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ORIGINAL ARTICLE

Relationship between baseline characteristics and response to risedronate treatment for osteoporosis: data from three Japanese phase III trials

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Abstract

Summary We evaluated the influence of baseline age, bone mineral density (BMD), and serum levels of vitamin D on the response to risedronate treatment. Risedronate consistently increased BMD, but our results suggest vitamin D supplementation may be necessary to achieve optimal treatment effect. Furthermore, early intervention may help prevent bone fractures.

Introduction We aimed to investigate the influence of baseline age, BMD, and vitamin D insufficiency on the response to risedronate treatment.

Methods Data regarding 1447 patients was obtained from the registries of three phase III clinical trials of risedronate. The response to treatment was expressed in terms of BMD increase and occurrence of new vertebral fractures. The patients were stratified by baseline values for age (<65, 65–72, and ≥72 years), lumbar spine BMD T-score (osteoporotic, <−2.5; and non-osteoporotic, ≥− 2.5), and serum levels of 25-hydroxyvitamin D (deficient, <21 ng/mL; and non-deficient, ≥21 ng/mL).

Results Risedronate consistently increased lumbar spine BMD in all the groups, with similar percentage and absolute increments in all the age tertiles. The percentage, but not absolute, increment in BMD was significantly higher ($p = 0.0003$) in the osteoporotic than that in the non-osteoporotic patients (baseline). Of the 1330 patients whose baseline serum levels of 25-hydroxyvitamin D were available, 44.7% had vitamin D deficiency (<20 ng/mL), while 89.2% had insufficiency (<30 ng/mL). The percentage and absolute increments in BMD were lower ($p < 0.05$ and $p < 0.01$, respectively) in the vitamin D-deficient than those in the non-deficient patients. New vertebral fractures occurred in 1.5 and 0.8% of the osteoporotic and non-osteoporotic patients, respectively (end of the treatment).

Conclusions Therapeutic response in elderly patients is consistent, but early initiation of risedronate treatment may help prevent fractures. Risedronate-induced increase in BMD is lower in patients with vitamin D deficiency, suggesting that vitamin D supplementation is important to achieve optimal treatment response.

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Introduction

Bisphosphonates are widely used to treat osteoporosis, and the treatment is effective in most osteoporosis patients, although there are some patients known as "non-responders" [1, 2]. Previous reports have indicated that factors involved in insufficient response include secondary osteoporosis [2–6], advanced age [7, 8], vitamin D deficiency [2, 4–6, 9–12], and poor compliance [2–5].

While some studies [7, 8, 13] have examined the relationship between age and fracture reduction in the context of risedronate treatment, there is little information on whether

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risedronate-induced increase in bone mineral density (BMD) is consistent in elderly patients.

Furthermore, while it was shown that the percentage increase in BMD is related to the baseline BMD [14], absolute increments in BMD have not been described. Finally, although it was shown that vitamin D levels are correlated with the response to treatment for postmenopausal osteoporosis in terms of BMD changes and fracture rates [15], this relationship has not been fully described.

Risedronate is a third-generation bisphosphonate containing a pyridinyl group. Risedronate has already been shown to benefit postmenopausal women with established osteoporosis [13, 16–21]. Similar efficacy has been reported in Japanese clinical trials for oral administration of daily, weekly, or monthly single doses (2.5, 17.5, and 75 mg, respectively) [19, 20, 22, 23]. Risedronate was approved for use in clinical practice in Japan following a series of phase III trials during which vitamin D was not supplemented in order to ensure consistency with previous trials [24]. Therefore, by analyzing the data collected during these trials, it is possible to explore the influence of vitamin D insufficiency and deficiency on the response to risedronate treatment.

The aim of the present study was to investigate the relationship between baseline characteristics (age, BMD, and serum levels of vitamin D) and therapeutic effects (change in BMD and incidence of new vertebral fractures) of risedronate treatment for osteoporosis by analyzing data from three phase III clinical trials in Japanese populations.

Methods

Study design

The present study analyzed combined data from three randomized, double-blind, clinical phase III trials for risedronate, namely CCT-003 [19], CCT-101 [22], and CCT-301 [23]. These trials were carried out as multicenter studies in Japan between March 1999 and August 2011. The primary efficacy endpoint was the percent change in mean lumbar spine BMD (LS-BMD), and the results were similar between CCT-003 and CCT-101, and between CCT-003 and CCT-301 [19, 22, 23].

