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## One Year of Alendronate after One Year of Parathyroid Hormone (1–84) for Osteoporosis

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### ABSTRACT

#### BACKGROUND

Since the use of parathyroid hormone as a treatment for osteoporosis is limited to two years or less, the question of whether antiresorptive therapy should follow parathyroid hormone therapy is important. We previously reported results after the first year of this randomized trial comparing the use of full-length parathyroid hormone (1–84) alone, alendronate alone, or both combined. In the continuation of this trial, we asked whether antiresorptive therapy is required to maintain gains in bone mineral density after one year of therapy with parathyroid hormone (1–84).

#### METHODS

In the data reported here, women who had received parathyroid hormone (1–84) monotherapy (100 µg daily) in year 1 were randomly reassigned to one additional year with either placebo (60 subjects) or alendronate (59 subjects). Subjects who had received combination therapy in year 1 received alendronate in year 2; those who had received alendronate monotherapy in year 1 continued with alendronate in year 2. Bone mineral density at the spine and hip was assessed with the use of dual-energy x-ray absorptiometry and quantitative computed tomography (CT).

#### RESULTS

Over two years, alendronate therapy after parathyroid hormone therapy led to significant increases in bone mineral density in comparison with the results for placebo after parathyroid hormone therapy, a difference particularly evident for bone mineral density in trabecular bone at the spine on quantitative CT (an increase of 31 percent in the parathyroid hormone–alendronate group as compared with 14 percent in the parathyroid hormone–placebo group). During year 2, subjects receiving placebo lost substantial bone mineral density.

#### CONCLUSIONS

After one year of parathyroid hormone (1–84), densitometric gains appear to be maintained or increased with alendronate but lost if parathyroid hormone is not followed by an antiresorptive agent. These results have clinical implications for therapeutic choices after the discontinuation of parathyroid hormone.

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WITH THE APPROVAL OF TERIPARATIDE, or human parathyroid hormone (1–34), two distinct classes of drugs became available for the treatment of osteoporosis. Antiresorptive drugs, such as the bisphosphonates, reduce bone resorption, whereas anabolic agents, such as teriparatide, primarily stimulate bone formation. However, it is not clear whether combining these therapeutic classes will improve efficacy. Two studies reported in the *Journal* in 2003<sup>1,2</sup> addressed that question in men and in postmenopausal women. One study,<sup>1</sup> of which the present report is an extension, involved full-length parathyroid hormone (1–84), and the other involved teriparatide.<sup>2</sup> Both reports indicated that the concurrent use of parathyroid hormone and alendronate offered no advantage over monotherapy in terms of changes in bone mineral density.<sup>1,2</sup> In fact, the concurrent use of alendronate blunted large parathyroid hormone–induced increases in trabecular bone mineral density.

The approval of teriparatide by the Food and Drug Administration for the treatment of osteoporosis was issued with the recommendation that therapy not last more than two years. However, there were no recommendations about what to do in the period after parathyroid hormone treatment. Observational studies in humans and studies in rat models suggest that gains in bone mineral density achieved with parathyroid hormone are lost if an antiresorptive agent is not administered after treatment.<sup>3–6</sup> The Parathyroid Hormone and Alendronate (PaTH) study was designed a priori to include a second year of therapy to test whether it is necessary to follow parathyroid hormone with a bisphosphonate in order to maintain gains in bone mineral density made during exposure to parathyroid hormone, as well as to address other questions with regard to two years of combination therapy with parathyroid hormone and alendronate. The present study examines this hypothesis in a controlled, double-blind, randomized, and prospective manner.

## METHODS

Study methods, previously described,<sup>1</sup> are summarized here.

### SUBJECTS

We recruited participants from four U.S. clinical centers: Bangor, Maine; Minneapolis; New York; and Pittsburgh. Postmenopausal women 55 to 85

years of age were enrolled if they had a T score for bone mineral density below  $-2.5$  at the femoral neck, total hip, or spine or if they had a T score below  $-2$  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 ever been treated with bisphosphonates for more than 12 months or for specified shorter intervals in recent periods.

### TREATMENTS

The treatments in this study were full-length parathyroid hormone (1–84) (100  $\mu\text{g}$  daily [NPS Pharmaceuticals] by subcutaneous injection), oral alendronate (10 mg daily [Fosamax, Merck]), calcium carbonate (500 mg of elemental calcium [Tums, GlaxoSmithKline]), and a multivitamin containing 400 IU of vitamin D (Rugby Laboratories).

### STUDY DESIGN

After a two-week run-in period, 238 women were randomly assigned to one of four treatment regimens for two years, as follows: parathyroid hormone in year 1 followed by alendronate in year 2 (hereafter referred to as the parathyroid hormone–alendronate group); parathyroid hormone in year 1 followed by placebo in year 2 (the parathyroid hormone–placebo group); parathyroid hormone plus alendronate in year 1 followed by alendronate in year 2 (the combination-therapy–alendronate group); and alendronate for two years (the continued-alendronate group). All participants received daily calcium and vitamin D. This report covers the entire 24 months of treatment. Parathyroid hormone or an injectable placebo was administered only during year 1.

