

ORIGINAL ARTICLE

# The Effects of Parathyroid Hormone, Alendronate, or Both in Men with Osteoporosis

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## ABSTRACT

### BACKGROUND

Because parathyroid hormone increases both bone formation and bone resorption, it is possible that combining parathyroid hormone with an antiresorptive agent will enhance its effect on bone mineral density.

### METHODS

We randomly assigned 83 men who were 46 to 85 years of age and had low bone density to receive alendronate (10 mg daily; 28 men), parathyroid hormone (40  $\mu$ g subcutaneously daily; 27 men), or both (28 men). Alendronate therapy was given for 30 months; parathyroid hormone therapy was begun at month 6. The bone mineral density of the lumbar spine, proximal femur, radial shaft, and total body was measured every six months with the use of dual-energy x-ray absorptiometry. Trabecular bone mineral density of the lumbar spine was measured at base line and month 30 by means of quantitative computed tomography. Serum alkaline phosphatase levels were measured every six months. The primary end point was the rate of change in the bone mineral density at the posteroanterior spine.

### RESULTS

The bone mineral density at the lumbar spine increased significantly more in men treated with parathyroid hormone alone than in those in the other groups ( $P < 0.001$  for both comparisons). The bone mineral density at the femoral neck increased significantly more in the parathyroid hormone group than in the alendronate group ( $P < 0.001$ ) or the combination-therapy group ( $P = 0.01$ ). The bone mineral density of the lumbar spine increased significantly more in the combination-therapy group than in the alendronate group ( $P < 0.001$ ). At 12 months, changes in the serum alkaline phosphatase level were significantly greater in the parathyroid hormone group than in the alendronate group or the combination-therapy group ( $P < 0.001$  for both comparisons).

### CONCLUSIONS

Alendronate impairs the ability of parathyroid hormone to increase the bone mineral density at the lumbar spine and the femoral neck in men. This effect may be attributable to an attenuation of parathyroid hormone–induced stimulation of bone formation by alendronate.

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**O**STEOPOROSIS AFFECTS MORE THAN 20 million people in the United States and leads to about 1.5 million fractures in this country each year.<sup>1</sup> Although osteoporotic fractures are more common in women, about 30 percent of such fractures occur in men.<sup>2</sup>

Alendronate, a potent nitrogen-containing bisphosphonate, inhibits osteoclastic bone resorption.<sup>3</sup> Alendronate increases bone mineral density and reduces the risk of fracture in women<sup>4-6</sup> and men<sup>7,8</sup> with osteoporosis. Once-daily administration of a parathyroid hormone fragment also increases bone mineral density in men with osteoporosis<sup>9,10</sup> and in estrogen-deficient women<sup>11-13</sup> and reduces the risk of fracture in postmenopausal women with osteoporosis.<sup>13</sup> Whereas all other available treatments for osteoporosis reduce bone resorption, parathyroid hormone therapy increases bone formation. Thus, combination therapy with parathyroid hormone and alendronate might increase bone mineral density more than the use of either agent alone. To test this hypothesis, we compared the effects of alendronate alone, parathyroid hormone alone, and the two agents combined in men with osteoporosis.

## METHODS

### STUDY SUBJECTS

We mailed 60,000 recruitment letters to men in the Boston area. Of 1730 men who returned the questionnaire, 575 were interested and were eligible for further screening. Of these men, 380 were disqualified because their bone density was too high, 14 on the basis of screening blood tests, and 83 because they missed screening appointments, leaving 98 men who were eligible for the study. Twenty declined to participate, and an additional five men were recruited from our clinic. Thus, the final cohort consisted of 83 men.

In order to be eligible, men were required to be 46 to 85 years of age and to have a bone mineral density of the lumbar spine in the posteroanterior or lateral projection or of the femoral neck that was at least 2 SD below the mean value for young normal men. They were also required to have a serum calcium level of less than 10.6 mg per deciliter (2.65 mmol per liter), a serum creatinine level of less than 2 mg per deciliter (177  $\mu$ mol per liter), a serum alkaline phosphatase level of less than 150 U per liter, a serum 25-hydroxyvitamin D level of at least 15 ng per milliliter (37 nmol per liter), serum

aspartate aminotransferase and alanine aminotransferase levels that were less than twice the upper limit of the normal range, and normal serum levels of parathyroid hormone, thyrotropin, and testosterone. Men who had disorders or were taking medications that are known to affect bone metabolism and men with nephrolithiasis, active peptic ulcer disease, severe reflux esophagitis, clinically significant cardiac, renal, or hepatic disease, or cancer were excluded.