Trial CCT-003 consisted of 48 weeks of treatment, whereby eligible patients were randomly assigned to receive either a daily oral dose of risedronate (2.5 mg) or an intermittent cyclical dosage regimen of etidronate (each cycle consisted of a 2-week period of treatment with 200 mg/day and a 10-week medication-free period). Trial CCT-101 also consisted of 48 weeks of treatment, but eligible patients were randomly assigned to receive either a weekly (17.5 mg) or a daily (2.5 mg) oral dose of risedronate. Finally, trial CCT-301 consisted of 12 months of treatment, whereby eligible patients

were randomly assigned to receive either a monthly (75 mg) or a daily (2.5 mg) oral dose of risedronate. In all the trials, blinding to the study drug was maintained by a double-dummy technique using active drugs and corresponding placebo tablets.

All the patients were treated in an ambulatory regime and supplemented with calcium lactate (1.54 g/day, corresponding to 200 mg of calcium per day) throughout the study period. However, vitamin D was not supplemented in order to ensure consistency with previous clinical trials [24]. Throughout the study period, concomitant use of any drugs known to affect bone metabolism was prohibited. The study protocols were approved by the Institutional Review Board of each institution prior to initiation of the study, and all the patients gave written informed consent before registration. The trials were conducted according to the Good Clinical Practice guidelines and in accordance with the Helsinki declaration. Details of the study design, patients involved, and protocols of these trials have been described elsewhere [19, 22, 23].
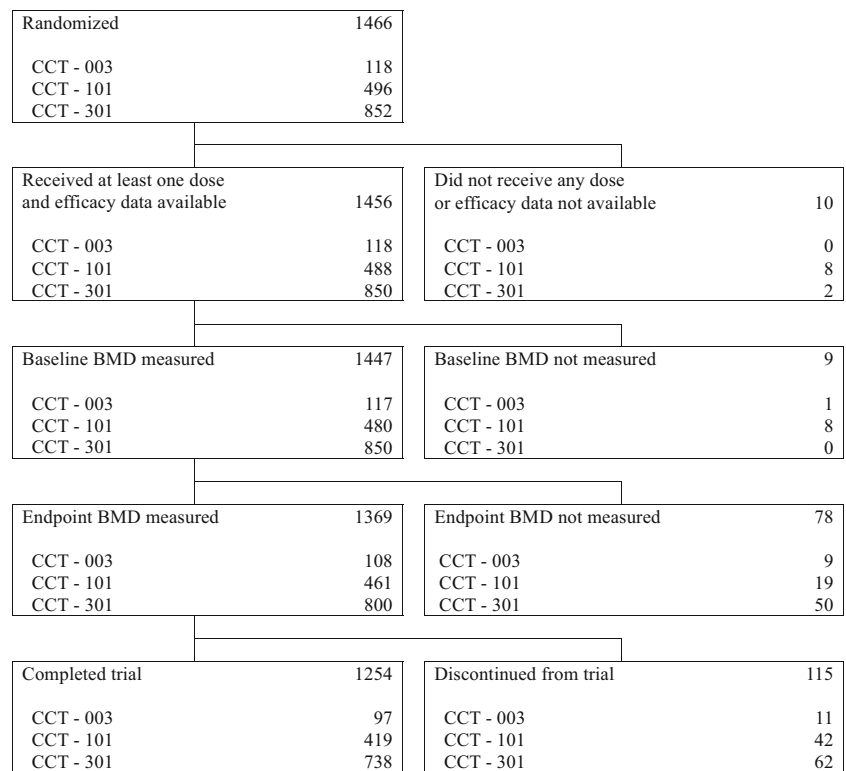
Selection of patients

The present study consists of a post-hoc analysis of data from 1447 osteoporosis patients who received treatment with risedronate within one of the risedronate trials described above. Ambulatory patients of either sex, aged 40–75 years (trial CCT-003) or ≥50 years (trials CCT-101 and CCT-301), with involutional osteoporosis were eligible if they met the diagnostic criteria for primary osteoporosis established by the Japanese Society for Bone and Mineral Research (JSBMR) [25, 26]. Exclusion criteria included the following: secondary osteoporosis or other diseases known to cause reduced bone mass; radiographic findings that might affect the LS-BMD; recent use of drugs known to affect bone metabolism; gastrointestinal diseases; hypocalcemia; hypercalcemia; serious renal, hepatic, or cardiac diseases; malignant tumors under treatment with antitumor agents; drug hypersensitivity; and history of radiotherapy to the lumbar spine or pelvis (Fig. 1).

