countries, partly because of the marked difference in prevalence. Recent clinical studies performed in Europe and the United States have shown that the second- and third-generation bisphosphonates are preferable to first-generation products because these are more effective at suppressing bone turnover, so these potent bisphosphonates are commonly used as first-line therapy in these countries [8–10]. In Japan, however, calcitonin and etidronate were the only pharmaceutical treatments approved for PDB until very recently, and there were no data about the efficacy of second- and third-generation bisphosphonates for Japanese patients.

Accordingly, the aim of this phase III clinical study was to evaluate the efficacy, tolerability, and safety of risedronate in Japanese patients with PDB by examining several biochemical markers of bone turnover and by bone scintigraphy.

Materials and methods

Patients

Eight male and 4 female patients aged 20–85 years with PDB diagnosed according to the standard clinical criteria of the Japanese Osteoporosis Society [11] were enrolled in this study. Enrolment criteria included a serum alkaline phosphatase (ALP) level more than twice the upper limit of the normal range and a period of at least 2 years since menopause in the female patients. Patients had not been treated or had failed to respond to bisphosphonate or to calcitonin.

Exclusion criteria were as follows: treatment with bisphosphonates within 8 weeks before the beginning of the study; treatment with other drugs that could affect bone metabolism (calcitonin and vitamin D preparations) within 4 weeks or for 4 weeks or more within 24 weeks before the beginning of the study; esophagitis and/or peptic ulcer (esophageal, gastric, or duodenal ulcer); disorders that could delay esophageal transit (e.g., dysphagia, esophageal stenosis, and achalasia); inability to maintain a standing or upright sitting posture for 30 min or more; hyperparathyroidism, hyperthyroidism, and/or osteomalacia within 1 year before the start of the study; serious renal, hepatic, or cardiac disease; and malignancy being treated with chemotherapy.

Study design

This was a phase III, multicenter, noncomparative, open-label study of oral risedronate (17.5 mg once daily for 8 weeks), with a 40-week posttreatment follow-up period, which was conducted between April 2006 and October 2007. The study protocol was approved by the Institutional Review Board of each participating institution, and all patients provided written informed consent. This study was conducted in compliance with Good Clinical Practice guidelines, and conformed to the ethical principles set out in the Declaration of Helsinki. The investigators who participated in this study are listed in the Appendix.

After a washout period for previous PDB treatments (8 weeks for bisphosphonates or 4 weeks for other agents such as calcitonin), each patient was given 17.5 mg risedronate orally once daily for 8 weeks. The dosage was based on the results of a phase III study from North America [12] and previous studies of risedronate performed in Japanese osteoporosis patients [13–16]. Risedronate was supplied by Ajinomoto and by Takeda Pharmaceutical Company. Throughout the 48-week study period, concomitant use of drugs known to influence PDB, such as other bisphosphonates or calcitonin, was prohibited.

Assessment of efficacy

Serum and urinary biochemical markers of bone metabolism were investigated to determine the percent changes of serum ALP, serum bone-specific ALP (BALP), urinary deoxypyridinoline (DPD), and urinary cross-linked N-telopeptide of type 1 collagen (NTX) from baseline to week 48. All urinary parameters were corrected for creatinine (CRN) excretion. Other outcome measures included the evaluation of pain and scintigraphic assessment of bone lesions.

Serum and urine samples were collected at baseline and in weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48 for the measurement of bone metabolism markers. All markers were measured at a central laboratory (SRL, Tokyo, Japan) by standard methods. Serum ALP was determined by the Japan Society of Clinical Chemistry (JSCC) method using Cica Liquid ALP (Kanto Chemical, Tokyo, Japan), and serum BALP was determined by an enzyme immunoassay (Osteolinks "BAP"; Quidel, San Diego, CA, USA). Urinary NTX was measured by an enzyme-linked immunosorbent assay (Osteomark; Inverness Medical Japan, Tokyo, Japan), and urinary DPD was determined by high-performance liquid chromatography (SRL, Tokyo, Japan).

Pain at rest was assessed by each patient with a visual analogue scale (VAS) on which 0 mm corresponded to no pain and 100 mm represented maximum pain. Pain was assessed at baseline, in week 8, and in week 24.

Paget's bone lesions were assessed and staging of the disease was done by plain radiography and bone scintigraphy at baseline and in week 24. Scintigraphy was done by performing a bone scan at 3 h after the injection of ^{99m}Tc-labeled methyl diphosphonate (MDP). Images were

input into digital analyzers, and the area and intensity of lesions were quantified through digital image processing. For scintigraphic assessment, the region of interest (ROI) was drawn around each bone lesion, and the radioisotope (RI) uptake ratio was calculated as the uptake in the ROI relative to that at a non-Paget's reference site, which was either the contralateral bone (if normal) or an unaffected humerus. The mean radioactivity per pixel of each lesional ROI was divided by that of the reference ROI to calculate the RI uptake ratio as described previously [17–20]. To perform staging of PDB, a Central Assessment Committee with four members was organized. To minimize variation in the assessment of imaging data, one committee member confirmed the eligibility of each patient and the ROIs on bone scintigraphy images at baseline. During the study, the four committee members independently viewed bone images to assess disease progression and then reached a consensus regarding the disease status by discussion.

Assessment of safety

Adverse events were recorded throughout the study. Vital signs and results of laboratory tests (i.e., hematology tests, biochemistry tests, and urinalysis) were also monitored. Each adverse event was assessed with regard to its frequency, severity (mild, moderate, or severe), timing of onset, and relationship to risedronate therapy.

Statistical analysis

A previous survey estimated that the total number of PDB patients in Japan was only a few hundred [7], so the sample size was set at ten, considering the feasibility of patient recruitment. The statistical power was calculated to be 100% with a group of ten patients when a one-sample t test was applied with significance accepted at $P < 0.05$ based on the percent changes of biomarkers during a phase III study performed in North America [12].

For efficacy variables, the changes from baseline to each time point were assessed with a one-sample t test, and $P < 0.05$ was considered as statistically significant. Results are presented as the mean ± standard deviation (SD).

Results

Twelve patients (8 men and 4 women, aged 68.6 ± 7.7 years) were enrolled in the study, and they were all treated with 17.5 mg risedronate orally once a day for 8 weeks. The demographic characteristics of the patients are described in Table 1.

One patient suffered from recurrence of bile duct cancer during this study. Because the recurrent cancer led to the elevation of serum ALP and BALP, we concluded that it was not appropriate to assess efficacy in this patient. Accordingly, the efficacy assessment was done in the remaining 11 patients who completed the 40-week follow-up period. With respect to the baseline bone metabolism markers of these 11 patients, the mean serum ALP and BALP levels were 1090.3 ± 616.6 and 189.7 ± 153.0 U/l, respectively; mean urinary DPD and NTX were 28.9 ± 14.3 pmol/μmol·CRN and 390.9 ± 164.1 nmol bone collagen equivalents (BCE)/mmol·CRN, respectively. These values were similar to the mean baseline values for the original 12 patients.

Biochemical markers of bone metabolism

The mean percent changes of bone formation markers (serum ALP and BALP) from baseline to week 48 are shown in Fig. 1. Both markers decreased significantly from week 8 to week 48 compared with baseline ($P < 0.001$). After 8 weeks of treatment, mean serum ALP and BALP levels were decreased by 45.8% and 49.1%, respectively, and the markers continued to decline during the subsequent 16-week period. The maximum mean reduction from baseline was seen in week 24, with a reductions of 63.2% for serum ALP and 71.6% for serum BALP. Similar levels were then sustained until week 48.

With respect to the serum ALP excess*, which is a parameter used in previous overseas studies to combine data from different laboratories where the normal range varied [21, 22], there was a reduction of 85.3% in week 24 and 82.1% in week 48.

* Serum ALP excess = serum ALP
− (upper limit of normal range
+ lower limit of normal range)/2

The mean percent changes of the bone resorption markers (urinary DPD and NTX) from baseline to week 48 are shown in Fig. 2. Both markers decreased significantly from week 2 to week 48 compared with baseline ($P < 0.001$). After 8 weeks of treatment, the mean urinary DPD and NTX levels were decreased by 56.4% and 78.3%, respectively, with similar levels being maintained until week 48.

Individual serum ALP levels were decreased by 47.7–82.7%, with the mean maximum reduction being 66.4%. During the period from week 8 after the initiation of treatment to week 40, 9 of 11 patients showed reduction to within the normal range, and the level was within the normal range until the final observation in week 48 for 7 patients. The 2 patients who did not show reduction to the reference level both had polyostotic disease. For these patients, the baseline value and the lowest value after

Table 1 Demographic and baseline characteristics of 12 Japanese patients with Paget's disease of bone

Variable	No. of subjects, *n* (%): mean ± SD	Min.–max.
Sex		
Male	8 (66.7)	–
Female	4 (33.3)	–
Age (years)	68.6 ± 7.7	57–81
Height (cm)	159.8 ± 8.4	150–177
Body weight (kg)	59.2 ± 9.8	43.5–75.5
BMI (kg/m^2)	23.2 ± 3.7	18.1–31.3
Years after menopause		
Only the four women	17.0 ± 2.9	14–20
Biochemical bone metabolism markers		
Serum ALP (U/l)	1093.9 ± 588.0	717–2770
Serum BALP (U/l)	188.7 ± 146.0	109–610
Urinary DPD (pmol/μmol·CRN)	28.0 ± 14.0	12.1–51.6
Urinary NTX (nmol BCE/mmol·CRN)	380.3 ± 160.6	201.5–680.5
Imaging findings		
Type of disease		
Monostotic	6 (50)	–
Polyostotic	6 (50)	–
Highest RI uptake ratio	12.4 ± 6.6	3.8–23.7
Visual analogue scale pain score (mm)	11.7 ± 14.4	0–50
History of treatment for PDB		
Yes/no	9/3 (75/25)	–
Etidronate		
Yes/no	4/8 (33.3/66.7)	–
Etidronate + calcitonin		
Yes/no	2/10 (16.7/83.3)	–
Other bisphoshonates		
Yes/no	3/9 (25/75)	–
Past medical history		
Yes/no	10/2 (83.3/16.7)	–
Current complications		
Yes/no	11/1 (91.7/8.3)	–

ALP alkaline phosphatase, *BMI* body mass index, *BALP* bone alkaline phosphatase, *BCE* bone collagen equivalent, *CRN* creatinine, *DPD* deoxypyridinoline, *NTX* cross-linked N-telopeptide of type 1 collagen, *RI* radioisotope, *SD* standard deviation

Normal range: serum ALP, 115–359 U/l; serum BALP, 13–33.9 U/l (male) and 9.6–35.4 U/l (female); urinary DPD, 2.9–9.7 pmol/μmol·CRN; urinary NTX, 13–66.2 nmol BCE/mmol·CRN (male) and 14.3–89 nmol BCE/mmol·CRN (postmenopausal female)

starting treatment were 2770 and 717 U/l versus 1429 (48.4% reduction) and 375 U/l (47.7% reduction), respectively.

