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Bisphosphonate Pre-Treatment Diminishes the Therapeutic Benefits of Teriparatide in Japanese Osteoporotic Patients

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Osteoporosis (OP) is the most common multifactorial metabolic bone disorder worldwide. It remains unclear whether bisphosphonate (BP) pre-treatment affects the anabolic bone metabolism in OP patients treated with teriparatide (TPTD), a recombinant form of parathyroid hormone 1-34. This study is the first to evaluate the clinical outcomes of daily TPTD administration in Japanese OP patients and aimed to clarify how BP pre-treatment influences the efficacy of TPTD. We enrolled 112 patients diagnosed as primary OP who received TPTD. Subjects were classified as OP treatment-naïve patients (TPTD alone group) or patients previously treated with BP (BP pre-treated group). We measured serum bone-specific alkaline phosphatase (BAP) as a bone formation marker, urinary cross-linked N-terminal telopeptide of type I collagen (NTX) as a bone resorption marker, and bone mineral density (BMD) of lumbar vertebrae (L-BMD) and bilateral total hips (H-BMD). In both groups, BAP and NTX increased until 6 months and then decreased thereafter. The percent changes of both markers in BP pre-treated group were more increased than those in TPTD alone group. L-BMD increased significantly in both groups. The percent increase of L-BMD in the TPTD alone group was significantly higher than that in the BP pre-treated group. H-BMD rose significantly in the TPTD alone group, but not in BP pre-treated group. BP pre-treatment appears to diminish the degree of the TPTD-mediated increase in BMD. Thus, it is preferable to administer TPTD ahead of BP treatment in patients with severe OP.

Keywords: bisphosphonate; bone mineral density; bone turnover markers; Japanese osteoporotic patients; teriparatide
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Introduction

Osteoporosis (OP) is a major public health issue among the elderly, especially post-menopausal women. Although the incidence of proximal femoral fractures appears to be decreasing in Europe and North America (Harvey et al. 2010), that of OP and OP-related fractures is increasing yearly in Japan (Ito 2014). Therefore, it is of national concern to reduce the burden of this debilitating disease.

The main goal of OP treatment is the prevention of fractures and ultimately death caused directly or indirectly by fractures. One of the best examinations to investigate the effects of osteoporotic treatment in OP patients is bone mineral density (BMD). Most drugs for OP, including bisphosphonates (BP), augment BMD through inhibition of bone resorption. Teriparatide (TPTD) (parathyroid hormone 1-34) is currently the only drug available in Japan to increase bone formation.

Neer et al. (2001) first described that once-daily TPTD injections decreased vertebral and non-vertebral fractures and increased BMD in vertebrae and hip joints. Others have reported that TPTD induces new bone formation and improves bone quality, which is beneficial in the treatment of OP (Arlot et al. 2005; Ma et al. 2006). Compared with conventional drugs, such as BP, TPTD has stronger effects on lumbar BMD (L-BMD) increase and the inhibition of spinal fractures (Neer et al. 2001). Therefore, TPTD may be preferential for osteoporotic patients who have greatly diminished BMD and/or multiple bone fractures.

Until recently, we had been prescribing BP treatment to all osteoporotic patients with low L-BMD and hip BMD (H-BMD) values. However, Obermayer-Pietsch et al. (2008) have reported on the effectiveness of TPTD therapy after BP treatment and concluded that TPTD was useful in increasing BMD regardless of successful or unsuccessful BP treatment. Accordingly, we have since been offering TPTD treatment to patients with severe OP with low

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L-BMD regardless of prior BP treatment.

We here report the clinical outcomes of 112 Japanese osteoporotic patients who were treated with daily TPTD over a 1-year observation period. We measured L-BMD and H-BMD as well as bone turnover markers in these groups and assessed whether BP pre-treatment affected the results of TPTD therapy. This study is first report to clarify that BP pre-treatment diminishes the beneficial effect of TPTD on BMD.

