

ORIGINAL ARTICLE

Daily and Cyclic Parathyroid Hormone in Women Receiving Alendronate

Felicia Cosman, M.D., Jeri Nieves, Ph.D., Marsha Zion, M.S., Lillian Woelfert, R.N., Marjorie Luckey, M.D., and Robert Lindsay, M.D.

ABSTRACT

BACKGROUND

We evaluated whether patients with osteoporosis treated with long-term alendronate have a response to parathyroid hormone treatment and whether short, three-month cycles of parathyroid hormone therapy could be as effective as daily administration.

METHODS

We randomly assigned 126 women with osteoporosis who had been taking alendronate for at least 1 year to continued alendronate plus parathyroid hormone (1–34) subcutaneously daily, continued alendronate plus parathyroid hormone (1–34) subcutaneously daily for three 3-month cycles alternating with 3-month periods without parathyroid hormone, or alendronate alone for 15 months.

RESULTS

In both parathyroid hormone groups, bone formation indexes rose swiftly. Among the women who were receiving cyclic parathyroid hormone, bone formation declined during cycles without parathyroid hormone and increased again during cycles with parathyroid hormone. Bone resorption increased in both parathyroid hormone groups but increased progressively more in the daily-treatment group than in the cyclic-therapy group. Spinal bone mineral density rose 6.1 percent in the daily-treatment group and 5.4 percent in the cyclic-therapy group ($P < 0.001$ for each parathyroid hormone group as compared with the alendronate group and no significant difference between parathyroid hormone groups). One woman in the daily-treatment group, two in the cyclic-therapy group, and four in the alendronate group had new or worsening vertebral deformities.

CONCLUSIONS

This study suggests that a regimen of three-month cycles of parathyroid hormone alternating with three-month cycles without parathyroid hormone causes the early phase of action of parathyroid hormone (characterized by pure stimulation of bone formation) to be dissociated from the later phase (activation of bone remodeling). The early phase may be more important to the increase in spinal bone mineral density. In patients with persistent osteoporosis after prior alendronate treatment, both daily treatment and cyclic treatment with parathyroid hormone increase spinal bone mineral density.

From the Clinical Research Center, Helen Hayes Hospital, West Haverstraw, N.Y. (F.C., J.N., M.Z., L.W., R.L.); the Department of Medicine, College of Physicians and Surgeons (F.C., R.L.), and the Department of Epidemiology, Mailman School of Public Health (J.N.), Columbia University, New York; Saint Barnabas Osteoporosis and Metabolic Bone Disease Center, Livingston, N.J. (M.L.); and the Department of Medicine, Mount Sinai Medical Center, New York (M.L.). Address reprint requests to Dr. Cosman at the Regional Bone Center, Helen Hayes Hospital, Route 9W, West Haverstraw, NY 10993, or at cosmanf@helenhayeshosp.org.

N Engl J Med 2005;353:566-75.
Copyright © 2005 Massachusetts Medical Society.

THE USE OF RECOMBINANT HUMAN parathyroid hormone is a novel therapy for osteoporosis with a unique mechanism of action. In contrast to antiresorptive agents, which reduce bone remodeling,¹⁻⁵ parathyroid hormone initially stimulates bone formation and later increases bone remodeling.⁶ Biochemical indexes of bone formation increase within one month.⁷⁻¹⁰ Within six months, indexes of bone resorption are similarly elevated.^{7,8} In addition, histomorphometric analyses indicate a dramatic increase in the formation of cancellous bone within four weeks,¹¹⁻¹³ providing evidence that parathyroid hormone stimulates formation without prior resorption. During daily administration of parathyroid hormone, indexes of bone remodeling peak and plateau over a period of 6 to 12 months and then decline.^{8,9} The cause of this apparent resistance to continued treatment is unknown. Multiple studies confirm that parathyroid hormone is highly effective at increasing bone mineral density in various populations,^{6-9,14-19} with the most rapid increment, consistent with the biochemical data, within the first 6 to 12 months.⁶⁻⁸ Both the early anabolic window (formation before resorption) and the subsequent resistance to parathyroid hormone suggest that to increase bone mineral density, parathyroid hormone might best be used for periods of 6 to 12 months or less.

Data from several recent studies raise questions about the effectiveness of administering parathyroid hormone with alendronate both in women who have not previously been treated for osteoporosis²⁰ and in those pretreated with alendronate.²¹⁻²³ Patients previously treated with alendronate constitute a large group for whom parathyroid hormone treatment might be indicated, and it is critical to determine whether parathyroid hormone works in these patients.

The objectives of this study were to determine whether parathyroid hormone therapy could improve bone mineral density and biochemical markers of bone turnover in women who had received and were still receiving alendronate and to determine whether short cycles of parathyroid hormone treatment, alternating with periods without parathyroid hormone, which take advantage of the widest window between bone formation and resorption, could produce increments in bone mineral density similar to those induced by daily therapy.

METHODS

SUBJECTS

Volunteers were recruited to Helen Hayes Hospital (West Haverstraw, N.Y.) through our osteoporosis screening center and osteoporosis clinic (1268 women), as well as through local newspaper advertisements and posters (65 women). Twelve potential subjects were identified at the Saint Barnabas Osteoporosis Center (Livingston, N.J.). Of these candidates, 736 were eligible for prescreening to determine their interest in the study and whether they met basic inclusion criteria. After undergoing a prescreening telephone interview, 499 women declined to participate or were ineligible and 209 women attended on-site screening to provide informed consent and undergo a medical interview, physical examination, laboratory evaluation, and measurement of bone mineral density.