Assessment of pain (VAS)

Table 2 shows the profile of VAS pain scores over time. The mean baseline VAS score was 12.0 ± 15.0 mm; it decreased to 10.0 ± 13.4 mm in week 8 and to 6.2 ± 11.8 mm in week 24. With respect to individual patient responses, there were 9 symptomatic patients with pain at baseline. The VAS score was decreased by week 8 in 7 patients and 5 patients had no pain (0 mm) in week 24; 1 patient was unchanged and 1 showed minimal deterioration.

Radiologic assessment

Plain radiography and bone scintigraphy revealed that Paget's disease was of the mixed type (lytic-sclerotic) in all lesions of all patients, with polyostotic disease in 6 patients and monostotic disease in the others. Abnormal RI uptake was detected at a total of 36 sites in 11 patients at baseline. The most common sites were the pelvis (n = 8), lumbar vertebrae (n = 5), femur (n = 4), and thoracic vertebrae (n = 4). The mean value of the highest RI uptake ratio for the bone lesions identified at baseline in each patient decreased from 12.7 ± 6.8 to 6.0 ± 2.3 by week 24. The mean change from baseline was –6.7 ± 6.1, and the reduction was significant (P = 0.004). Ten of the 11 patients (90.9%) showed a decrease of the RI uptake ratio,

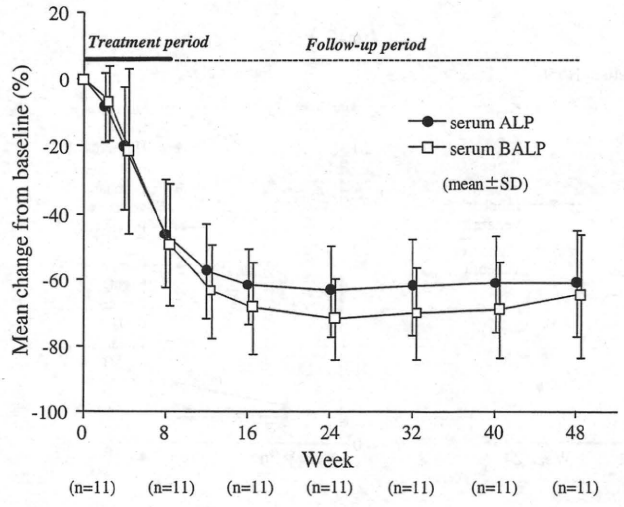

Fig. 1 Percent changes (mean ± SD) of serum alkaline phosphatase (*ALP*) and serum bone-specific ALP (*BALP*) in 11 Japanese patients with Paget's disease of bone treated for 8 weeks with risedronate (17.5 mg orally once daily) and observed for the following 40 weeks (to week 48)

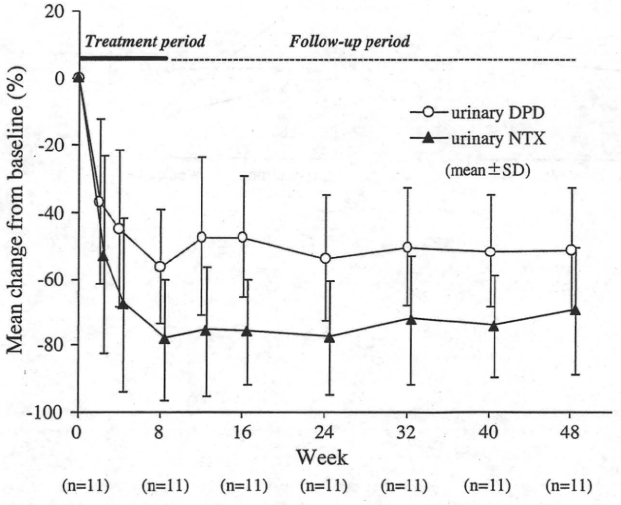

Fig. 2 Percent changes (mean ± SD) of urinary deoxypyridinoline (*DPD*)/creatinine and urinary cross-linked N-telopeptide of type 1 collagen (*NTX*)/creatinine in 11 Japanese patients with Paget's disease of bone treated for 8 weeks with risedronate (17.5 mg orally once daily) and observed for the following 40 weeks (to week 48)

although 1 patient had an increased uptake ratio for six of seven lesions.

Adverse events

The incidence of adverse events is summarized in Table 3. Except for one case of bile duct cancer recurrence, the adverse events were mild to moderate. Five events that were potentially related to risedronate occurred in 3 of the 12 patients (25.0%), and these events included three episodes of diarrhea and one each of stomach discomfort and peripheral edema. All these events were mild, and all resolved. With regard to upper gastrointestinal disorders, which are a well-known concern with bisphosphonate therapy, stomach discomfort occurred in 3 of the 12 patients (25.0%), but only one event was potentially related to risedronate therapy, as already noted. All these events were mild and all resolved.

With regard to the biochemical parameters, serum calcium decreased slightly during risedronate treatment because of the inhibitory effect on bone resorption, and

Table 2 Pain assessment by visual analogue scale (VAS) in 11 Japanese patients with Paget's disease of bone treated for 8 weeks with risedronate (17.5 mg orally once daily) and then observed for 16 weeks (to week 24)

Patient	VAS length (mm)		
	Baseline	Week 8	Week 24
1	8	8	8
2	50	44	38
3	0	0	0
4	0	0	0
5	24	15	0
6	1	0	0
7	8	7	5
8	4	1	0
9	16	20	17
10	19	15	0
11	2	0	0
Mean ± SD (mm)	12.0 ± 15.0	10.0 ± 13.4	6.2 ± 11.8
Mean change from baseline (mm) (*P* value)		−2.0 ± 3.5 ($P = 0.085$)	−5.8 ± 8.6 ($P = 0.049$)

Scores of 0 and 100 mm indicate no pain and maximum pain, respectively

Table 3 Summary of adverse events in 12 Japanese patients with Paget's disease of bone treated for 8 weeks with risedronate (17.5 mg orally once daily) and observed for the following 40 weeks (to week 48)

Item	No. of patients (%)
Evaluated for safety	12 (100)
Adverse events	11 (91.7)
Adverse events potentially related to risedronate	3 (25.0)
Serious adverse events	1 (8.3)
Serious adverse events potentially related to risedronate	0
Upper gastrointestinal adverse events	3 (25.0)

