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The Effect of Teriparatide [Human Parathyroid Hormone (1-34)] Therapy on Bone Density in Men With Osteoporosis

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ABSTRACT

Teriparatide [rhPTH(1-34)] increases bone mineral density and reduces the risk of vertebral fracture in women. We randomized 437 men with spine or hip bone mineral density more than 2 SD below the young adult male mean to daily injections of placebo, teriparatide 20 μg, or teriparatide 40 μg. All subjects also received supplemental calcium and vitamin D. The study was stopped after a median duration of 11 months because of a finding of osteosarcomas in rats in routine toxicology studies. Biochemical markers of bone formation increased early in the course of therapy and were followed by increases in indices of osteoclastic activity. Spine bone mineral density was greater than in placebo subjects after 3 months of teriparatide therapy, and by the end of therapy it was increased by 5.9% (20 μg) and 9.0% (40 μg) above baseline ($p < 0.001$ vs. placebo for both comparisons). Femoral neck bone mineral density increased 1.5% (20 μg; $p = 0.029$) and 2.9% (40 μg; $p < 0.001$), and whole body bone mineral content increased 0.6% (20 μg; $p = 0.021$) and 0.9% (40 μg; $p = 0.005$) above baseline in the teriparatide subjects. There was no change in radial bone mineral density in the teriparatide groups. Bone mineral density responses to teriparatide were similar regardless of gonadal status, age, baseline bone mineral density, body mass index, smoking, or alcohol intake. Subjects experienced expected changes in mineral metabolism. Adverse events were similar in the placebo and 20-μg groups, but more frequent in the 40-μg group. This study shows that teriparatide treatment results in an increase in bone mineral density and is a potentially useful therapy for osteoporosis in men. (J Bone Miner Res 2003;18:9–17)

Key words: teriparatide, osteoporosis, men, drug therapy, bone density

INTRODUCTION

ALTHOUGH LESS common than in women, osteoporosis in men is nevertheless a substantial public health problem.[1] Bone mineral density (BMD) is commonly low in older men and is closely linked to increased fracture risk.[2] Approximately 27% of hip fractures—the most devastating consequence of osteoporosis—occur in men, and the number is expected to increase as the elderly population expands.[3] The risk of symptomatic vertebral fracture also increases quickly with age in men.[4] Approximately 30% of older white men have prevalent vertebral deformities,[5] and men with vertebral fractures suffer disabilities, including pain and loss of function.[6] Hip fracture is four times more likely in men who have suffered a vertebral fracture than in the general population.[7]

Osteoporosis in men is commonly idiopathic,[8] and few potential treatments for the condition have been adequately evaluated. In one large trial, antiresorptive therapy with alendronate increased BMD and reduced vertebral fracture risk in osteoporotic men.[9] In postmenopausal women with prior vertebral fractures, parathyroid hormone of recombinant DNA origin [rhPTH(1-34)], or teriparatide, an amino-terminal analog of native parathyroid hormone, increases BMD and reduces vertebral and nonvertebral fracture incidence.[10] Although anabolic therapies have been less well studied in men, in small trials parathyroid hormone (1-34) therapy has increased BMD,[11,12] suggesting that it could

Drs Orwoll, Diez-Perez, and Kaufman have been consultants for Eli Lilly & Co. Ms Clancy and Dr Scheele, Paul, and Gaich are employees of Eli Lilly & Co. Drs Adami and Syversen have no conflicts of interest.

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be useful in the treatment of men with osteoporosis. In this trial, we determined the usefulness of teriparatide in a large group of men with bone density more than 2 SD below the mean for young adult males. In addition, we assessed the influence of sex steroid levels, smoking, and other factors on the response to teriparatide.

MATERIALS AND METHODS

Subjects

Men were recruited at 37 centers in 11 countries from hospital clinics and community practices. Subjects were eligible if they were aged 30–85 years, ambulatory, free of chronic, disabling conditions other than osteoporosis, and had lumbar spine or proximal femur (neck or total hip) BMD at least 2 SD below the average for young, healthy men (lumbar spine: 0.871 g/cm^2 for Hologic densitometers and 0.980 g/cm^2 for Lunar densitometers). Investigators were encouraged to enroll equal numbers of subjects with low and normal free testosterone.

