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## The Effects of Parathyroid Hormone and Alendronate Alone or in Combination in Postmenopausal Osteoporosis

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### ABSTRACT

#### BACKGROUND

Parathyroid hormone increases bone strength primarily by stimulating bone formation, whereas antiresorptive drugs reduce bone resorption. We conducted a randomized, double-blind clinical study of parathyroid hormone and alendronate to test the hypothesis that the concurrent administration of the two agents would increase bone density more than the use of either one alone.

#### METHODS

A total of 238 postmenopausal women (who were not using bisphosphonates) with low bone mineral density at the hip or spine (a T score of less than  $-2.5$ , or a T score of less than  $-2.0$  with an additional risk factor for osteoporosis) were randomly assigned to daily treatment with parathyroid hormone (1–84) (100  $\mu\text{g}$ ; 119 women), alendronate (10 mg; 60 women), or both (59 women) and were followed for 12 months. Bone mineral density at the spine and hip was assessed by dual-energy x-ray absorptiometry and quantitative computed tomography. Markers of bone turnover were measured in fasting blood samples.

#### RESULTS

The bone mineral density at the spine increased in all the treatment groups, and there was no significant difference in the increase between the parathyroid hormone group and the combination-therapy group. The volumetric density of the trabecular bone at the spine increased substantially in all groups, but the increase in the parathyroid hormone group was about twice that found in either of the other groups. Bone formation increased markedly in the parathyroid hormone group but not in the combination-therapy group. Bone resorption decreased in the combination-therapy group and the alendronate group.

#### CONCLUSIONS

There was no evidence of synergy between parathyroid hormone and alendronate. Changes in the volumetric density of trabecular bone, the cortical volume at the hip, and levels of markers of bone turnover suggest that the concurrent use of alendronate may reduce the anabolic effects of parathyroid hormone. Longer-term studies of fractures are needed to determine whether and how antiresorptive drugs can be optimally used in conjunction with parathyroid hormone therapy.

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**T**HE PREVENTION OF OSTEOPOROTIC fractures with the use of antiresorptive drugs represents an established therapeutic approach for patients with osteoporosis.<sup>1-3</sup> The results of double-blind, randomized, placebo-controlled trials have indicated that nitrogen-containing bisphosphonates such as alendronate and risedronate, which work principally by suppressing bone resorption, reduce the risk of fracture and increase bone mineral density.<sup>4-8</sup>

Unlike bisphosphonates, parathyroid hormone is anabolic when it is administered intermittently for osteoporosis. Both parathyroid hormone (1-34) and parathyroid hormone (1-84) increase bone density by stimulating bone formation rather than by reducing bone resorption.<sup>9-12</sup> Recently, the 34-amino-acid fragment, parathyroid hormone (1-34), was shown to reduce the risk of fracture<sup>9</sup> and is now available for the treatment of persons with established osteoporosis and a high risk of fracture.

Whether the use of a bisphosphonate and parathyroid hormone together would provide a therapeutic advantage by combining different mechanisms for the reduction of the risk of fracture is unknown. Parathyroid hormone (1-34) has been studied as an addition to ongoing therapy with estrogen (an antiresorptive agent),<sup>13,14</sup> but no similar trials have been conducted using bisphosphonates. Furthermore, no antiresorptive agent (including estrogen or a bisphosphonate) has been studied together with parathyroid hormone from the start of therapy in previously untreated patients. We conducted a multicenter, randomized, double-blind trial comparing monotherapy with parathyroid hormone (1-84) or alendronate with combination therapy consisting of both agents in postmenopausal women with osteoporosis. Here we report the results at 12 months.

## METHODS

### STUDY PARTICIPANTS

We recruited postmenopausal women 55 to 85 years of age from four clinical centers in the United States (Bangor, Me.; Minneapolis; New York; and Pittsburgh). Women were enrolled if they had a T score of less than -2.5 for bone mineral density at the femoral neck, total hip, or spine, or if they had a T score of less than -2.0 at one of these sites and at least one of the following risk factors: an age of 65 years or more, a history of postmenopausal fracture (vertebral or nonvertebral), and a maternal history of

hip fracture. We excluded women who had been treated with bisphosphonates for a total of more than 12 months or for more than 4 weeks during the previous 12 months or who had diseases or took medications that are known to affect bone metabolism. The institutional review board at each clinical center approved the study protocol, and all women provided written informed consent before enrollment.