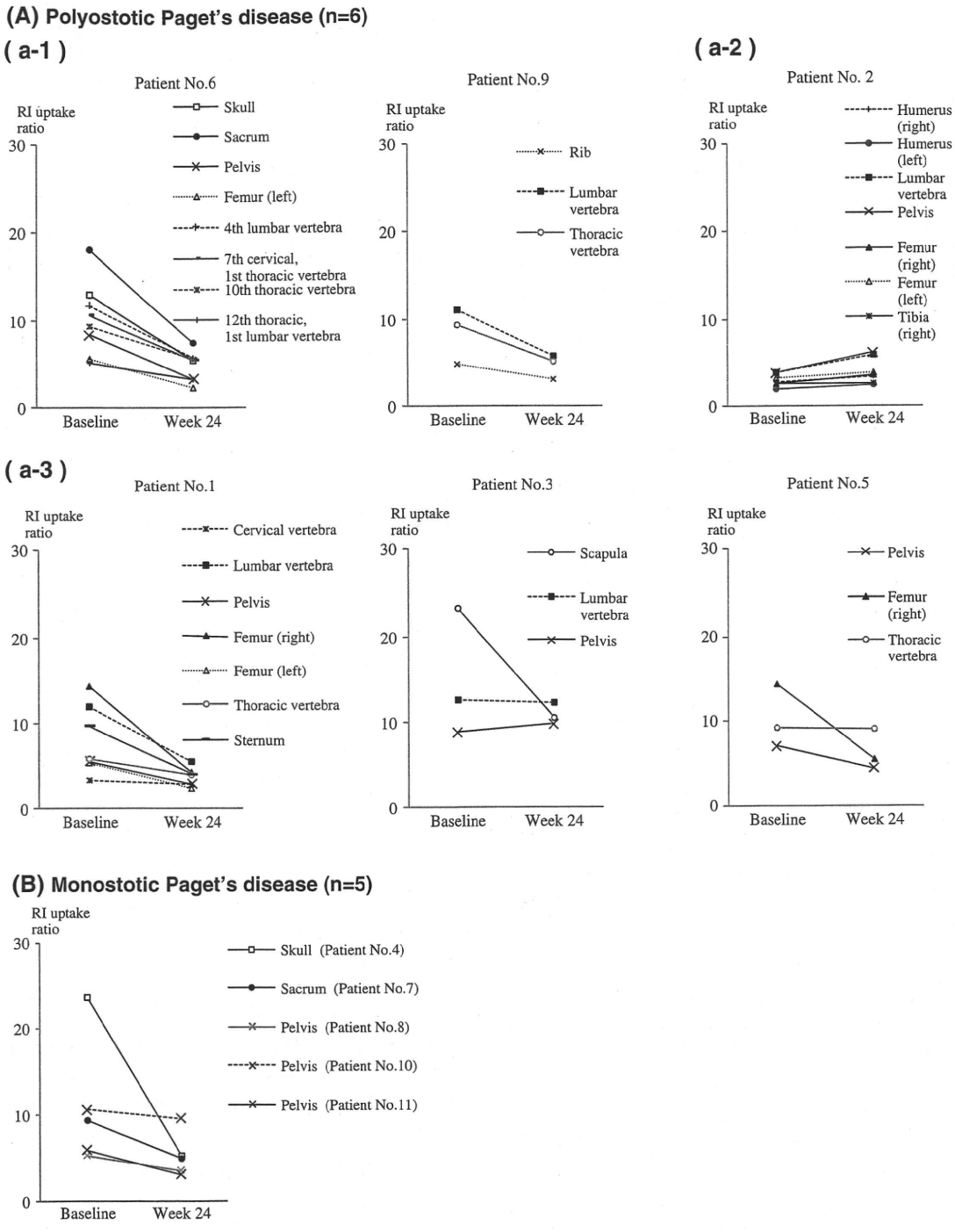

Fig. 3 Bone scintigraphy radioisotope (*RI*) uptake ratios for the individual lesions of 6 Japanese patients with polyostotic Paget's disease (**A**) and 5 Japanese patients with monostotic Paget's disease (**B**) treated for 8 weeks with risedronate (17.5 mg orally once daily) and observed for the following 16 weeks (to week 24): *a-1*, patients with a similar reduction; *a-2*, a patient with no response; *a-3*, patients with a different response

serum intact parathyroid hormone (PTH) increased as a compensatory mechanism to restore the serum calcium level. Serum calcium and intact PTH levels returned to baseline after the completion of treatment. None of the patients developed symptomatic hypocalcemia.

Discussion

This Japanese phase III study demonstrated that oral risedronate at a dose of 17.5 mg once daily for 8 weeks could significantly decrease the abnormal levels of

biochemical markers that had been increased by activation of bone metabolism associated with PDB, and the improvement was maintained for up to 40 weeks after the cessation of drug treatment. Risedronate normalized the serum ALP level in 9 of 11 patients (81.8%) during the 48-week study period and reduced the pain scores of most patients in week 24.

Bone lesions were assessed by quantitative bone scintigraphy in the present study. Risedronate reduced the RI uptake ratio of bone lesions in the majority of patients over 24 weeks, with a reduction to approximately half of baseline for the mean RI uptake ratio. Figure 3 shows the time course of the RI uptake ratio for the individual lesions of 6 patients with polyostotic disease (Fig. 3A) and 5 patients with monostotic disease (Fig. 3B). The RI uptake ratios of polyostotic lesions showed the following three distinct patterns (Fig. 3A): 2 patients had a similar reduction of the ratio in all bone lesions (a-1), 1 patient exhibited no response (a-2), and 3 patients had differing responses of different lesions (a-3). In the patients with a different response of each lesion (Fig. 3A, a-3), the greatest reduction was seen for the lesion with highest uptake at baseline. Possible factors explaining this finding include the preferential uptake of bisphosphonate (risedronate) by the most severely affected lesion [20, 23, 24], as is seen with diagnostic ^{99m}Tc-labeled MDP for bone scintigraphy, and/or a difference in the lytic, blastic, and mixed components of each bone lesion. Despite the suppression of biochemical markers, 1 patient exhibited no response to treatment based upon bone scintigraphic assessment (Fig. 3A, a-2). Avramidis et al. [20] reported one similar case in a study of zoledronic acid treatment. The overall findings of bone scintigraphy suggested that ^{99m}Tc-labeled MDP uptake is not necessarily decreased selectively in Paget's bone compared with healthy bone and that the reduction of bone uptake after bisphosphonate treatment could depend on the severity and/or the stage of each lesion. Therefore, biochemical markers of bone metabolism may be more sensitive and useful for monitoring the response to treatment.

Serum ALP, serum BALP, urinary DPD, and urinary NTX were simultaneously measured in this phase III study to evaluate the impact of drug therapy on biochemical markers of bone turnover. It was demonstrated that urinary NTX, a bone resorption marker, showed a significant decrease of 53.0% in week 2 ($P < 0.001$). Its response to risedronate was faster and more prominent than that of the other markers (see Figs. 1, 2), reflecting the antiresorptive mechanism of action of bisphosphonates. This finding suggests that urinary NTX might be a useful marker for monitoring the response of PDB to treatment.

Our results for the biochemical markers showed that the effects of risedronate at 17.5 mg daily in Japanese PDB patients were almost equivalent to those obtained with 30 mg daily in Europe and the United States [12, 25, 26], at which dosage the drug exhibited a stronger and more prolonged effect than etidronate [12]. Our results for biochemical markers were similar to the findings obtained with other second- and third-generation bisphosphonates, including alendronate [27], ibandronate [28], pamidronate [25, 27, 29], and zoledronic acid [20, 30]. Moreover, risedronate at 17.5 mg daily had a scintigraphic effect in Japanese PDB patients that was similar to other second- and third-generation bisphosphonates [18–20], and greater improvement was observed than had been seen in a previous Japanese study of etidronate [31]. With regard to the optimal dose of risedronate, previous pharmacokinetic studies demonstrated that the maximum plasma concentration (C_{max}) and the area under the plasma concentration–time curve (AUC) of risedronate were two to three times higher in Japanese subjects compared with Caucasians because of bioavailability differences [32, 33]. This finding has been confirmed clinically: dosages of 2.5 mg once daily and 17.5 mg once weekly produce results in Japanese osteoporosis patients equivalent to 5 mg once daily and 35 mg once weekly in Caucasian patients [13–16]. Because risedronate acts on PDB via the same mechanism as for osteoporosis, mainly by suppressing excessive bone turnover through the inhibition of bone resorption, approximately half the clinical dose of risedronate used in Europe and the Unites States for PDB should exhibit sufficient efficacy in Japanese PDB patients.

In this Japanese phase III study, risedronate was well tolerated despite the fact that the dosage of 17.5 mg once daily is seven times higher than the approved dosage for osteoporosis in Japan. No clinically significant adverse drug reactions were observed. These results are consistent with overseas clinical trials, in which the tolerability of risedronate was the same as that of etidronate [12].

This study demonstrated the efficacy and safety of risedronate for Japanese PDB patients by assessing biochemical markers, quantitative scintigraphy of bone lesions, and symptoms over 48 weeks, although the sample size was relatively small because of the low prevalence of PDB in Japan. Our findings will contribute to improved understanding of the risk/benefit ratio for risedronate in PDB patients and will also help to identify the long-term clinical outcome.

Acknowledgments This study was supported by the Joint Development Program of Ajinomoto and Takeda Pharmaceutical Company.

Appendix

Please refer to the following Table 4.

Table 4 Investigators in the phase III study of risedronate for Paget's disease of bone

Institution	Department	Investigators
Hyogo College of Medicine	Orthopedic Surgery	Yoshiya S, Kanazawa M, Yokoi H, Fukunishi S
Teikyo University School of Medicine	Orthopedic Surgery	Abe S
Osaka University Graduate School of Medicine	Orthopedic Surgery	Hashimoto J
Osaka City University Graduate School of Medicine	Metabolism, Endocrinology and Molecular Medicine	Imanishi Y, Tanaka K, Yamada S, Kobayashi K
Keio University School of Medicine	Orthopedic Surgery	Yabe H, Morioka H, Suzuki Y
University of Tokushima Graduate School	Orthopedics, Institute of Health Biosciences	Takata S, Nakano S
Nagoya University Graduate School of Medicine	Orthopedic Surgery	Nishida Y, Yamada Y, Tsukushi S
Tokyo Medical Center	Orthopedic Surgery	Yokoi A
Saga Prefectural Hospital Kouseikan	Orthopedic Surgery	Mae T
Tokyo Women's Medical University	Orthopedic Surgery	Itoh T, Kato Y
Aichi Cancer Center	Orthopedic Surgery	Sugiura H, Kozawa E, Yamada K
Hakodate Central General Hospital	Orthopedic Surgery	Shigenobu K
Saiseikai Kanazawa Hospital	Orthopedic Surgery	Yokogawa A

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ORIGINAL ARTICLE

Capacity of endogenous sex steroids to predict bone loss in Japanese men: 10-year follow-up of the Taiji Cohort Study

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Abstract This prospective cohort study aimed to evaluate the capacity of endogenous sex steroids to predict male osteoporosis (OP) among community-dwelling inhabitants. Among 1,028 male residents aged 40–79 years, 50 men belonging to each age stratum (200 in total) were randomly selected from a resident registration list. In the years 1993, 1996, 2000, and 2003, bone mineral density (BMD) of the lumbar spine and proximal femur was measured by dual-energy X-ray absorptiometry. Serum total estradiol (E_2) and free testosterone (FT) were measured using samples extracted in 1993. Among the 200 participants at baseline, 153 subjects completed 10-year follow-ups. Mean values of serum E_2 and FT were 22.4 and 9.4 pg/ml, respectively. Rates of change for BMD at the lumbar spine and femoral neck were 0.8% and 0.5% during the first 3 years, 0.0% and 0.5% during 7 years, and 0.8% and –0.3% over 10 years, respectively. According to multivariate regression analysis after adjusting for age and body mass index, mean values of FT were significantly related to the rate of change of BMD at the femoral neck at 3 years (beta = 0.21; $r^2 = 0.05$; $P < 0.01$), but not at 7 or 10 years. Serum FT level could offer a useful predictor of bone loss within 3 years.