Men with secondary causes of metabolic bone disease, including glucocorticoid excess, were excluded. Other reasons for exclusion were the use of estrogen agonists or antagonists, coumarins and indandione derivatives, anticonvulsants (other than benzodiazepines), calcium- or aluminum-containing antacids, or any other drug known to affect bone metabolism; nephrolithiasis or urolithiasis within 2 years of randomization; sprue, inflammatory bowel disease, malabsorption syndrome, or any indication of poor intestinal absorption of calcium, such as the combination of low urinary calcium excretion and elevated serum intact parathyroid hormone level within 1 year of randomization; significantly impaired hepatic or renal function; or alcohol (>6 drinks/day) or drug abuse within 1 year of randomization. Subjects were excluded if within 1 year of randomization they had metabolic bone disorders other than primary osteoporosis, such as Paget's disease, renal osteodystrophy, osteomalacia, or other disorders that are known to affect bone metabolism. Serum calcium and endogenous serum parathyroid hormone levels, and 24-h urine calcium excretion, were normal in all subjects. Men who had received treatment within 6 months for osteoporosis with androgen or other anabolic steroid therapy, calcitonins, progestins, fluorides, oral bisphosphonates, vitamin D >50,000 IU/week, or calcitriol analogs were not eligible. However, hypogonadal patients whose doses of androgens or other anabolic steroids had been stable for at least 6 months before randomization were eligible and continued such therapy during the study. Subjects with growth hormone deficiency from any cause, including previous pituitary surgery, tumor, or radiation, were not eligible for enrollment. Men were also excluded if they had suspected carcinoma or a history of carcinoma (with the exception of skin cancer) within 5 years of randomization. Men with abnormalities of the lumbar spine severe enough to prohibit assessment of BMD were not eligible. Ethical review boards at each center approved the study, and patients gave written informed consent to participation.

Treatment

Subjects were assigned (by centralized block randomization with a block size of three) to receive placebo, 20 μg teriparatide, or 40 μg of teriparatide (produced using recombinant DNA technology; Eli Lilly and Co., Indianapolis, IN, USA). The randomization sequence was generated from a random number table and was stratified based on the initial morning testosterone measurement (normal vs. low for the patient's age). Investigators and patients were blinded to treatment assignment.

Patients self-administered daily subcutaneous injections of teriparatide or placebo using a HumaJect injection device (Eli Lilly and Co.). Compliance was assessed by counting the number of unused doses returned at study visits. Patients also received daily oral supplements of 1000 mg of calcium and 400-1200 IU of vitamin D beginning at least 1 month before randomization. The study was originally planned to last for 24 months, but was stopped early by the sponsor because of the finding of osteosarcomas during routine toxicology studies in Fischer 344 rats treated with teriparatide for near lifetime.[13]

Measurements

BMD was assessed using dual energy X-ray absorptiometry (DXA; Hologic Inc., Bedford, MA, USA, or Lunar, Madison, WI, USA). All scans were centrally reviewed and analyzed (Synarc, Portland, OR, USA), and vertebrae with fractures or artifacts were excluded from the analyses. Lumbar spine BMD was measured at baseline and at 3, 6, and 12 months and/or at a final study visit. Hip, whole body, and radial BMDs were measured at baseline and at 12 months and/or at a final study visit. Total body measurements excluded the head.

Biochemical markers of bone formation (serum bone alkaline phosphatase [bone ALP], serum procollagen I carboxyterminal [PICP]) and resorption (urinary N-telopeptide [NTX], urinary free deoxypyridinoline [fDPD]), and 1,25 dihydroxyvitamin D [1,25-$(OH)_2$D] were measured at baseline and 1, 3, 6, and 12 months. Bone ALP was measured by a two-site immunoradiometric assay (interassay CV $<$ 8%; Hybritech, San Diego, CA, USA); PICP was measured by an equilibrium radioimmunoassay (interassay CV $<$ 8%; DiaSorin, Stillwater, MN, USA), NTX was measured by a competitive-inhibition ELISA (interassay CV $<$ 11%; Ostex, Seattle, WA, USA), fDPD was measured by a competitive enzyme immunoassay (interassay CV $<$ 13%; Metra Biosystems, Mountain View, CA, USA), and 1,25-$(OH)_2$D was measured by a radioreceptor binding assay (interassay CV $<$ 10%; Quest Diagnostics, San Juan Capistrano, CA, USA). Serum calcium was measured 4–6 h after injection at 1, 3, 6, and 12 months. Calcium and creatinine excretion in 24-h urine specimens were measured at baseline and after 1, 6, and 12 months of treatment. If teriparatide-treated subjects had elevated serum calcium (uncorrected serum calcium $\geq$ 2.64 mM) or urinary calcium excretion exceeded 350 mg (8.8 mmol) per day, along with an increased urinary calcium-to-creatinine ratio, and if the increase occurred on retesting, the dose of the calcium supplement was reduced or discontinued, or the dose of the study drug was reduced by half at the discretion of the investigator.

