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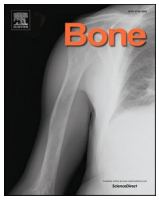

Full Length Article

Impact of baseline PINP on the BMD increase with romosozumab, teriparatide, and denosumab in treatment-naïve primary osteoporosis: A retrospective cohort study

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ABSTRACT

Purpose: To investigate the impact of baseline total N-terminal propeptide of procollagen (PINP) levels on increases in bone mineral density (BMD) after treatment with romosozumab (ROMO), teriparatide (TPTD), and denosumab (DMAb) in patients with treatment naïve primary osteoporosis.
Methods: This multicenter, retrospective cohort study included 462 treatment-naïve patients (88.7 % female; mean age, 75.5 years; baseline BMD T-scores: lumbar spine [LS], −3.0; total hip [TH], −2.7) who initiated treatment with ROMO ($n = 310$), TPTD ($n = 70$), or DMAb ($n = 82$). Patients were stratified by baseline total PINP levels into low ($\leq$ 70.1 μg/L) and high ($>$ 70.1 μg/L) groups. After adjusting for baseline characteristics using inverse probability of treatment weighting, changes in BMD were evaluated at 12 months.
Results: In the low PINP group, increases in LS BMD were similar between ROMO and TPTD; in the high PINP group, ROMO led to greater increases in LS BMD than TPTD. ROMO resulted in greater increases in TH BMD than TPTD, regardless of PINP level. Compared with DMAb, ROMO resulted in greater increases in LS BMD and TH BMD in the low PINP group, whereas no significant differences were observed in the high PINP group.
Conclusion: ROMO demonstrated robust increases in both LS and TH BMD across all PINP levels. TPTD led to increases in LS BMD comparable to those with ROMO in the low PINP group. DMAb led to increases in both LS and TH BMD comparable to those with ROMO in the high PINP group.

1. Introduction

As the global population ages, optimizing osteoporosis treatment has become an urgent challenge. Recently, numerous therapeutic agents, including romosozumab (ROMO) [1,2], teriparatide (TPTD) [3], and denosumab (DMAb) [4], have been introduced, particularly for severe osteoporosis characterized by extremely low bone mineral density (BMD) or high fracture risk [5]. However, even with these treatments,

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some patients do not achieve expected improvements in BMD, underscoring the need to refine treatment selection.

Bone turnover markers (BTMs), including bone formation markers such as N-terminal propeptide of type I procollagen (PINP) and bone resorption markers such as tartrate-resistant acid phosphatase 5b (TRACP-5b), are commonly used to evaluate osteoporosis treatment efficacy [6]. Recently, some studies have explored their potential to predict treatment outcomes. For example, previous reports suggest that higher baseline BTM levels correlate with greater BMD increases with ROMO or DMAb [1,7], and that greater increases in PINP three months after TPTD initiation correlate with improved TPTD efficacy [8]. However, no studies have yet directly compared the effects of increases in ROMO, TPTD, and DMAb on BMD among patients stratified by baseline BTM levels. We hypothesized that the anabolic agent TPTD would be more effective in patients with low bone turnover, whereas the antiresorptive agent DMAb would be more effective in patients with high bone turnover. Furthermore, although previous studies reported that ROMO has superior effects on increases in BMD compared with TPTD and DMAb [9,10], we also hypothesized that the agents might perform comparably, depending on bone turnover status at treatment initiation. PINP, a byproduct of collagen metabolism, is considered more stable than the enzyme TRACP-5b and reflects bone metabolic activity more directly [11,12]. Given its greater stability and broader evidence supporting its use in predicting anabolic agent efficacy [1,8,13,14], PINP was selected as the surrogate marker in this study.

This study aimed to compare increases in BMD with ROMO, TPTD, and DMAb in patients stratified into low- and high-turnover groups based on baseline PINP levels. This study also aimed to determine whether baseline BTM levels can reliably guide selection among these three agents.

2. Methods

2.1. Study design and patients

This multicenter, retrospective cohort study, conducted across seven medical centers, included 654 treatment-naïve patients with primary osteoporosis. These patients initiated treatment with ROMO, TPTD, or DMAb due to high fracture risk, as defined by the 1998 World Health Organization criteria or the 2011 Japanese Guidelines for the Prevention and Treatment of Osteoporosis (Figure SI1) [15]. As TPTD formulations, either the daily injection or the twice-weekly injection was administered. High fracture risk was defined as meeting one or more of the following criteria: (1) a BMD T-score below −2.5 with at least one fragility fracture; (2) a lumbar spine (LS) BMD T-score below −3.3; (3) two or more vertebral fractures; or (4) a semiquantitative Grade 3 vertebral fracture [16]. Patients with secondary osteoporosis, those previously treated with ROMO, TPTD, DMAb, selective estrogen receptor modulator (SERM), or bisphosphonates (BPs), or those lacking baseline BMD data were excluded. Patients were then classified into a low PINP group (PINP $\leqq$ 70.1 μg/L, n = 227) and a high PINP group (PINP >70.1 μg/L, n = 235) based on their baseline total PINP levels. The 70.1 μg/L cutoff value was determined using the upper limit of the reference range for premenopausal women, as defined by the assay kit (Roche Diagnostics, Basel, Switzerland). This approach was guided by previous studies recommending establishing BTM cutoff values using reference ranges from premenopausal women with normal bone turnover [17,18].

