

Original Article

Bone turnover rate and bone formation/resorption balance during the early stage after switching from a bone resorption inhibitor to denosumab are predictive factors of bone mineral density change

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Abstract

Objectives: This study aimed to investigate the correlation between bone mineral density (BMD) and the turnover rate [$\sqrt{(\text{MoMf}^2 + \text{MoMr}^2)}$], multiple of median formation (MoMf) was calculated as bone-specific alkaline phosphatase (BAP) value/18.6 and multiple of median resorption (MoMr) as tartrate-resistant acid phosphatase 5b (TRACP-5b) value/463] and the balance (MoMf/MoMr) and to compare differences in therapeutic effects evoked by differences in previous treatments.

Methods: In 51 osteoporotic women treated with bisphosphonates (BPs) or selective estrogen receptor modulators (SERMs), BMD was measured at 0, 24, and 48 weeks after denosumab administration. The values of BAP and TRACP-5b were measured at 0, 4, 12, 24, 36, and 48 weeks.

Results: The turnover rate decreased at week 4 and decreased further at week 12. The balance indicated a relative predominantly formative state at week 4. This balance became higher in the SERM group than in the BP group at week 4. A correlation was observed between the rate of BMD change and turnover rate at weeks 0 and 4.

Conclusions: It is necessary to evaluate the turnover rate and balance to determine the therapeutic effect of denosumab, which induces dissociation between the trends in the bone turnover markers. Turnover rate and balance during the early stages of denosumab treatment may be predictive factors of BMD. When switching from bone resorption inhibitors to denosumab, it was necessary to consider the beginning values that were affected by the previous treatment. The state of relative anabolism is greater at 4 weeks when the previous treatment involved SERMs rather than BPs.

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Keywords: Osteoporosis; Denosumab; Bone mineral density; Bone-specific alkaline phosphatase; Tartrate-resistant acid phosphatase 5b

1. Introduction

Denosumab is a powerful inhibitor of bone resorption and is reported to increase bone mineral density (BMD) and decrease the incidence of fragility fractures [1–5]. BMD and bone turnover markers (BTMs) have been used to evaluate the therapeutic effects of denosumab. BTMs have often been assessed by measuring either bone formation or resorption

markers or by separately evaluating both parameters [1–6]. However, during these assessments, it was difficult to assess bone turnover in terms of both bone formation and resorption, and it was also difficult to observe the balance between bone formation and resorption. Dissociation has been observed between bone formation and resorption markers immediately after treatment with denosumab [2,6,7]. In these cases, there is a possibility of erroneously evaluating bone metabolism without the simultaneous evaluation of bone formation and resorption markers. Furthermore, it is necessary to evaluate the balance between these two markers to determine therapeutic effects. Bieglmayer and Kudlacek [8] introduced a method for visually presenting the rate of bone turnover (referred to as

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turnover rate hereafter) with the balance between bone formation and resorption (referred to as balance hereafter) by depicting the levels of bone formation and resorption markers two-dimensionally on a graph. In this method, it becomes easy to evaluate the turnover rate and balance.

The present pilot study hypothesized that the simultaneous evaluation of bone formation and resorption markers is useful in determining the efficacy of denosumab treatment during which bone formation and resorption dissociation occur. The purpose of the study was to investigate whether future changes in BMD can be predicted from the early turnover rate and balance and to compare differences in therapeutic effects observable in BMD and BTMs evoked by differences in previous treatments.

