

EFFECT OF PARATHYROID HORMONE (1-34) ON FRACTURES AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

ROBERT M. NEER, CLAUDE D. ARNAUD, JOSE R. ZANCHETTA, RICHARD PRINCE, GREGORY A. GAICH, JEAN-YVES REGINSTER, ANTHONY B. HODSMAN, ERIK F. ERIKSEN, SOPHIA ISH-SHALOM, HARRY K. GENANT, OUHONG WANG, AND BRUCE H. MITLAK

ABSTRACT

Background Once-daily injections of parathyroid hormone or its amino-terminal fragments increase bone formation and bone mass without causing hypercalcemia, but their effects on fractures are unknown.

Methods We randomly assigned 1637 postmenopausal women with prior vertebral fractures to receive 20 or 40 μg of parathyroid hormone (1-34) or placebo, administered subcutaneously by the women daily. We obtained vertebral radiographs at base line and at the end of the study (median duration of observation, 21 months) and performed serial measurements of bone mass by dual-energy x-ray absorptiometry.

Results New vertebral fractures occurred in 14 percent of the women in the placebo group and in 5 percent and 4 percent, respectively, of the women in the 20- μg and 40- μg parathyroid hormone groups; the respective relative risks of fracture in the 20- μg and 40- μg groups, as compared with the placebo group, were 0.35 and 0.31 (95 percent confidence intervals, 0.22 to 0.55 and 0.19 to 0.50). New nonvertebral fragility fractures occurred in 6 percent of the women in the placebo group and in 3 percent of those in each parathyroid hormone group (relative risk, 0.47 and 0.46, respectively [95 percent confidence intervals, 0.25 to 0.88 and 0.25 to 0.86]). As compared with placebo, the 20- μg and 40- μg doses of parathyroid hormone increased bone mineral density by 9 and 13 more percentage points in the lumbar spine and by 3 and 6 more percentage points in the femoral neck; the 40- μg dose decreased bone mineral density at the shaft of the radius by 2 more percentage points. Both doses increased total-body bone mineral by 2 to 4 more percentage points than did placebo. Parathyroid hormone had only minor side effects (occasional nausea and headache).

Conclusions Treatment of postmenopausal osteoporosis with parathyroid hormone (1-34) decreases the risk of vertebral and nonvertebral fractures; increases vertebral, femoral, and total-body bone mineral density; and is well tolerated. The 40- μg dose increased bone mineral density more than the 20- μg dose but had similar effects on the risk of fracture and was more likely to have side effects. (N Engl J Med 2001;344:1434-41.)

Copyright © 2001 Massachusetts Medical Society.

TREATMENTS for postmenopausal women with osteoporosis include estrogens, selective estrogen-receptor modulators, bisphosphonates, calcitonin, vitamin D, and calcitriol. These treatments reduce bone resorption (and formation) and moderately increase bone density; some agents reduce the risk of fracture, but none routinely restore normal bone mass or strength. Treatments that stimulate bone formation may overcome these limitations.

Parathyroid hormone stimulates bone formation and resorption and can increase or decrease bone mass, depending on the mode of administration. Continuous infusions and daily subcutaneous injections of parathyroid hormone stimulate bone formation similarly but have different effects on bone resorption and bone mass.^{1,2} Continuous infusions, which result in a persistent elevation of the serum parathyroid hormone concentration, lead to greater bone resorption than do daily injections, which cause only transient increases in the serum parathyroid hormone concentration.³

Parathyroid hormone or its amino-terminal fragments and analogues prevent, arrest, or partially reverse bone loss in animals and humans.⁴ In animals, parathyroid hormone induces parallel increases in bone mass and bone strength,⁵ suggesting that treatment with parathyroid hormone may provide protection against fractures in humans. We tested this hypothesis in a study of parathyroid hormone (1-34) for the treatment of postmenopausal women with prior vertebral fractures. Parathyroid hormone (1-34) comprises the first 34 amino acids of the hormone and produces its chief biologic effects. The sponsor terminated the study early in order to evaluate the clinical relevance of the finding that osteosarcomas developed in Fisch-

From Massachusetts General Hospital and Harvard Medical School, Boston (R.M.N.); the University of California, San Francisco (C.D.A., H.K.G.); Fundación de Investigaciones Metabólicas, Buenos Aires, Argentina (J.R.Z.); the University of Western Australia and Sir Charles Gairdner Hospital, Perth, Australia (R.P.); Eli Lilly, Indianapolis (G.A.G., O.W., B.H.M.); Polycliniques Universitaires L. Brull, Liege, Belgium (J.-Y.R.); St. Joseph's Health Center, London, Ont., Canada (A.B.H.); Aarhus Amtssygehus, Aarhus, Denmark (E.F.E.); and Rambam Medical Center, Haifa, Israel (S.I.-S.). Address reprint requests to Dr. Mitlak at Eli Lilly, Inc., Lilly Corporate Center, Indianapolis, IN 46285-2680, or at b.mitlak@lilly.com.