### STUDY PROTOCOL

The men were randomly assigned by a computerized system to receive alendronate alone (10 mg orally once daily; 28 men), human parathyroid hormone (1-34) alone (40  $\mu$ g subcutaneously once daily; 27 men), or both (28 men). The men were stratified into blocks on the basis of age (<65 years of age or  $\geq$ 65 years of age) and according to the bone mineral density of the spine (higher or lower than 2 SD below the mean for the man's age). Alendronate therapy was begun at the base-line visit and continued for 30 months. Parathyroid hormone therapy was begun at the 6-month visit and continued for 24 months. The study was not double-blind, because the institutional review board at Massachusetts General Hospital considered it unethical to administer placebo injections for two years. The level of calcium intake was estimated by a research dietitian and was maintained at 1000 to 1200 mg daily through diet or supplementation. All the men received 400 U of vitamin D daily.

Blood was collected at base line and at 1, 2, 3, 6, 7, 8, 9, 12, 18, 24, and 30 months for routine chemical analysis, including measurement of serum calcium. Serum calcium was measured before and four to six hours after the administration of a parathyroid hormone injection. Twenty-four-hour urinary calcium excretion was measured every six months and one month after parathyroid hormone therapy began (month 7). Bone mineral density was measured with the use of dual-energy x-ray absorptiometry at base line and every six months thereafter. A standardized questionnaire was administered at each visit to assess side effects that had occurred since the previous study visit. Compliance with the study treatment was assessed with the use of medication diaries and counts of residual medication supplies.

The study was approved by the institutional review board of Massachusetts General Hospital. All the men provided written informed consent.

**PARATHYROID HORMONE PREPARATION AND DOSE ADJUSTMENTS**

Good Manufacturing Practices (GMP)–grade synthetic human parathyroid hormone (1–34) (Bachem) was placed in vials as a sterile freeze-dried powder (with mannitol) under GMP conditions by Ben Venue Laboratories in Bedford, Ohio. Analysis of amino acids and high-pressure liquid chromatography of the parathyroid hormone preparation revealed that each vial contained 37  $\mu\text{g}$  rather than the intended 40  $\mu\text{g}$ .

The dose of parathyroid hormone was reduced by 25 percent if any serum calcium measurement was 10.6 mg per deciliter or higher or if the investigators thought that the man was having a side effect of therapy. If hypercalcemia or symptoms persisted, the dose of parathyroid hormone was reduced by another 25 percent. If hypercalcemia or symptoms persisted after two reductions in the dose, parathyroid hormone therapy was discontinued. If the 24-hour urinary calcium excretion was more than 400 mg per day (10.0 mmol per day), the dietary calcium intake, the dietary sodium intake, or both were reduced by 25 to 50 percent. If hypercalciuria persisted, the dose of parathyroid hormone was reduced by 25 to 50 percent, as described above. If hypercalciuria persisted after a 50 percent reduction in the dose, parathyroid hormone therapy was discontinued.

**MEASUREMENTS OF BONE MINERAL DENSITY**

The bone mineral density of the lumbar spine in the posteroanterior and lateral projections, the proximal femur, the distal one third of the radial shaft, and the total body was measured with the use of dual-energy x-ray absorptiometry and a densitometer (Hologic QDR 4500A, Hologic). For the radial shaft, two measurements were obtained at each visit, and the mean of the two values was used in all analyses. The standard deviations for our short-term *in vivo* measurements were 0.005 g per square centimeter for the posteroanterior spine, 0.014 g per square centimeter for the lateral spine, 0.007 g per square centimeter for the femoral neck, and 0.006 g per square centimeter for the total hip. Individual vertebrae with obvious deformities or areas of focal sclerosis were excluded from analyses. Spine scans were excluded if the estimate of the x-ray attenuation exceeded the manufacturer's recommended limit. Total-body scans were analyzed without inclusion of the head region, because scans of this region often contain artifacts.<sup>14</sup> All bone-density

scans were analyzed by persons who were unaware of the treatment-group assignments.

Trabecular bone mineral density of the lumbar spine was determined with the use of quantitative computed tomography (CT) (General Electric Model QXI or Lightspeed Plus scanner). Axial scans of the first four lumbar vertebrae were obtained through the midbody. The density of trabecular bone was determined by means of comparison with an internal hydroxyapatite standard, and the values obtained for the vertebrae were then averaged. The precision error for this technique is 3 to 5 mg per cubic centimeter.<sup>15</sup>

**STATISTICAL ANALYSIS**

The predetermined primary end point was the change in the bone mineral density of the posteroanterior lumbar spine. Our prespecified analysis was to use data on the bone mineral density measured only while the men were receiving active therapy — that is, from month 0 to month 30 in the alendronate group and the combination-therapy group and from month 6 to month 30 in the parathyroid hormone group — and to assess changes in the serum alkaline phosphatase level only while it was changing monotonically (i.e., until month 12). A mixed-model analysis of variance was used to assess the effect of treatment on each variable. Our analysis assumes that the bone mineral density at each skeletal location changes at a different pace in each man.