Materials and Methods

Patient characteristics

Osteoporotic patients who were being treated at our hospital for very low L-BMD (i.e., less than −3.0 SD) were recommended to commence TPTD treatment. Only patients with primary OP were included in this study. Patients with obvious complications, such as renal or liver dysfunction, were not offered this therapy.

In total, we collected the data of 149 subjects who underwent TPTD treatment between November 2010 and December 2012. Fourteen of the 149 subjects dropped out of the study without prior notice. Eight patients discontinued TPTD treatment due to suspected adverse effects (AEs), such as nausea, low appetite, or dizziness, as advised by their principal physician. Nine subjects halted treatment because of economic or personal reasons, mental disorders, or exponential values of cross-linked N-telopeptide of type I collagen (NTX). Six subjects were excluded due to the prior fracture or nonunion (Fig. 1). Ultimately, 112 patients who continued TPTD treatment for at least 1 year were included in this investigation (Table 1). Gender comparison was performed using Fisher's exact test. The average data of age, body weight, height, and body mass index were analyzed using Welch's-t test (Table 1).

Patient classification

Subjects were classified into one of the following groups: 1) patients with primary OP who had not previously taken medication that may have affected bone or calcium metabolism (TPTD alone group), or 2) patients with primary OP who had taken BP prior to this study for low BMD. There was no washout period for BP in the BP pre-treated group (BP pre-treated group). The diagnosis of primary OP was made in accordance with the revised criteria established by the Japanese Society of Bone and Mineral Research (Orimo et al. 2012). In addition, the BP pre-treated group was classified into 3 groups (< 1 year, 1-2 years, and > 2 years) based on the BP administration period, and then we compared the increased values of BMD among them. The mean BP pre-treatment period for each group was 6.1 ± 1.1 months, 15.4 ± 1.5 months, and 56.7 ± 2.4 months, respectively.

TPTD (20 μg) was subcutaneously injected daily by the patients themselves over a period of at least 1 year. Adherence to therapy was confirmed at scheduled follow-ups. Alendronate, Risedronate, or Minodronate had been adopted for BP treatment. We could not examine the effects of individual BP drugs since they were sometimes changed for patients who exhibited low responsiveness.

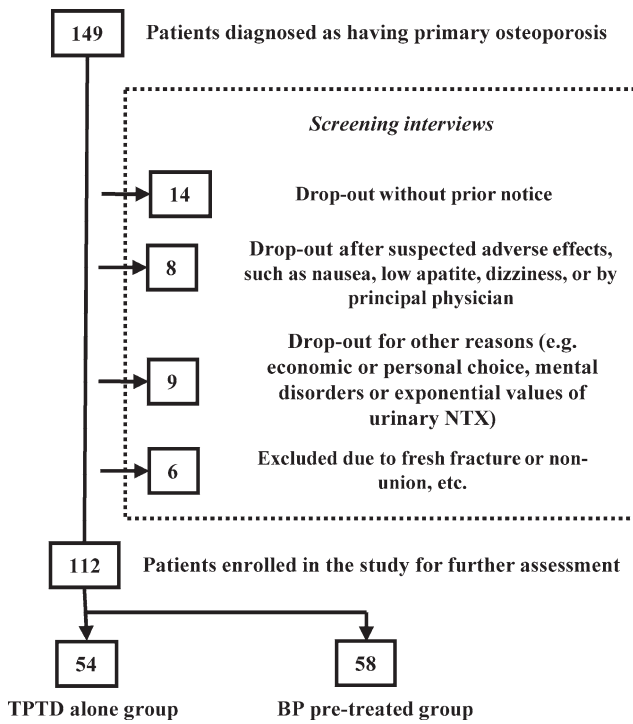

Fig. 1. Patient recruitment in the study.
The data of 149 primary osteoporotic patients were collected. However, 37 cases were excluded due to adverse effects, economic reasons, or other. The remaining 112 patients were divided into the TPTD alone group (54 patients) and the BP pre-treated group (58 patients) for further assessment.

Table 1. Baseline patient characteristics in the TPTD alone and BP pre-treated groups.