Other authors were Dan Mellström, Department of Geriatrics, University of Göteborg, Göteborg, Sweden; Erik S. Oefjord, Bergen Osteoporosecenter, Paradis, Norway; Ewa Marcinowska-Suchowierska, Klinika Chorob Wewnętrznych, Warsaw, Poland; Jorma Salmi, Koskiklinikka, Tampere, Finland; Henk Mulder, Medisch Onderzoekscentrum Gcp, De Bilt, the Netherlands; Johan Halse, Betanien Med Lab, Oslo, Norway; and Andrzej Z. Sawicki, Warszawskie Centrum Osteoporozy, Warsaw, Poland.

er 344 rats during a long-term toxicologic study of parathyroid hormone (1-34). Subsequent evaluation of the clinical data revealed that parathyroid hormone (1-34) was effective in preventing fractures and was well tolerated.

METHODS

Study Subjects

We screened postmenopausal women at 99 centers in 17 countries for enrollment in the study. Women were eligible for enrollment if they were ambulatory, if a period of at least five years had elapsed since menopause, and if they had at least one moderate or two mild atraumatic vertebral fractures on radiographs of the thoracic and lumbar spine, and an ambulatory status.⁶ For women with fewer than two moderate fractures, an additional criterion for enrollment was a value for bone mineral density of the hip or lumbar spine that was at least 1 SD below the mean value in normal premenopausal white women (age range, 20 to 35 years). We excluded women with illnesses that affect bone or calcium metabolism, urolithiasis within the preceding 5 years, impaired hepatic function, a serum creatinine concentration exceeding 2 mg per deciliter (177 μ mol per liter), or alcohol or drug abuse, as well as women who had taken drugs that alter bone metabolism within the previous 2 to 24 months (depending on the drug). The study was approved by the ethics committee at each participating center, and all women gave written informed consent.

Treatment Protocol and Follow-up Studies

All enrolled women received daily supplements of 1000 mg of calcium and 400 to 1200 IU of vitamin D. The women gave themselves daily injections of placebo for two weeks and were then randomly assigned to receive placebo or 20 or 40 μ g of recombinant human parathyroid hormone (1-34) in a regimen of daily, self-administered injections. We measured serum calcium before and 4 to 6 hours after injection at base line and after 1, 3, 6, 12, 18, and 24 months of treatment, and we measured calcium and creatinine excretion in 24-hour urine specimens at base line and after 1, 6, 12, and 24 months of treatment. All tests of serum and urine samples from an individual woman were performed at one of three laboratories that used identical, cross-calibrated methods of measurement. If the post-injection serum calcium concentration was high or if urinary excretion of calcium exceeded 350 mg (8.8 mmol) per day, and if the increase persisted on repeated testing, the calcium supplement was discontinued permanently or the volume of the injected study drug was halved until the abnormality had disappeared.

All women underwent anteroposterior and lateral radiography of the thoracic and lumbar spine at base line and at the end of the study. Radiologists at a central location who knew the temporal sequence of the radiographs, but not the treatment assignments, graded each woman's vertebrae as normal (i.e., normal height) or as mildly, moderately, or severely deformed (i.e., a decrease in height of approximately 20 to 25 percent, 26 to 40 percent, or more than 40 percent, respectively).⁶ A vertebra was not graded if scoliosis, fusion, or another anomaly prevented radiographic assessment. A new vertebral fracture was reported if a normal vertebra became deformed; worsening of preexisting deformities was not analyzed. Nonvertebral fractures were documented by a review of radiographs or radiologic reports and were classified as fragility fractures (the protocol-specified end point) if the associated trauma would not have resulted in the fracture of a normal bone, in the opinion of the local investigator.

We measured the bone mineral density of the lumbar spine, proximal femur, and radius and the total-body bone mineral by dual-energy x-ray absorptiometry with the use of Hologic, Lunar, or Norland equipment. The measurements were analyzed centrally, and the results were not reported to the participating centers. We measured the bone density of the spine at base line and at 12 and 18 months, and at the end of the study in all women (as well as at

3 and 6 months in a subgroup of women); we measured the bone density of the hips (in all women), forearms (in a subgroup), and total body (in a subgroup) at base line, at 12 months, and at the end of the study. Spine and hip values are reported in grams per square centimeter, although they have been converted to standardized units, which eliminate differences in measurements attributable to the manufacturer's calibrations.⁷ Measurements of the spine excluded vertebrae with fractures or focal sclerosis. Total-body bone measurements excluded the head in order to avoid dental artifacts. The consistency of serial measurements was assessed with serial measurements of a spine phantom at each center, and the consistency of measurements among centers was assessed with measurements of a standard phantom circulated to all centers. Measurements of the phantoms were used to adjust for minor changes in the performance of the densitometer.⁸

We measured height with a stadiometer at base line and every 12 months; blood counts, serum chemical tests, and urinalysis were performed at base line and at 1, 6, 12, and 24 months. Tests of serum antibodies to parathyroid hormone (1-34), based on the specific binding of radioiodinated parathyroid hormone (1-34), were performed at base line and at 3, 12, and 24 months.

Statistical Analysis

We analyzed data for all women with at least one follow-up visit after enrollment. The rates of side effects and the proportions of women with fractures in the three study groups were compared with the use of Pearson's chi-square test. All laboratory data and bone mineral measurements were evaluated by analysis of variance, with the inclusion of terms for the treatment assignment and country. All statistical tests were two-sided.