2.2. Bone mineral density assessment

Lumbar spine (LS; L2–L4) and total hip (TH) BMD were assessed using dual-energy X-ray absorptiometry (DXA) equipment (Horizon, Hologic, Inc., Marlborough, MA, USA; or PRODIGY, GE Healthcare, Madison, WI, USA). The percentage coefficient of variation for L2-L4 BMD was 0.63 % with the Horizon system and 0.41 % with the PRODIGY system. Measurements were taken at baseline and every 6 months after treatment initiation. BMD data were standardized using Japanese population reference values for each DXA device, following the correction method recommended by the Japan Osteoporosis Society and guidance from the International Society for Clinical Densitometry [19]. Regions with severe sclerosis, degenerative spinal conditions, vertebral fractures, or surgical sites were excluded from BMD measurements [4].

2.3. Biochemical markers of bone turnover

BTMs were assessed at baseline and at 6 and 12 months during therapy after treatment initiation. Total PINP served as a bone formation marker (inter-assay coefficient of variation $\leq$5.0 %; Roche Diagnostics, Basel, Switzerland) [20]. TRACP-5b was measured as a bone resorption marker (inter-assay coefficient of variation $\leq$9.0 %; Nittobo Medical Co. Ltd., Tokyo, Japan) [20]. Serum 25-hydroxycholecalciferol [25(OH)D] levels were assessed by electrochemiluminescence using the Elecsys system (Roche Diagnostics, Basel, Switzerland) [20].

2.4. Radiographs

Spinal radiographs were obtained at baseline and every 6 months after treatment initiation. Vertebral fractures of grade 1 or higher were identified using a semiquantitative method [16]. For patients with symptoms suggestive of clinical vertebral or nonvertebral fractures, attending investigators evaluated unscheduled radiographs.

2.5. Statistical analysis

Prior to comparing baseline characteristics among the study groups, normality tests were performed for continuous variables. As many variables did not follow a normal distribution, the Kruskal–Wallis test was applied for continuous variables, and the chi-square test was used for categorical variables. Changes in BMD were assessed by calculating the percentage change from baseline. Changes in BMD and BTM levels within each group from baseline to specific time points were assessed using the Wilcoxon signed-rank test.

Inverse probability of treatment weighting (IPTW) was used to adjust for baseline patient characteristics [21,22]. Since simultaneously adjusting baseline characteristics for all three groups using IPTW was not feasible, two sets of pairwise adjustments and comparisons were performed: ROMO vs. TPTD and ROMO vs. DMAb. First, logistic regression analysis was conducted to calculate propensity scores, which were then used to compute the weights [22]. The propensity score for receiving the reference drug was estimated using a multivariable logistic regression model. Covariates in the logistic regression model, selected based on their previously reported influence on BMD improvements, included age at treatment initiation [7], baseline BMD [23], body mass index (BMI), [24], and baseline total PINP and TRACP-5b levels. Baseline LS BMD were adujsted when comparing LS BMD changes, and baseline TH BMD were adujsted when comparing TH BMD changes. Weighting was performed using the inverse probability of the treatment actually received (1/PS for patients receiving the reference drug and 1/(1–PS) for patients receiving the comparator drug). After IPTW adjustment, differences in increases in BMD between the two groups were tested using generalized estimating equations (GEE) [25,26].

Standardized mean differences (SMDs) were calculated to evaluate whether IPTW adequately adjusted for baseline characteristics. A SMD <0.1 was considered indicative of good adjustment, whereas a SMD <0.2 was regarded as acceptable [27]. Furthermore, previous reports indicate that an adjusted total sample size of 40 or more is sufficient to maintain a Type I error rate below 0.05 [28]. It was confirmed that the adjusted total sample size did not fall below this threshold.

Statistical analyses were conducted using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical

user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [29]. *P*-values <0.05 were considered statistically significant.

2.6. Ethical statement

This study adhered to the ethical standards of the Declaration of Helsinki and received approval from the institutional ethical review board of Osaka University Graduate School of Medicine (approval no. 18258) and from the review boards of all participating institutes. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article; opt-out information was provided on the respective hospital websites.

3. Results

3.1. Baseline characteristics

Baseline patient characteristics before adjustment are presented in Table 1 (low PINP group) and Table 2 (high PINP group). Significant differences in patient characteristics were observed among the three treatment groups, including age, BMI, lumbar spine BMD, and estimated glomerular filtration rate (eGFR). Baseline characteristics after IPTW adjustment are shown in Tables SI1 and SI2. All SMDs for the adjusted variables were below 0.2, indicating appropriate balance across variables after adjustment.

3.2. Bone turnover markers

Changes in BTMs (ROMO vs. TPTD) after treatment initiation and IPTW adjustment are shown in Fig. 1. In the low PINP group, PINP levels significantly increased from baseline at 6 months in both treatment groups; at 12 months, the TPTD group maintained higher PINP levels than the ROMO group (Fig. 1a). In contrast, in the high PINP group, PINP levels at 6 and 12 months were similar between the two groups (Fig. 1b). ROMO administration was associated with decreased TRACP-5b levels in both PINP groups (Fig. 1c, d). Conversely, after TPTD administration, no significant change in TRACP-5b levels was observed in the low PINP group, whereas the high PINP group showed a significant decrease in these levels at both 6 and 12 months (Fig. 1c, d).

