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ORIGINAL ARTICLE

Potential association with early changes in serum calcium level after starting or switching to denosumab combined with eldecalcitol

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Abstract

The aims of this study are to investigate changes in serum calcium (Ca) level after switching from either non-therapy, bisphosphonate, selective estrogen receptor modulators (SERM) or teriparatide treatments to a combination therapy of denosumab (DMAb), and eldecalcitol, and the association between early changes in serum calcium and changes in bone metabolic markers and bone mineral density (BMD). 129 patients with postmenopausal osteoporosis (32 non-pretreatment, 50 bisphosphonates, 18 SERM, and 29 teriparatide) were recruited and switched to DMAb plus eldecalcitol. Serum calcium levels, bone metabolism markers, and BMD measurements of the lumbar spine and femoral neck were evaluated. All groups showed an increase in BMD 6 months and 1 year after DMAb administration compared to baseline via suppression of bone metabolism markers. The TPD group showed a significant decrease in serum calcium level 1 week after the first injection of DMAb and eldecalcitol compared to baseline and the bisphosphonate group. Changes in serum calcium level from baseline to 1 week after the first injection of DMAb trended to correlate with changes in bone metabolism markers and lumbar BMD. The risks of DMAb-induced hypocalcemia are different between starting and switching from bone resorption inhibitors and bone formation promoters. Therefore, appropriate assessment before administration of DMAb, including pretreatment therapy as well as serum Ca and bone metabolic markers will help identify the risk of hypocalcemia following DMAb in combination with eldecalcitol. Our findings also showed that early change in serum Ca level after DMAb initiation could potentially predict the efficacy for therapy reaction.

Keywords Postmenopausal osteoporosis · Denosumab · Hypocalcemia · Bene metabolic marker · Teriparatide

Introduction

Osteoporosis is a chronic and progressive condition characterized by decreased bone mass and micro-architectural deterioration, leading to increased bone fragility and a consequential increased risk of fracture. An estimated 9 million new osteoporosis-related fractures occurred worldwide in the year 2000 [1], and as many as 75 million people in the United States, Europe, and Japan are affected by osteoporosis [2]. Osteoporosis treatments are focused on the prevention of fractures to maintain daily living activities and thereby reduce mortality.

Therapies for osteoporosis are based on an understanding of bone biology. Denosumab (DMAb), an anti-bone resorptive drug, is a complete human-type monoclonal antibody that targets the osteoclast differentiation factor receptor activator of the NF-kB ligand (RANKL) [3]. Several studies showed that it caused a greater increase in bone mineral density (BMD) and a greater reduction in bone resorption than bisphosphonate [4–6]. The FREEDOM open-label extension study demonstrated that vertebral, non-vertebral, and hip fractures were decreased for up to 10 years after DMAb treatment and that bone

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mineral density (BMD) values increased linearly [7]. Therefore, as DMAb is also effective for bisphosphonate (BP)-unresponsive primary osteoporosis [8], it is considered one of the best therapeutic options for osteoporotic patients with respect to increase in BMD, improvement in bone turnover markers, and prevention of fractures [9].

Despite this demonstrated efficacy, several serious adverse effects of DMAb have been reported, including hypocalcemia [10, 11] in 2–20% of women with postmenopausal osteoporosis [12, 13]. One recent study demonstrated an association between high bone turnover and risk of denosumab-induced hypocalcemia [14]. Therefore, it is of great interest if there could be differences in the risk for hypocalcemia during DMAb therapy switching from various treatments for osteoporosis. Moreover, although bone turnover markers were reported to be associated with BMD during DMAb [15], it is unknown if hypocalcemia during DMAb could be associated with therapeutic reaction.

The hypotheses of this study are that the early changes in serum calcium (Ca) level after DMAb initiation are different between bone resorption inhibitors and bone formation promoters and that these changes might be associated with changes in bone turnover makers and BMD in the longer period. To address of these hypotheses, the objectives of this study are to investigate (1) changes in serum calcium (Ca) level after switching from either nontherapy (naive), bisphosphonate (BPs), selective estrogen receptor modulators (SERMs) or teriparatide (TPD) treatments to a combination therapy of DMAb and eldecalcitol, which has a longer half-life with lower clearance rate and stronger vitamin D receptor-mediated effects than alfacalcidol [16] and (2) the association between early changes in serum calcium and changes in bone metabolic markers and BMD.