RESULTS

Of 9347 women who were screened for the study, 7710 were not eligible or were not interested in participating. The remaining 1637 women were randomly assigned to receive placebo (544 women) or parathyroid hormone (1-34) at a dose of 20 μ g per day (541 women) or 40 μ g per day (552 women). The base-line characteristics of the women in the three study groups were similar (Table 1). In December 1998, all women were invited to a termination visit because the sponsor had stopped the study. The interval during which women were at risk for vertebral fractures (the period from enrollment to the final radiographic study of the spine) and nonvertebral fractures (the period from enrollment to the final visit) did not differ significantly among the three groups (Table 2 and Table 3, respectively). The cumulative duration of the study treatment in the group that received placebo, the group that received 20 μ g of parathyroid hormone (1-34) per day, and the group that received 40 μ g per day was 798, 779, and 774 patient-years, respectively, and the mean (\pm SD) duration of treatment in the three groups was 18 ± 5 , 18 ± 6 , and 17 ± 6 months, respectively. The average rate of compliance with the regimen of injections, assessed on the basis of returned medication, ranged from 79 to 83 percent at each visit, and the rates did not differ significantly among the three groups.

Vertebral Fractures and Changes in Height

Base-line and follow-up radiographs were available for 1326 of the 1637 women (81 percent); follow-up radiographs were not available for 249 women, and

TABLE 1. BASE-LINE CHARACTERISTICS OF 1637 POSTMENOPAUSAL WOMEN ACCORDING TO WHETHER THEIR SPINAL RADIOGRAPHS WERE ADEQUATE FOR EVALUATION.*

CHARACTERISTIC	WOMEN WITH ADEQUATE RADIOGRAPHS†			WOMEN WITHOUT ADEQUATE RADIOGRAPHS		
	PLACEBO (N=448)	PTH, 20 µg (N=444)	PTH, 40 µg (N=434)	PLACEBO (N=96)	PTH, 20 µg (N=97)	PTH, 40 µg (N=118)
White race (%)	99	99	98	99	98	98
Age (yr)	69±7	69±7	70±7	69±8	71±8	71±7
Years since menopause	21±8	21±9	21±8	21±10	24±9	24±8
Body-mass index‡	26.7±4.7	26.8±4.2	26.6±4.3	26.1±5.0	26.4±4.4	26.5±4.1
Calcium intake (mg/day)	762±433	786±443	757±449	745±460	675±432	758±432
Current smoker (%)	18.5	15.8	14.8	19.8	19.6	20.3
Previous osteoporosis therapy (%)	15	16	13	14	14	14
No. of vertebral fractures	2.3±1.8	2.3±1.8	2.3±1.8	2.6±1.8	2.7±1.7	2.3±1.7
Lumbar-spine BMD (mg/cm ²)	820±170	820±170	820±170	810±170	840±160	840±160

*Plus-minus values are means ±SD. PTH denotes parathyroid hormone (1-34), and BMD bone mineral density.

†P>0.05 for all comparisons among women with radiographs that could be evaluated.

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

TABLE 2. RADIOGRAPHIC EVIDENCE OF NEW VERTEBRAL FRACTURES.*

VARIABLE	PLACEBO (N=448)	PTH, 20 µg (N=444)	PTH, 40 µg (N=434)
No. of months at risk (randomization to final radiograph)	21±3	21±3	20±4
≥1 Fracture			
No. of women (%)	64 (14)	22 (5)†	19 (4)†
Relative risk (95% CI) vs. placebo	—	0.35 (0.22–0.55)	0.31 (0.19–0.50)
Percent reduction in absolute risk	—	9	10
>1 Fracture			
No. of women (%)	22 (5)	5 (1)†	3 (<1)†
Relative risk (95% CI) vs. placebo	—	0.23 (0.09–0.60)	0.14 (0.04–0.47)
Percent reduction in absolute risk	—	4	4
≥1 Moderate or severe fracture			
No. of women (%)	42 (9)	4 (<1)†	9 (2)†
Relative risk (95% CI) vs. placebo	—	0.10 (0.04–0.27)	0.22 (0.11–0.45)
Percent reduction in absolute risk	—	9	7

*Plus-minus values are means ±SD. PTH denotes parathyroid hormone (1-34), and CI confidence interval.

†P≤0.001 for the comparison with placebo.

an additional 62 women had pretreatment radiographs that were inadequate for evaluation. Base-line risk factors for new vertebral fractures were similar in the three groups (Table 1), as were serum 25-hydroxyvitamin D concentrations and indexes of bone turnover (data not shown). Of the 1326 women for whom adequate radiographs were available, 105 had one or more new vertebral fractures. As compared with placebo, parathyroid hormone (1-34) at the 20-µg and 40-µg doses reduced the risk of one or more new vertebral fractures by 65 and 69 percent, respectively; the risk of two or more fractures was reduced by 77

and 86 percent, respectively, and the risk of at least one moderate or severe vertebral fracture was reduced by 90 and 78 percent, respectively (Table 2). Treatment with parathyroid hormone (1-34) also reduced the total number of vertebral fractures: the number of fractures per 1000 patient-years of treatment was 136 in the placebo group, 49 in the 20-µg parathyroid hormone group, and 30 in the 40-µg group. With the 20-µg dose, a vertebral fracture was prevented for every 12 patient-years of treatment, and with the 40-µg dose, a vertebral fracture was prevented for every 10 patient-years of treatment.

