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Denosumab significantly improves lumbar spine bone mineral density more in treatment-naïve than in long-term bisphosphonate-treated patients

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ABSTRACT

The purpose of our study was to compare the skeletal responses to 3-year denosumab treatment in bisphosphonate (BP)-naïve and long-term BP-treated patients with postmenopausal osteoporosis. Female patients who were BP treatment-naïve (treatment-naïve group: 25 cases) or who received long-term BPs (BP pre-treated group: 24 cases) were compared for serum bone alkaline phosphatase (BAP), tartrate-resistant acid phosphatase (TRACP)-5b, and urinary N-terminal telopeptide of type I collagen (NTX) at baseline and at 4, 8, 12, 15, 18, 21, 24, 27, 30, 33, and 36 months of denosumab therapy. Lumbar 1–4 (L) spine bone mineral density (BMD), total hip (H)-BMD, and femoral neck (FN)-BMD values were measured at baseline and at 4, 8, 12, 18, 24, 30, and 36 months. The percentage changes of bone turnover markers were significantly decreased throughout the study period by a larger margin in the treatment-naïve group than in the BP pre-treated group. L-BMD, H-BMD, and FN-BMD were all significantly increased in the treatment-naïve and BP pre-treated groups at 36 months (12.9% and 7.5%, 5.9% and 6.0%, and 7.6% and 4.5%, respectively), compared with pre-treatment levels. There were significant differences for L-BMD at 12, 24, 30, and 36 months between the groups. Our findings suggest that the BMD response to denosumab, especially that of L-BMD, was diminished following BP therapy relative to treatment-naïve patients, thus providing evidence supporting the use of denosumab as a first-line therapy.

1. Introduction

As the number of osteoporosis (OP) cases increases in aging populations, there has been a concerted effort to address this health condition. The main goal of OP treatment is the prevention of fractures to maintain activities of daily living and thereby reduce mortality.

Denosumab, a human monoclonal antibody inhibitor of receptor-activator of nuclear factor kappaB ligand (RANKL), is also a very effective anti-resorptive agent. Denosumab treatment has been associated with significant reductions in the risk of vertebral, non-vertebral, and hip fractures by 68%, 20% and 40%, respectively (Cummings et al., 2009). Moreover, the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology Medical Guidelines for Practice very recently declared that alendronate (ALN), risedronate (RIS), zoledronic acid, and denosumab were appropriate initial therapies for patients at high fracture risk (Camacho et al., 2016).

We reported in 2016 that denosumab increased bone mineral density (BMD) even in bisphosphonate (BP)-unresponsive cases (Kamimura et al., 2017). Among the non-responsive patients, many of whom having taken BPs for over 5 years, both lumbar spine (L1–4) BMD (L-BMD) and total hip BMD (H-BMD) had become significantly decreased over time, and a switch to denosumab markedly increased BMD values. We concluded that patients exhibiting a diminished BP therapy response should immediately change to denosumab. Since the bone turnover markers that had been inhibited by BPs also further decreased significantly, denosumab was considered a good therapeutic option not only for primary OP, but also for BP non-responsive OP. However, there have been no direct comparisons between treatment-naïve and BP pre-treated OP patients to date.

According to AACE guidelines, BPs and denosumab are first-line drugs for OP treatment since they improve bone turnover and BMD and prevent fractures (Camacho et al., 2016; Black and Rosen, 2016). While both drugs inhibit osteoclastic bone resorption, they have very different mechanisms of action on osteoclastogenesis, i.e., abolished by denosumab and minimally affected by BPs. However, current clinical therapeutic treatments are insufficient to inhibit long-term bone loss and bone fracture risk, and thus, sequential therapies with anti-OP drugs have become an inevitable trend.

BMD determination by dual-energy X-ray absorptiometry (DXA) is presently the most reliable form of diagnosing OP and managing

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Table 1
Baseline patient characteristics in the BP pre-treated group and treatment-naïve group prior to denosumab treatment.