2. Methods

Subjects were diagnosed with primary osteoporosis according to the revised Japanese diagnostic criteria for primary osteoporosis (Primary osteoporosis is diagnosed based on the presence of any fragility fractures at various sites, including spine and proximal femur or another fragility fractures with BMD < 80% young adult mean (YAM). If there is no fragility fracture, BMD \leq 70% of YAM or \leq -2.5 standard deviation (SD) is also diagnosed as primary osteoporosis) [9]. The study was approved by the ethics committee at the Asahi General Hospital. Fifty-one postmenopausal women (68–92 years of age, mean age: 80.9 ± 6.6 years) were recruited, each with reduced lumbar vertebral or femoral BMD compared with that present 24 weeks prior (lumbar vertebral BMD was reduced in 27 subjects and femoral BMD was reduced in 30 subjects), irrespective of whether they were receiving treatment with bisphosphonates (BPs) or selective estrogen receptor modulators (SERMs). Of these, 44 women took alfacalcidol [BP and alfacalcidol ($n = 24$) and SERM and alfacalcidol ($n = 20$)] and one took SERM and calcium aspartate. The previous treatment was discontinued for all subjects, and they were administered 60 mg of denosumab every 24 weeks as treatment for osteoporosis. In addition, subjects were administered a combined formulation containing calcium (305 mg), natural vitamin D₃ (5.0 μ g), and magnesium (15 mg). Subjects receiving medications that could influence bone metabolism, those with hypocalcemia or secondary osteoporosis, and those with a history of surgery on the lumbar vertebrae (L2–4) were excluded. All recruited subjects showed no fracture within 100 days of the study initiation.

BMD of L2–4 and the left proximal femur (total) was measured by dual-energy X-ray absorption (DXA, Discovery A, Hologic, Inc, Bedford, MA, USA, Coefficient of variations are 1% at both the AP spine and the total hip) at the beginning of denosumab administration (week 0) and at weeks 24 and 48. Further, BMD of subjects with surgery or coxarthrosis of the left hip joint was measured on the right proximal femur if there was no surgery or coxarthrosis of the right hip joint. The values of bone-specific alkaline phosphatase (BAP) and tartrate-resistant acid phosphatase 5b (TRACP-5b) were measured at 0, 4, 12, 24, 36, and 48 weeks after the initial administration of denosumab. These measurements were divided by median values for

untreated postmenopausal women with osteoporosis (18.6 μ g/L for BAP and 463 mU/dL for TRACP-5b) to determine the multiple of median formation (MoMf, measured BAP value/18.6) and multiple of median resorption (MoMr, measured TRACP-5b value/463). These values were then plotted onto a graph using the Bieglmayer method [8,10]. The turnover rate was calculated as $\sqrt{(\text{MoMf}^2 + \text{MoMr}^2)}$ and the balance as MoMf/MoMr. There was no washout period between the discontinuation of the previous treatment and initiation of denosumab administration.

IBM SPSS Statistics version 20J (IBM, Armonk, NY, USA) was used for all statistical analyses. Time-dependent changes were compared using the Wilcoxon signed rank test, and differences between the two groups were evaluated using the Mann–Whitney test. Spearman's rank correlation coefficient was used to determine correlations between the two groups. The probability ellipse for the two-dimensional normal distribution was obtained from an electronic source. (This probability ellipse program was made by Shigenobu Aoki who resigned from the assistant professor at Gunma University society information department. <http://aoki2.si.gunma-u.ac.jp/R/scatter.html>) and created using Microsoft Excel.

3. Results

Ten of the 51 subjects were excluded for the following reasons: six failed to appear for follow-up at the hospital, two experienced fractures, one died, and one underwent articular surgery. The remaining 41 (68–92 years of age) were included for analysis. Previous treatments involved BPs for 22 subjects (BP group: alendronate, 17 subjects; risedronate, one subject; minodronic acid, three subjects; and ibandronate, one subject) and SERMs for 19 subjects (SERM group: raloxifene, 17 subjects and bazedoxifene, two subjects; Table 1).

3.1. Changes in BMD

Lumbar BMD increased in 35 subjects (BP group, 19 subjects and SERM group, 16 subjects) at week 24 and in 33 subjects (BP group, 16 subjects and SERM group, 17 subjects) at week 48 compared with that at week 0. Femur BMD increased in 26 subjects (BP group, 12 subjects and SERM group, 14 subjects) at week 24 and in 31 subjects (BP group, 15 subjects and SERM group, 16 subjects) at week 48 compared with that at week 0. The percent change of increase in lumbar BMD at weeks 24 and 48 were $4.8 \pm 4.2\%$ and $4.8 \pm 5.9\%$, respectively, whereas those of femur BMD were $5.8 \pm 16.3\%$ and $6.7 \pm 17.2\%$, respectively. The values of both parameters significantly increased compared with those at the beginning of the treatment, with the increases exceeding the least significant change (Table 2).

