

# Comparative effects of teriparatide and ibandronate on spine bone mineral density (BMD) and microarchitecture (TBS) in postmenopausal women with osteoporosis: a 2-year open-label study

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## Abstract

**Summary** Treatment effects over 2 years of teriparatide vs. ibandronate in postmenopausal women with osteoporosis were compared using lumbar spine bone mineral density (BMD) and trabecular bone score (TBS). Teriparatide induced larger increases in BMD and TBS compared to ibandronate, suggesting a more pronounced effect on bone microarchitecture of the bone anabolic drug.

**Introduction** The trabecular bone score (TBS) is an index of bone microarchitecture, independent of bone mineral density (BMD), calculated from anteroposterior spine dual X-ray absorptiometry (DXA) scans. The potential role of TBS for monitoring treatment response with bone-active substances is not established. The aim of this study was to compare the effects of recombinant human 1–34 parathyroid hormone (teriparatide) and the bisphosphonate ibandronate (IBN), on lumbar spine (LS) BMD and TBS in postmenopausal women with osteoporosis.

**Methods** Two patient groups with matched age, body mass index (BMI), and baseline LS BMD, treated with either daily subcutaneous teriparatide ( $N=65$ ) or quarterly intravenous IBN ( $N=122$ ) during 2 years and with available LS BMD measurements at baseline and 2 years after treatment initiation were compared.

**Results** Baseline characteristics (overall mean  $\pm$  SD) were similar between groups in terms of age  $67.9\pm 7.4$  years, body mass index  $23.8\pm 3.8$  kg/m<sup>2</sup>, BMD L1–L4  $0.741\pm 0.100$  g/cm<sup>2</sup>, and TBS  $1.208\pm 0.100$ . Over 24 months, teriparatide induced a significantly larger increase in LS BMD and TBS than IBN ( $+7.6\%\pm 6.3$  vs.  $+2.9\%\pm 3.3$  and  $+4.3\%\pm 6.6$  vs.  $+0.3\%\pm 4.1$ , respectively;  $P<0.0001$  for both). LS BMD and TBS were only weakly correlated at baseline ( $r^2=0.04$ ) with no correlation between the changes in BMD and TBS over 24 months.

**Conclusions** In postmenopausal women with osteoporosis, a 2-year treatment with teriparatide led to a significantly larger increase in LS BMD and TBS than IBN, suggesting that teriparatide had more pronounced effects on bone microarchitecture than IBN.

**Keywords** Bone mineral density · Open-label study · Osteoporosis · Parathyroid hormone · Teriparatide · Trabecular bone score · Treatment

## Introduction

Osteoporosis and osteoporosis-related fractures represent a worldwide disease burden, especially in North America and Europe [1–5]. With much of this burden stemming from the morbidity and mortality related to the roughly nine million osteoporotic fractures that occur each year [4, 5], the primary goal of treatment has long been fracture prevention [6–8].

As recommended by the World Health Organization (WHO) since 1994 [9], bone mineral density (BMD), measured by dual X-ray absorptiometry (DXA) is the current gold standard for diagnosing osteoporosis and monitoring treatment, supported by the fact that BMD is a major determinant of bone strength and fracture risk [10]. However, considerable

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overlap exists between BMD values in individuals who develop fractures and those who do not [11], indicating that other factors influence both bone strength and fracture risk. To cite just but a few: macrogeometry of cortical bone, microarchitecture of trabecular bone, as well as bone microdamage, mineralization, and turnover [12–14].

The trabecular bone score (TBS) is derived from a simple anteroposterior LS DXA scan and can be used for the noninvasive assessment of intravertebral cancellous bone microarchitecture [15–18]. The TBS was shown to discriminate between patients with incident hip, nonvertebral, or vertebral fracture and nonfractured patients with osteoporosis in several prospective and retrospective cohort studies [19–24], with odds ratios ranging between 1.6 and 2.05 with a similar order of magnitude than lumbar spine BMD [19, 21, 22, 24]. In addition, in these studies, the combination of TBS and lumbar spine BMD (LS BMD) was generally superior to either measurement alone with regard to fracture risk prediction [19, 20, 22–24]. Furthermore, the TBS was responsive to treatment with antiresorptive drugs in a large cohort study [25] and in the retrospective analysis of a randomized placebo-controlled trial with the aminobisphosphonate zoledronate [26].

