were followed up for a mean of 8.4 (1–14) years were included in the study.

The Committee for the Ethics of Human Research at Mie University approved the study protocol, and all participants provided written, informed consent before enrollment.

Baseline data obtained from standard questionnaires administered by orthopedic surgeons included information regarding age, gender and medical history. Body–mass index (BMI) was calculated from height and weight. Other medical examinations comprised radiography of the thoracic and lumbar spine and assessments of BMD at the distal third of the non-dominant side radius using dual energy X-ray absorptiometry (DCS-600EX; Aloka, Tokyo, Japan). We defined OP as T scores of BMD < 2.5 standard deviations (SD) below peak bone mass according to the World Health Organization criteria [20]. Central DXA of the lumbar spine or femoral neck is generally used to diagnose OP. However, many elderly individuals have vertebral deformities. Thus, lumbar DXA tends to show high BMD. Positioning (degree of internal rotation) of the femoral neck for DXA is difficult and thus reproducibility is poor and femoral DXA is unsuitable for longitudinal studies. Therefore, we assessed the participants using radial DXA.

We assessed VF from lateral radiographs of the thoracic and lumbar spine in terms of a wedge, biconcave or crushed appearance according the Japanese Society of Bone and Mineral Research criteria [21].

Based on the baseline OP and VF criteria, the participants were allocated to the following groups: with OP and without VF (OP group), with VF and without OP (VF group), with OP and VF (OP + VF group) and without OP and VF (Control group).

We assessed the survival/mortality rates of the participants until 2011 by reviewing their medical histories and death certificates with the help of local hospital staff. Causes of death were determined from death certificates.

Statistical analysis

Means ± SD were calculated for variables unless otherwise noted. Significant differences in baseline characteristics between the OP and Control groups, between the VF and Control groups, and between the OP + VF and Control groups were determined using t and χ^2 tests. Survival curves for the OP, VF, OP + VF and Control groups were constructed based on the Kaplan–Meier method. We also used Cox proportional hazards analyses to determine age–gender-adjusted mortality (as hazard ratios [HR] and 95% confidence intervals [CI]) among three groups (OP, VF and OP + VF groups) and the Control group. The Control group served as the reference for the Cox proportional hazards analyses. The period of the Cox model was measured in months. The significance level for entry into the model was 0.05. All data were statistically analyzed using PASW Statistics version 18 software (SPSS, Chicago, IL, USA).
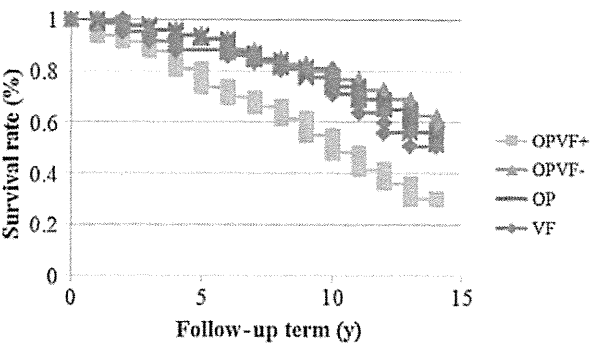

Figure 1. Survival rates for all groups. OP, osteoporosis; VF, vertebral fractures.

Results

The overall mean age of participants was 72.1 ± 6.5 years (average for men and women, 72.4 ± 6.3 and 72.0 ± 6.7, respectively). During a mean follow-up of 8.4 years, 304 participants (29.7%) had died. Table 1 compares the physical characteristics among the four groups. Height, weight and BMI were significantly lower, whereas the ratio of females and age were significantly higher for the OP + VF and OP groups than for the Control group.

Figure 1 shows the Kaplan–Meier survival curves for the four groups. The respective 5- and 10-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2% and 54.9%, 77.4%, 80.7% and 79.8%. Table 2 shows the results of the age and gender-adjusted Cox proportional hazards analyses. The mortality was significantly worse for the OP + VF group than for the Control group. The HR for the OP + VF group was 1.89 (95% CI, 1.27–2.77). The mortality rate tended to be worse for the OP group, but the difference did not reach significance.

Table 3 shows the causes of the 304 deaths. Malignant tumors, heart disease, old age, accidents, suicide, other and unknown causes accounted for 24.7%, 18.8%, 3.3%, 3.6%, 2.0%, 12.5% and 8.9%, respectively, of the deaths. These data were similar to the national data for Japan during 2009 [22]. The causes of death did not significantly differ among the four groups.

Discussion

We recognized the combination OP and VF (OP + VF group) as osteoporotic VF, and found that this combination was associated with high mortality rates among a Japanese village community.

Johnell et al. [15] and Cooper et al. [6] reported 5-year survival rates for individuals with VF of 28% in Sweden, and 61% in the USA, respectively. Our rates of all groups were higher than these findings, which might have been due to our study cohort being generally healthier.

Some authors [4,5] have reported that low BMD is a risk factor for death, and that it is probably related to comorbidity in affected patients. Of course, OP predisposes bones to easy breakage and

Table 1. Baseline physical characteristics of all groups.

	OP + VF n = 125	OP n = 356	VF n = 59	Control n = 484
Gender (M/F)	9/116*	33/323*	40/19	281/201
Age (y)	77.1 ± 7.6*	72.2 ± 6.6*	72.1 ± 6.1	70.8 ± 5.6
Height (cm)	143.1 ± 7.6*	147.7 ± 7.0*	154.5 ± 7.4	154.8 ± 7.5
Weight (kg)	46.9 ± 10.0*	49.9 ± 8.4*	55.6 ± 10.1	56.6 ± 8.4
BMI (kg/m²)	22.8 ± 3.9†	22.8 ± 3.3*	23.2 ± 3.6	23.6 ± 3.0

BMI, body–mass index; F, female; M, male; OP, osteoporosis; VF, vertebral fractures.

*p < 0.01 and †p < 0.05 versus Control.

Table 2. Age and gender-adjusted Cox proportional hazards findings versus Control.

	Alive	Dead	HR	95% CI	DF	P
					3	0.01
Control	360	124	1			
OPVF+	64	61	1.88	1.27–2.77	1	<0.005*
OP	255	101	1.33	0.98–1.81	1	0.07
VF	41	18	0.91	0.55–1.49	1	0.70

95% CI, 95% confidence intervals; HR, hazard ratio; OP, osteoporosis; VF, vertebral fractures.

*p < 0.005 versus Control.

Table 3. Causes of death.

	OP + VF n = 125	OP n = 356	VF n = 59	Control n = 484	Total n = 1024
Malignant tumor	11	21	3	40	75
Heart disease	10	18	3	26	57
Pneumonia	6	17	5	22	50
Brain disease	4	14	2	10	30
Old age	4	5	0	1	10
Accident	2	5	2	2	11
Suicide	2	2	1	1	6
Other	17	9	1	11	38
Unknown	5	10	1	11	27
Total	61	101	18	124	304

OP, osteoporosis; VF, vertebral fractures.

the relationship between OP and subsequent mortality might explain why survival decreases after sustaining osteoporotic fractures such as those of the hip [23]. In fact, a few studies have found that increased mortality is indeed associated with hip fractures [23–25]. Kanis et al. [26] reported that about 23% of deaths involving hip fractures might be causally related to the fracture itself. However, some [27–29] have shown that OP is associated with atherosclerosis, whereas others [30,31] have shown that OP does not increase the risk of mortality associated with fractures but is rather due to cardiovascular disease. The present study found that only OP without VF tended to associate with mortality, but a significant relationship was not identified ($p = 0.07$). Further study is needed to clarify this issue.

In term of causes of death, Kado et al. [14] reported that women with VF were 2- to 3-fold more likely to die of pulmonary causes than those without fractures. They also explained that severe kyphosis was highly predictive of pulmonary death, perhaps because those with underlying lung disease and decreased respiratory reserves might not be able to tolerate restrictive changes in thoracic anatomy resulting from VF. Indeed, Leech et al. [32] described a 9% decrease in predicted forced vital capacity per VF. Our preliminary report [19] associated the number of VF with mortality. Moreover, multiple VF might cause esophageal hiatal hernia and esophagitis [33,34], and restrict physical function, activities of daily living and quality of life [35,36]. Kado et al. [14] and Cooper et al. [6] also associated VF with increased cancer mortality. Thus, previous reports have associated VF with various causes of death. The present study associated the combination of VF and OP with increased mortality, but without relevance to a specific cause of death. Further investigation is needed to clarify the causes of death associated with osteoporotic VF.

