occurred less often</td>
</tr>
<tr>
<td>2001</td>
<td>with PTH+HRT vs HRT alone (P = .001). Combination therapy decreased the percentage</td>
</tr>
<tr>
<td></td>
<td>of women with incident vertebral fractures from 37.5% vs 8.3% (P &lt; .02).</td>
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<td></td>
<td>Radiographs not routinely performed 1 y after therapy, but no clinical fractures</td>
</tr>
<tr>
<td></td>
<td>occurred.</td>
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<tr>
<td>Neer et al, 24</td>
<td>20-µg and 40-µg doses decreased risk of ≥1 new vertebral fracture by 65% and</td>
</tr>
<tr>
<td>2001</td>
<td>69%, respectively. Risk of ≥2 fractures was reduced by 77% and 86%, respectively,</td>
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<td></td>
<td>and risk of ≥1 moderate or severe vertebral fracture was reduced by 90% and 78%</td>
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<tr>
<td></td>
<td>respectively. PTH also decreased the total number of vertebral fractures. The 20-µg</td>
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<td></td>
<td>and 40-µg groups were 35% and 40% respectively. Less likely to have ≥1 new</td>
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<tr>
<td></td>
<td>nonvertebral fragility fracture.</td>
</tr>
<tr>
<td>Lindsay et al, 24</td>
<td>Fewer vertebral fractures with estrogen + PTH vs estrogen alone, P = .09. Number</td>
</tr>
<tr>
<td>1997</td>
<td>of women with vertebral fractures not significantly different between groups, P</td>
</tr>
<tr>
<td></td>
<td>= .12.</td>
</tr>
<tr>
<td>Fujita et al, 30</td>
<td>Radiographically detected spinal fractures in 3 subjects in 50-U, 5 subjects in</td>
</tr>
<tr>
<td>1999</td>
<td>100-U, and 0 in 200-U dosing. Difference between groups not significant.</td>
</tr>
<tr>
<td>Kurland et al, 32</td>
<td>Numbers of radiographically detected vertebral fractures too small to establish</td>
</tr>
<tr>
<td>2000</td>
<td>significance.</td>
</tr>
<tr>
<td>Reeve et al, 35</td>
<td>P = .28 for number of patients having new vertebral deformity for HRT vs PTH+PTH.</td>
</tr>
</tbody>
</table>

PTH indicates parathyroid hormone; HRT, hormone replacement therapy; and CT, salmon calcitonin.

* Absolute risk of ≥1 nonvertebral fractures was 10% with placebo vs 6% with PTH. This translated to a relative risk of 0.47. The numbers of women with new nonvertebral fractures were too small to estimate the incidence of each type of fracture.

† Study was not powered to measure effect of treatment on vertebral fractures, although new vertebral fractures were observed radiologically.

at the trochanter and radius. One year after cessation of PTH, with continuation of HRT alone, gains in BMD were maintained. The specific hormone regimen used in this trial was conjugated equine estrogen, 0.625 mg/d orally, or estradiol, 50 µg/d transdermally, combined with sequential medroxyprogesterone acetate. In contrast, the 1-year trial already described did not specify exact hormone dosage and preparation.

A briefer duration of therapy also results in increased BMD (Table 2). Therefore, overall effects of 48 weeks to 3 years of therapy with PTH appear to be more marked at the spine than at other sites, may be detrimental at the radius, may be enhanced by combination with estrogen, and may be advantageous when combined sequentially with alendronate vs alendronate alone. The longest duration of therapy involved 3 years of PTH combined with HRT and showed benefit at the spine and total hip. It may take 12 months after treatment cessation for the maximal anabolic effect of PTH to manifest at the hip. (Combinations of PTH and other medications are the focus of the “PTH in Combination With Other Agents” subsection of the “Results” section.)

EFFECT BY STUDY SIZE

The largest studies involved 2202 and 1637 patients. Both trials made use of several different dosages of PTH. The first found that each of the dosages tested (15, 30, and 60 µg/d SC) increased spine BMD during 48 weeks and that the increases were dose-related. The other study described BMD increases at the spine, femoral neck, total hip, and trochanter, but decreases at the radius, with dosages of 20 and 40 µg/d SC vs placebo. Therefore, results of larger trials were conflicting as to whether effects were limited to the spine and suggested detrimental effects on radius BMD. In contrast, although smaller studies reported positive hip and lumbar effects, they generally suggested only minor bone loss at the radius (Table 2).