Table 1. Baseline Subject Characteristics (Mean ± SD or Percentages)

Characteristic	*Placebo (N = 147)*	*Teriparatide, 20 μg (N = 151)*	*Teriparatide, 40 μg (N = 139)*
White race (%)	100	99	99
Age (years)	59 ± 13	59 ± 13	58 ± 13
Body mass index (kg/m^2)	25 ± 4	25 ± 4	25 ± 4
Calcium intake (g/day)	0.86 ± 0.57	0.84 ± 0.54	0.80 ± 0.50
Current smoker (%)	32	30	27
Current alcohol use (%)	69	76	65
Previous osteoporosis therapy (%)	12	15	18
Low serum free testosterone (%)	50	48	49
Vertebral BMD (g/cm^2)	0.85 ± 0.14	0.89 ± 0.15	0.87 ± 0.14
T-scores			
Lumbar spine	−2.4 ± 1.2	−2.0 ± 1.3	−2.2 ± 1.2
Femoral neck	−2.7 ± 0.8	−2.6 ± 0.8	−2.7 ± 0.8
Total hip	−1.9 ± 0.8	−1.8 ± 0.8	−1.9 ± 0.9

If the elevation remained on repeat testing, the study drug was discontinued.

Free testosterone levels were measured in two baseline serum samples, and the results were averaged for subsequent analyses. Testosterone levels were compared with age-matched normal reference ranges. Free testosterone was estimated using a specific, competitive radioimmunoassay (interassay CV $<$ 16%; Diagnostic Products Corp., Los Angeles, CA, USA). Serum levels of estradiol were also determined on baseline samples using a specific, double-antibody, sequential radioimmunoassay (interassay CV $<$ 10%; limit of detection, 1.4 pg/ml; Diagnostic Products Corp.). Complete blood count, serum chemistry, and urinalysis were measured at baseline, at 6 and 12 months, and/or at a final study visit. Intact serum parathyroid hormone (1-84) was assessed by a validated immunoradiometric assay (Phoenix International, Montreal, Canada) at baseline and 12 months. Serum antibodies to teriparatide were measured at baseline and 12 months using an indirect radioimmunoassay. Spontaneous adverse events were recorded at each study visit. Alcohol consumption and smoking were assessed at baseline and at the end of the study.

Statistical analysis

The primary objective of the study was the assessment of changes from baseline to endpoint in lumbar spine BMD over 2 years of treatment. Secondary objectives were to measure changes from baseline to endpoint in BMD of the total hip, femoral neck, intertrochanter, trochanter, radial, and whole body, and whole body bone mineral content (BMC). The results were analyzed on an intention-to-treat basis with the last observation carried forward to final point, and for longitudinal analyses included all patients with at least one postbaseline value. Continuous measures were analyzed by ANOVA, including terms for treatment and country. Because the distribution of the biochemical markers was highly skewed, ranked ANOVA was used, and medians were presented as measure of central tendency. For categorical measures, treatments were compared using Pearson's χ^2 test. All tests were two-tailed with a significance level of 0.05. Additional exploratory subgroup analyses were performed to assess relationships between baseline variables (such as baseline demographics, smoking and alcohol intake, sex hormones, BMD, and biochemical markers of bone turnover and formation) on changes from baseline to endpoint in BMD and biochemical markers of bone turnover. ANOVA with treatment, country, subgroup, and subgroup by treatment interaction was used to perform the subgroup analyses, and the interaction was tested at the 0.10 significance level. Statistical analyses used SAS v6.09 for MVS (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Of 959 men who were screened, 437 were eligible for enrollment and randomly assigned to either placebo (147 men) or teriparatide at a dose of 20 μg per day (151 men) or 40 μg per day (139 men). The baseline characteristics of the men in the three study groups were similar (Table 1). Two hundred eleven subjects (49%) had baseline serum free testosterone levels below age-matched reference groups. Nineteen men were receiving stable doses of androgens: seven in the placebo group, five in the 20-μg group, and seven in the 40-μg group.

Treatment duration for all patients in the analysis ranged from less than 2 months to 15 months. The median treatment exposure was 11 months but was somewhat less in the teriparatide groups than placebo (median of 328 days for placebo, 313 days for teriparatide 20 μg, and 302 days for teriparatide 40 μg; $p = 0.046$). Three hundred eleven (71.2%) subjects received teriparatide or placebo for at least 9 months: 114 (77.6%) in the placebo group, 106 (70.2%) in the 20-μg group, and 91 (65.5%) in the 40-μg group. Based on the number of unused injection devices returned at study visits, the average percentage of study medication taken in each treatment group was 79%.

