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Note	

Highlights

- Treatment response to romosozumab was evaluated by the change of bone mineral density and bone turnover markers

- Prior bone-resorption inhibitors' treatment attenuates early treatment response to romosozumab

- Early treatment response to romosozumab was highest in treatment-naïve cases

- Early treatment response to romosozumab was predicted by the early change of bone turnover markers

1 **Rapid Commumication**

2 Effects of prior osteoporosis treatment on early treatment response of romosozumab in

3 patients with postmenopausal osteoporosis

4

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38

39

Abstract

Purpose

To investigate the effects of prior treatment and the predictors of early treatment

response to romosozumab (ROMO) in patients with postmenopausal osteoporosis.

Methods

In this prospective, observational, multicenter study, 130 treatment-naïve patients

(Naïve; n = 37) or patients previously treated with bisphosphonates (BP; n = 33),

denosumab (DMAb; n = 45), or teriparatide (TPTD; n = 15) (age, 75.0 years; T-scores

of the lumbar spine [LS] −3.2 and femoral neck [FN] −2.9) were switched to ROMO

based on their physician's decision. Bone mineral density (BMD) and serum bone

turnover markers were evaluated for six months.

Results

At six months, LS BMD changes were 13.6%, 7.5%, 3.6%, and 8.7% ($P < 0.001$

between groups) and FN BMD changes were 4.2%, 0.4%, 1.6%, and 1.5% ($P = 0.16$

between groups) for Naïve, BP, DMAb, and TPTD groups, respectively. Changes in

N-terminal type I procollagen propeptide (PINP; μg/L) levels from baseline→one

month were 72.7→139.0, 33.5→85.4, 30.4→54.3, and 98.4→107.4, and those of

isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b) (mU/dL) were

474.7→270.2, 277.3→203.7, 220.3→242.0, and 454.1→313.0 for Naïve, BP, DMAb,

and TPTD groups, respectively. Multivariate regression analysis revealed that

significant predictors of LS BMD change at six months were prior treatment difference

($r = −3.1$, $P = 0.0027$) and TRACP-5b percentage change ($r = −2.8$, $P = 0.0071$) and

PINP value at one month ($r = 3.2$, $P = 0.0021$).

3

63 *Conclusion*

64 Early effects of ROMO on the increase in LS BMD are significantly affected by the

65 difference of prior treatment and are predicted by the early change in bone turnover

66 markers.

67

68 **Keywords**

69 romosozumab; prior treatment; predictor; bone turnover marker; postmenopausal

70 osteoporosis

71

72 **Mini Abstract**

73 Early effects of ROMO on the increase in LS BMD at six months is significantly

74 affected by the difference of prior treatment and also predicted by the early change of

75 bone turnover markers in patients with postmenopausal osteoporosis.

76

77 **Introduction**

78 With the advent of various novel anti-osteoporosis agents, goal-directed treatment for

79 osteoporosis has been recommended to reduce imminent fracture risk [1]. One novel

80 anabolic agent is romosozumab (ROMO), a monoclonal anti-sclerostin antibody that

81 promotes bone formation and inhibits bone resorption [2]. Because of this unique dual

82 effect, the anabolic window (i.e., the difference between bone formation and bone

83 resorption), which determines the effects of osteoporosis treatment, is assumed to be

4

84   larger in ROMO than other osteoporosis treatments [3]. Indeed, in postmenopausal

85   women, ROMO has shown superior effects in increasing lumbar spine (LS) bone

86   mineral density (BMD) than alendronate or teriparatide (TPTD) [2]. In addition, the

87   increase in the bone formation markers and decrease in the bone resorption markers

88   become largest within a month after treatment induction [2], suggesting that this early

89   bone turnover response may be beneficial in predicting early treatment response to

90   ROMO.

91   The effects of prior treatment on bone anabolic agents have been reported. Prior

92   antiresorptive treatment such as bisphosphonates (BP) blunted the hip BMD response to

93   TPTD [4,5], and switching from denosumab (DMAb) to TPTD led to a transient

94   increase in the bone resorption markers and a consequent decrease in BMD [6]. On the

95   other hand, only a few studies have demonstrated the effects of subsequent treatment of

96   ROMO after administration of other osteoporosis agents, such as alendronate [7] or

97   DMAb [8]. We recently reported a case in which ROMO was not effective in

98   preventing multiple spontaneous clinical vertebral fractures after DMAb discontinuation

99   [9]. However, patients transitioned from oral BP to ROMO showed gains in hip BMD

100   that were not observed with TPTD, suggesting the difference of sequential effects

101   between these two agents [10].

102   Taken together, we hypothesized that prior antiresorptive treatment (such as BP or

103   DMAb) may diminish the effects of ROMO, although may differ from that of TPTD.

104   However, there has been no direct comparison between prior treatment-naïve cases or

105   prior treatment by TPTD cases.

