HSSJ (2017) 13:171–177
DOI 10.1007/s11420-016-9537-1

HSS Journal®
The Musculoskeletal Journal of Hospital for Special Surgery

ORIGINAL ARTICLE

Bone Mineral Density Response from Teriparatide in Patients with Osteoporosis

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Received: 5 September 2016/Accepted: 22 November 2016/Published online: 1 February 2017
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Abstract *Background:* A review of data from large clinical trials reported more than 90% of subjects significantly improved their bone mineral density (BMD) at the lumbar spine (LS) with teriparatide (TPTD) (bone 39:1268–1275, 1). However, our clinical experience suggests that many patients may be non-responders, raising questions as to the true efficacy of TPTD in improving BMD in osteoporotic patients. *Questions/Purposes:* The purpose of the study is to determine the rate of improvement in BMD following 18–24 months of teriparatide (TPTD) in patients with osteoporosis within an orthopedic hospital setting. *Methods:* This is a retrospective chart review of patients with osteoporosis who completed 18–24 months of TPTD therapy. The primary endpoint was the change in BMD at lumbar spine (LS) and hip-femoral neck (FN) and total hip (TH) following treatment. Secondary endpoints included the effect of prior bisphosphonate therapy, age, body mass index (BMI) and family history of fracture on BMD response, and the changes in bone-specific markers during active treatment. *Results:* Seventy-eight women and men with mean T-scores at the LS = −2.63 met the inclusion criteria. The overall group showed a 10.7% increase in LS-BMD after 24 months of TPTD. Eighty-three percent were considered responders defined as ≥3.0% increase in LS-BMD. Non-responders (16.7%) had mean LS-BMD change = −1.41%. No difference in baseline vitamin D, calcium, creatinine, BMI, age, gender, prior fracture history, or bisphosphonate use was observed between responders and non-responders. No consistent pattern of change in measures of bone markers was noted between responders and non-responders. *Conclusion:* Eighty-three percent of patients with osteoporosis showed a >3% increase in BMD after TPTD treatment. Baseline parameters, prior bisphosphonate therapy, and the changes in bone markers showed no correlation with final BMD outcome.

Keywords bone · osteoporosis · teriparatide treatment · clinical outcome · bone markers

Work performed at Hospital for Special Surgery.

Electronic supplementary material The online version of this article (doi:10.1007/s11420-016-9537-1) contains supplementary material, which is available to authorized users.

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Introduction

A review of data from several clinical trials reported more than 90% of subjects showed a greater than 3% increase in areal bone density (BMD) at the lumbar spine (LS) with teriparatide (TPTD) treatment [14]. In one large clinical trial, only 8 out of 354 patients (2%) failed to achieve an increase of 3% in the LS BMD after 24 months of daily teriparatide treatment. These patients were identified as non-responders [26]. Given the duration, effort, and expense of TPTD therapy, there is a strong incentive to ascertain response rates in specific patient populations and strive to improve

therapeutic outcomes. Early identification of patients likely to show a poor outcome to TPTD therapy alone might benefit by a change in therapy as recent evidence from combined therapeutic interventions have been shown to augment or prolong the anabolic effect of TPTD [2, 3, 10, 18, 25, 32–34]. In principle, the primary goal of osteoporosis therapy is to reduce fracture risk. However, fracture incidence is low and a surrogate measure such as areal BMD has been shown to have sufficient precision to follow overall response to therapy (11–21). The utility of following BMD was especially true with regard to TPTD since BMD changes were shown to account for up to 41% of the vertebral fracture reduction effect (19).

In the current study, the response rates to TPTD therapy in postmenopausal women and men with osteoporosis presenting to an orthopedic hospital were examined. Baseline parameters reported to affect response rate were assessed. Bone-specific markers were monitored during therapy in an effort to correlate osteoblast and osteoclast activity with response rate.

