A Fracture Does Not Adversely Affect Bone Mineral Density Responses after Teriparatide Treatment

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Abstract

Background Fracture leads to local and systemic catabolic physiologic changes. As teriparatide is an agent used to treat osteoporosis in patients with fragility fractures, it is unclear whether teriparatide treatment alters bone mineral density (BMD) and bone markers when given to patients with fractures.

Questions/purposes We asked whether BMD and bone marker responses would be blunted in patients with

fractures placed on teriparatide after fracture compared with patients without fractures on teriparatide.

Patients and Methods We retrospectively collected data from 141 patients treated with teriparatide for osteoporosis. Seventy-seven patients received teriparatide after fractures (fracture group), whereas 64 were treated for other indications (nonfracture group). We determined BMD at the lumbar spine and at the proximal femur before and 12 and 24 months posttreatment. Bone markers (urine N-telopeptide [urine NTX], bone-specific alkaline phosphatase [BALP]) were measured at baseline and 3, 12, and 24 months posttreatment.

Results Mean lumbar spine and hip BMDs at last followup increased from baseline with no differences between groups to approximately 9% and 4% at 24 months, respectively. Both bone markers increased from baseline in the nonfracture group, peaking at 12 months. For the fracture group, only urine NTX increased at 3 and 12 months posttreatment. Although the peak levels of both bone markers in the nonfracture group were greater, there was no difference between the two groups.

Conclusions Fracture does not have a negative effect on the BMD and bone marker responses to teriparatide treatment. Clinicians should anticipate comparable BMD responses when treating patients with teriparatide for osteoporotic fractures and for other indications.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

This work was performed at the Hospital for Special Surgery.

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Introduction

Teriparatide (human recombinant parathyroid hormone, 1–34) is the only anabolic agent available in the United States for treating osteoporosis. The anabolic effect

of teriparatide is reflected by increases of bone markers and increases in volumetric BMD of 4% at the femoral neck to 19% at the spine after 18 months of treatment [29]. It increases bone formation, resulting in a rapid increase in bone mass [13, 19, 23], and reportedly reduces the fracture risk in women with osteoporosis [28, 34]: in one study the risks of fracture were reduced by 65% and 53% for vertebral and nonvertebral fractures, respectively [34]. Owing to the medication's cost, this agent is reserved as a second-line drug for treating postmenopausal osteoporosis. Currently, the indications of teriparatide include (1) osteoporotic fracture despite bisphosphonate treatment, (2) declining BMD despite bisphosphonate treatment, and (3) low-turnover osteoporosis [17, 18]. Although treatment with teriparatide is associated with an increase in bone formation markers within 3 months and bone resorption markers within 6 months [30, 41], conditions such as long-term bisphosphonate therapy could adversely affect the anabolic responses to this agent. Prolonged bisphosphonate treatment temporarily suppresses bone markers [50] and thus reduces the skeletal responses to teriparatide [9, 15, 17, 24, 37, 43].

Several studies show fracture and trauma lead to a change in protein metabolism and produce a catabolic state [26, 27, 39, 51]. There is an increased demand for amino acids for fracture repair processes and a tendency to increase protein synthesis in the uninjured tissues [47]. These amino acids could become limiting if they are required simultaneously for fracture-healing processes and increased protein synthesis in the body. Protein repletion after fracture reportedly attenuates bone loss and leads to shorter recovery from fracture as measured by length of hospital stay, especially in the elderly population [40, 44]. Fracture injury and the physiologic stress of surgery lead to an increase in resting energy expenditure and a systemic catabolic state [35]. Concurrently, bone turnover markers of resorption and formation also vary after fracture [21, 22]. Fractures cause focal changes such as altered protein synthesis in uninjured tissue [47] and systemic physiologic changes including a cytokine-driven inflammatory response [38, 52].

Currently, teriparatide is used as an alternative medication for secondary prevention after a fragility fracture [4, 8]. The question remains whether BMD and bone marker responses will diverge in this particular group of patients. However, owing to the catabolic effects of fracture, we presume the anabolic activities of teriparatide as measured by BMD and bone markers would be blunted or delayed in patients with fractures who are treated for osteopenia/osteoporosis with teriparatide. However, it is unclear whether or how teriparatide treatment alters BMD and bone markers when given to patients with fractures.