3.2. Changes in turnover rate and balance

With the exception of BAP values at week 4, both BAP and TRACP-5b values significantly changed beyond a minimum significant change [11] during the treatment period

Table 1
Patient characteristics.

	All (n = 41)	BP group (n = 22)	SERM group (n = 19)	Difference between BP and SERM groups (p-value)
Age (years)	80.6 ± 7.0	83.2 ± 6.0	77.7 ± 7.0	<0.05
Height (cm)	143.8 ± 6.4	143.6 ± 6.2	144.1 ± 6.7	NS
Body weight (kg)	44.5 ± 8.1	44.0 ± 8.5	45.2 ± 7.9	NS
BMI (kg/m ²)	21.5 ± 3.4	21.3 ± 3.6	21.7 ± 3.2	NS
Serum calcium (mg/dL)	9.4 ± 0.4	9.4 ± 0.4	9.3 ± 0.4	NS
Serum phosphorus (mg/dL)	3.6 ± 0.5	3.6 ± 0.6	3.6 ± 0.5	NS
Serum alkaline phosphatase (U/L)	206 ± 66	184 ± 62	231 ± 63	<0.05
Turnover rate	1.04 ± 0.40	0.87 ± 0.31	1.23 ± 0.43	<0.01
Balance	0.85 ± 0.30	0.82 ± 0.31	0.90 ± 0.30	NS
Serum BAP (µg/L)	11.9 ± 5.2	9.7 ± 4.2	14.4 ± 5.3	<0.01
Serum TRACP-5b (mU/dL)	369.7 ± 158.7	316.2 ± 114.4	431.7 ± 182.1	<0.05
Lumbar BMD (g/cm ²)	0.693 ± 0.124	0.703 ± 0.148	0.682 ± 0.091	NS
Femur BMD (g/cm ²)	0.560 ± 0.096	0.554 ± 0.093	0.569 ± 0.101	NS

Results are shown as mean ± standard deviation.

BP, bisphosphonate; SERM, selective estrogen receptor modulator; NS, not significant; BMI, body mass index; BAP, bone-specific alkaline phosphatase; TRACP-5b, tartrate-resistant acid phosphatase 5b; BMD, bone mineral density.

compared with those at week 0 (Table 2). The turnover rate was significantly decreased at week 4 and decreased further by week 12. Thereafter, the turnover rate fluctuated; it increased at week 24, decreased at week 36, and increased again at week 48. At week 0, the calculated balance value (0.85) indicated a relative predominantly resorptive state. At week 4, this had increased to 2.40, indicating a relative predominantly formative state. Thereafter, the balance decreased to 1.86 at week 12 and 1.28 at week 24, indicating that the relative predominantly formative state fluctuated over time. However, the data indicated a relative predominantly formative state during the study (Table 2). MoMf and MoMr variance was great at week 0 and decreased over time at weeks 4 and 12. However, the variance increased again at week 24 (Fig. 1a–d).

3.3. Correlation between BMD change rate and turnover rate and between BMD change rate and balance at weeks 0 and 4

A significant correlation was observed between the rate of lumbar and femur BMD change and turnover rate

($|\rho| = 0.327–0.510$) at weeks 0 and 4 and between the rate of lumbar BMD change and balance in week 4 (Table 3).

3.4. Comparison by differences in previous treatments

Compared with the subjects in the BP group, those in the SERM group were significantly younger and had a significantly higher turnover rate and BAP and TRACP-5b values at the initial administration of denosumab (Table 1). Furthermore, the balance became significantly higher in the SERM group at week 4. The rate of change in balance was $142.0 \pm 72.0\%$ in the BP group and $263.7 \pm 166.3\%$ in the SERM group at week 4. Furthermore, the rates of increase in the SERM group were approximately two-times higher (Fig. 2a and b). In addition, BAP values were significantly higher in the SERM group at weeks 4 and 12 (Fig. 2c). Meanwhile, there was no difference in TRACP-5b values between the two groups at week 4 (Fig. 2d).

The lumbar and femur BMD values increased at weeks 24 and 48 compared with those at week 0 in both groups. A significant increase of the lumbar BMD was observed in the BP group ($p < 0.01$ at week 24, $p < 0.05$ at week 48) and that

Table 2
Periodic changes in turnover rate, balance, bone turnover markers, and lumbar and femur bone mineral density.