Eighty-one patients withdrew early (17 in the placebo group, 28 in the 20-μg group, and 36 in the 40-μg group). Withdrawals occurred most often because of adverse events (39 patients) and patient decision (25 patients) and were more frequent in the teriparatide groups. Other reasons for

TABLE 2. PERCENT CHANGE IN BONE MINERAL DENSITY AND CONTENT FROM BASELINE TO STUDY ENDPOINT

	Placebo	*Teriparatide, 20 μg*		*Teriparatide, 40 μg*		
Skeletal measurement	*Percent change (mean ± SD)*	*Percent change (mean ± SD)*	p *value vs. placebo*	*Percent change (mean ± SD)*	p *value vs. placebo*	p *value, teriparatide 20 vs. 40 μg*
Bone mineral density (g/cm^2)						
Lumbar spine	0.52 ± 3.90	5.87 ± 4.50	<0.001	9.03 ± 6.46	<0.001	<0.001
Femoral neck	0.31 ± 4.1	1.53 ± 3.95	0.029	2.93 ± 6.34	<0.001	0.023
Trochanter	1.09 ± 3.30	1.33 ± 4.15	NS	2.08 ± 5.32	NS	NS
Intertrochanter	0.61 ± 2.87	1.18 ± 3.09	NS	2.34 ± 4.41	<0.001	0.012
Total hip	0.54 ± 2.70	1.17 ± 2.94	NS	2.33 ± 4.41	<0.001	0.009
Distal radius	−0.15 ± 1.87	−0.46 ± 2.39	NS	−0.56 ± 2.36	NS	NS
Ultradistal radius	−0.29 ± 3.17	−0.48 ± 3.21	NS	0.22 ± 5.82	NS	NS
Whole body	−0.36 ± 2.72	0.40 ± 2.93	NS	0.51 ± 2.43	0.023	NS
Whole body bone mineral content (g)	−0.45 ± 2.75	0.64 ± 3.65	0.021	0.87 ± 3.65	0.005	NS

NS, not significant.

discontinuation were use of excluded medication, clinically significant abnormalities of clinical laboratory values, lack of efficacy caused by progressive disease, noncompliance, loss to follow-up, moving away, physician decision, failure to meet an entry criterion, and death.

BMD and whole body BMC

Daily treatment with teriparatide at both the 20-μg and 40-μg doses dose-dependently increased lumbar spine and femoral neck BMD (Table 2). Whole body BMC also increased in both teriparatide groups. Lumbar spine BMD was greater in the teriparatide groups than in placebo beginning at 3 months (Fig. 1). Approximately 40% of patients in the placebo group had a net decrease in lumbar spine BMD at the end of the study, whereas lumbar spine BMD decreased in 7.1% of patients in the teriparatide 20 μg group and 6.2% in the teriparatide 40 μg group. Lumbar spine BMD increased by 5% or more in 55% of patients in the 20-μg group and in 71% of patients in the 40-μg group compared with 9.8% in the placebo group. At study endpoint, the percent changes in total hip, intertrochanteric, and whole body BMD in the 40-μg group were greater than that observed in the placebo group (Table 2). BMD measures at the distal and ultradistal radius were not different between the teriparatide and placebo groups.

Biochemical markers of bone remodeling

Treatment with teriparatide was associated with dose-dependent increases in biochemical indices of bone formation (bone ALP, PICP) and resorption (NTX, fDPD) (Fig. 2). Markers of osteoblastic activity were increased after 1 month of teriparatide treatment ($p < 0.001$), but were stable (PICP) or declined slightly (bone ALP) in the placebo group. In the teriparatide groups, bone ALP concentrations reached a maximum after 6–12 months of therapy and were 29% and 59% above baseline in the 20- and 40-μg groups, respectively, at 12 months ($p < 0.001$ for both comparisons). Serum PICP levels peaked after 1 month of teriparatide therapy in both the 20-μg and 40-μg groups ($p <$ 0.001) and declined thereafter. Bone resorption markers (NTX and fDPD) were stable in the placebo group but increased in both teriparatide groups. The urinary excretion of both NTX and fDPD was above that in the placebo group at 1 month and remained elevated throughout the rest of the trial.

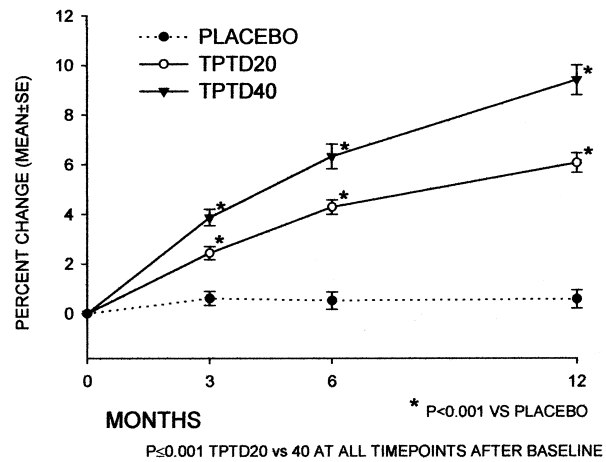

FIG. 1. Percent change (mean ± SE) in lumbar spine bone mineral density from baseline to endpoint for observed cases at 3, 6, and 12 months. TPTD20, teriparatide 20 μg; TPTD40, teriparatide 40 μg.