TABLE 3. NEW NONVERTEBRAL FRACTURES AND NEW NONVERTEBRAL FRAGILITY FRACTURES.*

VARIABLE	PLACEBO (N=544)	PTH, 20 μ g (N=541)	PTH, 40 μ g (N=552)
No. of months at risk from randomization to last visit	19 \pm 5	19 \pm 6	18 \pm 6
No. of patient-years at risk	857	837	833
\geq 1 Fracture (no. of women)			
Total	53	34 \dagger	32 \ddagger
Fragility	30	14 \ddagger	14 \S
Site of fracture (no. of women)			
Hip			
Total	4	2	3
Fragility	4	1	3
Wrist			
Total	13	7	10
Fragility	7	2	3
Ankle			
Total	4	2	2
Fragility	3	1	1
Humerus			
Total	5	4	3
Fragility	2	2	2
Rib			
Total	10	5	5
Fragility	5	3	2
Foot			
Total	4	1	4
Fragility	1	0	3
Pelvis			
Total	3	1	0
Fragility	3	0	0
Other			
Total	16	14	9
Fragility	8	6	3

*Some women had a new fracture at more than one skeletal site or had more than one new fracture at the same site (e.g., in both extremities). The total numbers of nonvertebral fractures in the placebo group and the 20- μ g and 40- μ g parathyroid hormone groups were 62, 36, and 37, respectively, and the total numbers of nonvertebral fragility fractures were 33, 15, and 17, respectively. Plus-minus values are means \pm SD. PTH denotes parathyroid hormone (1-34).

\dagger P=0.04 for the comparison with placebo.

\ddagger P=0.02 for the comparison with placebo.

\S P=0.01 for the comparison with placebo.

New or worsening back pain was reported by 23 percent of the women in the placebo group but by only 17 percent and 16 percent of those in the 20- μ g and 40- μ g parathyroid hormone groups, respectively (P=0.007). These data were consistent with the radiographic findings. Among the 105 women with one or more new vertebral fractures, the mean loss in height was greater in the placebo group (-1.1 cm) than in the 20- μ g and 40- μ g parathyroid hormone groups (-0.2 and -0.3 cm, respectively; P=0.002). Because most women did not have new vertebral fractures, the overall mean loss in height was small and did not differ significantly among the three groups.

Nonvertebral Fractures

New nonvertebral fractures occurred in 119 women and were considered fragility fractures in 58 (Ta-

ble 3). Women treated with the 20- μ g dose of parathyroid hormone (1-34) and those treated with the 40- μ g dose were 35 and 40 percent less likely to have one or more new nonvertebral fractures, respectively, than the women in the placebo group, and were 53 and 54 percent less likely to have one or more new nonvertebral fragility fractures. The absolute risk of one or more nonvertebral fractures was 10 percent in the placebo group and 6 percent in each parathyroid hormone group; the absolute risk of one or more nonvertebral fragility fractures was 6 percent in the placebo group and 3 percent in the two parathyroid hormone groups (relative risk, 0.47 and 0.46, respectively [95 percent confidence intervals, 0.25 to 0.88 and 0.25 to 0.86]). The cumulative incidence of one or more new nonvertebral fractures or nonvertebral fragility fractures was initially similar in the three study groups; the protective effects of parathyroid hormone treatment became evident after 9 to 12 months (Fig. 1). Although the numbers of women with new nonvertebral fractures at specific skeletal sites were too small to estimate the incidence of each type of fracture, the numbers in the parathyroid hormone groups were generally smaller than — and in no case exceeded — the numbers in the placebo group (Table 3).

Bone Mineral Density and Total-Body Bone Mineral

At base line, bone mineral density was similar among the three groups at all skeletal sites; total-body bone mineral was also similar (Table 4). The mean bone mineral density of the spine was 2.6 SD below the mean value in normal young white women (mean T score, -2.6). Treatment with parathyroid hormone (1-34) resulted in significant dose-dependent increases in the bone mineral density of the spine and hip and in total-body bone mineral (Table 4). The bone mineral density of the shaft of the radius decreased from the base-line values in all three groups; the percent change in the 40- μ g group, but not that in the 20- μ g group, differed significantly from the percent change in the placebo group (P<0.001). As previously reported by other investigators,^{9,10} this difference arose during the first year of treatment; subsequently, the bone mineral density of the radial shaft changed in parallel in all three groups (data not shown). The density of the distal radius did not differ significantly among the three groups.

