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Teriparatide for Idiopathic Osteoporosis in Premenopausal Women: A Pilot Study

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Context: Premenopausal women with idiopathic osteoporosis (IOP) have abnormal cortical and trabecular bone microarchitecture.

Objective: The purpose of this study was to test the hypotheses that teriparatide increases bone mineral density (BMD) and bone formation and improves trabecular microarchitecture and stiffness in women with IOP.

Design: This was an open-label pilot study.

Setting: The setting was a tertiary care referral center.

Patients: Participants were 21 premenopausal women with unexplained fragility fractures or low BMD.

Intervention: Teriparatide was administered at 20 μg daily for 18 to 24 months.

Main Outcome Measures: The primary endpoint was within-subject percent change in lumbar spine BMD. Secondary endpoints included percent change in hip and forearm BMD, transiliac biopsy parameters (trabecular bone volume, microarchitecture, stiffness, and adipocytes), serum N-terminal propeptide of procollagen type 1 (P1NP), and C-telopeptide.

Results: BMD increased at the spine (10.8 $\pm$ 8.3% [SD]), total hip (6.2 $\pm$ 5.6%), and femoral neck (7.6 $\pm$ 3.4%) (all $P < .001$). Serum P1NP doubled by 1 month, peaked at 6 months, and returned to baseline by 18 to 24 months. Transiliac biopsies demonstrated significant increases in cortical width and porosity and trabecular bone volume and number increased, mirrored by a 71% increase in trabecular bone stiffness ($P < .02$–$.001$). Adipocyte area, perimeter, and volume/marrow volume decreased, with no change in adipocyte number. Four women had no increase in BMD and a blunted, delayed increase in serum P1NP. Nonresponders had markedly lower baseline bone formation rate (0.002 $\pm$ 0.001 vs 0.011 $\pm$ 0.006 mm^2/mm/y; $P < .001$) and higher serum IGF-1 (208 $\pm$ 54 vs 157$\pm$ 44 ng/mL; $P = .03$).

Conclusions: Teriparatide was associated with increased spine and hip BMD and improved trabecular microarchitecture and stiffness at the iliac crest in the majority of women with IOP. **(*J Clin Endocrinol Metab* 98: 0000–0000, 2013)**

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CTx, C-telopeptide; DXA, dual-energy X-ray absorptiometry; IOP, idiopathic osteoporosis; μCT, microcomputed tomography; μFE, microfinite element analysis; 25-OHD, 25-hydroxyvitamin D; P1NP, N-terminal propeptide of procollagen type 1.

Idiopathic osteoporosis (IOP) affects young, otherwise healthy individuals with intact gonadal function and no secondary cause of bone loss or fragility (1). Compared with normal premenopausal women, those with IOP have abnormal bone microarchitecture with thinner cortices; fewer, thinner, more widely separated and heterogeneously distributed trabeculae (2); more rod-like trabecular structure; lower trabecular stiffness (2); and higher marrow fat (3). Bone remodeling, assessed by serum bone turnover markers (1) or transiliac biopsies (2), showed normal or high bone turnover in some, whereas others had low bone formation and higher serum IGF-1 concentrations. IGF-1 is anabolic for osteoblasts, which suggests that osteoblast dysfunction, possibly related to osteoblast IGF-1 resistance, may contribute to the pathogenesis of IOP in some women (2). The osteoanabolic agent, teriparatide, increases bone mineral density (BMD) and reduces fracture incidence in postmenopausal women (4) and glucocorticoid-induced osteoporosis (5, 6), and increases BMD in men with IOP (7, 8). We hypothesized that teriparatide would increase bone formation and BMD and improve trabecular microarchitecture and stiffness in premenopausal women with IOP.

Subjects and Methods

Patient population and treatment regimen

Premenopausal women, aged 20 to 48 years, with a history of 1 or more documented low trauma fracture(s) more than 6 months before enrollment and/or low spine or hip areal BMD by dual-energy X-ray absorptiometry (DXA) (Z-score ≤ -2.0) were recruited at Columbia University Medical Center (New York, New York) and Creighton University (Omaha, Nebraska) by advertisement, self-referral, or physician referral. Fractures were ascertained by review of radiographs or reports and categorized as fragility (equivalent to a fall from a standing height or less) by physician panel (E.S., A.C., R.R.R., and E.M.S.). All had regular menses without hormonal contraception and early follicular phase FSH levels <20 mIU/mL. Women with secondary osteoporosis related to estrogen deficiency, eating disorders, endocrinopathies, celiac or gastrointestinal disease, hyperparathyroidism, marked hypercalciuria (>300 mg/g creatinine), serum 25-hydroxyvitamin D (25-OHD) levels <20 ng/mL and drug exposures were excluded (1, 2).

All subjects (n = 21) received 20 μg of teriparatide daily in the morning or evening according to their preference, 630 mg of calcium, and 800 U of vitamin D. The study was planned for a duration of 18 months. During the study, it became possible to provide teriparatide for 24 months, and 16 women agreed. All used contraception during the study and provided informed consent. The institutional review boards of both institutions approved this study.