EFFECT BY AGE, SEX, AND BASELINE DISEASE

Only one study was designed to formally compare bone density changes according to age and sex. Parathyroid hormone benefits on bone density were similar with subjects 65 years and older vs younger than 65, at a weight of at least 50 kg vs less than 50 kg, whether baseline vertebral fracture was present or not, and regardless of time since menopause.

Most studies pertained to older men and women with established osteoporosis, with 2 exceptions. In the first study, PTH was added in an effort to prevent bone loss induced by GnRH agonists in young women with endometriosis (Table 1). Although lumbar BMD was increased with baseline in subjects receiving PTH along with the usual GnRH agonist treatment, femoral neck and trochanter BMD decreased with PTH and radius BMD did not change (with or without inclusion of PTH) compared with baseline. The second study investigated bone marker changes in older men with advanced prostate cancer. Augmentation of bone resorption associated with GnRH agonist–induced hypogonadism was blunted by PTH administration. All other studies included older men and women already affected by osteoporosis (Table 1).

Specifically, osteoporosis was postmenopausal osteoporosis, idiopathic male osteoporosis, or glucocorticoid-induced osteoporosis. These 3 clinical scenarios are individually reviewed herein.

Postmenopausal osteoporosis is the setting of most studies. In this setting, PTH consistently increased lum-
bar BMD. This was observed when PTH was given alone or with sequential calcitonin, HRT, calcitriol, or alendronate. Effects were less consistently seen at the total hip, femoral neck, trochanter, and radius (Table 2). Second, glucocorticoid-induced osteoporosis was studied in 1 trial. Combined PTH and HRT had no advantage over estrogen alone at the hip or radius. Furthermore, the benefit of PTH at the lumbar spine was only apparent after 1 year, and the benefit at the total hip was only apparent 1 year after cessation of PTH. The benefit at the femoral neck or trochanter was not statistically significant. Effects of combination therapy on the radius showed an insignificant decrease compared with estrogen alone.22,24

Femoral trochanter BMD loss caused by nafarelin was only partly prevented by PTH.19 Parathyroid hormone increased lumbar spine BMD in all studies, at several dosages, for any duration, in different clinical situations, and in combination with multiple agents (Table 2). However, results at the different hip sub-sites were conflicting. Femoral neck bone loss induced by nafarelin was only partly prevented by PTH.19 Parathyroid hormone was protective against bone loss at the radius. In other settings, no changes in femoral neck BMD were attributable to PTH therapy.20,22,24,30,31,35 In other studies,28,32 femoral neck BMD increased with PTH therapy.

Femoral trochanter BMD loss caused by nafarelin was not prevented by PTH, and significant BMD changes at this site were not found in several trials.22,24,35 Femoral trochanter BMD increased in other PTH trials.28,29 Therefore, PTH effects at the hip vary across studies and clinical diseases (see the “Effect by Age, Sex, and Baseline Disease” subsection of the “Results” section).

In summary, increases in lumbar BMD are induced by PTH (alone and possibly combined with other medications, as shown in the “PTH in Combination With Other Agents” subsection of the “Results” section) in postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, and idiopathic osteoporosis. Effects at other sites are insignificant or conflicting. Parathyroid hormone may protect against GnRH agonist-related bone loss. Although BMD end points were beneficially affected by PTH in all studies, with some variability between sites, little data specifically analyzed the effects of PTH in older vs younger subjects or directly compared effects according to sex.

### EFFECT BY ANATOMICAL SITE

Parathyroid hormone increased lumbar spine BMD in all studies, at several dosages, for any duration, in different clinical situations, and in combination with multiple agents (Table 2). However, results at the different hip sub-sites were conflicting. Femoral neck bone loss induced by nafarelin was only partly prevented by PTH.19 Parathyroid hormone was protective against bone loss at the radius. In other settings, no changes in femoral neck BMD were attributable to PTH therapy.20,22,24,30,31,35 In other studies,28,32 femoral neck BMD increased with PTH therapy.