Daily subcutaneous injections of recombinant human 1–34 N-terminal fragment of parathyroid hormone (teriparatide) were shown to increase BMD and to reduce the risk of new vertebral and nonvertebral, but not hip, fractures in patients with postmenopausal and glucocorticoid-induced osteoporosis [27, 28]. The observed increases in LS BMD with teriparatide accounted for approximately 30–41 % of the achieved vertebral fracture risk reduction, suggesting other mechanisms accounting for the remainder [27, 29]. Teriparatide was recently shown to improve trabecular microarchitecture in iliac crest bone biopsies of postmenopausal women [29], confirming earlier preclinical data showing improved histomorphometric cancellous bone parameters and vertebral bone strength in ovariectomized rats [30] and monkeys [31]. The effects of teriparatide on the TBS are unknown.

Bisphosphonates, such as the aminobisphosphonate ibandronate (IBN), are inhibitors of bone resorption belonging to the mainstay of osteoporosis treatment. Histomorphometric data in postmenopausal women treated during 2 years with intravenous ibandronate showed no increase in trabecular number or volume and no decrease in intertrabecular separation [32]. In line with these findings, an earlier study performed with the intravenous aminobisphosphonate zoledronate in postmenopausal women showed an only modest increase in TBS consistent with a preservation of vertebral bone microarchitecture [26].

The aims of this study were: (1) to compare the effects of subcutaneous teriparatide and intravenous ibandronate on LS BMD and TBS in postmenopausal women with osteoporosis;

(2) to assess whether the changes in TBS are independent of those of BMD; and (3) to evaluate the changes in TBS in terms of possible clinical relevance at the individual patient level.

## Methods

The study was conducted at the Department of Osteoporosis of the University Hospital of Berne, Switzerland as an open-label, retrospective, nonrandomized, treatment-controlled study comparing the effects of an up to 2-year treatment with subcutaneous teriparatide (Forsteo<sup>®</sup>, Eli Lilly, USA) vs. a 2-year treatment with intravenous IBN (Bonviva<sup>®</sup>, Roche, Switzerland) on LS BMD and TBS in two groups of postmenopausal women with osteoporosis matched for age, body mass index (BMI), and LS BMD.

### Study population and treatment schemes

Postmenopausal women with primary osteoporosis referred for evaluation to the osteoporosis consultation of the Department of Osteoporosis of University Hospital of Berne, Switzerland, between 2007 and 2009, who were subsequently treated with teriparatide 20 µg self-injected daily, were evaluated if they had LS BMD measurements performed by DXA at baseline and after 2 years of therapy ( $n=70$ ). Women treated with teriparatide usually had experienced a vertebral fragility fracture during a prior therapy with an antiresorptive, independently of their LS BMD value. The reimbursed duration of treatment with teriparatide was increased from 18 to 24 months during the course of the study. As a consequence, one sixth of the patients treated with teriparatide were treated during 18 months followed by an intravenous infusion of zoledronate 5 mg, the other five sixth were on teriparatide during 24 months. The control group consisted of postmenopausal women with primary osteoporosis in whom a treatment with intravenous ibandronate 3 mg every 3 months was initiated between 2007 and 2009 and monitored during at least two following years at the Department of Osteoporosis of Berne. Women treated with ibandronate usually had a BMD T-score at or below  $-2.5$  or one or more prevalent vertebral fractures. Women on ibandronate were matched for age, BMI, and LS BMD with women in the teriparatide group, following a 2:1 ratio ( $n=140$ ). All subjects were vitamin D-replete and received adequate calcium and vitamin D3 supplementation. Women currently on glucocorticosteroids or presenting other secondary forms of osteoporosis were not eligible. Prior therapies with bisphosphonates, estrogens, or other bone active substances including vitamin D were allowed. Only women with evaluable DXA scans for both LS BMD and TBS at baseline and after 2 years in the teriparatide and the ibandronate groups, respectively, were included in the analysis.