Laboratory assessments

To exclude secondary osteoporosis, fasting morning blood samples and 24-hour urine samples were collected during the early follicular phase with participants receiving their usual calcium intake (Quest Diagnostics, Madison, New Jersey). Fasting morning serum samples were collected before the daily teriparatide dose at baseline, at 2 weeks, and at 1, 3, 6, 12, 18, and 24 months and stored at −80°C for batch analyses of serum N-terminal propeptide of procollagen type 1 (P1NP), osteocalcin, C-telopeptide (CTx), and IGF-1 as described previously (1, 2). Fasting serum calcium was assessed at each visit, and 24-hour urinary calcium was assessed at 6, 12, and 18 months (Quest Diagnostics).

Areal BMD

Areal BMD was measured by DXA (Discovery; Hologic Inc, Walton, Massachusetts) at baseline and at 6, 12, 18, and 24 months at the spine, femur, and radius as described previously (1). The short-term coefficients of variation were 0.7% (spine) and 1.4% (femoral neck) at Columbia and 1.5% (spine and femoral neck) at Creighton. Phantoms were circulated at 6-month intervals. Z-scores were generated using the manufacturer's database. Lack of response to teriparatide was defined as an absolute change in 12-month spine BMD below the least significant change based on densitometer precision (<0.026 g/cm^2).

Transiliac bone biopsy

Double tetracycline-labeled, transiliac biopsies were obtained from opposite iliac crests before and after 18 months of teriparatide as described previously (9). Specimens were scanned by microcomputed tomography (μCT) (μCT40; Scanco Medical AG, Brüttisellen, Switzerland) with a nominal resolution of 8 μm (2, 9, 10). Trabecular indices were determined using a direct three-dimensional approach (11): trabecular bone volume fraction, thickness, separation, and number. The apparent Young's modulus (stiffness) of the biopsy samples was calculated by microfinite element analysis (μFE) of μCT trabecular images as described (2, 10–12). After μCT and μFE, biopsy specimens were embedded, sectioned, and stained using established procedures (9, 13). Histomorphometry was performed with a digitizing image analysis system (OsteoMeasure, version 4.00C; OsteoMetrics, Inc, Atlanta, Georgia). All variables were calculated according to the American Society for Bone and Mineral Research recommendations (14, 15). Adipocyte number, perimeter, and area, volume/marrow volume, and density were analyzed according to the method of Syed et al (16), as we had reported previously (3).

Statistical analysis

Statistical analyses was performed with SAS software (SAS Institute, Cary North Carolina). The prespecified primary endpoint was within-subject average percent change in lumbar spine BMD from baseline to 12 and 18 months, adjusted for baseline BMD. Prespecified secondary endpoints included 12-, 18-, and 24-month percent change in BMD at the femoral neck, total hip, and one-third radius by DXA; cortical width, trabecular bone volume, number, thickness, separation, and stiffness, and static and dynamic indices of bone formation and resorption on transiliac crest biopsy specimens; and serum IGF-1 and serum P1NP and CTx, all adjusted for baseline measurements. Exploratory endpoints included all adipocyte parameters. We used ANOVA to examine serial changes in BMD and biochemical analytes. Baseline and 18-month biopsy samples were compared with

paired Student *t* tests. Because not all variables were normally distributed (Kolmogorov-Smirnov test), Spearman correlations were used to test associations between baseline characteristics and response to teriparatide. Student *t* tests were used to compare responders and nonresponders. All data are expressed as means ± SD, unless otherwise indicated. Values of $P < .05$ were considered significant.

Results

Subject characteristics

On average, participants were in their late 30s and of normal weight (Table 1). Mean Z-scores were at the lower end of normal at the spine and hip and normal at the forearm. Eighteen (86%) participants had a history of low-trauma fractures of the hip or pelvis (both n = 4), vertebrae (n = 3), ribs (n = 4), upper extremity (n = 7), and lower extremity (n = 5); 11 participants had multiple fractures. All had normal calciotropic hormones and bone turnover markers.

BMD and bone turnover markers

By 6 months, there were significant increases in BMD (Figure 1, A–C). At 18 months, the largest increase in BMD was at the lumbar spine (9.8 ± 5.2%; $P < .001$). Significant increases also occurred at the total hip (2.9 ± 3.6%; $P < .001$) and femoral neck (3.5 ± 5.3%; $P < .01$). A similar pattern was seen at 24 months (spine, 10.8 ± 6.4%; total hip, 6.2 ± 5.7%, femoral neck, 7.6 ± 3.4%; all $P < .001$). At the forearm, there was a transient decrease at 6 months (−0.2 ± 1.6%; $P < .01$) that recovered by 12 months (not shown).

Serum P1NP doubled by 1 month, peaked at 150% above baseline at 6 months, and then declined toward baseline at 18 and 24 months (Figure 1D). Serum osteocalcin changed similarly (not shown). Serum CTx increased more gradually and to a lesser extent than P1NP, peaking at 75% above baseline at 6 months, and returning to baseline by 18 months.