	TPTD alone group	BP pre-treated group	p-value
Age (years)	68.1 ± 8.5	75.1 ± 7.1	< 0.001*
Gender (Male:Female)	3:51	2:56	0.671
Body weight (kg)	47.3 ± 6.8	46.2 ± 6.9	0.388
Height (cm)	152.1 ± 8.0	149.6 ± 6.6	0.086
BMI	20.4 ± 2.2	20.6 ± 2.7	0.695

Values are expressed as mean ± standard deviation (SD).
Gender comparison was performed using Fisher's exact test. The average data of age, body weight, height, and BMI were analyzed using Welch's-t test.
TPTD, daily teriparatide; BP, bisphosphonate; BMI, body mass index.
*Statistically significant.

Bone turnover markers and BMD

Serum bone alkaline phosphatase (BAP) was measured as a bone formation marker using a chemiluminescent enzyme immunoassay. Urinary NTX (Osteomark, Osteox International, Seattle, WA) was determined as a marker of bone resorption using the enzyme-linked immunosorbent assay (ELISA). After overnight fasting, serum and urine, except for the first morning samples, were collected between 8:30 a.m. and 11:00 a.m. Immunoassays were performed by SRL Inc. (Tokyo, Japan). Bone turnover markers were examined before administration and at 3, 6, and 12 months of TPTD administration. Overall, basic bone turnover marker values were significantly lower in the BP pre-treated group than those in the TPTD alone group, indicating the enhanced inhibition of bone metabolism by BP (Table 2).

BMD was measured using a Dual-energy X-ray Absorption (DXA) fan-beam bone densitometer (Lunar Prodigy; GE Healthcare Bio-Sciences Corp., Piscataway, NJ, USA) at the L1-4 levels of the postero-anterior spine and bilateral hips. Fracture sites were avoided for evaluation of BMD. H-BMD was calculated as the average BMD of the right and left hips. BMD was examined before administration and at 4, 8, and 12 months of TPTD administration.

Statistical analysis

For both groups, we compared the changes in urinary NTX, serum BAP, and BMD at each time point using linear mixed models and Bonferroni's correction method for multiple comparisons. Each value was individually adopted as a response variable: the timing of the measurement was used as a fixed effect, while the individuality of the measurement was adopted as a random effect. Comparisons between the results at each measuring point were performed using Welch's t-test. Since there was a significant difference between the 2 groups regarding the age of the patients, we performed multiple linear regression analysis. The percent change at 12 months was applied to a response variable; the existence of pre-treatment with BP and patients' age were applied to explanatory variables. The α error was designated as 0.05. Statistical analyses were performed using the statistical package R version 3.0.1 (R Development Core Team, http://www.r-project.org). All of the significant data were shown as p-value (Tables 1, 2 and 3).

The current study was approved by the Institutional Ethics Committees at Shinshu University School of Medicine and Showa Inan General Hospital, and informed consent was obtained from all patients. The methods were carried out in accordance with the approved guidelines. The clinical trial registration number is NCT02156960 and the date of registration was May 31, 2014.

Results

Patient distribution

In total, there were 54 patients (3 men and 51 women) in the TPTD alone treatment group and 58 patients (2 men and 56 women) in the BP pre-treated group. The mean period of BP pre-treatment prior to TPTD therapy was 44.1 ± 1.5 months. The characteristic baseline features of the subjects are shown in Table 1. The average age in the

Table 2. BMD and bone turnover marker values at each point.