Exclusion criteria included rheumatoid arthritis, multiple prior renal stones or a kidney stone within the preceding five years, or current use of glucocorticoids, antiepileptic medications, or estrogen. Subjects were required to have a bone mineral density T score of -2.5 or less at the lumbar spine (two or more vertebrae could be evaluated), femoral neck, or total hip or a T score of -2 or less at any of these sites plus a history of fracture in adulthood (defined as an age of at least 40 years) or vertebral fracture (identified by radiography), but excluding fractures caused by trauma (motor vehicle accidents) and finger, toe, and skull fractures. Normal levels of serum creatinine, total calcium (upper limit, 10.6 mg per deciliter [2.65 mmol per liter]), parathyroid hormone, and thyrotropin; normal liver function and complete blood count; and a ratio of urinary calcium to creatinine of less than 0.35 mg per milligram (1.0 mmol per millimole) after an overnight fast were prerequisites. Subjects with 25-hydroxyvitamin D levels of less than 20 ng per milliliter (50 nmol per liter) received supplements of vitamin D and were enrolled after levels rose to at least 20 ng per milliliter. Seventy-eight women were excluded from the study: 43 did not meet criteria for bone density, fracture, or both; 31 had abnormal laboratory values; and 4 were taking other medications concomitantly. Five women chose not to participate in the study after meeting eligibility criteria.

This study was approved by the institutional review board of Helen Hayes Hospital; all participants

provided written informed consent. A data and safety monitoring board designated by the National Institutes of Health (National Institute of Arthritis, Musculoskeletal, and Skin Diseases) monitored the conduct, safety, and progress of the study. The study began February 24, 2000, and was completed January 7, 2004. Dr. Cosman designed the study, with advice from Drs. Lindsay and Nieves. Drs. Cosman and Lindsay obtained funding. Dr. Cosman and Ms. Woelfert recruited subjects, with help from Drs. Lindsay and Luckey. Dr. Cosman and Ms. Woelfert were responsible for patient care and supervision of data collection, and Dr. Lindsay monitored safety and outcome data. Ms. Zion performed all primary data analyses with advice from Dr. Nieves, and they both vouch for the integrity of the data and analyses. Dr. Cosman wrote the manuscript with help from Drs. Lindsay, Nieves, and Luckey and Ms. Zion. There were no pharmaceutical sponsors, and the influence of the sponsor, the National Institute of Arthritis, Musculoskeletal, and Skin Diseases, was limited to the data and safety monitoring board.

Baseline Measurements

Baseline serum samples were obtained from the women the morning after an overnight fast. Serum levels of intact parathyroid hormone were measured by an iodine-125 radioimmunoassay (Nichols Institute). Serum levels of 25-hydroxyvitamin D were measured by an iodine-125 radioimmunoassay (Diasorin). Indexes of bone formation were determined as follows: bone-specific alkaline phosphatase was measured by enzyme immunoassay (Quidel), osteocalcin was measured by an immunoradiometric assay (Immutopics), and N-terminal propeptide of type I procollagen was measured by an Osteomark enzyme-linked immunosorbent assay (Ostex International). Baseline second-void fasting urine samples were analyzed for bone resorption by measuring the levels of cross-linked urinary N-telopeptide with the use of an enzyme-linked immunosorbent assay (Ostex International) and creatinine. Serum and urinary calcium and urinary creatinine were assayed by standard automated methods. All intra-assay coefficients of variation were less than 8.3 percent, and interassay coefficients of variation were less than 13.7 percent.

Baseline bone mineral density at the spine, at the hip, and of the total body was measured with the use of the Lunar Prodigy (General Electric/Lunar). In vivo the short-term precision of this approach

was 0.7 percent for spinal measurements and 0.9 percent for total-hip measurements; the long-term precision (two years) of this approach was lower than 1.7 percent for all sites. Lateral thoracic and lumbar spine radiographs were obtained at baseline for the determination of the prevalence of vertebral fractures.

Treatment

Subjects were randomly assigned by a computer, in blocks of 18, to receive 70 mg of alendronate weekly (43 women), daily parathyroid hormone plus alendronate (43 women), or cyclic parathyroid hormone plus alendronate (40 women) for 15 months. Daily parathyroid hormone was administered subcutaneously as synthetic human parathyroid hormone (1–34) in a daily dose of 25 µg. Cyclic parathyroid hormone was administered in the same fashion at the same dose, except that each treatment cycle lasted three months and was followed by three months without parathyroid hormone. Calcium intake was assessed by means of a food-frequency questionnaire, and all subjects maintained their total calcium intake (with supplements given when necessary) between 1200 and 1500 mg per day. Vitamin D supplementation was provided to achieve levels of 25-hydroxyvitamin D of more than 20 ng per milliliter. There were no placebo injections. Both the study nurse and the physician were aware of a woman's treatment-group assignment but were unaware of study outcomes. Those responsible for outcome measurements were unaware of the women's treatment assignments.