Changes in BTMs (ROMO vs. DMAb) after treatment initiation and IPTW adjustment are presented in Fig. 2. Changes in BTMs with ROMO administration showed a trend consistent with that observed in Fig. 1. Following DMAb administration, both PINP and TRACP-5b levels decreased at 6 and 12 months (Fig. 2a–d). Notably, the reduction in PINP tended to be greater in the high PINP group (6 months: −72.8 ± 3.0 %; 12 months: −74.2 ± 3.0 %; mean ± standard error) than in the low PINP group (6 months: −61.0 ± 2.5 %; 12 months: −58.6 ± 3.1 %). In both the low and high PINP groups, DMAb induced a more pronounced reduction in both PINP and TRACP-5b at 6 and 12 months post-treatment compared to ROMO.

Absolute changes in BTM values before IPTW adjustment are presented in Figure SI2.

3.3. Changes in BMD After IPTW adjustment

When comparing ROMO and TPTD (Fig. 3), increases in LS BMD in the low PINP group did not differ significantly between treatments (ROMO: 13.9 ± 0.8 %; TPTD: 12.1 ± 3.6 %; $P = 0.63$) (Fig. 3a). However, in the high PINP group, ROMO led to significantly greater increases in LS BMD than TPTD (ROMO: 17.6 ± 1.0 % vs. TPTD: 6.8 ± 1.5 %; $P < 0.001$) (Fig. 3b). For TH BMD, ROMO led to significantly greater increases than TPTD in both the low PINP group (ROMO: 4.8 ± 0.7 % vs. TPTD: 1.4 ± 1.1 %; $P = 0.006$) (Fig. 3c) and the high PINP group (ROMO: 6.3 ± 0.5 % vs. TPTD: 1.6 ± 1.1 %; $P = 0.037$) (Fig. 3d).

When comparing ROMO and DMAb (Fig. 4), ROMO led to greater increases in LS BMD than DMAb in the low PINP group (ROMO: 12.9 ± 0.8 % vs. DMAb: 5.6 ± 0.8 %; P < 0.001) (Fig. 4a), whereas no significant difference was observed in the high PINP group (ROMO: 16.4 ± 1.0 % vs. DMAb: 11.0 ± 3.4 %; $P = 0.13$) (Fig. 4b). Similarly, ROMO demonstrated greater increases in TH BMD than DMAb in the low PINP group (ROMO: 4.8 ± 0.7 % vs. DMAb: 2.2 ± 0.7 %; $P = 0.005$) (Fig. 4c), whereas no significant difference was observed in the high PINP group (ROMO: 6.2 ± 0.6 % vs. DMAb: 4.5 ± 1.1 %; $P = 0.16$) (Fig. 4d).

A comparison of BMD increases between the TPTD and DMAb groups is presented in Figure SI3, while Figure SI4 shows the comparison between the baseline low and high PINP groups across the three treatments: ROMO, TPTD, and DMAb. These figures were generated using IPTW; however, due to the small sample size, some covariates have not been adequately adjusted. Therefore, these figures should be interpreted for reference purposes only.

Table 1
Clinical characteristics of patients in low PINP group (PINP ≦ 70.1 μg/L) at treatment initiation with each agent.

Variable	ROMO ($n = 135$)	TPTD ($n = 37$) Daily: $n = 27$ Twice weekly: $n = 10$	DMAb ($n = 55$)	*P* value
Age (years)	74.6 ± 7.8	68.6 ± 13.3	77.2 ± 7.6	<0.001
Female sex (%)	97.7	97.3	65.5	<0.001
Body Mass Index (kg/m²)	20.6 ± 3.3	19.5 ± 2.7	21.6 ± 2.8	0.005
Prior vertebral fracture (%)	35.7	71.4	61.7	<0.001
Prior nonvertebral fracture (%)	18.8	16.1	27.7	0.491
Lumbar spine BMD (g/cm²)	0.734 ± 0.147	0.708 ± 0.144	0.860 ± 0.172	<0.001
Lumbar spine BMD (T-score)	−3.02 ± 1.13	−3.18 ± 1.28	−1.97 ± 1.36	<0.001
Total hip BMD (g/cm²)	0.628 ± 0.091	0.631 ± 0.144	0.635 ± 0.097	0.814
Total hip BMD (T-score)	−2.56 ± 0.75	−2.53 ± 1.28	−2.59 ± 0.69	0.828
Femoral neck BMD (g/cm²)	0.569 ± 0.090	0.582 ± 0.122	0.583 ± 0.097	0.239
Femoral neck BMD (T-score)	−3.18 ± 0.78	−2.81 ± 0.99	−2.90 ± 0.76	0.006
Corrected serum calcium (mg/dL)	9.2 ± 0.4	9.3 ± 0.4	9.2 ± 0.3	0.138
eGFR (mL/min/1.73m²)	74.1 ± 19.0	82.3 ± 22.5	63.7 ± 18.0	<0.001
PINP (μg/L)	50.1 ± 13.9	39.1 ± 15.3	48.0 ± 13.5	<0.001
TRACP-5b (mU/dL)	478.7 ± 169.1	420.7 ± 209.2	457.3 ± 175.3	0.141
25(OH)D (ng/mL)	17.2 ± 5.9	17.0 ± 7.9	19.1 ± 5.7	0.115

Values are presented as mean ± standard deviation or percentage. *P* values were calculated using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables.
Abbreviations: BMD, bone mineral density; DMAb, denosumab; eGFR, estimated glomerular filtration rate; PINP, N-terminal type I procollagen propeptide; ROMO, romosozumab; TPTD, teriparatide; TRACP-5b, tartrate-resistant acid phosphatase 5b.

Table 2
Clinical characteristics of patients in high PINP group (PINP >70.1 μg/L) at treatment initiation with each agent.