Keywords Testosterone · Estrogen · Bone loss · Male osteoporosis · Population-based cohort study

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Introduction

Osteoporosis (OP) is associated with impairment of activities of daily living (ADL) and quality of life (QOL), leading to increased morbidity and mortality in the elderly [1, 2]. As the proportion of the elderly population is rapidly increasing, an urgent need exists for the development of methods to prevent OP. The estimated number of patients with OP in Japan is about 10 million [3], and cases of hip fracture, as the most severe complication of OP and a key cause of bedridden status, are increasing annually, according to the results of a national survey [4].

Although OP is widely considered as a disorder that mainly affects women, 13% of cases of lumbar spine OP and 24% of cases of femoral neck OP involve men [3]. Up to 20% of hip fractures occur in men, and the number of men with fractures has been rising in Japan [3, 4]. In addition, several studies have shown higher mortality rates after hip fracture in men than in women [5–8], suggesting that male OP warrants urgent attention.

Estrogen is a well-known determinant of low bone mass, bone loss, and osteoporotic fracture in women [9–12]. Reports from the study of osteoporotic fracture suggest that in elderly women, undetectable levels of estradiol, which occur in about one-third of the population, are strongly associated with low bone mineral density (BMD), rapid

bone loss, and increased fracture risk [13–15]. In addition, lower androgen concentrations are reportedly weakly associated with lower BMD and rapid bone loss at some skeletal sites [13].

By contrast, less epidemiological evidence has been gathered regarding the influence of serum sex hormone levels on bone loss, OP, and osteoporotic fracture in men. Some studies of BMD in men have reported positive associations with endogenous androgen levels [16–19], but others have found no significant association [20, 21]. The influence of endogenous sex hormone concentrations on bone loss in men thus remains controversial.

In the present study, to clarify the age distribution of serum levels of endogenous sex steroids and to explore the predictive capacity of these levels for bone loss in men for the early detection of male OP, we measured baseline concentrations of endogenous sex steroids in male subjects randomly selected from a rural population in Japan and conducted follow-up for 10 years.

Materials and methods

Establishment of baseline cohort

This survey was performed in the Japanese town of Taiji. The Taiji cohort has been profiled in detail elsewhere [22–24] and so is summarized here only briefly. Taiji is located in the southern coastal area of Wakayama Prefecture. A list of all inhabitants born in 1913–1952, and therefore aged between 40 and 79 years old in 1993, was compiled based on resident registrations as of the end of 1992. A cohort of 2,261 inhabitants (1,028 men, 1,233 women) was identified, and all members of the cohort completed a self-administered, 125-item questionnaire addressing topics such as dietary habits, smoking habits, alcohol consumption, and physical exercise (whole cohort).

From the whole cohort, 50 men in each of four age groups between 40 and 79 years by decade of birth year (1913–1922, 1923–1932, 1933–1942, and 1943–1952), for a total of 200 participants, were randomly selected. BMD was measured for these 200 participants in 1993. At this time, blood samples of all participants were taken. An interviewer administered a second questionnaire to these 200 participants covering items of past medical history, including questions related to osteoporotic fractures and falls, family history, calcium intake, dietary habits, physical exercise, occupational activities, sun exposure, and, for women, additional questions about reproductive variables (baseline study).

Measurements of endogenous sex steroids

At the baseline study in 1993, blood samples were taken from all participants. After centrifugation of blood samples, sera were immediately placed in dry ice, transferred to a freezer within 24 h, and kept at –80°C until assayed. Serum levels of total estradiol (E_2) and free testosterone (FT) were measured using an immunoradiometric assay (DPC-free estradiol kit and DPC-free testosterone kit, respectively; Mitsubishi Kagaku, Tokyo, Japan). The lowest measurable levels of E_2 and FT were 10 and 0.4 pg/ml, respectively, and percent of coefficient of variation (CV%) for E2 and FT were both less than 15% (unpublished data).

BMD measurements

Baseline BMD was measured in 1993 using dual-energy X-ray absorptiometry (DXA) (QDR 1000; Hologic, Bedford, MA, USA), providing anteroposterior images of lumbar vertebrae L2–L4 and the proximal femur (femoral neck, Ward's triangle, trochanter). These measurements were repeated on the same participants after 3, 7, and 10 years (1996, 2000, and 2003).

To control for the precision of DXA, the equipment was checked at every examination in 1993, 1996, 2000, and 2003 using the same phantom, and BMD of the phantom was regulated to 1.030 ± 0.016 g/cm^2 (1.5%) during all examinations. All BMD measurements were performed by the same medical doctor (N.Y.). Intraobserver variability for DXA scans by this investigator was 0.35% using the phantom, as reported previously [25].

Annual rates of change for BMD during 3-, 7-, and 10-year observations were calculated as follows:

$$\text{Annual rate (\%/year)} = [(\text{BMD follow-up} - \text{BMD baseline})/\text{BMD baseline/follow-up years}] \times 100$$

All examinations were performed with the full consent of the participants. These studies were approved by the ethics committees of both Wakayama Medical University and the University of Tokyo.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA, College Station, TX, USA). Differences were tested for significance using analysis of variance for comparisons among multiple groups, and Scheffe's least significant difference (LSD) test for pairs of groups. Significant items were selected, and multiple regression analysis was performed with adjustment of suitable variables.

Results

Eligible participants and baseline characteristics

Background data including physical characteristics for all male participants at baseline are shown in Table 1. Mean weight and height in their fifties, sixties, and seventies, and mean body mass index (BMI) in their seventies were significantly lower than those in their forties ($P < 0.05$).

Among the 200 male participants at baseline, 1 man in his sixties declined to undergo blood and urinary examinations for endogenous hormones. Examinations at baseline were thus performed on 199 men. The second visit, aimed at evaluating changes in BMDs over 3 years, obtained measurements for 181 of the 200 initially recruited participants (90.5%). The following reasons were given for the loss of 19 participants at the 3-year follow-up: 8 men had died, 1 man had moved, 1 man was ill, 4 men declined to participate, and 2 men were away from the area at the time of follow-up. The third visit, aimed at evaluating changes in BMDs over 7 years, evaluated 170 of the 200 initially recruited participants (85%). Loss of 30 participants at the 7-year follow-up was explained as follows: 14 men had died, 3 men had moved, 6 men were ill, 5 men declined to participate, and 2 men were away from the area at the time of follow-up. Among the 200 male participants initially recruited, 153 men participated in the fourth visit held in 2003 (76.5%). Loss of 47 participants at the 10-year follow-up was explained as follows: 33 men had died, 6 men had moved, 4 men were ill, 2 men declined to participate, and 2 men were away from the area at the time of follow-up.

Mean levels of serum concentration of sex steroids at baseline

Age distributions of mean E_2 and FT levels at the initial survey are also shown in Table 1. Because data below the measurable range were excluded from analysis, E_2 and FT data could be obtained for 178 and 198 participants, respectively. Mean serum levels of E_2 and FT were 22.4 and 9.4 pg/ml, respectively. Although no significant age-related trends were seen for E_2, a significant trend toward low values of FT was noted according to age ($P < 0.001$). In addition, mean serum FT was significantly higher for men in their forties than for men in their sixties and seventies ($P < 0.05$).

Predictive capacity of endogenous sex steroids for bone change

Initial mean values and rates of change in L2–L4 BMD over the 3-, 7-, and 10-year periods, classified by age stratum, are shown in Table 2. BMD values at L2–L4 for men had increased slightly by the 10-year follow-up in their fifties and sixties but had decreased a little in the forties and seventies. BMD values at the femoral neck over 10 years had decreased for men in their forties and fifties and had increased considerably in their seventies.

According to multivariate regression analysis using each rate of change for BMD at the lumbar spine over 3, 7, and 10 years as an objective factor and serum levels of E_2 as an explanatory factor after adjusting for age and BMI, beta values for the rate of change for BMD for the first 3, 7, and 10 years were 0.02, 0.04, and –0.02, respectively. Similarly, on multivariate regression analysis using each rate of change for BMD at the femoral neck over 3, 7, and 10 years as an objective factor and serum levels of E_2 as an explanatory factor after adjusting for age and BMI, beta values for the rate of change for BMD for the first 3, 7, and 10 years were –0.07, 0.09, and –0.01, respectively. Total E_2 values could not predict bone change at the lumbar spine or femoral neck at 3, 7, or 10 years.