Our study has several limitations. First, Miyagawa village is a rural mountain community, and many of the inhabitants are typically engaged in forestry. Thus, whether the present findings reflect the general population of Japan is doubtful. Second, participants who could attend the hospital were generally healthier than non-participants. Third, this investigation was based on a relatively small cohort. Therefore, the statistical significance of the risk factors might be relatively low. Fourth, since VF was evaluated only by radiographic morphometry and not clinically, we could not investigate differences between clinical and morphological VF.

In conclusion, the respective 5-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2%. The mortality rate was worse for elderly individuals with than without OP combined with VF (osteoporotic VF). Since osteoporotic VF increased the mortality rate 2-fold, efforts should be directed toward preventing such fractures in elderly populations to decrease mortality rates and increase life expectancy.

Conflict of interest

None.

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ORIGINAL ARTICLE

An algorithm using the early changes in PINP to predict the future BMD response for patients treated with daily teriparatide

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A. Matsumine · T. Nakamura · T. Kono · A. Sudo

Abstract
Summary About two thirds of patients with a procollagen type I N-terminal propeptide (PINP) increase of >80 μg/l at 1 month after starting teriparatide therapy showed a ≥10 % increase in lumbar spine (LS) bone mineral density (BMD) from baseline at 12 months. We recommend this algorithm as an aid in the clinical management of patients treated with daily teriparatide.
Introduction An algorithm using PINP is provided in osteoporotic patients with teriparatide treatment. The correlations between the early changes in PINP and the subsequent BMD changes after daily teriparatide therapy were studied to develop an algorithm to monitor patients.
Methods We evaluated whether early changes in PINP correlated with the changes in BMD at 12 months and developed an algorithm using the early changes in PINP to predict the upcoming BMD increases.
Results The highest correlation coefficient for the relationship between PINP and LS BMD response was determined for the absolute change in PINP at 1 month and the percent change in LS BMD at 12 months ($r=0.36, p <0.01$). Using a receiver operator curve analysis, we determined that an 80 μg/l increase in PINP was the most convenient predictor of a 10 % increase in LS BMD from baseline (area under curve=0.72). Using a cut-off value of 80 μg/l, the positive predictive value for predicting a 10 % increase in LS BMD from baseline to 12 months was 65 %.

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Conclusion Greater short-term changes in PINP with teriparatide therapy are associated with greater 12-month increases in LS BMD. About two thirds of patients with a PINP increase of >80 μg/l at 1 month after starting treatment showed a ≥10 % increase in LS BMD from baseline at 12 months. We recommend this algorithm as an aid in the clinical management of patients treated with teriparatide.

Keywords BMD · Clinical trials · Osteoporosis · PINP · Teriparatide

Introduction

Fractures in patients with osteoporosis are a global burden for both individuals and health-care systems. Among postmenopausal females aged 60 years and older, the mortality-adjusted residual lifetime risk of fractures has been estimated to be 44–65 % [1]. Fractures in the elderly are associated with high morbidity and mortality; pain and immobility lead to a loss of quality of life and an increase in general frailty. Daily injection of teriparatide [human parathyroid hormone PTH(1-34) is known to increase the bone mineral density (BMD) and markers of bone formation, and to reduce the fracture risk. The vertebral fracture risk was reduced in the teriparatide group by 84 % compared to the placebo group [2]. Miyauchi et al. [3] assessed the efficacy of teriparatide in Japanese males and females with osteoporosis during a 12-month period, and reported that teriparatide significantly increased BMD at the lumbar spine (LS) by 10.0 % and BMD at femoral neck (FN) by 2.2 %.

Bone turnover markers provide information on the rates of bone formation and resorption, and correlate with the rate of bone loss. Bone turnover markers also have the potential to provide early feedback on the progress of the patient, and allows for changes to be made in the management of

osteoporosis. For example, patients treated with osteoporosis therapy who have a positive marker response can be given a positive message, which may increase their compliance and persistence with osteoporosis therapy [4–6]. Some reports showed that early changes in bone turnover markers represent a dynamic response to treatment and would correlate with upcoming BMD increases in patients treated with antiresorptive agents [7, 8]. We found several reports concerning the relationship between the early bone marker changes and subsequent BMD increases during the treatment with daily teriparatide [6, 7, 9, 10]. Tsujimoto et al. [6] reported that the mean procollagen type I N-terminal propeptide (PINP) change was 49.4 µg/l at 1 month after starting treatment, and they revealed that there was a correlation between the early changes in PINP and later changes in LS BMD. However, a clinical problem persists in which clinicians have little guidance concerning how a bone turnover marker change would predict a future remarkable BMD increase in patients under treatment with daily teriparatide.

The primary objective of this study was to determine whether early changes in PINP correlate with changes in BMD at 12 months in osteoporotic patients with teriparatide. The secondary objective was to provide an algorithm with regard to 12-month BMD increase that can be expected in clinical practice by using the early changes in the levels of PINP.

Materials and methods

Study subjects

One hundred fifty-four patients diagnosed with osteoporosis participated in this study. The inclusion criteria for the present study were postmenopausal females and males diagnosed with osteoporosis and at high risk of fracture. A high risk of fracture was defined when patients met at least one of the following criteria [3]: (1) BMD at lumbar spine L1—4<80 % of the young adult mean (YAM; for all subjects reported in the Japanese Normative Female Database [11]), with a minimum of one prevalent fragility fracture; (2) BMD at L1—4<70 % of YAM and age ≥65 years; (3) BMD at L1—4<65 % of YAM and age ≥55 years or (4) more than three previous osteoporotic fractures. The exclusion criteria were patients with illnesses affecting bone and calcium metabolism or other bone disorders other than osteoporosis, and patients with serious cardiovascular, renal, or hepatic dysfunction. Patients with a high concentration of serum calcium (>11 mg/dl) at baseline were also excluded.

Measurements

We measured BMD of the LS and FN using dual-energy x-ray absorptiometry on the DPX-Bravo instrument (GE Healthcare,

Madison, WI) at baseline at 4, 8, and 12 months after starting treatment, and measured the level of the biochemical bone formation marker, PINP using a radioimmunoassay (Orion Diagnostica, Espoo, Finland), at baseline and 1 and 4 months after starting treatment.

Statistical analysis

As many of the patients who were started on teriparatide therapy had previously been treated with antiresorptive agents, we first compared these previously treated patients with osteoporosis treatment-naïve patients in terms of the changes in LS and FN BMD after 12 months of teriparatide treatment. The changes in PINP at 1 and 4 months after starting treatment were also compared. Subsequently, the relationship between the changes in PINP, measured as both absolute and percent values, and the absolute and percent changes in BMD were also evaluated by a Spearman rank correlation analysis.

To determine the clinical performance of the PINP assays, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false positive rate, false negative rate, agreement (true positive and true negative rate), and odds ratios were calculated. In this study, we used three PINP cut-off values. The cut-off values of 10 and

Table 1 Baseline clinical characteristics (n=154)

Variable	Mean (SD), n (%)
Age (years)	76.1±8.0
Gender, n (%)	
Females	142 (92 %)
Males	12 (8 %)
Height (cm)	150.7±7.1
Weight (kg)	47.8±8.8
BMI (kg/m²)	21.1±3.5
Pre-treatment, n (%), mean period (range)	
Alendronate	70 (45 %), 37 months (3–76 months)
Risedronate	12 (8 %), 19 months (4–73 months)
SERM	13 (8 %), 30 months (5–70 months)
Previous osteoporotic fractures, n (%)	
Vertebral body	114 (74 %)
Proximal femur	26 (17 %)
Distal radius	7 (5 %)
Proximal humerus	3 (2 %)
BMD	
Lumbar spine (g/cm²)	0.808±0.148
Femoral neck (g/cm²)	0.627±0.116
Bone turnover marker	
Serum PINP (µg/L)	50.7±39.5

SD standard deviation, *BMI* body mass index, *BMD* bone mineral density, *PINP* procollagen type I N-terminal propeptide