Table 1. Characteristics of the Study Population

Subject Characteristics	Value (Mean ± SD)
Age, y	39.6 ± 5.4
Height, cm	163.6 ± 6.9
Weight, kg	59.4 ± 9.2
BMI, kg/m^2	22.1 ± 3.3
Baseline BMD *Z*-scores	
Lumbar spine	−1.9 ± 0.8
Total hip	−1.7 ± 0.5
Femoral neck	−1.9 ± 0.7
Distal radius	0.1 ± 0.7
Adult low trauma fractures, n (%)	18 (86)
No. of adult low trauma fractures	1.7 ± 1.6
Serum 25-OHD, ng/mL	41.9 ± 11.2
Serum PTH, pg/mL	33.7 ± 9.6
Serum calcium, albumin adjusted, mg/dL	9.0 ± 0.3
Urine calcium, mg Ca/g creatinine	216 ± 89
Serum CTx, ng/mL	0.387 ± 0.181
Serum P1NP, pg/L	43.6 ± 16.9
Serum osteocalcin, ng/mL	18.1 ± 8.2
Serum IGF-1, ng/mL	166 ± 48

Transiliac crest bone biopsies

Nineteen subjects had a second bone biopsy at 18 months. By μCT and μFE, there were substantial improvements in trabecular bone microstructure and stiffness (Table 2 and Figure 2, A and B). Trabecular bone volume and number increased by 34% and 18%, respectively, and trabecular separation decreased by 9%, reflected in a 71% increase in trabecular stiffness. There were significant increases in cortical width and porosity (22% and 46%, respectively). Wall width, the amount of bone formed in each remodeling cycle, also increased on cancellous (16%) and endocortical (12%) surfaces but not on intracortical surface (Figure 2C). Formation parameters, including osteoblast number, mineralizing perimeter, bone formation rate, mineral apposition rate, or adjusted apposition rate, did not change consistently. However, osteoclast number decreased by 46%. Adipocyte area, perimeter, and volume/marrow volume declined significantly, with no change in adipocyte number or density.

Predictors of response to teriparatide

The baseline bone formation rate tended to be associated with the 12-month percent change in spine BMD ($r = 0.42$; $P = .095$). The 1-month change in bone turnover markers significantly predicted percent change in spine BMD at 12 months (osteocalcin: $r = 0.55$, $P = .02$; PINP: $r = 0.50$, $P = .04$; CTx: $r = 0.46$, $P = .046$) and 24 months (osteocalcin: 0.58, $P = .02$; PINP: $r = 0.52$, $P = .046$) but not in hip BMD or trabecular bone volume.

Four women (19%) had no increase in spine BMD at 12 months (Figure 3A) and no response at the hip (not shown). At 12, 18, and 24 months, lumbar spine BMD increased by 0.6 ± 1.1%, 4.1 ± 2.7%, and 2.5 ± 3.7%, respectively, in nonresponders and by 9.2 ± 4.2%, 11.1 ± 4.7%, and 12.8 ± 5.2% in responders. At baseline, nonresponders weighed more than responders and had slightly higher body mass index (BMI) and BMD, but the differences were not significant. Nonresponders and responders did not differ by age, calciotropic hormones, or trabecular bone volume (Table 3). In contrast, the baseline bone formation rate was markedly lower (by 80%) in nonresponders as was serum osteocalcin (by ~38%) and CTx