Characteristic	BP pre-treated (n = 24)	Treatment-naïve (n = 25)	P value
Age (years)	75.5 ± 2.1	75.7 ± 1.9	0.9534
BMI (kg/m^2)	21.3 ± 0.6	21.5 ± 0.8	0.8563
Serum corrected Ca (mg/dl)	9.2 ± 0.1	9.2 ± 0.1	0.7202
Serum phosphorus (mg/dl)	3.6 ± 0.1	3.6 ± 0.1	0.7432
Serum BAP (μg/l)	12.1 ± 1.2	20.1 ± 1.9	0.0013
Serum TRACP-5b (mU/dl)	306.7 ± 30.9	558.3 ± 30.9	0.0001
Urinary NTX (nmol BCE/mmol/CRE)	23.6 ± 2.3	57.7 ± 8.2	0.0001
Serum whole PTH (pg/ml)	32.6 ± 5.0	30.3 ± 3.4	0.7031
Serum 1,25(OH)$_2$D$_3$ (pg/ml)	57.8 ± 6.6	56.5 ± 4.5	0.8702
Duration of BP use (years)	4.8 ± 1.1		
Lumbar 1–4 BMD (g/cm^2)	0.812 ± 0.02	0.804 ± 0.02	0.8454
Total hip BMD (g/cm^2)	0.647 ± 0.03	0.649 ± 0.02	0.9472
Femoral neck BMD (g/cm^2)	0.619 ± 0.03	0.624 ± 0.02	0.8569

pharmacological treatment regimens. BMD values generally increase during the initial few years of BP treatment (Cummings et al., 2009), however, become can plateau or even decrease over the long term in some cases, regardless of the BP used (Cummings et al., 2009; Camacho et al., 2016; Kamimura et al., 2017; Miller et al., 2016). Although denosumab was shown to greatly increase BMD in primary OP as well as in long-term BP-treated OP (Kamimura et al., 2017), direct comparative data with or without BP pre-treatment for denosumab therapy is needed.

In this study, we compared the skeletal responses of treatment-naïve and long-term BP pre-treated primary OP patients receiving denosumab for 3 years.

2. Patients and methods

This study retrospectively enrolled postmenopausal OP patients who received denosumab therapy between 2014 and 2017 at our facilities. After excluding drop-out cases, we obtained informed consent and further analyzed 24 BP treatment-naïve patients and 25 long-term BP treatment patients with low L-BMD or H-BMD values matched on the basis of age and body mass index (BMI) (Table 1). Both groups possessed primary OP only based on careful differential diagnosis.

The inclusion criteria for the study were primary OP with low L-BMD and/or H-BMD (i.e., less than −2.5 SD). The exclusion criteria were chronic renal failure (estimated glomerular filtration rate < 40 [ml/min/1.73 m^2]) with metabolic bone disorder or diabetes mellitus that affected OP. One patient in the BP pre-treated group experienced a patella fragility fracture during the study and was excluded due to possible alterations in bone metabolism. Ultimately, the patients were enrolled into the following groups prior to denosumab therapy: 24 cases in the BP pre-treatment group (BP pre-treated group) and 25 cases in the denosumab alone group (treatment-naïve group) (Table 1). The diagnosis of primary OP was made in accordance with revised criteria established by the Japanese Society of Bone and Mineral Research (Nakamura et al., 2012). In the BP pre-treated group, 11 patients had been taking ALN, 7 patients took RIS, 4 patients took minodronate (MIN), and 2 patients took ibandronate (IBN). Combinations of ALN, RIS, MIN, and IBN had been adopted in various regimens as part of long-term BP pre-treatment. We did not examine the effects of individual BP drugs since they were routinely changed for patients exhibiting low response.