### Measurement of bone mineral density

Bone mineral density (BMD) was assessed by DXA (Hologic QDR 4500A®, Hologic, Bedford, MA, USA) at the single study centre of the Department of Osteoporosis of the University Hospital of Berne, Switzerland. All DXA scans were performed in accordance with manufacturer recommendations. Lumbar spine BMD measurements were recorded for L1 through L4 (L1–L4). BMD was expressed as grams per square centimeter of hydroxyapatite and as T-scores (standard deviation [SD] from the mean of a healthy young female population). The manufacturer's normative database was used as reference for the LS after analysis according to International Society for Clinical Densitometry (ISCD) rules [33]. Individual vertebrae were excluded in case of fractures or degenerative changes, in accordance with ISCD rules for individual vertebrae exclusion (more than 1 standard deviation from immediately adjacent vertebrae). Quality control was performed daily (anthropometric spine phantom supplied by the manufacturer).

### Measurement of trabecular bone score

The trabecular bone score (TBS) is a grey-level texture measurement that can be applied to DXA images for quantifying local variations in grey level [15–17]. Using experimental variograms of two-dimensional (2D) projection images, TBS can differentiate between three-dimensional (3D) microstructures that exhibit the same bone density, but different trabecular characteristics [15, 18]. The TBS is obtained by direct (re-)analysis of an acquired lumbar spine DXA image, without need for further imaging. All TBS determinations were performed in a blinded manner within the Bone Disease Unit at the University Hospital of Lausanne, Lausanne, Switzerland using TBS iNsight® Software version 1.8.2 (Med-Imaps, Bordeaux, France). Lumbar spine TBS (LS TBS) was evaluated in the same vertebrae and regions of measurement as those used for LS BMD, with LS TBS calculated as the mean value of the individual measurements for vertebrae L1–L4. The coefficient of variation for LS BMD measurements at the Department of Osteoporosis of the University Hospital of Berne is 0.90 % when applying with ISCD recommendations (15 outpatients representative of our daily routine with triplicate measurements after repositioning) with a corresponding coefficient of variation of 1.12 % for TBS. Thus, the least significant change (LSC) is 2.49 % for LS BMD and 3.10 % for TBS.

### Statistical analysis

Descriptive analysis included means and percentages with standard deviations. The percent changes in BMD and TBS were calculated for each subject as the absolute change from baseline to 2-year follow-up, divided by the baseline value. Bivariate intergroup comparisons were performed between

those treated with IBN vs. teriparatide using Student's *t* tests and Pearson  $\chi^2$  analysis for continuous and noncontinuous variables, respectively. Pearson correlation coefficients were calculated for BMD vs. TBS and for change from baseline in BMD vs. change from baseline in TBS. All inferential tests were two-tailed and  $P < 0.05$  was set as the threshold for statistical significance. All statistical analyses were performed using Stata® software (Version 12, StataCorp, Texas, USA).

### Results

Overall, 65 (93 %) and 122 (87 %) patients had evaluable DXA scans for LS BMD and TBS at baseline and after 2 years in the teriparatide and the ibandronate groups, respectively, and were included in the analysis. In total, 40, 40, and 20 % of the patients had four, three, and two vertebrae evaluated, respectively. As a result of matching, baseline characteristics (mean  $\pm$ SD) were similar between groups in term of age, body mass index, baseline LS BMD T-score and LS TBS (Table 1). Patients in the teriparatide group were more likely having had prior therapy with a bisphosphonate (95.4 vs. 80.3 %,  $P = 0.005$ ), having prevalent vertebral fractures or a positive history of fracture during adulthood (90.5 vs. 44.3, and 73.8 vs. 41.0 %, respectively;  $P = 0.0001$  for both), and had a significantly higher clinical fracture risk score for hip and major osteoporotic fractures assessed by FRAX®.