In the mixed-model analysis of variance, the factors were the particular man, time, the treatment, and the interactions between the man and time and the treatment and time. The F ratio was the ratio of the interaction between the treatment and time to the interaction between the man and time (i.e., the error term). This model was used to test whether the differences in the average slopes among treatment groups were greater than expected, given the differences in slopes among individual men. Our analysis prespecified that if the F ratio was statistically significant (indicated an overall difference among treatment groups), we would then examine the average slopes of specific treatment groups in pairwise comparisons, using the least-squares means from the same analysis of variance. Baseline values were compared with the use of analysis of variance. Rates of adverse events were compared with the use of Fisher's exact test.

Data were analyzed in two ways: first with the inclusion of only those data obtained while the men

were taking their assigned treatment (per-protocol analysis) and then separately with the inclusion of all data, regardless of whether the men continued to take their assigned treatment (intention-to-treat analysis). Ten men (seven in the parathyroid hormone group and three in the combination-therapy group) discontinued participation before any follow-up measurements of bone density could be obtained during treatment with their assigned study medication, and data for these men are not included in any longitudinal analyses. An additional six men (one in the alendronate group, three in the parathyroid hormone group, and two in the combination-therapy group) discontinued the study treatment before any repeated measurements of bone density could be obtained but did return for bone-density measurements. Their data are included only in the intention-to-treat analyses. Four men (two in the alendronate group and two in the combination-therapy group) discontinued the study treatment after at least one repeated measurement of bone density had been obtained during treatment with their assigned medication. Results in these men are included in both the per-protocol analysis and the intention-to-treat analysis for the period when they were taking their assigned study medication but are included only in the intention-to-treat analysis thereafter. Because the results of the two types of analysis were essentially identical, only the results of the intention-to-treat analysis are presented.

One interim analysis was performed. It did not affect any aspects of the study. All P values are two-sided, and no adjustments were made for multiple statistical tests. Unless otherwise noted, data are presented as means  $\pm$ SD.

## RESULTS

### CHARACTERISTICS OF THE MEN

The base-line characteristics of the 73 men included in the intention-to-treat analysis (28 in the alendronate group, 20 in the parathyroid hormone group, and 25 in the combination-therapy group) are shown in Table 1. Two men were Asian, 2 were Indian, 1 was black, 1 was a Pacific Islander, and the remaining 67 were non-Hispanic white. There were no significant differences in base-line characteristics among the treatment groups. The base-line characteristics were also similar among all 83 men who underwent randomization (data not shown). None of the men had received previous drug therapy for osteoporosis.

### ADHERENCE TO STUDY TREATMENT

Of the 20 men who discontinued treatment, 3 were in the alendronate group, 10 in the parathyroid hormone group, and 7 in the combination-therapy group. Most of these men discontinued parathyroid hormone therapy because of discomfort or inconvenience related to the injections.

All but three of the remaining men took at least 95 percent of their doses of alendronate, and all but nine took at least 95 percent of their doses of parathyroid hormone. However, these 12 men took at least 80 percent of their doses of medication. As noted above, 10 men discontinued treatment before any follow-up measurements of bone density could be obtained during treatment with their assigned study medication. Five men in the parathyroid hormone group and five in the combination-therapy group had their dose of parathyroid hormone reduced by 25 percent, and five men in each of these groups had their dose reduced by 50 percent.

### BONE MINERAL DENSITY AND ALKALINE PHOSPHATASE

The bone mineral density at the posteroanterior spine increased more in men treated with parathyroid hormone alone than in those treated with alendronate alone or with the combination of the two ( $P < 0.001$  for both comparisons), even though the period of active treatment was six months shorter with parathyroid hormone alone than with alendronate (Fig. 1 and Table 2). The bone mineral density at the posteroanterior spine increased more with combination therapy than with alendronate alone ( $P < 0.001$ ). The bone mineral density at the lateral spine also increased more in the parathyroid hormone group than in the alendronate group or the combination-therapy group ( $P < 0.001$  for both comparisons) and increased more in the combination-therapy group than in the alendronate group ( $P = 0.02$ ).

