Original Article

Baseline serum PINP level is associated with the increased bone mineral density in hip by romosozumab in patients with treatment-naïve postmenopausal osteoporosis

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Abstract

Purpose

Some patients fail to obtain a sufficiently increased hip bone mineral density (BMD) by romosozumab (ROMO) treatment. This study aimed to investigate the prognostic factor for increased hip BMD with ROMO in patients with treatment-naïve postmenopausal osteoporosis.

Methods

This prospective, observational, and multicenter study included patients (n = 63: mean age, 72.6 years; T-scores of the lumbar spine [LS], −3.3; total hip [TH], −2.6; femoral neck [FN], −3.3; serum type I procollagen N-terminal propeptide [PINP], 68.5 μg/L) treated by ROMO for 12 months. BMD and serum bone turnover markers were evaluated at each time point. A responder analysis was performed to assess the patient percentage, and both univariate and multivariate analyses were performed to investigate the factors associated with clinically significant increased BMD (≥3%) in both TH and FN.

Results

Percentage changes of BMD from baseline in the LS, TH, and FN areas were 17.5%, 4.9%, and 4.3%, respectively. In LS, 96.8% of patients achieved ≥6% increased LS-BMD, although 57.1% could not achieve ≥3% increased BMD in either TH or FN. Multiple regression analysis revealed that only the baseline PINP value was significantly and independently associated with ≥3% increased BMD in both TH and FN (p = 0.019, 95% confidence interval = 1.006–1.054). The optimal cut-off PINP value was 53.7 μg/L with 54.3% sensitivity and 92.3% specificity (area under the curve = 0.752).

Conclusions

In a real-world setting, baseline PINP value was associated with increased BMD of TH and FN by ROMO in treatment-naïve patients.

Keywords: Bone mineral density, Type I procollagen N-terminal propeptide, Postmenopausal osteoporosis, Responder analysis, Romosozumab

Mini Abstract

Baseline serum PINP value was significantly and independently associated with increased bone mineral density (≥3%) in both total hip and femoral necks by 12 months of romosozumab treatment in patients with treatment-naïve postmenopausal osteoporosis.

Introduction

Osteoporosis is a metabolic disease that is characterized by a progressive loss of bone mass and microarchitectural deterioration, leading to an increased risk of fragility fractures [1]. Among all osteoporotic fractures, the hip fracture has the greatest impact on morbidity, mortality, and health care costs [2,3]. Recent meta-regression analyses revealed that increased treatment-related bone mineral density (BMD), especially in the total hip (TH) and femoral neck (FN), was more strongly associated with all types of fracture reduction compared to the lumbar spine (LS) [4]. Thus, obtaining sufficient BMD in TH and FN is of great interest.

Initiating treatment with anabolic agents, such as teriparatide, abaloparatide, and romosozumab (ROMO), is recommended in patients at a high risk of fracture to promptly reduce the imminent fracture risk [1,5,6]. ROMO is a humanized monoclonal antisclerostin antibody that rapidly increases bone mass by increasing bone formation and decreasing bone resorption, in contrast to teriparatide and abaloparatide, which stimulate both bone formation and bone resorption [7,8]. Presently, ROMO is recommended as a first-line drug for osteoporosis with extremely low BMD in both LS and hip [9]. The FRAME study revealed that ROMO treatment for 12 months increased BMD by approximately 13.3%, 6.9%, and 5.9% in LS, TH, and FN, respectively, in patients with treatment-naïve postmenopausal osteoporosis [10]. Previous studies identified the clinically significant increased BMD, which represents the least significant change, as 3% in three measured sites by ROMO treatment [11,12]. Previous well-organized studies showed the positive effects of ROMO in increasing hip BMD [7,10,11,12,13], and 96% and 78% of patients who obtained ≥3% increased BMD by 12 months of ROMO treatment was in LS and TH, respectively [11].

In March 2019, Japan became the first country to approve the use of ROMO, and its clinical data based on the real-world setting is of great interest. We previously reported that BMD increase induced by ROMO was significantly diminished by the prior anti-bone resorptive treatment [14,15], and the increased BMD in LS, TH, and FN in treatment-naïve patients was similar to that reported in Japanese populations of the FRAME study [12]. However, we realized that some patients show difficulty in increasing TH or FN-BMD by ROMO treatment in a real-world setting. Tominga et al. reported that the mean percent change in the TH-BMD was below the least significant change and suggested that ROMO showed minor effect in TH-BMD increase of treatment-naïve patients [16]. Therefore, this study aimed to investigate surrogate biomarkers for predicting increased hip BMD to distinguish the therapeutic responders from nonresponders by ROMO treatment.