Materials and methods

Study design and subjects

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by Hokkaido University Hospital Institutional Review Board (#017-0241). This 12-month retrospective study was performed at three centers. One hundred and thirty patients [32 treatment-naive patients, 50 patients previously treated with bisphosphonate (BPs) therapy, 18 patients previously treated with selective estrogen receptor modulators (SERM) therapy, and 29 patients previously treated with teriparatide (TPD) daily] with postmenopausal osteoporosis who met the criteria of the 2011 Japanese guidelines for prevention and treatment of osteoporosis were enrolled in the study. The criteria for switching from BPs and SERM were showing no increases in bone mineral density despite these treatments. Exclusion criteria at baseline were (1) %YAM value over 70% in both lumbar and femoral neck, (2) under 50 years, (3) male, (4) severe chronic kidney disease (CKD) (stages 4 and 5), and (5) abnormal serum calcium (Ca) level corrected by serum albumin level (less than 8.3 or more than 10.3 mg/dl) at baseline. All patients were switched to DMAb (60 mg subcutaneously every 6 months) in combination with orally administered 0.75 µg eldecalcitol (Edirol; Chugai Pharmaceutical, Tokyo, Japan) daily. At baseline clinical information including blood sample including calcium (Ca) corrected by albumin, renal function and bone metabolic markers, and bone mineral density (BMD) evaluated by dual-energy X-ray absorptiometry (DXA) were obtained. Serum Ca, intact type 1 procollagen-N-propeptide (P1NP), and tartrate-resistant acid phosphatase 5b (TRACP 5b) levels were monitored every 3 months (12 weeks). Serum Ca monitors were added on 1 and 25 weeks after DMAb initiation for evaluating changes in Ca level (Fig. 1).

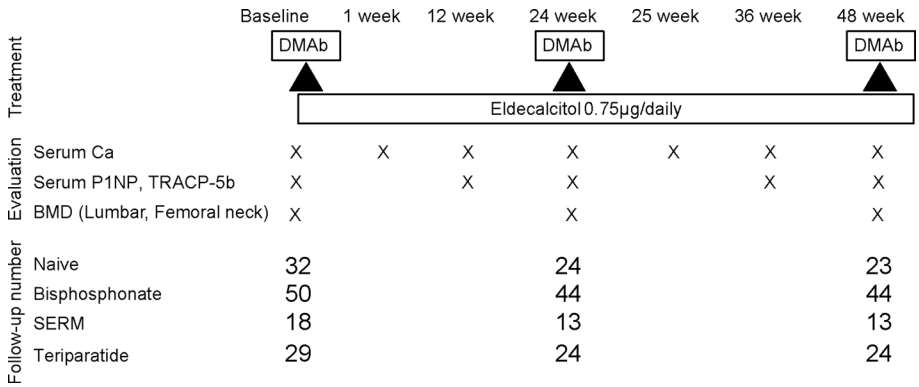

Fig. 1 Treatment and evaluation course of study participants

BMD assessments

Areal BMD in the lumbar spine (LS, L2–L4) and femoral neck (FN) were assessed by DXA (Discovery A, Hologic Japan, Inc, Tokyo, Japan) at baseline and after 6 and 12 months of treatment. Regions of severe scoliosis, previous vertebral fracture, and postoperative sites were excluded from BMD measurements, and at least two of the lumbar vertebrae L2–L4 had to be evaluable for BMD [17]. Subjects were excluded from the BMD analyses if the area was fractured or operated on during the study.

Statistical analysis

Comparisons of data among the groups and timepoints were performed using a one-way analysis of variance and Tukey tests. Linear regression models adjusted for age and body mass index (BMI) were built to evaluate the association between the change in serum Ca level from baseline to 1 week and changes in bone metabolic markers and BMD from baseline to 48 weeks after DMAb initiation. All statistical analyses were performed using SPSS Statistics version 23.0 (IBM Corporation, Armonk, NY) with a significance level set at 0.05.