	Week 4	Week 12	Week 24	Week 36	Week 48
Turnover rate	0.69 ± 0.26*	0.59 ± 0.19*	0.67 ± 0.23*	0.55 ± 0.20*	0.63 ± 0.24*
Balance	2.40 ± 1.12*	1.86 ± 0.72*	1.28 ± 0.42*	1.55 ± 0.35*	1.14 ± 0.50*
Serum calcium (mg/dL)	9.2 ± 0.5**	9.3 ± 0.5	9.4 ± 0.5	9.3 ± 0.4	9.2 ± 0.4**
Serum phosphorus (mg/dL)	3.2 ± 0.5*	3.3 ± 0.5*	3.3 ± 0.5*	3.3 ± 0.5*	3.3 ± 0.4*
Serum alkaline phosphatase (U/L)	204 ± 58	189 ± 56**	187 ± 55**	177 ± 56*	185 ± 59**
Serum BAP (µg/L)	11.6 ± 5.1	9.4 ± 3.5*	9.3 ± 3.0*	8.5 ± 3.4*	8.2 ± 2.7*
Serum TRACP-5b (mU/dL)	126.5 ± 34.0*	131.9 ± 34.2*	199.1 ± 89.6*	138.7 ± 41.0*	204.6 ± 102.1*
Lumbar BMD (g/cm ²)			0.725 ± 0.136*		0.727 ± 0.135*
Femur BMD (g/cm ²)			0.583 ± 0.077*		0.587 ± 0.072*

Results are shown as mean ± standard deviation.

Significantly different compared with week 0 (* $p < 0.01$, ** $p < 0.05$).

BAP, bone-specific alkaline phosphatase; TRACP-5b, tartrate-resistant acid phosphatase 5b; BMD, bone mineral density.