### TREATMENTS

The study treatments were full-length parathyroid hormone (1-84) (100 µg daily [NPS Pharmaceuticals]), alendronate (10 mg daily [Fosamax, Merck]), calcium carbonate (500 mg of elemental calcium [Tums, SmithKlineBeecham]), and a multivitamin containing 400 IU of vitamin D (Rugby Laboratories). The women injected parathyroid hormone (1-84) or matching placebo in the morning using a cartridge-loaded pen. Cartridges were changed every two weeks. Alendronate or matching placebo was taken each morning with a full glass of water after an overnight fast.

### STUDY DESIGN

After a two-week run-in phase, 238 women were randomly assigned to one of three treatment regimens to be followed for one year. A total of 119 women were assigned to take parathyroid hormone plus placebo that matched the alendronate, 59 women were assigned to take parathyroid hormone plus alendronate, and 60 women were assigned to take alendronate plus placebo that matched the parathyroid hormone. All participants received daily doses of calcium and vitamin D. In the second year of the study, which is ongoing, women in the original parathyroid hormone group were randomly assigned to receive either alendronate or matching placebo, and women in the other two original groups received alendronate. Because the original parathyroid hormone group was to be split into two groups during the second year of the study, it was twice as large as each of the other original groups. This report covers the first 12 months of the study, the only period during which parathyroid hormone was administered. Participants, clinicians, and investigators remained unaware of the treatment-group assignments, except for a clinician at the coordinating center who was responsible for reports to the data and safety monitoring board. Although support for drug products and quantitative computed tomography (CT) was provided by various pharmaceuti-

cal companies, they had no role in the design or interpretation of the study.

#### EFFICACY OUTCOME VARIABLES

Areal bone mineral density (in grams per square centimeter) was assessed with the use of dual-energy x-ray absorptiometry (Hologic QDR-4500A or Delphi densitometers). Bone mineral density was measured at the hip (femoral neck and total hip regions), the posteroanterior lumbar spine (L1 to L4), and the radius (the distal one third of the radial shaft) at base line and at 12 months. The coefficient of variation for the areal density is 1 to 2 percent.<sup>15</sup>

Volumetric bone mineral density (in grams per cubic centimeter) and the bone geometry in trabecular and cortical compartments were assessed with the use of quantitative CT at the spine (L1 and L2) and the hip (femoral neck and total hip regions). Findings on quantitative CT, performed at three clinical centers at base line and at 12 months, were evaluated by a central imaging facility (University of California, San Francisco) according to methods that have been described previously.<sup>16,17</sup> The coefficient of variation is 2 to 4 percent for volumetric density<sup>15</sup> and 5 to 6 percent for cortical volume.

Serum drawn after an overnight fast was stored (at  $-70^{\circ}\text{C}$ ) until it was assayed in a central laboratory (Synarc, Lyons, France). Serum C-terminal telopeptide of type I collagen (a marker of bone resorption) and N-propeptide of type I collagen (a marker of bone formation) were measured with two-site immunoassays on an automatic analyzer (Eleclys, Roche Diagnostics). Intraassay and interassay coefficients of variation for serum N-propeptide and serum C-terminal telopeptide are approximately 4 percent and 6 percent, respectively. Bone-specific alkaline phosphatase was measured with the use of the Ostase assay (Beckman).

#### ADHERENCE, SAFETY ASSESSMENT, AND ADVERSE EVENTS

Adherence to treatment was assessed by means of the return of unused cartridges (parathyroid hormone) and tablets (alendronate). Full adherence to treatment was defined as the use of at least 80 percent of the injections or tablets for at least 11 months.

Fasting serum calcium concentrations were measured at base line and at 1, 3, and 12 months. Participants were instructed not to take the injection the day of these clinic visits. Twenty-four-hour urinary excretion of calcium and creatinine was

measured at base line and at three months. Specific ordered algorithms for use in women in whom the serum or urinary calcium level became elevated (repeated assessment, discontinuation of calcium supplementation, reduction of the dose of parathyroid hormone, and then discontinuation of parathyroid hormone treatment) were followed if the serum calcium concentration was more than 10.5 mg per deciliter (2.62 mmol per liter), if the urinary calcium excretion was more than 400 mg per 24 hours (9.98 mmol per day), or if the ratio of the urinary calcium concentration to the urinary creatinine concentration was more than 0.4.