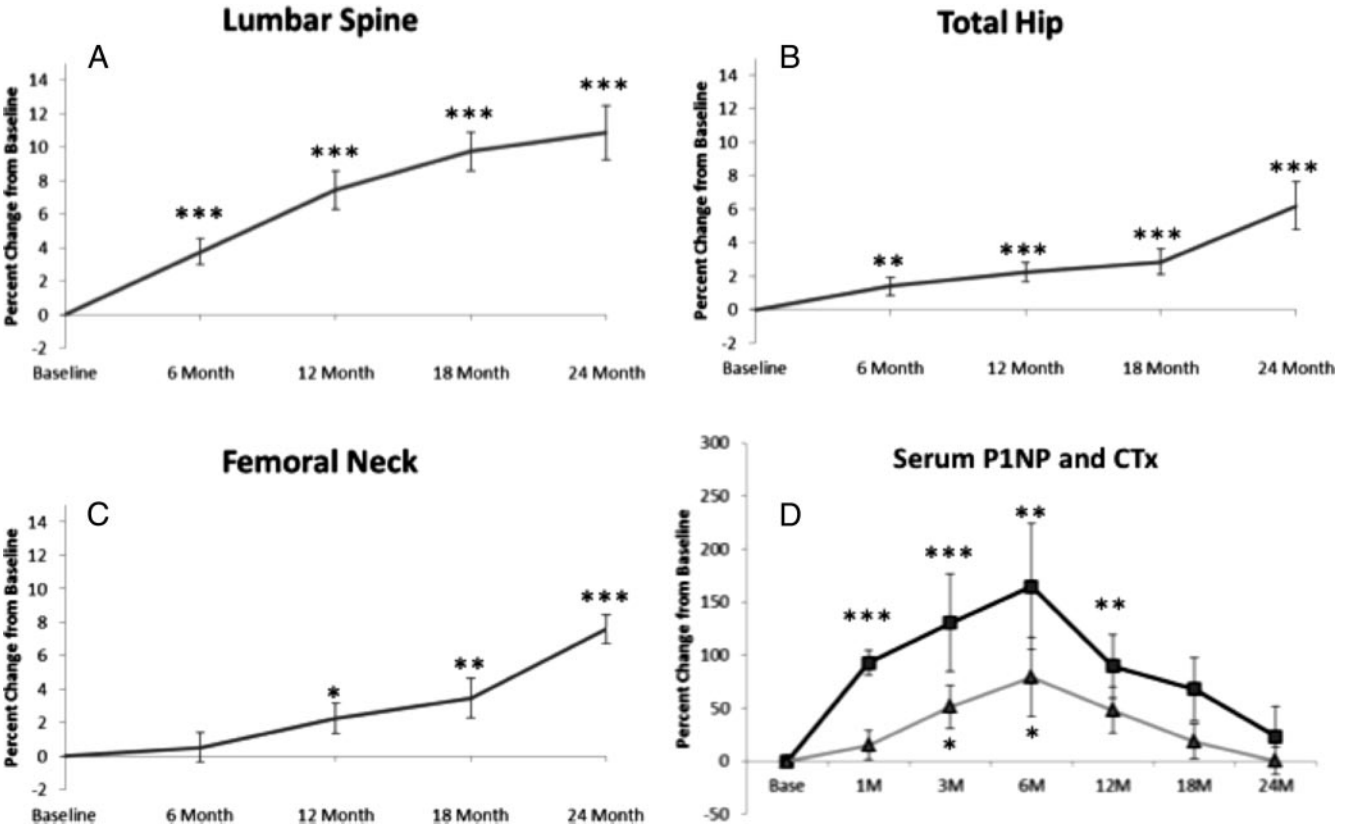

Figure 1. BMD and bone turnover markers after teriparatide: percent change from baseline: A, Lumbar spine. B, Total hip. C, Femoral hip. D, Bone turnover markers serum P1NP (■) and serum CTx (▲). $*P < .05$; $**P < .01$; $***P < .001$; significant percent change from baseline.

(by ~53%). Age-adjusted IGF-1 was 32% higher in nonresponders than in responders ($P = .03$).

Nonresponders and responders also differed by pattern of bone marker change. In Responders (Figure 3B), serum PINP increased by 62% at 2 weeks, peaked at 180% above baseline by 6 months, and did not differ from baseline at 18 or 24 months. In nonresponders (Figure 3C), the PINP peak was blunted (108% above baseline) and delayed, not differing significantly from baseline until 6 months. The pattern was similar for osteocalcin (not shown). Serum CTx rose comparably in both groups but peaked earlier in responders (6 vs 12 months). Serum IGF-1 did not change, but baseline serum IGF-1 was inversely associated with 12-month percent change in spine BMD (Figure 4), before ($r = -0.46$; $P = .05$) and after adjustment for age ($r = -0.50$; $P = .03$).

Although 12-month BMD did not increase in nonresponders, some biopsy parameters improved. Cortical width increased from 612 ± 308 to 858 ± 399 μm ($P = .04$), trabecular separation decreased from 0.717 ± 0.103 to 607 ± 0.086 μm ($P = .04$), and there was a nonsignificant increase in trabecular bone volume (19.2 ± 4.5 to 27.0 ± 4.7%; $P = .1$).

Adverse events and compliance

Adverse events and compliance with teriparatide injections were assessed at each visit by interview and journal. Teriparatide injections were well tolerated. One participant had a single episode of hypercalcemia (serum calcium >10.2 mg/dL) and 6 participants had 7 episodes of hypercalciuria (>300 mg/g creatinine) that resolved after per protocol reduction of calcium supplements. No serious adverse events were reported. One participant sustained a distal radius fracture after falling from a stool during the second 12 months. The most common complaints were mild injection site reactions (bruising, erythema, and pruritus), fatigue, headache, nausea, postinjection dizziness, palpitations and anxiety, leg cramps, and headaches. No subject withdrew because of these symptoms. Compliance exceeded 90% and did not differ between responders and nonresponders.

Discussion

Teriparatide was associated with marked improvements in lumbar spine, total hip, and femoral neck BMD in most women with IOP. The formation marker, serum P1NP, increased promptly, peaked at 6 months, and returned to baseline by 18 to 24 months. Paired transiliac bone biopsies demonstrated substantial increases in cortical width, wall width of completed bone packets, and trabecular bone volume and number. The resulting 71% increase in

Table 2. Microstructural, Stiffness, and Remodeling of Transiliac Crest Biopsy: Response to Teriparatide

	Baseline	18 Mo	% Difference	*P* Value
Cortical microstructure by two-dimensional histomorphometry				
Cortical width, μm	558 ± 209	680 ± 242	+22	.009
Cortical porosity, % cortical area	5.0 ± 1.5	7.3 ± 3.7	+46	.01
Trabecular microstructure and stiffness by three-dimensional μCT and μFE				
Trabecular bone volume fraction, %	20.8 ± 6.9	27.8 ± 7.3	+34	<.001
Trabecular number, n/mm	1.5 ± 0.2	1.8 ± 0.3	+18	<.001
Trabecular thickness, μm	177 ± 40	184 ± 27	+4	.5
Trabecular separation, μm	711 ± 72	650 ± 61	−9	<.001
Trabecular separation SD, mm	199 ± 27	207 ± 34	+4	.2
Connectivity density, 1/mm^3	10.1 ± 12.7	20.7 ± 21.9	+105	.7
Stiffness, Young modulus (E)	401 ± 234	685 ± 358	+71	<.001
Bone remodeling				
Osteoid width, no. lamellae	3.5 ± 1.3	2.8 ± 1.0	−20	.1
Cancellous wall width, μm	34 ± 5	40 ± 5	+16	<.001
Endocortical wall width, μm	39 ± 5	44 ± 5	+12	.002
Intracortical wall width, μm	53 ± 7	54 ± 4	+2	.6
Mineralizing perimeter, %	3.8 ± 2.8	3.1 ± 2.7	−19	.2
Bone formation rate, mm^2/mm/y	0.009 ± 0.007	0.008 ± 0.007	−16	.3
Mineral apposition rate, μm/d	0.623 ± 0.078	0.603 ± 0.125	−3	.4
Adjusted apposition rate, μm/d	0.519 ± 0.400	0.599 ± 0.503	+15	.6
Bone cells and marrow fat				
Osteoblast number, no./mm bone surface	1.15 ± 0.5	1.24 ± 0.9	+31	.70
Osteoclast number, no./mm bone surface	0.043 ± 0.03	0.023 ± 0.03	−46	.04
Adipocyte area, mm^2	0.325 ± 0.09	0.267 ± 0.08	−15	.01
Adipocyte perimeter, mm	31.5 ± 7.8	26.5 ± 5.9	−13	.008
Adipocyte number, no./mm^2 of marrow + bone	207 ± 46	198 ± 40	−1	.44
Adipocyte volume/marrow volume, %	34.6 ± 9.0	29.1 ± 8.8	−13	.02
Adipocyte density, no./mm^2 marrow tissue	220.1 ± 46.0	216.0 ± 44.7	−1	.69