Femoral trochanter BMD loss caused by nafarelin was not prevented by PTH, and significant BMD changes at this site were not found in several trials.22,24,35 Femoral trochanter BMD increased in other PTH trials.28,29 Therefore, PTH effects at the hip vary across studies and clinical diseases (see the “Effect by Age, Sex, and Baseline Disease” subsection of the “Results” section).

A single study,26 documented increases at all of the multiple sites (ie, spine and all hip sites). It was also the only trial comparing the effect of different dosages of PTH vs placebo at multiple sites for treatment of postmenopausal osteoporosis. This study was the largest, most recent, well-designed trial and was the only trial comparing different dosages of PTH with placebo, as opposed to sex.
to use in sequential or combination regimens. This trial confirmed the detrimental effect of PTH on radius BMD suggested in other studies.\textsuperscript{7,32} of postmenopausal osteoporosis. However, 1 trial\textsuperscript{29} reported a small BMD increase with PTH plus estrogen compared with estrogen alone at the radius. Because of the paucity of data, there is as yet no proof that the decrement in radius BMD translates into increased radius fractures.

In summary, when used for postmenopausal osteoporosis treatment, PTH compared with placebo increases BMD at the spine and at multiple sites of the hip. Effects are less clear at nonspine sites when PTH is used as part of combination or sequential therapy or for treatment of glucocorticoid-induced osteoporosis.

### HISTOMORPHOMETRIC EFFECTS

Bone quality must be assessed by histomorphometry to prevent unintentional augmentation in fracture risk, even if BMD increases occur. As an example, fluoride increased fracture risk, despite inducing impressive increases in BMD.\textsuperscript{11-13} Histomorphometric findings have been used as an indicator of bone quality.

Histomorphometric consequences of PTH use were investigated in 1 trial\textsuperscript{21} (Table 5). In women with postmenopausal osteoporosis, cyclical PTH increased trabecular bone turnover and induced positive remodeling balance, without detrimentally affecting cortical bone.\textsuperscript{31} The improvement of cortical and cancellous microarchitect-

### Table 5. Adverse Effects of Parathyroid Hormone Therapy\textsuperscript{*} (cont)

<table>
<thead>
<tr>
<th>Source</th>
<th>Histomorphometric Effects</th>
<th>Hypercalcemia</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dempster et al,\textsuperscript{26} 2001</td>
<td>Cancellous bone area was maintained in women and increased in men ( P = .07 ). Wall width of trabecular packets was maintained in women and significantly increased in men. Cortical width increased slightly in women and significantly in men, ( P &lt; .02 ). Most patients had increased trabecular connectivity by 3-dimensional scan.</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Neer et al,\textsuperscript{29} 2001</td>
<td>Mild hypercalcemia (( &gt;10.6 ) mg/dL) in 2%, 11%, and 28% of placebo, 20 µg, and 40-µg PTH groups, respectively. Of the high serum calcium values, 95% were &lt;11.2 mg/dL. Only one third had persistence of hypercalcemia on confirmatory retesting. Women who did not have hypercalcemia during the first 6 months of treatment rarely developed hypercalcemia later on.</td>
<td>No significant differences among the 3 groups in serious AEs. Cancer incidence was higher in the placebo than PTH groups. More withdrawals with PTH than placebo (11% for 40 µg vs 6% each for placebo and 20 µg). Nausea and headache were more common with PTH 40 µg than placebo (( P &lt; .001 ) and ( P = .01 ), respectively), but incidence was similar with 20 µg compared with placebo.</td>
<td>Pain and redness at injection site. One PTH withdrawal because of back pain, another because of a subcutaneous nodule at the injection site. No medication-related systemic effects, no serious AEs. No hypercalciuria.</td>
</tr>
<tr>
<td>Lindsay et al,\textsuperscript{29} 1997</td>
<td>Calcium decreased vs baseline with all dosages of PTH. Remained ( &gt;9 ) mg/dL in all dosage groups.</td>
<td>No significant changes in PTH and PTH + CT groups analyzed together.</td>
<td>...</td>
</tr>
<tr>
<td>Fujita et al,\textsuperscript{30} 1999</td>
<td>No significant change. Two patients had hypercalcemia (( &gt;10.5 ) mg/dL) in PTH group, leading to dose titration. Those patients still had increase in spinal BMD.</td>
<td>No difference from baseline or between groups in urinary calcium. Redness at injection site.</td>
<td>...</td>
</tr>
<tr>
<td>Kurland et al,\textsuperscript{32} 2000</td>
<td>No significant change.</td>
<td>No significant difference from baseline in change in urinary calcium, but difference between groups was significant (( P = .03 )).</td>
<td>...</td>
</tr>
<tr>
<td>Leder et al,\textsuperscript{33} 2001</td>
<td>No significant change. (Checked just before infusion at 6 mo.) (( P = .24 )).</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