Methods

Study design and participants

This open-label, prospective study was conducted in six centers. Female patients who were firstly diagnosed with postmenopausal osteoporosis with a high risk of osteoporotic fracture, and were never administrated osteoporosis agents were recruited from March 2019 to October 2021. All patients were subcutaneously administered ROMO at 210 mg every month for 12 months, and completed this treatment. A high risk of osteoporotic fracture is defined according to the World Health Organization 1998 definition or the diagnostic criteria for primary osteoporosis used by the Japanese Society of Bone Metabolism and the Japanese Osteoporosis Society [17]: patients with (1) BMD T-score of <-2.5 and ≥ 1 fragility fracture, (2) LS-BMD

T-score of <−3.3, (3) ≥2 vertebral fractures, (4) semiquantitative grade of 3 vertebral fracture [18]. The exclusion criteria were as follows: patients who received previous osteoporosis agents, patients with contraindications to ROMO (who had major cardiovascular events within a past year), patients with diseases affecting bone metabolisms, such as thyroid or parathyroid diseases, those undergoing hormone replacement therapy, those with cancer undergoing radiation therapy involving the skeleton, those with suspicion of osteomalacia (who showed low serum levels of 25(OH)D, calcium, and phosphorus, and also high serum levels of alkaline phosphatase and intact parathyroid hormone), or those with severely impaired renal function (estimated glomerular filtration rate of <30 mL/min/1.73 m^2).

The study was conducted following the Declaration of Helsinki and with the approval of the ethical review boards of Osaka University Graduate School of Medicine (approval no. 18258; Osaka University, Graduate School of Medicine) and each of the institutes involved. Informed consent was obtained from the patients, and opt-out information was posted on the hospital's homepage.

Clinical assessments

Age, height, weight, and body mass index (BMI) were recorded for all study participants at recruitment. Medical history, including osteoporotic fracture history and the presence or absence of prevalent vertebral or nonvertebral fractures, was assessed.

Radiological assessment

Frontal and lateral whole-spine radiographs (T4–L4) were obtained at baseline and 12 months

after ROMO administration. The presence or absence of vertebral deformity in the coronal and sagittal planes occurring after vertebral fractures was also assessed.

BMD values were measured by dual-energy X-ray absorptiometry (DXA) (Horizon W; Hologic, Inc., Marlborough, MA, USA / PRODIGY; GE Healthcare, Tokyo, Japan) at baseline and 12 months after ROMO administration. Areal BMD of LS (L1–4), FN, and TH were assessed by DXA. A BMD T-score was calculated for all measured sites. Percent coefficient of variation for L1-L4 was 0.63% in Horizon, and 0.41% in PRODIGY. BMD data were standardized using the reference data obtained from the Japanese population by each equipment according to the correction method proposed by the Japan Osteoporosis Society and the International Society for Clinical Densitometry Guidance [19]. The BMD measurements excluded the regions of severe sclerosis with a degenerative spine, vertebral fractures, and surgical sites.

Biochemical examination

Blood samples were collected in the morning after an overnight fast, and routine serum chemistry tests were performed using standard automated techniques. Bone turnover markers were measured at baseline and 1, 6, and 12 months during the ROMO treatment. Total type I procollagen N-terminal propeptide (PINP; interassay coefficient of variation ≤5.0%; Roche Diagnostics, Basel, Switzerland) was assessed as a bone formation marker. Tartrate-resistant acid phosphatase 5b (TRACP-5b; Osteolinks TRAP5b; interassay coefficient of variation ≤ 9.0%; SB Bioscience Co. Ltd., Tokyo, Japan) was measured as a bone resorption marker. Serum 25-dihydroxy vitamin D (25[OH]D) was measured by electrochemiluminescence immunoassay

(Roche Diagnostics) as previously described [20].

Statistical analysis

BMD and bone turnover marker changes were evaluated based on the percentage change from baseline. The primary efficacy outcome was the percentage change in BMD from baseline in the LS, TH, and FN areas at 12 months. A responder analysis was performed to assess the percentage of patients with any BMD changes from baseline of varying magnitudes (≥0%, ≥3%, ≥6%, and ≥10% from baseline) at the LS, TH, and FN areas at 12 months [12]. A recent meta-regression analysis revealed that more than 3.18% increase in TH BMD by osteoporosis treatment was significantly associated with hip fracture reduction [4]. The clinically significant increased BMD, which represents the approximate least significant change, was set as 3% in three measured sites according to the previous studies [11,12]. The cut-off value to distinguish the responder and nonresponder regarding the increased hip area BMD was set as 3%, and various parameters were analyzed between the two groups.

Categorical variables are presented as frequencies and percentages. Continuous data were expressed as means or means ± standard deviation. Two-sided probability values of $P < 0.05$ were considered statistically significant. The Mann–Whitney U test, chi-square test, and Fisher exact test were used for the statistical analysis of comparisons between the two groups. Changes in paired data were analyzed using the Wilcoxon signed-rank test.

Multivariate logistic regression analysis was performed to identify the prognostic factors for ≥3% of increased hip area BMD. Univariate analysis was initially performed to identify explanatory variables (including all items of medical history, biochemical examination, and

radiographic examination) with *P*-values of <0.20. Then, multivariate analysis was performed using possible variables, such as age and BMI [21], and also explanatory variables which were selected by univariate analysis. We computed the odds ratio and 95% confidence interval (CI) using the proportional odds model in logistic regression to express the associations between ≥3% of increased hip area BMD and explanatory variables. Receiver operating characteristic (ROC) curves were constructed to determine the best cut-off value of baseline serum PINP levels discriminating hip BMD responder and non-responder subsets (≥3% increase in both TH and FN BMD). The area under the ROC curve (AUC) was calculated as a measure of the overall discriminative ability of baseline serum PINP levels. The cut-off point was identified as the one closest to the sensitivity 1.0 and specificity 1.0 ~~(0, 1)~~ point [22], and also using Youden's index. Statistical analyses were performed using JMP software (version 12.2.0; SAS Institute, Inc., Cary, NC, USA).

