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Risk factors for nonresponse to 2 years of denosumab administration in patients with osteoporosis: A retrospective single-center cohorts study

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Abstract

Background and Aims: To investigate the factors associated with changes in bone mineral density (BMD) and the incidence of fractures in osteoporotic patients treated with denosumab.

Methods: This retrospective study included 162 osteoporotic patients treated with denosumab for 24 months between 2013 and 2019. Patients were divided according to the changes in BMD as nonresponders (N_L group: <3% increase in lumbar spine BMD [LBMD], N_H group: <0% increase in femoral neck BMD [FNBMD]) or responders (R_L group: ≥3% increase in LBMD, R_H group: ≥0% increase in FNBMD).

Results: The respective changes in the LBMD and FNBMD after 24 months of denosumab treatment were 9.3% (95% confidence interval [CI]: 8.1–10.6) and 3.3% (95% CI: 2.1–4.5). Twenty-eight (17.3%) patients were in the N_L group, and 134 (82.7%) were in the R_L group. A history of bisphosphonate treatment was a risk factor for being in the N_L group (odds ratio [OR]: 3.84, 95% CI: 1.38–10.71, $p = 0.007$; adjusted OR: 3.21, 95% CI: 1.01–10.19, $p = 0.048$). Although the N_H ($n = 48$; 30.8%) and R_H ($n = 108$; 69.2%) groups had similar baseline characteristics, the N_H group had a significantly higher baseline FNBMD than the R_H group ($p = 0.003$). The change in FNBMD was negatively associated with the FNBMD at baseline ($r = -0.34$, $p < 0.001$). No new osteoporotic fractures occurred in either group during follow-up.

Conclusion: In osteoporotic patients receiving denosumab treatment, a history of bisphosphonate treatment was a risk factor for a lack of increase in LBMD, and a higher FNBMD at baseline was negatively associated with the change in FNBMD.

KEYWORDS

bone mineral density, denosumab, nonresponder, osteoporosis, responder

1 | INTRODUCTION

As the older adult population in Japan grows, the number of osteoporotic patients is continuously increasing. Population-based epidemiologic studies estimate that there are approximately 13 million patients with osteoporosis in Japan, although only 20% are receiving treatment.[1] Osteoporosis is a well-known condition that results in low bone mineral density (BMD) and high risk of fracture[2,3] and is influenced by diverse epidemiological factors including age, sex, lower body mass index (BMI), transition to menopause, lower calcium intake, vitamin D deficiency, and less physical activity. Osteoporotic individuals commonly develop fractures of the vertebral body, forearm bone, and proximal femur, and the treatment strategies are an important social issue.

There are currently many available therapeutic agents that aim to prevent fractures associated with osteoporosis.[4,5] The two main types of osteoporotic agents are bone anabolic agents and bone resorption inhibitors. Although bone resorption inhibitors are widely used worldwide and reportedly achieve good outcomes regarding increased bone density and prevention of fractures, the existence of nonresponders have been reported.[6,7] Denosumab is a bone resorption inhibitor that is a fully human monoclonal antibody against receptor activator of nuclear factor-κB ligand,[8–10] which is a key activator of osteoclast formation, function, and survival. Denosumab was launched in Japan in June 2013 as a therapeutic option for osteoporosis. A domestic phase III clinical trial of patients with primary osteoporosis with vertebral fractures demonstrated that up to 2 years administration of denosumab decreases the incidence of vertebral fractures, increases bone density, and positively influences bone metabolism markers.[11] However, in clinical practice, the BMD of certain patients does not increase after denosumab administration. As few studies have reported nonresponders to denosumab treatment, their background characteristics are unknown.

We conducted this retrospective cohort study to investigate the risk factors for a low BMD increase rate among osteoporotic patients treated with denosumab.