106 Japan was the first country to approve ROMO on March 2019, and its clinical data

107 based on real-world settings is of great interest. This study aims to clarify the effects of

108 prior treatment and determine predictors for early treatment response of ROMO in

109 patients with postmenopausal osteoporosis.

110

Materials and methods

111 **Materials and methods**

112 *Study design and subjects*

113 This prospective, observational, nonrandomized study was conducted in six centers in

114 accordance with the Japanese Guidelines for Prevention and Treatment of Osteoporosis

115 2011 [11]. A total of 130 postmenopausal patients with osteoporosis who were

116 treatment naïve (Naïve; n = 37) or previously treated by BP (n = 33), DMAb (n = 45),

117 or TPTD (n = 15) were switched to ROMO based on the decision of the patients'

118 physicians (mainly judged by insufficient increase of BMD associated with prior

119 treatment). Patients were supplemented with vitamin D and calcium in principle (table

120 1), and followed up for six months.

121

122 *BMD assessment*

123 Areal BMD in the LS (L2–L4), total hip (TH), and femoral neck (FN) were assessed by

124 dual-energy X-ray absorptiometry (Discovery, Hologic, Inc., Waltham, MA, USA) at

125 baseline and six months after ROMO induction. We excluded regions of severe

126 sclerosis, vertebral fracture, and surgical sites from BMD measurements, as previously

127 described [12]. BMD data was standardized by correction method proposed by Japan

128 Osteoporosis Society in reference to the International Society for Clinical Densitometry

129 Guidance [13].

130

131 *Biochemical markers of bone turnover*

132 Bone turnover markers were measured at baseline, one month, and six months after

133 ROMO induction. Serum was obtained from each patient in the morning after an

134 overnight fast. We measured the N-terminal type I procollagen propeptide (PINP;

135 interassay coefficient of variation, 3.2%−5.2%; Intact UniQ assay; Orion Diagnostica,

136 Espoo, Finland) as a bone formation marker and isoform 5b of tartrate-resistant acid

137 phosphatase (TRACP-5b; interassay coefficient of variation, 5.0%−9.0%;

138 Immunodiagnostic Systems Ltd., Boldon, UK) as a bone resorption marker using

139 enzyme-linked immunosorbent assay, as previously described [14]. (A previous report

140 demonstrated that TRACP-5b levels are a useful bone resorption marker that

141 demonstrates higher clinical sensitivity and signal-to-noise ratio as compared to serum

142 CTX levels [15]). Serum 25-hydroxycholecalciferol [25(OH)D] levels were measured

143 by electrochemiluminescence using the Elecsys system (Roche Diagnostics, Basel,

144 Switzerland).

145

146 *Radiographs*

147 Spinal radiographs were obtained routinely at baseline and six months after ROMO

148 administration as well as at unscheduled times if the subject had symptoms suggesting

149 clinical vertebral fracture during follow-up. For subjects with symptoms of incidental

150 nonvertebral fractures, radiographs were assessed by the investigator.

Statistical analysis

Differences between study groups were tested using analysis of variance (between four groups) and the Steel-Dwass test (between two groups) for continuous variables and using the Fisher's exact test (between four groups) for categorical variables. Changes in BMD and bone turnover marker levels from baseline to the specified time points within each study group were compared using the Wilcoxon signed-rank test. Spearman's correlation coefficients were calculated, and multivariate logistic regression analysis with a forward stepwise procedure was performed to identify significant indicators of change in LS or FN BMD. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [16]. A *P* value <0.05 was considered significant.

Ethical statement

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the institutional ethical review board of Osaka University Graduate School of Medicine (approval no. 18258; Osaka University, Graduate School of Medicine) and each institute. The board waived the requirement for patient informed consent by posting the opt-out information in the hospitals' home page.

Results

173 Table 1 shows patient clinical backgrounds at ROMO induction. Among the groups, no

174 significant difference was observed in baseline age, body mass index, prior vertebral

175 and nonvertebral fracture incidence ratio, combined vitamin D and calcium dose or

176 usage or serum calcium, estimated glomerular filtration rate, and 25(OH)D levels,

177 whereas there was a significant difference in the duration of prior treatment ($P < 0.001$),

178 LS BMD (g/cm^2; $P = 0.04$), FN BMD (g/cm^2; $P = 0.006$), T-score ($P = 0.03$), and

179 serum levels of PINP ($P < 0.001$) and TRACP-5b ($P < 0.001$).

180

181 *Bone turnover markers*

182 Figure 1 shows the serum PINP level (Fig. 1a) and its percentage change (Fig. 1b) as

183 well as the TRACP-5b value (Fig. 1c) and its percentage change (Fig. 1d).