The study medications were provided by NPS Pharmaceuticals (parathyroid hormone and matching placebo), Merck (alendronate and matching placebo), and GlaxoSmithKline (calcium). Supplementary funds for quantitative computed tomography (CT) were provided by Merck. Merck and NPS Pharmaceuticals provided (nonbinding) comments on one draft of the manuscript.

The study design, data accrual, and writing of the manuscript were managed entirely by the investigators, who hold the data. The study was implemented in all facets, including data collection and analysis, by the University of California, San Francisco, coordinating center. Except for one clinician (D. Bauer), who was responsible for reports

to the data and safety monitoring board, participants, clinicians, and investigators remained blinded to the study treatments.

#### EFFICACY OUTCOME VARIABLES

Areal bone mineral density (in grams per square centimeter) at the lumbar spine, hip, and distal one third of the radius was assessed with the use of dual-energy x-ray absorptiometry (Hologic QDR 4500A or Delphi densitometers) at baseline, 12 months, and 24 months. Volumetric bone density (in grams per cubic centimeter) and bone geometry in trabecular and cortical compartments were assessed with the use of quantitative CT at the spine (L1 and L2) and total hip in a subgroup of 204 patients.<sup>1,7</sup> Specific outcomes from quantitative CT included trabecular bone mineral density at the spine and total hip as well as cortical bone density, content (in grams), and volume at the total hip.

After an overnight fast, serum samples were drawn and stored (at  $-70^{\circ}\text{C}$ ) until they were assayed for N-propeptide of type I collagen (a marker of bone formation) and serum C-terminal telopeptide of type I collagen (a marker of bone resorption) in a central laboratory (by P. Garnero at Synarc, Lyon, France). The baseline and 12-month assays were performed simultaneously, and the assay at 24 months was performed separately.

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

Adherence to treatment was assessed by means of the return of unused cartridges (parathyroid hormone, year 1) and tablets (alendronate, years 1 to 2). Full adherence to treatment each year was defined as the use of study medication (pills or injections) for at least 11 of the 12 months of that year and as the use of at least 80 percent of the prescribed medications during that period.

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)* and classified by a single clinician at the University of California, San Francisco, who was unaware of the treatment-group assignments. The preferred terms from *MedDRA* were categorized according to the types of adverse events anticipated on the basis of previous trials of parathyroid hormone<sup>8</sup> and alendronate<sup>9,10</sup>; the adverse events were also assigned to broader categories according to organ systems. These categories were then compared across treatment groups by the

data and safety monitoring board and reviewed for this report.

#### 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 treatment regimens. Analyses were performed according to the intention-to-treat principle unless otherwise stated. Means within treatment groups, 95 percent confidence intervals, and t-tests for the percent change from baseline to 24 months and from 12 months to 24 months in variables measured by dual-energy x-ray absorptiometry and by quantitative CT were used to assess the significance of changes within groups. Geometric means and 95 percent confidence intervals are shown for changes in bone markers. For the period from baseline to 24 months, two sets of comparisons were made: the first was between the parathyroid hormone–alendronate group and the other three treatment groups, and the second was between the combination-therapy group and the other three treatment groups. We also compared changes from 12 to 24 months between the two groups that received parathyroid hormone therapy alone in the first year (parathyroid hormone–alendronate vs. parathyroid hormone–placebo). For all comparisons, a significance level of 0.05 (not adjusted for multiple comparisons) was used, but the comparisons for which  $P < 0.001$  are generally noted in the text. A complete listing of the changes within groups and the differences between groups is given in the Supplementary Appendix (available with the full text of this article at [www.nejm.org](http://www.nejm.org)).

On the basis of standard deviations from the results at 24 months in a previous trial,<sup>9</sup> with a power of 0.90 and a significance level of 0.05, we expected to be able to detect a difference between any two treatment groups in areal bone mineral density of 4 percent at the spine and 2.4 percent at the total hip.

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## RESULTS

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#### CHARACTERISTICS OF THE PATIENTS AND ADHERENCE TO TREATMENT

Baseline characteristics of the participants are shown in Table 1. There were no significant differences in baseline characteristics among the four treatment groups, with the exception of areal bone mineral density of the spine, which differed signif-