Variable	ROMO (n = 175)	TPTD (n = 33) Daily: n = 18 Twice weekly: n = 15	DMAb (n = 27)	P value
Age (years)	76.6 ± 9.1	73.2 ± 9.2	81.1 ± 8.0	0.027
Female sex (%)	92.0	100.0	70.4	<0.001
Body Mass Index (kg/m²)	20.9 ± 3.0	21.3 ± 3.9	20.7 ± 2.8	0.837
Prior vertebral fracture (%)	61.2	73.3	62.5	0.666
Prior nonvertebral fracture (%)	24.4	33.3	34.8	0.710
Lumbar spine BMD (g/cm²)	0.721 ± 0.141	0.656 ± 0.104	0.808 ± 0.150	<0.001
Lumbar spine BMD (T-score)	−3.14 ± 1.03	−3.64 ± 0.79	−2.51 ± 1.18	<0.001
Total hip BMD (g/cm²)	0.590 ± 0.089	0.605 ± 0.116	0.604 ± 0.090	0.634
Total hip BMD (T-score)	−2.86 ± 0.70	−2.63 ± 0.95	−2.84 ± 0.71	0.352
Femoral neck BMD (g/cm²)	0.550 ± 0.092	0.570 ± 0.106	0.563 ± 0.085	0.315
Femoral neck BMD (T-score)	−3.38 ± 0.78	−3.01 ± 0.92	−3.14 ± 0.85	0.052
Corrected serum calcium (mg/dL)	9.1 ± 0.4	9.2 ± 0.4	9.2 ± 0.4	0.541
eGFR (mL/min/1.73m²)	71.4 ± 23.9	74.6 ± 22.8	57.5 ± 26.2	0.129
PINP (μg/L)	120.3 ± 123.4	101.5 ± 36.0	145.0 ± 218.6	0.780
TRACP-5b (mU/dL)	710.9 ± 245.6	691.5 ± 221.7	677.9 ± 315.2	0.531
25(OH)D (ng/mL)	16.1 ± 6.4	19.0 ± 5.3	15.6 ± 5.4	0.012

Values are presented as mean ± standard deviation or percentage. P values were calculated using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables.
Abbreviations: BMD, bone mineral density; DMAb, denosumab; eGFR, estimated glomerular filtration rate; PINP, N-terminal type I procollagen propeptide; ROMO, romosozumab; TPTD, teriparatide; TRACP-5b, tartrate-resistant acid phosphatase 5b.