2 | MATERIALS AND METHODS

2.1 | Subjects

This retrospective observational study was approved by the Ethics Committee of Juntendo University Hospital (approval number: H18-0037) and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Patients with osteoporosis were recruited from the outpatient clinic of our university hospital between September 2013 and November 2019. The Juntendo University Hospital has a 1051-bed (as of 2023) and is regional core hospital located in central of Tokyo. Participants were also provided the opportunity to opt-out.

The sample size was determined based on the number of eligible patients enrolled during the study period. All enrolled patients were diagnosed with osteoporosis and had received denosumab for 24 months or longer. Subjects were excluded if they did not have available BMD data at either baseline or after 24 months of denosumab treatment. Patients who had either lumbar spine (L2–L4) BMD (LBMD) data or femoral neck BMD (FNBMD) data were eligible for study inclusion.

All BMD measurements were carried out using DXA densitometry (Discovery A, Hologic Inc.). The final study cohort comprised 162 men and women with osteoporosis who were aged 50 years or older and were administered denosumab (60 mg/6 months) for 24 months. Patients were categorized as nonresponders or responders in accordance with the criteria used in previous studies.[7,12] We defined nonresponders as those with a LBMD increase of <3% in 2 years (N_L group) and a FNBMD increase of <0% in 2 years (N_H group). We defined responders as those with a LBMD increase of ≥3% in 2 years (R_L group) and those with a FNBMD increase of ≥0% in 2 years (R_H group). Additionally, the osteoporosis outpatient clinic was managed by specialists in osteoporosis treatment.

2.2 | Variables

The following data were obtained from the medical records: age, sex, height, weight, BMI, presence or absence of pretreatment with bisphosphonates, supplementation with either native or active vitamin D_3 during the treatment period, history of fracture, baseline LBMD and FNBMD, baseline serum calcium and tartrate-resistant acid phosphatase 5b (TRACP-5b) levels, and incidence of clinical vertebral fracture during the study period.

2.3 | Statistical analysis

The baseline patient characteristics and relevant bone turnover biomarkers were summarized. A pairwise comparison was performed to examine the differences in baseline characteristics among the groups. The distribution of the variables was examined using the Shapiro–Wilk test. Height, BMI, and baseline FNBMD were compared between two groups using the two-sample *t*-test; age, weight, baseline LBMD, serum calcium level, and serum TRACP-5b level were compared between two groups using the Wilcoxon rank sum test. The χ^2 test was used for intergroup comparisons of the presence or absence of pretreatment with bisphosphonates. The supplementation with either native or active vitamin D_3 was compared between groups using a test of difference in proportions. The differences between groups in sex and history of fracture were examined using Fisher's exact test. The association between the pretreatment BMD and the changes in the LBMD and FNBMD after 2 years of denosumab treatment was examined using Spearman's rank correlation coefficient. The correlation between various variables and the changes in the LBMD and FNBMD after 2 years of denosumab treatment was examined using partial correlation analysis. The odds ratio (OR) was obtained using logistic regression analysis after

adjusting for age, sex, and BMI. A two-sided 5% α level was used to assess the statistical significance. Cases with missing data in the analyzed population were excluded from the analysis. All data were analyzed using statistical software for Windows, STATA version 16.1 (Stata Corp LLC).

3 | RESULTS

The baseline characteristics of the osteoporotic patients treated with denosumab for 24 months are shown in Table 1. The percentage of women was 94% (152/162) and the average age was 73.1 ± 8.1 years. The administration of denosumab for 24 months increased the LBMD and FNBMD by 9.3% (95% confidence interval [CI]: 8.1–10.6) and 3.3% (95% CI: 2.1–4.5), respectively.