Patients and Methods

The charts of 78 osteoporotic patients treated with TPTD from a single clinician's practice that met the inclusion criteria of a Hospital for Special Surgery approved IRB retrospective study were reviewed. To be included, patients had to receive TPTD, 20mcg/day by subcutaneous injection for 18 to 24 months and have Dual-energy X-ray absorptiometry (DXA) scans the beginning and end of treatment. Patients with concurrent bisphosphonate, denosumab, or strontium use, underlying metabolic bone disorders, degenerative disc disease, or confounding lumbar scoliosis were excluded from the study. All subjects had bone markers monitored every 4 months. The specific markers included bone specific alkaline phosphatase (BSAP) measured by a two-site immunoradiometric assay (interassay CV, 7.4–7.9%; Hybritech, Beckman Beckman-Coulter, Brea, CA, USA and urinary cross-linked N-telopeptide of type I collagen (NTx) by a competitive-inhibition ELISA (interassay CV, 6.7–14.8%; Ostex, Seattle, WA, USA). Areal BMD measured by DXA-Hologic (Bedford, MA, USA) or GE-Lunar (Madison, WI, USA) equipment. The % change in standardized BMD (sBMD) values [26, 35] before and after 18–24 months of treatment were compared for each patient.

Patient data that were collected and assessed included age, BMI, gender, medical co-morbidities, tobacco history, prior bisphosphonate use, BMD at lumbar spine, femoral neck, total hip (LS, FN, TH), fracture history, serum calcium, creatinine, 25 hydroxy vitamin D (25OHD), and estrogen or selective estrogen receptor modulator (SERM) history. Patients were calcium and vitamin D replete, which was verified at the quarterly encounters to ensure that they maintained a total calcium intake between 1000 and 1500 mg/day from diet and supplements. 25-OH vitamin D levels were checked during TPTD treatment with the goal of maintaining the level above 30 ng/ml.

Statistical Analyses

All patients were included in the outcome analyses since prior studies had demonstrated that response to TPTD was independent of age, history of prior fracture, prior bisphosphonate therapy, or gender [23, 24, 27]. Demographics, baseline, and end of study characteristics were summarized across treatment groups using descriptive statistics. Baseline and end of study characteristics were compared using paired *t* test or Wilcoxon signed rank test. Percentage of change in sBMD between prior bisphosphate users and non-users was compared using two-sample *t* test or Wilcoxon rank sum test.

At the inception of the study, patients were identified as "responders" if they showed a 3% or greater increase in areal BMD at the lumbar spine from start to the completion of TPTD treatment. "Non-responders" were patients who showed less than a 3% gain in BMD at the lumbar spine at the end of TPTD treatment based on previously established criteria of least significant change (LSC) [5, 7, 9, 11, 14, 16, 19–21, 23, 24, 26–28, 31]. Baseline and follow-up characteristics were summarized and compared between responders and non-responders. The comparison methods included two-sample *t* test or Wilcoxon rank sum test for continuous variables and Chi-squared test or Fisher's exact test for categorical variables.

Linear mixed effect model with random intercept was used to compare the mean NTx over time between TPTD responders and non-responders after controlling for time and other clinical confounders and/or effect modifiers (age, gender, history of prior fracture or family history of fracture) [15, 22, 35]. The same model was also applied to compare the mean BSAP over time between responders and non-responders. Stepwise selection method and Akaike Information Criteria (AIC) were used for the model selection. The model with smallest AIC was chosen as the final model. All the statistical analyses were calculated by SAS 9.2.

Results

The patients in this study were predominately female in their mid sixties with osteoporosis as assessed by DEXA scan. BMD measurements recorded at the initiation of TPTD treatment and at the end (18–24 months) improved for the entire population (Table 1). The changes in bone density at the LS, FN, and TH for the entire patient group were statistically significant. The patients remained calcium and vitamin D replete for the duration of the study.