Results

Baseline characteristics

Table 1 shows the demographic data for all 63 females (mean age, 72.6 years) who met the criteria for high risk of osteoporotic fracture. The mean BMI was 20.9 kg/m^2, and BMD T-score was −3.3 in LS, −2.6 in TH, and −3.3 in FN. Regarding serum bone turnover markers, PINP was 68.5 μg/L and TRACP-5b was 510 mU/dL. The active form of vitamin D supplementation (alfacalcidol: 28.5%, eldecalcitol: 66.7%) was given to 60 (95.2%) patients, and 74.6% of all patients received calcium supplementation. The average level of serum 25(OH)D was 15.7 ng/mL, and 49 (78%) patients were vitamin D-deficient (25(OH)D level < 20 ng/mL).

Changes in BMD and responder analysis

The increased BMD from baseline was 17.5% in LS, 4.9% in TH, and 4.3% in FN, respectively, after 12 months of ROMO treatment. Regarding LS-BMD, 98.4%, 96.8%, and 82.5% of patients achieved ≥3%, ≥6%, and ≥10% increase, respectively (Fig. 1a). Only one patient experienced a <0% increase.

Conversely, regarding TH-BMD, only 59.3%, 35.2%, and 16.7% of patients achieved ≥3%, ≥6%, and ≥10% increased BMD, respectively (Fig. 1b). Regarding FN-BMD, similar to TH, only 54.5%, 32.7%, and 18.2% of patients achieved ≥3%, ≥6%, and ≥10% increased BMD, respectively (Fig. 1c). A clinically significant increased BMD (≥3%) in either TH or FN could not be achieves by 57.1% of patients, and 44.4% failed to achieve the ≥0% increased BMD in either TH or FN.

Bone turnover markers

The serum PINP level (Fig. 2a) and its percentage change (Fig. 2b) as well as TRACP-5b level (Fig. 2c) and its percentage change (Fig. 2d) are shown. PINP level reached its highest value at 1 month, followed by a gradual decrease from 6 months onwards. TRACP-5b level showed marked decrease from 1 month onwards.

Prognostic factor which affects the treatment response for hip BMD

We made three pairings responder and nonresponder groups according to the treatment response for hip BMD as follows: 1) ≥3% TH-BMD vs. <3% TH-BMD, 2) ≥3% FN-BMD vs.

<3% FN-BMD, and 3) ≥3% BMD in both TH and FN vs. <3% BMD in either TH or FN (Table 2). Among all three configured parings, univariate analysis revealed that absolute PINP value at baseline was significantly higher in the responder group than in the nonresponder group (mean PINP value; ≥3% TH-BMD [79.0] vs. <3% TH-BMD [55.5], p = 0.004; ≥3% FN-BMD [78.3] vs. <3% FN-BMD [58.7], p = 0.017, ≥3% TH- and FN-BMD [81.9] vs. <3% TH- or FN-BMD [58.1], p = 0.004). In comparison between the "≥3% TH-BMD vs. <3% TH-BMD" and "≥3% TH- and FN-BMD vs. <3% TH- or FN-BMD," the absolute PINP level at 1 month after ROMO administration was significantly higher in the responder group than in the nonresponder group, but without significant differences in both percentage changes from baseline, as well as the amount of PINP change from baseline (Table 2). Furthermore, no significant differences were found between the responder and nonresponder groups regarding bone resorption marker, TRACP-5b. In comparison between the "≥3% FN-BMD vs. <3% FN-BMD" and "≥3% TH- and FN-BMD vs. <3% TH- or FN-BMD," the FN-BMD T-score at baseline was significantly lower in the responder group than in the nonresponder group. Results were similar when the cut-off value was changed from 3% to 0% (data not shown).

The multiple regression analysis using explanatory variables (age, BMI, presence of prevalent nonvertebral fracture, FN-BMD T-score at baseline, and PINP value at baseline) revealed that only PINP value (/1 μg/L) at baseline was significantly and independently associated with ≥3% increased both TH- and FN-BMD (odds ratio = 1.028, p = 0.019, 95% CI = 1.006–1.054) (Table 3).

The ROC curves and AUC results for predicting ≥3% increase in both TH- and FN-BMD are shown in Fig. 3. The optimal PINP cut-off at baseline was 53.7 μg/L with 54.3% sensitivity and

92.3% specificity (AUC = 0.752). When cut-off value was set at 53.7 μg/L, positive predictive value was 58.5% (n = 24/41), and negative predictive value was 90.9% (n = 20/22).

Discussion

To our best knowledge, this is the first study to investigate the surrogate biomarker for increased hip BMD in osteoporosis treatment-naïve patients treated with ROMO. This study revealed that the baseline serum level of PINP, which is a bone formation marker, was identified as a unique factor to distinguish the therapeutic responders from nonresponders for increased BMD. A Higher PINP level before treatment predicts a greater increased hip BMD, and its optimal cut-off value for clinically significant increased BMD (≥3%) at both TH and FN was 53.7 μg/L.

The average percent change at 12 months was 17.5% for the efficacy of ROMO for increased LS-BMD, and 96.8% of subjects experienced ≥6% increase. Compared with the FRAME study results [10,11,12], these results in LS were similar, and the number of poor responders to ROMO in LS-BMD was minimal.