**Table 1. Baseline Characteristics of the Women.\***

Characteristic	Parathyroid Hormone– Placebo Group (N=60)	Parathyroid Hormone– Alendronate Group (N=59)	Combination-Therapy– Alendronate Group (N=59)	Continued- Alendronate Group (N=60)	P Value†
Age — yr	70.1±7.3	68.7±7.4	70.2±6.8	70.7±6.8	0.44
Age according to subgroup — no. (%)					0.46
50–59	7 (11.7)	8 (13.6)	5 (8.5)	2 (3.3)	
60–69	21 (35.0)	23 (39.0)	23 (39.0)	26 (43.3)	
70–79	27 (45.0)	24 (40.7)	28 (47.5)	24 (40.0)	
80–89	5 (8.3)	4 (6.8)	3 (5.1)	8 (13.3)	
Age at menopause — yr	45.8±7.2	47.5±5.6	47.2±7.2	48.4±5.1	0.17
Race — no. (%)‡					0.25
White	54 (90.0)	57 (96.6)	57 (96.6)	58 (96.7)	
Other	6 (10.0)	2 (3.4)	2 (3.4)	2 (3.3)	
Height loss since age of 25 yr — mm	–45.8±31.6	–34.7±22.4	–40.8±27.2	–34.5±25.3	0.07
Body-mass index§	25.9±4.3	25.4±4.9	27.1±5.6	25.1±4.5	0.13
Clinical fracture since age of 45 yr — no. (%)	27 (45.0)	30 (50.8)	30 (50.8)	25 (41.7)	0.65
Previous alendronate use — no. (%)	6 (10.0)	7 (11.9)	4 (6.8)	10 (16.7)	0.39
For >12 mo or >4 wk in last 12 mo	1 (1.7)	0	2 (3.4)	2 (3.3)	0.52
Areal bone mineral density on dual- energy x-ray absorptiometry — g/cm <sup>2</sup>					
Total spine	0.76±0.10	0.79±0.10	0.82±0.12	0.78±0.12	0.02
Total hip	0.71±0.10	0.71±0.09	0.74±0.08	0.71±0.09	0.23
Femoral neck	0.59±0.09	0.61±0.08	0.61±0.07	0.60±0.07	0.40
Distal one third of radius	0.55±0.08	0.56±0.07	0.57±0.07	0.55±0.07	0.70
Volumetric density on quantitative CT — g/cm <sup>3</sup> ¶					
Total spine	0.17±0.02	0.18±0.02	0.18±0.03	0.18±0.03	0.49
Trabecular bone at spine	0.08±0.02	0.08±0.02	0.08±0.02	0.08±0.02	0.61
Total hip	0.21±0.03	0.21±0.03	0.22±0.03	0.22±0.03	0.38
Trabecular bone at total hip	0.07±0.02	0.07±0.02	0.07±0.02	0.07±0.02	0.96

\* Plus–minus values are means±SD.

† P values were calculated with the use of the one-way analysis-of-variance method for continuous variables and the chi-square method for binary variables.

‡ Race was self-reported.

§ The body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

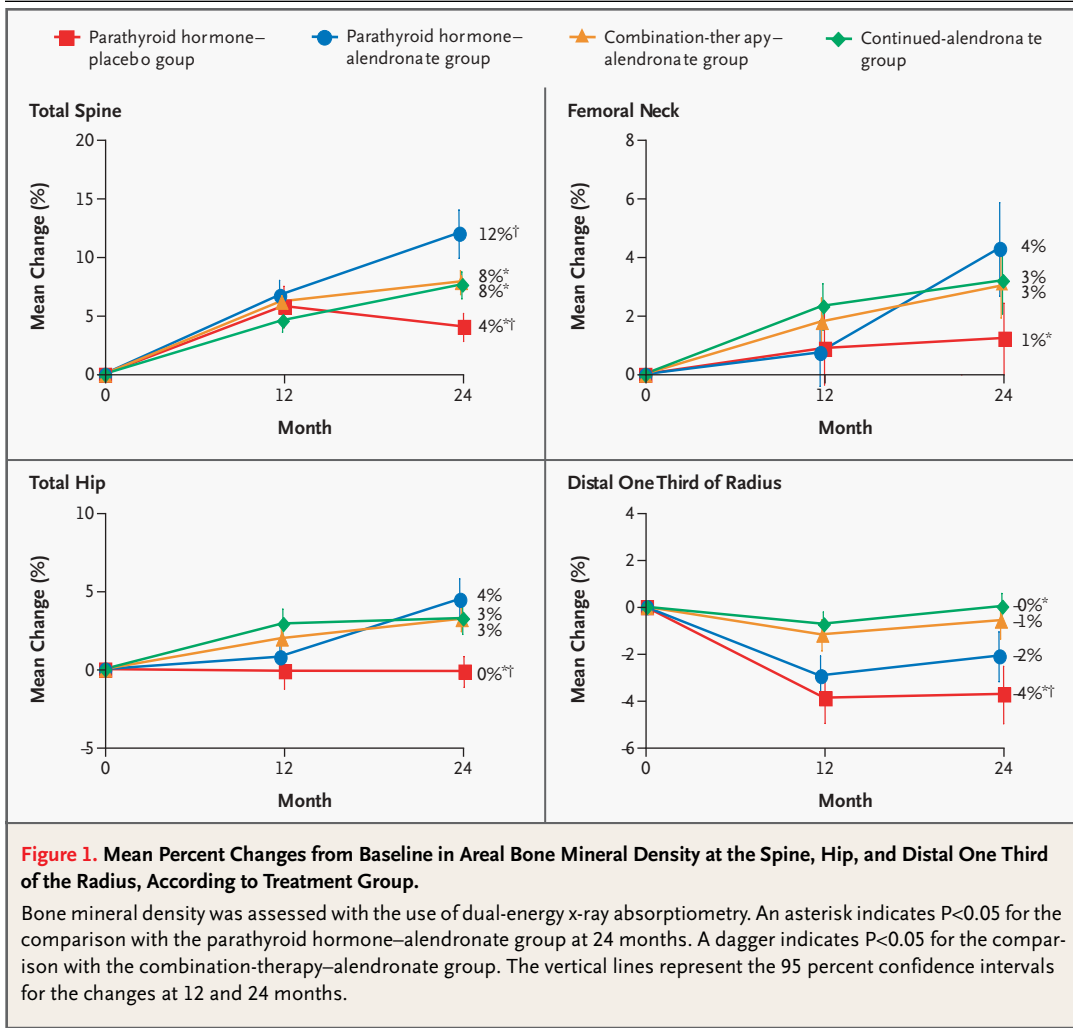
¶ Quantitative CT was performed in a total of 204 participants at three clinical sites.