	Month	TPTD alone	p-value	BP pre-treated	p-value	Group comparison p-value
Urinary NTX (nmol BCE/mmol Cr)	0	60.1 ± 5.1		30.4 ± 2.2		< 0.001*
	3	98.4 ± 8.5	< 0.001*	57.1 ± 6.7	< 0.001*	< 0.001*
	6	108.1 ± 9.7	< 0.001*	71.0 ± 6.6	< 0.001*	0.002*
	12	91.7 ± 9.5	< 0.001*	64.4 ± 6.9	< 0.001*	0.022*
BAP (μg/L)	0	21.0 ± 1.1		12.4 ± 0.8		< 0.001*
	3	27.0 ± 1.6	< 0.001*	15.3 ± 0.7	0.001*	< 0.001*
	6	28.1 ± 2.0	< 0.001*	19.5 ± 1.0	< 0.001*	< 0.001*
	12	24.3 ± 1.7	0.021	19.5 ± 1.4	< 0.001*	0.029*
L-BMD (g/cm^2)	0	0.692 ± 0.012		0.705 ± 0.011		0.434
	4	0.738 ± 0.012	< 0.001*	0.722 ± 0.012	< 0.001*	0.346
	8	0.766 ± 0.012	< 0.001*	0.731 ± 0.012	< 0.001*	0.038*
	12	0.787 ± 0.011	< 0.001*	0.736 ± 0.013	< 0.001*	0.003*
H-BMD (g/cm^2)	0	0.666 ± 0.013		0.640 ± 0.013		0.164
	4	0.673 ± 0.013	0.004*	0.644 ± 0.013	0.748	0.105
	8	0.685 ± 0.012	< 0.001*	0.640 ± 0.012	0.156	0.008*
	12	0.699 ± 0.012	< 0.001*	0.638 ± 0.013	0.705	< 0.001*

Values are expressed as mean ± standard error (SE).

TPTD, daily teriparatide; BP, bisphosphonate; NTX, cross-linked N-telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase; L-BMD, bone mineral density of the L1-4 vertebrae; H-BMD, bone mineral density of bilateral hips; BCE, bone collagen equivalent.

*Statistically significant.

Table 3. Changes in BMD and bone turnover marker values at each point.

		TPTD alone		BP pre-treated		
	Month	Percent change from month 0 (mean ± SE)	p-value	Percent change from month 0 (mean ± SE)	p-value	Group comparison p-value
Urinary NTX (nmolBCE/mmol Cr)	3	91.1 ± 20.0	< 0.001*	108.3 ± 21.3	< 0.001*	0.616
	6	119.5 ± 20.1	< 0.001*	166.5 ± 21.1	< 0.001*	0.203
	12	81.5 ± 21.0	< 0.001*	131.3 ± 22.1	< 0.001*	0.236
BAP (μg/L)	3	33.3 ± 6.9	< 0.001*	35.3 ± 7.8	< 0.001*	0.956
	6	40.3 ± 6.9	< 0.001*	70.6 ± 7.9	< 0.001*	0.027*
	12	24.5 ± 7.2	0.001*	64.1 ± 8.1	< 0.001*	0.009*
L-BMD (g/cm^2)	4	6.9 ± 0.7	< 0.001*	2.0 ± 0.6	< 0.001*	< 0.001
	8	10.7 ± 0.7	< 0.001*	3.6 ± 0.6	< 0.001*	< 0.001*
	12	13.0 ± 0.7	< 0.001*	4.7 ± 0.6	< 0.001*	< 0.001*
H-BMD (g/cm^2)	4	1.2 ± 0.4	0.004*	0.2 ± 0.4	0.586	0.040*
	8	2.9 ± 0.4	< 0.001*	−0.3 ± 0.4	0.373	< 0.001*
	12	4.4 ± 0.4	< 0.001*	0.3 ± 0.4	0.372	< 0.001*

Values are expressed as mean ± standard error (SE).
TPTD, daily teriparatide; BP, bisphosphonate; NTX, cross-linked N-telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase; L-BMD, bone mineral density of the L1-4 vertebrae; H-BMD, bone mineral density of bilateral hips.
*Statistically significant.

TPTD group (68.1 ± 8.5 years) was significantly lower than that in the BP pre-treated group (75.1 ± 7.1 years) ($p < 0.001$; Welch's t-test). Patient height, body weight, and body mass index were comparable between the groups, as was gender distribution.