We specifically asked: (1) Does BMD increase less in patients with fractures than it does in patients without

fractures? (2) Are the responses of biochemical bone markers blunted in patients with fractures receiving teriparatide treatment when compared with patients without fractures? (3) Are there any differences in BMD and biochemical bone marker responses among different types of fractures?

Patients and Methods

We retrospectively reviewed the medical records of 559 patients treated with teriparatide in our metabolic bone diseases clinic between January 2003 and January 2009. Patients were included if they received teriparatide therapy for at least 12 months and had followup data for more than 12 months after the initiation of treatment. We excluded 418 patients with incomplete medical records, lack of pretreatment BMDs or posttreatment BMDs at either 1 or 2 years, who were noncompliant with treatment, who received teriparatide less than 12 months, and who had BMD measured by different machines. Using the aforementioned criteria, we identified 141 patients for our study. Patients were divided into two groups based on indication for teriparatide treatment: fracture and nonfracture. The fracture group included patients who were treated because of fragility fractures ($n = 77$), whereas the nonfracture group ($n = 64$) included patients who had declining BMDs even with prior osteoporosis treatment with bisphosphonates ($n = 38$) or patients with low-turnover osteoporosis ($n = 26$). For the fracture group, there were 77 patients with 92 fragility fractures. Of these, 33 patients (42.9%) had vertebral compression fractures, 38 patients (49.4%) had long-bone fractures (upper and lower extremities), and six patients (7.7%) had fractures of the peritrochanteric area. All patients received self-administered subcutaneous injections of teriparatide (20 $\mu\text{g/day}$) using automatic injection pen devices that held a 4-week supply of the drug. For the fracture group, the median time from first diagnosis with fracture to the initiation of teriparatide was 35.5 days with interquartiles of 21.0 and 96.8 days (range, 6–926 days). In addition, all patients during the study period were instructed to take calcium (1200 mg/day) and vitamin D (1000–2000 IU/day) supplementation. The goal was to keep the serum calcium level greater than 9.2 g/dL and the 25-hydroxyvitamin D (25(OH)D) level at 32 ng/mL or greater. The minimum followup was 12 months (mean, 23 months; range, 12–34 months). No patients were lost to followup. No patients were recalled specifically for this study; all data were obtained from medical records and imaging. We had prior approval from our Institutional Review Board.

At baseline, we obtained information on demographics, health history, fracture history, and medication use. All

patients had hematology, routine blood chemistry, serum 25(OH)D, intact parathyroid hormone levels, BMD, and biochemical bone marker measurements before starting teriparatide therapy. BMDs were obtained from dual-energy xray absorptiometry of the L₂ to L₄ lumbar spine and the entire proximal femur. Parameters of biochemical bone markers were obtained, including a serum marker for bone formation (BALP) and a urine marker for bone resorption (NTX).

Patients' demographic characteristics were presented as means and 95% confidence intervals for continuous variables and frequencies and percentages for categorical variables. At baseline, the mean age of patients in the fracture group was 67 years (95% CI, 64.9–69.5); 87% were female (Table 1). The mean body mass index (BMI) of patients with fractures was 24.9 kg/m² (95% CI, 24.0–25.8). For the nonfracture group, the mean age and BMI of the patients were 63 years (95% CI, 60.6–66.0) and 22.6 kg/m² (95% CI, 21.6–23.5), respectively. Ninety-four percent of the patients in the nonfracture group were female. Approximately 90% of the patients in each group had a comorbidity index score of 0 or 1 and a history of bisphosphonate treatment. The average duration patients received bisphosphonates before starting teriparatide was 57.5 months (95% CI, 50.3–64.7) for the fracture group, and 47.6 months (95% CI, 41.3–54.0) for the nonfracture group. The differences in baseline metabolic chemical profiles and pretreatment BMDs at the lumbar spine and proximal femur between the fracture and nonfracture groups were evaluated using independent sample t-tests

(Table 2). As expected, the fracture group had higher levels of pretreatment biochemical bone markers of bone formation (BALP; $p = 0.015$) and bone resorption (urine NTX; $p < 0.001$). Nutritional status as assessed by serum albumin ($p = 0.093$) and creatinine clearance ($p = 0.898$) was comparable.