Again, using the results of multivariate regression analysis to clarify associations between serum FT and

Table 1 Summary characteristics for male participants at baseline classified by age

Birth cohort	Age-group (years)	*n*	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	E2 (pg/mL)		FT (pg/mL)	
			Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
1943–1952	40–49	50	44.2 (2.6)	168.8 (5.2)	69.0 (10.4)	24.2 (3.2)	46	22.1 (7.4)	50	10.9 (2.8)
1933–1942	50–59	50	54.8 (2.7)	165.6 (5.0)[a]	63.5 (9.4)[a]	23.1 (2.9)	43	22.2 (7.0)	50	9.8 (2.6)
1923–1932	60–69	50	64.6 (2.5)	163.0 (4.8)[a]	62.9 (9.6)[a]	23.6 (3.2)	46	23.1 (8.5)	49	8.8 (2.6)[a]
1913–1922	70–79	50	74.0 (2.7)	160.7 (5.4)[a,b]	57.5 (8.3)[a,b,c]	22.2 (2.8)[a]	43	22.3 (7.7)	49	8.2 (3.1)[a]
1913–1952	40–79	200	59.4 (11.4)	164.5 (5.9)	63.2 (10.2)	23.3 (3.1)	178	22.4 (7.6)	198	9.4 (2.9)

BMI body mass index, *E2* total estradiol, *FT* free testosterone, *n* number of participants, *SD* standard deviation

[a] Significantly different ($P < 0.05$) from values of participants in their forties

[b] Significantly different ($P < 0.05$) from values of participants in their fifties

[c] Significantly different ($P < 0.05$) from values of participants in their sixties

Table 2 Mean values (SD) of bone mineral density (g/cm^2) and change rate (%) at lumbar spine L2–L4 and femoral neck over 3, 7, and 10 years, classified by age and gender

Birth cohort	Age-group (years)	L2–L4								Femoral neck			
		Baseline		2nd visit (3-year follow-up)		3rd visit (7-year follow-up)		4th visit (10-year follow-up)		Basesline	2nd visit	3rd visit	4th visit
		n	BMD (g/cm^2)	*n*	Change rate (%/3 years)	*n*	Change rate (%/7 years)	*n*	Change rate (%/10 years)	BMD (g/cm^2)	Change rate (%/3 years)	Change rate (%/7 years)	Change rate (%/10 years)
1943–1952	40–49	50	1.05 (0.15)	48	0.6 (3.8)	46	−0.6 (5.1)	43	−0.2 (5.8)	0.86 (0.09)	0.3 (4.6)	−1.8 (4.8)	−1.5 (10.9)
1933–1942	50–59	50	0.98 (0.17)	47	1.0 (3.3)	46	−0.0 (6.3)	46	1.6 (8.0)	0.80 (0.13)[a]	−0.2 (4.9)	0.7 (10.0)	−3.0 (6.8)
1923–1932	60–69	50	1.04 (0.21)	49	1.3 (3.6)	47	1.4 (7.1)	41	2.3 (9.4)	0.77 (0.11)[a]	1.0 (7.0)	−0.1 (9.3)	0.3 (12.5)
1913–1922	70–79	50	0.97 (0.19)	37	0.1 (5.3)	31	−1.2 (7.9)	23	−1.5 (9.2)	0.71 (0.08)[a,b,c]	0.9 (6.3)	4.6 (10.2)[a]	6.6 (16.2)[b]
1913–1952	40–79	200	1.01 (0.18)	181	0.8 (4.0)	170	0.0 (6.6)	153	0.8 (8.1)	0.79 (0.12)	0.5 (5.7)	0.5 (8.9)	−0.3 (11.7)

SD standard deviation, *BMD* bone mineral density, *n* number of participants

[a] Significantly different ($P < 0.05$) from values of subjects in their forties

[b] Significantly different ($P < 0.05$) from values of subjects in their fifties

[c] Significantly different ($P < 0.05$) from values of subjects in their sixties

BMD changes at the lumbar spine and femoral neck, beta values of FT for the rate of change for BMD at the lumbar spine at the first 3, 7, and 10 years were 0.08, 0.08, and 0.03, respectively, and those at the femoral neck were 0.21, 0.14, and 0.06, respectively. Mean FT levels were significantly related to the rate of change for BMD at the femoral neck during the first 3 years ($R^2 = 0.05$, $P < 0.01$), but could not predict bone change at any site at 7 or 10 years.

Discussion

The present study examined endogenous hormone levels among men in Japan, measuring changes in BMD over spans of 3, 7, and 10 years. The present study clarified the age distribution of endogenous sex steroids, and a significant trend was seen toward low FT levels with age. FT tended to be significantly lower in the sixties and older when compared with levels in the forties in the present study. Our results support the findings of other reports. Orwoll et al. [26] showed that testosterone levels, particularly FT levels, for 2,623 men 65 years or older were associated with increasing age. Similar findings have been described in other cross-sectional and longitudinal studies [27–29]. Based on these results, we concluded that older men tended to show lower testosterone levels than younger men, similar to the situation with E_2 in women. Some men might display testosterone insufficiency, as seen in women with E_2 insufficiency. However, we do not yet have enough evidence regarding normal ranges in young men and thresholds for testosterone insufficiency. In addition, levels of testosterone may vary among individuals and be influenced by body composition such as adipose tissue, muscle, and bone.

In contrast to testosterone, no significant age-related trend in E_2 was found in the present study. Little information is available regarding E_2 levels in older men. Orwoll et al. [26] reported that E_2 concentrations decreased as age increased, and similar findings have been described in various reports [30–33]. However, other studies have noted stable [34–36] or rising [37] E_2 levels with increasing age. Although the reasons for these discrepancies are unclear, E_2 levels may vary among individuals and may be influenced by body composition such as adipose tissue, muscle, and bone, as well as testosterone.

Regarding the ethnic variations in serum sex steroid levels, as most previous reports have been based on studies of Caucasian men, ethnic variations in FT levels among men remain unclear. To the best of our knowledge, the Osteoporotic Fractures in Men Study (MrOS) is the only study in which a sufficient number of Asian men have participated [26]. For reasons of differences in measurement methods, direct comparison of the present results and

those from the MrOS study is inappropriate, but FT levels among Japanese men tended to be lower than those in MrOS participants, although no significant difference in E_2 levels was apparent. Orwoll et al. [26] analyzed ethnic differences in the MrOS study and stated that FT levels were lower in Asian men than in other races such as Caucasian, African-American, and Hispanic subjects, but no such differences were seen for E_2. The present results support these findings.

The present study found that serum levels of FT could offer a useful predictor of bone loss at the femoral neck within 3 years, but this effect was diluted with longer observation. Regarding the effects of testosterone on bone loss at the hip, Cauley et al. [38] reported, in an epidemiological study of 1,327 men ≥65 years old, that men in the lowest FT category experienced greater hip bone loss over 1.8 years. In addition, Ensrud et al. [39] reported that among men with weight loss, the rate of decline in total hip BMD showed a stepwise increase in magnitude with greater decreases in bioavailable testosterone from baseline. In the present study, the effect of FT levels on bone loss within the relatively short term up to 3 years was observed at the femoral neck, independent of age and BMI, supporting previous reports. Although reasons for site-specific differences in the predictive capacity of FT remain uncertain, we have already reported that bone loss rate differs depending on the site involved in another cohort study [40]. We have also reported that characteristics differ between fast bone losers at the lumbar spine and femoral neck [41]. One reason for site-specific differences might be because degenerative changes that increase BMD, such as osteophytosis or sclerotic change, are observed more frequently at the lumbar spine than at the femoral neck. These results suggest that the predictive capacity of FT might differ according to the sites involved.

A recent study showed that older men with total testosterone or E_2 deficiency were more likely to be osteoporotic [19], but no report evaluated the capacity of serum sex steroids to predict occurrence of OP. Regarding the relationship between testosterone and fracture risk, Mellstrom et al. [42] reported that FT within the normal range was independently associated with the presence, but not occurrence, of osteoporotic fracture in elderly men. In contrast, an analysis from the Rotterdam Study failed to confirm any association between testosterone and fracture risk [43]. Data from the Framingham study indicated that men with low serum testosterone and E_2 levels were at increased risk for incident hip fractures [44]. A recent report from the Dubbo osteoporosis epidemiology study revealed that in men older than 60 years, serum testosterone is independently associated with the risk of osteoporotic fracture [45]. We also tried to evaluate the predictive capacity of serum levels of sex steroids and occurrence of OP based on WHO criteria [46] and osteoporotic fractures, but only identified 7 cases of OP and 10 cases of osteoporotic fractures including 1 vertebral fracture, 1 hip fracture, 2 wrist fractures, 3 costal fractures, 2 ankle fractures, and 1 finger fracture. After analysis using Cox proportional hazards models adjusted for age and BMI, serum levels of FT were significantly related to incidence of OP (hazard ratio, 0.42; 95% confidence interval, 0.19–0.90), but not to incidence of osteoporotic fractures. This analysis suggests the possibility of serum FT as a predictor for OP occurrence over 10 years. However, the number of occurrences of OP seems to be too small to reach any conclusion regarding the presence or absence of associations between sex steroids and OP or osteoporotic fractures.

There are several limitations in the present study. First, the small sample size seemed to be the most severe weakness. In fact, as already noted, only 7 cases of OP and 10 cases of osteoporotic fractures were accumulated during the 10 years of the study. Longer observation in the present cohort might be required to confirm the association between sex steroids and OP or osteoporotic fracture. Second, the dropout rate over 10 years for patients in their seventies was considerably high (54.0%). This high dropout rate might cause bias. In fact, the tendency toward an increase in BMD at the femoral neck for patients in their seventies was skewed by withdrawal bias. On the basis of this hypothesis, we reanalyzed the multivariate regression analysis to assess the change rate of BMD at the femoral neck and serum FT with exclusion of subjects in their seventies. However, the results were similar, with serum levels of FT predicting bone loss at the femoral neck within 3 years (beta = 0.17, $P = 0.05$), but diluted effects with longer observation (7 years: beta = 0.8, $P = 0.38$; 10 years: beta = 0.03, $P = 0.77$). Third, all serum samples were extracted between 0900 and 1500, not at a fixed time in the morning, although samples for measurement of FT are recommended to be collected in the morning. Serum levels of testosterone tend to increase toward night, peaking in the early morning, then decreasing rapidly and reaching a nadir between 1300 and 2300. We collected samples when FT levels would probably have been decreasing toward the nadir. The present study might thus have underestimated FT values compared to collection at a fixed time in the morning.

Conversely, the study design shows several notable strengths. In this population-based cohort study, subjects were selected randomly from the resident registration list. BMD was carefully measured by a single observer (N.Y.), and measurements were repeated 3, 7, and 10 years later with high participation rate by the same device and same observer. Another strength was that the effect of serum levels of sex steroids on changes in BMD could be estimated directly.