Patients were questioned at each visit about adverse events, which were coded with the use of preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA)<sup>18</sup> and classified by a clinician at the University of California, San Francisco, who was unaware of the treatment-group assignments. The preferred terms were categorized according to anticipated types of adverse events whose rates had been increased in previous trials of parathyroid hormone<sup>9</sup> and alendronate,<sup>4,5</sup> as well as according to organ systems; the treatment groups were then compared in terms of the rates of adverse events in previous trials as well as those affecting each organ system.

#### STATISTICAL ANALYSIS

We attempted to follow all the women who underwent randomization for all study visits and procedures, regardless of their level of adherence to the assigned treatment regimen. Analyses were performed according to the intention-to-treat principle unless otherwise indicated. Group means and 95 percent confidence intervals are given for the percent changes from base line in variables measured by dual-energy x-ray absorptiometry and quantitative CT; these values were used to assess the significance of changes within each group. Medians and interquartile ranges are reported for changes in the levels of markers of bone turnover; t-tests were used to compare the combination-therapy group with each of the other two groups in terms of the mean percent change, and Wilcoxon tests were used to compare the groups in terms of markers of bone turnover. No adjustments were made for multiple comparisons. The statistical significance of differences among the treatment groups in the frequency of base-line risk factors and the rates of adverse events was assessed with the use of one-way analysis of variance for continuous variables and

two-by-three chi-square tests for dichotomous variables. Given the standard deviations in this trial, with a power of 90 percent, we could detect a difference in the areal bone mineral density of about 2.8 percent for the spine and 2.2 percent for the hip.

## RESULTS

### CHARACTERISTICS OF THE WOMEN AND ADHERENCE TO TREATMENT

Table 1 summarizes the base-line characteristics of the women. The mean ( $\pm$ SD) T score for the bone mineral density of the femoral neck was  $-2.2\pm 0.7$ . A total of 165 women (69 percent) had at least one T score below  $-2.5$ , and 112 (47 percent) reported a fracture after menopause. There were no significant differences among the treatment groups in base-line characteristics, except for the areal bone mineral density of the spine (which was about 6 percent higher in the combination-therapy group than in either of the other groups;  $P=0.03$  for the three-way comparison). No similar trend was evident with regard to the volumetric density of the spine.

A total of 227 women (95 percent) completed the 12-month visit. For the first 12 months of the study, 75 percent of the women had full adherence to treatment involving injections, and 81 percent had full adherence to treatment involving tablets. There were no differences in adherence according to treatment group.

### AREAL AND VOLUMETRIC BONE MINERAL DENSITY

The areal bone mineral density of the lumbar spine (as measured by dual-energy x-ray absorptiometry) increased significantly within each treatment group (Fig. 1). Changes were similar in the parathyroid hormone group and the combination-therapy group (increases of 6.3 percent and 6.1 percent, respectively) and were somewhat smaller in the alendronate group (4.6 percent; difference between the combination-therapy group and the alendronate group, 1.5 percentage points; 95 percent confidence interval,  $-0.5$  to  $3.6$ ). At the total hip and the femoral neck, the bone mineral density remained essentially unchanged in the parathyroid hormone group but increased in the combination-therapy group and