Surgery was performed for 37 of the 77 patients with fractures (48.1%), whereas the remaining patients were treated nonsurgically. Of a total of 37 patients, 12 had vertebral compression fractures, 20 had long-bone fractures, and five had peritrochanteric fractures. Each patient had symptoms related to the fractures at the time of diagnosis and initiation of teriparatide. All fractures healed without complications. Fracture healing was assessed by the senior author (JML) at followup. A fracture was considered healed if, on clinical assessment, there was no pain at the fracture site or no pain at the fracture site with full weightbearing. Radiographic criteria used to define healing of long-bone and peritrochanteric fractures were bridging of the fracture by bone at three of four cortices and obliteration of the fracture line with cortical continuity [14]. For patients with vertebral compression fractures and insufficiency lesions, fracture union was determined on MRI by the absence of bone marrow edema.

Followup laboratory data were reviewed at 3, 12, and 24 months after treatment, and BMD measurements were recorded at 12 and 24 months posttreatment. Our primary outcome was the percent changes in BMD at 1 and 2 years after treatment with teriparatide. Because of the patients' insurance plans, BMD measurements at both followups

Table 1. Descriptive characteristics of the fracture and nonfracture groups

Variables	Fracture (n = 77)		Nonfracture (n = 64)	
	Mean $\pm$ SD or N (%)	95% CI	Mean $\pm$ SD or N (%)	95% CI
Age (years)*	67.2 $\pm$ 10.3	(64.9, 69.5)	63.3 $\pm$ 10.9	(60.6, 66.0)
Female (%)	67 (87%)		60 (94%)	
Body mass index (kg/m ²)*	24.9 $\pm$ 4.0	(24.0, 25.8)	22.6 $\pm$ 3.7	(21.6, 23.5)
Charlson Comorbidity Index				
0	51 (66.2%)		45 (70.3%)	
1	21 (27.3%)		13 (20.3%)	
2	4 (5.2%)		6 (9.4%)	
3	1 (1.3%)		0 (0%)	
Prior bisphosphonate therapy	70 (90.9%)		58 (90.6%)	
Type of bisphosphonate				
Alendronate	48 (62.3%)		31 (48.4%)	
Risedronate	16 (20.8%)		13 (20.3%)	
Zoledronic acid or pamidronate	0 (0%)		8 (12.5%)	
Ibandronate	2 (2.6%)		2 (3.1%)	
Raloxifene	4 (5.2%)		4 (6.3%)	
Duration of bisphosphonate treatment (months)*	57.5 $\pm$ 30.3	(50.3, 64.7)	47.7 $\pm$ 24.2	(41.3, 54.0)

* Values are expressed as mean $\pm$ SD; 95% CI = 95% confidence interval.

Table 2. Baseline levels of laboratory tests and bone mineral densities

Baseline levels	Fracture (n = 77)	Nonfracture (n = 64)	p Value
Biochemistries and biochemical bone markers			
Serum calcium (mg/dL)	9.51 ± 0.48	9.79 ± 1.22	0.068
25-hydroxyvitamin D (ng/mL)	37.91 ± 14.73	42.12 ± 19.17	0.160
Serum parathyroid hormone (pg/mL)	34.38 ± 19.05	28.50 ± 15.01	0.060
Serum albumin (g/dL)	4.20 ± 0.39	4.30 ± 0.33	0.093
Creatinine clearance (mL/minute)	67.95 ± 20.66	67.47 ± 22.76	0.898
Urine NTX (nmol/L BCE/mmol/L creatinine)	32.28 ± 14.68	22.33 ± 10.30	< 0.001
BALP (µg/L)	15.39 ± 13.75	11.01 ± 4.33	0.015
Bone mineral densities			
Lumbar spine BMD (g/cm ²)	0.829 ± 0.156	0.797 ± 0.145	0.219
Lumbar spine BMD T score	−2.34 ± 1.21	−2.67 ± 1.12	0.093
Total hip BMD (g/cm ²)	0.674 ± 0.113	0.639 ± 0.110	0.076
Total hip BMD T score	−2.21 ± 0.879	−2.32 ± 0.812	0.445

Values are expressed as mean ± SD; BMD = bone mineral density; urine NTX = urine cross-linked N-telopeptide of type I collagen; BALP = bone-specific alkaline phosphatase.

were not available for all patients. Of 141 patients, 107 and 102 patients had hip BMDs at 1 and 2 years posttreatment, respectively. Lumbar spine BMDs at 1 and 2 years posttreatment were available for 105 and 99 patients, respectively. The secondary outcome of our study was the changes in biochemical bone marker levels (urine NTX and BALP) at 3, 12, and 24 months after treatment with teriparatide compared with baseline levels. We analyzed data only from patients who had complete bone marker levels at all times (before, 3, 12, and 24 months after treatment). Of 141 patients, 71 and 65 had urine NTX and serum BALP measurements, respectively, completed at all times.