icantly among the four treatment groups ( $P=0.02$ ). A similar trend was not evident for volumetric bone mineral density of the spine.

A total of 223 patients (94 percent) completed the 24-month follow-up. During the first 12 months, 75 percent of participants fully adhered to treatment by injection and 81 percent to treatment with tablets. In the second year, 80 percent fully adhered to treatment with tablets. There were no significant differences in adherence according to treatment group.

#### TWO-YEAR CHANGES IN BONE MINERAL DENSITY

Over 24 months, areal bone mineral density at the lumbar spine increased significantly ( $P<0.001$ ) in all four treatment groups (Fig. 1). The largest cumulative increase was seen in the parathyroid hormone–alendronate group (12.1 percent), and the smallest in the parathyroid hormone–placebo group (4.1 percent; 8 percent difference; 95 percent confidence interval, 5.6 to 10.3 percent). The increase in the parathyroid hormone–alendronate group was significantly greater than in the other three treat-



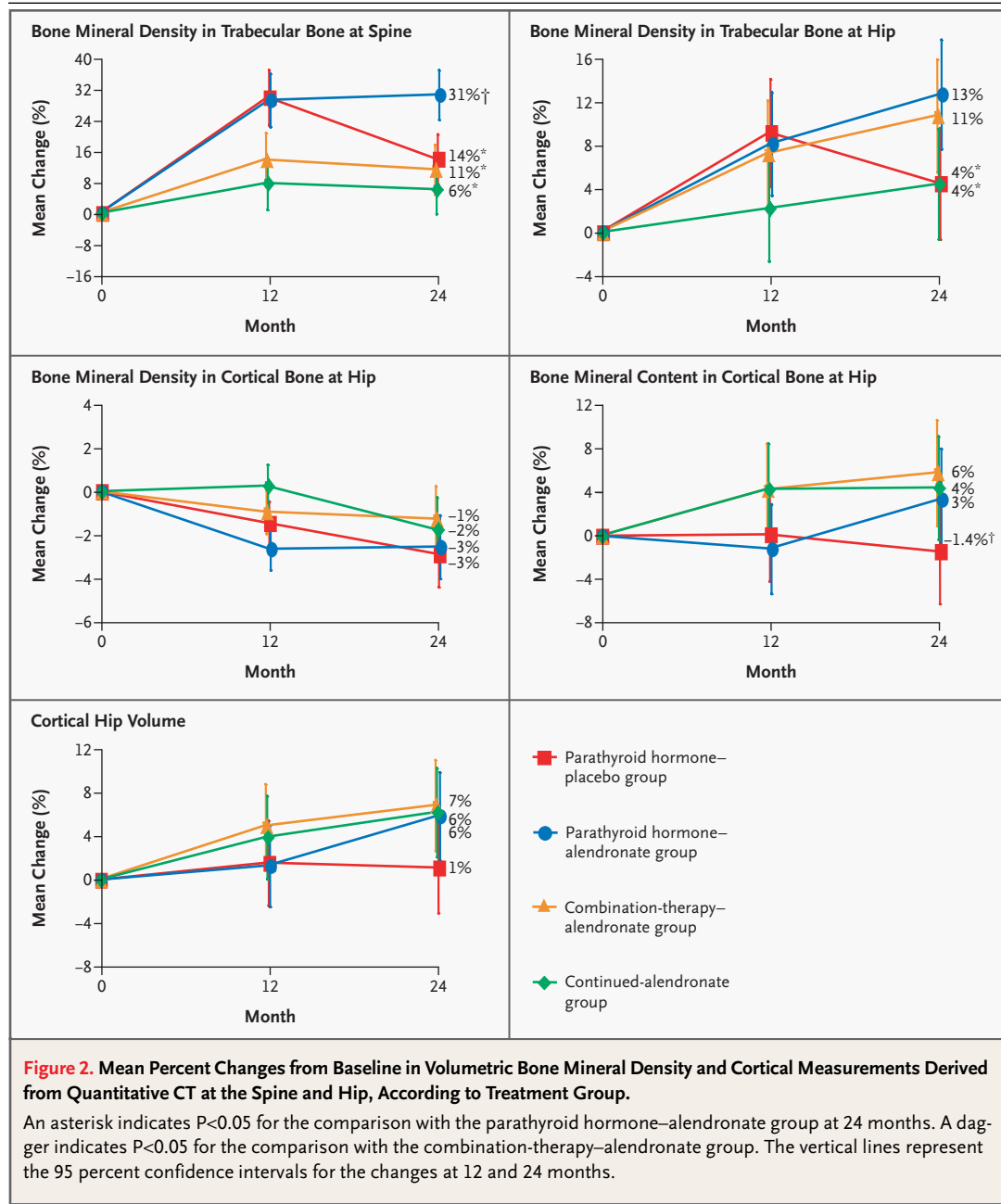
ment groups ( $P < 0.001$ ). The increase in the combination-therapy–alendronate group was significantly greater than that in the parathyroid hormone–placebo group ( $P = 0.002$ ), smaller than that in the parathyroid hormone–alendronate group ( $P < 0.001$ ), and similar to that in the continued-alendronate group.