The bone mineral density at the femoral neck increased more in the parathyroid hormone group than in the alendronate group ( $P < 0.001$ ) or the combination-therapy group ( $P = 0.01$ ). There was no significant difference between the alendronate group and the combination-therapy group in the changes in the bone mineral density at the femoral neck ( $P = 0.18$ ). The bone mineral density at the total hip increased more in the parathyroid hormone group than in the alendronate group ( $P = 0.005$ ). There were no significant differences in the changes in the density at the total hip between the alendronate

**Table 1. Base-Line Characteristics of Men with Osteoporosis Treated with Alendronate Alone, Parathyroid Hormone Alone, or Both.\***

Characteristic	Alendronate Group (N=28)	Parathyroid Hormone Group (N=20)	Combination-Therapy Group (N=25)	P Value
Age (yr)	58±7	57±9	58±8	0.84
Height (cm)	174.6±5.4	175.7±4.9	174.8±5.5	0.78
Weight (kg)	77.4±9.5	79.3±12.8	77.1±8.0	0.74
Body-mass index	25.3±2.6	25.7±4.3	25.2±2.6	0.87
Calcium intake (mg/day)	1115±688	1051±542	1249±588	0.55
Serum testosterone level (ng/dl)	485±137	456±85	546±146	0.06
Serum 25-hydroxyvitamin D level (ng/ml)	24±10	23±8	27±12	0.33
Serum parathyroid hormone level (pg/ml)	39±12	38±13	32±12	0.17
Serum alkaline phosphatase level (U/liter)	71±17	76±26	76±15	0.56
Bone mineral density (g/cm <sup>2</sup> )				
Posteroanterior spine	0.851±0.113	0.885±0.122	0.852±0.093	0.49
Lateral spine	0.646±0.078	0.676±0.075	0.667±0.053	0.39
Femoral neck	0.670±0.106	0.703±0.085	0.695±0.075	0.43
Total hip	0.835±0.113	0.889±0.097	0.876±0.090	0.15
Radial shaft	0.751±0.066	0.760±0.052	0.772±0.060	0.45
Total body	0.977±0.106	1.011±0.097	0.993±0.090	0.51
Spinal trabecular bone density on quantitative CT (mg/cm <sup>3</sup> )	92±23	96±22	96±24	0.70

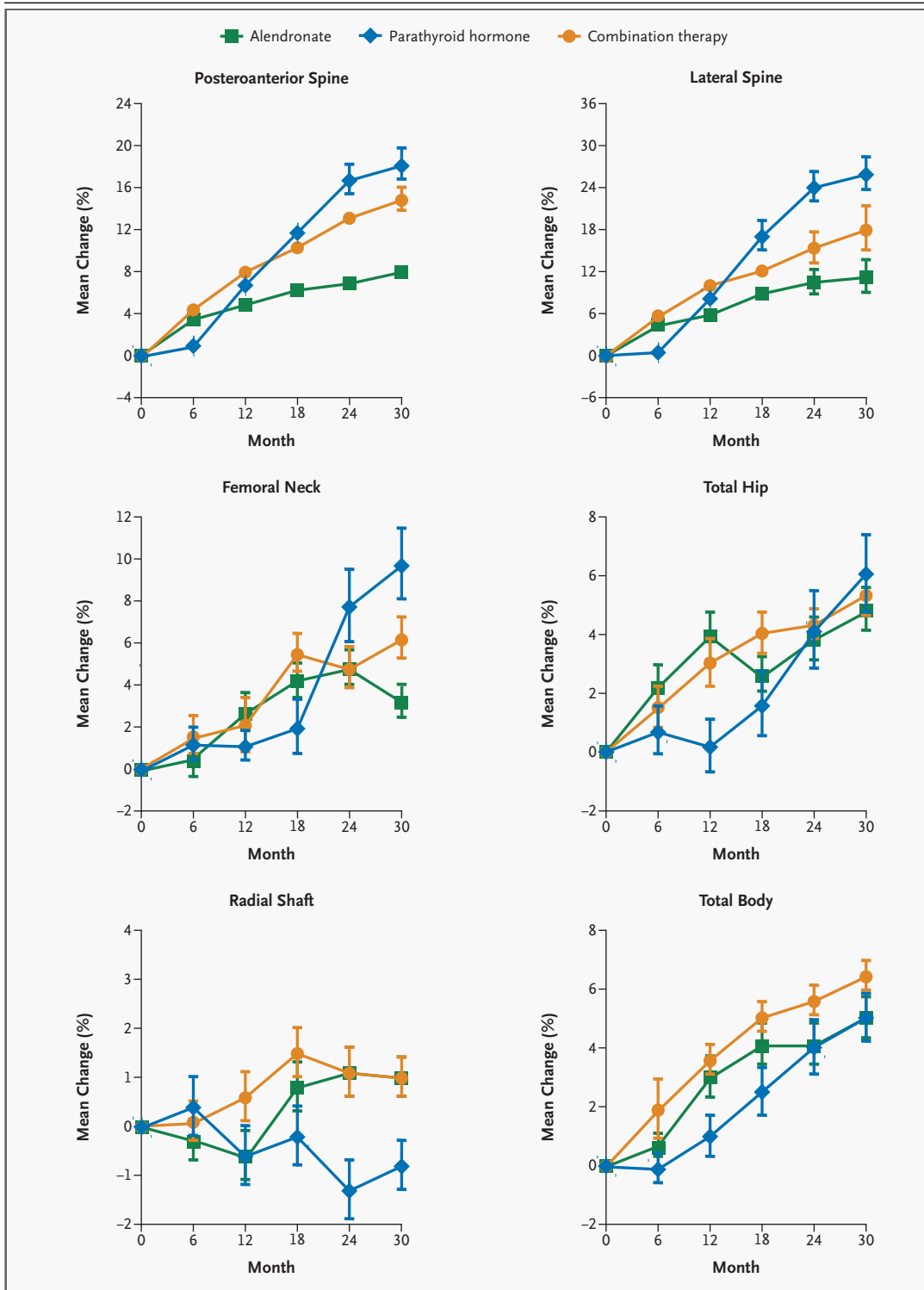
\* The data shown are for the men in the intention-to-treat population. Plus–minus values are means ±SD. P values are for the three-way comparisons and were determined by analysis of variance. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert values for testosterone to nanomoles per liter, multiply by 0.0347. To convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.