Mineral metabolism

Mean serum calcium concentrations measured at 4–6 h after injection of teriparatide were higher in the teriparatide groups at all time points ($p < 0.001$ vs. placebo; Fig. 3). Serum calcium levels were above the upper limit of normal (>2.64 mM) in 6.2% of subjects receiving 20 μg of teriparatide ($p = 0.003$ vs. placebo) and in 16.8% receiving 40 μg of teriparatide ($p < 0.001$ vs. placebo). Nearly all of these episodes occurred in the first 28 weeks of the trial (89% and 91% in the 20-μg and 40-μg groups, respectively). Two patients in the 20-μg group and eight in the 40-μg group

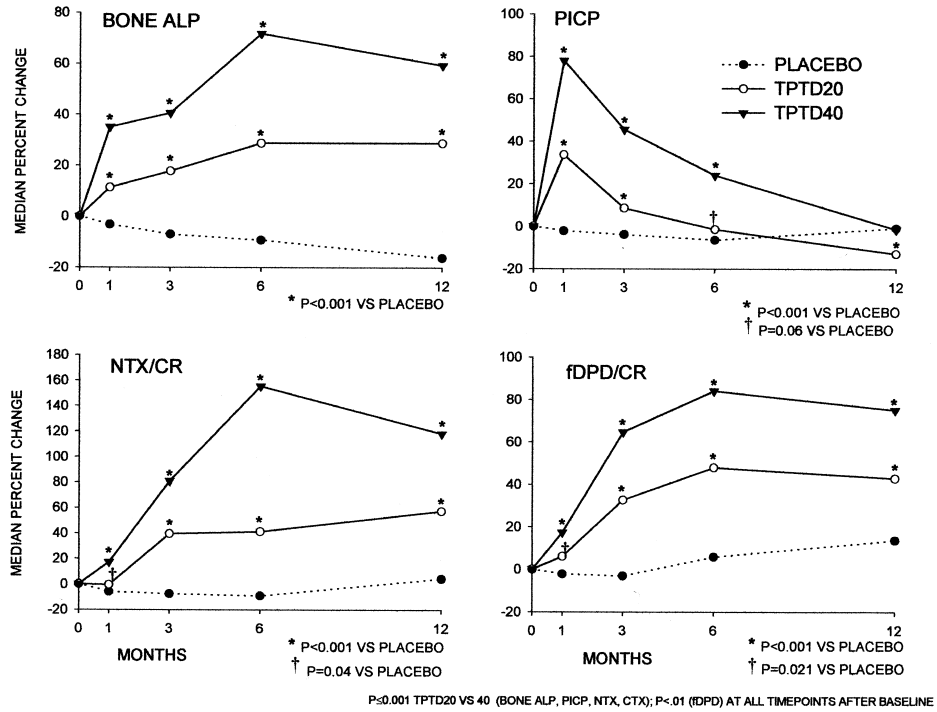

FIG. 2. Median percent changes from baseline in biochemical markers of bone formation (top) and resorption (bottom) from baseline to endpoint for observed cases at 1, 3, 6, and 12 months. Bone ALP, bone alkaline phosphatase; PICP, procollagen I carboxy-terminal; NTX/CR, urinary N-telopeptide/creatinine ratio; fDPD/CR, free deoxypyridinoline/creatinine ratio; TPTD20, teriparatide 20 μg; TPTD40, teriparatide 40 μg.

experienced elevated postdose serum calcium concentrations more than once. Calcium supplementation was reduced in 4 patients in the 20-μg group and in 12 patients in the 40-μg group because of elevated postdose serum calcium levels, increased 24-h urine calcium excretion, or symptoms such as nausea or headache. The dose of teriparatide was reduced from 40 to 20 μg in seven patients. Three patients (2%) in the 20-μg group and six patients (4%) in the 40-μg group were withdrawn from the study because of elevated postinjection serum calcium levels.

Treatment increased the mean urinary calcium excretion in all groups (20–40 mg/day above baseline; Fig. 3), but the increase occurred after calcium and vitamin D supplementation began at the start of the study and did not increase further with the institution of teriparatide or placebo therapy. There were no differences among treatment groups in the frequency of abnormal urine calcium excretion (>350 mg [8.8 mmol] per 24 h) or urinary calcium to creatinine ratio (>1.0 mmol calcium/mmol creatinine).

Concentrations of serum 1,25-$(OH)_2$D increased in both teriparatide groups compared with placebo (Fig. 4). In both teriparatide groups, 1,25$(OH)_2$D peaked at 1 month ($p <$ 0.001 vs. placebo for both teriparatide groups) and remained elevated throughout the study. By month 12, serum intact parathyroid hormone (1-84) was reduced below the limit of quantitation (16 pg/ml) in 91.9%, 89.8%, and 88.1% of patients in the placebo, 20-μg, and 40-μg groups, respectively. Serum from two patients had binding activity for antibodies to teriparatide in an initial assay, but neither patient had a positive test for antibody specific to teriparatide on subsequent testing.