*PTH indicates parathyroid hormone; hPTH, human PTH; AE, adverse effect; and BMD, bone mineral density. To convert serum calcium from micrograms per deciliter to millimoles per liter; multiply micrograms per deciliter by 0.25.

†The earlier trials by the same authors are not included because the 1998 trial is the continuation.

‡Reactions to PTH included subcutaneous hemorrhage, whole-body reddening, facial flush, eczema, itching, lumbago, headache, dizziness, nausea, vomiting, abdominal pain, belching, yawning, thirst, anorexia, febrile sensation, febrile episode, sensation of weakness, general malaise, chills, and sleepiness. No comment regarding significant difference between groups or compared with placebo, nor whether reactions were thought to be medication-related.

§PTH and PTH + CT groups analyzed together.
ture with daily PTH administrations has been reported in humans.26

In a sex-comparative analysis after 3 years of combined PTH and HRT, cancellous bone area was maintained in women and increased in men26 (Table 5). Wall width of trabecular packets was maintained in women and significantly increased in men. Cortical width increases slightly in women and significantly in men. Most patients had increased trabecular connectivity by threedimensional scan.

EFFECTS ON BONE FORMATION MARKERS

Bone turnover markers are sometimes used as surrogates to assess therapeutic effects of osteoporosis medications, although whether such application is clinically relevant is a matter of active controversy. Bone markers can give useful insights into medication mechanisms. Markers of bone formation include serum alkaline phosphatase, serum osteocalcin, and C-terminal propeptide of type I procollagen. Parathyroid hormone would be expected to increase alkaline phosphatase on the basis of its mechanism of action on collagen. Parathyroid hormone would be expected to increase serum osteocalcin, and C-terminal propeptide of type I procollagen. Bone formation markers can include serum alkaline phosphatase, serum osteocalcin, and C-terminal propeptide of type I procollagen. A single trial16 found an increase in serum osteocalcin with PTH alone and PTH plus alendronate vs alendronate alone, or with PTH vs placebo.

EFFECTS ON BONE RESORPTION MARKERS

Markers of bone resorption that increase during PTH therapy include urinary pyridinoline,19,20,30,32 deoxypyridinoline,19,22,30 and N-telopeptide,20,29,31,32 excretion.

Induction of hypogonadism in older men may cause changes in skeletal sensitivity to PTH.33 The increase in urinary N-telopeptide excretion (but not deoxypyridinoline) during PTH infusion was greater after 6 months of leuprolide acetate therapy than before induction of hypogonadism caused by leuprolide. Data regarding urinary hydroxyproline are conflicting. A decrease was reported in 1 trial.30 Other trials19-20 reported increases in urinary hydroxyproline in women with endometriosis. One trial19 found no change from baseline with PTH therapy alone, although levels at the study end were lower after sequential PTH plus calcitonin vs PTH alone. Some data suggest that the increase in bone formation and resorption is disproportionate, suggesting that PTH could be uncoupling bone formation and resorption.22 This idea may be supported by the observation that PTH plus HRT (compared with HRT alone) did not increase resorption as much as formation.20