group and the combination-therapy group ( $P=0.20$ ) or between the parathyroid hormone group and the combination-therapy group ( $P=0.08$ ). The bone mineral density at the radial shaft increased slightly in the alendronate group and the combination-therapy group and decreased slightly in the parathyroid hormone group ( $P=0.002$  for the comparison between the parathyroid hormone group and the alendronate group;  $P=0.009$  for the comparison between the parathyroid hormone group and the combination-therapy group). There were no significant differences among groups in the changes in total-body bone mineral density ( $P=0.60$  for the three-way comparison).

The trabecular bone mineral density at the spine increased more in the parathyroid hormone group than in the other two groups ( $P<0.001$  for both comparisons) and also increased more in the combination-therapy group than in the alendronate group ( $P=0.005$ ) (Fig. 2). The serum total alkaline phosphatase level decreased in the alendronate group,

**Figure 1 (facing page). Mean Percent Changes in the Bone Mineral Density of the Posteroanterior Spine, the Lateral Spine, the Femoral Neck, the Total Hip, the Distal One Third of the Radial Shaft, and the Total Body, as Determined with Dual-Energy X-Ray Absorptiometry.**

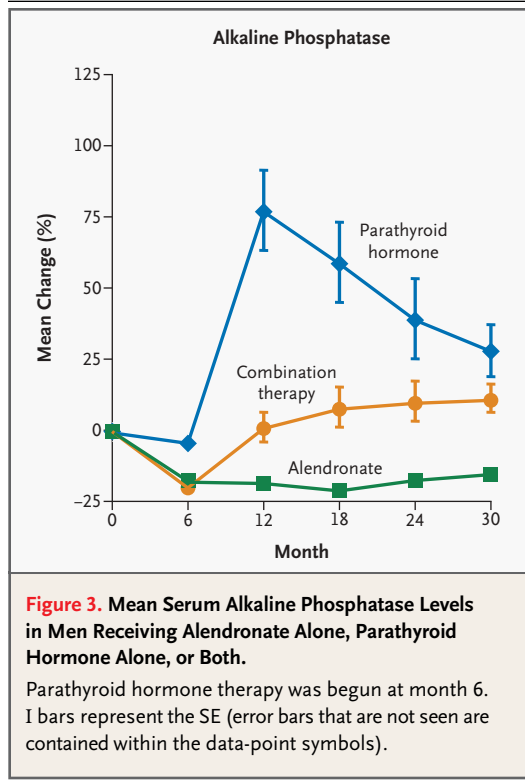
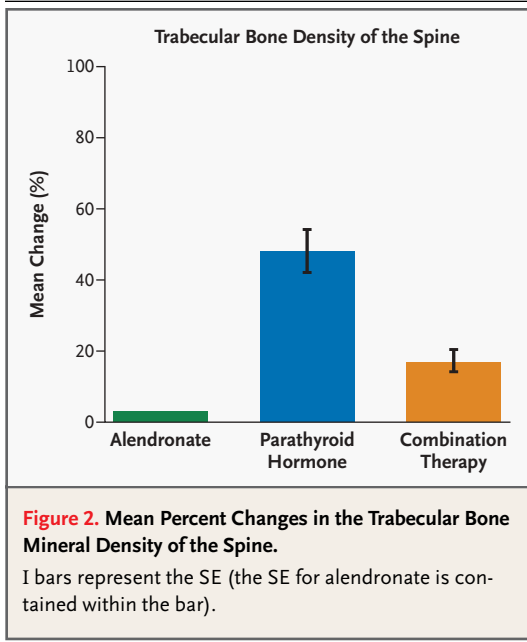
Parathyroid hormone therapy was begun at month 6. For the posteroanterior spine, each plotted value is based on 27 or 28 men in the alendronate group, 18 to 20 in the parathyroid hormone group, and 22 to 25 in the combination-therapy group. For the lateral spine, each plotted value is based on 22 to 24 men in the alendronate group, 15 or 16 in the parathyroid hormone group, and 16 to 21 in the combination-therapy group. For the femoral neck and the total hip, each plotted value is based on 26 or 27 men in the alendronate group, 18 to 20 in the parathyroid hormone group, and 22 to 25 in the combination-therapy group. For the distal one third of the radial shaft and the total body, each plotted value is based on 27 or 28 men in the alendronate group, 17 to 20 in the parathyroid hormone group, and 22 to 25 in the combination-therapy group. I bars represent the SE (error bars that are not seen are contained within the data-point symbols).