Parathyroid hormone was synthesized by Bachem, inserted into vials by Bionebraska/Restoragen, and tested for bioactivity with the use of the chick hypercalcemia assay (TNO Bibra International). Subjects self-injected parathyroid hormone, rotating sites, with 56 percent of the women using both the abdomen and thighs, 30 percent using solely the thighs, and 14 percent using solely the abdomen. Most subjects administered the medication in the morning, though two administered it in the evening. There were no significant differences in the changes in bone mineral density at the lumbar spine among women injecting parathyroid hormone primarily into their thigh, women who used primarily abdominal sites, and women who used both sites.

Follow-up Measurements

Fasting morning blood samples and second-void urine samples were obtained approximately 24

hours after the last injection. Efficacy biochemical analyses (bone formation and resorption variables), selected safety biochemical analyses (serum calcium and ratio of urinary calcium to creatinine), and measurements of bone mineral density at the spine and hip were performed every three months. Additional safety biochemical analyses (creatinine levels, liver-function tests, and a complete blood count) were performed at 12 months with the use of standard automated techniques. Measurement of bone mineral density of the total body and lateral thoracolumbar radiography were repeated at 15 months.

Determination of Vertebral Fractures

Spine radiographs were digitized by BioImaging Technologies. Points were placed on end plates of T4 to L5, and height ratios were calculated.²⁴⁻²⁶ Prevalent fractures were defined by ratios 3 or more SD below the mean of a reference population.²⁷ Incident vertebral fractures (new or worsening) were defined by a decrease of at least 20 percent in one of the heights by morphometric assessment,^{28,29} if also confirmed by semiquantitative review by two investigators, who were unaware of the results of quantitative analyses. One subject was found to have an incidental vertebral fracture by semiquantitative review alone. Radiographs were reviewed in chronologic sequence, with treatment-group assignment and patient identifiers removed.

Statistical Analysis

The preplanned primary hypothesis was that both parathyroid hormone regimens would induce an increase in spinal bone mineral density as compared with alendronate alone and that the magnitude of this increment would be similar in the two groups. The study had a statistical power of 90 percent to detect an absolute difference of 3 percent in the spinal bone mineral density increment between the two parathyroid hormone groups, given the enrollment of 33 women in each group, and greater statistical power to identify differences in either parathyroid hormone group as compared with the alendronate group. Analyses were based on the 108 women who completed the 15-month protocol, since 56 percent of withdrawals occurred before the three-month visit. Analyses based on the intention to treat did not differ significantly from those based on treatment actually received.

Data were evaluated for normality and log-transformed where necessary. Baseline differences were evaluated by means of analysis of variance for continuous variables and the chi-square test for categorical variables. A mixed-model analysis of variance was used to assess the primary hypothesis of the effect of treatment on bone mineral density. Bone mineral density was analyzed as the percent change from baseline. To assess whether the primary unadjusted hypothesis test was robust with

Table 1. Characteristics of the Women.*

Characteristic	Daily Parathyroid Hormone + Alendronate (N=43)	Cyclic Parathyroid Hormone + Alendronate (N=40)	Alendronate Only (N=43)
Age — yr	67.1±7.6	67.4±8.0	70.7±7.1
Years from menopause	19.5±10.6	20.7±8.7	22.1±8.9
Height — in.	63.2±3.5	62.8±3.6	62.2±2.6
Weight — lb	139.2±25.7	130.9±22.0	136.3±22.4
Spine			
Bone mineral density — g/cm ²	0.838±0.11	0.847±0.08	0.833±0.10
T score	-2.9±0.9	-2.8±0.8	-2.9±0.8
Total hip			
Bone mineral density — g/cm ²	0.761±0.11	0.739±0.09	0.768±0.01
T score	-2.0±0.9	-2.1±0.7	-1.9±0.8
Prior nonspinal fracture in adulthood — no. (%)	26 (60)	23 (58)	13 (30)†
Prevalent vertebral fractures — no. (%)	22 (51)	18 (45)	21 (49)
Years of alendronate therapy	2.8±0.2	3.5±0.3	3.0±1.0

* Plus-minus values are means ±SD. To convert height to centimeters, divide by 0.3937. To convert weight to kilograms divide by 2.2.

† P<0.001 for the comparison with the parathyroid hormone groups.

respect to potential confounders, including age, years from menopause, weight, height, body-mass index (defined as the weight in kilograms divided by the square of the height in meters), years of prior alendronate therapy, and presence or absence of a history of fracture, these variables were assessed in separate models. Biochemical variables were analyzed by repeated-measures analysis of variance. Exact logistic regression, controlling for the presence or absence of fracture in adulthood, was used to evaluate whether the number of new or worsening vertebral fractures differed among the three groups. All analyses were two-sided, with an alpha value of 0.05.

RESULTS

BASELINE CHARACTERISTICS

Baseline characteristics are shown in Table 1. The mean (\pm SD) age of the women was 68.4 \pm 7.6 years. Overall, 48 percent of the women had vertebral compression deformities at baseline (no significant differences among the groups). The only significant baseline difference among the groups was in the number of prior nonspinal clinical fractures during adulthood. However, if fractures of the feet, toes, fingers, and ankles were excluded, there were no significant differences among the groups. Baseline biochemical data (Table 2) were similar across groups, except for the mean ratio of urinary calcium to creatinine, which was slightly higher in the group

given daily parathyroid hormone ($P<0.001$). Mean bone turnover levels were all in the low normal range, with no significant group differences.