Results of combination therapy trials confirm what would be predicted according to medication mechanism. Neither alendronate nor HRT increased formation markers when administered alone.25,27 Rather, only combination PTH with alendronate or HRT increased formation markers. Parathyroid hormone–induced increase in bone resorption and formation peaked at 6 months.25 They returned to baseline by 30 months. Subsequently, when patients were maintained on HRT alone for another year, no significant changes in turnover markers occurred.25

It may be possible to make use of serial bone marker measurements to identify skeletal responders to anabolic therapy in estrogen-replete women with glucocorticoid-induced osteoporosis.23 One study23 suggests that the response of bone markers predicted a gain in BMD resulting from PTH therapy with high diagnostic accuracy, although it did not predict the magnitude of the gain.

In summary, PTH increases bone formation markers. The increase in bone formation is probably larger in magnitude and may have a different time of onset compared with the increase in resorption.

ANTIFRACTURE EFFICACY

Antifracture efficacy is the single most critical efficacy outcome for osteoporosis treatment. As it is difficult to include adequate numbers of subjects to yield substantial numbers of fracture events, fracture outcome data for PTH are sparse. Although not a satisfactory state of affairs, this has historically been the case with other osteoporosis therapies as well. Often, fractures are only monitored as part of adverse outcome assessment, as opposed to constituting a primary outcome. Table 4 summarizes fracture outcome data for PTH. Rates of radiographically detected fractures were generally low. Fracture rates were sometimes so low as to prevent statistical analysis.20,22,32,35

Rates of radiographically detected spinal fractures were not different among different doses of PTH over a 50- to 200-U dose range.30 The incidence of radiographically detected vertebral fractures was not different with sequential PTH plus calcitonin compared with PTH alone, although differences between groups were not significant and the number of events was small.28 When HRT was compared with HRT plus PTH, differences between groups in vertebral fracture incidence were not significant.35 The vertebral fracture incidence was lower with PTH plus estrogen vs estrogen alone, although differences between groups were not significant.20 Rates of nonvertebral fracture were lower, making analysis of reduced fracture rates difficult or impossible20,22 (Table 4).

The largest trial28 reported an impressive reduction in the rate of new vertebral fractures with PTH dosages of 20 and 40 µg/d SC for 17 months. The risk of 2 or more vertebral fractures was reduced, as was the risk of at least 1 moderate or severe vertebral fracture, regardless of which PTH dosage was used. Nonvertebral fractures were also decreased by PTH. Parathyroid hormone recipients were 35% to 40% less likely to have at least 1 new nonvertebral fracture compared with placebo and 53% to 54% less likely to have at least 1 new nonvertebral fragility frac-
tion. 

The numbers of nonvertebral fractures were too low to be broken down by individual site. It could not be concluded from the study if the notable decrease in radius BMD in this trial may have led to increased fracture rates.

These findings are replicated in the longest and most recent trial. 

Radiographically detected vertebral fractures were significantly decreased with PTH plus HRT during 3 years compared with HRT alone. The percentage of women with incident vertebral fractures decreased from 37.5% to 8.3% by PTH plus HRT compared with HRT alone. Again, the rate of nonvertebral fractures was low.

In summary, when data were robust enough to allow adequate statistical power, PTH decreased the incidence of radiographically detected spinal fractures, decreased the incidence of nonvertebral fractures, and may have added to the fracture reduction ability of estrogen replacement therapy.

ADVERSE EFFECTS AND COMPLIANCE

Adverse effects of PTH are summarized in Table 5. No serious medication-related adverse effects were attributed to PTH. In some trials, 

PTH increased calcium levels, but they remained in the normal range. One trial reported minor decreases in calcium levels with PTH therapy. Other trials reported no change in calcium levels. The largest trial reported mild hypercalcemia (>10.6 mg/dL [>2.65 mmol/L]) in 2%, 11%, and 28% of the placebo, 20-µg, and 40-µg PTH groups, respectively. Of the high serum calcium values, 95% were less than 11.2 mg/dL (2.80 mmol/L).

Monitoring of serum calcium levels varied across trials. In some trials, subjects were monitored every 3 months or every 6 months, whereas other subjects were monitored more frequently at the beginning and less frequently later on. Women who did not manifest hypercalcemia during the first 6 months of treatment rarely developed hypercalcemia later on. 