Fig. 1 The mean percent changes in lumbar spine and femoral neck BMD during teriparatide treatment (*$p < 0.01$, **$p < 0.05$ vs. baseline; paired t test). Data are mean + SD
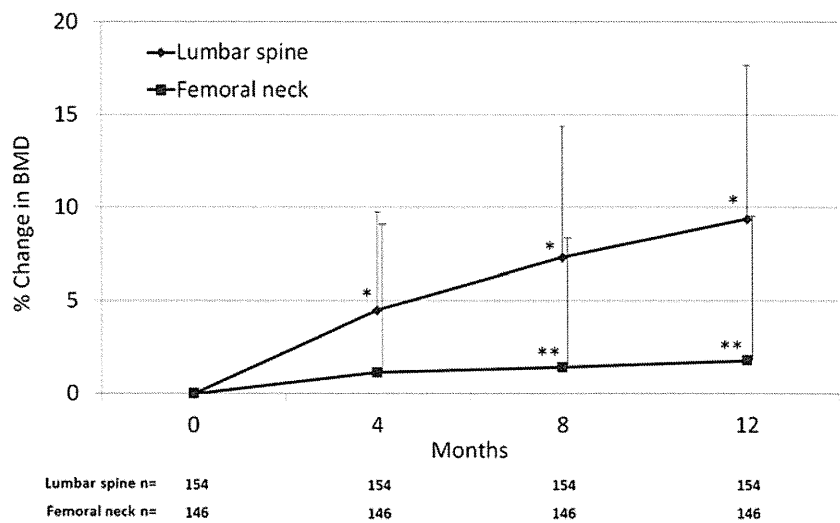
50 μg/l was based on previous values reported in the literature [5, 6, 12], while the other cut-off value was determined by using a receiver operator characteristic (ROC) analysis. The overall diagnostic accuracy for predicting the BMD changes was assessed by the area under the ROC curves (AUC). The analyses were performed using the SAS software program, version 9.1 (SAS Institute, Inc., Cary, NC, USA), and values of $p < 0.05$ were considered to be statistically significant.

Compliance

The medication compliance was assessed at each visit. Participants were queried regarding the number of missed doses of medication and were considered compliant if they consumed ≥85 % of the study drug.

The protocol was in compliance with the ethical principles stated in the Declaration of Helsinki, and was approved by the Ethics Committee of Tomidahama Hospital. Written informed consent was obtained from the patients.

Results

Baseline characteristics

The age, gender, height, weight, body mass index (BMI), previous treatments, previous osteoporotic fractures, and baseline BMD at the LS and FN and baseline PINP levels are presented in Table 1. Ninety-five patients (61 %) had been previously treated with antiresorptive agents for at least 3 months just before beginning the teriparatide treatment. The most common antiresorptive agents used were as follows: alendronate ($n=70$), risedronate ($n=12$), and selective estrogen receptor modulator ($n=13$).

The changes in BMD and PINP in response to teriparatide treatment

There were no significant differences between the patients previously treated with antiresorptive agents and the osteoporosis treatment-naïve patients in terms of LS and FN BMD

Fig. 2 The mean changes in PINP during teriparatide treatment (*$p < 0.01$ vs. baseline; paired t test). Data are mean ± SD
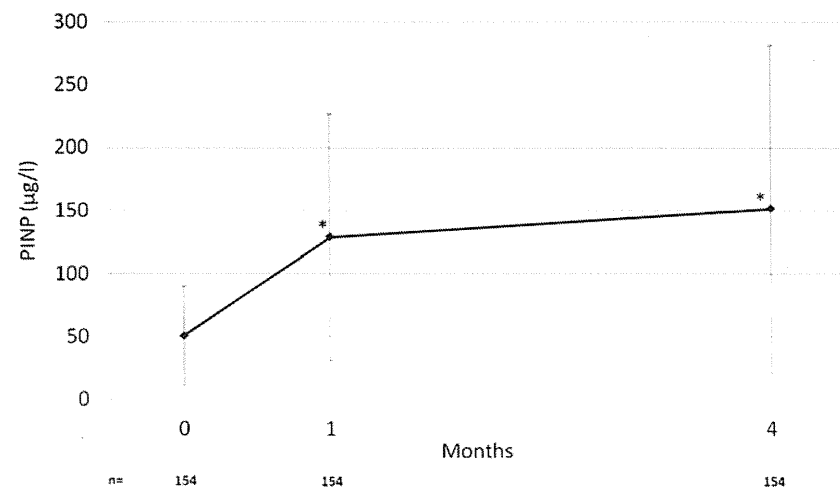
Table 2 Spearman correlation coefficients between the absolute or percent changes in PINP and BMD response at LS and FN BMD at 12 months of treatment

Change	Time (months)	Percent change in LS BMD		Absolute change in LS BMD		Percent change in FN		Absolute BMD change in FN BMD	
		r	p	r	p	r	p	r	p
PINP									
Absolute	1	0.36	<0.01	0.34	<0.01	0.17	<0.05	0.17	<0.05
Percent	1	0.17	<0.05	0.17	<0.05	0.13	n.s.	0.13	n.s.
Absolute	4	0.34	<0.01	0.32	<0.01	−0.03	n.s.	−0.03	n.s.
Percent	4	0.21	<0.05	0.19	<0.01	−0.06	n.s.	−0.06	n.s.

PINP procollagen type I N-terminal propeptide, *LS* lumbar spine, *FN* femoral neck, *r* correlation coefficient, *p* p value, *n.s.* not significant

at baseline (data not shown). Patients who had been previously treated with antiresorptive agents had significantly lower PINP values at baseline than treatment-naïve patients (34.7±27.1 vs. 76.3±42.9 μg/l, p <0.01, Mann–Whitney U test) [mean ± standard deviation (SD)]. No significant differences were observed in the increase in LS and FN BMD at 12 months between the previously treated patients and the osteoporosis treatment-naïve patients (data not shown). Comparisons of absolute PINP changes at 1 and 4 months after starting teriparatide treatment also showed no significant differences between the antiresorptive-treated patients and the osteoporosis treatment-naïve patients except on the percent change in PINP values at 1 and 4 months (data not shown). Previous antiresorptive agents-treatment did not have any significant impact on the absolute changes in PINP values at 1 and 4 months compared with treatment-naïve patients (data not shown).

Based on the results of the above analyses, we performed the subsequent analyses with a focus on all patients. The LS BMD after 12 months of teriparatide therapy showed a 9.4±8.3 % increase, and the FN BMD after 12 months showed a 1.8±7.7 % increase (Fig. 1). The proportions of patients with a LS BMD increase from baseline ≥3, 5, and 10 % at 12 months were 79, 71, and 38 %, respectively. The

mean absolute PINP change was 78.1±82.4 μg/l at 1 month and 100.7±122.2 μg/l at 4 months after starting the treatment (Fig. 2). The proportions of patients with a PINP increase at 1 month from baseline >10, 50, and 80 μg/l were 94, 56, and 31 %, respectively.

Statistically significant correlations were observed between absolute PINP changes at 1 month and LS and FN BMD changes at 12 months (both absolute and percent changes), and between absolute PINP changes at 4 months and LS BMD changes at 12 months (both absolute and percent changes) (Table 2). The absolute changes in PINP at 1 month after starting treatment were more strongly correlated with 12-month BMD changes than that of the other changes in PINP. The highest correlation between PINP and BMD response was observed between the absolute changes in PINP at 1 month and the percent changes in LS BMD at 12 months (r=0.36, p <0.01) (Fig. 3). The second highest correlation coefficient value was observed between the absolute changes in PINP at 1 month and the absolute changes in LS BMD at 12 months (r=0.34, p <0.01).

The above analyses indicated that the absolute change in PINP was the most useful potential aid in the management of patients treated with teriparatide, so we performed additional analyses with a focus on the absolute changes in PINP.