**Table 1. Base-Line Characteristics of the Women.\***

| Characteristic   | Parathyroid Hormone Group (N=119) | Combination-Therapy Group (N=59) | Alendronate Group (N=60) | P Value |
|--|-----------------------------------|----------------------------------|--------------------------|---------|
| Age — yr   | 69.4 $\pm$ 7.3                    | 70.2 $\pm$ 6.8                   | 70.7 $\pm$ 6.8           | 0.47    |
| Age at menopause — yr  | 46.7 $\pm$ 6.5                    | 47.2 $\pm$ 7.2                   | 48.3 $\pm$ 5.2           | 0.27    |
| Race — no. (%)   |                                   |                                  |                          | 0.50    |
| White  | 111 (93.3)                        | 57 (96.6)                        | 58 (96.7)                |         |
| Other  | 8 (6.7)                           | 2 (3.4)                          | 2 (3.3)                  |         |
| Height loss since 25 yr of age — mm  | 40.3 $\pm$ 27.8                   | 40.8 $\pm$ 27.2                  | 34.5 $\pm$ 25.3          | 0.35    |
| Body-mass index  | 25.6 $\pm$ 4.6                    | 27.1 $\pm$ 5.6                   | 25.1 $\pm$ 4.5           | 0.07    |
| Clinical fracture since 45 yr of age — no. (%)                                     | 57 (47.9)                         | 30 (50.8)                        | 25 (41.7)                | 0.64    |
| Any previous alendronate use — no. (%)   | 13 (10.9)                         | 4 (6.8)                          | 10 (16.7)                | 0.23    |
| Areal bone mineral density on dual-energy x-ray absorptiometry — g/cm <sup>2</sup> |                                   |                                  |                          |         |
| Lumbar spine   | 0.771 $\pm$ 0.104                 | 0.819 $\pm$ 0.120                | 0.778 $\pm$ 0.125        | 0.03    |
| Total hip  | 0.710 $\pm$ 0.098                 | 0.738 $\pm$ 0.077                | 0.712 $\pm$ 0.092        | 0.13    |
| Femoral neck   | 0.599 $\pm$ 0.084                 | 0.612 $\pm$ 0.067                | 0.596 $\pm$ 0.072        | 0.50    |
| Distal one third of radius   | 0.556 $\pm$ 0.076                 | 0.566 $\pm$ 0.071                | 0.551 $\pm$ 0.073        | 0.49    |
| Volumetric density on quantitative CT — g/cm <sup>3</sup> †                        |                                   |                                  |                          |         |
| Integral spine   | 0.174 $\pm$ 0.023                 | 0.178 $\pm$ 0.026                | 0.178 $\pm$ 0.028        | 0.56    |
| Trabecular spine   | 0.083 $\pm$ 0.022                 | 0.087 $\pm$ 0.025                | 0.085 $\pm$ 0.024        | 0.68    |
| Integral total hip   | 0.211 $\pm$ 0.028                 | 0.220 $\pm$ 0.031                | 0.217 $\pm$ 0.025        | 0.14    |
| Trabecular total hip   | 0.073 $\pm$ 0.022                 | 0.074 $\pm$ 0.025                | 0.076 $\pm$ 0.019        | 0.71    |

\* Plus-minus values are means  $\pm$ SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.

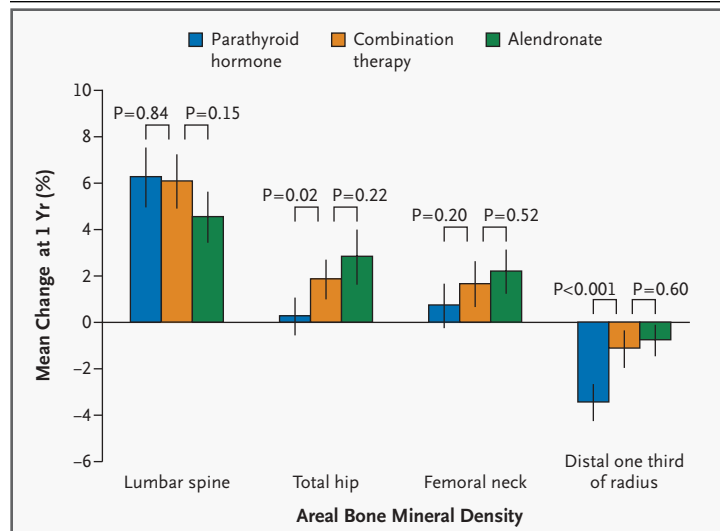
† Data on quantitative CT measurements were available for 178 women.

the alendronate group. The increase at the total hip in the combination-therapy group was significantly greater than that in the parathyroid hormone group (1.9 percent vs. 0.3 percent; difference, 1.6 percentage points; 95 percent confidence interval, 0.3 to 2.9). The bone mineral density at the distal radius decreased significantly in the parathyroid hormone group (a 3.4 percent reduction), but the reduction appeared to be mitigated by the presence of alendronate in the combination-therapy group (a 1.1 percent reduction; difference, 2.3 percentage points; 95 percent confidence interval, 1.2 to 3.5). The loss in the alendronate group was similar to that in the combination-therapy group.