For patients who had never received bisphosphonate therapy before TPTD ($n = 28$), a mean increase in bone mineral density of 12.6% at LS, 4.3% at FN, and 3% at TH was seen. Patients who had received bisphosphonate therapy in the past ($n = 50$), a mean increase in BMD of 9.65% at LS, 3.98% at FN, and 4.34% at TH was seen. The

Table 1 Baseline and end of study parameters for entire patient population

	Baseline Mean (std.)	End of Treatment Mean (std.)	*p* value*
Age (years)	62.62 (8.53)	64.62	N/A
Male (%)	10.26%	10.26%	N/A
BMI	22.42 (4.00)	22.11 (8.07)	0.47
sBMD_LS (g/cm^2)	0.83 (0.16)	0.91 (0.20)	<0.001
T score-LS	−2.63 (1.38)	−1.98 (1.68)	<0.001
sBMD-FN (g/cm^2)	0.67 (0.11)	0.70 (0.11)	<0.001
sBMD-TH (g/cm^2)	0.73 (0.11)	0.75 (0.10)	<0.001
25OHD (ng/Ml)	38.37 (11.40)	41.10 (10.23)	0.29
Serum Ca (mg/dL)	9.73 (0.47)	9.61 (0.45)	0.14
NTx (Nm BCE/Mm Cr)	37.04 (33.94)	46.75 (26.69)	0.048
BSAP (units/L)	14.95 (8.75)	20.04 (11.21)	0.08

differences in the change in BMD between the two groups were not statistically significant at lumbar spine, femoral neck, and total hip.

Thirteen (16.7%) patients were TPTD non-responders in that they showed less than a 3% change in LS BMD, (mean = −1.4%), (median = −1.29%) with a mean duration of TPTD treatment of 24 months. Sixty-five (83.3%) patients were TPTD responders and gained more than 3% in lumbar spine BMD, (mean = 13.1%) (median = 9.84%) with a mean TPTD treatment duration of 23.29 months. The % change in BMD at the LS between non-responders and responders was highly significant ($p < 0.0001$). The % change in BMD between non-responders and responders was also significant at the FN ($p = 0.04$) but was not statistically significant at the TH. The baseline characteristics of the non-responders and responders are summarized in Table 2.

A peak response in bone marker NTx was observed at 4–8 months in both non-responders and responders while the peak response in BSAP was observed at 8–12 months in non-responders and at 4–8 months in responders (Table 3 and Fig. 1a, b). During the 24 months of TPTD, BSAP remained higher in the non-responders. However, the magnitude of BSAP was significantly higher in the non-responders compared to TPTD responders only at 4 months ($p = 0.04$). The magnitude of NTX was significantly higher in the TPTD non-responders compared to the responders only at the end of TPTD at 24 months. Although the differences were not statistically significant, the NTx/BSAP ratio was higher in the TPTD non-responders at 4–12 months, indicative of greater resorptive activity compared to bone formation (Fig. 2).

Two separate linear mixed effect models with random intercept were fitted for NTx and BSAP, controlling for time, time^2 (time-squared), responders/non-responders, age, gender, history of prior fracture, and family history of fracture [15, 22, 35]. Holding other factors constant, both NTx and BSAP changed over time ($p < 0.001$ in both