Fig. 3 The relationship between the absolute changes in PINP at 1 month after starting teriparatide treatment, and the percentage change in lumbar spine BMD after 12 months of treatment. The *solid lines* show the cut-off value at BMD 10 % and PINP 80 μg/l

$$y = 6.199 + 0.41 {}^* x$$
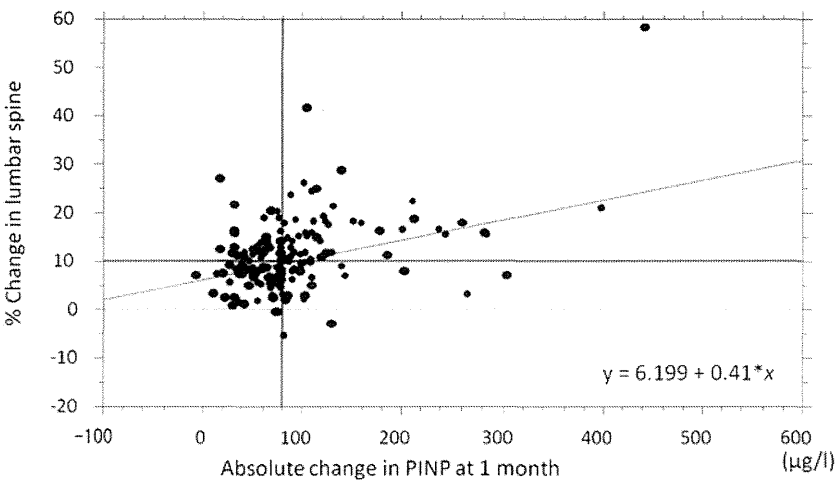
Prediction of LS BMD response based on the changes in PINP after 1 month of treatment

To further assess the potential of using PINP changes to predict the later percent changes in LS BMD at 12 months, an ROC analysis was performed. Using the ROC analysis, we determined that an 80 μg/l increase in PINP was the most convenient predictor of LS BMD response in clinical practice (area under the curve=0.72). Using a PINP cut-off value of 80 μg/l, the sensitivity for a ≥10 % increase in LS BMD from baseline to 12 months was 53 %, and the specificity was 82 %. The PPV was 65 %, the NPV was 74 %, the false positive rate was 18 %, the false negative rate was 47 %, the agreement was 71 %, and odds rate was 5.08 (associated 95 % confidence interval; 95 % CI, 2.44–10.57). In brief, if PINP increased more than 80 μg/l 1 month after treatment, the possibility of a more than 10 % increase in LS BMD at 12 months was 65 %. About two thirds of patients with a more than 80 μg/l increase in PINP at 1 month had a more than 10 % increase in LS BMD at 12 months. The performance of the absolute change in PINP at 1 month evaluated by the PPV for a 10 % increase in LS BMD at 12 months is shown in Table 3. The PPV was the highest (76 %) when using a PINP cut-off value of 110 μg/l.

To predict a 5 % increase in LS BMD, using a PINP cut-off value of 50 μg/l was the most convenient, with an AUC of 0.65, the sensitivity of 63 %, the specificity of 61 %, the PPV of 80 %, the NPV of 40 %, the false positive rate of 39 %, the false negative rate of 37 %, the agreement of 62 %, and the odds rate of 2.67 (associated 95 % confidence interval; 95 % CI, 1.30–5.49). Of note, four fifths of the patients with a more than 50 μg/l increase in PINP concentration at 1 month had a more than 5 % increase in LS BMD at 12 months.

Discussion

In this study of daily teriparatide among patients at high risk for osteoporotic fractures, we found that greater short-term treatment-related increases in PINP were associated with a greater increase in LS BMD at 12 months. The highest correlation between the PINP and BMD response was observed between the absolute change in PINP at 1 month and the percent change in LS BMD at 12 months. The correlation was reinforced by an AUC analysis. Using a ROC analysis, we determined that an 80 μg/l increase in PINP was the most convenient predictor of LS BMD response in clinical practice. Using a PINP cut-off value of 80 μg/l after 1 month of treatment, about two thirds of the patients had a more than 10 % increase in LS BMD at 12 months. Our results are in agreement with those of the previous analyses using pharmacodynamic modeling, where PINP concentration was

Table 3 The performance of the absolute change in PINP at 1 month for predicting a 10 % increase in LS BMD at 12 months

Cut-off value (μg/l)	0	10	20	30	40	50	60	70	80	90	100	110	120	130
Number of patients > cut-off value (%)	149 (97 %)	144 (94 %)	130 (84 %)	116 (75 %)	99 (64 %)	86 (56 %)	77 (50 %)	64 (42 %)	48 (31 %)	40 (26 %)	34 (22 %)	29 (19 %)	23 (15 %)	20 (13 %)
PPV	39.6 %	41.0 %	43.1 %	45.7 %	48.5 %	50.0 %	51.9 %	54.7 %	64.6 %	70.0 %	73.5 %	75.9 %	73.9 %	75.0 %

PPV positive predict value

identifies as a strong predictor of the percent increase in LS BMD. This study showed that PINP change at 1 month was the most sensitive and accurate predictor of the LS BMD response.

Bone turnover markers can rapidly provide information on the early response to osteoporosis therapy. The increases in bone turnover markers seen with teriparatide indicate that there is an early and profound effect on the bone turnover. The increase in the bone formation marker concentration signifies overall activation of the remodeling process. Because teriparatide also leads to early and sustained increases in LS BMD, a continuously positive coupling balance consistent with net bone formation predominates. In this clinical trial, most patients (94 %) treated with teriparatide had a >10 μg/l increase in PINP concentration after 1 month of treatment. This result confirms that PINP level is useful for assessing both the patient response to treatment, as well as their adherence to treatment. Patients with a significant increase in PINP level at 1 month can be provided with a positive message regarding their good compliance and/or immediate response to teriparatide (Fig. 4). Patients without a significant early increase in PINP concentration during teriparatide therapy may require evaluation of their adherence, how they are storing and injecting their teriparatide, and their underlying medical problems, such as vitamin D deficiency. If neither a significant increase in PINP level nor a significant increase in BMD is observed by 4 months after starting treatment, switching to a different treatment for osteoporosis should be considered.

Eastell et al. recommended selecting the absolute, rather than percent, changes in PINP to assess the teriparatide responsiveness for two reasons [5]. First, the absolute changes were easier to calculate and interpret in clinical practice.

Second, the percent is greatly affected by the baseline turnover. Our findings support Eastell et al.'s opinions, and we also recommend using the absolute change in PINP. In addition, we found that the absolute change in PINP at 1 month was a more accurate predictor of the increase in LS BMD than the percent change.

The diagnostic capacity of PINP was tested by an AUC analysis, and the absolute change in PINP at 1 month was confirmed to be the most reliable predictive marker. The AUC value, representing the predictive accuracy for a more than 10 % increase in LS BMD at 12 months, was the highest for PINP concentration at 1 month (0.72). Although the PPV was higher if the cut-off value was established at a >110 μg/l increase in PINP at 1 month, we suggest using a cut-off value of 80 μg/l because of a bias between the proportion of strong responders (>110 μg/l increase, 19 % of patients) and weak responders (≤110 μg/l increase, 81 % of patients). Chen et al. showed that the AUC value for PINP concentration at 3 months was high (0.81) using a cut-off value of a 3 % increase in LS BMD at 18 months [9]. They also showed that the AUC value for type I collagen C-terminal propeptide (PICP) at 1 month was the highest (0.83). In our study, the mean LS BMD increased at 12 months by 9.4 %, and the majority patients (77 %) had a ≥3 % increase. We recommended a cut-off value of a 10 % increase in LS BMD for two reasons. First, the mean increase in LS BMD after 12 months of teriparatide therapy was 9.4 %, which was similar to a previous report in Japanese subjects (10.0 % increase in LS BMD after 12-month treatment) [3]. The second advantage was that a cut-off value of a 10 % increase in LS BMD was a perspicuous indicator not only for the physicians but also for the patients. Improving adherence to medications is essential for osteoporosis treatment. Rapid and high increases in BMD
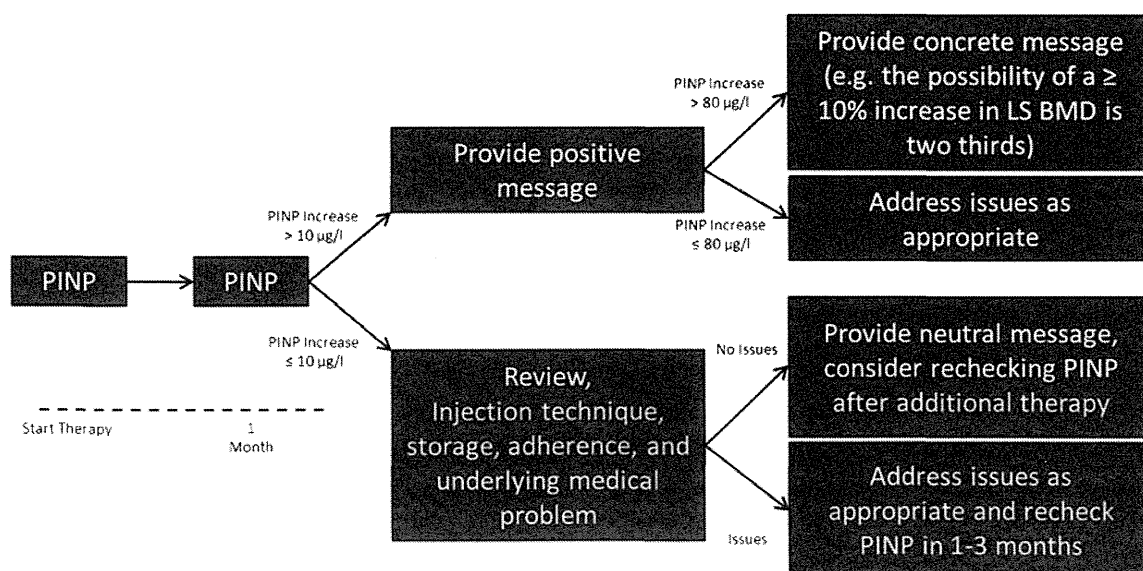