The mean duration of BP usage was 4.8 ± 1.1 years on average. All patients received denosumab (60 mg, subcutaneously) once every 6 months. We also prescribed newly approved vitamin D supplementation tablets (762.5 mg of precipitated calcium carbonate, 200 IU of cholecalciferol, 59.2 mg of magnesium carbonate) twice daily to all subjects during denosumab administration.

Serum levels of bone alkaline phosphatase (BAP) were measured as a bone-formation marker using a chemiluminescent enzyme immunoassay and antibody radioimmunoassay. Serum levels of tartrate-resistant acid phosphatase (TRACP)-5b and urinary levels of N-terminal telopeptide of type-I collagen (NTX) (Osteomark®; Ostex International, Seattle, WA, USA) were evaluated using an enzyme-linked immunosorbent assay as markers of osteoclast number and bone resorption, respectively. Each marker was assessed at baseline and at 4, 8, 12, 15, 18, 21, 24, 27, 30, 33, and 36 months of treatment. After overnight fasting, serum and first-void urine samples were collected between 8:30 am and 10:00 am. Immunoassays were carried out by SRL (Tokyo, Japan).

BMD was measured using a DXA fan-beam bone densitometer (Lunar Prodigy; GE Healthcare, Waukesha, UK, USA) at the L1–4 levels of the posteroanterior spine, the bilateral total hips, and the bilateral femoral neck (FN). The percentage changes of BMD were calculated based on the BMD values.

The results of BMD are expressed as the mean ± standard error. For both groups, we compared the changes in markers, L-BMD, H-BMD, and FN-BMD at each time point using the Bonferroni correction method for multiple comparisons. Comparisons of markers, L-BMD, H-BMD, and FN-BMD between the groups at each measurement point were performed using Welch's *t*-test. Differences were considered statistically significant at $P < 0.05$.

The study protocol was approved by the Ethics Committees of Shinshu University School of Medicine (Matsumoto, Japan) and Showa-Inan General Hospital (Komagane, Japan). This study was carried out in accordance with the ethical standards set forth in the Declaration of Helsinki (2014 revision). The study registration date was May 31, 2014. Written informed consent was obtained from all patients.

3. Results

There were no significant differences in baseline patient age or BMI between the groups (Table 1). The percentage changes in bone turnover serum levels are shown in Fig. 1. No serious adverse events, such as hypocalcemia or fracture, occurred during the treatment period.

3.1. Markers of bone turnover

3.1.1. Marker of bone formation

BAP values were significantly lower in the BP pre-treated group than in the treatment-naïve group prior to treatment (Table 1).

The percentage decrease in BAP was significant throughout the study period in the treatment-naive group at 4 ($P < 0.05$), 8 ($P < 0.01$), 15 ($P < 0.05$), and 21 ($P < 0.01$) months in the BP pre-treated group, compared with pre-treatment levels. We observed significant differences at every time point ($P < 0.01$ except for $P < 0.05$ at 27 months) between the groups (Fig. 1a).

3.1.2. Markers of bone resorption

Urinary NTX and serum TRACP-5b values were significantly lower in the BP pre-treated group than in the treatment-naïve group at baseline (Table 1). The percentage decreases in both markers were significant throughout the study period in the treatment-naive patients, while only TRACP-5b values decreased significantly in the BP-pre-treated group at 4, 8, 15, and 21 months, compared with pre-treatment levels. We observed significant differences for urinary NTX at 4, 8, and 21 months ($P < 0.01$) and at 15 and 18 months ($P < 0.05$) between the groups (Fig. 1b). There were significant differences for TRACP-5b at 4, 8, 15, 21, and 36 months ($P < 0.01$) and at 12 and 18 months