However, almost half of the patients in this study could not achieve a clinically significant increased BMD (≥3%) at either TH or FN areas, and 44.4% of the patients had no BMD gain (≥0%) at either TH or FN areas, contrary to the efficacy of ROMO for the LS-BMD. The global FRAME study revealed that 78% of the patients obtained ≥3% increased TH-BMD by ROMO treatment [11], although the percentage decreased to 65.5% in the Japanese population [12], which was similar to the present study (59%). The patients' background data of the Japanese population in the FRAME study was quite similar to that of our present study in age, BMI, and

TH-BMD T-score at baseline [12].

The differences between these studies were race, BMI (the global FRAME study [24.5 kg/m^2], Japanese population of the FRAME study [21.3 kg/m^2], and the present study [20.9 kg/m^2]), and serum 25(OH)D value (the global FRAME study [>20 ng/mL], Japanese population of the FRAME study [30.8 kg/m^2], and the present study [15.7 ng/mL]) [10,12].

Ominsky et al. advocated that increased FN-BMD by osteoporosis treatment may result from 1) modeling-based bone formation, 2) bone mineralization, and 3) remodeling space closure [23]. Regarding bone modeling, lower BMI may lead to decreased mechanical loading and consequent promotion of sclerostin expression with modeling inhibition [24], and lower BMI in the elderly is associated with the risk of osteoporosis [25]. At first, we speculated that lower BMI in the Japanese population may diminish the effects of ROMO, although BMI did not show any tendency or significant correlation with increased hip BMD in this study.

Regarding bone mineralization, patients with baseline 25(OH)D levels of <20 ng/mL were excluded from the global FRAME study [10]. In this study, 78% of patients showed vitamin D deficiency (25[OH]D <20 ng/mL) at baseline. However, 95.2% of subjects received an active form of vitamin D supplementation (alfacalcidol or eldecalcitol). These active forms of vitamin D showed superior effects in calcium uptake [26] and increased BMD in combination with bisphosphonates [27] or denosumab [28,29] compared to native vitamin D. Tominga et al. concluded that ROMO had minor effect on increased TH-BMD, but only 5% of patients received vitamin D supplementation, which may strongly affect their study results [16]. Additionally, serum 25(OH)D levels did not show any correlation with serum PINP levels in a large cohort study (n = 4822) of postmenopausal women although vitamin D may promote

osteoblast differentiation [30]. The present study revealed no significant correlation between baseline serum 25(OH)D and PINP levels (p = 0.26). Taken together, baseline vitamin D deficiency may not affect serum PINP level, and ROMO in combination with active vitamin D is in no way inferior to that of native vitamin D regarding bone mineralization.

Regarding remodeling space closure, serum TRACP-5b level decreased from 1 month after ROMO administration, although no significant differences were observed in both absolute value and decreasing value between the responder and nonresponder groups. Ominsky et al. investigated the effects of sclerostin antibody in cynomolgus monkeys and revealed bone histomorphometry analysis demonstrated that the initial rapid increase in bone formation on femur endocortical surfaces is mainly derived from modeling-based bone formation, not from remodeling-based bone formation [23,31]. The present study suggest that increased hip BMD in ROMO treatment may depends on the baseline bone formation status, but not on bone resorption inhibition. In addition, there was a significant difference in the absolute value of serum PINP levels at both baseline (P=0.004) and one month (P=0.010), although no significant difference was observed after 6 months between the responder and non-responder group (Table 2). These results were similar to our previous report demonstrating that increase of TH BMD by 18-months of daily teriparatide administration was significantly associated with baseline serum PINP levels, but not with its later change in patients with postmenopausal osteoporosis [32]. Taken together, individuals who have more active bone formation status at early time course (from baseline to 1 month) may have advantages in BMD increase of hip by 12-months ROMO administration.

This study has some limitations. First, this study included a relatively small number of subjects

which may weaken the statistical power, and further studies with larger sample sizes may be required in the future. Second, this study included only Japanese patients; thus, the results may not be generalizable to other populations. Third, this study was a single arm and not a randomized controlled study. Fourth, we failed to monitor serum CTX as a bone resorption marker. Fifth, difference of DXA data between Horizon W and PRODIGY was not corrected. However, this study focused on the change of BMD, so we assume that the difference of the DXA model may have minor effects on the results. In conclusion, this study demonstrated for the first time that baseline serum PINP level is significantly and independently associated with increased BMD in hip by ROMO treatment, which may provide useful information in predicting its effect in a real-world setting.

Statements and Declarations

Author contributions

Study design: MK and KE. Study conduct: MK, TK, and KE. Data collection: MK, TK, HT, YN, AM, and KE. Data analysis: MK and KE. Data interpretation: MK and KE. Drafting the manuscript: MK and KE. Approving the final version of the manuscript: MK, TK, HT, YN, AM, and KE. KE takes responsibility for the integrity of the data analysis.