Adverse Events

There were no significant differences among the three groups with respect to the numbers of deaths and hospitalizations or the numbers of women in whom cardiovascular disorders, urolithiasis, or gout developed during the study. There were no cases of osteosarcoma. Cancer developed in 40 women, with a higher incidence in the placebo group (4 percent) than in the 20- μ g and 40- μ g parathyroid hormone groups (2 percent in each group; P=0.02 and P=

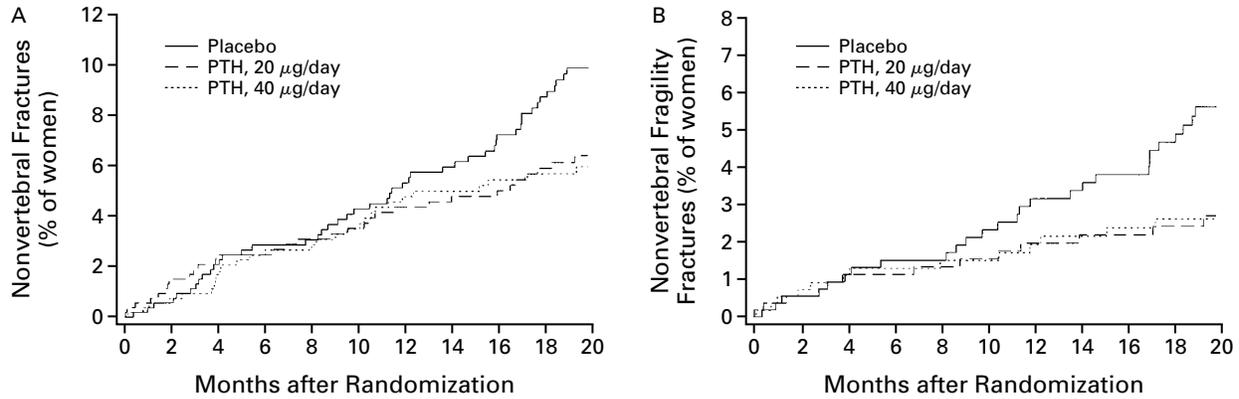


Figure 1. Cumulative Proportion of Women Assigned to Receive Placebo or Parathyroid Hormone (1-34) (PTH) at a Daily Dose of 20 µg or 40 µg Who Had One or More Nonvertebral Fractures (Panel A) and the Cumulative Proportion Who Had One or More Nonvertebral Fragility Fractures (Panel B) during the Study.

For both panels, the respective numbers of women in the placebo group and in the 20-µg and 40-µg PTH groups were 544, 541, and 552 at base line; 497, 492, and 486 at 6 months; 477, 465, and 456 at 12 months; and 404, 400, and 390 at 18 months. $P \leq 0.05$ for all pairwise comparisons with placebo, by the log-rank test.

TABLE 4. CHANGE FROM BASE LINE IN BONE MINERAL DENSITY AND TOTAL-BODY BONE MINERAL.*

SKELETAL MEASUREMENT	BASE LINE			LAST VISIT							
	PLACEBO	PTH, 20 µg	PTH, 40 µg	PLACEBO		PTH, 20 µg		P VALUE	PTH, 40 µg		P VALUE
				no. of women	% change	no. of women	% change		no. of women	% change	
Bone mineral density†											
Lumbar spine	0.82±0.17	0.82±0.17	0.82±0.17	504	1.1±5.5	498	9.7±7.4†	<0.001	497	13.7±9.7	<0.001
Femoral neck	0.64±0.11	0.64±0.11	0.64±0.11	479	-0.7±5.4	479	2.8±5.7†	<0.001	482	5.1±6.7	<0.001
Trochanter	0.57±0.12	0.57±0.12	0.57±0.12	479	-0.2±6.3	479	3.5±6.8†	<0.001	482	4.4±7.5	<0.001
Intertrochanter	0.86±0.16	0.85±0.16	0.85±0.14	257	-1.3±4.5	250	2.6±5.5†	<0.001	254	4.0±6.0	<0.001
Total hip	0.71±0.12	0.70±0.12	0.70±0.11	230	-1.0±4.3	222	2.6±4.9†	<0.001	232	3.6±5.4	<0.001
Distal radius	0.32±0.08	0.31±0.07	0.32±0.07	154	-1.6±8.3	152	-0.1±7.2	0.09	145	-1.5±8.4	0.74
Shaft of radius	0.58±0.11	0.58±0.10	0.59±0.11	154	-1.3±3.3	152	-2.1±4.2	0.09	145	-3.2±4.5	<0.001
Total-body bone mineral‡				140		134		<0.001	131		<0.001
Hologic	1303±263	1250±248	1324±276	61	-1.3±6.5	61	0.6±5.8	—	63	1.0±6.1	—
Lunar	1444±328	1453±293	1481±279	79	0.0±4.8	73	3.1±4.3	—	68	4.5±5.7	—

*Bone mineral density and total-body bone mineral were measured by dual-energy x-ray absorptiometry. PTH denotes parathyroid hormone (1-34). P values are for the comparisons with the placebo group.

†The data for the lumbar spine, femoral neck, trochanter, intertrochanter, and total hip are in standardized units⁷ and expressed in grams per square centimeter; the data for the distal radius and shaft of the radius are in grams per square centimeter.

‡Data are expressed in grams. Because manufacturers have not standardized measurements of total-body bone mineral, we report the values according to the instrument used for measurement. Since each woman's total-body bone mineral was measured serially with the same instrument, tests of statistical significance included all data and allowed for an effect of the instrument used.