In conclusion, we clarified that serum levels of FT could predict bone loss within 3 years, but not longer. Further observations are required to confirm the relationship between FT, E_2, and spinal OP and osteoporotic fractures. Other environmental and genetic factors should also be evaluated to develop strategies for the early prevention of OP.

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The Fracture and Immobilization Score (FRISC) for risk assessment of osteoporotic fracture and immobilization in postmenopausal women—A joint analysis of the Nagano, Miyama, and Taiji Cohorts

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ABSTRACT

Introduction: We aimed to (i) explore risk factors for major osteoporotic fracture or immobilization; (ii) develop a prediction model that can be used to assess the risk of fracture and immobilization; and (iii) assess external validity of the final model.

Methods: A total of 1787 postmenopausal Japanese women were followed in a hospital-based cohort study. Endpoints included the annual incidence of major osteoporotic fracture and immobilization. For each endpoint, multivariate Poisson regression models were fitted separately and risk factors were screened through backward variable selection. The predictive accuracy of the final model (FRISC) was evaluated in two independent community-based cohorts.

Results: Over a median follow-up of 5.3 years, a total of 383 major osteoporotic fractures (279 clinical vertebral, 44 hip, 60 distal forearm) and 83 immobilizations occurred in the developmental dataset. Backward variable selection confirmed that the following are risk factors for major osteoporotic fracture: age, weight, prior fracture, back pain, and lumbar bone mineral density (BMD). Age, prior fracture and dementia were significant risk factors for immobilization. Hosmer–Lemeshow tests did not indicate any significant deviation between the observed fracture frequency and prediction from the FRISC in the independent validation dataset. The C statistic for the FRISC was 0.727 (95% confidence interval: 0.660 to 0.794) and was higher than that for BMD alone significantly ($p = 0.03$).

Conclusions: We developed a novel prediction model for fracture and immobilization, FRISC, and the clinical risk factors in the FRISC allows better identification of populations at high risk of fracture than BMD alone. A web application is available at http://www.biostatistics.jp/prediction/frisc.

Introduction

Fracture due to osteoporosis results in increased mortality, morbidity and medical expense in the US and Japan [1–3]. As an adjunct to the development of effective treatments, early identification of populations at high risk of fracture is regarded as an effective strategy for decreasing both the burden of illness and the associated cost in countries with aging populations [4]. The US and Japanese guidelines both recommend that bone mineral density (BMD) should be used to determine when to intervene in patients with osteoporosis [5,6]. However, epidemiological studies have demonstrated that many major osteoporotic fractures occur among individuals with a BMD T score value above the intervention threshold value, although the incidence of fracture certainly increases with decreasing BMD [7,8]. As a solution to this problem, a WHO scientific group proposed the use of 10-year probabilities of osteoporotic or hip fracture, calculated using multiple risk factors. The result was the WHO fracture risk assessment tool (FRAX) [9]. Several other prediction models/risk assessment tools were also developed based on data from cohort studies and clinical trials [10–13].

Abbreviations: BMD, bone mineral density; FRAX, fracture risk assessment tool; FRISC, Fracture and Immobilization Score; CHD, coronary heart disease; CVD, cerebrovascular disease; ROC, receiver operating characteristic; CI, confidence interval.

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Although case-finding strategies optimized by risk assessment tool for fracture appear to be promising, there are several problems which must be addressed before clinical application. First, whether combination of BMD and clinical risk factors allows better discrimination of fracture than BMD alone is still controversial; the discriminatory power of the FRAX was excellent in eleven population-based cohorts [14] but was similar to BMD alone in a cohort study [15]. Second, since the Japanese version of FRAX was validated only in the community dwelling cohorts in Japan [9], there has been no available data whether the FRAX probability performs well in hospital-based population. As Justice et al. pointed out, the effectiveness of prediction models in clinical practice depends on the extent to which they can be generalized to the population in question [16]. In general practice, the FRAX was often adapted to assess fracture risk in a patient who has a more complicated risk for fracture, such as atherosclerosis, diabetes or other potential risks to deteriorate bone strength. In this regard, it is necessary to evaluate prediction models for fracture not only in community but also hospital-based populations. Third, outcomes other than fracture, such as immobilization, appear to be also important for optimizing osteoporotic treatment from the health economic perspective. In fact, we have found that osteoporotic fracture was an independent risk for immobilization and this morbid state would require a large amount of resources of care [17].

The present study was therefore performed with three main aims. The first was to explore risk factors for the incidence of major osteoporotic fracture or immobilization. This was done using data from the Nagano Cohort, a hospital-based cohort study of postmenopausal Japanese women. The second aim of this study was to develop a prediction model named as the Fracture and Immobilization Score (FRISC), to assess the risk of major osteoporotic fracture and immobilization, based on the risk factors confirmed in the first part of the study. Finally, we assess the external validity of the FRISC and investigate whether the predictive accuracy was improved from BMD alone using pooled data from the Miyama and Taiji Cohorts, which followed 400 Japanese women from communities over a 10-year period.

Methods

Development and validation datasets

We used two independent datasets in the current analysis; a developmental dataset from the Nagano Cohort and a validation dataset from the Miyama and Taiji Cohorts. Profiles of these three cohorts have been detailed previously [17–28]. The Nagano Cohort recruited and followed up postmenopausal women who were receiving medical care as outpatients or visitors at a medical institute in Nagano Prefecture, Japan since April 1993 [16–20]. A total of 1787 participants were included in the developmental dataset; exclusion criteria were (i) metabolic bone disease and (ii) secondary osteoporosis (e.g. hyperparathyroidism, hyperthyroidism other than patients on T4 replacement and with euthyroid for more than one year, chronic renal failure or osteomalacia). We excluded those who met the exclusion criteria regardless of BMD.

However, steroid users were enrolled to the present study because the history of steroid use was required in the FRAX. The protocol was approved by the ethics committee at the Research Institute and Practice for Involutional Diseases and we obtained written informed consent from all participants. The Miyama Cohort was set up in 1988 as subsets of nationwide community-based cohort studies sponsored by the Ministry of Education or Ministry of Health and Welfare [21–23]. A total of 1453 inhabitants aged 40–79 years in Miyama Village were listed from the resident registration in December 1988. Then, 200 men and 200 women were recruited and followed up between 1990 and 2000. The Taiji Cohort is a community-based cohort study in Taiji Town, Wakayama Prefecture, Japan [25–27]. From a list of 2261 inhabitants aged 40–79 years obtained from the resident registration in June 1992, 50 men and 50 women in each decade age group between 40 and 79 years (a total of 400 participants) were recruited randomly and followed up between 1993 and 2003. All the sampled participants were contracted and agreed to participate. The validation dataset included all the women in the Miyama and Taiji Cohorts.

Data collection in the Nagano Cohort

At baseline, anthropometric indices, including body weight and body height, were obtained for all patients. Subjects were also interviewed to obtain data about age at menopause, smoking habit, alcohol consumption, past and present occupation, presence of pain, medical history (including rheumatoid arthritis, diabetes mellitus, hypertension, dyslipidemia, cancer, dementia, coronary heart disease [CHD] and cerebrovascular disease [CVD]). Pain was defined as any symptom of pain in the back, hip muscles, ribs, legs, knees, neck, shoulders, wrists, or other joints. Back pain was defined as any symptom of pain in the back trunk area, regardless of the degree or consistency of the pain [18]. Rheumatoid arthritis was diagnosed according to the diagnostic criteria proposed by the American Rheumatism Association [28]. The Japanese version of the Mini-mental State Examination (MMSE) was performed in the subjects who were suspicious dementia and a subject with the total score of MMSE less than 20 points was considered to have obvious cognitive dysfunction [29]. A history of CHD was defined as any previous acute coronary symptoms or events requiring coronary intervention, and was confirmed by coronary angiography, echocardiogram, or MD-CT imaging study. A history of CVD was diagnosed based on evidence of apparent brain attack or an existing brain lesion as observed by magnetic resonance imaging or computer-assisted X-ray tomography. Self-reports of a history of malignancy were confirmed by referring to the patient's medical records [19]. The BMD of the lumbar spine was measured at baseline using dual-energy X-ray absorptiometry (Lunar DPX-L or DPX-IQ; Lunar Corporation, Madison, WI) and a quality assurance test was carried out for every measurement to detect machine drift. The inter-assay variance of the lumbar BMD measurements in our laboratory was $0.5 \pm 0.5\%$ (coefficient of variation $\pm$ standard deviation) [20]. T score was calculated by using Japanese standard values [30].

Data collection in the Miyama and Taiji Cohorts

A self-administered questionnaire was used for baseline data collection in the Miyama Cohort, while both self-administered and interviewer-administered questionnaires were used in the Taiji Cohort [22–27]. The items in these questionnaires included birth date, body weight, body height, current smoking status, current alcohol intake, presence of back pain, use of steroids, and medical history such as rheumatoid arthritis. Parental history of fracture was asked only in the Taiji Cohort. The BMD of L2-4 and BMD at femoral neck, Ward's triangle and the trochanteric region were measured by dual-energy X-ray absorptiometry (Lunar DPX; Lunar Corporation, Madison, WI in the Miyama Cohort, Hologic QDR-1000; Hologic Inc., Crosby Drive Bedford, MA in the Taiji Cohort) and treated as T scores. The incidence of clinical fracture was evaluated in both the cohorts. However, radiographs for morphometrical vertebral fracture were available only in the Miyama Cohort. Consequently, parental history or morphometrical vertebral fracture was missing data in either cohort systematically and thus we assumed that participants with these missing data did not have parental history or prior fracture. We calculated the 10-year probability of major osteoporotic fracture by entering the following data into online version of the FRAX; age, sex, weight, height, previous fracture, parental history of hip fracture, current smoking status, glucocorticoid use, rheumatoid arthritis, alcohol intake and femoral neck BMD.