Conflict of interest

MK has received payments for lectures from Amgen, Asahi-Kasei, Astellas, Mochida, and Teijin Pharma. KE is affiliated with the Department of Musculoskeletal Regenerative Medicine, Osaka University, Graduate School of Medicine, which is supported by Taisho. KE has received research grants from Amgen, Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, and Ono. KE has received payments for lectures from Amgen, Asahi-Kasei, Astellas, Chugai,

Daiichi Sankyo, Eisai, Eli Lilly, Ono, and Pfizer. HT has received a research grant from Chugai and has received payments for lectures from Asahi-Kasei, Astellas, Chugai, Eisai, Eli Lilly, and Pfizer. YN has received payments for lectures from Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, and Ono. TK and AM declare that they have no conflicts of interest. The funders had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Figure legends

Fig. 1 Percent change in bone mineral density (BMD) from baseline to 12 months after romosozumab administration [(a) Lumbar spine, (b) Total hip, (c) Femoral neck].

The x-axis represents each subject. Dotted horizontal lines reflect 3%, 6%, and 10% responses relative to baseline. Dotted vertical lines which cross the x-axis represent the percentage of patients with the indicated percent changes in BMD (≥3%, ≥6%, and ≥10%). The black arrow represents the percentage of patients with <0% change in BMD.

Fig. 2 Serum PINP level (a) and its percentage change (b); serum TRACP-5b level (c) and

its percentage change (d)

PINP, N-terminal type I procollagen propeptide; TRACP-5b, isoform 5b of tartrate-resistant acid phosphatase.

Fig. 3 Receiver operating characteristic (ROC) curve to determine the best cut-off value of baseline serum PINP level to predict ≥3% BMD increase in both TH and FN.

TH, total hip; FN, femoral neck; BMD, bone mineral density; AUC, area under the curve.

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Table 1. Baseline characteristics of osteoporosis treatment-naïve patients receiving romosozumab

Characteristics (n=63)	
Age (years)	72.6 ± 7.5
BMI (kg/m^2)	20.9 ± 2.9
Presence of prevalent OVF	29 (46.0%)
No. of prevalent OVF confirmed by whole-spine radiographs (T4-L4)	1.2 ± 1.8
Presence of prevalent nonvertebral fracture	13 (20.6%)
Combined active form of vitamin D supplementation (dose [μg/day])	Alfacalcidol: 28.5% (0.47 ± 0.27) Eldecalcitol: 66.7% (0.70 ± 0.10) None: 4.9%
Combined calcium supplementation (dose [mg/day])	74.6% (421 ± 192)
LS-BMD (g/cm^2)	0.65 ± 0.13
LS-BMD T-score	−3.3 ± 1.1
TH-BMD (g/cm^2)	0.61 ± 0.08
TH-BMD T-score	−2.6 ± 0.8
FN-BMD (g/cm^2)	0.51 ± 0.08
FN-BMD T-score	−3.3 ± 0.7
eGFR (ml/min/1.73m^2)	72.5 ± 15.5
PINP (μg/L)	68.5 ± 32.6
TRACP-5b (mU/dL)	510 ± 230
25 (OH) D (ng/mL)	15.7 ± 5.2

Values are shown as mean ± standard deviation.

BMD, bone mineral density; *BMI*, body mass index; *OVF*, osteoporotic vertebral fracture; *eGFR*, estimated glomerular filtration rate; *FN*, femoral neck; *LS*, lumbar spine; *PINP*, type I collagen N-terminal propeptide; *TRACP-5b*, tartrate-resistant acid phosphatase 5b; *25(OH)D*, 25-hydroxycholecalciferol.

Table 2

Table 2. Univariate analysis of characteristics of patients receiving romosozumab for 12 months: with or without ≥3% hip BMD increase

Valuables	**≥3% TH-BMD** (*N*=34)	**<3% TH-BMD** (*N*=29)	P value	**≥3% FN-BMD** (*N*=31)	**<3% FN-BMD** (*N*=32)	P value	**≥3% TH- and FN-BMD** (*N*=27)	**<3% TH- or FN-BMD** (*N*=36)	P value
Baseline									
Age (years)	72.2	73.1	0.641	71.5	73.7	0.270	70.9	73.79	0.107
BMI (kg/m^2)	20.6	21.2	0.558	21.3	20.5	0.254	21.3	20.6	0.324
Presence of prevalent vertebral fracture	41%	59%	0.064	48%	52%	0.892	44%	47%	0.827
Presence of prevalent nonvertebral fracture	27%	14%	0.215	32%	9%	0.025*	33%	11%	0.057
LS- BMD T-score	-3.6	-3.0	0.057	-3.4	-3.2	0.890	-3.5	-3.2	0.656
TH-BMD T-score	-2.7	-2.4	0.128	-2.7	-2.5	0.183	-2.8	-2.4	0.058
FN-BMD T-score	-3.3	-3.2	0.419	-3.5	-3.5	0.037*	-3.5	-3.1	0.014**
eGFR (ml/min/1.73m^2)	74.9	69.7	0.215	74.2	70.8	0.488	74.6	71.0	0.433
0M-PINP (μg/L)	79.0	55.5	0.004**	78.3	58.7	0.017*	81.9	58.1	0.004**
0M-TRACP-5b (mU/dL)	539	476	0.281	501	519	0.759	530	496	0.565
25 (OH) D (ng/mL)	16.5	14.8	0.221	15.4	16.0	0.645	15.7	15.8	0.923
1 month after starting Tx									
1M-PINP (μg/L)	144.5	115.6	0.034*	143.9	118.0	0.058	150.7	115.8	0.010**
ΔPINP (1M-0M)	65.3	59.0	0.545	65.7	59.0	0.516	68.8	57.3	0.263
% change of PINP (1M-0M)	101%	110%	0.367	101%	119%	0.347	100%	117%	0.408
1M-TRACP-5b (mU/dL)	320	295	0.487	323	293	0.406	332	290	0.235
ΔTRACP-5b(1M-0M)	-210	191	0.551	-178	-215	0.663	-197	-196	0.974
% change of TRACP-5b (1M-0M)	-31%	-33%	0.771	-30%	-34%	0.695	-32%	-32%	0.986
6 months after starting Tx									
6M-PINP	74.5	56.7	0.097	72.3	61.1	0.295	75.4	59.8	0.141
ΔPINP (6M-0M)	-4.5	0.8	0.582	-5.5	1.1	0.495	-6.5	1.3	0.423
% change of PINP (6M-0M)	2%	12%	0.544	3%	9%	0.729	-1%	11%	0.471
6M-TRACP-5b	312	279	0.283	296	299	0.925	306	290	0.611
12 months after starting Tx									
12M-PINP	51.7	49.1	0.817	48.9	53.0	0.704	50.3	51.1	0.936
12M-TRACP-5b	268	282	0.743	247	309	0.146	255	293	0.412