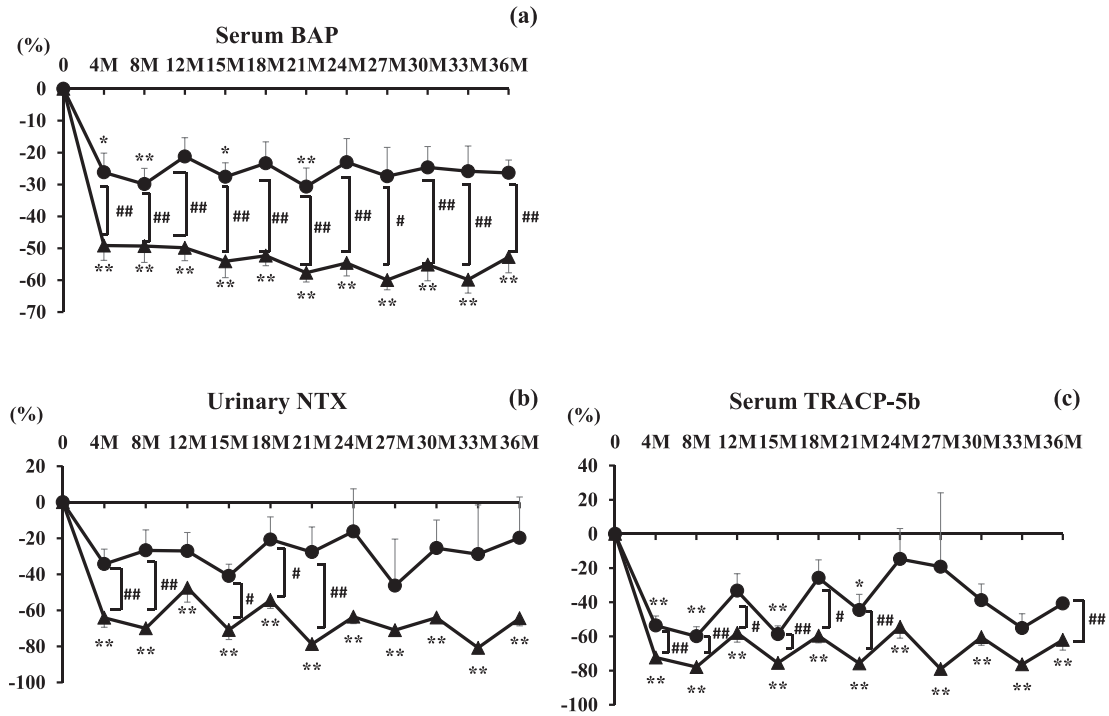

Fig. 1. Changes in serum bone alkaline phosphatase (BAP) (a), urinary N-terminal telopeptide of type-I collagen (NTX) (b), and serum tartrate-resistant acid phosphatase (TRACP-5b) (c). Circles indicate the BP pre-treated group and triangles indicate the treatment-naïve group. Double and single asterisks denote significant differences of $P < 0.01$ and $P < 0.05$, respectively, compared with pre-treatment values. Double and single hashtags denote significant differences of $P < 0.01$ and $P < 0.05$, respectively, between the groups at a given time point.

($P < 0.05$) between the groups (Fig. 1c).

3.1.3. Value changes of serum BAP, urinary NTX, and serum TRACP-5b

Despite significant differences for each marker prior to the start of the study (Table 1), the absolute value changes of each marker decreased to similar levels during 4 to 36 months for both groups (Fig. 2a–c).

3.2. L-BMD, H-BMD, and FN-BMD findings

L-BMD was significantly increased at 8 ($P < 0.05$) and 12, 18, 24, 30, and 36 (12.9%) ($P < 0.01$) months in the treatment-naïve group and at 12 ($P < 0.05$) and 18, 24, 30, and 36 (7.5%) ($P < 0.01$) months in the BP pre-treated group compared with pre-treatment levels. There were significant differences for L-BMD at 12 ($P < 0.05$), 24 ($P < 0.01$), 30 ($P < 0.01$), and 36 ($P < 0.05$) months between the groups (Fig. 3a).