Results

Clinical characteristics

Table 1 shows baseline characteristics. 10 cases in naive group, 27 cases in BPs' group, and 8 cases in SERM group used active vitamin D3 before administration of eldecalcitol. The number of patients who experienced fragility fracture were 21 cases in naive, 36 cases in BPs, 12 cases in SERM, and 23 cases in TPD. There were no differences in age, BMI, Ca, Cr, 25(OH)D, and % young adult mean (%YAM) of BMD at baseline between each group. BPs and SERM groups exhibited significantly lower P1NP and TRACP-5b levels compared to Naive group. On the other hand, TPD group exhibited significantly higher P1NP compared to Naive and BPs' groups and TRACP-5b compared to Naive group (Table 1). Of 129 patients, data could be obtained for 104 patients at 1 year after starting and switching to DMAb and eldecalcitol (follow-up ratio 80.6%) (Fig. 1). Of note, during DMAb treatment, one case in naive, 2 cases in BPs, and one case in TPD experienced fracture.

Longitudinal Ca, P1NP, and TRACP-5b level

The TPD group exhibited significantly lower serum Ca levels from baseline to 1 week, yet there were no differences between timepoints after 12 weeks. On the other hand, there were no significant differences in naive, BPs, and SERM groups between each timepoints (Fig. 2a). More specifically,

Table 1 Clinical characteristic at baseline

Variable	Naive	BPs	SERM	TPD
Age, years	74.0 (9.2)	75.6 (8.2)	73.9 (7.4)	72.3 (10.3)
BMI, kg/m^2	23.2 (3.4)	21.1 (3.4)	22.2 (2.8)	21.3 (3.8)
Duration of pretreatment, month	NA	44.8 (36.0)	33.6 (28.2)	19.8 (5.4)
Vitamin D3 use in pretreatment	10 cases	27 cases	8 cases	0
History of fragility fracture	21 cases	36 cases	12 cases	23 cases
Ca, mg/dl	9.39 (0.31)	9.65 (0.40)	9.49 (0.43)	9.67 (0.50)
Cr, mg/dl	0.68 (0.26)	0.67 (0.19)	0.62 (0.10)	0.76 (0.38)
eGFR, ml/min/1.73 mm^2	67.5 (26.3)	70.0 (18.3)	73.3 (11.4)	69.8 (35.6)
P1NP, ng/ml	59.3 (33.9)	20.8 (11.3)*	28.8 (11.0)*	93.8 (53.1)*†
TRACP-5b, mU/dl	529.3 (230.6)	307.3 (159.5)*	304.1 (165.7)*	677.2 (331.9)†
25(OH)D, ng/ml	23.6 (6.4)	24.0 (8.1)	26.0 (6.2)	24.0 (8.1)
%YAM lumbar, %	65.8 (14.3)	70.9 (11.8)	69.5 (8.3)	68.4 (12.9)
%YAM FN, %	57.5 (9.4)	59.5 (7.5)	62.5 (13.0)	58.6 (13.8)

Mean (SD)

BMI body mass index, *Ca* calcium, *Cr* creatinine, *eGFR* estimated glomerular filtration rate, *P1NP* intact type 1 procollagen-*N*-propeptide, *TRACP-5b* tartrate-resistant acid phosphatase 5b, *25(OH)D* 25-hydroxyl vitamin D, *YAM* young adult mean, *FN* femoral neck