WITHDRAWALS

Eighteen subjects withdrew from the study: five women in the group given daily parathyroid hormone, six in the group given cyclic parathyroid hormone, and seven in the alendronate group. Fifty-six percent of withdrawals occurred during the first three months of the study. Reasons for withdrawal are shown in Table 3.

ADHERENCE

Adherence to parathyroid hormone therapy was assessed by reviewing the women's diaries and counting the number of empty parathyroid hormone vials that were returned, and alendronate adherence was assessed by interviewing the women. Adherence to all treatment regimens exceeded 90 percent. Of the 108 women who completed the study, 99 percent completed 100 percent of study visits.

BIOCHEMICAL EFFICACY VARIABLES

There were no significant biochemical changes in the alendronate group during the study (Fig. 1). In the group given daily parathyroid hormone, markers of bone formation rose from 116 percent in the case of bone-specific alkaline phosphatase to 373 percent in the case of N-terminal propeptide of

Table 2. Baseline Biochemical Characteristics of the Women.*

Variable	Daily Parathyroid Hormone + Alendronate (N=43)	Cyclic Parathyroid Hormone + Alendronate (N=40)	Alendronate Only (N=43)
Serum			
Calcium (mg/ml)	9.3 \pm 0.3	9.3 \pm 0.4	9.3 \pm 0.3
Parathyroid hormone (1–84) (pg/ml)	34.8 \pm 16.3	37.5 \pm 16.5	40.1 \pm 14.6
25-Hydroxyvitamin D (ng/ml)	25.9 \pm 6.5	25.0 \pm 8.3	24.6 \pm 8.9
Bone-specific alkaline phosphatase (U/liter)	12.8 \pm 3.7	13.2 \pm 3.9	13.0 \pm 5.4
Osteocalcin (ng/ml)†	5.2 \pm 1.7	5.2 \pm 1.8	4.8 \pm 1.7
N-propeptide of type 1 procollagen (μ g/liter)	22.9 \pm 13.8	22.1 \pm 13.2	19.9 \pm 12.9
Urine			
Calcium:creatinine ratio‡	0.22 \pm 0.1	0.15 \pm 0.1	0.13 \pm 0.1
N-telopeptide:creatinine ratio	29.0 \pm 16.2	27.9 \pm 14.9	25.4 \pm 14.0

* Plus–minus values are means \pm SD.

† To convert values for osteocalcin to nanomoles per liter, multiply by 0.1724.

‡ Both calcium and creatinine were measured in milligrams. $P<0.001$ for the comparison of the daily-therapy group with the other two groups.

type I procollagen above baseline values. The bone-resorption marker cross-linked urinary N-telopeptide rose more slowly and to a lesser extent (93 percent above baseline values). Among the women who were receiving cyclic parathyroid hormone, markers increased similarly during the first three months of therapy and declined during the periods without parathyroid hormone therapy. During the second and third cycles of parathyroid hormone therapy, markers of bone formation rose to a similar degree as seen during the first cycle. Levels of urinary N-telopeptide did not rise to as great an extent as in the daily-therapy group during the second and third cycles of parathyroid hormone; in fact, there was a progressive separation in urinary N-telopeptide values between the daily-therapy and cyclic-therapy groups during the 15 months.

BONE DENSITY

At 15 months, bone mineral density at the lumbar spine (Fig. 2) had not changed significantly from baseline values in the alendronate group but increased 6.1 percent in the group given daily parathy-

roid hormone and 5.4 percent in the group given cyclic parathyroid hormone ($P < 0.001$). This increase did not differ significantly between the parathyroid hormone groups. Adjustment for covariates did not alter the significance of the effects of parathyroid hormone on bone mineral density. Eighty-five percent of women in the parathyroid hormone groups had an increase in spinal bone mineral density: 72 percent had an increase of at least 3 percent, 58 percent had an increase of at least 5 percent, 14 percent had an increase of at least 10 percent, and 6 percent had an increase of at least 15 percent. There was no relationship between the duration of prior alendronate use and the change in either spinal bone mineral density or biochemical markers. Baseline biochemical markers correlated weakly with changes in spinal bone mineral density ($r = 0.26$ for osteocalcin, $r = 0.25$ for bone-specific alkaline phosphatase, $r = 0.38$ for N-terminal propeptide of type I procollagen, and $r = 0.37$ for cross-linked urinary N-telopeptide; all $P < 0.05$). In the parathyroid hormone groups, an increase of more than 30 percent in any of the biochemical markers at 3 months had a posi-

Table 3. Withdrawals and Adverse Events.