Quantitative CT was used to measure volumetric bone mineral density of trabecular bone at the spine and the hip (Fig. 2) and volumetric bone mineral density and geometric variables in cortical bone at the hip (Fig. 3). The integral volumetric density (cortical plus trabecular bone) at the spine showed a pattern similar to that seen in the areal density of the spine. The volumetric density of the trabecular bone at the spine increased markedly in all groups. However, the increase in the parathyroid hormone group was approximately twice as great as that found in the combination-therapy group (25.5 percent vs. 12.9 percent; difference, 12.6 percentage points; 95 percent confidence interval, 2.8 to 22.4). The change in the alendronate group (10.5 percent) was similar to that in the combination-therapy group. The volumetric density of the trabecular bone at the hip increased in all treatment groups. Although the pattern of differences among the groups was similar to that observed in the volumetric density of trabecular bone at the spine, these differences did not reach statistical significance.

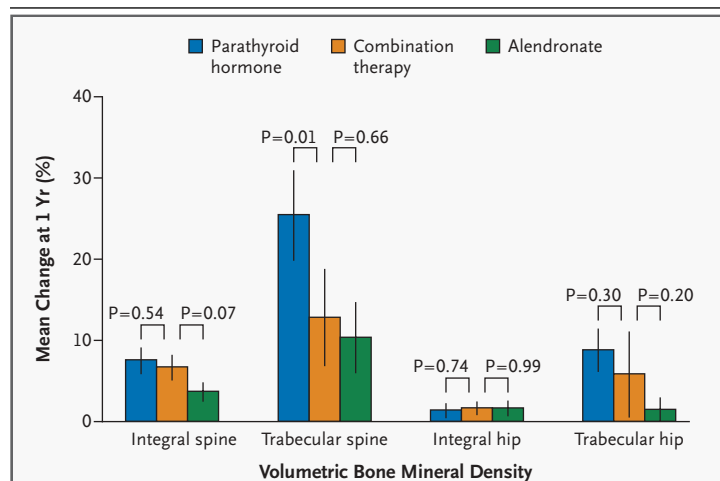
The pattern of changes in cortical-bone variables (Fig. 3) was different from that observed with trabecular bone. The volumetric density of cortical bone at the total hip decreased significantly in the parathyroid hormone group, whereas there was no significant change in the combination-therapy group (a reduction of 1.7 percent vs. an increase of 0.1 percent; difference, 1.8 percentage points; 95 percent confidence interval, 0.7 to 3.0), and there was an increase in the alendronate group (1.2 percent; alendronate group minus combination-therapy group, 1.1 percentage points; 95 percent confidence interval, -0.3 to 2.4). Patterns were similar for the volumetric density of cortical bone at the femoral neck. In the parathyroid hormone group, the cortical bone volume increased significantly at

the total hip (3.5 percent) and femoral neck (3.4 percent), but there were no significant increases in the other treatment groups. There was a significant difference between the parathyroid hormone group and the combination-therapy group in the change in cortical volume at the femoral neck (a 3.4 percent



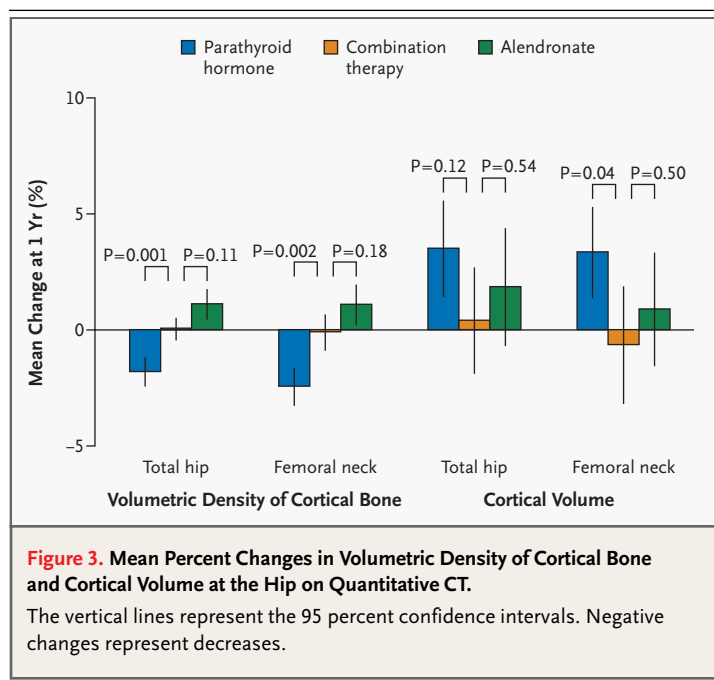
**Figure 1. Mean Percent Changes in Areal Bone Mineral Density on Dual-Energy X-Ray Absorptiometry.**

The vertical lines represent the 95 percent confidence intervals. Negative changes represent decreases.