The trial allowed adjustment of calcium intake in patients experiencing hypercalcemia. Examples of protocol adjustments triggered by hypercalcemia include a decrease in PTH dosage for calcium levels greater than 10.5 mg/dL (2.63 mmol/L), with subsequent documentation of normalization of calcium levels, or a decrease in medication dosage only for persistence of hypercalcemia, despite a decrease in dietary intake. In the latter trial, the numbers of subjects withdrawn for hypercalcemia were 1 in the placebo group, 1 in the 20-µg PTH group, and 9 in the 40-µg group.

Besides hypercalcemia, other adverse effects associated with PTH therapy include local injection site reactions, transient mild headaches, nausea, and arthralgia (Table 5). There was some suggestion that adverse effects increased with increasing dosage of PTH. However, the largest trial, which compared placebo, 20-µg PTH, and 40-µg PTH, reported no significant difference between groups in the incidence of serious adverse effects. Interestingly, the incidence of nausea and headache was higher with the 40-µg/d dosage compared with placebo, but were similar in the 20-µg/d and placebo groups. The longest (3-year) trial reported that nausea did not occur.

Hypercalcemia occurred infrequently in some trials, but by the study end returned to baseline in 1 study. Generally, hypercalcemia resolved with a decrease in calcium intake. Other studies reported no change from baseline in urinary calcium levels. One study reported that urinary calcium fell below the basal level.

There was sometimes difficulty with PTH injection technique or compliance (Table 5). The largest trial found more subject withdrawal from the study with PTH than with placebo treatment.

Rats that were given nearly lifetime daily injections of PTH manifested increased osteosarcoma incidence in a dose-dependent fashion as a result of PTH administration. However, this effect is absent in primates (eg, monkey models). Furthermore, chronic hyperparathyroidism is not associated with osteosarcoma in humans. None of the trials reviewed herein reported an increased cancer incidence associated with PTH, and the cancer incidence was higher with placebo vs PTH therapy. In summary, PTH administration is associated with hypercalcemia in a small percentage of patients, possibly in a dose-dependent fashion, and early in treatment. Other minor adverse effects are also associated with PTH. No published trial results have indicated that cancer risk is increased by PTH use in humans.

PTH IN COMBINATION WITH OTHER AGENTS

A 28-day “pulse” of daily hPTH–(1-34) injections at a dosage sufficient to elevate serum calcium levels to the upper normal reference range was proposed as a way of activating bone turnover and osteoblastic synthesis of new bone matrix. The underlying hypothesis is that, once bone turnover had been activated, the anabolic phase of bone remodeling would be left to complete itself during the remainder of the 90-day treatment cycle before initiation of the next cycle. Calcitonin given sequentially after the PTH pulse would be designed to limit the degree of PTH-induced bone resorption, thereby enhancing the net anabolic effect of PTH.

The idea of pairing PTH with calcitonin in such a manner did not yield the anticipated beneficial effects, in that the 2 groups (PTH alone vs PTH with calcitonin) had the same incremental gain in vertebral BMD at the end of a 2-year trial. The corresponding histomorphometric analyses for all the 29 treated patients vs a separate group of biopsies from control patients with untreated osteoporosis revealed an increase in trabecular bone turnover with a positive remodeling balance, without deleterious effect on cortical bone.

Six other trials studied PTH given in combination with an antiresorptive (Tables 1 and 2). These combined alendronate with PTH, estrogen replacement with PTH, or PTH with calcitriol. These trials reported a bone density benefit over individual therapy at the lumbar spine and had conflicting results regarding different areas of the hip.
ing 3 years of combined HRT plus PTH, the increases in BMD persisted.25

These studies of combination therapy can be considered according to whether the components are given concomitantly or sequentially. Concomitant therapy will be considered first. In the only study27 of combination therapy that reported fracture outcome, PTH was given simultaneously with HRT to treat postmenopausal osteoporosis. The concomitant use resulted in a decrease in radiographically detected vertebral fractures and in the percentage of women with incident vertebral fractures. Unfortunately, most studies of concomitant therapy had too few fractures to assess22,29,35 or were not designed to determine fracture outcome. These latter studies23,24,27 with bone density outcomes suggested that concurrent PTH and estrogen use had an advantage over estrogen alone at the spine in women with postmenopausal osteoporosis. The advantage may29,35 or may not35 exist at the hip.