Table 2 Baseline and follow-up characteristics for non-responders and responders

	Non-responder ($N = 13$) mean (std.)	Responder ($N = 65$) mean (std.)	*p* value*
Age (years)	63.08 (6.70)	62.52 (8.89)	0.91
Male (%)	0%	12.31%	0.34
Bisphosphates user (%)	76.92%	61.54%	0.36
Total months on any bisphosphates before Forteo	51.10 (48.98)	71.74 (38.73)	0.11
Total months of bisphosphates free period before Forteo	9.50 (14.03)	16.49 (24.57)	0.86
Fracture yes (%)	76.92%	69.23%	0.74
Fracture during therapy yes (%)	16.67%	4.65%	0.20
BMI_Bbaseline	20.84 (2.80)	22.74 (4.15)	0.17
sBMD_LS initial (g/cm^2)	0.78 (0.07)	0.83 (0.18)	0.53
sBMD_LS final (g/cm^2)	0.77 (0.07)	0.94 (0.20)	0.0008
% change in sBMD_LS	−1.41 (3.52)	13.15 (11.58)	<0.0001
T score initial (g/cm^2)	−2.98 (0.60)	−2.56 (1.49)	0.45
T score final (g/cm^2)	−3.28 (0.91)	−1.72 (1.69)	0.0005
sBMD_FN initial (g/cm^2)	0.69 (0.09)	0.66 (0.11)	0.53
sBMD_FN final (g/cm^2)	0.67 (0.08)	0.70 (0.12)	0.35
% change in sBMD_FN	−0.11 (4.33)	4.92 (8.48)	0.04
sBMD_TH Initial (g/cm^2)	0.72 (0.09)	0.73 (0.12)	1.00
sBMD_TH final (g/cm^2)	0.71 (0.07)	0.75 (0.10)	0.40
% change in sBMD_TH	1.25 (6.04)	4.17 (7.24)	0.39
25OHD Initial (ng/Ml)	42.80 (13.08)	37.51 (10.98)	0.29
25OHD Final (ng/Ml)	42.10 (7.46)	40.89 (10.81)	0.53

Table 3 NTx and BSAP over time for non-responders and responders

	Non-responder ($N = 13$) mean (std.)	Responder ($N = 65$) mean (std.)	p value*
NTx initial (Nm BCE/Mm Cr)	32.90 (15.00)	37.98 (37.00)	0.88
NTx 4 months (Nm BCE/Mm Cr)	71.00 (40.18)	63.58 (42.63)	0.44
NTx 8 months (Nm BCE/Mm Cr)	86.56 (57.44)	75.84 (55.32)	0.52
NTx 12 months (Nm BCE/Mm Cr)	83.91 (49.86)	75.16 (72.36)	0.29
NTx 16 months (Nm BCE/Mm Cr)	66.50 (36.98)	69.41 (55.37)	0.88
NTx 20 months (Nm BCE/Mm Cr)	57.10 (22.32)	63.70 (41.64)	0.81
NTx 24 months (Nm BCE/Mm Cr)	63.83 (38.40)	42.73 (21.74)	0.02
BSAP initial (units/L)	18.37 (9.17)	14.47 (8.82)	0.35
BSAP 4 months (units/L)	25.06 (8.86)	18.70 (9.96)	0.04
BSAP 8 months (units/L)	27.79 (10.87)	23.17 (14.20)	0.17
BSAP 12 months (units/L)	28.71 (14.18)	22.84 (13.69)	0.15
BSAP 16 months (units/L)	27.16 (13.33)	24.65 (14.84)	0.50
BSAP 20 months (units/L)	24.08 (12.60)	22.84 (13.74)	0.67
BSAP 24 months (units/L)	22.45 (10.88)	19.57 (11.31)	0.31

models); but no statistically significant differences were found between responders and non-responders over time (time taken as continuous variable) in either NTx ($p = 0.79$) or BSAP ($p = 0.27$).

The percentage of patients showing a greater than 3% increase in BMD (responder rates) after 2 years of TPTD treatment in our study was 83% using the spine as outcome, but only 40% at the femoral neck (Fig. 3.)

Discussion

Not every patient receiving 18–24 months of TPTD showed a significant increase in lumbar spine bone density. In the current study, 83% of patients were TPTD responders, demonstrating a greater than 3% increase in BMD, a value preselected to exceed the least significant change (LSC) used by prior investigators in distinguishing responders and non-responders based on LS BMD changes with TPTD treatment [9, 26].

In the current study, 16.7% of the patients were identified as non-responders, which is a significantly higher rate of non-responders to TPTD than previously reported [14, 26]. None of the initial characteristics including age, BMI, BMD, vitamin D status, or prior bisphosphonate use predicted response to TPTD. Interestingly, with regard to gender, all 8 men in the study were responders. Since so few men were in the study, this result could not be judged to be statistically significant.