**Figure 2. Mean Percent Changes in Volumetric Bone Mineral Density for Integral (Cortical plus Trabecular) and Trabecular Bone on Quantitative CT.**

The vertical lines represent the 95 percent confidence intervals.



increase vs. a 0.6 percent decrease; difference, 4.0 percentage points; 95 percent confidence interval, 0.1 to 7.9), but not in the change in cortical volume at the total hip (increases of 3.5 percent vs. 0.4 percent; difference, 3.1 percentage points; 95 percent confidence interval, -0.8 to 7.1). The cortical bone mineral content did not change in any of the treatment groups.

#### BIOCHEMICAL MARKERS OF BONE TURNOVER

The parathyroid hormone group had a rapid, large increase in the level of N-propeptide of type I collagen, a marker of bone formation; the increase was sustained over the 12-month period (an increase of 150 percent at 12 months) (Fig. 4). Treatment with parathyroid hormone was associated with an increase in the concentration of serum C-terminal telopeptide of type I collagen, a marker of bone resorption, although this increase was somewhat delayed in comparison with the change in the N-propeptide concentration. The combination-therapy group had an increase in the concentration of N-propeptide at 1 month, but the concentration had decreased to slightly below the base-line value by 3 months (and was 15.7 percent below base line at 12 months). In the combination-therapy group, the C-terminal telopeptide concentration had decreased by 50 percent at one month and remained at that level. In the alen-

dronate group, there was a rapid decrease in the C-terminal telopeptide level (a 58 percent decrease at one month), followed by a similar decrease (59 percent at three months) in the N-propeptide level. Changes in the concentrations of bone-specific alkaline phosphatase were similar to the changes in the N-propeptide concentrations (data not shown).

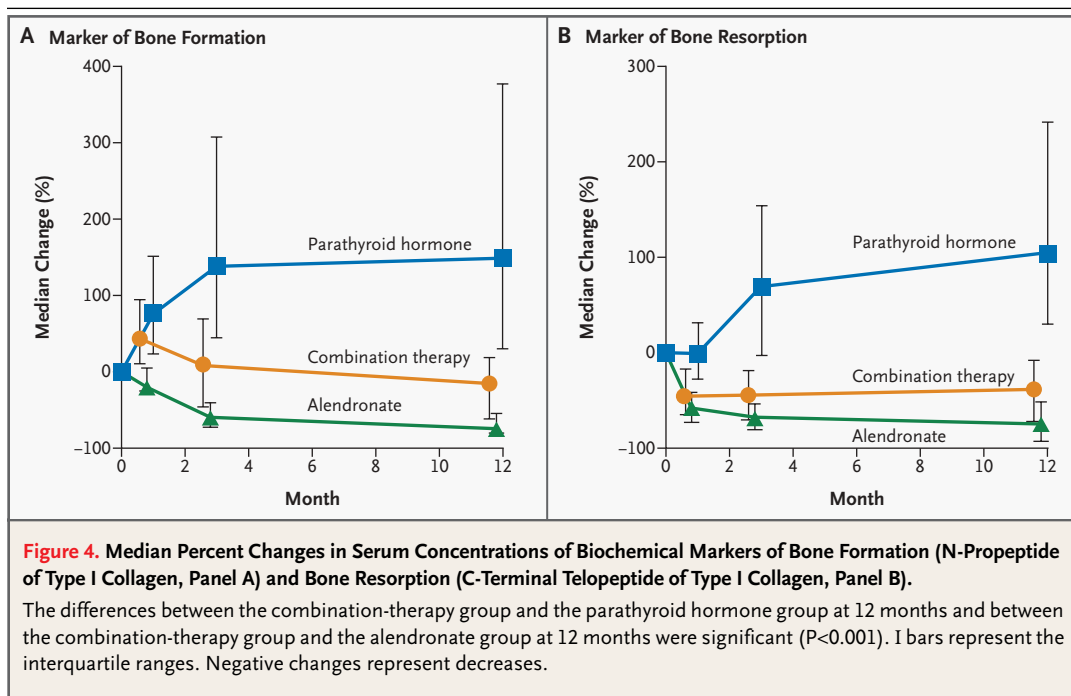
#### FRACTURES

Eight clinical fractures occurred during the trial. The incidence was similar in all three treatment groups (approximately 3 percent).