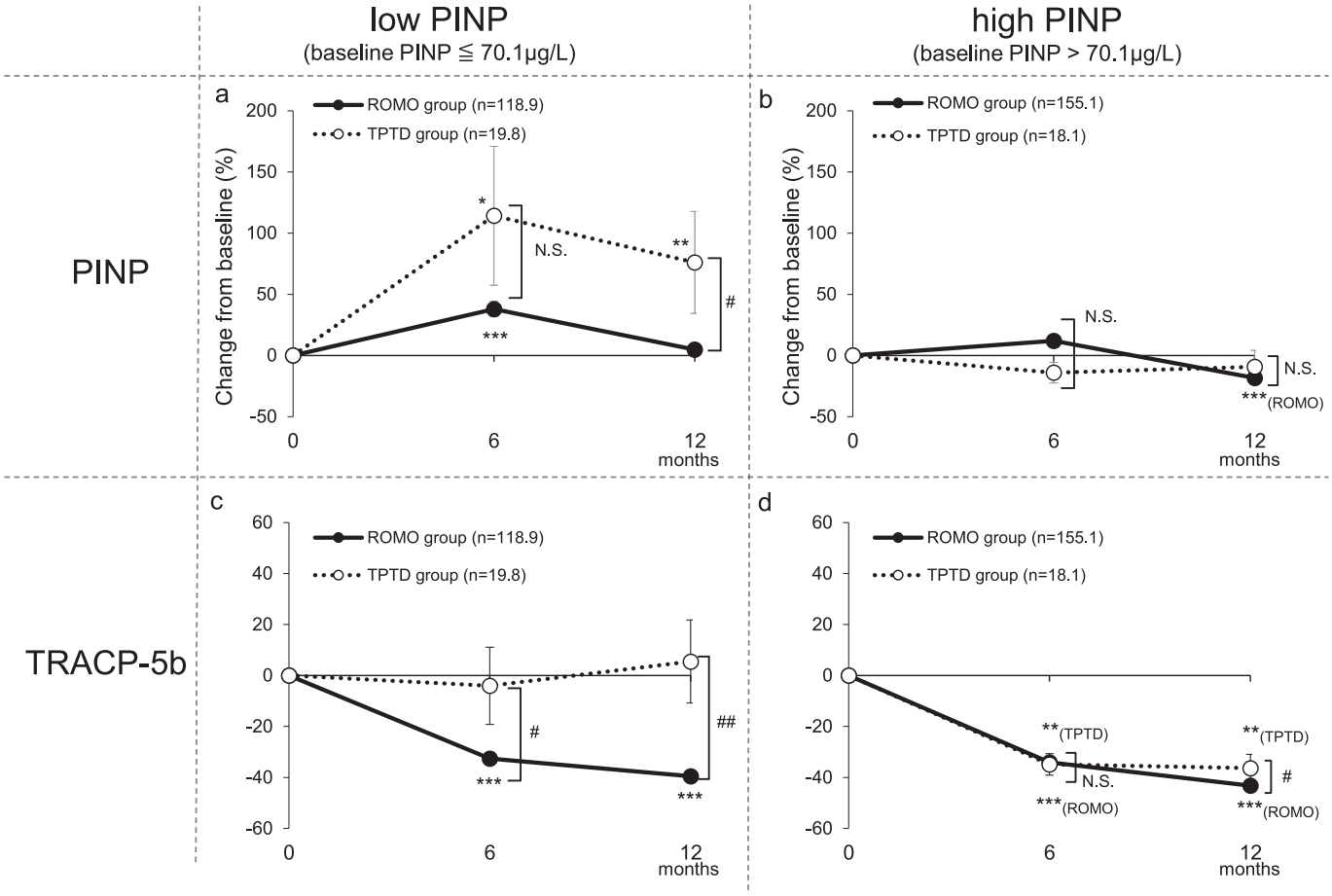

Fig. 1. Changes in serum PINP and TRACP-5b levels after IPTW: ROMO vs. TPTD
Abbreviations: IPTW, inverse probability of treatment weighting; PINP, N-terminal type I procollagen propeptide; ROMO, romosozumab; TPTD, teriparatide; TRACP-5b, tartrate-resistant acid phosphatase 5b.
Bars indicate mean ± standard error. * $P < 0.05$, vs. baseline, ** $P < 0.01$, vs. baseline, *** $P < 0.001$, vs. baseline, using Wilcoxon signed-rank test. # $P < 0.05$, ROMO vs. TPTD, ## $P < 0.01$ ROMO vs. TPTD, using generalized estimated equation.

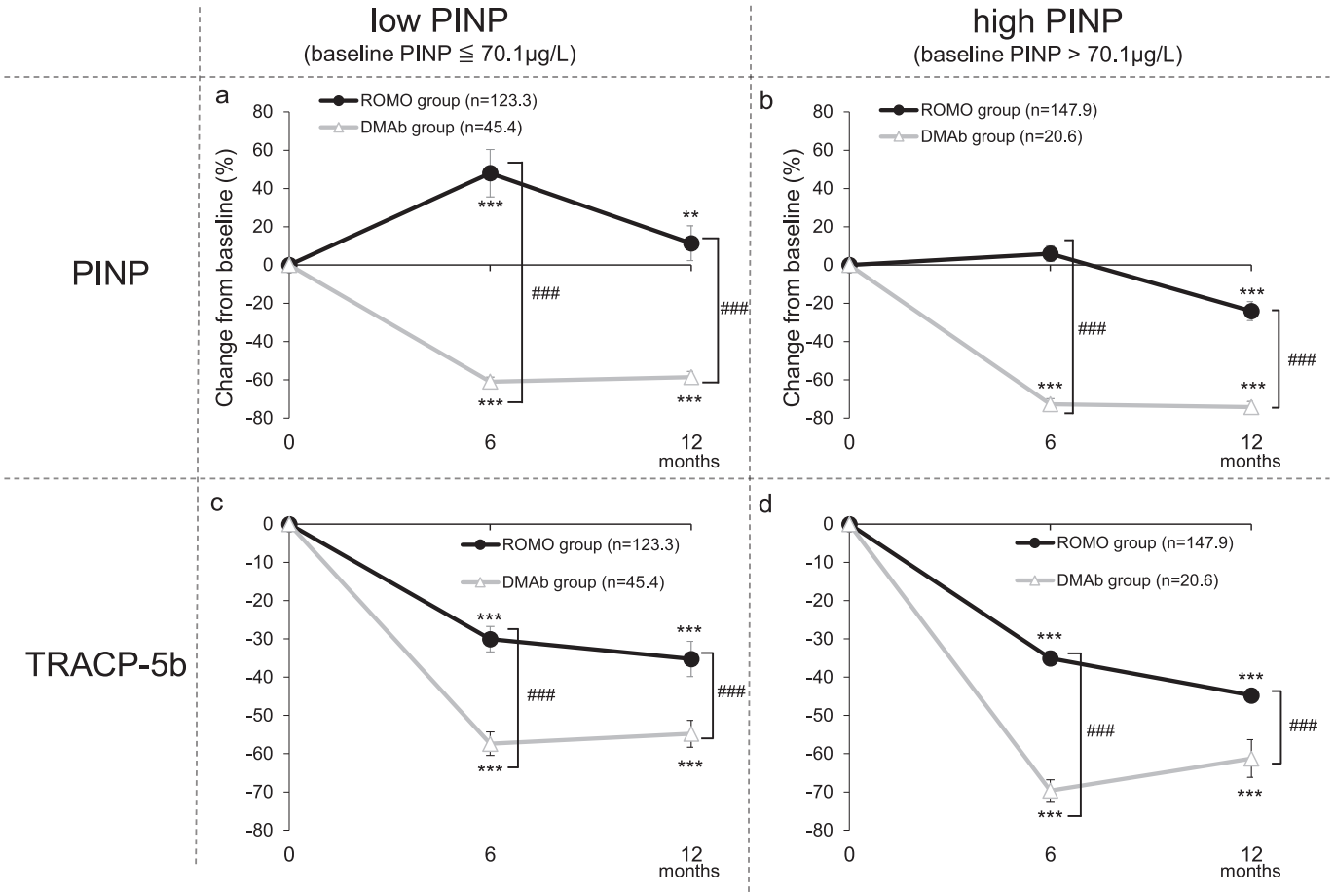

Fig. 2. Changes in serum PINP and TRACP-5b levels after IPTW: ROMO vs. DMAb
Abbreviations: DMAb, denosumab; IPTW, inverse probability of treatment weighting; PINP, N-terminal type I procollagen propeptide; ROMO, romosozumab; TRACP-5b, tartrate-resistant acid phosphatase 5b.
Bars indicate mean ± standard error. ** $P < 0.01$, vs. baseline, *** $P < 0.001$, vs. baseline, using Wilcoxon signed-rank test. ### $P < 0.001$ ROMO vs. DMAb, using generalized estimated equation.