Endpoints

Endpoints included the annual incidence of major osteoporotic fracture and immobilization. Major osteoporotic fracture was defined

as first occurrence of any clinical fracture (hip fracture, surgical neck fracture of the humerus, distal forearm fracture, or clinical vertebral fracture). We also evaluated a radiographical vertebral fracture by the semi-quantitative visual method [31], but major osteoporotic fracture does not include morphometrical fracture by definition. A validation analysis of our semi-quantitative method for analyzing incident vertebral fracture has been reported elsewhere [32]. Prior vertebral fractures were defined as those fractures for which the ratio of the height of the central or anterior vertebral body to that of the posterior vertebral body was less than 0.8, or when any of these three vertebral body heights was less than 80% of the height of the adjacent vertebral body [6]. Immobility was defined in accordance with the subject's locomotive ability. Subjects bed-bound at home (lying in bed almost all day) for more than 6 months or institutionalized in nursing homes (lying in bed or using a wheelchair for locomotion), were defined as immobile [17]. Some immobile subjects could be sitting on a bed and could be going to a portable toilet which located besides the bed. Participants who died from any cause, moved to the home of a relative because they were not able to perform the activities of daily living independently, were lost to follow-up, or were followed up until June 1, 2009 were treated as censored. For each endpoint, the accumulation of person-years at risk started from registration of each patient.

Statistical considerations

For each endpoint, we fitted multivariate Poisson regression models separately and rate ratios for risk factors estimated by the Poisson regression models were reported with 95% confidence intervals (CI) and p values. The following variables were initially identified from the literature as the traditional risk factors for osteoporotic fracture: covariates included in the FRAX other than femoral neck BMD (age, height, weight, prior fracture, parental history of fracture, current smoking status, use of steroids, rheumatoid arthritis, alcohol intake), lumbar BMD, presence of back pain, presence of any pain, and drug treatment for osteoporosis [9,18,22]. These covariates were screened via backward variable selection with a significance level of $p=0.2$. We constructed a prediction model for immobilization using the same procedure, except that three covariates (dementia, history of CVD, and history of malignancy) were used in addition to those used in the osteoporotic fracture analysis. Finally, the FRISC was developed using the following formula:

$$\mathrm{Prob}(t) = \int_0^t \lambda \exp(\mathbf{X}\boldsymbol{\beta}) \exp\left[-\int_0^u \{\lambda \exp(\mathbf{X}\boldsymbol{\beta}) + m(v)\} dv\right] du$$

Here, t is a time point for prediction (i.e. the formula calculates 10-year probability if $t=10$), $\boldsymbol{\beta}$ is a vector of log-rate ratios for covariates $\mathbf{X}$, λ denotes baseline incidence rate, and $m(v)$ is mortality at time v obtained from sex- and age-specific mortality in Vital Statistics of Japan in 2008 [33].

We assessed the predictive accuracy of the FRISC in terms of calibration and discrimination [34] using occurrence of major osteoporotic fracture within a 10-year period, which was treated as a binary event, in the validation dataset. Calibration, namely how closely the prediction reflects actual events, was assessed using ratio of observed and predicted events and the Hosmer–Lemehshow test. Discrimination, the ability to distinguish between those who experience the event and those who do not, was evaluated using receiver operating characteristic (ROC) curves and Harrell's C statistic. Improvement in the C statistics of the two models from BMD alone was assessed by using contrast tests.

All reported p values for statistical tests are two-tailed, and $p<0.05$ was taken to indicate statistical significance. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Characteristics of participants and follow-up

Baseline characteristics of participants in the Nagano, Miyama and Taiji Cohorts are summarized in Table 1. The Nagano Cohort included older participants and mean lumbar BMD in this cohort was lower than the other cohorts. Prior fracture, back pain and parental history were observed more frequently in the Miyama and Taiji Cohorts. In the Nagano Cohort, 37.4% of participants were being treated with bone resorption inhibitors (bisphosphonates or a selective estrogen receptor modulator), and 16.7% were receiving 1-alpha-OH vitamin D_3 or vitamin K_2 at baseline. Table 2 describes the incidence of fractures and immobilization. In the Nagano Cohort, over a median follow-up time of 5.3 years (range, 0.03–16.5 years), a total of 383 major osteoporotic fractures occurred (279 clinical vertebral fractures, 44 hip fractures, 60 distal forearm fracture, Table 2). In the Miyama and Taiji Cohorts, 337 of 400 participants completed the planned follow-up of the 10-year period (84%) and a total of 60 major osteoporotic fractures occurred (44 clinical vertebral fractures, 8 hip fractures, 8 distal forearm fracture, Table 2). Incidence rates of fractures in the two cohorts were much lower than the Nagano Cohort possibly due to the difference in average age and lumbar BMD at baseline (Tables 1 and 2). Immobilization occurred in 83 participants in the Nagano Cohort.

Risk factors for fracture and immobilization

We fitted multivariate Poisson regression models to the validation dataset of 1787 participants. Backward variable selection identified the following six risk factors for major osteoporotic fracture: age, weight, lumbar BMD, prior fracture and presence of back pain (Table 3). That is, parental history of fracture, smoking status, alcohol consumption, rheumatoid arthritis, and use of steroids, which are all

Table 1
Characteristics of participants in the three cohorts.

		The Nagano Cohort (N=1787)			The Miyama and Taiji Cohorts (N=400)		
		Mean	SD	5–95 percentile	Mean	SD	5–95 percentile
Age (years)		63.4	11.1	45–81	59.5	11.3	41–77
Height (cm)		150.9	6.6	140–161	150.2	6.2	140–159
Weight (kg)		51.1	8.5	38–65	51.2	9.3	37–66.5
Lumbar BMD (T score)		−1.55	1.22	−3.5–0.5	−1.36	1.19	−3.85–1.57
Femoral neck BMD (T score)		*			−1.61	1.84	−3.29–0.53
			Frequency	%	Frequency		%
Prior fracture			403	22.6	49†		25.0
Presence of pain	Back		572	32.0	251		63.0
	Other sites		449	25.1	†‡		
Parental history			22	1.2	20‡		10.0
Current smoker			38	2.1	16		4.0
Current alcohol drinker			137	7.7	46		11.5
Medication	Bone resorption inhibitors		369	37.4	†‡		
	Active vitamin D_3 or vitamin K_2		299	16.7	†‡		
	Steroids		27	1.5	0‡		0.0
Rheumatoid arthritis			224	12.5	0		0.0
Dementia			97	5.4	†‡		

SD: standard deviation; BMD: bone mineral density.
*Not measured in the Nagano Cohort. †Not measured in the Miyama Cohort (N=200).
‡Not measured in the Taiji Cohort (N=200).

Table 2
Frequencies and incidence rates of fracture and immobilization in participants in the three cohorts.

	The Nagano Cohort (N=1787)				The Miyama and Taiji Cohorts (N=400)			
	Frequency	IR	95% CI		Frequency	IR	95% CI	
Major osteoporotic fracture	383	34.1	30.9	37.7	60	16.1	12.5	20.7
Clinical vertebral facture	279	24.9	22.1	28.0	44	11.8	08.8	15.9
Hip fracture	44	3.9	2.9	5.3	8	2.2	1.1	4.3
Immobilization	83	7.4	6.0	9.2	–			

IR, incidence rate per 1,000 person-years; CI, confidence interval.

included in the FRAX, were excluded based on having p values less than 0.2. Importantly, incidence rate of major osteoporotic fracture increased as weight elevated and this direction is opposite to the FRAX and this trend remains significant even when all the other risk factors listed initially in the variable selection procedure are adjusted for (rate ratio for 10 kg increase in weight: 1.22, 95% CI: 1.07 to 1.40, $p<0.01$). Multivariate analysis for immobilization, using the same variable selection procedure, showed that age, prior fracture and dementia were associated with the incidence of immobilization (Table 3).

Input and output of the FRISC

All the risk factors that were retained through the variable selection procedure were incorporated into the final prediction model named as the FRISC. Interface of web application of the FRISC is displayed in Fig. 1. The input comprises the sex risk factors and, menopausal status and secondary osteoporosis which were used only for assessment of the applicability. The output comprises the 1, 3, 5 and 10-year probabilities of major osteoporotic fracture and those of immobilization and is calculated by using the algorithm described in Supplementary Data.

External validation of the FRISC

Fig. 2 displays histograms of the calculated 10-year probabilities of major osteoporotic fracture for the 400 participants in the validation dataset (upper: the FRISC, lower: the FRAX). An apparent difference was observed in the left tail of the two histograms; in the upper figure participants with fracture probability less than 0.05 were very few, while the FRAX gave the fracture probability less than 0.05 to a substantial portion of the participants. As a result, the fracture probabilities from the FRISC were much higher on average. Table 4 compares the predictive accuracy of the two prediction models and prediction from BMD alone. Over the 10-year follow-up, major osteoporotic fracture developed in 60 of 400 participants in the validation dataset. The predicted event frequency calculated from the FRISC was slightly higher than the observation (observed/predicted ratio: 0.74), while the FRAX tended to underestimate (observed/predicted ratio: 1.59). The Hosmer–Lemeshow test did not indicate any significant deviation between the observed event frequency and prediction from the FRISC. The C statistics for the FRISC was 0.727, indicating that the discriminatory power of the FRISC is moderate, while that for prediction from BMD alone was 0.651. That is, the discriminatory power of the FRISC, which combines BMD and additional clinical risk factors, was better than BMD alone significantly even in independent community-based cohort studies ($p=0.03$, Table 4). Fig. 3 shows ROC curves for major osteoporotic fracture probability from the FRISC (solid curve), the FRAX (dashed curve) and BMD alone (dotted curve). Both the ROC curves of the prediction models increased almost identically at first, but the curve for the FRISC was slightly above the curve for the FRAX where sensitivity is higher than 0.7 and where lower probability is used as a cutoff point (i.e. 16% or lower in the FRISC, 14% or lower in the FRAX), indicating that the FRISC is advantageous over the FRAX for screening of low-risk osteoporotic patients.