#### SAFETY AND ADVERSE EVENTS

There was a small but significant increase in the mean serum calcium concentration in the parathyroid hormone group at 1 and 3 months, but the concentration had returned to the base-line value by 12 months (9.5 mg per deciliter [2.38 mmol per liter] at base line; 9.7 mg per deciliter [2.42 mmol per liter] at 1 month; 9.8 mg per deciliter [2.45 mmol per liter] at 3 months). The combination-therapy group had a small increase at one month, but the concentration had returned to the base-line value by three months ( $P=0.004$  for the comparison with the parathyroid hormone group at three months). As expected, there was a decrease in the serum calcium concentration among the women in the alendronate group.

Twenty-two women (12 percent in the parathyroid hormone group, 14 percent in the combination-therapy group, and none in the alendronate group) met the criteria for an elevated serum calcium concentration on at least one occasion, but only five had values above 11.2 mg per deciliter (2.80 mmol per liter). Fifteen women (8 percent in the parathyroid hormone group, 10 percent in the combination-therapy group, and none in the alendronate group) met the criteria for elevated urinary calcium excretion. Both serum and urinary levels returned to normal in almost all women either after a confirmatory measurement (step 1 in the algorithm) or after the discontinuation of calcium supplementation (step 2). Only two women required a reduction in the dose of parathyroid hormone because of increased calcium levels. One additional woman who was receiving parathyroid hormone had a normal serum calcium concentration at all study visits but had transient hypercalcemia associated with an intercurrent illness; the hypercalcemia resolved within 24 hours with intravenous hydration.



A total of 226 women reported at least one adverse event, and 20 reported at least one serious adverse event. The proportions did not differ according to treatment group, nor did the rates of adverse events that were previously found to be associated with parathyroid hormone treatment (injection-site complications, nausea, fatigue, headache, dizziness, or limb pain).

Two deaths occurred during the trial, both due to rapidly progressing dementia and both in women in the parathyroid hormone group. One of these women had taken only one dose of parathyroid hormone. The data and safety monitoring board judged that the two deaths were unrelated to the study medication.

There was a significant increase in the mean serum uric acid concentration in both the parathyroid hormone group (1.03 mg per deciliter [61  $\mu\text{mol}$  per liter]) and the combination-therapy group (0.85 mg per deciliter [51  $\mu\text{mol}$  per liter];  $P < 0.001$  for both increases), whereas there was no change in the alendronate group. Three women had gout — one in the parathyroid hormone group and two in the combination-therapy group.

## DISCUSSION

Our randomized clinical trial was designed to assess whether combination therapy with parathy-

roid hormone and a bisphosphonate is superior to monotherapy with parathyroid hormone or a bisphosphonate. Daily injections of parathyroid hormone (1–34) and parathyroid hormone (1–84) have been shown to increase bone mineral density,<sup>9,12,13</sup> and parathyroid hormone (1–34) has been shown to reduce the risk of vertebral and nonvertebral fractures.<sup>9</sup> Although parathyroid hormone therapy increases both bone formation and bone resorption, bone formation is increased preferentially over resorption, at least initially. The bisphosphonate alendronate has also been shown to increase bone mineral density and reduce the risk of fracture, but its mechanism of action differs from that of parathyroid hormone; it preferentially suppresses bone resorption over bone formation.<sup>4,5</sup>

By stimulating bone formation and inhibiting bone resorption simultaneously, combination therapy might be more effective than therapy with parathyroid hormone or alendronate alone. We hypothesized that, as compared with parathyroid hormone therapy alone, combination therapy with parathyroid hormone and alendronate would induce larger increases in bone mineral density, preserve the increase in bone formation, and minimize increases in bone resorption. However, taken together, the changes in areal and volumetric bone mineral density, cortical volume, and the levels of biochemical markers of bone turnover found in our study pro-

vide little evidence that this combination is better than either drug alone.