Data are shown as mean ± SD for normally distributed variables and as median and interquartile ranges for not normally distributed variables. Following the descriptive analysis, differences between fracture and nonfracture groups on percent changes of BMD at 1 and 2 years were analyzed using independent samples t-tests. Changes of BMD measurements from baseline to 1 year and baseline to 2 years were assessed with paired t-tests. Hereafter, two-way repeated-measures ANOVA was used to assess the effect of time and fracture group (fracture versus nonfracture) and fracture type (vertebral, long-bone, and peritrochanteric) on the change of bone markers. Additional subgroup analyses based on fracture types on changes of BMD from baseline to 1 year and baseline to 2 years were evaluated using paired t-tests with one-way ANOVA used to analyze the differences between fractures types. Bonferroni technique was used to adjust critical p values for all multiple comparisons. All analyses were evaluated for normality and conducted using SPSS® software (Version 17.0; SPSS Inc, Chicago, IL, USA).

Results

Mean lumbar spine BMD increased ($p < 0.001$) from baseline at all times in both groups (Table 3). At 2 years, lumbar spine BMDs increased by averages of 9.0% and 8.6% compared with baseline in the fracture and nonfracture groups, respectively. We observed no differences in percent change in lumbar spine BMD between the two groups ($p = 0.883$ and 0.846 at 1 and 2 years posttreatment, respectively). At 1 year, mean percent changes in proximal femur BMD increased 1.3% in the fracture group and 0.3% in the nonfracture group. At 2 years, hip BMD increased means of 4.1% and 3.8% relative to baseline in the fracture and nonfracture groups, respectively (Table 3). We found no differences between the two groups ($p = 0.478$ at 1 year and $p = 0.875$ at 2 years posttreatment).

In response to teriparatide, biochemical bone markers for bone formation and resorption in the nonfracture group increased ($p < 0.001$, except for BALP at 24 months $p = 0.001$) from baseline at all times, with peak levels approximately 12 months after treatment (Fig. 1). Conversely, in the fracture group, urine NTX increased from baseline only at 3 and 12 months after treatment ($p = 0.022$ at 3 months and $p = 0.002$ at 12 months). Additionally, the increment of BALP levels in the fracture group was similar at all times when compared with that at baseline (Fig. 1). There were no differences in urine NTX levels between fracture and nonfracture groups at 12 and 24 months, but there was a borderline difference at 3 months posttreatment ($p = 0.034$, 0.065 , and 0.485 for 3, 12, and 24 months posttreatment, respectively) (Fig. 1).

Table 3. Measurements of bone mineral density after 1 and 2 years of teriparatide treatment

Bone mineral density measurement	Pairs	Fracture	Within group p value	Pairs	Nonfracture	Within group p value	Between groups p value
Lumbar spine							
At baseline (g/cm ²)		0.83 ± 0.16	Reference		0.81 ± 0.15	Reference	0.219
Percent change at 1 year	58	5.94 ± 8.11	< 0.001	47	6.17 ± 7.20	< 0.001	0.883
Percent changes at 2 years	46	9.00 ± 11.16	< 0.001	53	8.62 ± 8.56	< 0.001	0.846
Total hip							
At baseline		0.67 ± 0.11	Reference		0.64 ± 0.11	Reference	0.076
Percent change at 1 year	60	1.26 ± 7.55	0.548	47	0.29 ± 6.27	0.707	0.478
Percent change at 2 years	48	4.08 ± 10.40	0.028	54	3.82 ± 6.78	0.001	0.875

Values are expressed as mean ± SD; Pairs = patients with data available at baseline and the indicated time at 1 or 2 years; adjusted critical p value = 0.025.