184 Regarding PINP value, the Naïve group reached its highest value compared with other

185 groups at one month after ROMO induction, although only the DMAb group remained

186 within the reference range (14.9–68.8 μg/L) at one month and then continuously

187 increased until six months. The tendency in the BP group was similar to that of the

188 Naïve group, although the BP group's value remained in a smaller range. The TPTD

189 group maintained its value at one month, which then markedly decreased at six months.

190 The tendency of percentage change of PINP was similar between the Naïve, BP, and

191 TPTD groups, although only the DMAb group showed a continuous increase during this

192 period.

193 Regarding TRACP-5b value and percentage change, the Naïve and TPTD groups

194 showed marked decreases from one month to six months. This tendency was similar in

195 the BP group, although its decreasing rate was smaller than that of the other two groups

9

196 at six months. On the other hand, the DMAb group demonstrated a continuous increase

197 from one month to six months.

198

Changes in BMD

200 Regarding the change in LS BMD (Fig. 2a), the Naïve group had the highest increase

201 (mean ± standard errors; P-value compared with baseline; 13.6% ± 1.0%; $P < 0.001$),

202 followed by TPTD (8.7% ± 1.0%; $P < 0.001$), BP (7.5% ± 1.0%; $P < 0.001$), and

203 DMAb (3.6% ± 0.6%; $P < 0.001$). There was a significant difference between the

204 groups ($P < 0.001$).

205 Regarding the change in TH BMD (Fig. 2b), the Naïve group had the highest increase

206 (4.1% ± 0.8%; $P < 0.001$), followed by TPTD (2.7% ± 1.3%; $P = 0.031$), BP (2.1% ±

207 0.7%; $P = 0.032$), and DMAb (1.1% ± 0.8%; $P = 0.44$). There was a significant

208 difference between the groups ($P = 0.033$).

209 Regarding the change in FN BMD (Fig. 2c), the Naïve group had the highest and most

210 significant increase (4.2% ± 1.1%; $P = 0.002$), followed by DMAb (1.6% ± 1.1%; $P =$

211 0.37), TPTD (1.5% ± 1.4%; $P = 0.24$), and BP (0.4% ± 1.1%; $P = 0.43$). However, there

212 was no significant difference between the groups ($P = 0.16$).

213

Significant predictor variables of the change in LS or FN BMD

215 Spearman's correlation coefficient revealed that the significant confounders ($P < 0.05$)

216 of LS BMD change at six months were the PINP value at baseline ($r = 0.60$, $P < 0.001$)

217 and at one month ($r = 0.67$, $P < 0.001$), TRACP-5b value at baseline ($r = 0.57$, $P <$

218 0.001) and its percentage change at one month ($r = -0.55$, $P < 0.001$) and six months (r

219 $= -0.57$, $P < 0.001$), and baseline LS BMD T-score ($r = -0.20$, $P = 0.039$). Significant

220 confounders of FN BMD change at six months were PINP value at baseline ($r = 0.27$, P

221 $= 0.004$) and one month ($r = 0.24$, $P = 0.014$), TRACP-5b value at baseline ($r = 0.22$, P

222 $= 0.02$) and its percentage change at one month ($r = -0.19$ $P = 0.049$) and six months (r

223 $= -0.25$, $P = 0.010$), and baseline FN BMD T-score ($r = -0.33$, $P < 0.001$).

224 To investigate the early predictor of BMD response, the above significant confounders

225 (including prior therapy before ROMO [categorized as Naïve (1), TPTD (2), BP (3),

226 and DMAb (4)]; PINP [value of baseline and one month], TRACP-5b [value of baseline

227 and percentage change at one month], and baseline BMD [LS or FN T-score]) were

228 subjected to stepwise multivariable linear regression analysis.

229 Regarding the LS BMD change, the significant predictor was found to be the difference

230 of prior therapy before ROMO (partial regression coefficient = -3.1, $P = 0.0027$),

231 percentage change of TRACP-5b at one month (partial regression coefficient = -2.8, P

232 $= 0.0071$), and value of PINP at one month (partial regression coefficient = 3.2, $P =$

233 0.0021). As for FN BMD change, the significant predictor was value of PINP at

234 baseline (partial regression coefficient = 3.1, $P = 0.0030$).

235

Incidence of fragility fracture

237 During this period, a 74-year-old female patient who was switched from BP to ROMO

238 suffered a proximal humerus fracture as a result of a fall. Another 59-year-old female

239 patient who was switched from DMAb after a 9-month interval suffered multiple

240 vertebral fractures [17].

Discussion

To the best of our knowledge, this is the first study to demonstrate the effects of prior

treatment and predictors of ROMO in patients with postmenopausal osteoporosis. It has

been reported that in addition to the apoptosis of osteoclasts by BP uptake, osteoblasts

also uptake BP, and animal studies have demonstrated that BP suppress bone formation

by the lining cells (i.e., bone modeling) [17]. Indeed, the BP group showed smaller

percent decrease of TRACP-5b compared to the Naïve group. However, although the

BP group tended to show smaller absolute value of PINP, percent increase of PINP at

one month was similar to the Naïve group.