Fig. 4 The algorithm for using PINP value to monitor patients being treated with teriparatide

had a positive impact on osteoporotic patient's adherence [13]. As adherence to PTH(1-84) treatment for up to 24 months is associated with greater efficacy [14], we recommended a cut-off value of a 10 % increase in LS BMD. Therefore, a cut-off value of a 10 % increase in LS BMD was more useful when taking into account the clinical significance. The PICP was not evaluated in this study, so further studies will be needed to examine the AUC value for a 10 % increase in LS BMD at 12 months, and to compare the diagnostic accuracy between PINP and PICP and other markers.

This study has several limitations that should be kept in mind when interpreting the results. First, the investigation was not large enough to examine the fracture outcomes by teriparatide treatment. To reveal the impact on fracture prevention by teriparatide treatment, a larger sample size would be needed. However, this study confirms that increases in LS BMD have previously been found to account for a 30–41 % reduction in the risk of the vertebral fractures following teriparatide treatment [15]. The second limitation was that we only evaluated PINP, while there are various other bone turnover markers, such as PICP, bone alkaline phosphatase, carboxyterminal telopeptide, osteocalcin, and so on. However, the previous reports have emphasized the relationship between early PINP changes and later increases in LS BMD [5, 6, 9, 10], so, we believe that this marker is particularly useful for the early evaluation of patient being treated with teriparatide. Third, in routine medical practice, the background of patients might vary widely than that of the patients in this study. For instance, patients who have suffered a fracture just before beginning teriparatide treatment might exhibit differences in their PINP changes. Accordingly, it is unclear whether our algorithm will be useful in a wider variety of patients. Future studies in a larger number of patients with more diverse backgrounds will be needed. Fourth, due to the limited number of patients in this study, the relationship between the fracture risk and changes in PINP could not be assessed. A large fracture trial in which all patients undergo PINP testing would be helpful to directly assess the relationship between the changes in PINP and the fracture risk reduction during teriparatide therapy. Fifth, although the greater short-term treatment-related increases in PINP were associated with a greater increase in LS BMD at 12 months, two thirds of the patients with a >80 μg/l increase in PINP concentration had a ≥10 % increase in LS BMD. While one fourth of the patients with a ≤80 μg/l increase in PINP concentration had a ≥10 % increase in LS BMD. So, clinicians should use this algorithm in consideration of the results.

In conclusion, we have developed a new treatment algorithm based on our results. We recommend that physicians should use this algorithm in clinical practice so that they can make more accurate treatment decisions based on the patient response and can provide a simple message to their patients regarding their treatment adherence.

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ORIGINAL ARTICLE

Efficacy of the dynamic radiographs for diagnosing acute osteoporotic vertebral fractures

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Abstract

Summary We investigated the efficacy of dynamic radiographs for diagnosing acute osteoporotic vertebral fractures (OVFs) compared with supine radiographs or sitting radiographs alone. Evaluation of the dynamic radiographs was superior to the other evaluations. Dynamic radiographs provide a convenient and useful method of diagnosing acute OVFs.

Introduction Identifying acute OVFs on plain radiographs is difficult. We studied a new approach to identify acute OVFs on the basis of fracture mobility.

Methods We performed a retrospective radiographic analysis of 472 acute OVFs (<3 weeks after onset), which were diagnosed on the basis of magnetic resonance imaging of T5 through L5 (a total of 5,239 vertebrae). Supine lateral radiographs were compared with sitting lateral radiographs to determine the presence or absence of mobility. Vertebrae showing changes in the vertebral body height were diagnosed as acute OVFs. We analyzed the diagnostic accuracy on the basis of comparative supine and sitting lateral radiographs and compared it with that of radiographs obtained in the supine or the sitting position alone.

Results Of the 472 acute OVFs diagnosed, 313 (66 %) exhibited vertebral mobility on supine lateral and sitting lateral radiographs. Correct diagnoses of acute OVFs or no acute OVFs were made in 4,883 vertebrae. There were 159 unreadable OVFs (3 %), and 197 previous OVFs (4 %) were misdiagnosed as acute OVFs. The sensitivity was 66 % and the specificity was 96 %. Evaluation of the mobility of acute OVFs in the supine and the sitting position was superior to evaluation using radiographs in either the supine or the sitting position alone.

Conclusions Dynamic radiographs provide a convenient way to identify acute OVFs.

Keywords Mobility · Osteoporosis · Radiograph · Vertebral fracture assessment

Introduction

Osteoporosis is a skeletal disorder characterized by a loss of bone strength—comprising bone quality and bone mineral density—and an increased risk of fractures. Osteoporotic vertebral fractures (OVFs) are the most common type of fragility fracture. The prevalence of OVFs increases steadily with age, reaching 40 % in 80-year-old females [1, 2]. OVFs not only cause height loss but also are a strong predictor of future fractures and mortality [2, 3]. Therefore, diagnosing OVFs is crucial for the proper treatment of acute back pain and prevention of postfracture sequelae.

The diagnosis of OVFs largely relies on the observation of vertebral deformations on plain radiographs. In order to minimize the subjective biases intrinsic to qualitative reading and to standardize data analyses, a number of morphometric systems have been developed. Currently, three general approaches are used to identify OVFs: (1) visual identification of fracture; (2) visual identification using either the semiquantitative assessment (SQ) grading developed by Genant et al. [4] or the algorithm-based approach for qualitative identification of vertebral fracture (ABQ) developed by Jiang et al. [5]; and (3) quantitative morphometry (QM), which was first developed in the 1960s [6]. Although SQ grading and QM assessment have been considered the gold standard methods for OVF assessment, they have limitations. Distinguishing acute OVFs from other conditions with a similar radiographic appearance, such

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as non-fracture deformities or previous OVFs, can be difficult in many cases if no previous radiograph is available for comparison. Moreover, in clinical practice, OVF does not always result in decreased vertebral height on lateral radiographs in the lateral position (Genant's Grade 0 deformation [4]) at presentation although acute OVFs can be confirmed by magnetic resonance imaging (MRI) [7]. Pham et al. reported that 63 % of acute OVFs displaying no visible deformation of the vertebral body on initial radiographs (Genant's grade 0), confirmed by MRI, worsened and eventually resulted in a reduction of vertebral height (Genant's grade ≥ 1) [7].

MRI has a high degree of accuracy for making a definite diagnosis of acute OVF and it continues to be used as the most useful tool. However, because of limitations in equipment as well as considerations that must be given to the economics of medical treatment, it is not possible to use MRI in all patients. Therefore, conventional radiography is still the mainstay of diagnosis when assessing OVFs in daily clinics.

Mobility refers to a change of vertebral height or configuration with changes in body positioning [8]. There have been occasional reports that many OVFs are mobile [9–11]. Comparative radiographs taken in weight-bearing positions (standing or sitting) and in supine positions have been used to determine the indication of percutaneous vertebroplasty for delayed union or nonunion of OVF [12–14]. Because many acute OVFs also exhibit mobility, comparative supine and sitting lateral radiographs help to identify acute OVFs [9]. In the present study, in which diagnoses were made on the basis of MRI, we analyzed the diagnostic accuracy of comparative supine and sitting lateral radiographs for diagnosing acute OVFs and evaluated their efficacy for predicting any subsequent reduction in vertebral height.