Bone turnover markers

Bone resorption marker: In both groups, urinary NTX increased and peaked at 6 months, and then decreased until the study end point (Fig. 2a, Table 2). The change patterns of urinary NTX were similar for both groups (Fig. 2a). From 3 months after TPTD administration, urinary NTX was significantly higher compared with baseline in both groups (Table 2). However, urinary NTX values in the BP pre-treated group were significantly lower than those in the TPTD alone group over the whole observation period (Table 2). On the other hand, the percent changes of urinary NTX were not significantly different between the two groups ($p = 0.616$, 0.203, and 0.236 at 3, 6, and 12 months, respectively) (Table 3).

Bone formation marker: In both groups, serum BAP increased and peaked at 6 months, and then decreased until the study end point (Fig. 2b, Table 2). The change patterns of BAP were similar for both groups (Fig. 2b). From 3 months after TPTD administration, BAP was significantly higher compared with baseline in both groups (Table 2). However, serum BAP values in the BP pre-treated group were significantly lower than those in the TPTD alone group over the whole observation period (Table 2). The percent changes of serum BAP were not significantly different at 3 months TPTD administration ($p = 0.956$). However, after 6 months of administration, the percent changes of BAP in the BP pre-treated group were significantly higher than those in the TPTD alone group ($p = 0.027$ and 0.009 at 6 and 12 months, respectively) (Table 3).

L-BMD: L-BMD increased steadily for 12 months in the TPTD alone group ($p < 0.001$ at 4, 8, and 12 months; 13.0% increase) and in the BP pre-treated group ($p < 0.001$ at 4, 8, and 12 months; 4.7% increase) (Fig. 2c). At the study onset, the values of L-BMD tended to be lower in the TPTD group. However, after 8 months of TPTD administration, L-BMD in the TPTD alone group were significantly higher than that in the BP pre-treated group ($p = 0.038$ and 0.003 at 8 and 12 months, respectively) (Table 2). The percent changes of L-BMD in the TPTD alone group (13.0%) were significantly higher than those in the BP pre-treated group (4.7%) after 4 months of TPTD administration ($p < 0.001$) (Table 3).

H- BMD: In the TPTD alone group, H-BMD rose moderately until the study endpoint ($p = 0.004$ at 4 months and $p < 0.001$ at 6 and 12 months; 4.4% increase) (Fig. 2d, Table 2). However, H-BMD did not change noticeably ($p = 0.748$, 0.156 and 0.705 at 4, 8, and 12 months, respectively; 0.3% increase) in the BP pre-treated group during follow-up (Fig. 2d, Table 2). At base line and 4 months after TPTD administration, H-BMD was not significantly different between the two groups. However, after 8 months of administration, H-BMD values in the TPTD alone group