In a human clinical trial, patients receiving second-line treatment with ROMO after

DMAb demonstrated a continuous increase in serum PINP and β-CTX levels, which

was associated with a decreased or maintained BMD level at six months, and the BMD

increase was relatively small compared with patients with treatment washout [8]. In

addition, we have recently reported that a patient who was switched from DMAb to

ROMO at nine months had increased bone turnover and multiple vertebral fractures [9].

Taken together, it seems that increased bone turnover from DMAb discontinuation

cannot be fully compensated by ROMO in the early period. Regarding TPTD, Lindsay

et al. demonstrated that TPTD was able to stimulate not only bone remodeling but also

bone modeling [18]. In that report, 70% of bone formation by TPTD was based on

remodeling, whereas 20%−30% was modeling-based (modeling was especially

dominant within first two months after TPTD induction). In our study, switching from

TPTD to ROMO led to a maintained PINP level and a rapidly decreasing TRACP-5b

12

264 level at one month. Taken together, prior treatment with TPTD may leave little room for

265 further bone modeling by ROMO (as TPTD promotes bone modeling in relatively early

266 phase), although enhanced bone resorption by TPTD can be suppressed by ROMO (as

267 ROMO promotes osteoprotegerin production from both osteoblasts and osteocytes),

268 which resulted in a significant increase in LS BMD second to the Naïve group.

269 Another point of interest is the identification of the early predictors of the effects of

270 ROMO. It has been reported that both the increase in bone formation markers and the

271 decrease in bone resorption markers are largest within one month after ROMO

272 induction [2], suggesting that this early bone turnover response might be beneficial in

273 widening the anabolic window and predicting the treatment response. Takada et al.

274 reported that in patients with postmenopausal osteoporosis who were switched from BP

275 to ROMO, 91% of patients showed more than 3% increase in LS BMD at 12 months

276 when PINP increased more than 10 µg/L at 1 month [7]. This result suggests the

277 usefulness of early PINP response in predicting LS BMD increase (PINP was not useful

278 in predicting BMD increase of patients switched from BP to TPTD, suggesting the

279 difference between ROMO and TPTD), although this study included only patients

280 switched from BP and didn't evaluate the correlation with bone resorption markers.

281 From this study's multivariable linear regression analysis results, the significant

282 predictors of an increase in LS BMD at six months were the difference of prior

283 treatment before ROMO, percentage change of TRACP-5b at one month, and value of

284 PINP at one month. The significant predictor of FN BMD change was the value of

285 PINP at baseline. These results indicate that an early treatment response of ROMO may

286 be predicted by (1) difference of prior treatment, (2) bone turnover response at one

287 month, and (3) baseline bone formation status. Concerning sequential treatment, Saag et

288 al. demonstrated that switching ROMO to alendronate lead to maintained BMD [19],

289 while switching ROMO to DMAb lead to continuous BMD increase [20]. Taken

290 together, preceding ROMO to DMAb may be more hopeful treatment strategy

291 compared to preceding DMAb to ROMO.

292 There are several limitations to this study. Because of the small number of patients

293 included, the statistical power of the results (especially for the TPTD group) might be

294 attenuated. TPTD was treated for relatively short period (mean 10.7 months) with two

295 regimens (daily and weekly), BP group was heterogeneous (including both oral and

296 intravenous, with different frequency regimens), and relatively short duration of each

297 prior treatment may affect the results. Some patients received a different treatment prior

298 to the entry, although detailed information was unavailable. Because this was not a

299 randomized study, differences in patients' backgrounds may potentially affect the

300 physicians' treatment selection and subsequent effects. Larger randomized studies with

301 longer follow-up periods should be conducted in the future.

302 In conclusion, in this short-term follow-up study of postmenopausal patients with

303 osteoporosis who were introduced to ROMO, the Naïve group demonstrated the highest

304 treatment response as compared to the other groups, as evaluated by the increase in LS

305 and FN BMD. Prior antiresorptive treatment may attenuate the treatment response, and

306 prior anabolic treatment may have a smaller influence as compared with antiresorptive

307 treatment. These results may contribute to the selection of adequate subsequent

308 treatment by ROMO, although further investigations are required.

309

14

Availability of data and material

331 The dataset used or analyzed in the current study are available from the corresponding

332 author on reasonable request.