Clinical examinations

The effect of risedronate treatment was evaluated in terms of LS-BMD and the incidence of new, non-traumatic vertebral fractures (including worsening of pre-existing fractures) throughout the duration of treatment.

The LS-BMD (L_2–L_4) was determined at baseline and at designated time points via dual-energy X-ray absorptiometry, using QDR type instruments (trial CCT 301) or QDR type, XR type, or DPX type instruments (trials CCT-003 and CCT-101). These LS-BMD results were assessed by a specialized central review committee blinded to patient information.

Fig. 1 Patient inclusion flow chart. Data were collected from three randomized, double-blind, clinical phase III trials for risedronate (CCT-003, CCT-101, and CCT-301). *BMD* bone mineral density

Randomized	1466
CCT - 003	118
CCT - 101	496
CCT - 301	852

Received at least one dose and efficacy data available	1456		Did not receive any dose or efficacy data not available	10
CCT - 003	118		CCT - 003	0
CCT - 101	488		CCT - 101	8
CCT - 301	850		CCT - 301	2

Baseline BMD measured	1447		Baseline BMD not measured	9
CCT - 003	117		CCT - 003	1
CCT - 101	480		CCT - 101	8
CCT - 301	850		CCT - 301	0

Endpoint BMD measured	1369		Endpoint BMD not measured	78
CCT - 003	108		CCT - 003	9
CCT - 101	461		CCT - 101	19
CCT - 301	800		CCT - 301	50

Completed trial	1254		Discontinued from trial	115
CCT - 003	97		CCT - 003	11
CCT - 101	419		CCT - 101	42
CCT - 301	738		CCT - 301	62

Chest and lumbar spine X-rays were taken at baseline and at the end of the trial. A specialized central review committee decided whether there were pre-existing and new fractures, or if worsening of pre-existing fractures occurred. Vertebral fractures were judged based on the JSBMR diagnostic criteria for primary osteoporosis [25, 26]. An incident vertebral fracture was considered to have occurred if: the ratio of the central to anterior vertebral height (C/A) was <0.8; the ratio of central to posterior vertebral body height (C/P) was <0.8; the ratio of anterior to posterior vertebral height (A/P) was <0.75; or A, C, or P decreased by at least 20% from their baseline values. In trials CCT-003 and CCT-101, a pre-existing vertebral fracture was considered to have worsened if C/A, C/P, or A/P decreased by 20% or more from their baseline values [27]. In trial CCT-301, a semi quantitative assessment method was used to detect worsening of an existing fracture based on whether A, C, or P had decreased by at least 20% (or 4 mm) from their baseline values, in which case the condition was labeled to have progressed by one grade or more [28]. In addition, serum levels of 25-hydroxyvitamin D (further referred to as vitamin D) were measured at baseline by the radioimmunoassay method.

Statistical analyses

In order to examine the influence of baseline characteristics including age and BMD, the patients were stratified in groups according to age tertiles at baseline (<65, 65–72, and ≥72 years) and to LS-BMD T-score at baseline (osteoporotic, <−2.5; non-osteoporotic, ≥−2.5). To determine the most appropriate cutoff level of serum levels of vitamin D relevant for achieving optimal increase in BMD in response to risedronate treatment, the Akaike's information criterion (AIC) was employed [29]. A smaller AIC value indicated a more reliable model for predicting the outcome, and the serum levels of vitamin D for the smallest AIC value were used as the cutoff.