When the subjects were divided into two groups according to the changes in the LBMD after denosumab treatment, the R_L group contained 134 of 162 subjects (66.7%; 124 women, 10 men) and the N_L group contained 28 subjects (33.3%; 28 women). The change in the LBMD was 11.2% (95% CI: 9.9–12.5) in the R_L group and 0.2% (95% CI: −0.9–1.3) in the N_L group ($p < 0.001$). There were no significant differences between the R_L and N_L groups in age, history of fracture, baseline LBMD and FNBMD, calcium level, and TRACP-5b level. However, pretreatment with bisphosphonate before the initiation of denosumab treatment was significantly more common in the N_L group (82%; 23/28) than the R_L group (54%; 73/134) ($p = 0.007$) (Table 1). We showed the differences in the types of bisphosphonates between the NL group and RL group (Supporting Information: Table 1). Univariate analysis showed that pretreatment with bisphosphonate was a risk factor for a <3% increase in the LBMD after 24 months of denosumab treatment (OR: 3.84, 95% CI: 1.38–10.71, $p = 0.01$); multivariate logistic analysis adjusted for age, sex, and BMI showed a similar result (OR: 3.21, 95% CI: 1.01–10.19, $p = 0.048$).

One-hundred-and-forty-four of 162 subjects (88.9%) received either native vitamin D_3 ($n = 46$) or active vitamin D_3 ($n = 98$) in addition to denosumab treatment for 24 months, while 14 subjects (8.6%) received both native and active vitamin D_3; the remaining four subjects (2.5%) did not receive either native or active vitamin D_3. Of the 144 subjects who received either native vitamin D_3 or active vitamin D, 121 (84.0%) were in the R_L group (40 (33.1%) received native vitamin D_3 and 81 (66.9%) received active vitamin D_3), while 23 (16.0%) were in the N_L group (6 (26.1%) received native vitamin D_3 and 17 (74.0%) received active vitamin D_3). The distribution of the two types of vitamin D_3 did not significantly differ between the R_L and N_L subgroups ($p = 0.056$).

When the subjects were divided into two groups according to the changes in the FNBMD after denosumab treatment, the R_H group contained 108 of 156 subjects (69.2%; 102 women, 6 men) and the N_H group contained 48 subjects (30.8%; 44 women, 4 men). Eleven subjects (7.1%) were included in both the N_L and N_H groups. The change in the FNBMD was 6.5% (95% CI: 5.2–7.7) in the R_H group and −3.8% (95% CI: −5.0 to −2.6) in the N_H group ($p < 0.001$). There were no significant differences between the R_H and N_H groups in the history of spine, hip, and other fractures. Although the LBMD at baseline did not significantly differ between the R_H and N_H groups, the FNBMD at baseline was significantly lower in the R_H group than the N_H group ($p = 0.003$). There were no significant differences between the R_H and N_H groups in the serum levels of calcium and TRACP-5b. The frequency of pretreatment with bisphosphonate did not significantly differ between the N_H and R_H groups (63% (30/48) in the N_H group and 56% (61/108) in the R_H group) (Table 1).

One-hundred-and-forty of 156 subjects (89.7%) received either native vitamin D_3 ($n = 45$) or active vitamin D_3 ($n = 95$) in addition to denosumab treatment for 24 months, while 14 subjects (9.0%) received both native and active vitamin D_3; the remaining two subjects (1.3%) did not receive either native or active vitamin D_3. Of the 140 subjects who received either native vitamin D_3 or active vitamin D, 42 (30.0%) were in the N_H group (15 (35.7% received native vitamin D_3 and 27 (64.3%) received active vitamin D_3), while 98 subjects (70.0%) were in the R_H group (30 (30.6%) received native vitamin D_3 and 68 (69.4%) received active vitamin D_3). The distribution of the two types of vitamin D_3 did not significantly differ between the R_H and N_H subgroups ($p = 0.19$).

The change in the LBMD was associated with the change in the FNBMD in osteoporotic patients who received 24 months of denosumab treatment (Spearman's $\rho = 0.19$, $p = 0.02$). The change in the LBMD was positively associated with the serum level of TRACP-5b at baseline (Spearman's $\rho = 0.34$, $p < 0.001$) and negatively associated with the serum level of calcium at baseline (Spearman's $\rho = -0.18$, $p = 0.02$) (Table 2). The FNBMD at baseline was also negatively associated with the change in the FNBMD in osteoporotic patients treated with denosumab for 24 months ($r = -0.34$, $p < 0.001$) (Figure 1).