*$P < 0.05$ vs naive group

$^{\dagger}P < 0.05$ vs BPs' group

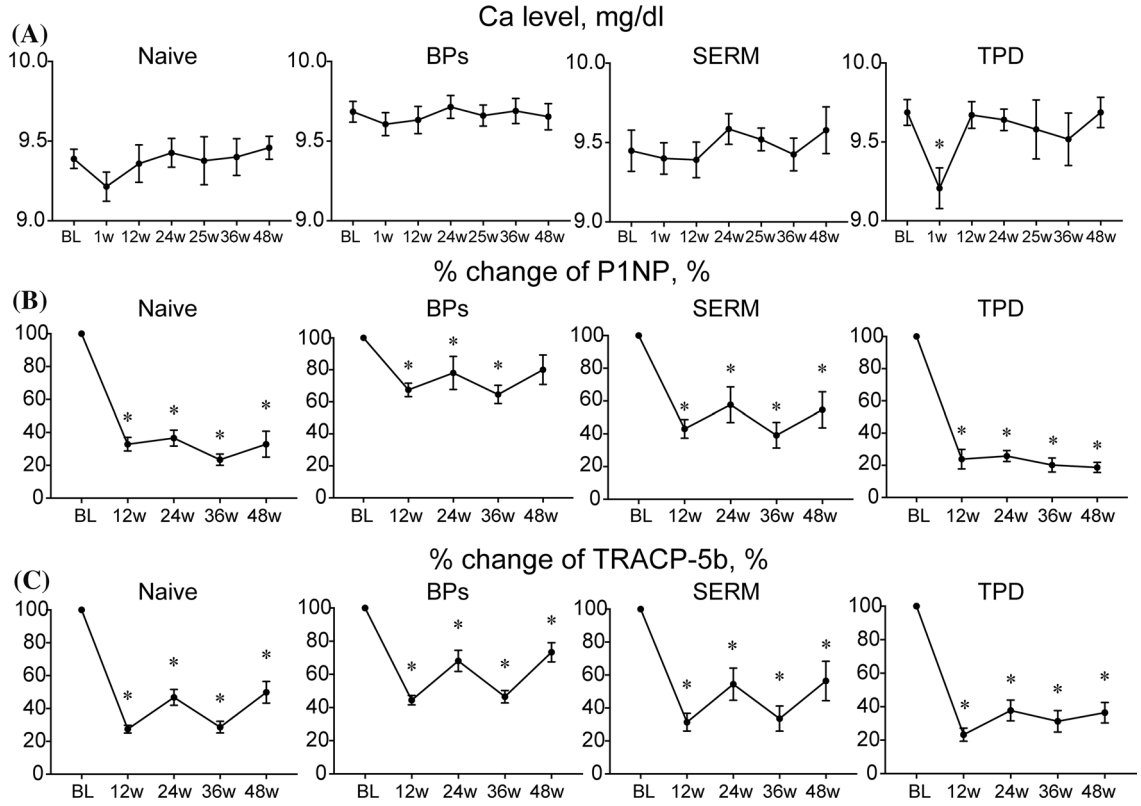

Fig. 2 Longitudinal changes in **a** serum Ca level and % change in **b** serum P1NP and **c** serum TRACP-5b level. Data show mean ± SD, $*P < 0.05$ vs baseline (BL)

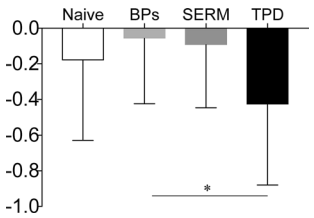

Fig. 3 Comparison of changes in serum Ca level from baseline to 1 week after DMAb initiation. Data show mean ± SD, $*P < 0.05$

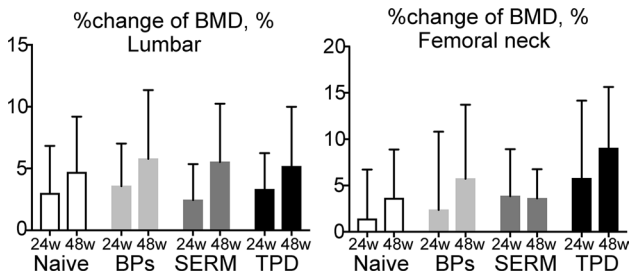

Fig. 4 Longitudinal changes in % change in BMD lumbar and femoral neck. Data show mean ± SD