15

333

Consent for publication

335   Not applicable.

336

Figure legend

338   **Figure 1. Serum PINP value (a) and its percentage change (b), serum TRACP-5b**

339   **value (c) and its percentage change (d).**

340   PINP, N-terminal type I procollagen propeptide; TRACP-5b, isoform 5b of

341   tartrate-resistant acid phosphatase; BP, bisphosphonate; DMAb, denosumab; TPTD,

342   teriparatide. Bars indicate mean ± standard errors. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$;

343   difference between the two indicated groups. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$;

344   change from baseline within each treatment group.

345

346   **Figure 2. Percentage change of BMD in the lumbar spine (a), total hip (b), and**

347   **femoral neck (c).**

348   BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; BMD, bone mineral

349   density. Bars indicate mean ± standard errors. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$;

350   difference between the two indicated groups. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$;

351   change from baseline within each treatment group.

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1 **Table 1. Patients' clinical characteristics at baseline**

Variable	Naïve group (n = 37)	BP group (n = 33)	DMAb group (n = 45)	TPTD group (n = 15)	P-value
Age (years)	74.2 ± 6.6	74.4 ± 7.4	76.1 ± 7.7	75.5 ± 6.0	0.64
Body mass index (kg/m^2)	19.1 ± 1.5	18.8 ± 1.7	19.7 ± 1.8	20.0 ± 2.6	0.14
Prior vertebral fracture (%)	48.6	45.5	53.3	60.0	0.79
Prior non-vertebral fracture (%)	24.3	21.2	15.6	26.7	0.67
Prior osteoporosis treatment	None	ALN (weekly p.o. n = 8/monthly i.v. n = 1) RIS (weekly and monthly p.o. n = 15) IBN (monthly p.o. n = 2/monthly i.v. n = 2) MIN (monthly p.o. n = 3) ZOL (yearly i.v. n = 2)	DMAb 60mg (every 6 months)	Daily TPTD 20μg (n = 11) Weekly TPTD 56.5μg (n = 4)	N.A.
Duration of prior treatment (months)	0	28.0 ± 23.9	24.1 ± 15.8	10.7 ± 7.4	<0.001
Interval from final prior treatment prescription (months)	0	2.6 ± 3.5	6.2 ± 1.3	1.4 ± 1.3	<0.001
Combined VD, (n)	None (n = 0) ALF (n = 15) ELD (n = 22)	None (n = 2) ALF (n = 10) ELD (n = 21)	None (n = 0) ALF (n = 18) ELD (n = 27)	None (n = 0) ALF (n = 2) ELD (n = 13)	0.16
Combined VD, μg/day	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.7 ± 0.1	0.15
Combined Ca, % (n/N)	83.8 (31/37)	69.7 (23/33)	77.8 (35/45)	93.3 (14/15)	0.28
Combined Ca, mg/day	378.4 ± 304.7	430.3 ± 433.4	613.3 ± 594.5	380.7 ± 308.3	0.15
Lumbar spine BMD (g/cm^2)	0.652 ± 0.089	0.727 ± 0.121	0.705 ± 0.138	0.703 ± 0.109	0.04
Lumbar spine BMD (T-score)	−3.5 ± 0.8	−3.0 ± 0.9	−2.9 ± 1.2	−3.2 ± 0.9	0.09
Total hip BMD (g/cm^2)	0.615 ± 0.074	0.633 ± 0.081	0.573 ± 0.087	0.607 ± 0.095	0.03
Total hip BMD (T-score)	-2.5 ± 0.7	-2.4 ± 0.7	-2.7 ± 0.9	-2.6 ± 0.8	0.36
Femoral neck BMD (g/cm^2)	0.519 ± 0.076	0.568 ± 0.108	0.484 ± 0.087	0.539 ± 0.095	0.006

Femoral neck BMD (T-score)	−3.1 ± 0.6	−2.6 ± 0.7	−3.1 ± 0.8	−2.9 ± 0.9	0.03
Corrected serum Ca (mg/dl)	9.3 ± 0.4	9.5 ± 0.4	9.6 ± 0.6	9.5 ± 0.3	0.08
eGFR (ml/min/1.73 m^2)	70.8 ± 14.5	70.3 ± 18.3	65.1 ± 20.4	74.2 ± 17.6	0.34
PINP (μg/l)	72.7 ± 34.2	33.5 ± 30.1	30.4 ± 30.9	98.4 ± 75.7	<0.001
TRACP-5b (mU/dl)	474.7 ± 214.9	277.3 ± 140.7	220.3 ± 142.9	454.1 ± 200.7	<0.001
25(OH)D (ng/ml)	15.0 ± 4.4	16.1 ± 5.3	15.3 ± 7.0	14.2 ± 5.0	0.69

2   Mean ± standard deviation. % = number of patients with measurements / total number of patients.

3   Differences between the groups were determined by ANOVA or the Fisher's exact test.

4   BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; p.o., oral administration; i.v, intravenous;

5   ALN, alendronate; RIS, risedronate; MIN, minodronate; ZOL, zoledronate; VD, vitamin D; ALF,

6   alfacalcidol; ELD, eldecalcitol; Ca, calcium; BMD, bone mineral density; eGFR, estimated glomerular