One-way ANOVA was used for comparing the percentage and absolute increments in LS-BMD between patient groups defined according to age. Two-tailed Student's t tests were conducted comparing the percentage and absolute changes in LS-BMD between the two groups defined based on baseline LS-BMD T-score. Chi-square tests were conducted for comparing the incidence of new vertebral fractures between the patient groups defined based on endpoint LS-BMD T-score. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Out of the 1466 randomized patients (118 from the CCT-003 trial, 496 from the CCT-101 trial, and 852 from the CCT-301 trial), we assessed 1447 patients whose LS-BMD was measured at baseline (Fig. 1). The baseline characteristics of all the patients included in our analysis are shown in Table 1. X-ray examinations at baseline exhibited fragility fractures in 335 out of 1406

Table 1 Baseline characteristics for patients undergoing treatment with risedronate for osteoporosis ($n = 1447$)

Characteristic	Value
Age (years)	67.5 ± 7.2
Height (cm)	150.8 ± 6.0
Weight (kg)	49.4 ± 7.0
BMI (kg/m^2)	21.8 ± 2.9
Sex (male/female)	31/1416
Use of risedronate (daily/weekly/monthly)	783/242/422
Lumbar spine BMD (g/cm^2)	0.652 ± 0.075
T-Score	−3.03 ± 0.65
Serum 25(OH)D levels (ng/mL)	20.9 ± 6.6[a]
Prevalent vertebral fractures (yes/no)	335/1071[b]

Data given as mean ± standard deviation, or number of subjects

BMI body mass index, *BMD* bone mineral density

[a] Data available for 1330 subjects

[b] Data available for 1406 subjects

patients for whom X-ray examinations were available. Baseline serum levels of vitamin D were <20 ng/mL for 595 patients (44.7%), and <30 ng/mL for 1187 patients (89.2%), out of the 1330 patients for whom these data were available (Fig. 2).

Following treatment with risedronate, LS-BMD increased significantly compared to baseline (5.62 ± 4.33%, $p < 0.0001$). There were no statistically significant differences among the age groups in terms of percentage ($p = 0.1720$) or absolute (g/cm^2) increments ($p = 0.3524$) in LS-BMD (<65 years, $n = 487$, 5.40 ± 4.44%, 0.0350 ± 0.0284 g/cm^2; 65–72 years, $n = 489$, 5.91 ± 4.20%, 0.0374 ± 0.0264 g/cm^2; ≥72 years, $n = 393$, 5.54 ± 4.33%, 0.0354 ± 0.0272 g/cm^2) (Fig. 3a, b). Results were similar when the patients were stratified into age groups using different cutoffs (<75, 75–80, and ≥80 years) rather than into tertiles (data not shown).
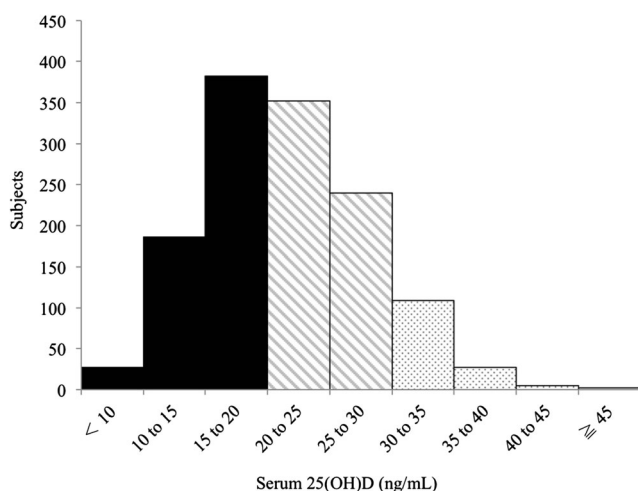
Fig. 2 Distribution of baseline serum levels of 25-hydroxyvitamin D ($n = 1330$). A significant number of patients had vitamin D deficiency (<20 ng/mL) or insufficiency (<30 ng/mL)

The percentage increment in LS-BMD was a significantly higher ($p = 0.0003$) in the osteoporotic than that in the non-osteoporotic patients (respectively: $n = 1171$, 5.80 ± 4.37%; $n = 198$, 4.59 ± 3.93%), while no significant difference ($p = 0.7524$) was observed regarding the absolute BMD increments (0.0361 ± 0.0267 and 0.0354 ± 0.0308 g/cm^2, respectively) (Fig. 3c, d).