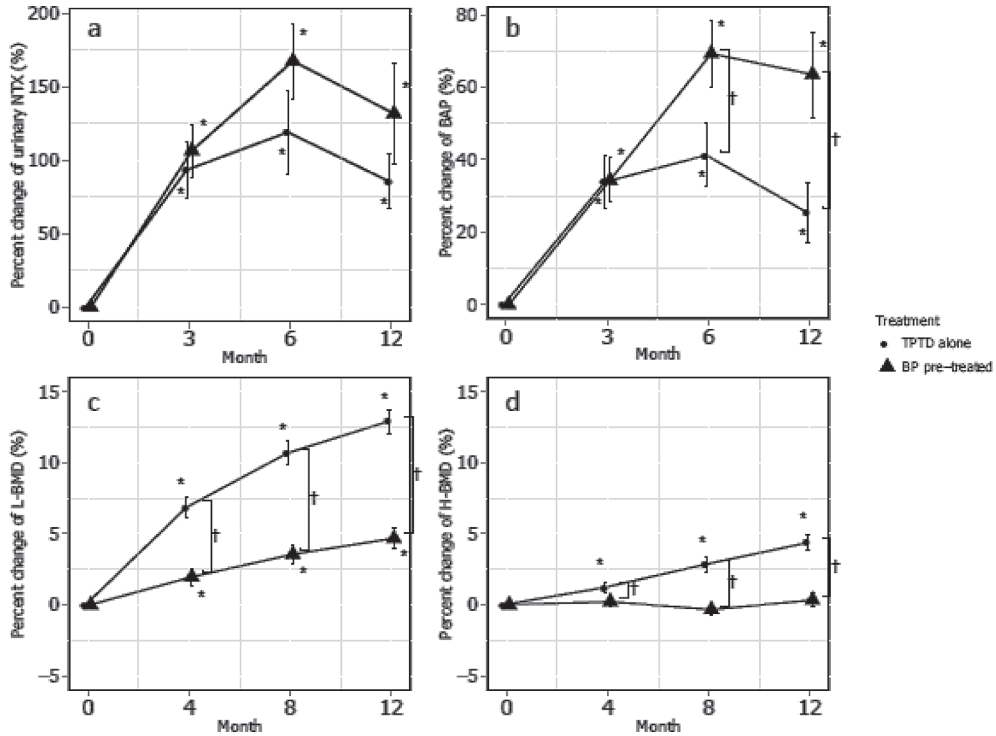

Fig. 2. Percent change of bone turnover markers and BMD.
a. Percent change of urinary NTX at 3, 6, and 12 months compared with the value at the first visit (shown as 0) in the TPTD alone and BP pre-treated groups. Standard error is shown as error bars at each time point. Asterisks (*) show significant differences.
b. Percent change of serum BAP at 3, 6, and 12 months compared with the value at the first visit (shown as 0) in the TPTD alone and BP pre-treated groups. Standard error is shown as error bars at each time point. Asterisks (*) show significant differences. Daggers (†) indicate significant differences between the TPTD alone and BP pre-treated groups.
c. Percent change of L-BMD at 4, 8, and 12 months compared with the value at the first visit (shown as 0) in the TPTD alone and BP pre-treated groups. Standard error is shown as error bars at each time point. Asterisks (*) show significant differences. Daggers (†) indicate significant differences between the TPTD alone and BP pre-treated groups.
d. Percent change of H-BMD at 4, 8, and 12 months compared with the value at the first visit (shown as 0) in the TPTD alone and BP pre-treated groups. Standard error is shown as error bars at each time point. Asterisks (*) show significant differences. Daggers (†) indicate significant differences between the TPTD alone and BP pre-treated groups.

were significantly higher than those in the BP pre-treated group ($p = 0.008$ and < 0.001 at 8 and 12 months, respectively) (Table 2). The percent changes of H-BMD in the TPTD alone group were significantly higher than those in the BP pre-treated group after 4 months of the TPTD administration (Table 3). The values of H-BMD were significantly improved in the TPTD alone group.

The percent changes of L-BMD of patients who only had earlier taken BP for less than 1 year were 5.1%, 6.8%, and 8.5% at 4, 8 and 12 months, respectively, for 1-2 years were -0.6%, 1.5%, and 3.1% at 4, 8, and 12 months, respectively, and for more than 2 years were 1.4%, 3.1%, and 4.1% at 4, 8, and 12 months, respectively (Fig. 3). Note that there was no significant difference in the percent change of the patients with more than 2 years and 1-2 years.

As a result of multiple linear regression analyses, BP pre-treatment decreased the BMD-increasing effects by TPTD. Patient age did not contribute significantly to the percent changes of BMD (Table 4).

Discussion

The present study describes the changes in BMD and bone turnover markers in 112 Japanese osteoporotic patients who were treated with the bone formation drug TPTD. Overall, the percent changes of bone turnover markers in the BP pre-treated group were higher than those in the TPTD alone group. During the 12-month treatment period, both L-BMD (13.0%) and H-BMD (4.4%) increased significantly in the TPTD alone group. In contrast, L-BMD rose by only 4.7% and H-BMD did not change appreciably in the BP pre-treated group. We also observed that the BMD increase achieved with TPTD was progressively diminished by longer BP treatment.