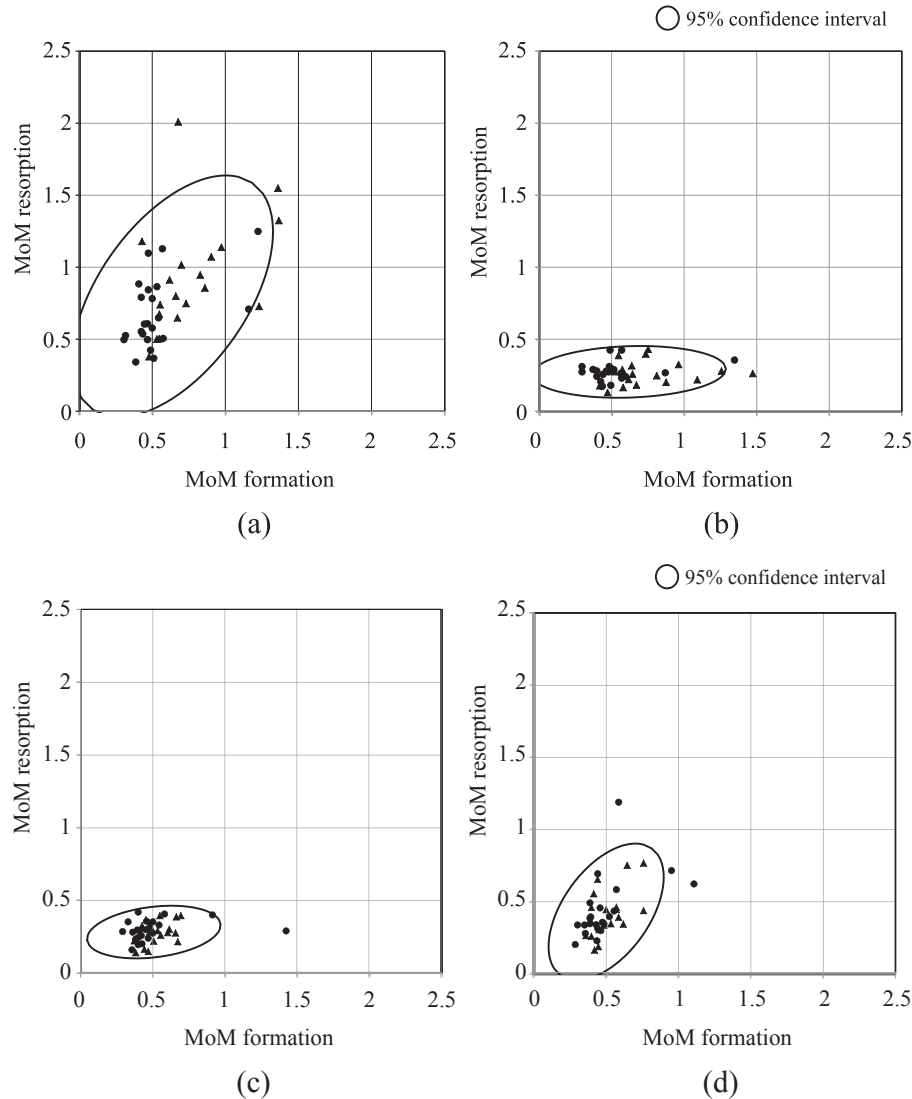


Fig. 1. Scatter diagram for multiple of median (MoM) formation and MoM resorption in the bisphosphonate group (●) and selective estrogen receptor modulator group (▲) at weeks 0 (a), 4 (b), 12 (c), and 24 (d).

of the lumbar and the femur BMD was observed in the SERM group ($p < 0.01$); however, no significant differences were observed between the two groups (Fig. 2e and f). The rate of lumbar BMD change at week 48 was significantly higher in the SERM group (BP group, $2.8 \pm 5.7\%$ and SERM group, $7.0 \pm 5.4\%$; $p < 0.05$).

In the SERM group, there were significant correlations ($|\rho| > 0.5$) between the lumbar BMD change rate and turnover rate and between lumbar BMD change rate and balance at week 4. In the BP group, a significant correlation was observed between the rate of lumbar BMD change at week 24 and balance at week 4 and between the femur BMD change rate at week 48 and the turnover rate at week 0 (Table 3).

4. Discussion

It is important to know which indicators to evaluate when using BTMs to determine therapeutic effects. Bone resorption

markers are useful for evaluating bone resorption inhibitors, such as BPs and SERMs, whereas bone formation markers are useful for evaluating bone formation promoters such as teriparatide [11]. However, it is insufficient to evaluate either the bone formation marker or bone resorption marker, when there is any dissociation between observed trends in both markers, such as that occurring in this study [12]. When the effect of denosumab was evaluated only in BAP at week 4, the balance might be underestimated, and when it was evaluated only in TRACP-5b, the turnover rate might be overestimated. To avoid this, it is important to simultaneously measure both markers and to assess them together. Thus, it seems to be useful to evaluate the turnover rate and balance together to determine the therapeutic effect in the early period after the first administration of denosumab. Furthermore, in the present study, BTMs (represented by MoMf and MoMr) were two-dimensionally expressed to reveal different changes with the turnover rate and balance at weeks 4, 12, and 24 after the first

Table 3

Correlation between the rate of BMD change and turnover rate and between the rate of BMD change and balance after 48 weeks of denosumab administration.

	Correlation to the rate of BMD change after 24 weeks				Correlation to the rate of BMD change after 48 weeks			
	Week 0		Week 4		Week 0		Week 4	
	p	Correlation coefficient	p	Correlation coefficient	p	Correlation coefficient	p	Correlation coefficient
Lumbar								
Total								
Turnover rate	<0.01	0.411	<0.01	0.51	<0.05	0.394	<0.01	0.456
Balance	NS	0.158	<0.01	0.516	NS	0.169	<0.01	0.466
BP group								
Turnover rate	NS	0.161	NS	0.242	NS	0.086	NS	0.12
Balance	NS	0.23	<0.05	0.515	NS	0.098	NS	0.183
SERM group								
Turnover rate	NS	0.406	<0.01	0.58	NS	0.394	<0.01	0.588
Balance	NS	−0.046	<0.05	0.537	NS	0.013	<0.05	0.56
Femur								
Total								
Turnover rate	<0.05	0.327	<0.05	0.342	<0.05	0.396	<0.05	0.394
Balance	NS	−0.125	NS	0.199	NS	−0.111	NS	0.196
BP group								
Turnover rate	NS	0.245	NS	0.205	<0.05	0.461	NS	0.326
Balance	NS	−0.101	NS	0.18	NS	−0.187	NS	0.064
SERM group								
Turnover rate	NS	0.17	NS	0.195	NS	0.137	NS	0.186
Balance	NS	0.369	NS	0.424	NS	−0.29	NS	0.1

BMD, bone mineral density; NS, not significant; BP, bisphosphonate; SERM, selective estrogen receptor modulator.

administration of denosumab. Because the turnover rate and balance are expressed in one figure, this expression is useful when they are evaluated together.