The cutoff for serum levels of vitamin D was calculated as 21 ng/mL, according to the AIC. For the patients with baseline serum levels of vitamin D of ≥21 ng/mL, both percentage and absolute (g/cm^2) increments of LS-BMD were significantly higher ($p = 0.0138$ and $p = 0.0078$, respectively) than those in the patients with baseline serum levels of vitamin D of <21 ng/mL (respectively: $n = 626$, 5.99 ± 4.17%, 0.0383 ± 0.0264 g/cm^2; $n = 635$, 5.39 ± 4.42%, 0.0343 ± 0.0277 g/cm^2) (Fig. 3e, f).

There was no statistically significant difference between the patients with endpoint LS-BMD T-score <−2.5 ($n = 871$, 13 cases, 1.5%) and those with endpoint LS-BMD T-score ≥−2.5 ($n = 481$, 4 cases, 0.8%) regarding the incidence of new vertebral fractures, but there was a trend for lower incidence in the group with higher BMD (Fig. 4). A similar trend was observed for the patients with baseline LS-BMD T-score <−2.5 ($n = 1159$), as those with endpoint LS-BMD T-score < −2.5 ($n = 869$, 13 cases, 1.5%) had a relatively lower incidence of new fracture ($n = 869$, 13 cases, 1.5%) than did the patients with endpoint LS-BMD T-score ≥−2.5 ($n = 290$, 2 cases, 0.7%) (Fig. 5); this difference did not reach statistical significance either.

Discussion

In our post-hoc analysis of data from a large-scale, strictly controlled, phase III clinical trial conducted in Japan, we found that risedronate consistently increased LS-BMD regardless of the baseline age, BMD, or vitamin D deficiency. The influence of such factors on the efficacy of osteoporotic treatment has been previously studied, with conflicting conclusions.