7   filtration rate; PINP, Type I collagen N-terminal propeptide; TRAP-5b, isoform 5b of tartrate-resistant

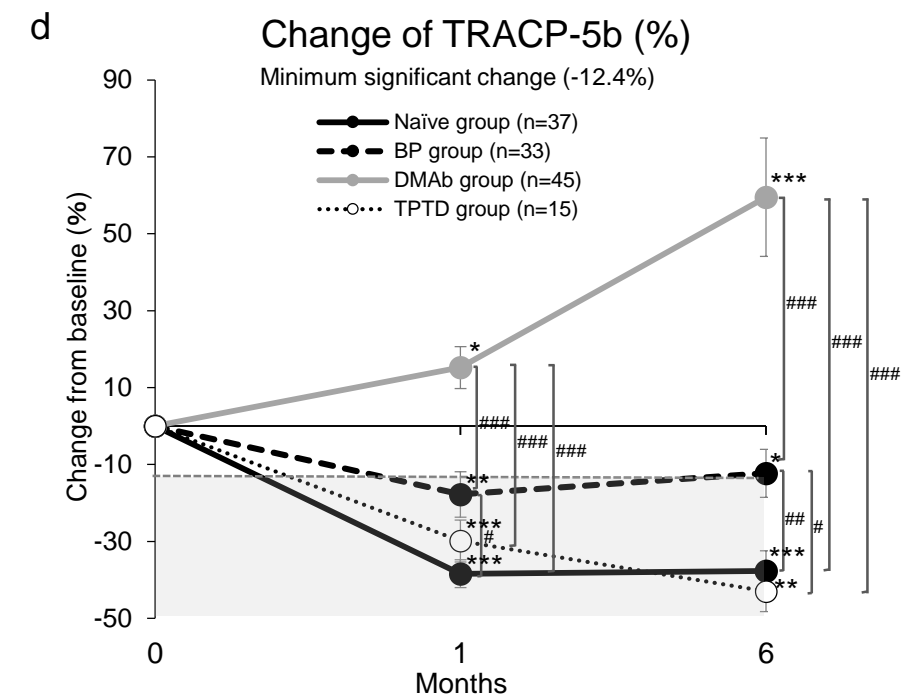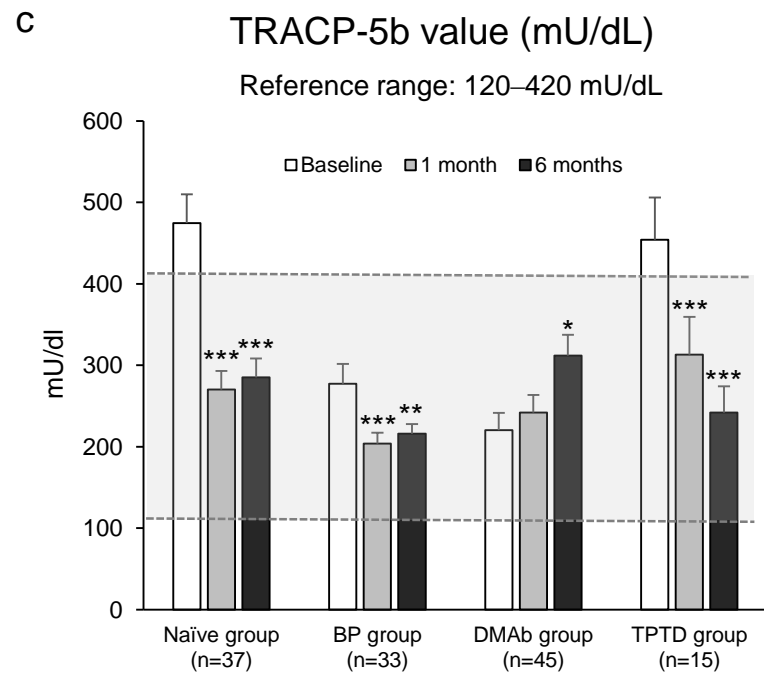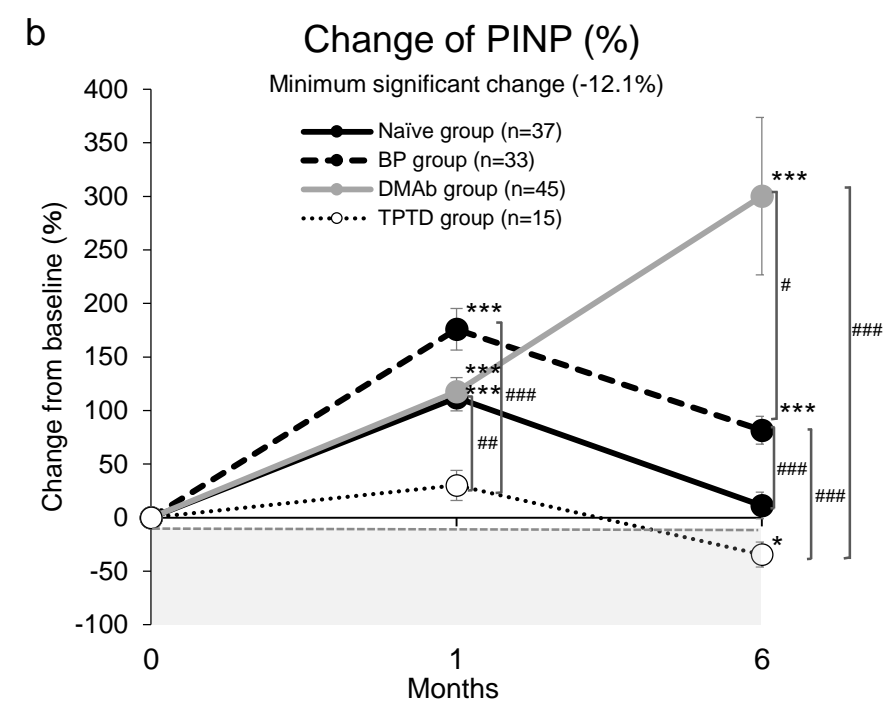8   acid phosphatase; 25(OH)D, 25-hydroxycholecalciferol.