At the femoral neck and total hip, there were significant increases ( $P < 0.001$ ) in areal bone mineral density over two years in all treatment groups except the parathyroid hormone–placebo group. Across treatment groups, the increases in the parathyroid hormone–alendronate group were significantly greater than those in the parathyroid hormone–placebo group ( $P = 0.005$  for the femoral neck and  $P < 0.001$  for the total hip).

Over two years, there were significant losses at

the distal one third of the radius in both the parathyroid hormone–alendronate and parathyroid hormone–placebo groups ( $P < 0.001$  for both groups) but no significant changes in the other two treatment groups. The two-year cumulative loss in the distal one third of the radius in the parathyroid hormone–placebo group was significantly greater than in the parathyroid hormone–alendronate group ( $P = 0.04$ ), the combination-therapy–alendronate group ( $P < 0.001$ ), and the continued-alendronate group ( $P < 0.001$ ). The only other significant difference between groups at this site was that between the parathyroid hormone–alendronate group ( $-2.1$  percent) and the continued-alendronate group (0 percent,  $P = 0.006$ ).

Volumetric bone mineral density in trabecular bone at both the spine and the hip increased in all



four treatment groups over the two years (Fig. 2). At the spine, the increases were significant ( $P < 0.001$ ) for three of the four treatment groups (the exception was the continued-alendronate group,  $P = 0.06$ ). The increase in volumetric bone mineral density at the trabecular spine was greatest in the parathyroid hormone–alendronate group (31 percent,  $P < 0.001$ ), which was significantly higher than in the other three groups ( $P < 0.001$  for all three comparisons). The increases in bone mineral density in trabecular

bone at the hip were greatest in the parathyroid hormone–alendronate group (13 percent,  $P < 0.001$ ) and the combination-therapy–alendronate group (11 percent,  $P < 0.001$ ). In the parathyroid hormone–placebo group and the continued-alendronate group, the increases were smaller (about 4 percent) and not statistically different from baseline values.

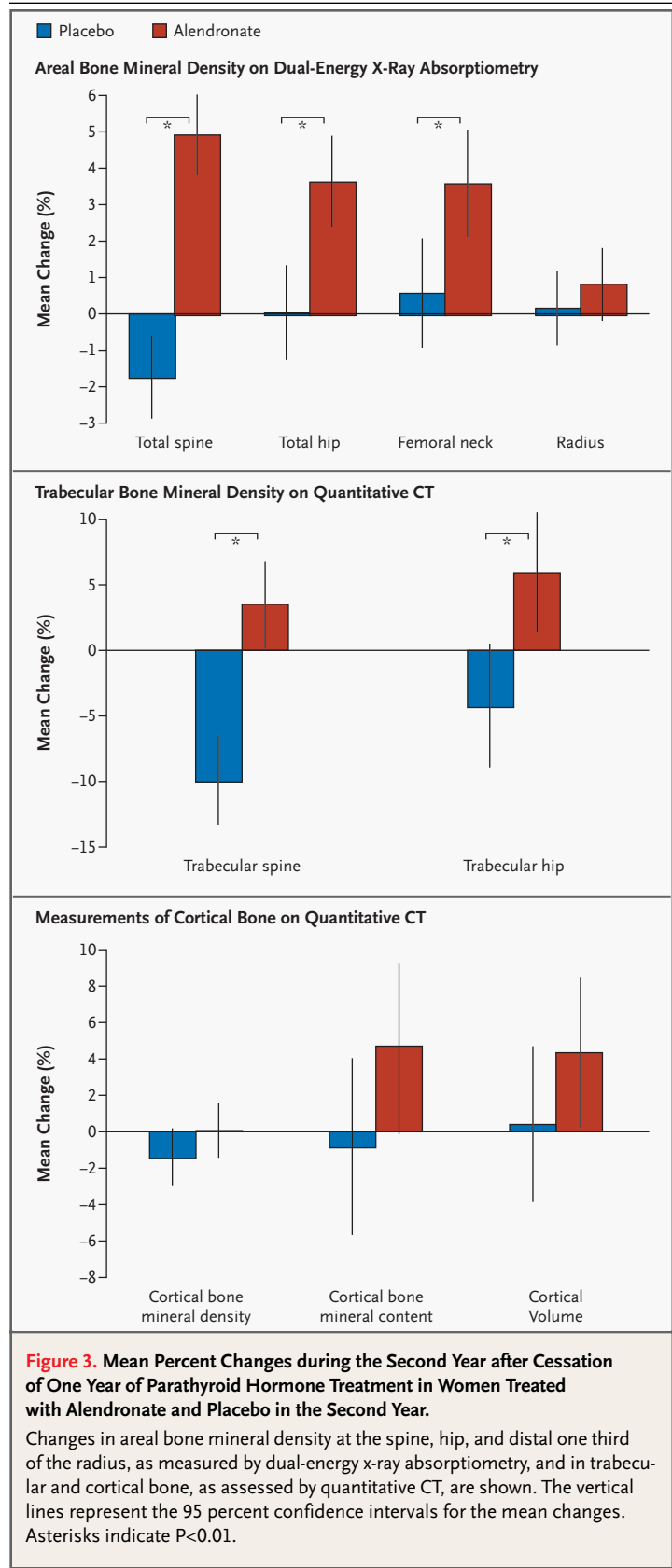
Over the two years, in all four treatment groups, there were small declines in volumetric bone mineral density in cortical bone at the hip (changes of