Event	Daily Parathyroid Hormone + Alendronate (N=43)	Cyclic Parathyroid Hormone + Alendronate (N=40)	Alendronate (N=43)
Reasons for withdrawal — no. (%) of randomized women			
Multiple nonspecific symptoms	5 (12)	5 (12)	2 (5)
Randomly assigned to alendronate alone group	0	0	2 (5)
New diagnosis of breast cancer	0	0	1 (2)
New diagnosis of rheumatoid arthritis	0	1 (2)	0
Death from complications of aortic-valve surgery	0	0	1 (2)
Practical or transportation issues	0	0	1 (2)
Total withdrawals	5 (12)	6 (15)	7 (16)
Adverse events — no. (%) of women who completed study			
Musculoskeletal symptoms*	10 (26)	4 (12)	2 (6)
Redness at injection site*	1 (3)	6 (18)	0
Gastrointestinal effects	9 (24)	7 (21)	4 (11)
Generalized fatigue	2 (5)	3 (9)	0
Cardiac symptoms	5 (13)	3 (9)	3 (8)
Vascular symptoms	2 (5)	1 (3)	0
Elevated total serum calcium	1 (3)	1 (3)	0
Elevated urinary calcium:creatinine ratio*	15 (39)	6 (18)	3 (8)
Elevated serum creatinine	0	0	0
Elevated liver-function tests	1 (3)	0	2 (6)
Abnormal complete blood count	5 (13)	4 (12)	2 (6)

* $P < 0.05$ for the difference among the groups.

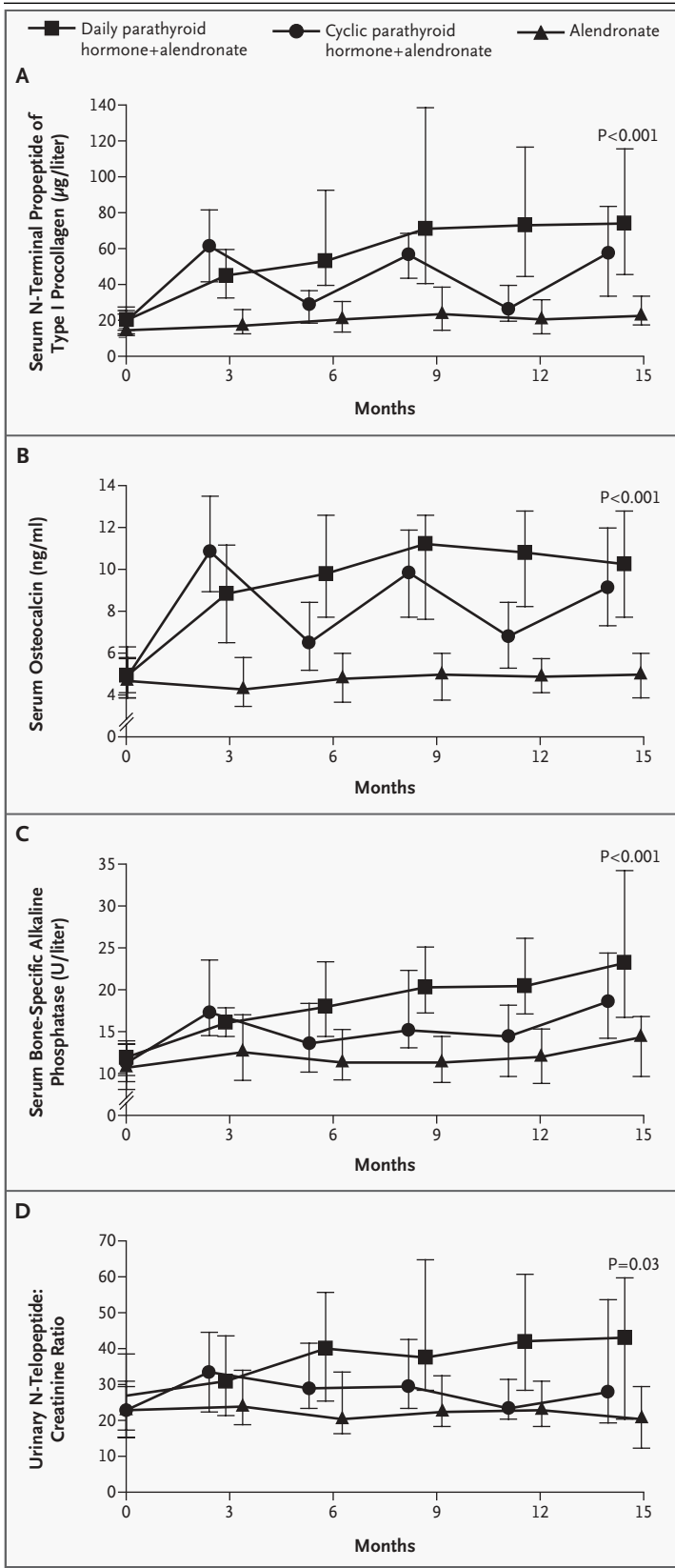


Figure 1. Median Changes in Indexes of Bone Formation (Panels A, B, and C) and Resorption (Panel D) among the Group Given Daily Parathyroid Hormone plus Alendronate, the Group Given Cyclic Parathyroid Hormone plus Alendronate, and the Group Given Alendronate Alone.

I bars denote the interquartile range. P values are for the time-treatment interactions among the three groups. To convert values for osteocalcin to nanomoles per liter, multiply by 0.1724.

tive predictive value of more than 73 percent for an increase in spinal bone mineral density of at least 3 percent at 15 months.

Bone mineral density at the hip (Fig. 2) increased slightly in all three groups ($P < 0.05$), with no significant differences among the groups. There were no significant changes in total-body bone mineral density in any of the three groups (data not shown).