Bone markers showed the typical increases with TPTD treatment that have been described in earlier studies [2–4, 8–10, 12, 17, 18, 23–27, 29, 32–34]. In general, both BSAP and NTx were higher in the TPTD non-responders compared to the responders.

The NTx marker measures a fragment of the cross-linking bridge between the type I collagen chains in bone. High values of the NTx reflect accelerated type I collagen breakdown associated with increased bone resorption [13]. BSAP is primarily derived from osteoblasts. Increased levels of BSAP reflect increased bone synthesis and anabolic activity. A rise in BSAP has been demonstrated during early anabolic response to TPTD treatment, which is subsequently followed by a rise in the resorptive markers [4]. This early osteoblast-mediated anabolic response to TPTD, which precedes the osteoclast-mediated resorption of type I collagen describes the so-called anabolic window [1, 6, 30]. Previous studies of TPTD combination therapy were aimed at improving BMD anabolic response by prolonging the anabolic window during which bone formation exceeds bone resorption [1, 6, 25, 30]. Based on the current study results, there were no significant differences in the BSAP or NTX markers between the TPTD responders and non-responders over time.

Identifying TPTD non-responders early in therapy would have great practical utility especially as there was a significant percentage of patients who failed to respond with a net increase in bone formation, 16.7% in our study. Previous reports suggest sequential addition of an anti-remodeling agent consistently leads to an increase in net bone formation [2, 3, 25] as does concurrent TPTD and zolendronate or denosumab [10, 18, 33, 34]. In the Muschitz et al. study, the accentuated BMD anabolic response with TPTD-alendronate therapy compared to TPTD monotherapy was accompanied by early suppression of bone resorptive marker CTx to pre-TPTD treatment levels along with partial suppression of P1NP [25]. This finding supported the hypothesis of re-opening of the anabolic window of TPTD, which is characterized by greater bone formation than resorption, resulting in net gain of BMD. In the more recent TPTD-denosumab combination trial, Tsai et al. demonstrated augmented BMD anabolic response with concurrent TPTD-denosumab therapy compared to TPTD or denosumab monotherapy, which was accompanied by complete suppression of CTx and only partial suppression of markers of bone formation, osteocalcin, and P1NP [34]. Furthermore, combined denosumab-TPTD