Fig. 1A–B The mean values of biochemical bone markers and within group and between group p values for (A) urine NTX and (B) BALP for the fracture and nonfracture groups at different times before treatment and at 3, 12, and 24 months after teriparatide therapy are

shown. The error bars indicate standard error. The adjusted critical p value = 0.025. Urine NTX = urine cross-linked N-telopeptide of type I collagen; BALP = bone-specific alkaline phosphatase.

Similarly, we found no differences in BALP levels between fracture and nonfracture groups ($p = 0.861$, 0.053 , and 0.095 for 3, 12 and 24 months posttreatment, respectively).

The mean lumbar spine BMD increased (p values ranged from < 0.001 to 0.01) from baseline in patients with vertebral and long-bone fractures (Table 4). Conversely, lumbar spine BMDs at 1 and 2 years posttreatment in patients with peritrochanteric fractures were similar to those at baseline ($p = 0.068$ and 0.647 at 1 and 2 years posttreatment, respectively). We found no differences in percent changes in lumbar spine BMD among these three fracture types ($p = 0.068$ and 0.156 at 1 and 2 years posttreatment, respectively). The percent changes in proximal femur BMD at 2 years increased by 5.4% and 3.7% for patients with vertebral and long-bone fractures, respectively; however, BMD decreased 1.4% in patients

with peritrochanteric fractures (Table 4). There were no differences in percent changes in proximal femur BMD by fracture type ($p = 0.099$ and 0.781 at 1 and 2 years posttreatment, respectively). Similar to percent change of BMD, posttreatment bone marker levels were similar (p values ranged from 0.157 to 0.887) between different fracture types (Table 5). We observed no differences in percent changes of BMD and bone marker responses between patients who received operative and nonoperative treatment.

Discussion

Teriparatide is the only anabolic agent approved in the United States for treating osteoporosis. It can result in as

Table 4. Percent change in bone mineral density based on type of fracture

Bone mineral density measurement	Type of fractures								Between groups p value
	Pairs	Vertebral (n = 33)	Within group p value	Pairs	Long-bone (n = 38)	Within group p value	Pairs	Peritrochanteric (n = 6)	Within group p value
Lumbar spine									
At baseline (g/cm ²)		0.82 (0.15)	Reference		0.84 (0.17)	Reference		0.84 (0.24)	Reference
Percent change at 1 year	23	8.92% (9.52)	< 0.001	29	3.72% (6.67)	0.010	6	5.27% (5.64)	0.068
Percent changes at 2 years	25	12.39% (13.21)	0.001	30	7.42% (9.22)	0.001	4	3.23% (13.13)	0.647
Total hip									
At baseline		0.65 (0.11)	Reference		0.69 (0.12)	Reference		0.66 (0.13)	Reference
Percent change at 1 year	18	3.71% (0.11)	0.018	24	−0.28% (6.76)	0.679	5	−1.74% (3.16)	0.332
Percent change at 2 years	20	5.35% (12.34)	0.100	25	3.74% (9.22)	0.093	3	−1.42% (3.30)	0.558

Values are expressed as mean (SD); pairs = patients with data available at baseline and the indicated time at 1 or 2 years; adjusted critical p value = 0.025.

Table 5. Change of bone turnover markers based on type of fractures

Within-patient change of bone turnover markers	Vertebral fracture	Long-bone fracture	Peritrochanteric fracture	Between group p value
Urine NTX (nmol/L BCE/mmol/L Cr)	N = 17	N = 13	N = 2	
3 months posttreatment	55.65 (41.86)	37.15 (15.81)	46.50 (29.00)	0.157
12 months posttreatment	46.76 (20.81)	52.62 (35.01)	100.00 (46.67)	0.323
24 months posttreatment	36.59 (18.69)	39.92 (17.67)	45.00 (4.24)	0.619
Within group p value	0.051	0.119	0.285	
BALP (µg/L)	N = 16	N = 12	N = 1	
3 months posttreatment	20.03 (12.69)	17.42 (7.05)	28.20 (0.00)	0.887
12 months posttreatment	20.49 (17.50)	16.98 (9.12)	32.50 (0.00)	0.546
24 months posttreatment	18.76 (14.71)	12.25 (5.08)	22.70 (0.00)	0.325
Within group p value	0.635	0.031	N/A	