trabecular stiffness brought treated women to a level comparable to that of normal premenopausal women (2). Four women (19%) had no increase in BMD at any site and a blunted and delayed rise in serum P1NP. At baseline, they were characterized by a markedly lower bone formation rate and higher serum IGF-1. Serum IGF-1 was inversely associated with the 12-month percent increase in spine BMD.

Teriparatide increases BMD and reduces fractures in postmenopausal (4), glucocorticoid-induced (5, 6), and male osteoporosis (8). In men with IOP randomly assigned to PTH(1–34), there were significant 13.5% and 2.9% increases in spine and femoral neck BMD, respectively (7). Orwoll et al (8) randomly assigned men with either idiopathic or hypogonadal osteoporosis to placebo or 20 or 40 μg of teriparatide for a median of 11 months. Spine BMD increased in both treatment groups (by 5.9% and 9.0%, respectively). These trials led to approval of teriparatide for male IOP.

Although ours is the only study of teriparatide in premenopausal women with IOP, PTH(1–34) has been evaluated in premenopausal women receiving gonadotropin-releasing hormone analogs (17) and glucocorticoids (6, 18). Premenopausal women with endometriosis randomly assigned to nafarelin alone sustained rapid bone loss, whereas BMD increased or remained stable in those who also received PTH(1–34) (17). Saag et al (6) compared alendronate and teriparatide for 18 months in patients with glucocorticoid-induced osteoporosis. Lumbar spine BMD increases were significantly greater in the teriparatide group than in the alendronate group in premenopausal women, similar to findings in men and postmenopausal women (18).

The evolution of bone turnover markers we observed resembles that for studies of teriparatide in other forms of osteoporosis (7, 8, 17, 19, 20), demonstrating evidence of an anabolic window during the first 6 months, the period