INCIDENCE OF FRACTURES

New or worsening vertebral deformities occurred in 1 of 38 women in the group given daily parathyroid hormone (3 percent), 2 of 34 women in the group given cyclic parathyroid hormone (6 percent), and 4 of 36 women in the alendronate group (11 percent; $P = 0.20$ for the difference among the groups). Clinical nonspinal fractures occurred in four women in the group given daily parathyroid hormone (calcaneus, toe and wrist, shoulder, and metatarsal), two in the group given cyclic parathyroid hormone (hip and elbow), and two in the alendronate group (two ribs and metatarsal).

SAFETY

Adverse events are reported in Table 3. One woman in each parathyroid hormone group had minimally elevated serum calcium levels during early treatment, and these levels returned to normal spontaneously by the next preplanned sampling one week later. All but 1 of 24 women with elevated ratios of urinary calcium to creatinine had a spontaneous return to normal values by the next sampling; the value normalized in this woman after the dose of her calcium supplement was decreased (according to the planned algorithm). None of the women required a reduction in the dose of medication.

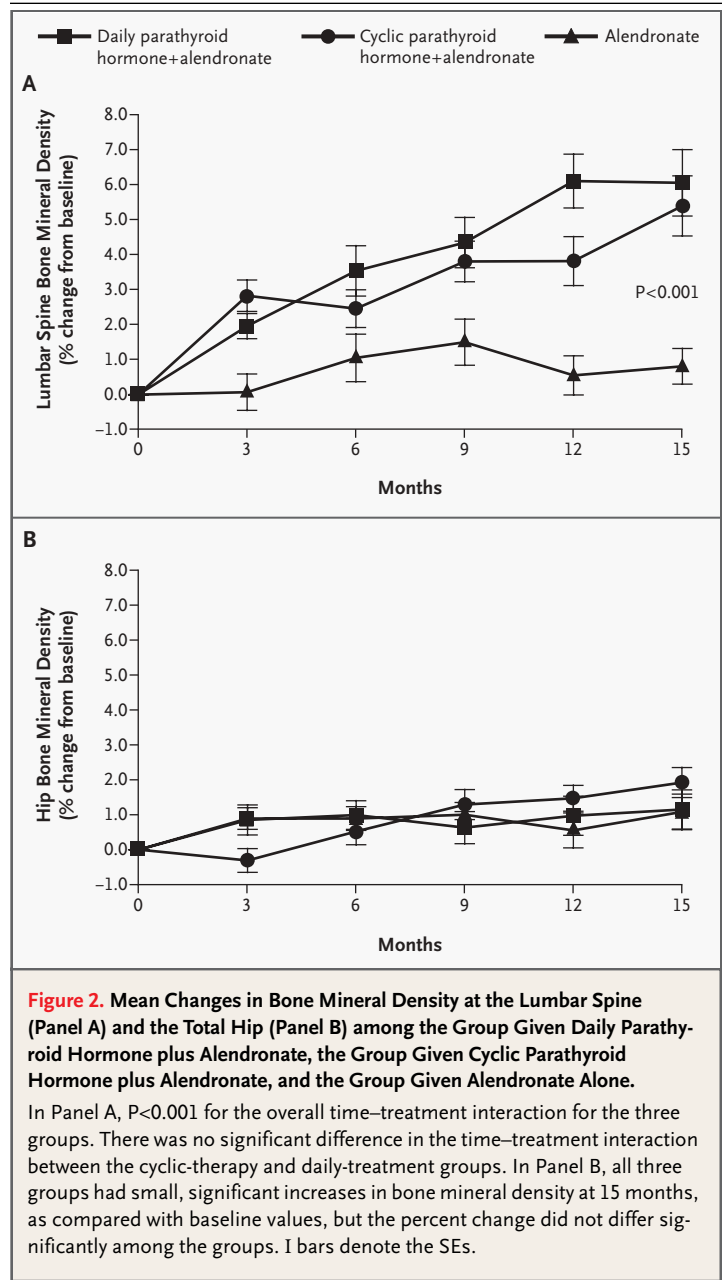
DISCUSSION

Our data suggest that, after prior and continuing treatment with alendronate, the administration of parathyroid hormone stimulates bone formation

and enhances spinal bone mass. Many women with osteoporosis, previously treated with bisphosphonates, might benefit from parathyroid hormone therapy because of the possibility of intercurrent fractures, active bone loss, persistently low bone mineral density, or an inability to tolerate ongoing bisphosphonate treatment. Whether the response to parathyroid hormone in these patients is identical to the response in patients who have never received treatment cannot be ascertained on the basis of the available data and is not clinically relevant for patients who have been previously treated with alendronate. Although small and not statistically powered to evaluate fracture outcomes, our study suggests that parathyroid hormone may further reduce the incidence of vertebral deformity in patients who have previously been treated with alendronate; this possibility needs to be confirmed in a larger trial.

The bone density findings in our study differ somewhat from those in an observational study of women who were given parathyroid hormone daily for 18 months after discontinuing alendronate or raloxifene therapy.²³ The baseline biochemical markers were lower in the alendronate group in that study than in ours, particularly for bone-specific alkaline phosphatase and cross-linked urinary N-telopeptide, and the baseline turnover may predict the bone mineral density response. However, the magnitude of change in remodeling biochemical variables with parathyroid hormone therapy was similar in the two studies.