As shown in Fig. 1, after 24 months of therapy, LS BMD and TBS increased significantly more with teriparatide compared to IBN (+7.6 %  $\pm$  6.3 vs. +2.9 %  $\pm$  3.3 and +4.3 %  $\pm$  6.6 vs. +0.3 %  $\pm$  4.1, respectively;  $P < 0.0001$  for both). Compared to baseline, increases in LS BMD were significant in both the teriparatide and IBN group ( $P < 0.0001$  for both), while increases in LS TBS were significant in the teriparatide group only ( $P < 0.0001$ ).

Baseline spine BMD and TBS were only weakly correlated, ( $r^2 = 0.04$ ), indicating that only 4 % of the variance in one parameter was explained by the other. There was no correlation between the 2-year changes in BMD and TBS from baseline ( $r^2 = 0.01$ ).

As shown in Table 2, LS BMD was more sensitive than LS TBS with regard to the proportion of patients achieving an increase above least significant change (LSC) in both treatment groups: 78.5 vs. 61.5 % (McNemar test  $P < 0.01$ ) and 51.6 vs. 26.3 % ( $P < 0.001$ ) with teriparatide and IBN, respectively. Interestingly, while only 11.0 % of the patients did not respond in terms of TBS below the LSC with teriparatide, this proportion reached 27.0 % with IBN. Furthermore, in the teriparatide group, 51.0 % of the patients were above the LSC for both LS BMD and TBS vs. only 28.0 % in the IBN group (results not shown in Table 2), suggesting a stronger effect on bone microarchitecture with the former.

**Table 1** Baseline Demographics and Clinical Characteristics (mean  $\pm$  SD)

	Teriparatide group	IBN group	<i>P</i> value
<i>N</i>	65	122	
Duration of active treatment (months)	22.9 $\pm$ 3.6	24.0 $\pm$ 4.7	0.10
Age (years)	68.9 $\pm$ 9.0	67.4 $\pm$ 6.5	0.20
BMI (kilogram per square meter)	23.7 $\pm$ 4.2	23.8 $\pm$ 3.5	0.92
Prior therapy with an oral/IV bisphosphonate (percent)	95.4	80.3	0.005
Duration of washout prior to study drug initiation (months)	0.23 $\pm$ 0.79	0.26 $\pm$ 0.85	0.23
Lumbar spine			
BMD (gram per square centimeter)	0.759 $\pm$ 0.153	0.732 $\pm$ 0.080	0.12
T-score	-2.66 $\pm$ 1.35	-2.77 $\pm$ 0.67	0.46
TBS	1.206 $\pm$ 0.100	1.209 $\pm$ 0.100	0.85
Total hip			
BMD (gram per square centimeter)	0.703 $\pm$ 0.113	0.729 $\pm$ 0.100	0.10
T-score	-1.96 $\pm$ 0.93	-1.75 $\pm$ 0.78	0.11
Femoral neck			
BMD (gram per square centimeter)	0.606 $\pm$ 0.105	0.622 $\pm$ 0.084	0.27
T-score	-2.09 $\pm$ 1.17	-2.11 $\pm$ 0.81	0.91
Prevalent vertebral fractures (percent)	90.5	44.3	0.0001
Positive history of nonvertebral fractures during adulthood (percent)	73.8	41	0.0001
Past use of glucocorticosteroids (percent)	9.0 %	4.6 %	0.28
10-year absolute risk for major osteoporotic fractures (FRAX <sup>®</sup> with BMD, percent)	26.7 $\pm$ 10.4	21.1 $\pm$ 10.1	0.0001
10-year absolute risk for hip fractures (FRAX <sup>®</sup> with BMD, percent)	8.15 $\pm$ 6.7	5.1 $\pm$ 5.1	0.0001