The incidence of urolithiasis was not different in placebo (0.7%) and teriparatide groups (1.3% and 1.4% in the 20-μg and 40-μg groups, respectively; $p = 0.81$). Uric acid levels reached a value above the upper limit of normal in 0.7% of patients in the placebo group, in no patients in the 20-μg group, and in 2.3% of patients in the 40-μg group. Values below the lower limit of normal were seen for serum chloride (2.1% of patients in the placebo group, 1.4% in the 20-μg group, and 1.5% in the 40-μg group) and for serum magnesium (2.3% in the 40-μg group), but these findings were not associated with an adverse clinical event.

Subgroup analyses

Lumbar spine BMD responses to treatment were independent of baseline free testosterone (interaction, $p = 0.288$) or estradiol (interaction, $p = 0.398$; Fig. 5). Changes in BMD at other sites and changes in biochemical markers of bone remodeling stimulated by therapy were also unrelated to baseline free testosterone or estradiol levels (data not shown). The response to treatment was unaffected by age, body mass index (BMI), baseline lumbar spine BMD, smoking, and alcohol intake (data not shown).

Adverse events

Two patients died during the study (both in the 20-μg group); neither death was considered related to study drug or procedures. Three cancers occurred in the placebo group, three in the 20-μg group and none in the 40-μg group. There were no cases of osteosarcoma. The overall incidence of adverse events was similar in the three groups. Thirty-nine patients (8.9%) withdrew from the study because of an adverse event, including 7 (4.8%) in the placebo group, 14 (9.3%) in the teriparatide 20 μg group, and 18 (12.9%) in the teriparatide 40 μg group ($p = 0.052$ by overall comparison). The most common drug-related reason for with-

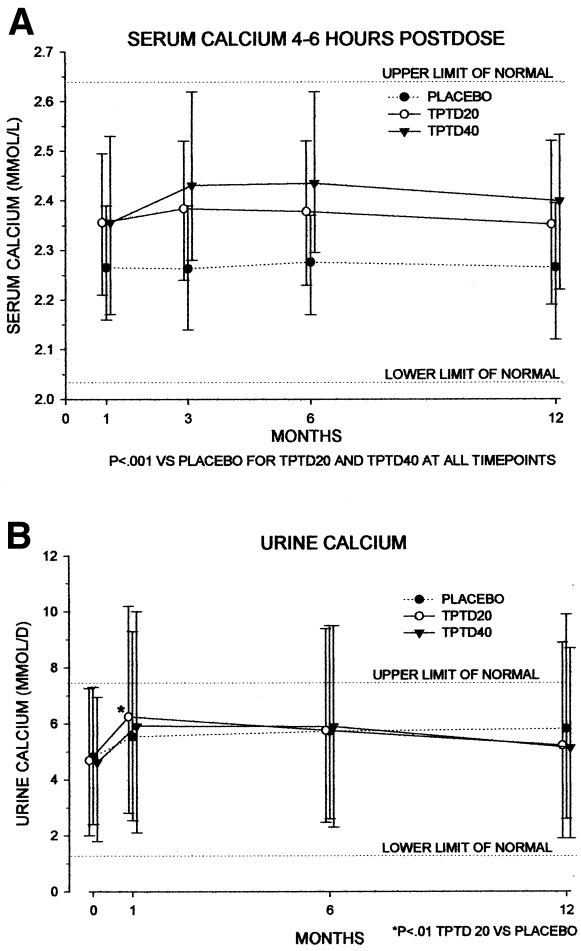

FIG. 3. (A) Serum calcium levels (mean and 10th to 90th percentiles) 4–6 h after teriparatide injection (postdose) during the trial. (B) Urine calcium excretion during the trial. Because some participants did not complete 12 months of study, the number of subjects included in the analyses at the 12-month time point represents approximately one-half those completing the trial. TPTD20, teriparatide 20 μg; TPTD40, teriparatide 40 μg.

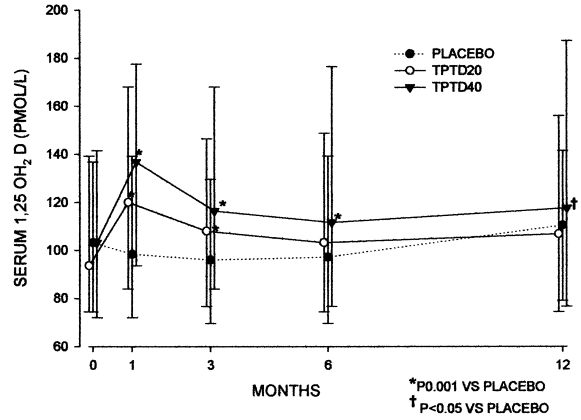

FIG. 4. 1,25-Dihydroxyvitamin D concentrations at 1, 3, 6, and 12 months (mean and 10th to 90th percentiles). Because some participants did not complete 12 months of study, the number of subjects included in the analysis at the 12-month time point represents approximately one-half those completing the trial. TPTD20, teriparatide 20 μg; TPTD40, teriparatide 40 μg.