In the other study, an initial slight decline in bone mineral density at the hip was seen in the group that had previously received alendronate, whereas our study showed no evidence of a loss of bone mineral density at the hip, perhaps because alendronate was continued during parathyroid hormone treatment. The discontinuation of alendronate, even after long-term treatment, results in a decline in the bone mineral density at the hip.³⁰ Stimulation of bone turnover by parathyroid hormone may further accelerate this loss after the withdrawal of alendronate. However, ultimately (after six months of parathyroid hormone treatment), bone mineral density at the hip returned to baseline values in that investigation.²³ A randomized trial to evaluate the effect of continuation or discontinuation of alendronate would be required to determine whether this is the cause of the difference in the change in bone mineral density at the hip between the studies. The changes we observed in spinal bone mineral density were greater (6.1 percent vs. 4.2 percent), despite



our use of a slightly shorter treatment period (15 vs. 18 months). This may relate to our use of a slightly higher dose of parathyroid hormone (25 μg per day vs. 20 μg per day), since the change in bone mineral density is dose dependent.⁶

Our study does not address the distinct clinical issue of concomitant treatment with parathyroid hormone and alendronate in patients who have never been treated for osteoporosis. Several recent investigations²⁰⁻²² indicate that in such patients,

administering parathyroid hormone with alendronate or providing a short course of alendronate treatment before parathyroid hormone therapy does not further augment the increase in spinal bone mineral density. The parathyroid hormone used in one of these studies²⁰ was a different molecule, the full, intact peptide, parathyroid hormone (1–84). Biochemical results in the group given parathyroid hormone plus alendronate in that study suggest that osteoblast activity is stimulated initially (within the first month), but then inhibition of bone resorption becomes the dominant effect, and when new remodeling sites are no longer initiated under the influence of alendronate, the rate of bone formation declines. Differences in the response of the osteogenic unit (committed precursors, mature bone cells, and their microenvironment) to simultaneous treatment with the two agents, as compared with sequential therapy, are likely to account for unique responses to parathyroid hormone administration in patients who have never received treatment, as compared with patients who have already received alendronate.

The concept of cyclic administration of parathyroid hormone was based on the hypothesis that early direct stimulation of bone formation by parathyroid hormone might be more important to the ultimate accrual of bone mineral density than later activation of bone remodeling by parathyroid hormone. The short cycle of parathyroid hormone largely dissociates the early anabolic effect from the latter remodeling-based effects of parathyroid hormone. The fact that the increase in bone mineral density at the spine was similar with cyclic and daily therapy, after only 60 percent of the daily dose had been given, suggests that this, indeed, might be true, at least for spinal bone mineral density. Furthermore, the biochemical data from the cyclic-therapy group confirm that a second course of parathyroid hormone can stimulate bone formation with a magnitude similar to that induced by the first course of parathyroid hormone after a short interval without therapy. Further study is warranted to determine whether short cycles of parathyroid hormone for a more extended period

would be superior to a single two-year course of therapy.

Our data confirm that parathyroid hormone can exert a biologically meaningful increase in bone mineral density and should be considered for patients who have previously received alendronate (and perhaps other bisphosphonates) who are still at high risk for fracture. The main end points of our study — bone turnover and bone density — reflect some, but not all, of the mechanisms (macroarchitecture and microarchitecture) underlying the parathyroid hormone–mediated increase in bone strength. The parathyroid hormone–induced increment in spinal bone mineral density may be slightly lower in women who have previously received alendronate than in women who have never received alendronate; however, the magnitude of the change in spinal bone mineral density is still impressive. Our data suggest that intermittent cyclic treatment with parathyroid hormone produces effects on bone mineral density similar to those induced by daily administration, but at a lower cost and with less effort on the part of patients. Use of the change in bone mineral density induced by the combination of these medications to predict the effect on fractures should be performed with caution and only after a fracture trial has been conducted.

Supported in part by a grant (AR39191) from the National Institutes of Health.

Dr. Cosman reports having received speakers' fees from Eli Lilly, Merck, Roche-GlaxoSmithKline, and Novartis; advisory or consulting fees from Eli Lilly, Merck, Novartis, Pfizer, NPS, and Roche-GlaxoSmithKline; and grants from Novartis, Merck, Roche-GlaxoSmithKline, and Eli Lilly. Dr. Lindsay reports having received speakers' fees from Procter & Gamble, Aventis, Eli Lilly, Roche-GlaxoSmithKline, Novartis, and Wyeth; advisory or consulting fees from NPS, Wyeth, Procter & Gamble, Aventis, Pfizer, Roche-GlaxoSmithKline, and Novartis; and grants from Wyeth, Aventis, Roche-GlaxoSmithKline, Novartis, and Ilex. Dr. Nieves reports having received speakers' fees from Merck. Dr. Luckey reports having received speakers' fees from Merck, Procter & Gamble, Aventis, and Eli Lilly; advisory or consulting fees from Wyeth, Roche, Procter & Gamble, and Merck; and grants from Amgen, Merck, Procter & Gamble, and Roche.

We are indebted to the trial participants for their courage and perseverance; to Patricia Garrett, radiologic technologist, Annette Moreno, laboratory technologist, and Don McMahon, statistician, for their excellent work on this project; and to the members of our data and safety monitoring board (Drs. Murray Favus, Sundeep Khosla, Karl Insogna, William Ershler, and Margaret Peterson).