All values are means  $\pm$  SD, except indicated otherwise

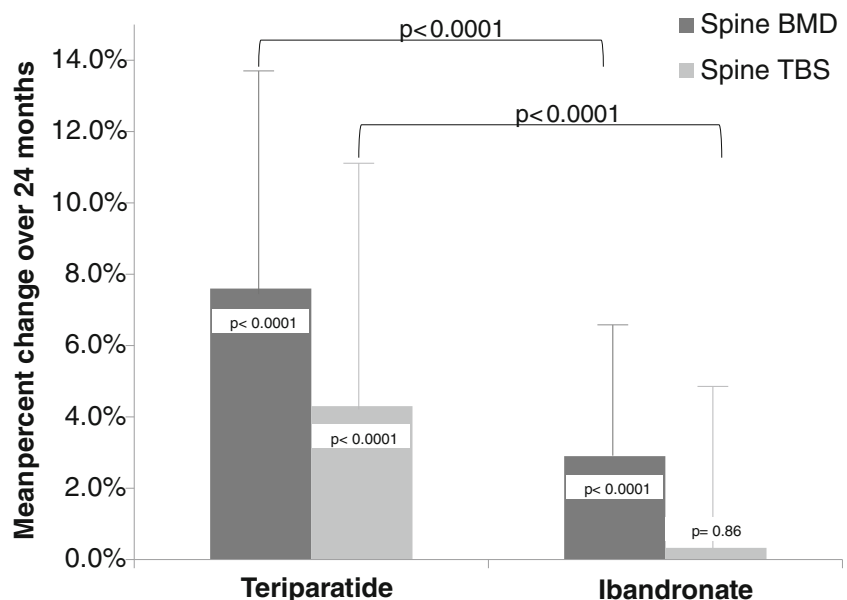
## Discussion

In postmenopausal women with primary osteoporosis, a 2-year treatment with teriparatide increased LS BMD and TBS significantly more and in a significantly greater proportion of patients than a 2-year treatment with intravenous ibandronate.

As the increase in LS TBS was largely independent from the BMD response, these results suggests that LS TBS may contribute to assess the effects of bone anabolic agents on vertebral microarchitecture.

Only few studies have investigated the effect of bone active substances on LS TBS [25, 26]. Taken together with the

**Fig. 1** Percent change in lumbar spine BMD and TBS at month 24 after treatment with teriparatide (22.9 months) and ibandronate (24 months). Mean values  $\pm$  standard deviation. *P* values above the bars refer to significance vs. baseline



**Table 2** Percentage of patients above, within and below the LSC for both teriparatide and IBN groups and LS BMD and LS TBS

	Above LSC (percent)	Within LSC (percent)	Below LSC (percent)
<i>Teriparatide</i>			
LS BMD	78.5	20.0	1.5
LS TBS	61.5	27.7	10.8
<i>Ibandronate</i>			
LS BMD	51.6	42.6	5.8
LS TBS	26.3	46.7	27.0

LSC least significant change, LS lumbar spine

Within LSC for LS BMD is between  $-2.49$  and  $+2.49$  %

Within LSC for LS TBS is between  $-3.10$  and  $+3.10$  %

present findings, these earlier reports are consistent with the concept that bisphosphonates allow for “positive maintenance” of bone microarchitecture rather than a major improvement in microarchitecture. For almost two decades, bisphosphonates have been the therapy of choice to treat osteoporosis and to prevent fractures, relying on solid evidence with regard to fracture risk reduction [2, 34–38]. However, the long-term bone safety of bisphosphonates has been recently questioned [39]. On one hand, bisphosphonates increase bone strength by increasing the mineralization of remodelled bone units, reducing cortical porosity and decreasing focal stress. On the other hand, they suppress the generation of new bone remodelling units and reduce bone turnover [39]. In the present study, the increase in LS BMD and TBS observed with IBN was of a lower order of magnitude than expected. In earlier studies, LS TBS increased by 0.25 to 0.5 % per year under antiresorptive therapy [25, 26], which is clearly more than the 0.3 % over 2 years reported in the present study. One of the possible explanations may be related to the fact that more than 80 % of the “real life” women included had been on bisphosphonate therapy before being switched to intravenous ibandronate after a very short or no washout period. This suggests not unexpectedly that, in patients under prior antiresorptive therapy, bisphosphonates may be more likely to maintain than to restore vertebral microarchitecture.