In considering sequential therapy, studies again had too few fractures to allow fracture outcome assessment10,20,32 or were not designed for assessment of fracture outcome.17,31 It seemed that the use of calcitonin following PTH therapy had no benefit in postmenopausal or idiopathic male osteoporosis,17,20 but that the use of alendronate following PTH protected the bone density gains incurred during PTH therapy of postmenopausal osteoporosis.25,31

Therefore, in comparing concurrent vs sequential PTH regimens, the data overall would support concurrent therapy with PTH plus estrogen to increase bone density and decrease the incidence of vertebral fractures, and sequential therapy with alendronate following PTH therapy to protect bone density gains. Data specifically do not support sequential therapy with PTH followed by calcitonin. These comments refer only to postmenopausal osteoporosis; data in other patient subgroups are lacking.

In summary, regarding the use of PTH in combination regimens for postmenopausal osteoporosis, the addition of PTH to combination HRT or alendronate had advantages over HRT alone at the lumbar spine, but effects at the radius, trochanter, and hip are conflicting. For glucocorticoid-induced osteoporosis, combined PTH and estrogen replacement may be of added benefit compared with estrogen replacement alone at the spine, but not necessarily at the total hip or radius. Because only one trial tested each regimen, conclusions cannot be made regarding any particular combination involving PTH or about relative advantages of sequential vs concomitant therapy. Effects of combining one HRT regimen vs another HRT regimen with PTH are not known.

**COMMENT**

The increase in BMD induced by PTH seems to be dose-dependent. Based on the results of 1 trial,25 BMD increases are similar for subjects 65 years and older vs younger than 65, weighing at least 50 kg vs less than 50 kg, with or without baseline vertebral fractures, and regardless of time since menopause. Parathyroid hormone protects against vertebral fracture.28 It not only decreases the incidence of radiographically detected vertebral fractures but also decreases the clinical corollary—pain. Preliminary findings indicate that there was improvement in backache associated with PTH treatment in one trial26 and that new or worsening back pain was reported less often with PTH than placebo in another trial.28 The protective effects of PTH against new nonvertebral fractures and nonvertebral fragility fractures were rapid; effects were evident after 9 to 12 months of therapy.26 Although direct comparisons have not been performed, approximately the same degree of fracture reduction results from PTH treatment as from risedronate sodium, alendronate, or raloxifene hydrochloride treatment in other trials.

When combined with standard oral or transdermal estrogen alone in postmenopausal osteoporosis, PTH induced increased BMD at the lumbar spine and femoral neck, but not at the femoral trochanter, compared with estrogen alone.20 However long-term studies are lacking, and different routes of administration and dosages may have different effects. Moreover, estrogen and progesterone components were not investigated separately.20,35 Each hormone component probably has different effects on bone metabolism. It is also conceivable that adding PTH to ongoing HRT may have effects different from those of initiating PTH and HRT concurrently.20 Based on the data reviewed, because of differing regimens and subject characteristics across trials, it is difficult to say if calcium and vitamin D administration affected BMD or fracture outcome effects of PTH.