The average subject age in the TPTD alone group was significantly lower than that in the BP pre-treated group. Since the patients in the latter group had earlier undergone BP treatment for 44 months on average, this was considered to at least partially account for a more advanced age among these subjects. Furthermore, osteoporotic patients were

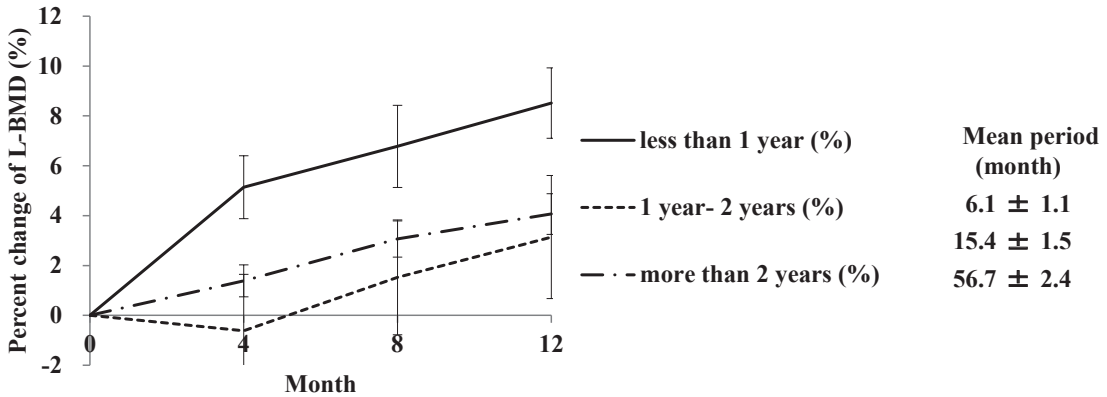

Fig. 3. L-BMD values in the BP pre-treated groups.
Percent change of L-BMD at 4, 8, and 12 months compared with the value at the first visit (shown as 0) in osteoporotic patients who were earlier treated with BP for less than 1 year, 1-2 years, or more than 2 years. Standard error is shown as error bars at each time point.

Table 4. Effects of BP pre-treatment and age for the increasing ratio of BMD (1 year after TPTD administration).

Factor	The increasing ratio of BMD (BP pre-treated – TPTD alone) (%)	
	L-BMD	H-BMD
BP pre-treatment	−8.2 ± 1.2 ($p < 0.001$*)	−4.3 ± 0.8 ($p < 0.001$*)
Age (increase of 1 year)	0.0 ± 0.1 ($p = 0.901$)	0.0 ± 0.0 ($p = 0.353$)

Values are expressed as mean ± standard error (SE).
*Statistically significant.

selected with respect to L-BMD for TPTD therapy, the levels of which were comparable at study onset. Thus, the age discrepancy in both groups (Table 1) might be explainable as 1) the L-BMD values may have been lower in the BP pre-treated group rather than those in the TPTD alone group at the time of BP usage, and 2) the low values of L-BMD ahead of the BP treatment in the BP pre-treated group suggested that the patients were more aged than those in the TPTD alone group. Although we examined whether or not the age discrepancy contributed to the increasing rate of BMD in both groups, there was no significant difference noted (Table 4).

A pressing question in recent OP management is whether BP pre-treatment influences the anabolic response to TPTD. In ovariectomized rats, TPTD increased new bone formation regardless of long-term exposure to Alendronate, estrogen, or Raloxifene (Ma et al. 2003). Several other trials have shown that prior BP treatment may slightly increase the anabolic effects of TPTD (Finkelstein et al. 2003, 2006). In the present study, bone turnover markers increased in both groups and percent changes were higher in the BP pre-treated group than in the TPTD alone group. This indicates that PTH exerts effects on osteoporotic bones in spite of earlier BP administration. As shown by the real values of serum BAP and urinary NTX in Table 2, even at 12 months of TPTD administration, turnover marker values were lower in the BP pre-treated group than in the TPTD alone group. These results suggest that BP therapy continuously affects bone turnover, even during TPTD treatment.