Because changes in BTMs are reversible following the administration of denosumab [2,13], the values of the turnover rate, balance, and TRACP-5b were fluctuated before and after the second administration of denosumab. However, the turnover rate and balance peaked at different times in the present study. Because the turnover rate is maximally suppressed at weeks 12 and 36 and the balance changes to the bone-formation-predominant state mostly at week 4, it seems necessary to evaluate the turnover rate and balance considering these characteristics. MoMr decreased in all subjects by week 4 during treatment with denosumab and there was little variation in the bone resorption-inhibiting effects at week 4, which is consistent with the findings reported by Eastell et al. [6]. However, there were outliers observed in the decrease of the turnover rate at week 12 (i.e., the decrease in MoMf), thus showing individual differences in the effects on bone formation markers. In addition, the variance of MoMf and MoMr values at week 24 was greater than that at week 12. Based on these data, denosumab demonstrated a clear inhibition of bone resorption with no individual differences at week 4 of administration, but thereafter, individual differences were observed in the persistence of effects and effects on BAP inhibition.

Denosumab treatment was associated with increasing serum sclerostin levels and declining serum Dickkopf-related protein 1 levels [14]. This might explain the slight positive imbalance between suppressed bone resorption and formation (relative anabolism) [15]. In this study, the balance at week 4 became

higher than that at week 0, which is caused by the relatively less inhibition of bone formation compared with that of bone resorption. This condition in which the bone formation relatively changed in predominance as compared with that at week 0 (hereafter referred to as “the relative bone-formation-predominant state”) induced by denosumab, reflects relative anabolism. It seems that BMD-increasing effects occur because of this relative anabolism [15]. Because the balance was maintained at a higher level during this study than that at week 0, it seems that the relative bone-formation-predominant state and BMD-increasing effects were maintained up to week 48.

BMD and BTMs are used to determine the effects of therapeutic agents. The larger increases in BMD and reductions in BTMs were associated with a reduction in the fracture risk during treatment with antiresorptive agents [16]. However, according to definitions from the U.S. National Institute of Health Consensus Development Program, BMD and bone quality are independent indicators of bone strength [17]. During osteoporosis treatment, BMD and BTMs measurements facilitate the observation of various dimensions of bone strength. This indicates the importance of evaluating BMD with BTMs when determining the therapeutic effects of osteoporosis treatment [11]. Denosumab has been reported to increase BMD after only 1 month of administration [7,18], although generally, BMD is measured at intervals of a few months [2,4]. Meanwhile, BTMs that begin to change from the early stages of treatment are generally used to determine early therapeutic effects [11]. The ability to use early BTMs to predict BMD changes that occur several months later will be a more effective determinant of therapeutic effects. Eastell et al. [6] reported a significant correlation between carboxyl-terminal collagen