Cortical and trabecular bone are the 2 main types of bone. Cortical bone constitutes the shell around cancellous bone. The peripheral skeleton is predominantly cortical bone, but the axial skeleton (eg, spine) is a combination of cortical and trabecular bone.30 Metabolism and rates of bone loss differ in the 2 types of bone, and diseases often differentially affect the 2 types of bone.30 The theoretical possibility of unintentionally causing a fracture (or decreased bone density as a possible surrogate for fracture) at one type of bone while simultaneously benefiting another type of bone is the reason for strict attention to differentiating cortical and trabecular effects. In 1 trial,35 cortical bone mass decreased 1.7% with PTH plus calcitriol vs 5.7% with calcium alone, but trabecular bone mass increased 32% with PTH plus calcitriol. The varying effects according to bone composition (ie, trabecular vs cortical) may relate to the varying results seen according to measurement technique. For example, spine BMD differences between estrogen and estrogen plus PTH groups were 9.8% by dual-energy x-ray absorptiometry and 33.5% by calcitonin treatment.22 There may be subtle differences between men and women in the degree of histomorphometric response to PTH.26 The suggestion in several studies,17,24,32,34 of a decrease in radius BMD in association with PTH use parallels the recognized differing effects of hyperparathyroidism on trabecular vs cortical bone. Even if BMD effects at different sites become well established, BMD changes during therapy are only a surrogate for fractures.25 We need to directly determine fracture rates site by site in prospective studies with adequate statistical power.

Strictly speaking, treatment with PTH should be limited to less than 2 years, given the lack of long-term safety and efficacy data. Parathyroid hormone treatment should
be followed by antiresorptive therapy, with the goal of maintaining BMD gains. Evidence supports continuation of HRT after combination PTH plus HRT to preserve increases in BMD. However, the latter medications must be continued long-term to preserve beneficial bone density effects. Long-term PTH effects are not clear; hence, optimal duration of therapy is not clear. Effects of intermittent vs continuous therapy are different and require additional elucidation. In the future, differences in response to PTH must be analyzed by sex. In addition, determination of a clinical algorithm regarding appropriate response to PTH-associated hypercalcemia will be necessary.

In placing future research into proper context, especially given that PTH will be studied in combination with other therapies, several potential pitfalls warrant mentioning. Identical bone density changes between 2 active treatment groups might signify that both regimens work to increase BMD or that neither regimen works to increase BMD. In addition, instead of being dismissed as proof of lack of efficacy, a lack of BMD change compared with baseline may signify that BMD is being preserved (ie, that bone loss is being prevented). Such considerations must determine appropriate comparison groups in the design and proper interpretation of results of randomized controlled trials.

Antifracture efficacy is the single most critical efficacy outcome for osteoporosis treatment, and fracture reduction data are not robust for PTH, especially at nonvertebral sites. Additional fracture data are anticipated and will be the ultimate proof of efficacy. Bone density effects of 48 weeks to 3 years of therapy with PTH appear more marked at the spine than at other sites, may be detrimental at the radius, may be enhanced by combination with estrogen, and may enhance effects of alendronate. Maximal anabolic effect of PTH may require 12 months after treatment cessation before manifesting at the hip. Dose-related bone density effects may exist in the dosage range of 50 to 100 µg/d SC. Although a few studies support the intranasal route of PTH administration to prevent bone loss in women receiving specific endometriosis therapies, most data available refer to the SC route. However, the SC route was associated with decreased compliance. Subjects in the trials reviewed had the support of clinical trial nurses. Older patients encountered in community practice may have difficulty with injections.

Results of larger trials were conflicting as to whether effects were limited to the spine and suggested detrimental effects on radius BMD. Little data analyzed the effects of PTH in older vs younger subjects or directly compared effects according to sex. Increases in lumbar BMD are induced by PTH in postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, and idiopathic osteoporosis. Effects at other sites are insignificant or conflicting. When data were robust enough to achieve adequate statistical power, PTH decreased the risk of new spinal fractures in women with postmenopausal osteoporosis by 65% to 70% and may have decreased the overall incidence of nonvertebral fractures. However, there were several drawbacks to the lack of data: numbers of nonvertebral fractures were too low to be broken down by individual site, it is unknown whether the decrement in radius BMD associated with PTH results in an increased risk of future radius fracture, and the only population definitely demonstrated to have vertebral fracture reduction associated with PTH is women with established postmenopausal osteoporosis.

Parathyroid hormone administration induces hypercalcemia in a small percentage of patients, possibly in a dose-dependent fashion, and early in treatment. Other minor adverse effects are also associated with PTH. Although concerns were raised from animal research, published trial results indicate that cancer risk is not increased by PTH use in humans. Because only one trial tested each individual regimen, conclusions cannot be made regarding any particular combination regimen involving PTH.

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