**Table 2. Mean Percent Changes in Bone Mineral Density at Month 30 and Rates of Change among Men Treated with Alendronate Alone, Parathyroid Hormone Alone, or Both.\***

Bone Site	Alendronate Group			Parathyroid Hormone Group			Combination-Therapy Group			P Value		
	Mean Percent Change (95% CI)	Mean Rate of Change (95% CI)	Mean Percent Change (95% CI)	Mean Rate of Change (95% CI)	Mean Percent Change (95% CI)	Mean Rate of Change (95% CI)	Mean Percent Change (95% CI)	Mean Rate of Change (95% CI)	Three-Way Comparison	Alendronate vs. Parathyroid Hormone	Alendronate vs. Combination Therapy	Parathyroid Hormone vs. Combination Therapy
Posteroanterior spine	7.9 (6.3 to 9.4)	0.063 (0.043 to 0.082)	18.1 (14.9 to 21.3)	0.146 (0.126 to 0.167)	14.8 (12.4 to 17.3)	0.125 (0.104 to 0.146)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Lateral spine	11.1 (6.3 to 15.8)	0.068 (0.038 to 0.098)	25.8 (20.9 to 30.6)	0.172 (0.140 to 0.203)	18.0 (11.4 to 24.7)	0.124 (0.092 to 0.156)	<0.001	<0.001	<0.001	<0.001	0.02	<0.01
Femoral neck	3.2 (1.5 to 4.8)	0.030 (0.015 to 0.044)	9.7 (6.1 to 13.4)	0.063 (0.046 to 0.079)	6.2 (4.0 to 8.4)	0.044 (0.029 to 0.059)	0.001	<0.001	0.001	<0.001	0.18	0.001
Total hip	4.8 (3.3 to 6.3)	0.031 (0.019 to 0.043)	6.4 (3.6 to 9.1)	0.050 (0.037 to 0.065)	5.3 (3.8 to 6.8)	0.043 (0.030 to 0.056)	0.02	0.005	0.02	0.005	0.20	0.08
Radial shaft	1.0 (0.2 to 1.8)	0.011 (0.003 to 0.019)	-0.8 (-2.3 to 0.6)	-0.012 (-0.022 to -0.001)	1.0 (-0.1 to 2.1)	0.007 (-0.001 to 0.016)	0.007	0.002	0.007	0.002	0.56	0.009
Total body	5.0 (3.6 to 6.3)	0.052 (0.038 to 0.065)	5.0 (3.2 to 6.7)	0.049 (0.034 to 0.064)	6.4 (5.4 to 7.4)	0.060 (0.046 to 0.074)	0.60	0.42	0.60	0.42	0.38	0.95
Spinal trabecular bone density on quantitative CT	3 (0 to 6)	2 (-4 to 8)	48 (35 to 61)	46 (39 to 53)	17 (10 to 24)	15 (8 to 21)	<0.001	<0.001	<0.001	<0.001	0.005	<0.001

\* The rates of change were determined by an analysis of the slopes; data for the rates of change are reported in grams per square centimeter per 30 months, except for the data for the rate of change in spinal trabecular bone density on quantitative CT, which are reported in milligrams per cubic centimeter per 30 months. P values are for comparisons of the rates of change; P values for the three-way comparisons were calculated by analysis of variance. Negative changes represent decreases. CI denotes confidence interval.



peaked at 12 months and then decreased in the parathyroid hormone group, and decreased until month 6 and then increased in the combination-therapy group (Fig. 3). The peak serum alkaline phosphatase levels at month 12 were significantly higher in the parathyroid hormone group than in the other two groups ( $P < 0.001$  for both comparisons) but did not differ significantly between the alendronate group and the combination-therapy group ( $P = 0.14$ ).