Materials and methods

Participants

Four hundred and three patients who presented with acute back pain and were diagnosed as having acute OVFs on MRI were enrolled in this study. OVFs were diagnosed in cases with no history of trauma or as a result of low-energy trauma (a fall on the ground or from a height of <1 m). Acute OVFs were defined within 3 weeks of injury or the onset of symptoms [15]. Patients who had a history of primary or metastatic bone tumors, infectious disease, or hematological disorders were excluded. Of the patients enrolled, 310 were female and 93 were male, with an average age of 80.4±8.9 years [mean ± standard deviation (SD)]. Two hundred and nine patients had experienced a simple fall, 100 patients were unable to identify the cause of their injury, and 94 patients sustained injuries with no history of trauma.

Measurements

All radiographs were taken at the initial visit at a film-focus distance of 100 cm with the X-ray beam centered at T8 for the thoracic spine and at L3 for the lumbar spine. Fracture mobility was determined by comparing cross-table supine lateral radiographs with sitting lateral radiographs (Fig. 1), as reported by previous studies [9–11]. In brief, vertebral body height was measured to the nearest millimeter in the lateral digitized radiographs. Mobility was considered present when a measurable change in vertebral body height occurred between supine and sitting radiographs. In this study, we defined "dynamic radiography" as the comparison of measured vertebral height between cross-table supine lateral and sitting lateral views. Fractures that were not mobile were considered fixed (i.e., measurable change in vertebral body height did not occur between supine and sitting radiographs). For each participant, we recorded the presence of OVFs identified between the levels of T5 and L5. Follow-up radiographs were obtained >3 months after the initial radiographs to evaluate any subsequent reduction in vertebral height and to exclude other causes of fracture.

T1-weighted images, T2-weighted images, and T2-weighted fat suppression images were used in MRI {1.5 T, T1-weighted images [spin-echo (SE): repetition time (TR)/ echo time (TE) = 550/12 ms]; T2-weigthed images [SE: TR/ TE=2500/100 ms]}. The criteria for the diagnosis of acute OVF were bone marrow signal anomalies in the form of a band-like homogenous bone marrow edema feature (low signal on T1-weighted and high signal on T2-weighted images), a horizontal linear fracture parallel to a vertebral plateau (low signal on all sequences) or both, and the absence of any tumor signs (nodular signal anomalies, posterior bulging of the vertebral body, involvement of the posterior elements of the vertebra, and epidural or soft tissue mass) [7]. Complete bone marrow signal replacement within the vertebral body did not rule out the diagnosis of osteoporotic collapse if a fracture line was identified and no other sign suggestive of a tumor was present [7]. In addition, vertebrae in which signal intensity was limited to the vicinity of the upper and lower end plates of the vertebral body were determined to be degenerative disk lesions. A diagnosis of acute OVF using MRI was made by two radiologists with >20 years of clinical experience, and by four orthopedic surgeons with >10 years of clinical experience. All assessors were blinded to the results of the plain radiographs. A diagnosis was considered correct when two investigators reached the same conclusion. MRI was performed within 3 days of the initial visit. A diagnosis of acute OVF using radiographs was made by the four orthopedic surgeons.

Differences in the ability of the four orthopedic surgeons to interpret spinal radiographs were investigated in advance. The subjects of this investigation were 50 patients with OVF, and
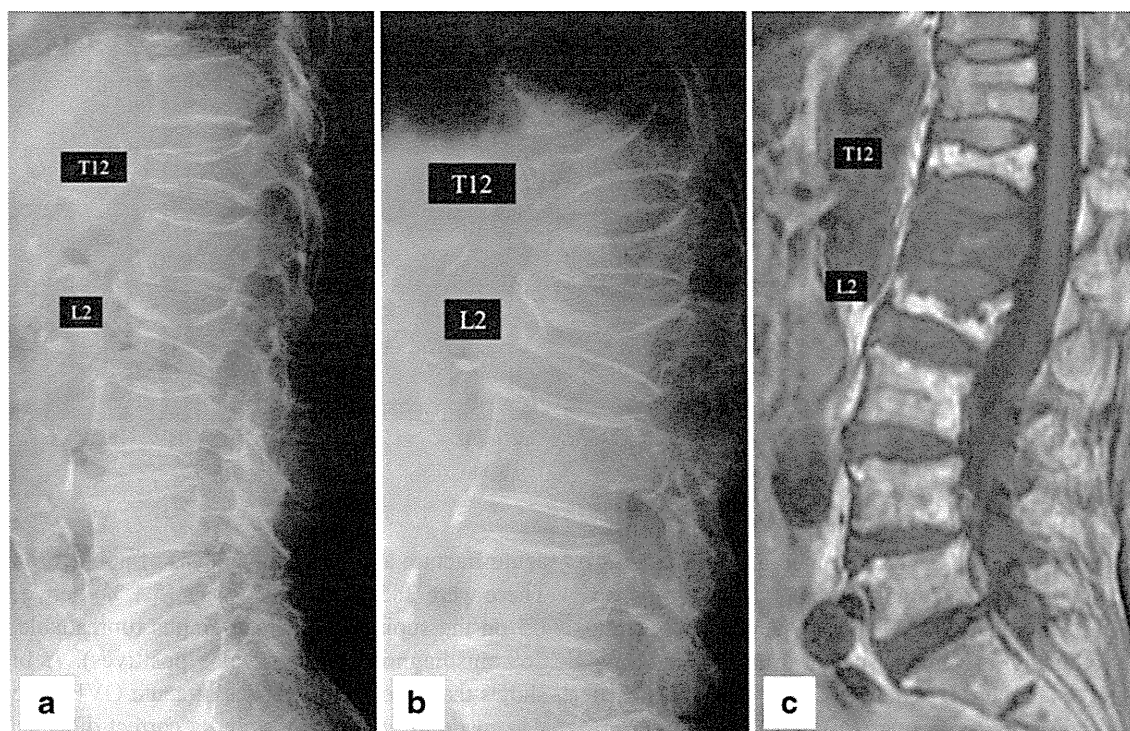
Fig. 1 A 96-year-old female patient sustained an L1 acute osteoporotic vertebral fracture (OVF) following a fall. **a** Supine cross-table lateral radiograph of severe *T12* and *L2* OVFs. **b** Sitting lateral view of an L1 OVF showing mobility, whereas no height change was observed at *T12* or *L2*. **c** Sagittal magnetic resonance imaging showing an acute OVF at L1 on a T1-weighted image

the surgeons received training to standardize their approach to diagnosis. To determine sample size, we used the recommendations of Loewen and Philp [16]. To determine the reliability of OVF assessment based on comparative supine and sitting lateral radiographs, we estimated the agreement corrected for chance using a simple kappa (*k*) coefficient inter-reader and intra-reader agreement and associated 95 % confidence interval (CI) [17]. All vertebrae were classified as either acute fracture or non-acute fracture. To interpret the agreement, we used the criteria described by Landis and Koch [18], which classified agreement as almost perfect (0.81–1.00), substantial (0.61–0.80), moderate (0.41–0.60), fair (0.21–0.40), slight (0.00–0.20), or poor (<0.00). The results revealed that inter-reader agreement was substantial with a *k* coefficient of 0.755 (95 % CI, 0.659–0.851), whereas intra-reader agreement was also substantial with a *k* coefficient of 0.730 (95 % CI, 0.651–0.809). Accordingly, we assumed that there was no difference in the ability of orthopedic surgeons to interpret radiographs using comparative supine and sitting lateral radiographs with good reproducibility.

Next, we analyzed the diagnostic accuracy of dynamic radiographs and compared this with radiographs obtained in the supine position alone or in the sitting position alone. A diagnosis of acute OVFs using plain radiographs (comparative supine and sitting position, supine position alone, or sitting position alone) was made by orthopedic surgeons who were blinded to the results of the other plain radiographs and MRI.