0.07, respectively). A total of 32 women in the placebo group (6 percent), 35 in the 20-µg parathyroid hormone group (6 percent), and 59 in the 40-µg group (11 percent) withdrew from the study because of an adverse event. Nausea was reported by 18 percent of women taking 40 µg of parathyroid hormone, and headache was reported by 13 percent, whereas only 8 percent of women taking placebo reported each of these symptoms ($P < 0.001$ and $P = 0.01$, re-

spectively); the frequencies of nausea and headache in the lower-dose parathyroid hormone group were similar to those in the placebo group. Nine percent of the women in the 20-µg parathyroid hormone group reported dizziness, and 3 percent reported leg cramps, but these symptoms were reported by only 6 percent and 1 percent of women in the placebo group, respectively ($P = 0.05$ and $P = 0.02$, respectively); the frequencies of dizziness and leg cramps in the 40-µg

parathyroid hormone group were similar to those in the placebo group. Preinjection blood pressure and heart rate, measured at each visit, were unaffected by treatment with parathyroid hormone (1-34).

Because subcutaneous injections of parathyroid hormone (1-34) have the greatest effect on serum calcium during the first four to six hours after injection, we measured serum calcium before and four to six hours after an injection of parathyroid hormone (1-34) at each visit. The preinjection measurements (performed 16 to 24 hours after the previous injection) were usually normal. Mild hypercalcemia (defined as a calcium concentration that exceeded 10.6 mg per deciliter [2.6 mmol per liter]) occurred at least once in 2 percent of the women in the placebo group, 11 percent of those in the 20- μ g parathyroid hormone group, and 28 percent of those in the 40- μ g group. Of the high serum calcium values, 95 percent were less than 11.2 mg per deciliter (2.80 mmol per liter) in the 20- μ g group, and 95 percent were less than 11.8 mg per deciliter (2.95 mmol per liter) in the 40- μ g group; in only about one third of the women with high serum calcium concentrations were the values high on retesting, which was usually performed within a few weeks. Women who did not have hypercalcemia during the first six months of treatment seldom had it later. The study protocol required permanently halving the injected dose of medication in women with persistent hypercalcemia after a reduction in calcium intake; this occurred in 3 women in the placebo group (<1 percent), 15 in the 20- μ g group (3 percent), and 62 in the 40- μ g group (11 percent). Treatment was withdrawn because of repeatedly elevated serum calcium concentrations in one woman in the placebo group, one in the 20- μ g group, and nine in the 40- μ g group.

Serum 25-hydroxyvitamin D and calcitriol concentrations were similar in the three groups at base line. Serum calcitriol concentrations increased significantly from the base-line values in each parathyroid hormone group and did not change in the placebo group. The mean 24-hour urinary calcium excretion increased slightly during parathyroid hormone (1-34) treatment (by 30 mg [0.75 mmol] per day), but the incidence of hypercalciuria (a value for urinary calcium excretion that exceeded 300 mg [7.5 mmol] per day) did not increase. Serum magnesium concentrations decreased slightly in both parathyroid hormone groups, and serum uric acid concentrations rose by 13 to 20 percent during treatment with parathyroid hormone at a dose of 20 μ g per day and by 20 to 25 percent at a dose of 40 μ g per day, without clinical sequelae. An average of five weeks after the cessation of treatment, serum calcium, magnesium, and uric acid concentrations had returned to or approached pretreatment values. Serum creatinine concentrations and creatinine clearance were unaffected by parathyroid hormone (1-34) treatment. Circulating antibodies to parathy-

roid hormone (1-34) developed in 1 woman in the placebo group (<1 percent), 15 women in the 20- μ g group (3 percent), and 44 in the 40- μ g group (8 percent), but these antibodies had no discernible effects on any of the other measurements.

DISCUSSION

Daily injections of parathyroid hormone (1-34) at a dose of 20 μ g and daily injections at a dose of 40 μ g increased the bone mineral density of the spine by 9 and 13 percentage points more than did placebo, and reduced the risk of new vertebral fractures by 65 and 69 percent, respectively, as compared with placebo. These benefits exceed those reported for other treatments in similar women. In studies using similar analyses, alendronate (10 mg per day) reduced the risk of new vertebral fractures by 48 percent,¹¹⁻¹³ risedronate (5 mg per day) by 41 percent,¹⁴ an intermittent regimen of cyclical etidronate by 44 percent,^{15,16} and raloxifene (60 mg per day) by 30 percent.¹⁷ Estimates of a 40 to 50 percent reduction in the risk of vertebral fractures with estrogen treatment are based on cohort and case-control studies or small placebo-controlled, prospective trials.^{18,19} Salmon calcitonin nasal spray has inconsistent effects on the risk of vertebral fractures,²⁰ and the effects of supplemental calcitriol,^{21,22} vitamin D,²³⁻²⁶ and calcium²⁷ on this end point cannot be estimated on the basis of the published data.