Table 3
Multivariate Poisson regression analysis of risk factors for major osteoporotic fracture and immobilization in the development dataset of 1,787 participants.

	Major osteoporotic fracture				Immobilization			
	Rate ratio	95% CI		p	Rate ratio	95% CI		p
Age, +10 years	1.62	1.43	1.83	<0.01	2.80	2.09	3.73	<0.01
Weight, +10 kg	1.25	1.10	1.42	<0.01	–	–	–	–
Lumbar BMD, +1 T score point	0.85	0.76	0.94	<0.01	–	–	–	–
Prior fracture, yes/no	2.00	1.57	2.54	<0.01	2.04	1.21	3.44	0.01
Back pain, yes/no	1.58	1.27	1.96	<0.01	–	–	–	–
Dementia, yes/no	–	–	–	–	2.09	1.32	3.29	<0.01

BMD: bone mineral density; CI: confidence interval.

Discussion

In the current study, we explored clinical risk factors for major osteoporotic fracture and immobilization and developed a novel prediction model, the FRISC. Importantly, the assessment of external validity showed that the FRISC allows accurate prediction of major osteoporotic fracture even in the community-based setting and after a long-term follow-up of ten years, although it was developed in a hospital-based cohort study (i.e. for outpatients and visitors to a clinic). Therefore, the FRISC is useful both not only for patients who have a more complicated risk for fracture, such as atherosclerosis, diabetes or other potential risks to deteriorate bone strength, but also general postmenopausal women. Further the discriminatory power of the FRISC was shown to be better than BMD alone. We have previously noted that there is a close relationship between bone fractures and subsequent immobilization in postmenopausal Japanese women, and that these two conditions are morbid states that require a large amount of health resources [17]. Therefore, an accurate measure to predict these two conditions is particularly valuable in the context of an aging society. A web application of the FRISC is available at http://www.biostatistics.jp/prediction/frisc (Fig. 1).

The major finding of the current study is that inclusion of the four clinical risk factors, namely age, weight, prior fracture and back pain, in addition to BMD significantly improved the accuracy of the prediction model for major osteoporotic fracture. In contrast, parental history of fracture, smoking status, alcohol consumption, rheumatoid arthritis and use of steroids, which are all included in the FRAX, were not associated with incidence of fracture in the present analysis. The reason for this observation does not appear to be a lack of power given the number of observed events in the Nagano Cohort. Diet and other lifestyle factors, which were Westernized among smokers in this cohort, may have contributed to this unexpected result. One implication of these findings is that the association between lifestyle factors and fracture risk is possibly biased due to confounding factors, and it is necessary for prediction models to reflect the multidimensional nature of lifestyles. Although there were smokers and drinkers in the present population, the extent of their smoking and drinking was very mild, and smaller percentages of patients had these habits than in comparable Caucasian populations. In the practical point of view, a more parsimonious model is desirable and the FRISC would therefore provide a simple but sufficiently accurate measure for prediction of major osteoporotic fracture.

The present results indicated that incidence of fracture increases with heavier body weight, although low BMI has been considered as a significant risk factor of fracture as proposed in the FRAX. This trend remained even after the adjustment for the other risk factors

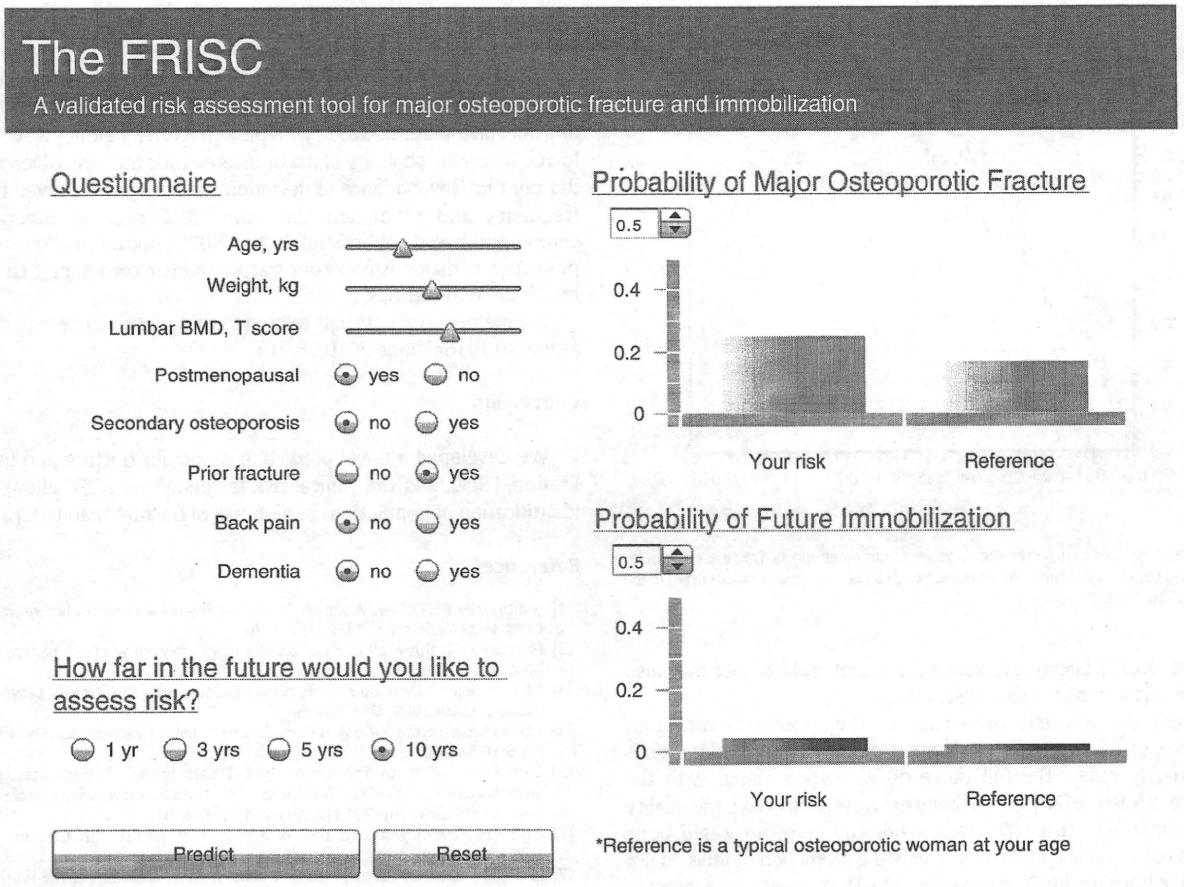

Fig. 1. Input and output of the web application of the FRISC.

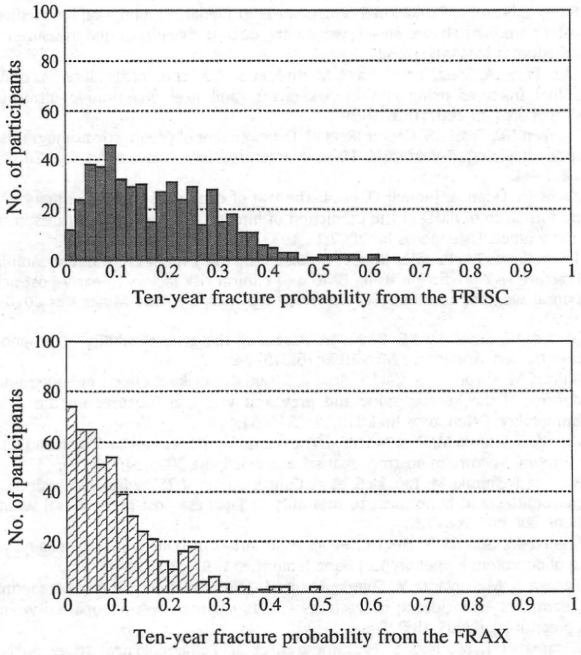

Fig. 2. Histogram of 10-year probabilities of major osteoporotic fracture from the FRISC (upper) and the FRAX (lower) in the Miyama and Taiji Cohorts.

($p<0.01$) and therefore seemed to be attributable to confounders. This may be one of the causes of discrepancy in 10-year probability between the FRAX and the actual fracture rate in the three cohorts. Recent report indicated that morbid obesity had a higher susceptibility of fractures comparing to the postmenopausal women with normal weight although the BMD of the obesity was higher than the controls [35]. As it is well known that obesity will connect to have diabetes mellitus or at least to have glucose intolerance and diabetes may deteriorate bone quality due to an increase in non-enzymatic glycation induced cross-links of collagen, which increased collagen

Table 4
Predictive accuracy of major osteoporotic fracture probability from the FRISC compared the FRAX evaluated in the validation dataset from general population.

	Calibration			Discrimination			
	Predicted no. of cases	Observed/ predicted ratio	p^*	C statistics†	95% CI		$p^‡$
BMD alone	–	–	–	0.651	0.575	0.728	–
The FRAX	37.8	1.59	<0.01	0.699	0.629	0.768	0.23
The FRISC	81.2	0.74	0.17	0.727	0.660	0.794	0.03

CI: confidence interval.
* Hosmer–Lemeshow test, p value less than 0.05 indicates a significant deviation between the observed and predicted event frequencies. Number of strata and degree of freedom are 10 and 8, respectively.
† The proportion of all patient pairs in which prediction and observed occurrence of event are concordant.
‡ Contrast test comparing C statistics of the FRAX and FRISC from that of BMD alone, p value less than 0.05 indicates a significant improvement from BMD alone.