During the 24 months of denosumab treatment, no patients developed new clinical vertebral body fractures as well as thoracic vertebra, femoral neck and other fractures.

4 | DISCUSSION

Denosumab has been reported to reduce the incidence of vertebral and nonvertebral fractures and increase BMD in patients with osteoporosis.[13,14] In the current study, new clinical vertebral fractures did not occur in patients who received denosumab for 2 years, and the mean increase rate was 9.3% for LBMD and 3.3% for FNBMD after 2 years. Denosumab was well tolerated in the present study and the mean BMD gains achieved were similar to those observed with the same denosumab regimen in other populations.[11,13] We found that 17.3% of the total patient cohort did not achieve more than a 3% increase in LBMD, and 30.8% did not achieve more than a 0% increase in FNBMD after 24 months of denosumab treatment, which is similar to the findings of a previous study.[15] In the present study, we considered nonresponders as no or little increase in the BMD of the lumbar spine and femoral neck and the word “non-responder” in this study does not mean clinically ineffective. Since no clinical fracture

TABLE 1 Baseline characteristics of the patients with osteoporosis.

	N_L group (n = 28)	R_L group (n = 134)	p Value
Change of LBMD, mean (95% CI) (%)	0.2 (−0.9–1.3)	11.2 (9.9–12.5)	<0.001***
Age, mean (SD, range) (years)	73.6 (8.4, 53–84)	73.0 (8.1, 50–88)	0.66
Female, *n* (%)	28 (100)	124 (92)	0.21
Height, mean (range) (cm)	150.9 (130–166)	152.6 (139–175)	0.22
Body weight, mean (range) (kg)	45.3 (35–55)	48.5 (31–73)	0.07
BMI, mean (range) (kg/m^2)	19.9 (14.5–23.8)	20.8 (14.3–29.4)	0.17
Prevalent fracture, *n* (%)			
Thoracic vertebra, *n* (%)	2 (7)	21 (16)	0.37
Lumber vertebra, *n* (%)	10 (36)	36 (27)	0.36
Femoral neck, *n* (%)	0 (0)	3 (2)	>0.99
Other, *n* (%)	1 (4)	9 (7)	>0.99
BMD			
Baseline LBMD, mean (95% CI) (g/cm^2)	0.72 (0.65–0.80)	0.71 (0.68–0.73)	0.93
Baseline FNBMD, mean (95% CI) (g/cm^2)	0.49 (0.46–0.52)	0.49 (0.48–0.50)	0.78
Serum calcium levels, mean (95% CI) (mg/dL)	9.5 (9.3–9.7)	9.4 (9.3–9.4)	0.34
Serum TRACP-5b levels, mean (95% CI) (mU/dL)	292.1 (233.2–351.0)	320.4 (292.7–348.1)	0.43
Bisphosphonate, *n* (frequency, %)	23 (82%)	73 (54%)	0.007**
	N_H group (n=48)	R_H group (n=108)	p Value
Change of FNBMD, mean (95% CI) (%)	−3.8 (−5.0 to −2.6)	6.5 (5.2–7.7)	<0.001***
Age, mean (SD, range) (years)	74.8 (7.5, 50–85)	72.9 (8.3, 50–88)	0.13
Female, *n* (%)	44 (92)	102 (94)	0.50
Height, mean (range) (cm)	153.0 (130–162)	151.9 (139–175.5)	0.35
Body weight, mean (range) (kg)	48.0 (35–63)	47.6 (31–73)	0.52
BMI, mean (range) (kg/m^2)	20.4 (14.5–26.7)	20.7 (14.3–29.4)	0.64
Prevalent fracture, *n* (%)			
Thoracic vertebra, *n* (%)	8 (17)	14 (13)	0.62
Lumber vertebra, *n* (%)	15 (31)	29 (27)	0.57
Femoral neck, *n* (%)	0 (0)	3 (3)	0.55
Other, *n* (%)	2 (4)	8 (7)	0.73
BMD			
Baseline LBMD, mean (95% CI) (g/cm^2)	0.73 (0.68–0.79)	0.70 (0.67–0.73)	0.40
Baseline FNBMD, mean (95% CI) (g/cm^2)	0.52 (0.50–0.53)	0.48 (0.47–0.49)	0.003**
Serum calcium, mean (95% CI) (mg/dLa)	9.4 (9.2–9.5)	9.4 (9.3–9.5)	0.89
TRACP-5b, mean (95% CI) (mU/dL)	285.1 (249.0–321.1)	329.9 (296.9–362.9)	0.22
Bisphosphonate, *n* (frequency, %)	30 (63%)	61 (56%)	0.48