Values are expressed as mean (SD); urine NTX = urine cross-linked N-telopeptide of type I collagen; BALP = bone-specific alkaline phosphatase; N/A = not applicable.

much as a 13.5% increase in lumbar spine BMD during 2 years of therapy [36], a greater increase than with bisphosphonate treatment [29]. Although teriparatide shows substantial benefits, some conditions may blunt teriparatide's anabolic effects, such as prior bisphosphonate treatment or a catabolic state after fracture. In the current study, we reviewed data for patients who received at least 1 year of teriparatide treatment to address the following questions: (1) Does BMD increase less in patients with fractures than it does in patients without fractures? (2) Are the responses of bone markers blunted in patients with fractures receiving teriparatide treatment when compared with patients without fractures? (3) Are there any differences in BMD and bone marker responses among different types of fractures?

There are limitations to this study. The first limitation relates to the power of the study. Owing to small sample sizes, the power was low and caution must be exercised in interpreting our results (Type II error). This would influence interpretations of bone marker changes between fracture and nonfracture groups after teriparatide treatment. Therefore, our study is best considered a preliminary study assessing the association between fractures and bone marker responses. Second, we used BMD as our primary outcome. Changes in BMD occur slowly and differences might not be detectable even several years after an intervention [6, 12, 42]. In addition, full assessment of teriparatide's skeletal effects would require a fracture endpoint study and comprehensive assessment of bone microarchitecture and geometry. Third, we measured only

Table 6. Summary of studies of the effect of teriparatide on bone mineral density after antiresorptive treatment

Study	Number of cases	Participants	Prior antiresorptive treatment		Duration of teriparatide treatment (months)	% change of lumbar spine BMD after treatment	% change of hip BMD after treatment
			Percent of total cases	Type (%)			
Blumsohn et al. [5]	209	Postmenopausal women	100%	BIS (83.7) Rlx (12.4) Others (23.0)	10 (2, 18)**	10.7%	3.2%
Cosman et al. [10]	99	Postmenopausal women	100%	Aln (50.5) Rlx (49.5)	Aln 45.7 (3.1)* Rlx	4.8% in Aln 8.1% in Rlx	0.9% in Aln 1.8% in Rlx
Eastell et al. [16]	305	Postmenopausal women	72.4%	BIS (62.6) Rlx (10.9) Others (26.5)	39.8 (3.0)* 24 (7, 52)**	10.7%	2.5%
Etinger et al. [17]	59	Postmenopausal women	100%	Aln (56) Rlx (44)	Aln 29.3 (5.2)* Rlx	4.1% in Aln 10.2% in Rlx	0.3% in Aln 1.8% in Rlx
Obermayer-Pietsch et al. [36]	134	Postmenopausal women	100%	BIS (86.6) Rlx (11.9) Others (25.3)	29.0 (5.5)* 11 (3, 21)**	10.2%	2.3%
Current study	141	90% female 10% male	91%	Aln (56) Ris (21) Others (23)	53 (27.9)*	8.8%	3.9%

* Values are expressed as mean (SD) **Values are expressed as median (interquartile range); Aln = alendronate; BIS = bisphosphonate; BMD = bone mineral density; Ris = risedronate; Rlx = raloxifene.

urine NTX and serum BALP, which we presumed would best reflect the effects of teriparatide. However, it is unknown which bone markers best reflect all anabolic responses to teriparatide treatment. Furthermore, many biologic and technical factors affect bone markers. Nonetheless, with improvements in technical methods, the analytic coefficient of variation is minimized to approximately 5% [45]. Fourth, we obtained bone marker values only at 3, 12, and 24 months after treatment. Although more frequent evaluation of bone markers could provide a better trend of responses to teriparatide treatment, it offers no additional clinical benefit to the patient as we aimed to treat these patients with teriparatide for at least 1 year. Finally, because fracture data were obtained retrospectively, some details regarding the course of fracture healing were not documented.