Specifically, the study by McClung et al. [16] included 5445 osteoporotic women aged 70–79 years and 3886 women aged ≥80 years. The study participants, each of whom had at least one clinical risk factor for hip fracture, received treatment with oral risedronate or placebo for 3 years. It was found that BMD response in the older patients was similar to that observed in the younger cohort, and the effect on hip fracture risk was apparent in the older patients whose baseline BMD was measured and was consistent with osteoporosis. Boonen et al. [7] also reported that risedronate consistently reduced the risk for vertebral fracture both in subjects younger than 80 years (hazard ratio, 0.61; $p < 0.001$) and in those aged 80 years or older (hazard ratio, 0.56; $p = 0.003$); nevertheless, the reduction in risk for nonvertebral fractures was statistically significant only in patients younger than 80 years, and no treatment effect was seen in patients aged 80 years or older. The authors speculated that the reduced treatment effect in terms of risk for nonvertebral
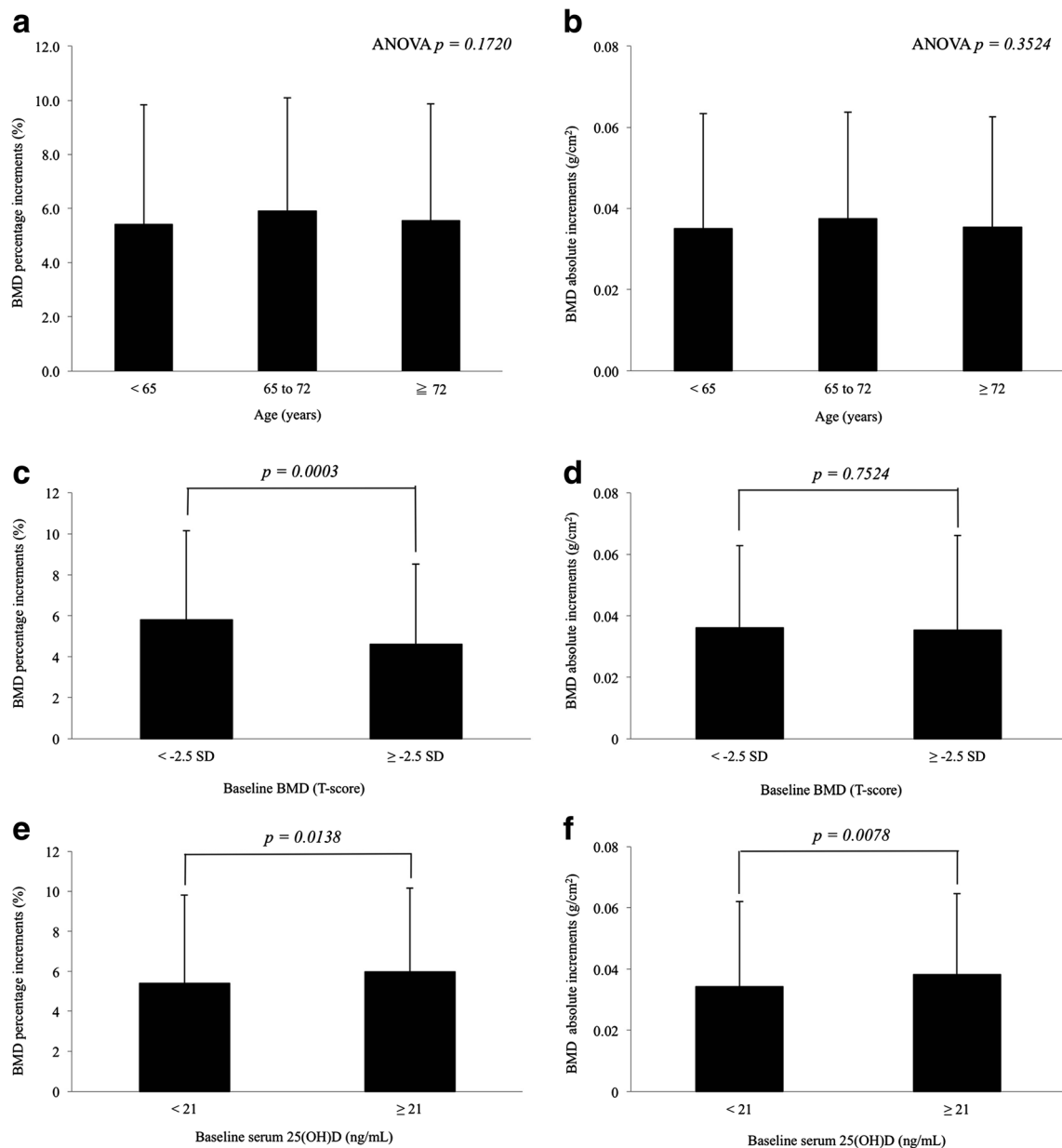
Fig. 3 Relationship between baseline characteristics and the increase in LS-BMD. Patients were divided into age tertiles based on the age at baseline. Percentage (**a**) and absolute (**b**) increments in LS-BMD from baseline are shown. The patients were stratified into two cohorts by LS-BMD (given by T-score) at baseline. Percentage (**c**) and absolute (**d**) increments in LS-BMD are shown. The patients were stratified into two cohorts by serum levels of 25-hydroxyvitamin D at baseline. Percentage (**e**) and absolute (**f**) BMD increments in LS-BMD from baseline are shown. *Error bars* represent standard deviation

fractures in the patients aged 80 years or older may reflect the age-related increase of the influence of nonskeletal risk factors (e.g., falling) for these types of fractures. Adami et al. [8] conducted a longitudinal study regarding the incidence of inadequate treatment response in osteoporosis patients, and concluded that those with inadequate clinical response to treatment with antiresorptive agents (alendronate, risedronate, and raloxifene) were significantly older ($p = 0.032$) and more frequently had multiple vertebral deformities ($p = 0.013$). Watts et al. [13] collected data on 3684 postmenopausal women involved in the