-1 to -3 percent). The declines were significant in all treatment groups ( $P=0.02$  to  $P<0.001$ ) except the combination-therapy-alendronate group (Fig. 2). None of the declines differed among treatment groups. There was a trend toward an increase in the cortical bone mineral content and a significant increase in the cortical volume ( $P=0.004$  to  $P=0.001$ ) in all treatment groups except the parathyroid hormone-placebo group.

**CHANGES IN YEAR 2**

During year 2, among women in the parathyroid hormone-alendronate group, there was a significant additional increase in areal bone mineral density at the spine (4.9 percent,  $P<0.001$ ) and hip (3.6 percent,  $P<0.001$ ) (Fig. 3). In contrast, in the parathyroid hormone-placebo group, there was a significant decrease in areal bone mineral density at the spine (-1.7 percent,  $P=0.002$ ) and no change at the hip or radius. The difference between further gains in year 2 in the parathyroid hormone-alendronate group and the decline in the parathyroid hormone-placebo group was significant at both the spine (6.6 percent;  $P<0.001$ ; 95 percent confidence interval, 5.1 to 8.2 percent) and the total hip (3.6 percent;  $P<0.001$ ; 95 percent confidence interval, 1.8 to 5.3 percent). During year 2, there were further increases in bone mineral density in trabecular bone at both the spine and the hip in the parathyroid hormone-alendronate group and decreases in the parathyroid hormone-placebo group (Fig. 3). At the spine, the decrease was almost 10 percent ( $P<0.001$ ). The differences between the gains in the parathyroid hormone-alendronate group and the losses in the parathyroid hormone-placebo group in bone mineral density were significant in trabecular bone at both the spine (-13.3 percent;  $P<0.001$ ; 95 percent confidence interval, -17.9 to -8.6 percent) and the hip (-10.1 percent;  $P=0.002$ ; 95 percent confidence interval, -16.5 to -3.7 percent).

No significant change in volumetric bone mineral density in cortical bone was noted in either the parathyroid hormone-alendronate group or the parathyroid hormone-placebo group. However, there were increases in both bone mineral content (4.6 percent,  $P=0.05$ ) and volume (4.4 percent,  $P=0.04$ ) in cortical bone in the parathyroid hormone-alendronate group, with no significant changes in either factor in the parathyroid hormone-placebo group. However, neither the change in bone mineral content nor the change in volume during year 2 differed significantly between the two treatment groups.



**MARKERS OF BONE REMODELING, FRACTURES, AND ADVERSE EVENTS**

The increases in bone resorption and formation that had occurred as a result of parathyroid hormone therapy at month 12 had declined significantly by 24 months in the groups receiving parathyroid hormone in year 1 (the parathyroid hormone–alendronate, parathyroid hormone–placebo, and combination-therapy–alendronate groups) (Fig. 4). Despite large differences between the parathyroid hormone groups and the combination-therapy–alendronate group at month 12, women in both groups who received alendronate during year 2 had levels of biochemical markers of bone turnover below those at baseline; these values were indistinguishable from those in the continued-alendronate group. At 24 months, markers of bone turnover in the parathyroid hormone–placebo group had returned to baseline levels and were higher than in the other groups ( $P < 0.001$ ).