the decrease in serum Ca level from baseline to 1 week in TPD groups was significantly higher compared to that in BPs' group (Fig. 3). Although 2 cases experienced hypocalcemia (Ca level < 8.4) and 11 cases experienced hypercalcemia (Ca level > 10.3), no subjects experienced the serious side effects related to hypercalcemia (such as short QT syndrome and renal diabetes insipidus) and hypocalcemia (such as tonic convulsions and tetany). After initiation of DMAb and eldecalcitol, all groups exhibited a significant decrease in P1NP levels compared to baseline (naive; approximately 30%, BPs; approximately 70%, SERM; approximately 50% and TPD; approximately 20%) (Fig. 2b). Similarly, all groups exhibited significant decrease in TRACP-5b levels compare to baseline (naive; approximately 30%, BPs; approximately 50%, SERM; approximately 40% and TPD; approximately 20%) (Fig. 2c).

Longitudinal BMD changes

At 24 weeks after DMAb initiation, all group showed an approximately 3% increase compared to baseline. At 48 weeks, all group showed an approximately 5% increase compared to baseline. There were no differences in % change in lumbar BMD between each group (Fig. 4). On the other

hand, TPD showed an increase, albeit not significantly, in % change in femoral neck BMD at 48 weeks compared to other groups (Fig. 4).

Correlations between the changes in serum Ca level and bone metabolic markers

To clarify why the TPD group showed significantly larger decreases of Ca level compared to BPs' group, we first investigated the correlations between the changes in serum Ca level from baseline to 1 week and serum P1NP and TRACP-5b levels at baseline. The change in serum Ca level from baseline to 1 week had significant correlations between serum P1NP level at baseline ($\beta = -0.446$, $P < 0.001$) and serum TRACP-5b level at baseline ($\beta = -0.375$, $P = 0.001$). However, there were no significant correlations between serum 25(OH)D level at baseline and changes in serum Ca level. In addition, we also investigated the correlation between changes in serum Ca level from baseline to 1 week and % change in bone metabolic markers and BMD from baseline to 48 weeks to address if early changes in serum Ca level were associated with therapeutic effects. Change in serum Ca level from baseline to 1 week had significant correlations between % change in PINP ($\beta = 0.500$, $P < 0.001$) and TRACP-5b ($\beta = 0.319$, $P = 0.007$) (Fig. 5). Although there was no significant correlation between change in serum Ca level and % change in BMD in femoral neck ($\beta = -0.253$, $P = 0.178$), change in serum Ca level from baseline to 1 week had significant correlation with % change in BMD in lumbar from baseline to 48 weeks ($\beta = -0.296$, $P = 0.019$).

Discussion

In this longitudinal study, we investigated risk factors and predictors related to change in serum Ca level after DMAb initiation in combination with daily eldecalcitol after switching from naive, BPs, SERM, and TPD therapies in postmenopausal osteoporosis. Although no subjects experienced the serious side effects related to hypocalcemia in this study, mean serum Ca levels decreased 1 week after first administration of DMAb. Specifically, the TPD group showed significant decrease from baseline to 1 week and compared to that of the BPs' group. Although one randomized control study reported that switching from TPD to DMAb in postmenopausal osteoporosis could continue to increase BMD and be an effective therapy for those who are at an acutely high risk of fragility fracture [18], our results suggested that patients switching from TPD to DMAb should be monitored more carefully for hypocalcemia, especially after the first administration.

The differences in the changes in serum Ca level after switching from the various treatment methods to DMAb could be explained by the influence of bone turnover. Consistent with one recent study [14], our results showed that bone metabolic markers at baseline had significant correlations with changes in serum Ca level from baseline to 1 week. In addition, we also found that there were no differences in serum Ca level from 24 weeks (second DMAb administration) to 25 weeks. Given that administration of DMAb could continue to suppress bone metabolic markers until 24 weeks after administration, these results could also support that bone metabolic markers are potentially useful for predicting hypocalcemia following DMAb treatment. On the other hand, secondary hyperparathyroidism has been suggested to increase the risk of hypocalcemia among patients with renal failure [10, 13]. Although 25(OH)D levels at baseline had no correlation with changes in serum Ca level, this study did not investigate intact parathyroid hormone (PTH) level and excluded severe CKD cases. Therefore, future studies switching to DMAb from other treatments are necessary to address the relationship between secondary hyperparathyroidism and change in serum Ca level. In addition, this study included the patients who used active vitamin D3 before administration of eldecalcitol. Although there were no differences in 25(OH)D level between groups at baseline, pretreatment of active vitamin D3 might affect the response of serum