Values are shown as mean ± standard deviation.

$p < 0.05$ was considered a statistically significant difference (*$p < 0.05$, **< 0.01).

BMD, bone mineral density; *BMI*, body mass index; *eGFR*, estimated glomerular filtration rate; *FN*, femoral neck; *LS*, lumbar spine; *PINP*, type I collagen N-terminal propeptide; *TRACP-5b*, tartrate-resistant acid phosphatase 5b; *Tx*, treatment; *25(OH)D*, 25-hydroxycholecalciferol; *Δ*, amount of change; *0M*, at baseline; *1M*, 1month after starting treatment; *6M*, 6months after starting treatment; *12M*, 12months after starting treatment.

Table 3

Table 3. Results of multiple regression analysis: factors associated with ≥3% increase in both total hip and femoral neck BMD ~~increase~~ versus without its increase

Explanatory variables	P value	OR (95%CI)
Age (/1 year)	0.341	0.959 (0.878－1.045)
BMI (/1 kg/m^2)	0.095	1.193 (0.976－1.485)
Presence of prevalent nonvertebral fracture (yes= 1, no= 0)	0.154	3.073 (0.683－16.081)
FN-BMD T-score (/1 unit)	0.253	0.584 (0.222－1.450)
0M-PINP (/1 μg/L)	0.019*	1.028 (1.006－1.054)

$p < 0.05$ was considered a statistically significant difference (*$p < 0.05$).

BMD, bone mineral density; *BMI*, body mass index; *CI*, confidence interval; *FN*, femoral neck; *OR*, odds ratio; *PINP*, type I collagen N-terminal propeptide; *0M*, at baseline.