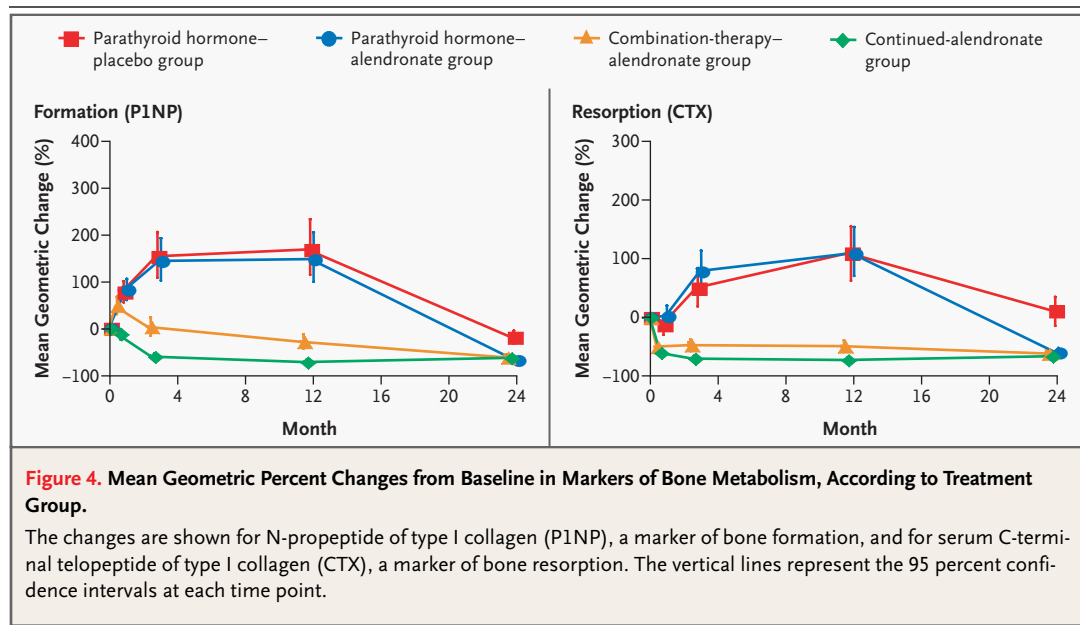
Over the two years, 21 women (8.8 percent) had one or more clinical fractures. The proportion of fractures did not differ among treatment groups. During year 2, a total of six women had a clinical fracture.

During year 2, there was no significant difference between the parathyroid hormone–placebo group and the parathyroid hormone–alendronate group in the occurrence of adverse events, serious adverse events, or adverse events associated with either alendronate (upper gastrointestinal events)

or parathyroid hormone (nausea, vomiting, fatigue, headache, or reaction at the injection site).

**DISCUSSION**

This double-blind, randomized trial was designed to examine several combination-treatment options for previously untreated, postmenopausal women with osteoporosis. In the first year of the PaTH study, we found that combining parathyroid hormone (1–84) with alendronate did not provide a clear advantage over either form of treatment alone when the end point of bone mineral density (as measured by dual-energy x-ray absorptiometry and quantitative CT) was evaluated.<sup>1</sup> Moreover, the concurrent use of alendronate blunted the effect of parathyroid hormone on trabecular bone mineral density.<sup>1</sup> During the second year of the PaTH trial, we addressed several additional questions regarding sequential, rather than concurrent, anabolic and antiresorptive combination therapy. In particular, we tested the hypothesis that in order for densitometric gains to be maintained, parathyroid hormone therapy must be followed by bisphosphonate therapy. Results from the PaTH study support this a priori hypothesis by showing that gains in bone mineral density at both the spine and hip are much larger if parathyroid hormone monotherapy is followed by alendronate rather than no therapy. These data indicate that if antiresorptive therapy does not follow parathyroid hormone therapy, much of the



skeletal gain in bone mineral density with parathyroid hormone is lost.

The salutary effects of antiresorptive therapy after treatment with parathyroid hormone are most striking for trabecular bone compartments. At the spine, the two-year cumulative increase was 31 percent among women in whom parathyroid hormone was followed by alendronate, as compared with only 14 percent among women in whom parathyroid hormone was followed by placebo. In addition, we noted positive changes in cortical bone (increases in volume and mineral content but not in density) in the group receiving alendronate after parathyroid hormone that were not seen in the group receiving placebo after parathyroid hormone.

One of the aims of our study was to assess whether two years of combination therapy was superior to two years of monotherapy. Parathyroid hormone followed by alendronate resulted in greater gains in areal bone mineral density than did alendronate alone at sites rich in trabecular bone (e.g., the spine — 12 percent for parathyroid hormone–alendronate therapy vs. 8 percent for continued-alendronate therapy). This was especially evident with regard to volumetric bone mineral density, particularly in the spine, where the parathyroid hormone–alendronate group gained 31 percent, as compared with 6 percent in the continued-alendronate group. However, at sites with more cortical bone, gains with alendronate alone were similar (at the total hip, 4 percent in the parathyroid hormone–alendronate group vs. 3 percent in the continued-alendronate group on dual-energy x-ray absorptiometry) or larger (at the radius). A comparison of the sequential combination with parathyroid hormone alone is more difficult, since our study did not include a group treated with parathyroid hormone alone for two years and, to our knowledge, no study has reported two-year data for parathyroid hormone. However, during 21 months of teriparatide monotherapy, Neer et al.<sup>8</sup> reported gains in bone mineral density similar to those for parathyroid hormone plus alendronate followed by alendronate (9.7 percent at the spine and 2.6 percent at the hip). Thus, from a clinical perspective, one year of parathyroid hormone followed by one year of alendronate would seem to be an effective means of increasing bone mineral density while minimizing the use of parathyroid hormone. However, the effect of this regimen on the risk of fracture is unknown and can be definitively ascertained only in a trial involving fractures.