**ADVERSE EVENTS**

Hypercalcemia did not occur in any man in the alendronate group. When serum calcium was measured approximately 24 hours after the administration of parathyroid hormone, no serum calcium values were elevated in the men in the parathyroid hormone group, and 0.9 percent of the values were elevated in the men in the combination-therapy group ( $P = 0.20$ ). When the level was measured approximately four hours after a dose of parathyroid hormone, 3.9 percent of serum calcium values in men in the parathyroid hormone group were elevated, as were 1.1 percent of the values in the men in the combination-therapy group ( $P = 0.15$ ). Only one serum calcium measurement was above 11 mg per deciliter (2.75 mmol per liter); this measurement was 11.5 mg per deciliter (2.88 mmol per liter). Urinary calcium excretion was greater than 400 mg per day in 2.1 percent of urine samples from the men in the

alendronate group, 6.0 percent of samples from the men in the parathyroid hormone group, and 10.5 percent of samples from the men in the combination-therapy group ( $P = 0.004$  for the comparison between the alendronate group and the combination-therapy group).

Table 3 shows the percentage of visits at which men reported side effects. There were several differences among the treatment groups, but these differences were generally small.

**DISCUSSION**

We found that the administration of alendronate, a potent inhibitor of bone resorption, is associated with a decrease in the ability of once-daily parathyroid hormone therapy to increase the bone mineral density at the spine and the femoral neck. Alendronate also reduced the parathyroid hormone-associated increase in the serum total alkaline phosphatase levels, which reflect the stimulation of osteoblast activity by parathyroid hormone.<sup>16</sup> This finding suggests that alendronate impairs the ability of parathyroid hormone to stimulate new bone formation in men. Although the combination of parathyroid hormone and alendronate increased

**Table 3. Percentage of Visits at Which Men Reported Side Effects.\***

Side Effect	Alendronate Group (N=28)	Parathyroid Hormone Group (N=20)	Combination-Therapy Group (N=25)	P Value			
				Three-Way Comparison	Alendronate vs. Parathyroid Hormone	Alendronate vs. Combination Therapy	Parathyroid Hormone vs. Combination Therapy
	<i>% of visits</i>						
Headache	11	16	21	0.002	0.05	<0.001	0.16
Dizziness	4	7	8	0.03	0.05	0.01	0.65
Mood swings	4	6	7	0.43	0.45	0.22	0.86
Joint pain	33	54	43	<0.001	<0.001	0.01	0.01
Bone pain	4	7	9	0.06	0.21	0.02	0.35
Back pain	26	38	29	0.008	0.003	0.47	0.03
Muscle aches	24	26	29	0.44	0.57	0.21	0.57
Chest pain	8	3	6	0.04	0.02	0.44	0.12
Shortness of breath	6	5	11	0.01	0.60	0.03	0.007
Nausea	3	5	7	0.05	0.14	0.02	0.49
Constipation	8	12	8	0.27	0.16	0.88	0.21
Bloating	6	7	10	0.15	0.73	0.07	0.18
Heartburn	18	20	25	0.10	0.46	0.04	0.23
Diarrhea	9	7	10	0.58	0.46	0.89	0.37
Gas	17	16	20	0.45	1.00	0.30	0.28
Frequent urination	25	22	22	0.67	0.50	0.45	0.92
Discomfort at injection site	NA	18	17	NA	NA	NA	0.75

\* P values were calculated with the use of Fisher's exact test. NA denotes not applicable.

the bone mineral density at the spine more effectively than alendronate alone, the combination was clearly inferior to parathyroid hormone alone. At the radial shaft, a skeletal site composed predominantly of non-weight-bearing cortical bone, the combination of parathyroid hormone and alendronate prevented the parathyroid hormone-induced decrease in bone density. All three treatments had similar effects on total-body bone mineral density. These effects are remarkably similar to those of alendronate monotherapy, parathyroid hormone monotherapy, and combination therapy on bone mineral density in women with postmenopausal osteoporosis.<sup>17,18</sup>