drawal was nausea, (3.6% in the 40-μg group but none in the 20-μg or placebo groups). Nausea was reported by 26 patients (18.7%) in the 40-μg group ($p < 0.001$ vs. placebo), 8 (5.3%) in the 20-μg group, and 5 (3.4%) in the placebo group. Headache occurred more frequently in the 40-μg group (15 patients, 10.8%; $p = 0.053$ by overall comparison), but was not more severe than in the other groups. Nonvertebral fractures occurred in three patients in the placebo group, two in the 20-μg group, and in one in the 40-μg group (differences statistically nonsignificant). One patient (in the 40-μg group) withdrew because of headache. There were no changes in blood pressure or pulse.

DISCUSSION

Daily injections of teriparatide increased spinal and femoral BMD and whole body BMC in men with osteoporosis. The increase in lumbar spine BMD occurred rapidly (by 3 months of therapy) and continued throughout the treatment period. These findings are similar to those reported by Kurland et al.[12], who noted increases in BMD in men with idiopathic osteoporosis treated with parathyroid hormone (1-34). The time course and magnitude of the change in spinal BMD in the current study was similar to that seen in a study of teriparatide in women.[10,14] Although the duration of therapy in the present trial was short (median, 11 months), the increases in BMD with teriparatide therapy exceeded those seen with alendronate therapy in men after 1 year.[9]

The rapid, dose-dependent increases in biochemical indices of bone turnover, similar to those previously reported,[12] are consistent with an anabolic mode of action for teriparatide. The increases indicate a global activation of remodeling, whereas the rapid and sustained gain in BMD during treatment with teriparatide indicates a continuously positive coupling balance in favor of bone formation. The early increase in BMD suggests a rapid stimulation of osteoblastic activity by teriparatide, possibly through a stimulation of existing osteoblasts or activation of lining cells.[15] This response is quite different than that occurring after antiresorptive therapy, when markers of bone turnover are suppressed, reflecting reduced bone remodeling.[16] The pattern of response of serum PICP, which was short-lived and distinct from that of serum bone ALP, supports the idea that not all markers provide interchangeable information on osteoblastic function. The reasons for these distinct patterns of response are uncertain, but effects of teriparatide on osteoblasts are complex and may include stimulation of active osteoblasts, activation of lining cells, recruitment and differentiation of osteoblast precursors, and reduction of osteoblast apoptosis.[12]

Teriparatide-treated subjects experienced expected changes in mineral homeostasis, including minor increases in serum calcium 4–6 h after injection and increased $1,25(OH)_2D$ levels 1 month after therapy began, indicating an independent action of teriparatide on mineral metabolism. Urine calcium increased in all groups after calcium

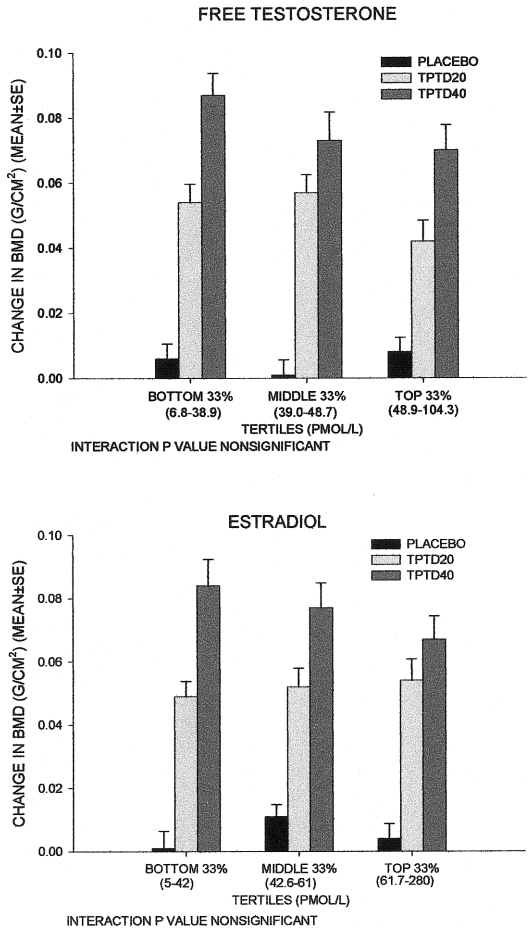

FIG. 5. Change (mean ± SE) in lumbar spine BMD from baseline to endpoint by tertiles of serum free testosterone and estradiol. TPTD20, teriparatide 20 μg; TPTD40, teriparatide 40 μg. (Interaction p values nonsignificant.)

and vitamin D supplementation began, suggesting that calcium and vitamin D supplementation had the major effect on calcium excretion. Endogenous PTH was suppressed below the limit of quantitation in the placebo and teriparatide groups. Kurland et al.[12] also found that endogenous PTH fell by 50% from baseline at 6 months in a group of osteoporotic men treated with 400 IU PTH (1-34) daily (approximately equivalent to 25 μg), and was 40% lower after 18 months of therapy ($p = 0.05$ vs. placebo). However, Cosman et al.[17] showed that postmenopausal women treated with teriparatide 400 IU daily for up to 3 years had no loss of endogenous PTH response.