Note: Patients were divided into two groups according to the changes in bone mineral density in the spine (A) and hip (B). N_L group: nonresponders regarding LBMD (<3% increase); N_H group: responders regarding LBMD (≥3% increase); R_H group: responders regarding FNBMD (≥0% increase); R_L group: responders regarding LBMD (≥3% increase).

Abbreviations: 95% CI, 95% confidence interval; BMD, bone mineral density; BMI, body mass index; FNBMD, femoral neck BMD; LBMD, lumbar spine BMD; SD, standard deviation; TRACP-5b, tartrate-resistant acid phosphatase 5b.

**p < 0.01; ***p < 0.001.

TABLE 2 Associations between the changes in LBMD and FNBMD and various baseline variables.

	ΔLBMD		ΔFNBMD	
Variable	***r***	***p* Value**	***r***	***p* Value**
Age (years)	*−0.09*	*0.26*	−0.16	0.053
Height (cm)	*0.06*	*0.40*	−0.14	0.09
Body weight (kg)	*0.07*	0.36	−0.03	0.76
BMI (kg/m^2)	*0.04*	0.63	0.05	0.54
Serum calcium level (mg/dLa)	*−0.18*	0.02*	0.02	0.81
TRACP-5b level (mU/dL)	*0.34*	<0.001***	0.14	0.08

Note: $p > 0.05$ is not significant are in italic. r values in italic indicate not coefficient of determination.

Abbreviations: BMD, bone mineral density; BMI, body mass index; FNBMD, femoral neck BMD; LBMD, lumbar spine BMD; TRACP-5b, tartrate-resistant acid phosphatase 5b.

***$p < 0.001$; *$p < 0.05$.

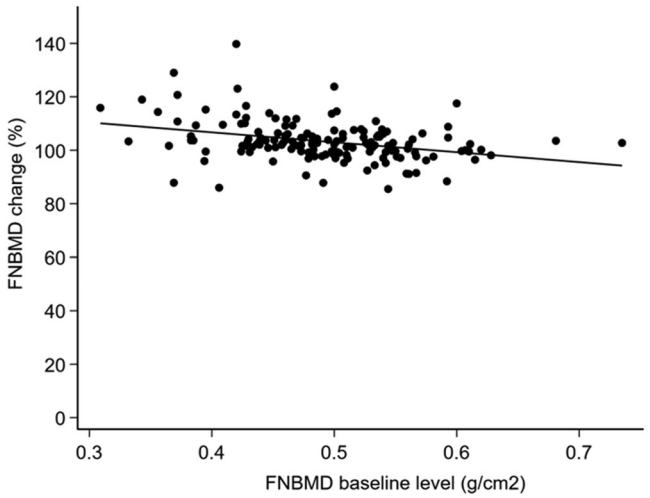

FIGURE 1 Association between baseline femoral neck bone mineral density (FNBMD) and the change in FNBMD after 2 years of denosumab treatment. The FNBMD increase rate was weakly negatively associated with the FNBMD at baseline ($r = −0.34$, $p < 0.001$).

occurred during the study period, we think that denosumab treatment is a useful option for the osteoporosis patients.