Secondly, vertebral height was calculated as the distance in millimeters between the points on the superior and inferior end plates at the anterior (Ha), middle (Hm), or posterior (Hp) location. The magnitude and percentage change of the vertebral height between the supine and the sitting positions were evaluated to determine diagnostic accuracy. For the analyses, precision error was calculated for each dimension, Ha, Hm, and Hp by blinded, triplicate measurements of 20 randomly selected fractured vertebrae evaluated in sitting and supine position and expressed as percent coefficient of variation (%CV) and SD. Precision errors expressed as %CV were 6.7, 8.0, and 4.6 % for Ha, Hm, and Hp, respectively, in sitting position, and 4.4, 6.1, and 4.6 % for Ha, Hm, and Hp, respectively, in supine position. The precision errors correspond to SDs of 1.2 mm for Ha, 1.3 mm for Hm, and 1.3 mm for Hp in sitting position and 1.0 mm for Ha, 1.2 mm for Hm, and 1.4 mm for Hp in supine position. Magnification error between radiographs in sitting position and radiographs in supine position was also calculated by blinded, triplicate measurements of 20 randomly selected non-fractured vertebrae. Magnification errors expressed as %CV were 3.7, 3.3, and 3.1 % for Ha, Hm, and Hp, respectively, and compared favorably with previous report [11]. The precision errors correspond to SDs of 1.1 mm for Ha, 1.0 mm for Hm, and 1.0 mm for Hp. Accordingly, we assumed that there was an allowable error in calculating vertebral height using dynamic radiographs. Third, the magnitude of the reduction in vertebral

Fig. 2 Distribution of acute
osteoporotic vertebral fractures
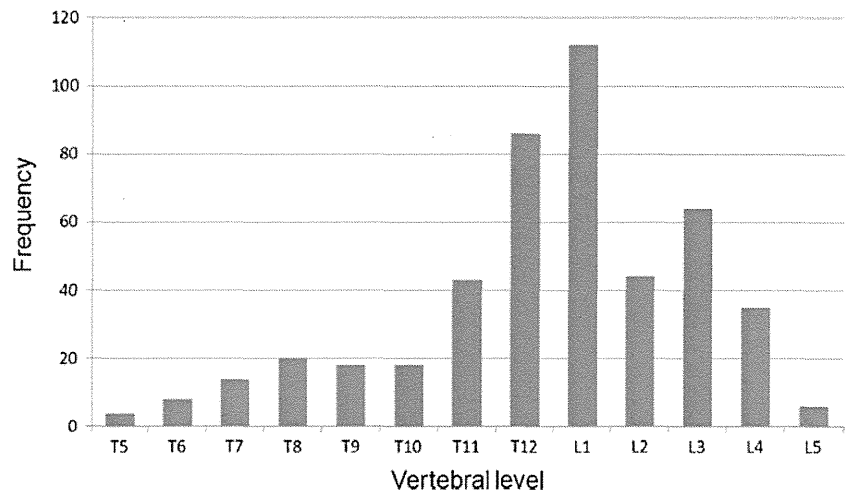
height on follow-up radiographs, obtained after >3 months, compared with the initial radiographs, was evaluated between the following subgroups to evaluate efficacy for predicting subsequent reduction in vertebral height using the initial radiographs: (1) subgroup of acute OVFs correctly diagnosed on initial radiographs (correct group) and (2) subgroup of acute OVFs incorrectly diagnosed on initial radiographs (incorrect group).

Statistical analysis

Statistical analysis was performed using the chi-square test and the Mann–Whitney U test. Differences with P values of <0.05 were considered significant. The analysis was performed using the StatView statistical software package (version 5.0; SAS Institute, Cary, NC).

The study was conducted according to the ethical principles stated in the Declaration of Helsinki and was approved by the ethical committee of our institution. Written informed consent was obtained from the patients.

Results

We observed 472 OVFs in 403 patients. Almost two-thirds of fractures were identified between T11 and L2 on MRI. L1 was the most commonly affected level, identified in 112 cases, with T12 being the next most commonly affected level with 86 cases followed by 64 fractures at L3, 43 fractures at T11 and L2, 35 fractures at L4; the remaining fractures were evenly distributed among other levels (Fig. 2).

Evaluation in the supine position

Table 1 depicts the results of evaluation of supine lateral radiographs. Overall, a correct diagnosis was made in 4,685 vertebrae (89.4 %) (agreement between correct diagnosis of

acute fracture and correct diagnosis of non-acute fractures). There were 285 unreadable OVFs (5.4 %) between T5 and L5 on the supine lateral radiographs (unreadable rate) and 269 misdiagnosed OVFs (false positives). A breakdown shows that a correct diagnosis of acute OVF (true positive) was made in 187 fractures, and a correct diagnosis of non-acute OVF, which included non-fractured vertebra and previous OVF (true negative) was judged to be present in 4,498 vertebrae. Therefore, overall, the sensitivity was 39.6 % and the specificity was 94.4 % (Table 2). The positive predictive value (PPV) was 41.0 % and the negative predictive value (NPV) was 94.0 %.

Evaluation in the sitting position

Table 3 depicts the results of evaluation of sitting lateral radiographs. Overall, a correct diagnosis was made in 4,696 vertebrae (89.6 %) (agreement). There were 269 unreadable OVFs (5.1 %) on sitting lateral radiographs (unreadable rate) and 274 misdiagnosed OVFs (false positives). The details are shown in Table 2.

Evaluation in supine and sitting positions

Table 4 depicts the results of evaluation of comparative supine and sitting radiographs. Of 472 acute OVFs diagnosed on

Table 1 The diagnostic accuracy of supine lateral thoracic/lumbar radiographs for acute osteoporotic vertebral fracture

		Acute OVF on MRI		Total
		Positive	Negative	
Acute OVF diagnosed by radiography	Positive	187	269	456
	Negative	285	4,498	4,783
	Total	472	4,767	5,239

Table 2 The diagnostic value of three methods

Evaluation method	Sensitivity	Specificity	PPV	NPV	False positive rate	False-negative rate	Uninterpretable rate	Agreement	Odds ratio [95 % CI]
Supine	39.6	94.4	41.0	94.0	5.6	60.4	5.4	89.4	10.97 [8.79–3.69]
Sitting	43.0	94.3	42.6	94.4	5.7	57.0	5.1	89.6	12.37 [9.94–15.40]
Dynamic	66.3	95.9	61.4	96.6	4.1	33.7	3.0	93.2	45.67 [35.98–57.95]

Uninterpretable rate means that the OVF overlooked by comparative radiographs

PPV positive predictive value, *NPV* negative predictive value, *Agreement* true positive + true negative rate, *CI* confidence interval

MRI, 313 vertebrae (66.3 %) exhibited mobility on supine lateral and sitting lateral radiographs. Overall, a correct diagnosis was made in 4,883 vertebrae (93.2 %) (agreement). There were 159 unreadable OVFs (3.0 %) between T5 and L5 on the supine lateral radiographs (unreadable rate) and 197 misdiagnosed OVFs (false positives). A breakdown shows that a correct diagnosis of acute fractures (true positive) was made in 313 OVFs, and non-acute OVFs (true negative) were judged to be present in 4,570 vertebrae. Therefore, the sensitivity was 66.3 % and the specificity was 95.9 % (Table 2). PPV was 61.4 % and NPV was 96.6 %. Prevalence of mobility based on location of the OVFs showed that mobility is the most common at the thoracolumbar junction. There was a significant difference of mobility based on location of OVFs ($P < 0.01$, Chi-square test) (Table 5)

Optimal cutoff value for diagnosis of acute OVF

We classified the 313 acute OVFs which exhibited mobility into two groups according to the magnitude or the rate of change of the vertebral height between the supine and the sitting positions. The results are shown in Table 6. The average reduction in vertebral height with mobile fractures was 5.4±4.4 mm. Among 313 acute OVFs diagnosed on dynamic radiographs, 262 vertebrae (83.7 %) exhibited a change of >2 mm, 220 vertebrae (70.3 %) exhibited a change of >3 mm, and 192 vertebrae (61.5 %) exhibited a change of >4 mm. With regard to the vertebral percent height reduction, 220 vertebrae (70.3 %) exhibited a change of >10 %, 106 vertebrae (33.9 %) exhibited a change of >20 %, and 55 vertebrae (17.6 %) exhibited a change of >30 %. A QM

assessment of OVFs suggested that a 2-mm reduction in vertebral height was the most reasonable cutoff value for screening for OVFs.

Subsequent reduction in vertebral height on follow-up radiographs

A mean reduction of 6.6±4.2 mm in vertebral height occurred on subsequent radiographs in the correct group and a reduction of 3.0±4.0 mm in vertebral height occurred in the incorrect group. There was a significant difference in the subsequent reduction in vertebral height between the correct group and the incorrect group ($P < 0.01$, Mann–Whitney U test). Therefore, a large future height loss of OVF was assumed when acute OVF was correctly diagnosed using dynamic radiographs, whereas a relatively small height loss was expected if acute OVF was not diagnosed using dynamic radiographs.

Discussion

This study attempted to analyze the potential benefits offered by dynamic radiographs in the diagnosis of acute OVFs compared with information obtained from supine lateral radiographs or sitting lateral radiographs alone. According to our results, the detection rate of acute OVFs was much higher on dynamic radiographs than on either supine lateral radiographs or sitting lateral radiographs alone. In addition, dynamic radiographs were useful for estimating the prognosis of acute OVFs.