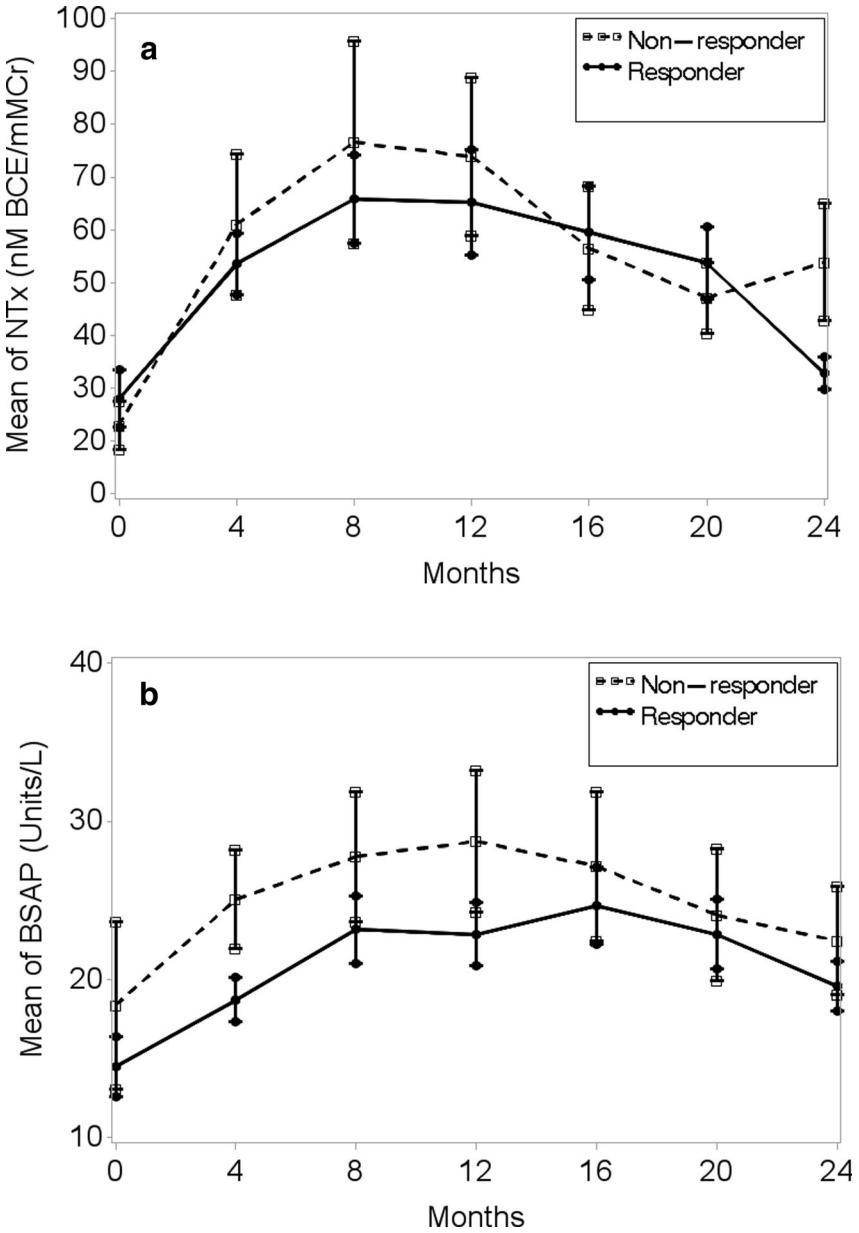

Fig. 1. **a** A peak response in bone marker NTx was observed at 4–8 months in both non-responders and responders while the peak response in BSAP was observed at 8–12 months in non-responders and at 4–8 months in responders. **b** The magnitude of BSAP was significantly higher in the non-responders compared to TPTD responders only at 4 months ($p = 0.04$).

therapy produced favorable changes in cortical parameters, such as less porosity, increased cortical thickness, and volume along with apparent filling of resorptive cavities at the endocortical surface [33].

Clinicians often rely on bone turnover markers to confirm that patients are responding to osteoporosis therapy, in this case, TPTD. Although our study results showed significantly higher BSAP levels in the TPTD non-responders at 4 months, there were no significant differences between the TPTD responders and non-responders over time (24 months). This finding suggests that the changes seen in the bone turnover markers during TPTD therapy may not correlate well with clinical outcome, such as improvement in BMD.

There are several limitations to the current study. First, the data are derived from a retrospective, open-label, small patient number cohort. However, the study being open label would not have influenced the changes in BTM and BMD. Those performing the laboratory measurements were blinded with regard to treatment. Furthermore, the primary endpoint of a BMD change greater than 3% for the study was predetermined and no differences in baseline characteristics or laboratory values were demonstrable in the responder and non-responder patient populations.