Teriparatide exerts primarily bone anabolic effects, which include increasing cancellous bone volume and connectivity, increasing cortical bone thickness, and enhancing trabecular morphology [39, 40]. Since the inaugural publication by Neer et al. [27] in 2001, several smaller studies have confirmed that teriparatide allows for strong BMD increases and for fracture risk reduction, suggesting that it may become an attractive alternative to bisphosphonates for strengthening and possibly restoring bone microarchitecture [41–44]. In the present study, a 2-year therapy with subcutaneous teriparatide induced a statistically significant increase in LS BMD and TBS of large

magnitude. The latter ( $+4.3$  % in only 2 years) exceeds by far the TBS increases reported with antiresorptive substances to date [25, 26]. Furthermore, the ratio of BMD to TBS increase was approximately 2:1 with teriparatide and 9:1 with ibandronate in the present study, compared to 10:1 with bisphosphonates in a retrospective study of 534 postmenopausal women treated with antiresorptive therapy in the Canadian province of Manitoba [25], and 4:1 in a 3-year randomized, controlled study with yearly intravenous zoledronate [26]. Taken together with the absence of a significant correlation between changes from baseline in BMD and changes from baseline in TBS [25, 26], these observations indicate that BMD and TBS measure different characteristics of bone and bone strength.

With regard to individual therapy monitoring, only 12–35 % of patients on bisphosphonates had an increase in TBS that was exceeding the LSC in earlier studies [25, 26], as compared to 26 % in the present analysis. In contrast, about 62 % of the patients on teriparatide were above LSC, primarily indicating that LS TBS may be more suitable for monitoring the effects of bone anabolic substances than for monitoring the effects of antiresorptives.

To date, only one direct comparison between teriparatide and a bisphosphonate (risedronate) has been published in postmenopausal women with osteoporotic spine compression fractures. In that study, teriparatide yielded a significantly greater increase in BMD from baseline in the lumbar spine and femoral neck and was associated with a lower incidence of vertebral fractures at 18 months (4 vs. 9 %, respectively;  $P=0.01$ ) and with less severe vertebral fractures ( $P=0.04$ ) [45]. There have, on the other hand, been several studies assessing the effects of teriparatide in patients in whom bisphosphonate treatment has failed or otherwise been terminated. In the most recently published study, postmenopausal women with severe osteoporosis who had failed treatment with a bisphosphonate responded well to 18 months of treatment with daily parathyroid hormone, with a 37 % reduction in the incidence of fractures in their second year of treatment relative to their first 6 months of therapy, and a 76 % reduction relative to baseline subsequent to this. Patients also reported reduced back pain and improved health-related quality of life while taking teriparatide [46]. These results are consistent with the results of several prior studies demonstrating some benefit of parathyroid hormones in the aftermath of bisphosphonate therapy [41, 44, 47] although it is the first time that results are reported with TBS.

The findings of the present study are limited by the retrospective nature of the analysis. Pretreatment with antiresorptives may have partially blunted some of the expected effects on LS BMD and TBS. In addition, the two groups were not comparable with respect to osteoporosis severity, which may have influenced the results. Keeping these limitations in mind, the results show, for the first time, that larger

effects on trabecular microarchitecture assessed by TBS may be expected when using bone anabolic substances and may open the way for future research in this direction including, but not limited to, the place of TBS alone and/or in combination with BMD and/or clinical risk factors for the choice and monitoring of treatments with bone-active substances and the identification of more individualized treatment schemes for patients with osteoporosis at increased risk of fracture.

## Conclusions

In women with postmenopausal osteoporosis, a 2-year treatment with teriparatide exerted more beneficial effects on lumbar spine BMD and microarchitecture assessed by TBS than ibandronate. Changes in LS BMD and TBS from baseline were not correlated, confirming that these two parameters measure different responses of bone to therapy. At the individual patient level, TBS was significantly more sensitive to bone anabolic substances than to antiresorptives, with almost two thirds of the patients on teriparatide showing TBS increases above the least significant change.

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**Conflicts of interest** Didier Hans is coowner of the TBS patent and has corresponding ownership shares. Christoph Senn, Beatrice Günther, Albrecht W. Popp, Romain Perrelet, and Kurt Lippuner declare that they have no conflict of interest.

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