We also asked whether combination therapy followed by alendronate alone might offer an advantage over other regimens. In the first year, we found no advantage to concurrent combination therapy. Similarly, over two years, gains in areal bone mineral density in the combination-therapy–alendronate group were similar to those in the continued-alendronate group but somewhat lower than those in women who received parathyroid hormone followed by alendronate. Gains in bone mineral density in trabecular bone at the spine were substantially smaller in the combination-therapy–alendronate group (11 percent) than in the parathyroid hormone–alendronate group (31 percent). Taken together, these data do not support the use of alendronate concurrently with parathyroid hormone but suggest that parathyroid hormone alone followed by alendronate alone may be a preferred method of combining these two agents.

Previous reports suggested that antiresorptive therapy after 12 to 21 months of parathyroid hormone therapy — both teriparatide and parathyroid hormone (1-84) — was beneficial in maintaining or increasing areal bone density, but those studies were uncontrolled, observational, and unblinded.<sup>3,5,6,11</sup> It is reassuring that the current findings from the PaTH trial are consistent with the results of those studies, suggesting that our findings are applicable to treatment with both teriparatide and parathyroid hormone (1-84) as well as to varying durations of treatment with parathyroid hormone.

Few previous trials have involved serial measurements of the trabecular and cortical compartments as determined on quantitative CT. Measuring these values may provide insights into how drugs for osteoporosis affect the structure and function of bone. For example, after the cessation of parathyroid hormone therapy, cortical density did not change in either the alendronate or placebo groups over 12 months. However, cortical volume and bone mass increased with alendronate but not with placebo. Increases in cortical volume and mass, with density remaining constant, could improve bone strength and might help explain discrepancies between the relatively small increases in bone density and the larger reductions in the rate of fractures that have been seen with antiresorptive treatments.<sup>12,13</sup> However, to explore more definitively the implications associated with changes in cortical and trabecular bone would require biomechanical modeling,<sup>14</sup> studies in animals, or trials involving fractures in humans.

There are several limitations to this trial. First, it was not large enough to assess the effects of treatment on the rate of fracture, and our conclusions are based on changes in bone mineral density and geometry. However, these changes are remarkably consistent in support of the value of antiresorptive therapy after treatment with parathyroid hormone. The only study of the risk of fracture after parathyroid hormone therapy is a recent 18-month observational, unblinded follow-up after 21 months of teriparatide treatment.<sup>6</sup> This study suggested that teriparatide afforded sustained protection against fracture whether or not antiresorptive therapy was initiated.<sup>6</sup> However, participants self-selected for the use of antiresorptive therapy after parathyroid hormone treatment, making the findings difficult to interpret. Furthermore, one would expect a residual but transient reduction in protection against fracture after treatment with parathyroid hormone without follow-up antiresorptive therapy that might wane over time. Additional studies should address this question. A second limitation is that we cannot be certain that our results are applicable to other types of antiresorptive therapy, including other bisphosphonates. Finally, our study could not address the clinically important question of whether parathyroid hormone can be used successfully after antiresorptive therapy. Some studies (neither randomized nor blinded) have suggested that parathyroid hormone after antiresorptive therapy still has a strong anabolic effect, although the response to parathyroid hormone may be delayed or blunted as a function of the potency and type of antiresorptive therapy.<sup>5,6,15,16</sup>

In summary, increases in bone mineral density during one year of treatment with parathyroid hormone appear to be rapidly lost after therapy is dis-

continued. Treatment with the bisphosphonate alendronate immediately after the discontinuation of parathyroid hormone either maintains or further increases bone mineral density in year 2. We found no evidence that a concurrent combination of parathyroid hormone and alendronate is superior to either agent alone. Our results are consistent with regard to a wide range of end points involving bone density and bone geometry, suggesting that treatment with parathyroid hormone should be followed by antiresorptive therapy to consolidate the gains made in trabecular and cortical bone density during treatment with parathyroid hormone alone.

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#### APPENDIX

In addition to the principal investigators, the following persons participated in the PaTH study: *Columbia University* — K. Lee and J. Sliney (study coordinators); *Minneapolis Veterans Affairs Medical Center* — V. Wyum and N. Michaels; *University of Pittsburgh Medical Center* — J.L. Ryan (study coordinator) and J.M. Wagner; *Maine Center for Osteoporosis Research—St. Joseph Hospital* — L. Fowler and D. Storm (study coordinators); *University of California, San Francisco* — T. Hue (project director), L. Palermo (statistician), D. Sellmeyer, and D.C. Bauer (study physicians); *Data Safety Monitoring Board* — L. Raisz, S. Hui, R. Recker, D. Kiel, and D. Hanley.

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