Figure 1

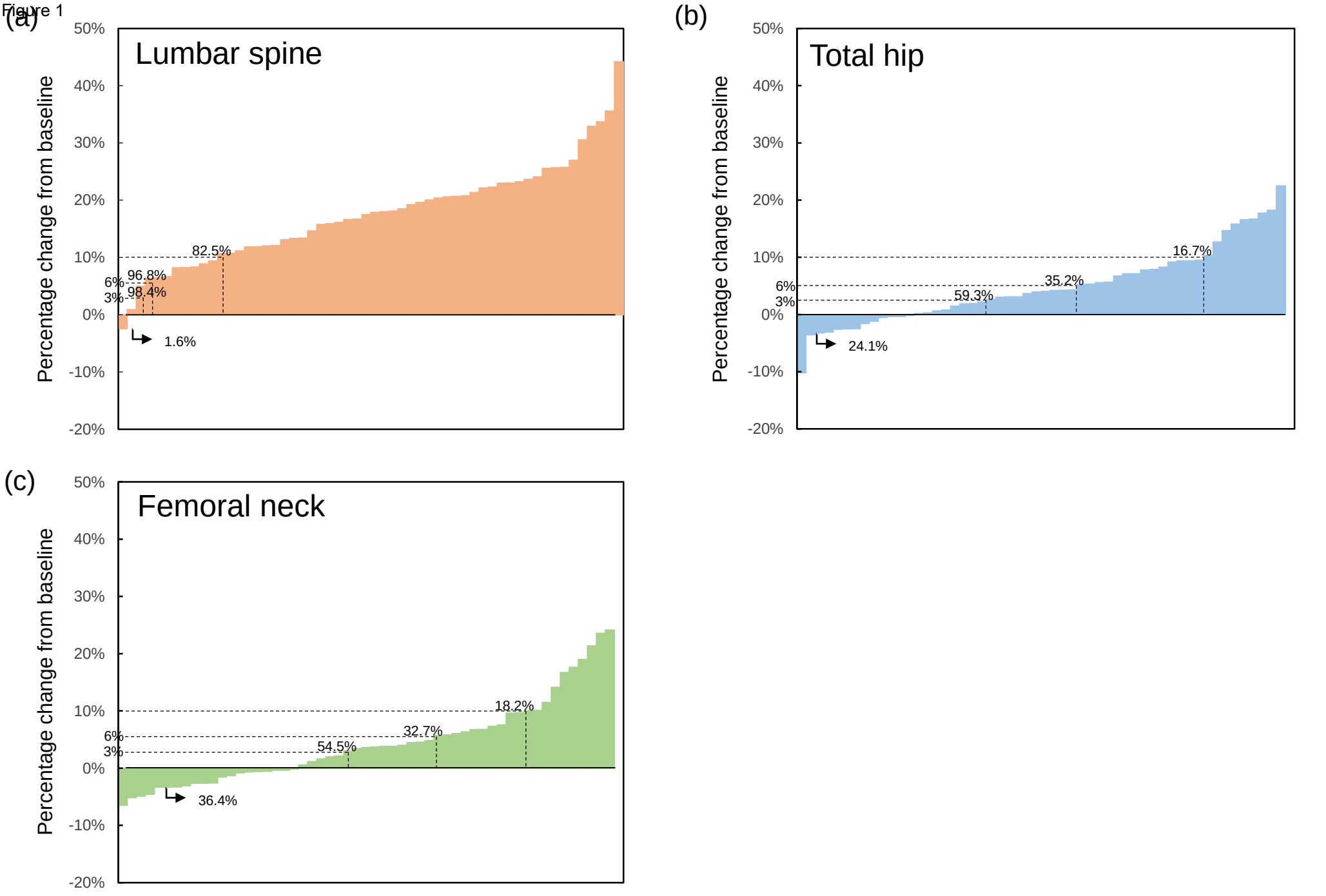

(a)
Lumbar spine
Percentage change from baseline
50%
40%
30%
20%
10%
6%
3%
0%
-10%
-20%
82.5%
96.8%
98.4%
1.6%
(b)
Total hip
Percentage change from baseline
16.7%
35.2%
59.3%
24.1%
(c)
Femoral neck
Percentage change from baseline
18.2%
32.7%
54.5%
36.4%