3.4. Changes in BMD before IPTW adjustment

Unadjusted increases in BMD before IPTW adjustment are shown in Figure SI5. The rate of change of BMD after treatment initiation showed a similar trend before and after IPTW adjustment. However, in the high PINP group before IPTW adjustment, the increase in LS BMD with DMAb was smaller than that observed with ROMO (ROMO: 16.7 ± 1.0 %; DMAb: 7.2 ± 2.8 %). This difference is likely attributable to the higher baseline BMD in the DMAb group before adjustment.

3.5. Incidence of fragility fractures

During the observation period, fragility fractures occurred in four patients (1.3 %) in the ROMO group: three vertebral fractures and one femoral trochanteric fracture. Two of the vertebral fractures occurred within the first 6 months after treatment initiation, while the other two fractures occurred within 12 months. One vertebral fracture (1.4 %) was reported in the TPTD group, and one distal radius fracture (1.2 %) was observed in the DMAb group. These fractures occurred between 6 and 12 months after treatment initiation. All of the above patients with fractures continued treatment based on discussions between the attending physician and the patient.

4. Discussion

To our knowledge, this is the first study to directly compare increases in BMD with ROMO, TPTD, and DMAb by stratifying patients according to their baseline PINP levels. ROMO demonstrated significant increase in BMD between baseline and 12 months regardless of baseline PINP. In patients with low baseline PINP levels, TPTD resulted in a LS BMD increase that did not differ significantly from that observed with ROMO, whereas its effect on TH BMD was significantly smaller than that of ROMO. Likewise, in patients with high baseline PINP levels, there were no statistically significant differences in the increases in LS and TH BMD between DMAb and ROMO. These findings suggest that baseline PINP levels may serve as a potential predictor of BMD response to treatment.

In the low PINP group, TPTD administration resulted in a significant increase in PINP, whereas no significant increase was observed in the high PINP group (Fig. 1a, b). TPTD acts on parathyroid hormone (PTH) receptors, enhancing the differentiation and proliferation of mesenchymal stem cells and osteoprogenitor cells [30,31]. In patients with low baseline PINP, a sufficient pool of these precursor cells may be available, allowing TPTD to stimulate bone formation effectively. However, when TPTD is administered to patients with consistently high baseline PINP, some progenitor cells may have already differentiated, potentially limiting the anabolic response to TPTD. However, this interpretation remains speculative, and further studies are needed to confirm these mechanisms.

With DMAb administration, both PINP and TRACP-5b levels markedly decreased. Notably, the reductions in PINP and TRACP-5b, as well as the increase in BMD, tended to be greater in the high PINP group. Previous studies have reported that greater decreases in