9   .

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Figure 1

a PINP value (µg/L)
Reference range: 14.9–68.8 µg/L

b Change of PINP (%)
Minimum significant change (-12.1%)

c TRACP-5b value (mU/dL)
Reference range: 120–420 mU/dL

d Change of TRACP-5b (%)
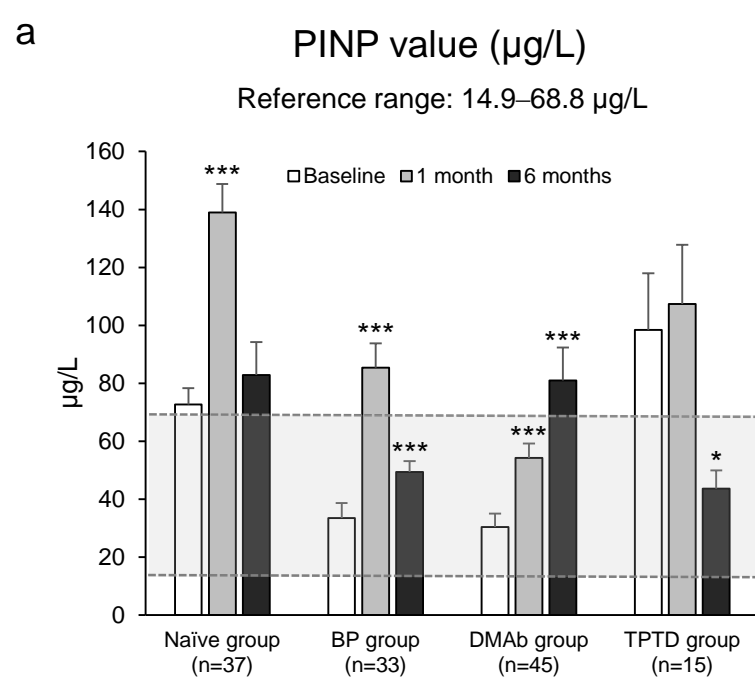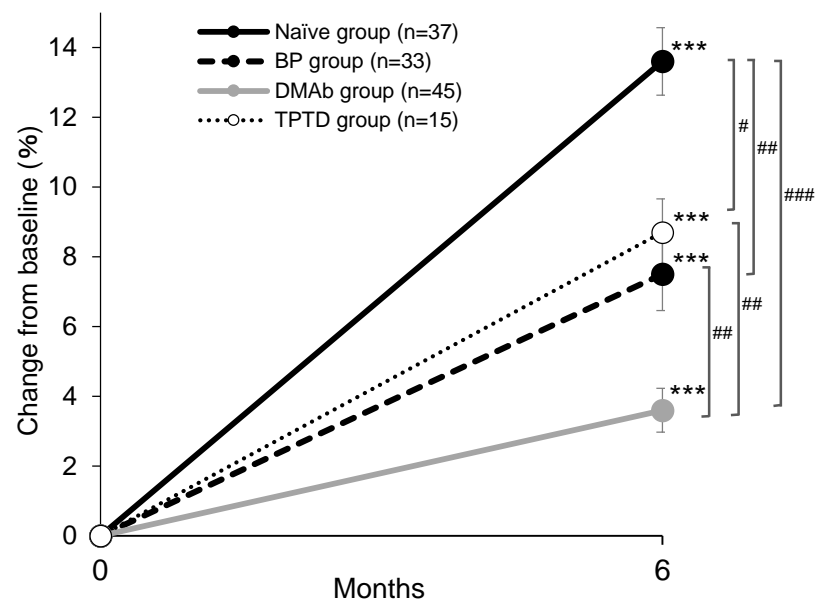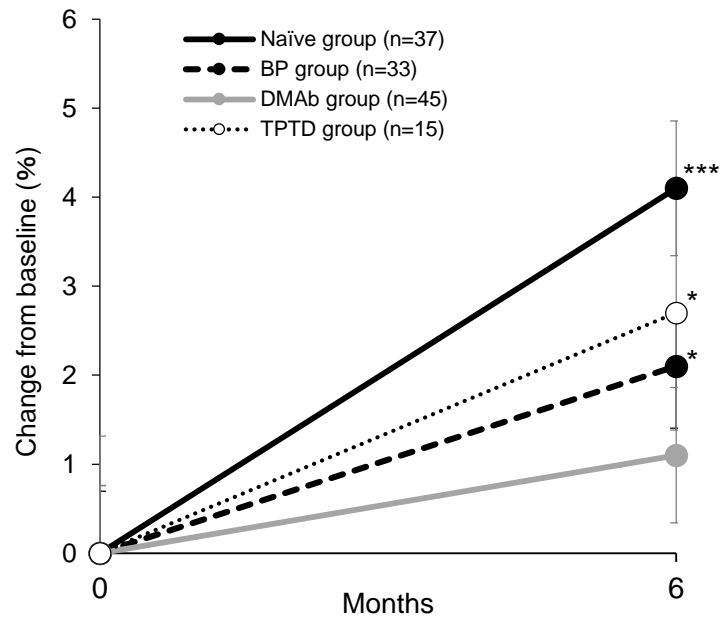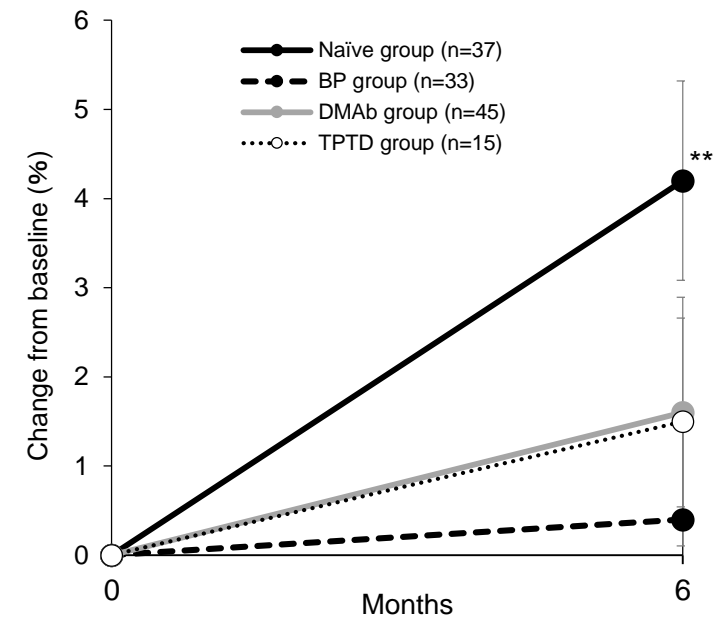Minimum significant change (-12.4%)

Figure 2

a   Change of lumbar spine BMD (%)

b   Change of total hip BMD (%)

c   Change of femoral neck BMD (%)

1 **Credit Author Statement**

2

3 **Kosuke Ebina:** Conceptualization, Data curation, Methodology, Validation, Visualization, Formal

4 analysis, Investigation, Resources, Project administration, Funding acquisition, Writing – Original

5 Draft, Writing – Review & Editing.

6 **Makoto Hirao:** Conceptualization, Project administration, Supervision.

7 **Hideki Tsuboi:** Data curation, Project administration, Supervision.

8 **Yoshio Nagayama:** Data curation, Project administration, Conceptualization.

9 **Masafumi Kashii:** Data curation, Conceptualization, Methodology, Writing – Review & Editing.

10 **Shoichi Kaneshiro:** Data curation, Methodology.

11 **Akira Miyama:** Data curation, Resources.

12 **Hiroyuki Nakaya:** Data curation, Resources.

13 **Yasuo Kunugiza:** Data curation, Resources.

14 **Gensuke Okamura:** Investigation, Resources.

15 **Yuki Etani:** Investigation, Resources.

16 **Kenji Takami:** Investigation, Resources.

17 **Atsushi Goshima:** Investigation, Resources.

18 **Ken Nakata:** Supervision, Funding acquisition.

19