Vertebral Efficacy with Risedronate Therapy trial. It was reported that the incidence of new fractures decreased to a similar extent in patients treated with risedronate and in those treated with placebos, and the effect was observed both in patients aged <70 years and in those aged ≥70 years. With respect to alendronate therapy, Ensrud et al. [30] performed post-hoc analyses of data from the Fracture Intervention trial, and reported that the alendronate-induced reduction in risk for fractures was similar for patients aged <75 years and for those aged ≥75 years. Hochberg et al. [31] analyzed data on 3658 postmenopausal women with
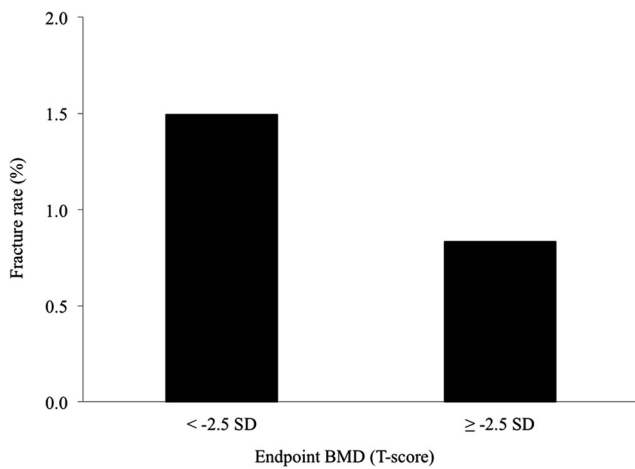
Fig. 4 Relationship between endpoint BMD and the incidence of new vertebral fractures

osteoporosis enrolled in the same Fracture Intervention trial, and showed that alendronate is effective in reducing the risk of symptomatic osteoporotic fractures across a spectrum of ages (55–80 years). In our study on the effect of risedronate therapy, both percentage increments and absolute increments in LS-BMD were similar across the age tertiles, which is in agreement with the previous reports on the effect of alendronate therapy [30, 31].

Regarding the influence of baseline BMD, Gordon et al. [14] performed a linear regression analysis of the relationship between baseline BMD and BMD percentage increase in the lumbar spine and femoral neck, and found a statistically significant negative correlation; however, the sample size in their study was modest ($n = 44$), and absolute BMD increments were not described. Ensrud et al. [30] also examined the consistency of the effect of alendronate in preventing fractures within groups of patients defined according to baseline BMD of the femoral neck (FN-BMD); with respect to reducing the risk of new vertebral fractures, the treatment appeared to be as
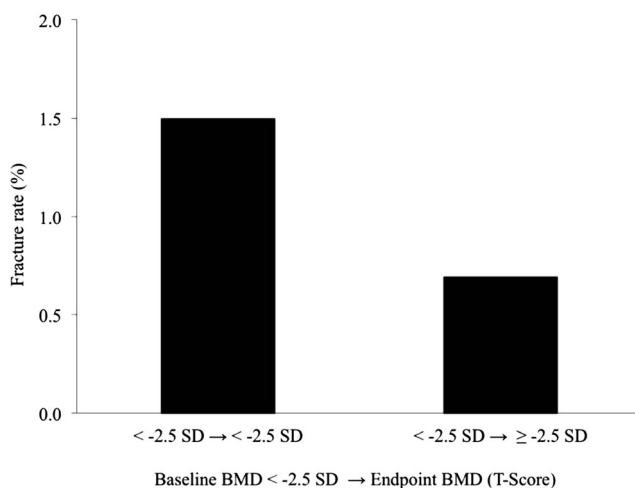
Fig. 5 Relationship between endpoint BMD and the incidence of new vertebral fractures for patients with baseline BMD <−2.5

effective in women with FN-BMD <0.59 g/cm^2 as in those with FN-BMD ≥0.59 g/cm^2. The authors concluded that alendronate effectively reduces fracture risk in postmenopausal women with vertebral fracture and low BMD, and the effect is stronger in women at highest risk because of advanced age or severe osteoporosis. Our results have shown that BMD percentage increments are 1.21% higher in the subjects who were osteoporotic at baseline (T-score <−2.5) than those in the non-osteoporotic subjects, while absolute increments did not differ. On the other hand, as shown in Figs. 4 and 5, the incidence of new vertebral fractures seems dependent on the endpoint BMD, suggesting that risedronate therapy consistently increases the absolute value of LS-BMD, but early intervention may be important to ensure optimal reduction in fracture risk.