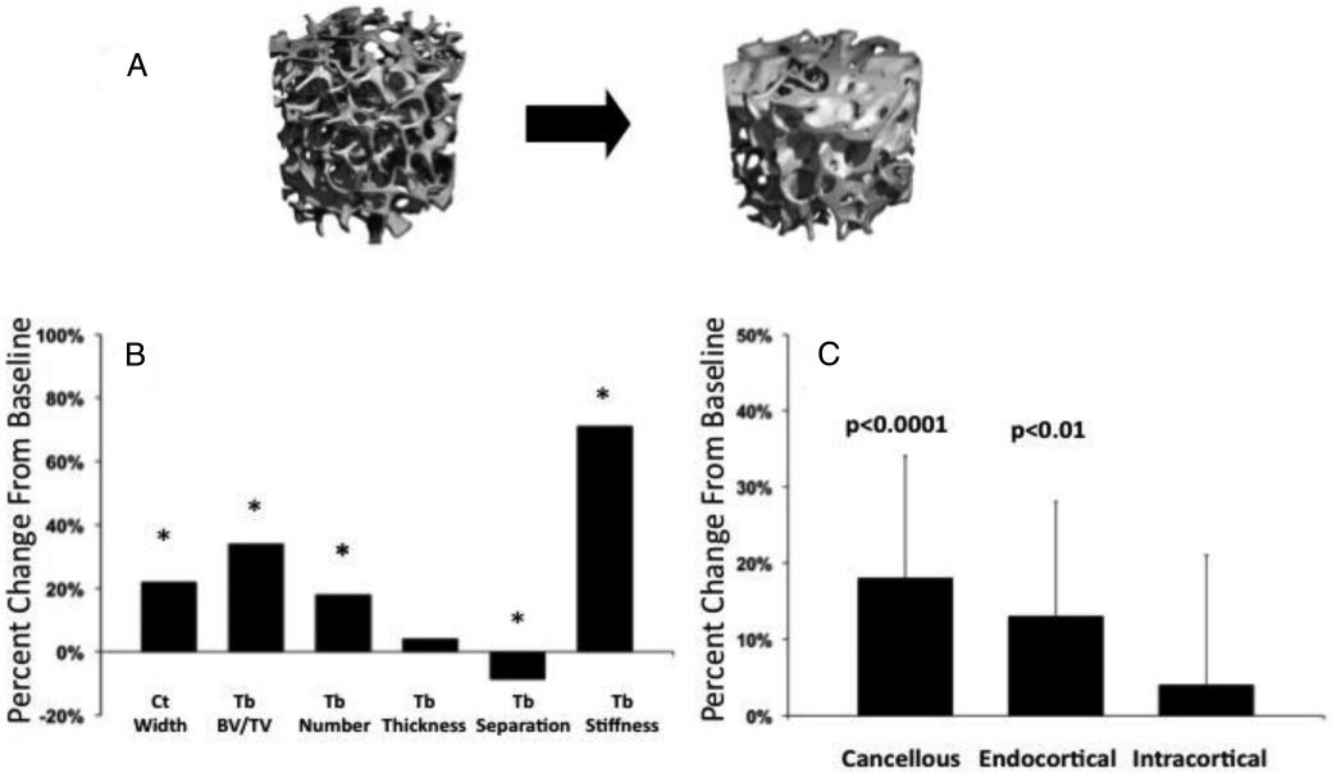

Figure 2. Bone histomorphometry at the iliac crest before and after teriparatide. A, Trabecular bone structure assessed by μCT of transiliac crest bone biopsy samples from opposite iliac crests before and after teriparatide treatment in a representative subject, whose trabecular bone volume increased from 12% to 17%. B, Mean change in structural parameters assessed by quantitative histomorphometry (cortical width) and μCT and μFE of transiliac crest bone biopsy samples. *, significant change from baseline to 18 months. Ct, cortical; Tb, trabecular; BV/TV, bone volume fraction. C, Percent change from baseline in mean wall width at 3 surfaces assessed by quantitative histomorphometry.

of time during which PTH stimulates bone formation more than resorption (19). Our data are also consistent with those in men with IOP (7, 8) and those in nafarelin-treated premenopausal women on PTH(1–34), in whom 3-month bone turnover markers also predicted a response to teriparatide (21). The increase in P1NP in our subjects was comparable to that in studies of postmenopausal women (22–25).

No other studies that have characterized teriparatide effects on iliac crest microarchitecture have included premenopausal women or evaluated stiffness (6, 26–33). Trabecular bone volume increased by 5.4% in 12 osteoporotic postmenopausal women after 1 year of PTH(1–34) (33). Paired biopsies in 8 estrogen-treated postmenopausal women treated with PTH(1–34) for 36 months and 8 men with IOP treated for 18 months (27) revealed increases in cortical width and wall width and decreases in eroded surface. In the Fracture Prevention Trial, postmenopausal women randomly assigned to PTH(1–34) had significant increases in trabecular bone volume and connectivity and cortical thickness and a shift to a more plate-like trabecular structure (30). Moreover, increases in lumbar spine and femoral neck BMD correlated with improvements in bone microarchitecture (26), and changes in formation markers predicted improvements in wall thickness, trabecular bone volume, and thickness (28). Our results agree with these studies. We also found an increase in cortical width and porosity, consistent with prior studies (25, 31), and for the first time report marked increases in trabecular bone stiffness and decreases in marrow adipocyte size. It is unclear whether the decrease in adipocyte size but not adipocyte number we observed is due to a direct effect of teriparatide on adipocytes or is mediated indirectly via the effects of teriparatide on osteoblasts. However, this pattern of change is consistent with the effects of estrogen on marrow adipocytes in postmenopausal women (16).

Four of our subjects (19%) had a minimal or no increase in BMD, blunted and delayed increases in serum P1NP and osteocalcin, and no evidence of an anabolic window, although there were microarchitectural improvements at the iliac crest. Other studies, all of postmenopausal women, have reported a lack of BMD increase with teriparatide (34, 35). Of 249 treatment-compliant women in 3 randomized trials of teriparatide (36–38), 6% to 9% did not exceed the least significant change in lumbar spine BMD (<3% increase) (34). Consistent with our results, the median 3-month change in P1NP was greater in responders than in nonresponders, but even nonresponders had a significant increase (34).