About one-half of the participants had serum levels of free testosterone below age-related normal ranges. Nevertheless, increases in BMD and bone turnover markers in response to teriparatide were independent of baseline testosterone and estradiol concentrations. This observation is notable because in in vitro and animal studies, sex steroids affect the responsiveness of osteoblastic cells to parathyroid hormone.[18–20] Low levels of testosterone and estrogen are common in men with osteoporosis,[21] but based on the results of this study, are not a factor in the response to teriparatide. Moreover, alcohol consumption and aging, conditions that have been associated with reduction in bone formation, did not reduce either the stimulation of bone remodeling or the increase in BMD induced by teriparatide.

The planned duration of the trial was 24 months, but the finding of osteosarcomas in rats given teriparatide in a standard carcinogenicity assay led to early termination of drug administration. The total exposure to teriparatide was limited to a median duration of 11 months. Extensive review has concluded that the finding in rats [exposed to daily doses of PTH(1-34) for most of their lives] is not predictive of an increased risk for humans treated in adulthood for relatively short periods.[22] No osteosarcomas were seen in nonhuman primates that underwent bilateral oophorectomy and were given daily doses of teriparatide 4–10 times the maximal dose in humans for 18 months. In several standard tests (the in vitro bacterial mutagenesis assay with and without metabolic activation, the mouse lymphoma assay for mammalian cell mutation, the chromosomal aberration assay in Chinese hamster ovary cells, and the in vivo micronucleus test in mice), teriparatide was neither mutagenic nor genotoxic. No osteosarcomas have been seen in men and women exposed to the drug for up to 18 months in clinical trials and followed for up to 3 years (approximately 2500 patients).[10,23–26] In addition, published epidemiological studies have reported no increase in the incidence of osteosarcoma in patients with primary hyperparathyroidism.[27,28] In an examination of the Swedish Cancer Registry, investigators found no increased risk of primary tumors of bone in 12,644 men and women with a history of parathyroid adenoma.[22]

In general, therapy with teriparatide was well tolerated, particularly in the 20-μg treatment group. Although hypercalcemia occurred 4–6 h after injection in a small number of subjects, the increase was transient, usually mild, and of limited clinical importance. In the 20-μg treatment group, elevated serum calcium levels led to a reduction in the dose of supplemental calcium in only four patients (3%) and discontinuation of participation in three patients (2%). A reduction in the dose of teriparatide was not needed in any patients treated with 20 μg. Other adverse events occurred with similar frequency in the placebo and 20-μg groups. The 40-μg dose of teriparatide resulted in greater changes in BMD than 20 μg, but at the expense of more frequent adverse effects. Nausea and headache were more common in the teriparatide treatment groups, accounting for most treatment withdrawals caused by adverse events. Hypercalcemia was also more common in those treated with 40 μg and led to teriparatide dose reductions and discontinuation of therapy in a small number of patients. Of note, hypercalciuria was not a problem, possibly because of the short duration of action of subcutaneously injected teriparatide or its intrinsic stimulation of renal calcium conservation. The small increases in urinary calcium excretion seemed to primarily be the result of calcium and vitamin D supplementation.

The study has several limitations; the primary one in its relatively short duration. In a previous trial in men, 400 IU daily of parathyroid hormone (1-34), approximately equivalent to 25 μg, increased lumbar spine BMD by

13.5% by month 18 of treatment. Such increases in BMD could be associated with a substantial reduction in fracture risk.[12] Another limitation is that the subject population was almost entirely white, and the effects of teriparatide on bone mass in other ethnic groups remains undetermined. Finally, the study was not designed to assess incident fractures.

In summary, once-daily administration of teriparatide resulted in increased BMD at the spine and proximal femur, and increased whole body BMC, after a median treatment duration of 11 months. Treatment was associated with few adverse effects, especially in the 20-μg treatment group, although occasional, transient hypercalcemia occurred 4–6 h after teriparatide injection and resulted in occasional reductions in the calcium (but not teriparatide dose) in the 20-μg group. The effects of teriparatide on markers of bone turnover and BMD were similar to those seen in a trial in postmenopausal women, who experienced dramatic reductions in the risk of vertebral and nonvertebral fractures.[10]

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