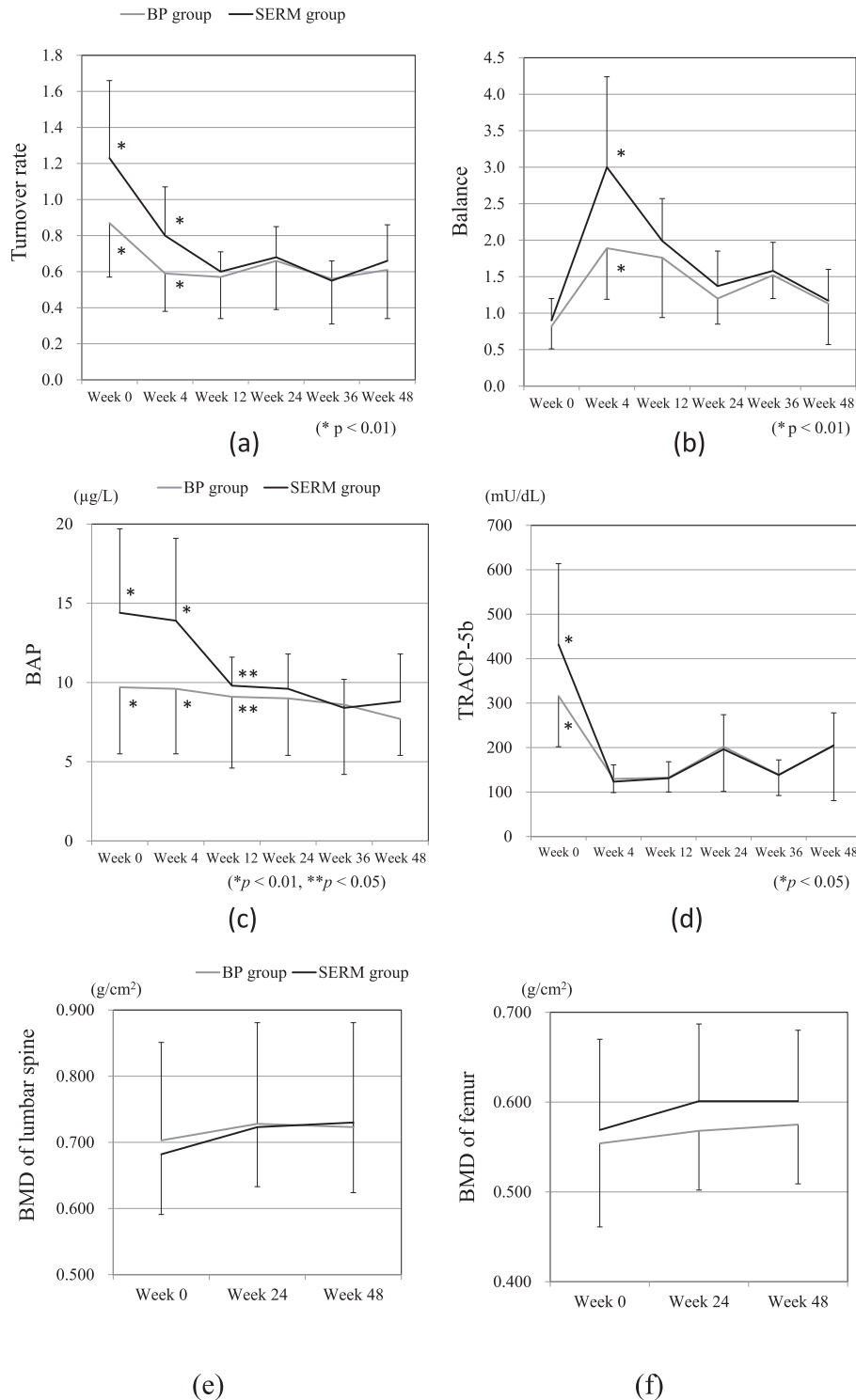


Fig. 2. Periodic changes in turnover rate (a), balance (b), bone alkaline phosphatase (BAP) (c), tartrate-resistant acid phosphatase 5b (TRACP-5b) (d), lumbar spine (e) and femur (f) bone mineral density (BMD) in the bisphosphonate (BP) and selective estrogen receptor modulator (SERM) groups.

crosslink (CTX) values at month 6 of treatment and BMD at month 36. In the present study, a significant correlation was observed between the BMD change rate at week 48 and the short-term turnover rates at weeks 0 and 4 and between the lumbar BMD change rate and the balance at week 4. These seem to be useful because they the future therapeutic effects on

BMD during earlier phases of denosumab treatment. BTMs cannot be measured frequently in Japan. However, the changes in the turnover rate and balance in the early stage after the switching of drugs seem to be useful not only to evaluate the effect of denosumab but also to predict the BMD change during clinical practice.