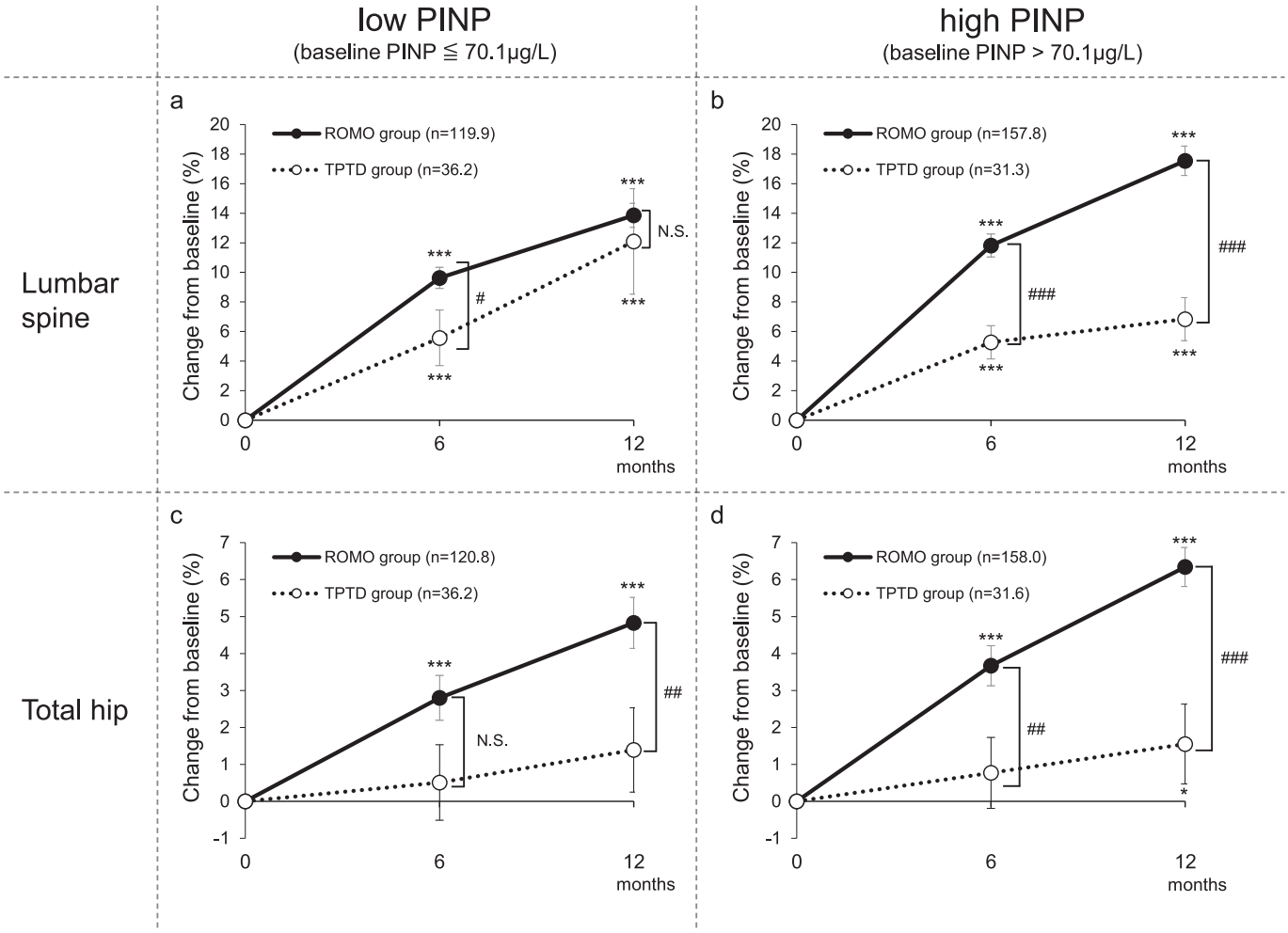

Fig. 3. Percent changes in BMD in the lumbar spine (a,b) and total hip (c, d) after IPTW: ROMO vs. TPTD
Abbreviations: BMD, bone mineral density; IPTW, inverse probability of treatment weighting; PINP, N-terminal type I procollagen propeptide; ROMO, romosozumab; TPTD, teriparatide.
Bars indicate mean ± standard error. * $P < 0.05$, vs. baseline, *** $P < 0.001$, vs. baseline, using Wilcoxon signed-rank test. # $P < 0.05$ ROMO vs. TPTD, ## $P < 0.01$ ROMO vs. TPTD, ### $P < 0.001$, ROMO vs. TPTD, using generalized estimated equation.

BTMs—particularly PINP—following DMAb administration are associated with greater increases in BMD [32]. The present findings are consistent with the findings of these reports.

A previous report found that higher baseline PINP levels are associated with greater increases in BMD with ROMO [1]; our present findings are consistent with those findings. However, a novel finding of this study is that baseline PINP levels had a weaker influence on treatment response in patients receiving ROMO, whereas treatment outcomes in those receiving DMAb were more strongly affected by baseline PINP levels.

ROMO, which exerts a dual effect by promoting bone formation and inhibiting bone resorption [33], demonstrated high efficacy in both low- and high-turnover states. However, the U.S. Food and Drug Administration and the European Medicines Agency recommend avoiding ROMO in high-risk patients, such as those who have experienced a major cardiovascular event within the past year [34]. In such patients, utilizing baseline PINP levels as a biomarker to guide the choice between TPTD and DMAb may represent a clinically useful strategy.

Previous studies have reported that weekly TPTD (56.5 μg per injection) formulations are associated with decreased serum sclerostin levels [35] and reduced levels of bone resorption markers after administration [36]. This effect is thought to result from suppressed osteoclastogenesis via sclerostin inhibition and consequent osteoprotegerin production [37]. Similar decreases in bone resorption markers have also been observed with twice-weekly TPTD formulations (28.2 μg per injection) [36]. In this study, the high PINP group included a larger proportion of patients treated with the twice-weekly formulation than did the low PINP group. This difference may explains why TRACP-5b levels decreased in the high PINP group.

In the high PINP group, changes in BTMs following TPTD and ROMO administration were largely comparable; however, a substantial difference in increases in BMD was observed between the two treatments. ROMO has been reported to enhance modeling-based bone formation and suppress bone resorption as early as one month after initiation [38]. In the present study, BTMs at one month were not measured, making it impossible to assess this early effect. However, it is possible that this early response influenced the observed differences in BMD increases between TPTD and ROMO at 6 and 12 months.

Previous reports have used bone formation markers to predict treatment response [1,7,8]; however, no studies using bone resorption markers for this purpose have been identified. Indeed, although data are not presented in this paper, our preliminary investigation revealed no correlation between baseline TRACP-5b levels and subsequent BMD increases when stratifying patients by these levels.

This study has several limitations. First, the evaluation period was limited to one year. Second, while the sample size was sufficient to detect differences in BMD, it may not have been large enough to detect smaller differences in fracture risk reduction. Future studies with larger