Daily treatment with parathyroid hormone (1-34) reduced the risk of nonvertebral fractures by 35 percent at the 20- μ g dose and by 40 percent at the 40- μ g dose and reduced the risk of nonvertebral fragility fractures by 53 and 54 percent, respectively. In similar women, alendronate reduced the risk of nonvertebral fractures by 20 percent,¹² risedronate by 39 percent,¹⁴ and raloxifene by 10 percent.¹⁷ The effects of etidronate^{15,16} and calcitonin²⁰ on the risk of nonvertebral fractures are not known. Vitamin D^{23,26} and calcitriol²² reduced the risk of nonvertebral fractures by 50 to 60 percent in some studies, but the effects of parathyroid hormone in our study are in addition to any effect of vitamin D, since all the women received vitamin D and calcium supplements.

These antifracture benefits make it important to understand the clinical relevance of the osteosarcomas found in rats given parathyroid hormone (1-34) in a standard carcinogenicity bioassay. In that study, the rats were given nearly lifetime daily injections of parathyroid hormone (1-34). The occurrence of osteosarcoma was dose-dependent, and the tumors developed after parathyroid hormone (1-34) had induced osteosclerosis. Parathyroid hormone (1-34) did not increase the incidence of tumors in other tissues in rats, nor were osteosarcomas found in monkeys that had undergone bilateral oophorectomy and then been given daily doses that were 4 to 10 times the maximal dose in humans over a period of 18 months. In stand-

ard tests, parathyroid hormone (1-34) is neither mutagenic nor genotoxic. In prior studies involving a total of nearly 1000 patients, treatment with parathyroid hormone (1-84), parathyroid hormone (1-34), or parathyroid hormone (1-38) for up to three years did not increase the incidence of bone tumors.²⁸ Osteosarcomas are rare in adults, and chronic primary hyperparathyroidism is not associated with an increased risk of osteosarcoma.^{29,30}

In summary, the clinical benefits of parathyroid hormone (1-34) reflect its ability to stimulate bone formation and thereby increase bone mass and strength. This hormone appears to be effective in preventing fractures in postmenopausal women with osteoporosis.

Supported by Eli Lilly.
Dr. Eriksen owns stock in Eli Lilly.

We are indebted to Drs. Hunter Heath III and John T. Potts, Jr., for their comments on the manuscript and to Ms. Michele Y. Hill for editorial assistance and assistance in the preparation of the manuscript.

APPENDIX

The following additional investigators participated in the study: *Argentina* — C.A. Mautalen, Buenos Aires; *Austria* — G. Leb, Astrid Fahrleitner, H. Dobnig, Graz; *Belgium* — J.P. Devogelaer, Brussels; J.-M. Kaufman, Ghent; *Canada* — J.P. Brown, Sainte-Foy, Que.; D.A. Hanley, Calgary, Alta.; R.G. Josse, G.A. Hawker, S. Mann, Toronto; W.P. Olszynski, Saskatoon, Sask.; L.G. Ste-Marie, Montreal; M.O. Al-Daker, Regina, Sask.; C.K. Yuen, Winnipeg, Man.; S. Kaiser, St. John's, Newf.; A.B. Cranney, Ottawa, Ont.; K.G. Siminoski, Edmonton, Alta.; *Czech Republic* — J. Stepan, Prague; O. Topolcan, V. Vyskocil, Plzen-Bory; V. Palicka, Kralove; *Denmark* — L. Hyldstrup, Hvidovre; P. Laurberg, Aalborg, Otto Grove, Varde; H. Beck-Nielsen, Odense; *Finland* — E. Alhava, Kuopio; M. Korhonen, Turku; P. Salmela, K. Rontgen, J.E. Heikkinen, Oulu; J. Salmi, Tampere; M. Valimaki, I. Arnala, Helsinki; J. Saltevo, Jyväskylä; *Hungary* — G. Poor, J. Szuecs, Budapest; L. Gaspar, Szeged; *Israel* — A. Karasik, I. Vered, Tel-Hashomer; E. Segal, Haifa; *Italy* — C. Gennari, Siena; G. Crepaldi, L. Sartori, Padua; A. Pinchera, Pisa; G. Mazzuoli, Rome; M. Passeri, Parma; G. Bianchi, Arezano; *New Zealand* — N.L. Gilchrist, Canterbury; *Norway* — J.B. Michelsen, Kristiansand; J.A. Falch, Oslo; E. Mohr, Haugesund; S.S. Gudnason, Bergen; U. Syversen, Trondheim; *Poland* — M. Talalaj, P. Kapuscinski, J. Borowicz, E. Sawicka, J. Lesnicki, A. Olak-Popko, Warsaw; T. Miazgowski, J. Ogonowski, S. Czekalski, Szczecin; *Sweden* — S. Ljung-hall, K. Larsson, Uppsala; M. Palmer, Orebro; G. Toss, Linkoping; M. Saaf, Stockholm; *United States* — M.A. Bolognese, Gaithersburg, Md.; C. McKeever, Houston; L. Avioli (deceased), St. Louis; E.S. Orwoll, Portland, Oreg.; M. Greenwald, Palm Springs, Calif.; R.D. Wasnich, Honolulu; S.R. Weiss, San Diego, Calif.; W. Briney, Denver; C. Gallagher, Omaha, Neb.; O.S. Gluck, Phoenix, Ariz.; M.H. Davidson, Chicago; S.C. English, Billings, Mont.; N.M. Lunde, Arden Hills, Minn.; M.R. Khairi, Indianapolis; J. Rosenstock, Dallas; A.A. Licata, Cleveland; A.L. Burshell, New Orleans; C.E. Lewis, Birmingham, Ala.; A.L. Mulloy, Augusta, Ga.; M.P. Ettinger, Stuart, Fla.; A. Virshup, West Palm Beach, Fla.; S.B. Ward, Philadelphia; N. Wei, Frederick, Md.; J. Stock, Morristown, N.J.; S. Wallach, R. Bockman, New York; C.J. Rosen, Bangor, Me.; C.E. Waud, Worcester, Mass.; R. Marcus, Palo Alto, Calif.; R. Levy, Olympia, Wash.; S.S. Miller, San Antonio, Tex.; S. Songcharoen, Jackson, Miss.; K.D. Schlessel, Willingboro, N.J.; L.M. Cohen, Sarasota, Fla.; V.K. Piziak, Temple, Tex.; S. Scumpia, Austin, Tex.; R.R. Stoltz, Evansville, Ind.