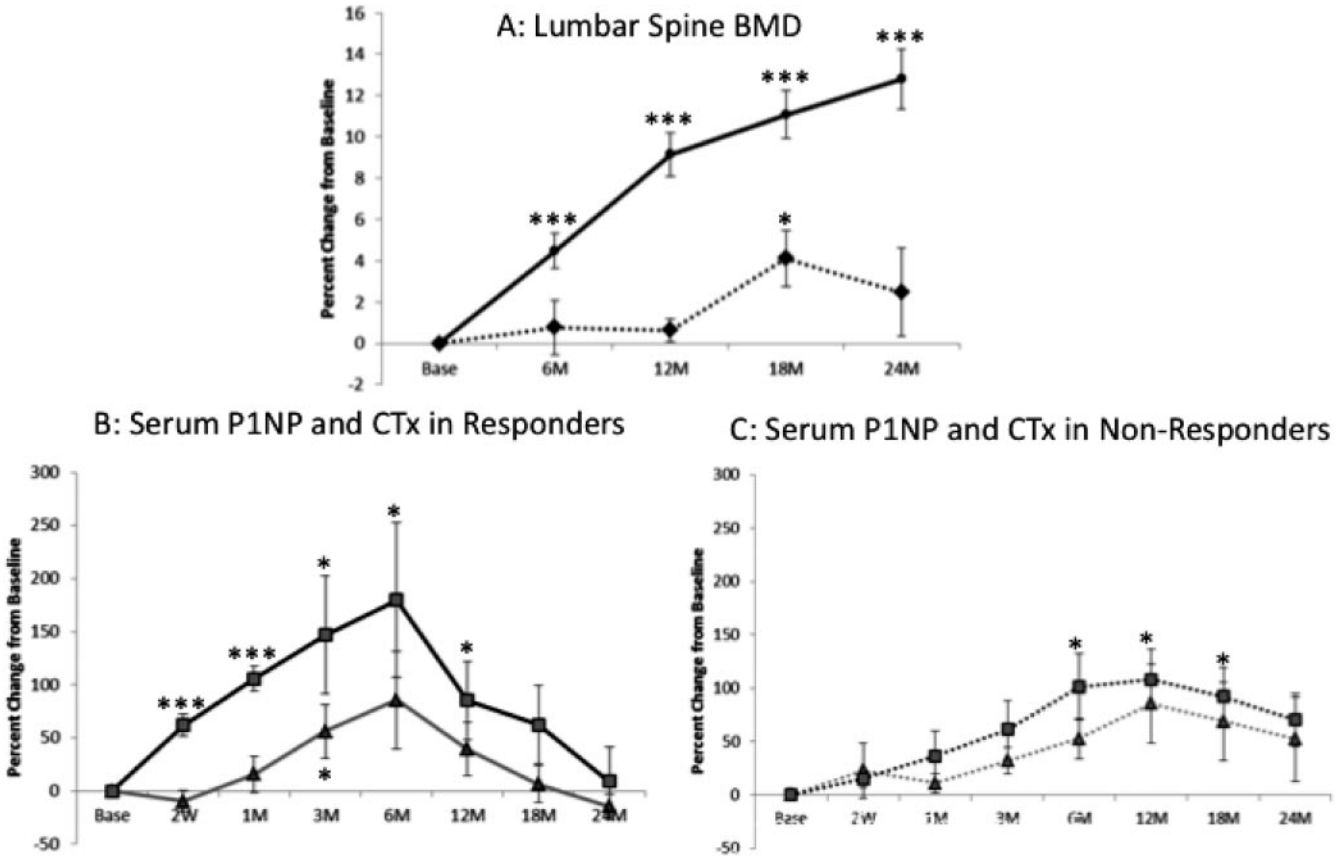

Figure 3. BMD and bone turnover markers after teriparatide: percent change from baseline in responders and nonresponders. A, BMD at the lumbar spine: ●, responders; ♦, nonresponders. $*P < .05$; $***P < .001$; significant percent change from baseline. B, Bone turnover markers in responders: ■, serum P1NP; ▲, serum CTx. $*P < .05$; $***P < .001$; significant percent change from baseline. C, Bone turnover markers in nonresponders: ■, serum P1NP; ▲, serum CTx. $*P < .05$; significant percent change from baseline.

Another study found no response to teriparatide in 15% of 203 postmenopausal women (35). Although no formation markers were measured (34, 35), both studies found direct relationships between baseline bone resorption markers and response at the spine. We also found that baseline bone remodeling, as assessed by bone formation rate on bone biopsy and bone formation and resorption markers, was much lower in nonresponders.

The mechanism for the lack of response to teriparatide in our patients is unclear. Given changes detected at the iliac crest, the lack of response may have been apparent rather than real, perhaps related to BMD measurement imprecision (35). Alternatively, teriparatide may increase bone area, which would automatically reduce the effect of an increase in areal BMD. Because we did not measure volumetric BMD, this remains a possible explanation. Nonresponders could also have been less compliant. However, several observations led us to hypothesize that their lack of responsiveness could be related to IGF-1, a key regulator of skeletal growth that acts both as a circulating GH-dependent hormone and a local autocrine/paracrine skeletal growth factor (19). Most men with IOP (39–45) have low serum IGF-1 concentrations that correlate with low bone formation on transiliac bone biopsies (43, 46–48), suggesting that male IOP is due to decreased osteoblast proliferation (49) or recruitment to remodeling sites (50) related to IGF-1 deficiency. In contrast, we found a subset of women with IOP with low bone turnover and significantly higher serum IGF-1 concentrations, suggesting that their osteoblasts may be resistant to IGF-1 (2). Our nonresponders appear to belong to this subset, because they had very low bone formation and slightly but significantly higher serum IGF-1 concentrations at baseline. Evidence is accumulating that the anabolic effects of PTH are, in part, mediated by local production of IGF-1 (19, 51–56). Thus, these women, whose osteoblasts may be less responsive to IGF-1, may also have a less robust response to PTH. In this regard, we also found that baseline serum IGF-1 was inversely associated with the 12-month percent change in spine BMD. Further studies are needed to evaluate this possibility.

Management of osteoporosis in premenopausal women should focus on identification and specific treatment of any secondary cause, adequate weight-bearing exercise and intake of calories, calcium, and vitamin D, and avoidance of tobacco and excessive alcohol (57, 58).