REFERENCES

1. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA* 1999;282:637-45. [Erratum, *JAMA* 1999;282:2124.]
2. Black DM, Cummings SR, Karpf DB, et al. Effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;348:1535-41.
3. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280:2077-82.
4. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral

- and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled clinical trial. *JAMA* 1999;282:1344-52.
5. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001;344:333-40.
 6. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434-41.
 7. Lindsay R, Nieves J, Formica C, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet* 1997;350:550-5.
 8. Cosman F, Nieves J, Woelfert L, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. *J Bone Miner Res* 2001;16:925-31.
 9. Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. *J Clin Endocrinol Metab* 2000;85:3069-76.
 10. Cosman F, Nieves J, Woelfert L, Shen V, Lindsay R. Alendronate does not block the anabolic effect of PTH in postmenopausal osteoporotic women. *J Bone Miner Res* 1998;13:1051-5.
 11. Dempster DW, Zhou H, Cosman F, et al. PTH treatment directly stimulates bone formation in cancellous and cortical bone in humans. *J Bone Miner Res* 2001;16:Suppl 1: S179. abstract.
 12. Hodsdman AB, Steer BM. Early histomorphometric changes in response to parathyroid hormone therapy in osteoporosis: evidence for de novo bone formation on quiescent cancellous surfaces. *Bone* 1993;14: 523-7.
 13. Lindsay R, Zhou H, Cosman F, et al. Short term response to parathyroid hormone (1-34hPTH) in human iliac crest bone using a unique quadruple (double double) tetracycline labeling regimen and single biopsy. *J Bone Miner Res* 2003;18:Suppl 1: S154. abstract.
 14. Lane NE, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. Bone mass continues to increase after parathyroid hormone treatment is stopped in glucocorticoid-induced osteoporosis: results of a randomized controlled clinical trial. *J Bone Miner Res* 2000;15:944-51.
 15. Roe EB, Sanchez SD, del Puerto GA, et al. Parathyroid hormone 1-34 (hPTH 1-34) and estrogen produce dramatic bone density increases in postmenopausal osteoporosis — results from a placebo-controlled randomized trial. *J Bone Miner Res* 1999;14: Suppl 1:S137. abstract.
 16. Finkelstein JS, Klibasnik A, Arnold AL, Toth TL, Hornstein HD, Neer RM. Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): a randomized controlled trial. *JAMA* 1998;280:1067-73.
 17. Slovick DM, Rosenthal DI, Doppelt JH, et al. Restoration of spinal bone in osteoporotic men by treatment with human parathyroid hormone (1-34) and 1,25-dihydroxyvitamin D. *J Bone Miner Res* 1986;1:377-81.
 18. Orwoll ES, Scheele WH, Paul S, et al. The effects of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 2003;18:9-17.
 19. Ste-Marie LG, Scheele WH, Jasqui S, et al. Effect of LY333334 [recombinant human parathyroid hormone (1-34), rhPTH(1-34)] on bone density when given to postmenopausal women receiving hormone replacement therapy (HRT). In: Program and abstracts of the Endocrine Society's 83rd Annual Meeting, Denver, June 20–23, 2001: 125. abstract.
 20. Black DM, Greenspan SL, Ensrud KE, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med* 2003;349:1207-15.
 21. Neer R, Hayes A, Rao A, Finkelstein J. Effects of parathyroid hormone, alendronate, or both on bone density in osteoporotic postmenopausal women. *J Bone Miner Res* 2002;19:Suppl 1:S98. abstract.
 22. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 2003;349: 1216-26.
 23. Ettinger B, San Martin J, Crans G, Pavo I. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. *J Bone Miner Res* 2004;19:745-51.
 24. Jergas M, Valentin RS. Techniques for the assessment of vertebral dimensions in quantitative morphometry. In: Genant HK, Jergas M, van Kuijk C, eds. *Vertebral fracture in osteoporosis*. San Francisco: University of California Osteoporosis Research Group, 1995:163-88.
 25. Nelson D, Peterson E, Tilley B, et al. Measurement of vertebral area on spine x-rays in osteoporosis: reliability of digitizing techniques. *J Bone Miner Res* 1990;5: 707-16.
 26. Melton LJ III, Lane AW, Cooper C, Eastell R, O'Fallon WM, Riggs BL. Prevalence and incidence of vertebral deformities. *Osteoporos Int* 1993;3:113-9.
 27. Black DM, Cummings SR, Stone K, Hudes E, Palermo L, Steiger P. A new approach to defining normal vertebral dimensions. *J Bone Miner Res* 1991;6:883-92.
 28. Guglielmi G, Diacinti D. Vertebral morphometry. In: Grampp S, ed. *Radiology of osteoporosis*. New York: Springer, 2003: 101-10.
 29. Smith-Bindman R, Cummings SR, Steiger P, Genant HK. A comparison of morphometric definitions of vertebral fracture. *J Bone Miner Res* 1991;6:25-34.
 30. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004;350:1189-99.

Copyright © 2005 Massachusetts Medical Society.

PHYSICIAN-JOURNALIST

The *Journal* is seeking a physician with substantial reporting experience to write occasional articles on timely topics in medicine and society for the Perspective section. Send curriculum vitae and writing samples to Perspective Editor, *New England Journal of Medicine*, 10 Shattuck St., Boston, MA 02115, or at writer@nejm.org.