The present study showed that a history of administration of bisphosphonates was associated with a nonresponse to denosumab regarding the LBMD after adjusting for age, sex, and BMI. In the process of suppressing bone resorption, denosumab does not have the same mechanism as bisphosphonates.[16] A previous phase 3 trial showed that denosumab has strong inhibitory effects on bone resorption despite prior bisphosphonate therapy and confirmed that denosumab produces more pronounced bone resorption inhibition; similar results were shown in other studies.[17–20] As the mean BMD increase rate in the present study was similar to these previous reports, our data were not inconsistent with previous reports. In the nonresponder cases, we speculate that the removal of highly mineralized bone during the initial treatment phase may account for the higher nonresponse rate to denosumab. From another perspective, 76.9% (73/96) of patients with a history of bisphosphonate treatment showed an increase in LBMD with denosumab therapy. Although the rate is lower than that observed in the group of patients without a history of bisphosphonate administration (92.4%, 61/66), denosumab was still effective for approximately three-quarters of the patients who had previously received bisphosphonate therapy. This result suggests that switching from bisphosphonates to denosumab may bring new therapeutic opportunities, even for patients categorized as nonresponders to bisphosphonates. However, there were cases in which neither bisphosphonates nor denosumab were sufficiently effective, and further investigation is warranted to identify the factors affecting the efficacy of denosumab in preventing osteoporotic fractures. It remains unclear why patients with prior bisphosphonate administration only showed a smaller BMD increase in the lumbar spine region, but not the femoral neck.

We showed that the FNBMD increase rate was negatively associated with the FNBMD at baseline. Patients with lower baseline FNBMD responded well to denosumab treatment, while those with high baseline FNBMD did not. We also found a significant association between the change in LBMD and the change in FNBMD from pretreatment to 2 years after denosumab initiation. These data suggest that denosumab works on the spine and femoral neck in patients with osteoporosis. However, it should be noted that 7.1% of patients in the present cohort were categorized as nonresponders regarding both LBMD and FNBMD.

To evaluate the effects of the denosumab treatment, many studies use TRACP-5b as a biomarker for bone resorption.[21–24] Previous research has shown that the concentration of TRACP-5b in blood increases with the increase in bone resorption and accurately reflects the state of bone resorption.[25] Our study revealed a significant positive correlation between the change in LBMD and the TRACP-5b level at the time of denosumab initiation. This suggests that patients with a high TRACP-5b level at baseline are likely to respond to the denosumab treatment and their BMD is likely to increase. We consider this an understandable result because the main action of denosumab is as a bone resorption inhibitor and the effect may not be sufficient in patients whose bone resorption is already suppressed. In other words, our results suggest that the TRACP-5b level at denosumab initiation may be a predictable biomarker of BMD increase. However, the TRACP-5b level did not significantly differ between nonresponders and responders in terms of both LBMD and FNBMD. Future studies may be needed to interpret the results.

Vertebral fractures and hip fractures are considered to be strongly associated with reductions in spine BMD and hip BMD, respectively.[26] Previous research has shown that denosumab reduces the risk of new radiographic vertebral fractures.[11,13] In the FREEDOM trial, 36 months of denosumab treatment significantly reduced the risk of vertebral fractures by 68%, nonvertebral fractures by 20%, and hip fractures by 40% compared with placebo.[13] In the present study, no patient developed a new clinical fracture. As there

were no new fractures in either group, we could not conclude that the BMD increase rate was a predictor of the increased incidence of new clinical fractures within 24 months. However, denosumab might have a preventive effect on new fractures even for patients whose BMD does not increase. This notion is supported by a previous study that reported no major fractures after 2 years of denosumab treatment, regardless of the response to denosumab based on the spine BMD.[15] We will monitor the cohort to determine whether the BMD level continues to stay stable or decreases in the future and whether the incidence of new fractures decreases over the longer term.