H-BMD was significantly increased at 8 ($P < 0.05$) and 12, 18, 24, 30, and 36 (5.9%) ($P < 0.01$) months in the treatment-naïve group and at 12 ($P < 0.05$) and 18, 24, 30, and 36 (6.0%) ($P < 0.01$) months in the BP pre-treated group compared with pre-treatment values. There were no significant differences between the groups (Fig. 3b).

FN-BMD was significantly increased at 24 ($P < 0.05$), 30 ($P < 0.01$), and 36 (7.6%) ($P < 0.01$) months in the treatment-naïve group and at 30 ($P < 0.01$) and 36 (4.5%) ($P < 0.01$) months in the BP pre-treated group versus baseline levels. We observed no significant differences between the groups (Fig. 3c).

4. Discussion

This is the first report presenting comparative data on denosumab therapy with or without BP pre-treatment in Japanese post-menopausal patients with primary OP. Compared with denosumab following long-term BP pre-treatment, denosumab without prior BPs produced larger percentage changes in BMD, especially L-BMD. However, denosumab had significantly increased BMD in both groups at 36 months compared with pre-treatment levels. These findings indicate that denosumab is a good option for primary OP, preferentially before long-term BP therapy with respect to an increase in L-BMD.

Our study revealed significant differences in bone turnover marker values between the groups just prior to denosumab, likely due to long-term BP therapy inhibition (Table 1). However, despite significant differences in percentage changes at several time points (Fig. 1), the bone turnover marker values were reduced to approximately the same levels after 4 months (Fig. 2).

While the marker levels achieved by denosumab therapy were similar between the groups, the changes were much greater in treatment-naïve patients (Fig. 2). Previous studies have demonstrated that the BMD increases in response to most OP therapies were related to bone turnover marker levels at therapy commencement (Kamimura et al., 2017; Miller et al., 2016; Nakamura et al., 2012; Eastell et al., 2018; Chen et al., 2005). Since the present investigation showed lower turnover markers in patients previously treated with BPs, smaller BMD percentage increases in this group are consistent with earlier studies (Kamimura et al., 2017; Miller et al., 2016; Nakamura et al., 2012; Eastell et al., 2018; Chen et al., 2005).

To the best of our knowledge, there are no reports comparing the effect of denosumab in previously BP treated and treatment-naïve osteoporosis patients. Denosumab alone significantly increased L-BMD, but not H-BMD or FN-BMD, compared with BP pre-treated patients (Fig. 3a). The mechanism for greater L-BMD gains in the treatment-naïve group is currently unknown, but is likely related to alterations in the remodeling space, as reflected by bone markers, and to the degree of mineralization. Thus, in terms of increasing L-BMD, denosumab may be preferable prior to long-term BP therapy. The agent may also provide gains in H-BMD and FN-BMD to prevent femoral fractures in both treatment-naïve and long-term BP pre-treated OP.

Lastly, although the FN-BMD increases were not significantly different between the treatment-naïve and BP pre-treated groups, their trends were consistent with those of L-BMD ($P < 0.05$). An inadequate

