Geriatric Depression Scale (GDS)

The GDS was administered and scored according to published procedures [29, 30]. GDS scores were interpreted as indicating no depression (GDS score ≤ 5), probable depression (GDS score >5 and ≤ 10), or definite depression (GDS score >10).

Modified Fall Efficacy Scale (MFES)

The MFES is a 14-item "balance efficacy" questionnaire that measures a person's confidence in their ability to avoid a fall during each of 14 essential, non-hazardous activities of daily living (ADLs) [31]. A higher score indicates greater independence or ability to balance (score range, 14–140, with 14 being worst). Full score means the patient has no fear of falling [32]. The MFES has been found to be internally consistent and demonstrates good test–retest reliability [33, 34].

Statistical analysis

All data are expressed as mean ± SD. Patients were classified as either "non-fallers" or "fallers" (one or more falls) based on data gathered during the prospective 6-month observation.

Differences between groups were determined using Pearson's chi-square test. The non-paired *t* test and Mann–Whitney U test were conducted to compare grading scales between non-fallers and fallers.

Both multivariate and univariate analyses were performed. Variables with a significance level of $P < 0.05$ as determined by univariate analysis were selected for multivariate analysis. Multivariate logistic regression was used to provide adjusted odds ratio estimates for associations with falls.

All data were analyzed using PASW statistical software (version 18 for Windows; SPSS Inc., Japan). For all analyses, a P value <0.05 was considered significant.

This study was approved by the local ethics committees of the Faculty of Medicine, Tottori University (No1264), and Hakuai Hospital.

Results

Of the 74 patients enrolled, 70 (94.6%) completed a 6-month prospective observation. One patient was unable to follow-up. Three patients were withdrawn from the study because contralateral TKA was performed during the study period.

Incidence of falls

Twenty-three of 70 patients (32.9%) fell during the observational period; 6 subjects fell twice each, while 4 subjects fell 3 times each. One patient sustained a dislocated shoulder and two patients had bruises and slight injuries due to falling. There were no fall-related fractures during the 6-month observational period.

Patient characteristics

Characteristics of non-fallers and fallers are presented in Table 2. There was no significant difference between the two groups except for the number of patients with eye problems, cardiac disease, and diabetes, which tended to be higher in fallers than non-fallers ($P = 0.051$, $P = 0.065$, $P = 0.058$, respectively).

Physical examinations and performance tests

Physical examination and performance test variables are presented in Table 3. Postoperative range of knee flexion (range 80–140°) was significantly lower in fallers than in non-fallers ($P = 0.016$). Six of 70 patients (8.6%) had less than 100° of knee flexion, 23 of 70 patients (32.9%) had less than 120° and more than 100° of knee flexion. 41 of 70 patients (58.6%) had more than 120° of knee flexion.

Postoperative ranges of knee flexion and extension (range 60–135°) and ankle plantar flexion (range 40–70°) were significantly lower in fallers than in non-fallers ($P = 0.037$, $P = 0.014$, respectively). Preoperative knee flexion (range 80–145°) and ankle dorsal flexion (range 5–30°) tended to be lower in fallers than non-fallers ($P = 0.055$, $P = 0.070$, respectively).

Two of 70 patients (2.9%) had more than moderate instability of the knee that had undergone TKA. 27 of 70 patients (38.6%) had hallux valgus (scale of 2–4) and 18 of 70 patients (25.7%) had limited ankle mobility. Mean index of kyphosis was 8.3 ± 3.6% (range 2–20%). There were no significant differences between the two groups in terms of preoperative range of knee extension, preoperative range of knee flexion and extension, postoperative range of knee extension, knee instability, muscle strength during knee extension, hallux valgus, degree of limitation of ankle mobility, and degree of kyphosis.

One-leg standing time (range 0–32.5 s), mean gait speed (range 0.3–1.53 s/m) and step length (0.2–0.71 m) showed no significant differences between the two groups.