In Japan, both active vitamin D and native vitamin D supplementation with denosumab treatment are covered by national healthcare insurance. Patients receiving denosumab are recommended to take combination treatment with vitamin D to prevent hypocalcemia caused by the pharmacological action of denosumab.[27–29] We found no difference in the response to denosumab (in terms of the LBMD and FNBMD increase rates) depending on the type of vitamin D used. A previous study reported that the denosumab plus active vitamin D group and the denosumab plus native vitamin D group showed similar increases in the BMD of the lumbar spine (6.5% vs. 6.4%) and total hip (3.4% vs. 3.3%) from baseline to 12 months after treatment, but showed different increases in the BMD of the femoral neck (1.0% vs. 4.9%).[28] Although we do not know how much vitamin D affects the rate of BMD increase, the administration of both types of vitamin D with denosumab had a similar effect on the BMD increase in our study.

The present study had some limitations. First, the choice of patients who received denosumab depended on each physician's preference. Although we adjusted the analysis to remove the effects of some key baseline characteristics (age, sex, and BMI), there were other potential confounders such as exercise, diet, smoking, alcohol drinking history, medication including steroids or warfarin and prevalence of osteoarthritis or rheumatoid disease. Second, in our study, although the BMD change did not influence the incidence of new clinical fractures, the observation period was relatively short. Therefore, a further long-term longitudinal study is needed. Third, the data regarding whether patients had primary osteoporosis or not was not available. Lastly, the serum calcium levels were negatively correlated with the changes in LBMD, the TRACP-5b levels were positively correlated with the changes in LBMD, and the baseline FNBMD was negatively associated with the change in FNBMD after 2 years of denosumab therapy; although these factors may have been influenced by the baseline renal function, the renal function was not assessed. Fourth, we consider the inability to incorporate C-terminal telopeptide and either Pepin or bone-specific alkaline phosphatases into the analysis as a limitation of this study. Fifth, while it would have been preferable to perform a sample size calculation, we utilized all the data registered across the research institution, and therefore, a sample size calculation was not conducted. Sixth, as the target was outpatient care at a university hospital, there is a possibility that patients with multiple comorbidities were gathered. Furthermore, excluding cases with missing data may have introduced selection bias. Seventh, there was no information on the duration of bisphosphonates administration in our database and we were unable to include the administration period in the analysis. The difference in duration of bisphosphonates could be important factor influencing the results. Eighth, it was not feasible to perform adjusted multivariate analysis for the use of bisphosphonates due to the small sample size. Ninth, we initially considered the definition of the nonresponder in FNBMD as 3%. However, in the present study, the number of responders in FNBMD has been very small and it was difficult to perform adequate analysis. We have decided to adopt a cutoff value of 0% for responders and nonresponders in FNBMD based on the previous studies.[30,31]

5 | CONCLUSION

Denosumab is a clinically useful option for osteoporotic patients with an inadequate response to bisphosphonates; however, a history of bisphosphonate administration is suggested to be a risk factor for a lack of increase in the LBMD with denosumab treatment. In addition, a higher FNBMD at baseline was negatively associated with the change in FNBMD caused by denosumab treatment in patients with osteoporosis. As no patients experienced new clinical vertebral body fractures in the 24 months after denosumab initiation, denosumab might have a preventive effect against new fractures even in patients whose BMD does not increase.

AUTHOR CONTRIBUTIONS

Akiko Yamamoto: Data curation; investigation; formal analysis; writing—original draft. **Masashi Nagao**: Conceptualization; methodology; software; data curation; investigation; formal analysis; supervision; project administration; visualization; writing—review & editing. **Yuji Nishizaki**: Conceptualization; investigation; validation; supervision; resources; project administration; writing—review & editing; funding acquisition. **Eri Maeda**: Writing—review & editing; data curation; validation; investigation. **Muneaki Ishijima**: Writing—review & editing; conceptualization; supervision; project administration; investigation; methodology; resources. All authors have read and approved the final version of the manuscript. Dr. Masashi Nagao had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The public sharing of the data for this study is not possible because consent was not obtained for the public sharing of participants' data. The corresponding author is going to responding to requests regarding data analyses.

TRANSPARENCY STATEMENT

The lead author Masashi Nagao affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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