Vitamin D plays an essential role in the maintenance of bone strength and muscle function. Vitamin D repletion is pre-requisite inclusion criteria, and vitamin D is usually supplemented in most of the current clinical trials of osteoporosis treatments, though that is not always the case in routine clinical practice. Therefore, the role of vitamin D in bisphosphonate therapy is an important clinical question. Adami et al. [15] studied data on 1515 women with postmenopausal osteoporosis undergoing treatment with antiresorptive agents including alendronate, risedronate, and raloxifene for over 13 months; they reported that vitamin D-deficient and -repleted subjects differed significantly with respect to annual changes in spine and hip BMD; the adjusted odds ratio measuring the risk for incident fractures in vitamin D-deficient women relative to that in vitamin D-repleted women was 1.77 (95% confidence interval, 1.20–2.59; $p = 0.004$). In our present study, 595 out of the 1330 patients (44.7%) had serum levels of vitamin D <20 ng/mL, while 1187 out of the 1330 patients (89.2%) had serum levels of vitamin D <30 ng/mL (Fig. 2). According to the guidelines of the American Society of Endocrinology [32], vitamin D deficiency and insufficiency are defined when the serum levels of vitamin D are <20 and 21–29 ng/mL, respectively, suggesting that 90% of the patients in our cohort had vitamin D deficiency or insufficiency. These results are almost consistent with those of Ishijima et al., who reported that vitamin D levels were <30 ng/mL in 82% of Japanese postmenopausal osteoporosis patients ($n = 52$) undergoing a 6-month trial of alendronate therapy [33]. Okazaki et al. reported even higher percentage of vitamin D deficiency: <20 ng/mL in 75.7% of the Japanese population [34].

On the other hand, Peris et al. reported that 30% of Spanish postmenopausal osteoporotic women ($n = 120$) receiving alendronate or risedronate showed inadequate response to treatment, with significantly lower levels of vitamin D (22.4 ± 1.3 vs. 26.6 ± 0.3 ng/mL, $p = 0.01$) and higher incidence of vitamin D levels <30 ng/mL (91 vs. 69%, $p = 0.019$). Patients with values of vitamin D >30 ng/mL had a greater increase in LS-BMD than patients with values of vitamin D <30 ng/mL (3.6 vs. 0.8%, $p < 0.05$) [10].

Ishijima et al. administered alendronate to 52 Japanese postmenopausal women for 6 months; serum levels of vitamin D of ≥25 ng/mL were determined to be the minimum levels necessary to achieve an adequate effect of alendronate treatment. The increase in LS-BMD after a 6-month alendronate treatment was significantly lower in patients with serum vitamin D levels <25 ng/mL (3.3%; 95% confidence interval, 1.7–5.0%) than in those with serum vitamin D levels ≥25 ng/mL (6.8%; 95% confidence interval, 3.8–9.4%) [33].

In accordance with those reports, both of the percent and absolute increments in LS-BMD after risedronate treatment were significantly higher for patients with serum levels of vitamin D ≥21 ng/mL when compared to the those seen in patients with serum levels of vitamin D <21 ng/mL (respectively; $5.99 \pm 4.17\%$, 0.0383 ± 0.0264 g/cm^2; and $5.39 \pm 4.42\%$, 0.0343 ± 0.0277 g/cm^2; respectively, $p = 0.0138$ and $p = 0.0079$), suggesting the importance of vitamin D repletion in osteoporosis treatment.

The current study is limited by its post-hoc design. Another limitation of this study is that no placebo groups were available for comparison in the trials considered, and therefore, the effectiveness of risedronate on reducing fracture risk could not be compared between younger and older patients. Furthermore, other confounding factors remain to be investigated. We believe that a further prospective study is necessary to elucidate whether taking natural vitamin D supplements or alfacalcidol is able to increase the therapeutic effects of bisphosphonates against osteoporosis.

In conclusion, the results of this study suggest that risedronate administration consistently increases the absolute value of LS-BMD, regardless of age or baseline BMD. However, early start of the treatment seems to be important in order to prevent new fractures. Vitamin D deficiency and insufficiency are common conditions, and the BMD change in response to risedronate treatment seems to be smaller in the patients with serum levels of vitamin D <21 ng/mL when compared to the change seen in the patients with serum levels of vitamin D ≥21 ng/mL. This suggests that vitamin D supplementation may be important to achieve optimal LS-BMD response to risedronate treatment.

Compliance with ethical standards

Conflicts of interest Dr. Mawatari and Dr. Iwamoto have no conflict of interest to declare with respect to the work described herein.

Mr. Muraoka discloses an employment relationship with EA Pharma Co., Ltd., Tokyo, Japan.

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