We found no differences in percent changes in BMD after 1 and 2 years of teriparatide treatment between fracture and nonfracture groups. When performing post hoc analysis, our study had 61% and 99% power to detect accepted minimal clinically important differences in BMD changes of 3% and 5% [34], respectively. As our sample size was adequately powered ($\geq 80\%$) to detect a difference within this range, we believe that the lack of difference in percent change of BMD between the two groups is genuine. Interestingly, approximately 90% of patients in each group had a history of bisphosphonate therapy. This reflects the nature of patients we saw at our institution. Average percent changes in BMD at 2 years after treatment in our study were approximately 8.8% at the lumbar spine and 3.9% at the entire proximal femur in both

groups. These findings were similar to previous reports of teriparatide's effects on BMD in patients with a history of antiresorptive therapy [10] (Table 6). The percent changes of BMD in our patients with prolonged bisphosphonate treatment of approximately 4 to 5 years were comparable to those of studies that reported the effect of teriparatide in patients who received a shorter duration of antiresorptive medication [5, 16] (Table 6).

After teriparatide treatment, urine NTX in our patients increased 1.5- to threefold from baseline, whereas BALP increased approximately 1.2- to 1.5-fold from baseline. These findings are similar to those of other studies of bone marker responses after teriparatide treatment in patients who received prior bisphosphonate therapy [7, 10] (Table 7). It also is important to point out that the baseline urine NTX and BALP levels were greater in the fracture group. A previous study showed that fracture healing increased bone marker responses [11]. Thus, it is possible that the pretreatment bone marker levels in the fracture group were already elevated to maximal or submaximal levels, contributing to smaller degrees of change in both bone markers during posttreatment followup. However, as peak levels of the bone markers in the nonfracture group were greater than in the fracture group, this may imply that responses to teriparatide treatment in the fracture group are blunted.

Several investigators have suggested the type and location of a fracture might affect expression of bone markers during the fracture healing process, with bone markers in diaphyseal tibial fractures taking greater time to elevate than ankle [48, 49] or distal radial fractures [25].

Table 7. Summary of studies of the effect of teriparatide on biochemical bone markers after antiresorptive treatment

Study	Number of cases	Duration of therapy (months)	Biochemical bone markers	Peak levels (months)	Magnitude of change at peak levels compared with baseline
Blumsohn et al. [5]	209	24	PINP	6*	↑ fourfold-fivefold
			BALP	6*	↑ 1.5-twofold
Boonen & Singer [7]	245	24	PINP	6*	↑ fourfold-sevenfold
			BALP	6*	↑ 1.2-twofold
Cosman et al. [10]	99	18	PINP	6	↑ 3.5-sevenfold
			BALP	12	↑ 1.4-twofold
			Serum CTX	6	↑ twofold-fourfold
Ettinger et al. [17]	59	18	Osteocalcin	12	↑ threefold
			PINP	6	↑ fourfold-fivefold
			BALP	6	↑ twofold-threelfold
			Serum NTX	6	↑ twofold-threelfold
Current study	141	24	BALP	12	↑ 1.2–1.5-fold
			Urine NTX	12	↑ 1.5-threefold

* Levels reported at the latest time; PINP = N-terminal propeptide of type I collagen; BALP = bone-specific alkaline phosphatase; NTX = cross-linked N-telopeptide of type I collagen; CTX = cross-linked C-telopeptide of type I collagen.

Nakagawa et al. [31] also suggested that a larger bone surface and longer time to union might contribute to different degrees of bone marker changes. Our patients with vertebral fractures had higher increments of BMD at 1 and 2 years after teriparatide treatment than patients with long-bone and peritrochanteric fractures. However, as the number of patients with each fracture type was small, the analysis lacked statistical power to assess the association between fracture type and changes of BMD and bone markers. Although we did not study the association between teriparatide treatment and rate of fracture healing, all patients with fractures achieved healing without complications despite 90% of them having had prior bisphosphonate therapy. Numerous studies document that teriparatide provides additional benefits to enhance fracture healing [1–3, 20, 32, 33, 46, 53]. Therefore, this agent may be suitable in patients with fractures who have high risks of delayed union, nonunion, or with a history of prolonged bisphosphonate therapy.

Our preliminary data suggest a fracture does not adversely affect BMD and bone marker responses to teriparatide treatment. After 2 years of teriparatide treatment, the mean changes of lumbar spine and hip BMDs were approximately 9% and 4% respectively in both groups. Therefore, clinicians should anticipate comparable BMD responses when treating patients with teriparatide for osteoporotic fractures and for other indications.

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