Obermayer-Pietsch et al. (2008) have reported that BP pre-treatment mildly reduced TPTD efficacy in a 2-year prospective study. In the TPTD alone group, the percent change of L-BMD and H-BMD increased by 13.1% and 3.8%, respectively. In the BP pre-treated group, these parameters increased by 10.2% and 2.3%, respectively; BP pre-treatment mildly decreased the percent change of BMD. Furthermore, they stated that L-BMD increased by 9.8% with TPTD in BP non-responders after 24 months of treatment, and concluded that TPTD was useful to increase BMD regardless of earlier or unsuccessful BP treatment. Why were the effects of TPTD diminished due to BP pre-treatment? The authors hypothesized that long-term BP pre-treatment inhibited strongly bone metabolism and the anabolic effects of TPTD in the first few months of TPTD administration by a yet unknown mechanism. Their hypothesis has since been supported by EUROFORS and other trials (Neer et al. 2001; Eastell et al. 2009).

In our study, the percent changes of bone turnover markers in the BP pre-treated group were higher than those in the TPTD alone group. However, L-BMD increased by 13.0% in the TPTD alone group versus only 4.4% in

patients following BP treatment, and H-BMD rose by 4.7% with TPTD alone compared with no change in the BP pre-treated group. Our findings suggest that prior BP treatment greatly reduces the effects of TPTD with respect to BMD increase in Japanese osteoporotic patients.

We witnessed that the inhibitory effects on TPTD-induced bone formation by BP pre-treatment in this study were stronger that those in another study (Obermayer-Pietsch et al. 2008). As the change patterns of bone turnover markers did not show any remarkable differences, TPTD may have functioned in a similar manner. However, the average BP pre-treatment period in this study was 44.1 ± 1.5 months, which was considerably longer than that in other reports (Finkelstein et al. 2003, 2006; Obermayer-Pietsch et al. 2008). As the half-life of BP in bone deposits is relatively long, the residual BP in bones and excess calcification caused by BP also may have reduced the effects of increased values of BMD by TPTD in this study.

Since we hypothesized that there was a correlation between BP treatment period and increasing values of BMD based on the report of Obermayer-Pietsch et al. (2008), BP treatment was classified into 3 groups (< 1 year, 1-2 years, and > 2 years). We observed that while the percent change of L-BMD tended to be mildly decreased even in < 1 year patients, it was greatly diminished in ≥ 1 year patients; whereas L-BMD percent change increased by 13.0% in the non-pretreated group, it was only 3.8% higher in patients with more than 2 years of BP therapy at the end of follow-up. Thus, it appeared that ≥ 1 year of BP pre-treatment resulted in greater bone calcification, greater residual BP in bones, and diminished TPTD efficacy in Japanese patients.

It has been reported that pre-treatment with BP in osteoporotic patients showed little change in the values of L-BMD at 12 months of treatment (Finkelstein et al. 2006; Minne et al. 2008). Thus, the BP pre-treated bones might have been densely mineralized. Also, since the bulky increase in L-BMD in BP pre-treated patients occurred between 18 and 24 months (Finkelstein et al. 2006; Minne et al. 2008), the "lack response" in L-BMD observed in this study might have been a timing issue.

The limitation of this study is that it is single-center, observational, and retrospective in nature. Future prospective, double-blinded investigations are needed to confirm our results. However, it will be challenging to perform such studies ethically since BP pre-treatment greatly decreases the increased effects of BMD caused by TPTD among Japanese.

In conclusion, TPTD is an effective drug for OP treatment because of its ability to increase BMD with few AEs. In both groups, the values of bone turnover markers were greatly improved by TPTD therapy. However, BP pre-treatment appears to markedly diminish the BMD benefits of TPTD.

Author Contributions

Y.N. directed this study. M.K. collected the patients' data. M.K. and Y.N. wrote the main manuscript text. S.I. performed statistical analyses. S.U. and H.K. gave suggestions on this study. All authors reviewed the manuscript. We thank Mr. Trevor Ralph who provided medical writing services on behalf of EZ communications.

Conflict of Interest

The authors declare no conflict of interest.

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