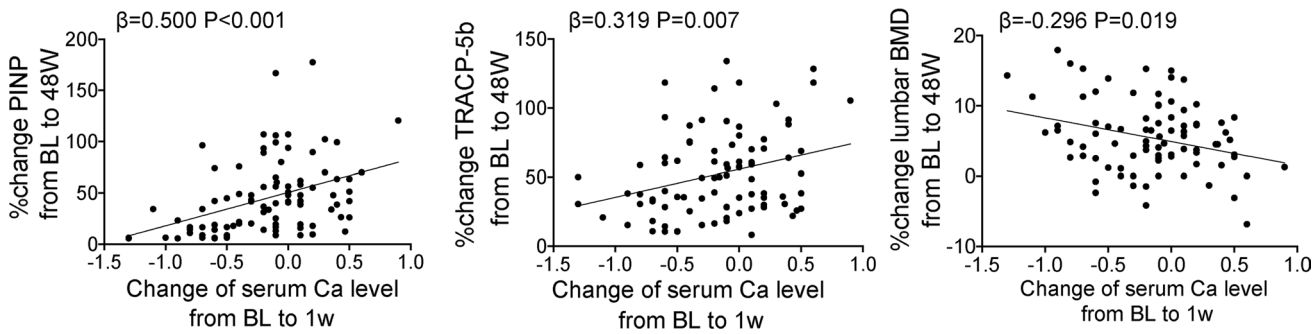

Fig. 5 Correlations between the changes in serum Ca level, bone metabolic markers and BMD

calcium to eldecalcitol. Therefore, future studies should compare patients who did not use active vitamin D3 for pretreatment.

Interestingly, we found that changes in serum Ca level from baseline to 1 week had significant correlations with changes in bone metabolic markers and BMD from baseline to 48 weeks after DMAb initiation. A recent study reported that bone metabolic markers, especially bone alkaline phosphatase (BAP), represent a useful marker to evaluate BMD during DMAb therapy [15]. However, to the best of our knowledge, there are no reports about predictors of bone metabolic markers or BMD during DMAb therapy. Ca status is strictly regulated by intestinal Ca absorption, bone resorption, and renal re-absorption. Nevertheless, serum Ca level decreased drastically, particularly after the first administration of DMAb in this study, and these changes had significant correlations with change in bone metabolic markers and BMD, suggesting that early change in serum Ca levels might potentially surrogate the reactivity for bone metabolism. Therefore, routine monitoring for serum Ca level after administration of DMAb is thought to be recommended with respect to predicting the therapeutic reactivity as well as hypocalcemia.

There are some limitations in this study. First, we did not investigate longitudinal 25(OH)D and intact-PTH levels. Although there were no differences in 25(OH)D at the baseline and all patients received eldecalcitol therapy to prevent secondary hyperparathyroidism in this study, future studies should address the influence of secondary hyperparathyroidism. Second, this study had a small sample size and short observation period. Further studies are needed to ascertain whether BMD continuously increases upon DMAb treatment and to what extent fractures can be prevented.

In conclusion, the risks of DMAb-induced hypocalcemia are different between starting and switching from bone resorption inhibitors and bone formation promoters. Therefore, appropriate assessment before administration of DMAb, including pretreatment therapy as well as serum Ca and bone metabolic markers, will help identify the risk of hypocalcemia following DMAb even in combination with eldecalcitol. In addition, our findings also showed that early change in serum Ca level after DMAb initiation could potentially predict the efficacy for therapy reaction.

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Compliance with ethical standards

Conflict of interest Tsuyoshi Asano, Tomohiro Shimizu, Daisuke Takahashi, Masahiko Takahata, Hiroki Hamano, Masahiro Ota, Shigeto Hiratsuka, Dai Sato, and Norimasa Iwasaki declare that they have no conflict of interest.

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