The use of quantitative CT allowed us to evaluate trabecular bone separately from cortical bone. The volumetric density of trabecular bone at the spine increased more with parathyroid hormone alone than with combination therapy or alendronate alone. In the parathyroid hormone group, the cortical volume at the hip increased, the volumetric density decreased, and the bone mineral content was unchanged — observations that are consistent with the findings of other studies<sup>19-21</sup> and with the previously demonstrated actions of parathyroid hormone, including the induction of new bone that is not fully mineralized, as well as the increasing cortical porosity.<sup>19,22,23</sup> In studies in nonhuman primates,<sup>19</sup> these changes were not associated with decreases in bone strength. However, in humans, it is not known whether the changes we observed in cortical bone with parathyroid hormone therapy have a positive, negative, or neutral effect on bone strength and the risk of fracture. Overall, the changes that were induced by parathyroid hormone therapy in cortical and trabecular bone were not seen with combination therapy or with alendronate monotherapy, which suggests that combination therapy alters the distinct effects of parathyroid hormone on bone. Ultimately, further study is needed to determine the effect of parathyroid hormone–based combination therapy on the risk of fracture.

The parathyroid hormone group had a clear and early increase in the levels of the marker of bone formation, with a somewhat delayed but substantial increase in the levels of the marker of resorption. These observations are consistent with the findings of previous studies.<sup>10-13</sup> The expectation that combination therapy would maintain the increased bone formation seen with parathyroid hormone alone while dampening increases in resorption was not substantiated by the data. Although the levels of the marker of bone resorption did decrease substantially with combination therapy and the levels of the marker of bone formation remained relatively constant over the 12-month period, the expected large and sustained increases in bone formation were negated after 1 month. If increases in bone formation are indicative of the effects of parathyroid hormone on bone, these results suggest that the anabolic actions of parathyroid hormone might not be optimally realized with combination therapy.

We examined the concurrent administration of

antiresorptive therapy and parathyroid hormone therapy only in women who were not already taking medication for osteoporosis; therefore, we cannot address questions regarding antiresorptive therapy initiated before or after the initiation of parathyroid hormone therapy. Little is known about the use of parathyroid hormone therapy after antiresorptive therapy. However, the addition of parathyroid hormone to ongoing estrogen therapy apparently did not reduce the ability of parathyroid hormone to increase bone turnover.<sup>13,14</sup> Increases in bone mineral density achieved with combined estrogen and parathyroid hormone were similar to those observed with parathyroid hormone monotherapy. A recent study of combination alendronate and parathyroid hormone (1–34) (40 µg) therapy in men, initiated after 6 months of alendronate monotherapy, showed that the increases in bone mineral density over 24 months of combination therapy were less than those observed over 24 months of parathyroid hormone monotherapy.<sup>24</sup> However, there have been no studies of parathyroid hormone monotherapy initiated after the discontinuation of any type of antiresorptive therapy. Our report cannot provide insight about whether antiresorptive therapy administered after a course of parathyroid hormone therapy is of clinical benefit. Although one small, nonrandomized study of alendronate therapy given after therapy with parathyroid hormone (1–84) showed an additional increase in bone mineral density,<sup>12</sup> it is unclear whether antiresorptive drugs should be used after parathyroid hormone therapy.

We used the full-length 84-amino-acid parathyroid hormone molecule. The effects of parathyroid hormone (1–84) on the bone mineral density at the spine and the hip in our study are similar to those that have been found with 20 µg (the approved dose) of parathyroid hormone (1–34) in other 1-year studies<sup>10,11</sup> and are somewhat smaller than those found in one longer (21-month) study.<sup>9</sup> However, the generalizability of our results with the concurrent initiation of parathyroid hormone (1–84) and alendronate combination therapy to therapy with parathyroid hormone (1–34) is uncertain. Whether our results with the concurrent initiation of alendronate therapy and parathyroid hormone therapy apply to other bisphosphonates or other antiresorptive drugs is unknown. Taken together, these results do not support the concurrent initiation of alendronate with parathyroid hormone treatment.



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## APPENDIX

The following persons participated in the PaTH Study: Columbia University — J.P. Bilezikian (principal investigator), K. Lee, J. Sliney (study coordinators); Minneapolis Veterans Affairs Medical Center — K.E. Ensrud (principal investigator), V. Wyum, N. Michaels; University of Pittsburgh Medical Center — S.L. Greenspan (principal investigator), J.L. Ryan (study coordinator), J.M. Wagner; Maine Center for Osteoporosis Research—St. Joseph's Hospital — C.J. Rosen (principal investigator), L. Fowler, D. Storm (study coordinators); University of California, San Francisco — D.M. Black (principal investigator), T. Hue (project director), L. Palermo (statistician), D. Sellmeyer and D.C. Bauer (study physicians); Data and Safety Monitoring Board — L. Raisz (chair), S. Hui, R. Recker, D. Kiel, D. Hanley.

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