REFERENCES

- Podbesek R, Edouard C, Meunier PJ, et al. Effects of two treatment regimes with synthetic human parathyroid hormone fragment on bone formation and the tissue balance of trabecular bone in greyhounds. *Endocrinology* 1983;112:1000-6.
- Hock JM, Gera I. Effects of continuous and intermittent administration and inhibition of resorption on the anabolic response of bone to parathyroid hormone. *J Bone Miner Res* 1992;7:65-72.
- Tam CS, Heersche JN, Murray TM, Parsons JA. Parathyroid hormone stimulates the bone apposition rate independently of its resorptive action: differential effects of intermittent and continuous administration. *Endocrinology* 1982;110:506-12.
- Dempster DW, Cosman F, Parisien M, Shen V, Lindsay R. Anabolic actions of parathyroid hormone on bone. *Endocr Rev* 1993;14:690-709. [Erratum, *Endocr Rev* 1994;15:261.]
- Turner CH, Wang T, Hirano T, et al. In primates, treatment with PTH (1-34), LY333334, increases bone strength at trabecular bone sites without compromising the strength of cortical bone. *J Bone Miner Res* 1999;14: Suppl 1:S414. abstract.
- Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993;8:1137-48.
- Lu Y, Ye K, Mathur AK, Hui S, Fuerst TP, Genant HK. Comparative calibration without a gold standard. *Stat Med* 1997;16:1889-905.
- Lu Y, Mathur AK, Blunt BA, et al. Dual X-ray absorptiometry quality control: comparison of visual examination and process-control charts. *J Bone Miner Res* 1996;11:626-37.
- Neer R, Slovik D, Daly M, Lo C, Potts J, Nussbaum S. Treatment of postmenopausal osteoporosis with daily parathyroid hormone plus calcitriol. In: Christiansen C, Overgaard K, eds. *Osteoporosis 1990: proceedings of the Third International Symposium on Osteoporosis*. Copenhagen, Denmark: Osteopress ApS, 1990:1314-7.
- Hodsman AB, Steer BM, Fraher LJ, Drost DJ. Bone densitometric and histomorphometric responses to sequential human parathyroid hormone (1-38) and salmon calcitonin in osteoporotic patients. *Bone Miner* 1991;14:67-83.
- Liberman UA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995;333:1437-43.
- Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;348:1535-41.
- 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.
- 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 trial. *JAMA* 1999;282:1344-52.
- Storm T, Thamsborg G, Steiniche T, Genant HK, Sørensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990;322:1265-71.
- Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990;323:73-9.
- 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.]
- Lufkin EG, Wahner HW, O'Fallon WM, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992;117:1-9.
- Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomized women. *Lancet* 1980;2:1151-4.
- Chesnut CH, Silverman SL, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures study. *Am J Med* 2000;109:267-76.
- Ott SM, Chesnut CH. Calcitriol treatment is not effective in postmenopausal osteoporosis. *Ann Intern Med* 1989;110:267-74.
- Tilyard MW, Spears GFS, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med* 1992;326:357-62.
- Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D₃ and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992;327:1637-42.
- Heikkinen RJ, Inkovaara JA, Harju EJ, et al. Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int* 1992;51:105-10.
- Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. *Ann Intern Med* 1996;124:400-6.
- Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997;337:670-6.
- Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in post-

menopausal women: a randomized controlled trial. *Am J Med* 1995;98:331-5.

28. Horwitz M, Stewart A, Greenspan SL. Sequential parathyroid hormone/alendronate therapy for osteoporosis — robbing Peter to pay Paul? *J Clin Endocrinol Metab* 2000;85:2127-8.

29. Palmer M, Adami HO, Krusemo UB, Ljunghall S. Increased risk of

malignant diseases after surgery for primary hyperparathyroidism: a nationwide cohort study. *Am J Epidemiol* 1988;127:1031-40.

30. Wermers RA, Khosla S, Atkinson EJ, et al. Survival after the diagnosis of hyperparathyroidism: a population-based study. *Am J Med* 1998;104:115-22.

Copyright © 2001 Massachusetts Medical Society.