Several studies in animals have examined the effects of antiresorptive agents on the anabolic effect of parathyroid hormone on bone. In rats, neither calcitonin nor estrogen nor bisphosphonates block the anabolic activity of parathyroid hormone, which suggests that bone resorption is not essen-

tial for this activity.<sup>19-23</sup> In contrast, tiludronate completely blocks the ability of parathyroid hormone to increase bone formation and bone mass in sheep.<sup>24</sup>

In postmenopausal women who were receiving long-term postmenopausal hormone therapy, the addition of parathyroid hormone increased the bone mineral density of the lumbar spine, total hip, and total body more than the continuation of hormone therapy alone.<sup>25,26</sup> Because neither of these studies<sup>25,26</sup> included a group of subjects who were treated with parathyroid hormone alone, it is not possible to determine whether postmenopausal hormone therapy augments, has no effect on, or reduces the ability of parathyroid hormone to increase bone mineral density. In postmenopausal women, the cyclic administration of parathyroid hormone alone tended to increase the bone mineral density at the spine more than cyclic therapy with parathyroid hormone followed by calcitonin, although the difference was not significant.<sup>27,28</sup> Parathyroid hor-

hormone therapy also increased bone formation and bone mineral density less in postmenopausal women who had previously been treated with alendronate than in those who had previously been treated with raloxifene.<sup>29</sup> Because alendronate is a more potent antiresorptive agent than raloxifene, these results are consistent with the idea that antiresorptive agents mitigate the anabolic effects of parathyroid hormone.

Parathyroid hormone therapy was particularly effective at increasing the bone mineral density in the spine, a skeletal site composed mainly of trabecular bone, as was the case in previous studies in humans and animals.<sup>13,30</sup> This treatment clearly caused a greater increase in the spinal bone mineral density in men than alendronate monotherapy—a finding that is similar to that in a previous report on postmenopausal women.<sup>31</sup> Parathyroid hormone therapy reduced the bone mineral density at the radial shaft, an effect that is also similar to the effect at this site in postmenopausal women.<sup>13,17,27,32</sup> In contrast, parathyroid hormone therapy increased the total-body bone mineral density (a skeletal measurement that primarily involves cortical bone), an effect again similar to that of parathyroid hormone therapy in postmenopausal women.<sup>13</sup>

The increases in femoral-neck bone mineral density in our study were most marked between 12 and 24 months after the start of parathyroid hormone therapy. Thus, parathyroid hormone may need to be administered for more than 12 months in order to achieve optimal benefits at this site.

Parathyroid hormone may exert its anabolic effect on bone either through a direct stimulatory effect on osteoblastic bone formation or indirectly through a mechanism that requires it to increase osteoclastic bone resorption. For example, parathyroid hormone might stimulate bone formation directly by increasing the local production of insulin-like growth factor I or other bone-stimulating growth factors.<sup>33,34</sup> If parathyroid hormone stimulates bone formation directly, a reduction in bone resorption should not mitigate its anabolic effect on bone. Parathyroid hormone also stimulates bone resorption, thereby releasing preformed growth factors that are adsorbed to bone matrix, such as insulin-like growth factor I and transforming growth

factor  $\beta$ .<sup>35</sup> If these growth factors participate in the mechanism whereby parathyroid hormone stimulates bone formation, suppressing bone resorption should impair the anabolic activity of parathyroid hormone. Our findings that alendronate reduces the ability of parathyroid hormone to increase the activity of serum alkaline phosphatase and reduces the ability of parathyroid hormone to increase the bone mineral density at the spine and femoral neck are consistent with the hypothesis that the anabolic effect of parathyroid hormone depends, at least in part, on its ability to induce bone resorption.

The dose of parathyroid hormone used in this study (37  $\mu$ g) was higher than that currently approved by the Food and Drug Administration (20  $\mu$ g) but similar to the dose used in many clinical studies of parathyroid hormone.<sup>10-13,36</sup> Thus, alendronate might further impair the ability of a lower dose of parathyroid hormone to increase bone mineral density. Differences in changes in bone density between men treated with alendronate alone and those treated with parathyroid hormone alone might also be less evident with a lower dose of parathyroid hormone. The start of parathyroid hormone therapy was delayed for six months so that bone resorption would be maximally suppressed by alendronate in the men who received combination therapy.<sup>37</sup> Different effects might be observed if parathyroid hormone therapy and alendronate therapy were begun simultaneously.

In summary, alendronate impairs the ability of parathyroid hormone to increase bone mineral density at the lumbar spine and femoral neck in men with osteoporosis. Alendronate prevents parathyroid hormone–induced mineral loss from non-weight-bearing cortical-bone sites. The consequences of these complex effects on the risk of fracture are unknown. Additional studies are needed before combinations of antiresorptive agents and parathyroid hormone can be recommended for the treatment of men with osteoporosis.

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