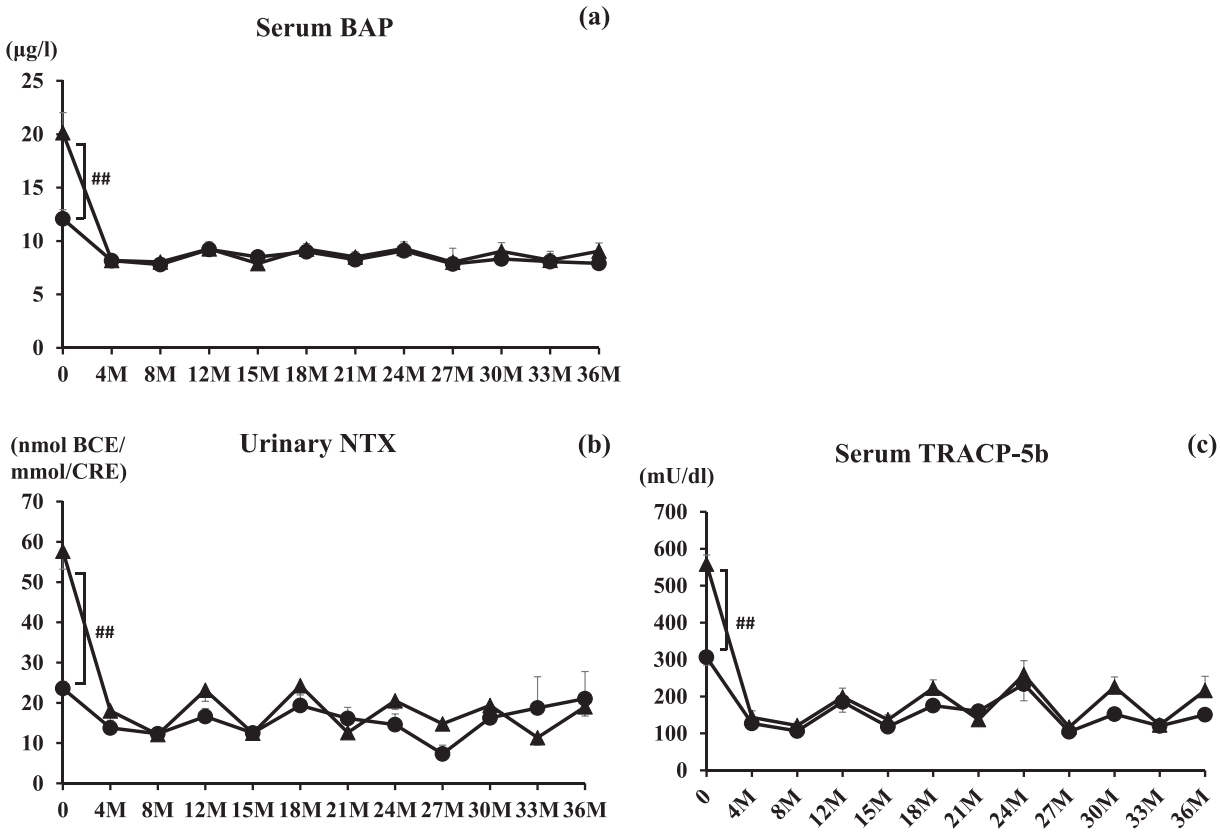

Fig. 2. Value changes in serum bone alkaline phosphatase (BAP) (a), urinary N-terminal telopeptide of type-I collagen (NTX) (b), and serum tartrate-resistant acid phosphatase (TRACP-5b) (c). Circles indicate the BP pre-treated group and triangles indicate the treatment-naïve group. Double hashtags denote a significant difference of $P < 0.01$ between the groups at baseline.