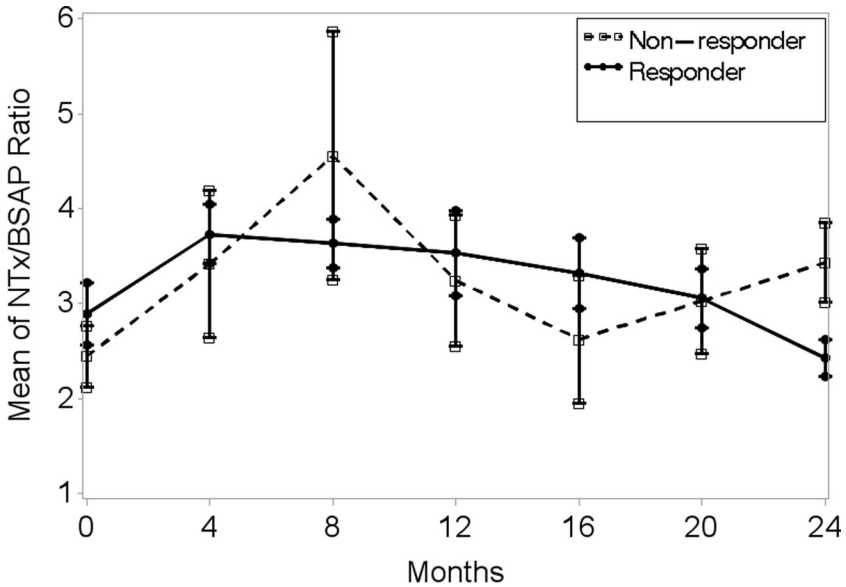

Fig. 2. Although the differences were not statistically significant, the NTx/BSAP ratio was higher in the TPTD non-responders at 4–12 months, indicative of greater resorptive activity compared to bone formation.

Second, there was limitation in racial and ethnic diversity in the study population. This was an unavoidable consequence of the patient population coming from a single physician's practice and reflects the typical regional and referral patient population to this academic practice for treatment of osteoporosis. In fact, it is a strength that the patients/subjects were drawn from a real-life medical practice in which the choice to treat with TPTD was based solely on the clinical presentation.

Third, these changes in bone markers do not provide a true insight into biological mechanism of BMD changes. Finally, too few fractures occurred during the study so no correlation of BTM or BMD changes with fracture incidence can be made. However, it is important to remember that the strongest correlation of BMD change with fracture risk is seen with TPTD treatment more than with any of the other therapeutic interventions for osteoporosis [7].

It would appear that there is a complex balance of osteoclast-mediated resorptive activity and osteoblast-mediated bone formation modulating the anabolic response. The current study suggests that the bone turnover markers BSAP and NTx do not correlate well with clinical response to teriparatide therapy, and puts into question the role of monitoring BTM during therapy. Recently proposed TPTD combination therapy with denosumab or zolendronate may be an effective treatment option for patients who do not respond to TPTD monotherapy. However, additional studies dedicated to identifying TPTD non-responders early in therapy are necessary so that this subset of osteoporotic patients can be treated earlier and more effectively with combination or sequential therapy.

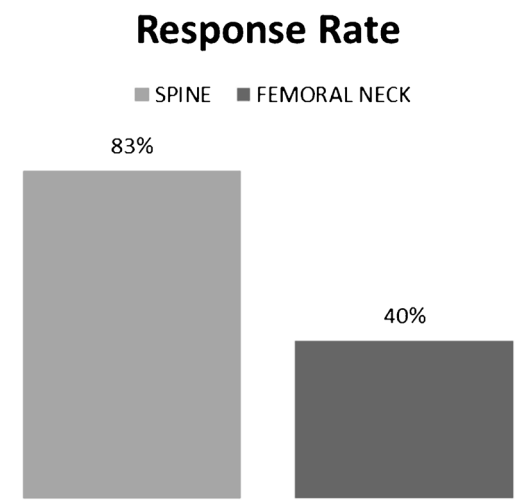

Fig. 3. Eighty-three percent of the lumbar spine and 40% of the femoral neck showed significant response to teriparatide therapy with more than 3% increase in BMD.

Acknowledgements The authors thank Mr. Erik Nielsen for his assistance in collating the early patient data.

Compliance with Ethical Standards

Conflict of Interest: So-Young Kim, MD, Meng Zhang, PhD, and Richard Bockman, MD, PhD, have declared that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent: Informed consent was waived from all patients for being included in the study.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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