The turnover rate at weeks 0 and 4 showed a positive correlation to the rate of lumbar and femur BMD change. It seems that this was because the higher the bone turnover rates during the early treatment period with denosumab were, the greater were the bone turnover-inhibiting effects demonstrated by denosumab. This suggests that the early bone turnover rate seems to be a predictive factor for BMD changes up to 48 weeks. Furthermore, denosumab administration inhibits bone resorption with long-term BMD gains associated with sustained modeling-based formation [19]. Therefore, the increase of the balance at week 4 seems to be useful to predict an increase in lumbar BMD. However, the correlation between the femur BMD change rates and the turnover rates was weaker than that between the lumbar BMD change and turnover rates. In addition, there was no significant correlation between the femur BMD change rates and the balance. Although cortical and cancellous porosities were reduced by denosumab, the action points of denosumab were different in the cortical and cancellous bone (osteoclast on the Haversian canal of cortical bone and on the canopy of cells lining the cancellous bone) [20]. This may be one of the reasons for those differences between lumbar BMD, which had a high ratio of cancellous bones, and femur BMD, which had a high ratio of cortical bones. Therefore, it seemed necessary to evaluate femur BMD and BTMs together for determining the effect of denosumab.

This was an observational study to evaluate the effects of switching from BPs and SERMs to denosumab. Therefore, it was necessary to consider the relative effects of the previous treatment. A difference in the changes in turnover rate depending on whether BPs or SERMs were administered was previously reported [10]. Although the subjects of this study responded poorly to the previous treatment in BMD, there were differences between the BP and SERM groups in terms of turnover rate and BAP and TRACP-5b values at the beginning of the present study. These differences may be affected by the bias of the two groups, which included the effects of the previous treatment. Therefore, it is important to consider the effects of the differences in initial or reference values to compare relative changes over time. Furthermore, there were differences between the two groups in terms of turnover rate and BAP values at 4 and 12 weeks, respectively. Thus, it seems necessary to consider the residual effects of the previous treatment on the turnover rate and BAP values up to 4 and 12 weeks, respectively, to determine the therapeutic effects based on these values. No significant difference was observed in balance between the BP and SERM groups at the beginning of the study. However, there was a greater change in balance in the SERM group than in the BP group at week 4, showing a relative bone-formation-predominant state. The rate of change was two-times larger. In addition, a significant but moderate correlation was observed between the balance at week 4 and the rate of lumbar BMD change in the SERM group. This suggests the following when switching from bone resorption inhibitors to denosumab: 1) relative anabolism increases more when the prior treatment is with an SERM than when it is a BP, which is a stronger bone resorption inhibitor and 2) the lumbar BMD can increase more in the SERM group than in the BP group.

There were five limitations to the present study. First, because the turnover rate and the balance were calculated on the basis of the values of BTMs of untreated postmenopausal women with osteoporosis as reference, the effects of treatment could be relatively evaluated with them. However, enough examination is not accomplished to evaluate the absolute values of the turnover rate and the balance. Therefore, they could only be used to observe the relative change of the bone metabolism. Second, BAP and TRACP-5b were used as the BTMs. A significant advantage of using these two markers is that they are rarely affected by food intake or decreased renal function, that there is little diurnal variation or day-to-day variation, and that simultaneous sample collection is possible [11,21,22]. Therefore, these two markers were selected because they are easy to use in a clinical setting. However, Eastell et al. [6] reported greater changes in CTX than in TRACP-5b following denosumab administration, suggesting that CTX is more useful in determining the therapeutic effects of denosumab. In addition, because BTMs were not measured at week 28, it could not be determined whether the second administration of denosumab caused the same changes in turnover rate and balance as the first administration. Furthermore, because this was a clinical study, the mean age of the subjects in the BP and SERM groups could not be made consistent. Finally, because the present study lasted only 1 year, it was not possible to elucidate whether and for how long the correlation between the early turnover rate or balance and the rates of BMD change would be observed in the future.

In conclusion, it is useful to evaluate the turnover rate and balance to determine the therapeutic effect of denosumab, which induces dissociation between the trends in the bone formation marker and the bone resorption marker. It was suggested that turnover rate and balance during the early stages of denosumab treatment might be predictive factors of BMD up to week 48. When switching from bone resorption inhibitors to denosumab, it was necessary to consider the beginning values that were affected by the previous treatment bias. The state of relative anabolism might be greater at 4 weeks when the previous treatment involved an SERM rather than a BP.

Conflict of interest

The author has no conflict of interest.

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