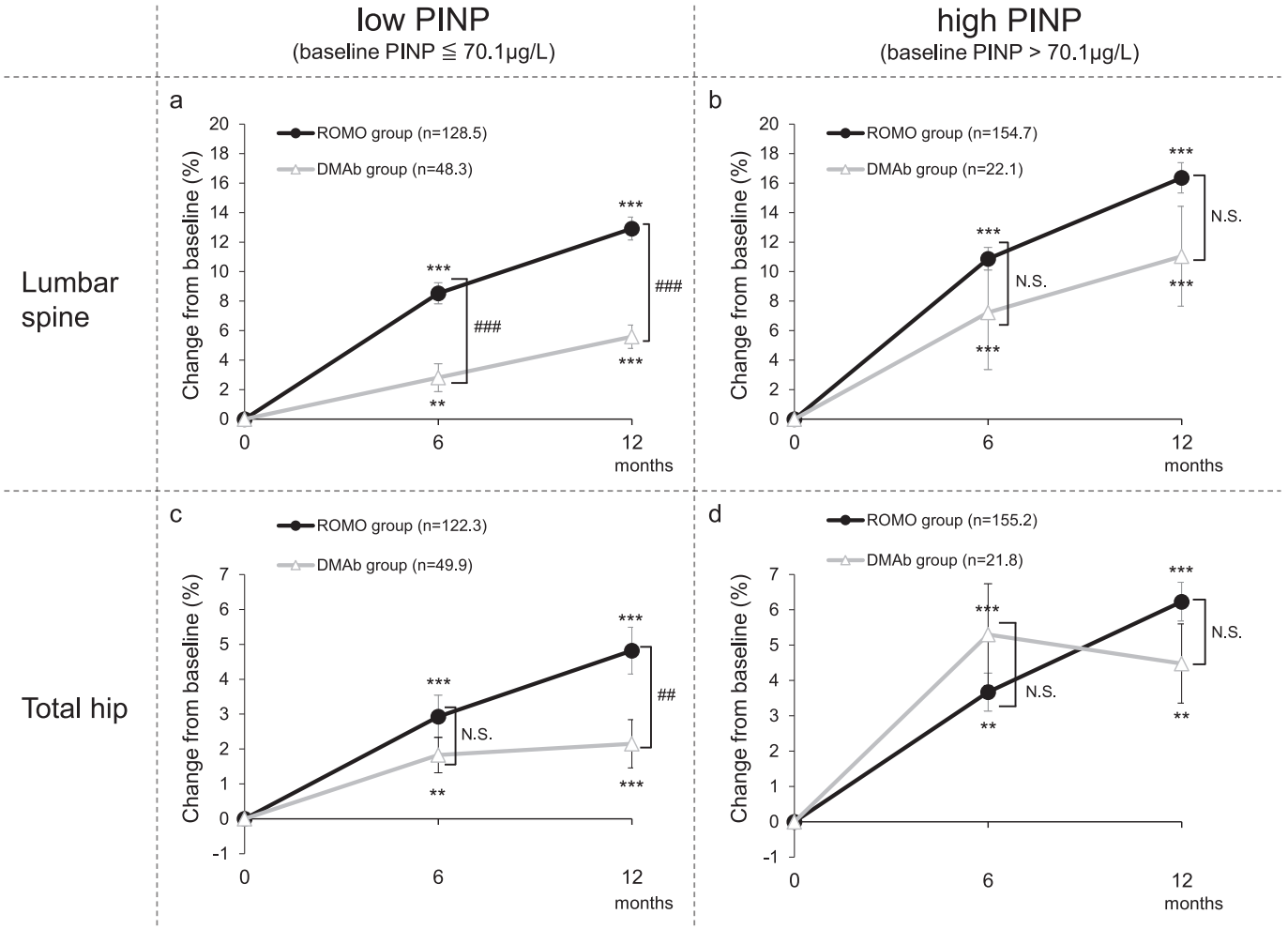

Fig. 4. Percent changes in BMD in the lumbar spine (a, b) and total hip (c, d) after IPTW: ROMO vs. DMAb
Abbreviations: BMD, bone mineral density; DMAb, denosumab; IPTW, inverse probability of treatment weighting; PINP, N-terminal type I procollagen propeptide; ROMO, romosozumab; TPTD, teriparatide.
Bars indicate mean ± standard error. ** $P < 0.01$, vs. baseline, *** $P < 0.001$, vs. baseline, using Wilcoxon signed-rank test. ## $P < 0.01$ ROMO vs. DMAb. ### $P < 0.001$, ROMO vs. DMAb, using generalized estimated equation.

sample sizes and longer follow-up periods, including sequential treatment, are needed. Third, the TPTD group included multiple formulations (daily and twice-weekly injections), which may have influenced the results. Fourth, due to the limited sample size, the number of covariates that could be adjusted for was restricted, and factors such as sex could not be included in the adjustment. Fifth, in cases where treatment was initiated shortly after a fracture, baseline PINP levels are likely to be influenced by the fracture itself; however, it was difficult to collect reliable data on the timing of fractures. However, despite these limitations, a major strength of this study is the direct comparison of increases in BMD among the three agents after adjusting for baseline characteristics.

5. Conclusion

ROMO demonstrated robust increases in BMD, irrespective of baseline PINP levels. In the low PINP group, TPTD showed an increase in LS BMD comparable to ROMO's, although its effect on TH BMD was inferior to that of ROMO. In the high PINP group, DMAb exhibited increases in LS and TH BMD comparable to those with ROMO. These findings suggest that, depending on baseline PINP level, TPTD or DMAb may achieve increases in BMD comparable to those with ROMO at specific skeletal sites.

CRediT authorship contribution statement

Yuki Etani: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Takaaki Noguchi:** Investigation, Data curation. **Toshitaka Yukishima:** Investigation, Data curation. **Tomonori Kobayakawa:** Project administration, Investigation, Data curation, Conceptualization. **Masafumi Kashii:** Investigation, Data curation. **Gensuke Okamura:** Investigation, Data curation. **Atsushi Goshima:** Investigation, Data curation. **Makoto Hirao:** Investigation, Data curation. **Taihei Miura:** Investigation, Data curation. **Takuya Kurihara:** Investigation, Data curation. **Yuji Fukuda:** Investigation, Data curation. **Atsushi Sugimoto:** Investigation, Data curation. **Seiji Okada:** Supervision, Resources. **Ken Nakata:** Supervision, Resources. **Kosuke Ebina:** Writing – review & editing, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2025.117627.

Data availability

The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

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