Table 3. Baseline Characteristics of Women Who Did and Did Not Respond to Teriparatide

	Responders (n = 17)	Nonresponders (n = 4)	*P* Value
Age, y	39 ± 6	41 ± 4	.7
Height, cm	163.6 ± 7.6	163.5 ± 2.5	.9
Weight, kg	57.6 ± 8.5	65.4 ± 10.6	.1
BMI, kg/m^2	21.1 ± 3.4	23.4 ± 4.2	.2
Baseline BMD, g/cm^2			
Lumbar spine	0.799 ± 0.072	0.847 ± 0.129	.3
Total hip	0.701 ± 0.060	0.764 ± 0.082	.1
Femoral neck	0.593 ± 0.069	0.640 ± 0.115	.3
Cancellous BV/TV, % by μCT	21.3 ± 7.1	19.2 ± 4.5	.6
Serum calcium, albumin-adjusted, mg/dL	9.0 ± 0.3	8.9 ± 0.2	.7
Serum PTH, pg/mL	33.8 ± 9.8	33.3 ± 10.4	.9
Serum 25-OHD, ng/mL	41.4 ± 9.6	44.3 ± 18.1	.6
Serum 1,25(OH_2D), pg/mL	57.2 ± 13.9	59.8 ± 30.0	.9
Cancellous BFR/BS, mm^2/mm/y	0.011 ± 0.006	0.002 ± 0.001	<.0001
Cancellous wall width, μm	34.8 ± 4.4	32.7 ± 5.4	.4
Serum CTx, ng/mL	0.431 ± 0.170	0.201 ± 0.160	.001
Serum P1NP, pg/L	46 ± 17	32 ± 13	.12
Serum osteocalcin, ng/mL	19.5 ± 8.5	12.0 ± 1.5	.003
Serum IGF-1, age-adjusted; ng/mL	157 ± 44	208 ± 54	.03

Abbreviations: 1,25(OH_2D), 1,25-dihydroxyvitamin D; BFR/BS, bone formation rate/bone surface; BV/TV, trabecular bone volume fraction.

Pharmacological therapy is reserved for severely affected women with major fracture(s), very low BMD, and/or progressive bone loss. Selective estrogen receptor agonists should not be used to treat osteoporosis in premenopausal women because they cause bone loss (59–61). Bisphosphonates should be avoided in women of childbearing potential, because they have a prolonged residence in bone, cross the placenta, and have adverse effects on the fetal rodent skeleton (62). However, in our experience, many premenopausal women with osteoporosis have already taken bisphosphonates (63). Teriparatide, in contrast, is not retained in the skeleton and is not likely to affect a fetus conceived after its discontinuation (19). However, although clearly effective in increasing BMD in premenopausal women with idiopathic or secondary osteoporosis (17, 18), teriparatide has not been shown to reduce fractures in premenopausal women (17, 18), nor are there data on long-term effects. Teriparatide is associated with osteosarcoma in rodents and is therefore approved only for patients with fused epiphyses and for 2 years of use, although recent analyses suggest no association with teriparatide in patients with osteosarcoma (64, 65).

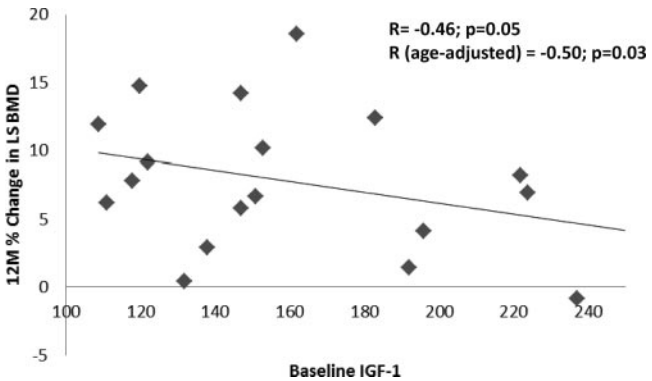

Figure 4. Relationship between serum IGF-1 at baseline and percent change in lumbar spine (LS) BMD at 12 months.

The effects of teriparatide on BMD gradually dissipate after discontinuation unless followed by antiresorptive drugs, usually bisphosphonates, which are undesirable for premenopausal women. However, endogenous estrogen also has antiresorptive effects. Although no studies have evaluated the duration of teriparatide effects in menstruating premenopausal women with IOP, an extension study of human PTH(1–34) in premenopausal women with endometriosis treated with nafarelin found a persistent benefit in women who regained normal menses (21). BMD also remained stable in postmenopausal women taking estrogen for 2 years after teriparatide discontinuation (66) and postmenopausal women taking estrogen who received PTH for glucocorticoid-induced osteoporosis (67). Thus, in premenopausal women with IOP and normal menses, teriparatide-induced increases in BMD may be sustained after discontinuation, although ongoing follow-up studies are needed for confirmation.

This study has several limitations. Without an untreated control group, we cannot attribute the observed effects to teriparatide with certainty. We could not evaluate the effects of teriparatide on fractures. Six women

received teriparatide for 18 months rather than for 24 months. It is possible that nonresponders were less compliant. We did not measure volumetric BMD at the spine, which might have detected a response when DXA did not. However, the marked baseline differences in bone formation rate and turnover markers between responders and nonresponders argue against this interpretation. Higher baseline serum IGF-1 concentrations in nonresponders may not reflect marrow IGF-1. We did not measure IGF-1 binding proteins that modulate IGF-1 action.

In summary, teriparatide was associated with large increases in BMD in most premenopausal women with IOP, accompanied by typical increases in the formation marker P1NP and the resorption marker CTx. Paired transiliac biopsies detected significant increases in cortical width, increases in trabecular bone volume and number, decreases in trabecular separation, and increased stiffness. Participants with no increase in BMD had markedly lower baseline bone formation, slightly higher serum IGF-1, and a blunted and delayed rise in P1NP, suggestive of a defective osteoblast response to teriparatide. Although pharmacological therapy should be reserved for women with fractures or severe and progressive bone loss, these results provide evidence that, should specific bone-active therapy be necessary, teriparatide increases BMD in most premenopausal women with IOP.

Acknowledgments

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