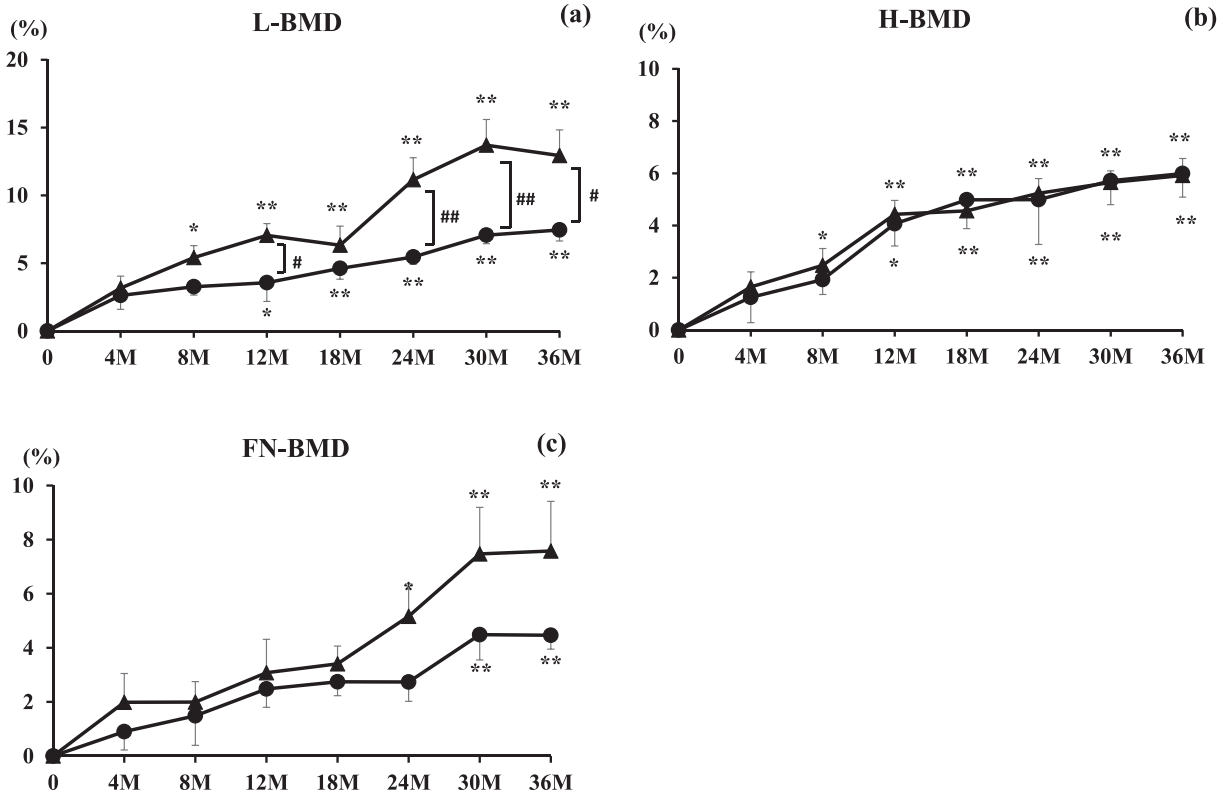

Fig. 3. Changes in lumbar 1–4 spine bone mineral density (L-BMD) (a), bilateral total hip BMD (H-BMD) (b), and bilateral femoral neck BMD (FN-BMD). Double and single asterisks denote significant differences of $P < 0.01$ and $P < 0.05$, respectively, compared with pre-treatment values. Circles indicate the BP pre-treated group and triangles indicate the treatment-naïve group. Double and single hashtags denote significant differences of $P < 0.01$ and $P < 0.05$, respectively, between the groups at a given time point.

sample size and no serum 25(OH)D data were the major limitations of this study. Further evaluation of fracture protection will also be required in the future.

5. Conclusions

This is the first comparative study of denosumab therapy with or without long-term bisphosphonate (BP) pre-treatment in post-menopausal Japanese osteoporosis patients. Denosumab decreased markers of bone turnover and increased bone mineral density (BMD) in patients previously treated with BPs (BP pre-treated group) as well as in treatment-naïve patients (treatment-naïve group). As expected, baseline marker values were lower in BP-treated prior to the start of this study patients. While the degree of bone turnover marker decrease was greater in treatment-naïve patients, the absolute values achieved with denosumab were similar between the groups. Lumbar spine BMD was significantly increased by 3-year denosumab without BP pre-treatment compared with denosumab following BP pre-treatment. Our findings provide supportive evidence that denosumab may be a first-line drug for OP, as women who had not previously been treated with BP respond more pronounced to treatment with denosumab.

Author contributions

T.S. and Y.N. wrote the main manuscript text. M.K. and T.S. prepared the table and figures. M.K. and H.K. gave suggestions on the study design.

Additional information

All of the authors have declared no competing financial interests in this study.

Transparency document

The Transparency document associated with this article can be found, in online version.

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