Table 3 The diagnostic accuracy of sitting lateral thoracic/lumbar radiographs for acute osteoporotic vertebral fracture

		Acute OVF on MRI		Total
		Positive	Negative	
Acute OVF diagnosed by radiography	Positive	203	274	477
	Negative	269	4,493	4,762
	Total	472	4,767	5,239

Table 4 The diagnostic accuracy of dynamic lateral thoracic/lumbar radiographs for acute osteoporotic vertebral fracture

		Acute OVF on MRI		Total
		Positive	Negative	
Acute OVF diagnosed by radiography	Positive	313	197	510
	Negative	159	4,570	4,729
	Total	472	4,767	5,239

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Table 5 The prevalence of dynamic mobility based on location of the OVFs (*n*=472)

| | | Location* | | |
		T5–T10	T11–L2	L3–L5
Number of OVFs diagnosed by MRI	Dynamic mobility positive	41 (50 %)	206 (72 %)	66 (63 %)
	Dynamic mobility negative	41 (50 %)	79 (28 %)	39 (37 %)

*P<0.01, Chi-square test

Plain radiographs are the mainstay for initial diagnosis of OVFs. Nonetheless, reaching a clear diagnosis of acute OVFs is difficult in many vertebrae. Identifying acute OVFs on plain radiographs is problematic because (1) "normal" radiological appearances in the spine vary greatly both among and within individuals, (2) "abnormal" appearances due to non-fracture deformities and normal variants are common but can be difficult to differentiate from true OVFs, (3) osteoporosis can often cause asymptomatic OVFs and make it difficult to distinguish between acute OVFs and previous OVFs, and (4) OVFs do not always result in a reduction in vertebral height on lateral radiographs. Therefore, a correct diagnosis of acute OVFs can be difficult. Ito et al. reported that acute OVF was correctly diagnosed in 51.5 % of cases [19]. The false-negative rates of diagnosis of acute OVFs on conventional radiographs have been reported to range from 27 to 48.5 % [20, 21]. Hence MRI is often performed in elderly patients with vertebral disease because it is currently the only available definitive diagnostic tool; however, it is costly and not always immediately available.

On the basis of the problems raised above, we investigated whether the correct diagnostic rates for acute OVFs using radiographic diagnosis could be improved by the use of dynamic radiographs compared with either supine lateral radiographs or sitting lateral radiographs alone. To the best of our knowledge, this type of comparison has not been carried out to date; however, a search of the literature has revealed that various datasets are available on the diagnostic rate of acute OVF using radiographs. Ito et al. evaluated

diagnosis of acute OVFs using the criteria of Genant et al. [4], which are commonly used in the diagnosis of acute OVFs, but only 45.5 % of acute OVFs could be diagnosed correctly [19]. Nakano et al. also evaluated diagnosis of acute OVFs using Japanese guidelines [22] which are essentially the same as those used for QM assessment [6]. They reported that sensitivity was 45.9 %, specificity was 89.3 %, PPV was 41.5 %, and NPV was 91.2 %. In contrast, Kanchiku et al. reported a high correct diagnosis rate of 87 % [23]. In this study, using dynamic radiographs, we demonstrated sensitivity of 66 %, specificity of 96 %, PPV of 61 %, and NPV of 97 % for diagnosing acute OVFs. These results were superior to evaluation using either supine or sitting radiographs alone. However, it is necessary to keep in mind the fact that many factors, such as the skill levels of the examiners, the background of the patients, or radiographic conditions, make the simple comparison of a correct diagnosis rate difficult. However, these results offer concrete insights, and we therefore recommend that dynamic radiographs should be used in the management of patients with acute low back or back pain who are suspected of having acute OVFs.

Dynamic radiographs identify acute OVFs on the basis of fracture mobility. This method differs in concept from conventional morphology-based fracture diagnosis such as SQ, ABQ, and QM. Identifying the presence of mobility by dynamic radiography furthers our understanding of the pathophysiology of OVF and provides clinicians with an opportunity to correctly identify the cause of an elderly

Table 6 The accuracy of acute osteoporotic vertebral fracture based on quantitative morphometry assessment of comparative supine and sitting lateral radiographs

Cutoff value	Sensitivity	Specificity	PPV	NPV	False positive rate	False negative rate	Uninterpretable rate	Agreement	Odds ratio [95 % CI]
2 mm	83.7	53.3	74.0	67.3	46.7	16.3	10.0	72.0	5.86 [3.89–8.84]
3 mm	70.3	72.1	80.0	60.4	27.9	29.7	18.2	71.0	6.11 [4.11–9.06]
4 mm	61.5	84.3	86.1	58.0	15.7	38.5	23.6	70.3	8.57 [5.48–13.39]
10 %	70.3	72.1	80.0	60.4	27.9	29.7	18.2	71.0	6.11 [4.11–9.06]
20 %	33.9	93.9	89.8	47.2	6.1	66.1	40.6	57.1	7.89 [4.21–14.81]
30 %	17.6	97.0	90.2	42.5	3.0	82.4	50.6	48.2	6.79 [2.86–16.09]

Uninterpretable rate means that the OVF overlooked by comparative radiographs

PPV positive predictive value, *NPV* negative predictive value, *Agreement* true positive + true negative rate, *CI* confidence interval

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osteoporotic patient's back pain by requesting an axially loaded (standing or sitting) radiographs than simply requesting the standard radiographs which may well be a non-axially loaded lateral decubitus film. Kawaguchi et al. [9] analyzed 41 acute OVFs diagnosed on dynamic radiographs and revealed dynamic vertebral mobility in 81 % of fractures. In this study, dynamic vertebral mobility was found in 66 % of fractures, with an average reduction in vertebral height of 5.4±4.4 mm on subsequent radiographs observed in the mobile acute OVFs.

Dynamic radiographs are useful for estimating the subsequent loss in vertebral height of acute OVFs. To the best of our knowledge, this is also the first attempt to evaluate this parameter. Why some OVFs did not result in mobility is unclear. OVFs that could not be diagnosed on dynamic radiographs might contain micro-trabecular fracture, which are considered to be a step prior to OVF with mobility. Otherwise, OVFs that could be diagnosed on dynamic radiographs exhibited severe breakage of interconnected bone fibers of both cortical and cancellous bone; therefore, the mobile OVFs collapsed easily compared with OVFs that were not mobile.

There are two major drawbacks of dynamic radiographs. One is radiation exposure. The other is back pain during examination. Assessment by fracture mobility requires radiographs in weight-bearing position and supine position. Back pain during radiographic examination (e.g., lie down on the X-ray table, adjust the position on the table, and sit up from the table) has the possibility to disturb the later radiographic examination. Back pain during radiographic examination was common in the lateral decubitus position, but back pain in the supine positions is partially stronger than the lateral decubitus position. Although there were no patients who could not take radiographic examination due to back pain in our institution, Kawaguchi et al. reported one of 38 patients was unable to sit up for the radiographs due to back pain [9].

This study has several limitations that should be kept in mind when interpreting its results. First, although the k coefficients of inter-reader and intra-reader agreement were acceptable, the manual measurement of the images might have caused intra-observer and inter-observer error. The second limitation was that the manual measurement of the images also might have caused the precision and magnification errors, although they were acceptable. The third limitation was that although we compared the accuracy of dynamic radiographs with information obtained from either supine lateral radiographs or sitting lateral radiographs alone in this study, with the results revealing that comparative evaluation was superior to the other evaluations, there was no control group. Lateral radiographs are usually obtained in the lateral decubitus position in most institutions which has neither the features of the axially loaded (standing or sitting) lateral views or the hyperextended (cross table) lateral views. Comparison

of the accuracy between dynamic radiographs and standard lateral radiographs in the lateral decubitus position is required. Fourth, distortion of the vertebral body and end plates in oblique projection might reduce the accuracy, which is a common problem in other methods of OVF assessment [21, 24, 25]. Fifth, the dynamic radiography has not previously been discussed and needs to be standardized. Further study is warranted.

In conclusion, dynamic radiographic examinations are an effective tool for correctly identifying acute OVFs. By incorporating these scans into routine clinical assessments, clinicians can reduce costs and MRI examination which is occasionally painful for the patients, and thereby enhance the care of patients suspected of having OVFs.

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V. 資　料