Figure 2

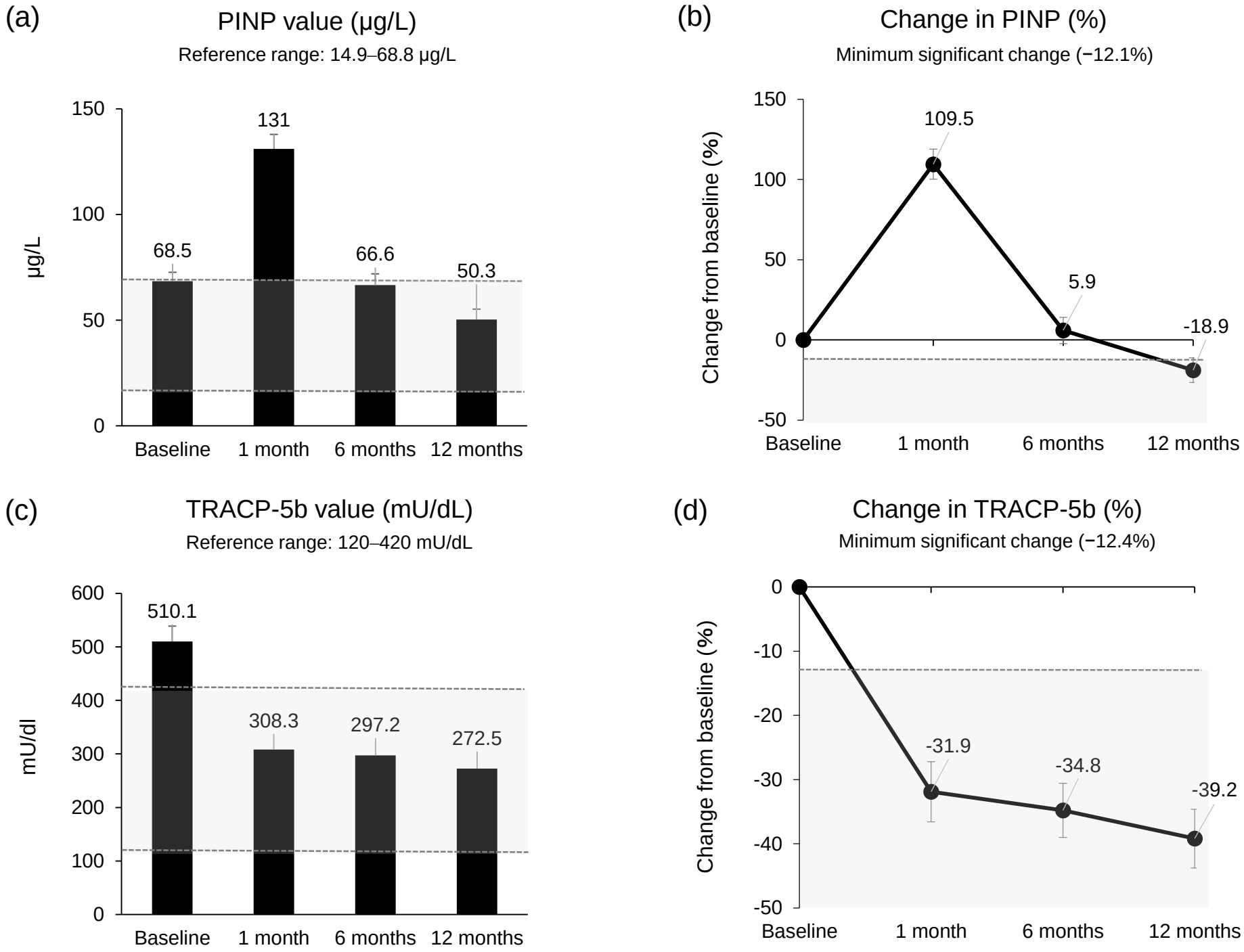
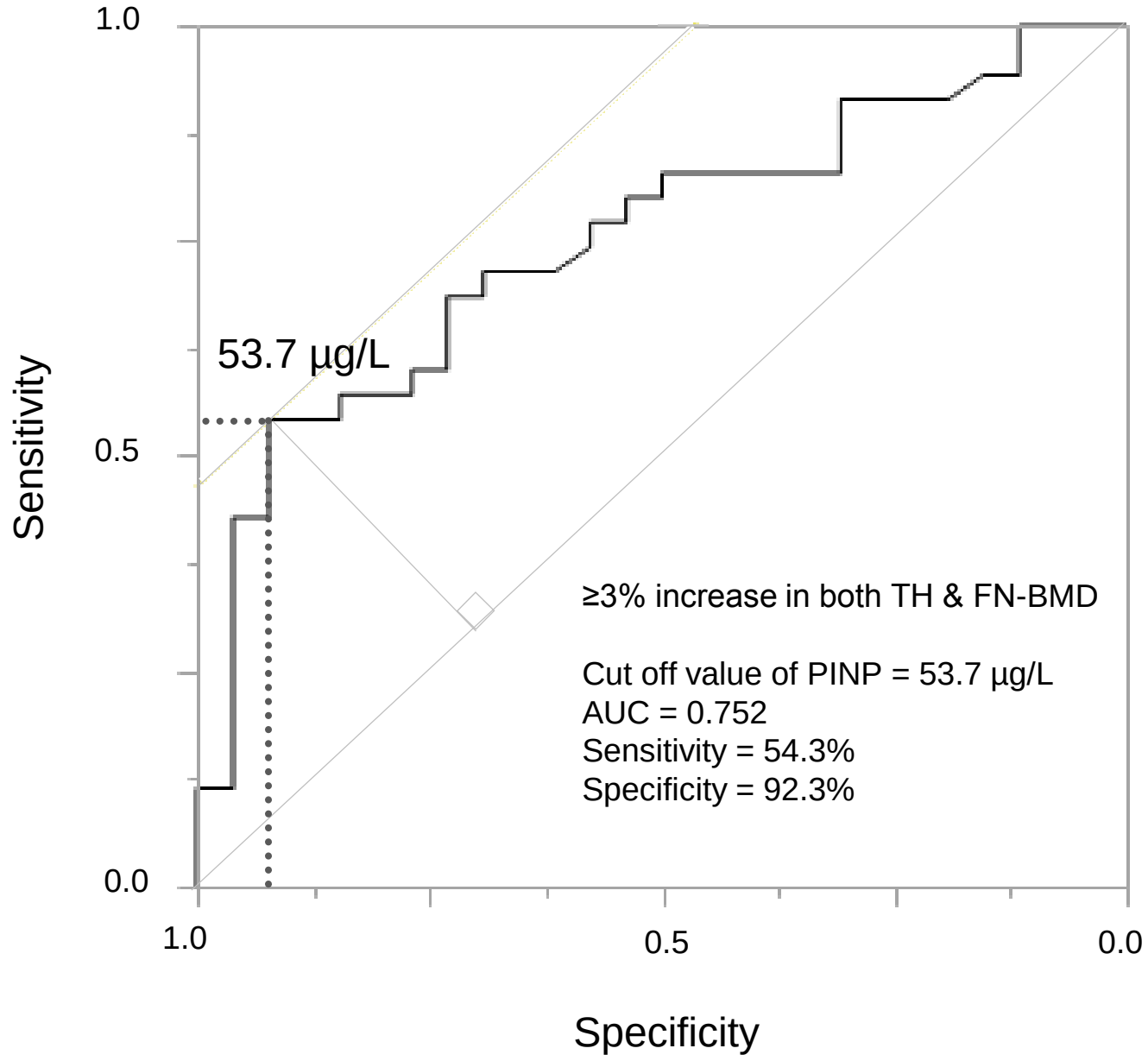

(a)
PINP value (μg/L)
Reference range: 14.9–68.8 μg/L
μg/L
150
100
50
0
68.5
131
66.6
50.3
Baseline
1 month
6 months
12 months
(b)
Change in PINP (%)
Minimum significant change (−12.1%)
Change from baseline (%)
150
100
50
0
-50
109.5
5.9
-18.9
Baseline
1 month
6 months
12 months
(c)
TRACP-5b value (mU/dL)
Reference range: 120–420 mU/dL
mU/dl
600
500
400
300
200
100
0
510.1
308.3
297.2
272.5
Baseline
1 month
6 months
12 months
(d)
Change in TRACP-5b (%)
Minimum significant change (−12.4%)
Change from baseline (%)
0
-10
-20
-30
-40
-50
-31.9
-34.8
-39.2
Baseline
1 month
6 months
12 months

Figure 3


1.0
0.5
0.0
Sensitivity
53.7 µg/L
≥3% increase in both TH & FN-BMD
Cut off value of PINP = 53.7 µg/L
AUC = 0.752
Sensitivity = 54.3%
Specificity = 92.3%
1.0
0.5
0.0
Specificity