Self-administered questionnaires

The results of the self-administered questionnaires (JKOM, GDS, and MFES) are presented in Table 4. 44 of 70 patients (62.9%) scored less than 50 on the JKOM (range 29–95). Based on GDS score, 21 of 70 patients (30.0%) had probable depression (GDS score >5 and ≤ 10) while 6

Table 2 Characteristics of non-fallers and fallers

	Total ($n = 70$)	Non-fallers ($n = 47$)	Fallers ($n = 23$)	P value
Age (years)	75.5 ± 6.0	76.2 ± 5.4	74.1 ± 6.9	0.156
Sex ratio (M:F)	(8:62)	(5:42)	(3:20)	0.766
Height (cm)	152.0 ± 7.5	152.5 ± 7.2	151.0 ± 8.3	0.435
Weight (kg)	57.4 ± 9.1	56.9 ± 8.9	58.5 ± 9.5	0.494
BMI (kg/m^2)	24.8 ± 3.2	24.4 ± 3.0	25.6 ± 3.3	0.142
TKA side				
Right (%)	31.4	31.9	30.4	0.969
Left (%)	22.9	23.4	21.7	
Bilateral (%)	45.7	44.7	47.8	
Diagnosis OA:RA	(66:4)	(44:3)	(22:1)	0.730
Mean time since surgery (month)	8.2 ± 2.7	8.1 ± 2.7	8.6 ± 2.7	0.444
Prior hip surgery (%)	4.3	2.1	8.7	0.986
Total no. of prescribed regular medications (number)	3.3 ± 2.6	3.3 ± 2.8	3.4 ± 2.5	0.843
Hearing problems (%)[a]	40.0	42.5	34.8	0.533
Eye problems (%)[a]	48.6	40.4	65.2	0.051
Complications				
Cardiac disease (%)	5.7	2.1	13.0	0.065
Diabetes (%)	11.4	6.3	21.7	0.058
Hypertension (%)	34.3	36.1	30.4	0.422
Ambulation				
Walking without device (%)	68.6	70.2	65.2	0.466
One cane (%)	30.0	29.8	30.4	
Walker (%)	1.4	0.0	4.3	

Data are mean ± SD (range)

[a] Self reported

of 70 patients (8.6%) had definite depression (GDS score >10). 45 of 70 patients (64.3%) did not achieve full scores on the MFES (range 22–140). There were no significant differences between the two groups in terms of JKOM, GDS, or MFES scores.

Multivariate logistic regression analysis

Postoperative range of knee flexion was divided into 6 groups of 10 degrees each (range 80–140°). Postoperative range of knee flexion and extension was similarly divided into 8 groups of 10 degrees each (range 60–135), and range of ankle plantar flexion was divided into 6 groups of 5 degrees each (range 40–70°).

In the multivariate analysis, postoperative range of knee flexion and ankle plantar flexion were determined to be significant risk factors (Table 5). Patients with a higher postoperative range of knee flexion were less likely to fall; a 10-degree increase significantly reduced the odds of falling during the observation period by 72.3%. Similarly, patients with a higher range of ankle plantar flexion were less likely to fall; a 5-degree increase significantly reduced the odds of falling by 40.6%.

Discussion

The present study examined for the first time the relationship between falls and physical function among elderly persons who had undergone TKA. Our prospective investigation demonstrated that 23 out of 70 elderly TKA patients fell at least once during the 6-month observation period. The incidence of falls was 32.9%, which was higher than one study's previously reported incidence range of 10–20%[35] among elderly in Japan, and another study's annual incidence of 29.3% among people between the ages of 75 and 79 [36], similar ages to the subjects in this study.

Swinkels et al. [14] examined whether or not the incidence of falls changed before and after TKA in patients with OA or RA. They found an incidence of 24.2% both before and after TKA. The authors speculated that TKA lowers fall incidence because the estimated incidence for community-dwelling elderly people was 33% and the number of falls was reduced after TKA. The annual incidence of falls among patients with RA was reported to be 50% [37], indicating that these patients are at risk. The incidence of falls among patients with OA is also speculated to be high. Levinger et al. [15] reported that 48% of

Table 3 Physical examinations and performance tests in fallers and non-fallers

	Total (n = 70)	Non-fallers (n = 47)	Fallers (n = 23)	P value
ROM of the knee (°)				
Preoperative				
Flexion	118.4 ± 13.0	120.3 ± 12.2	113.2 ± 14.0	0.055
Extension	−7.7 ± 6.6	−7.6 ± 7.3	−8.5 ± 4.6	0.561
Range of flexion and extension	110.5 ± 17.3	112.7 ± 16.9	104.7 ± 17.3	0.105
Postoperative				
Flexion	116.4 ± 15.3	119.5 ± 14.1	110.2 ± 16.1	0.016
Extension	−9.7 ± 4.6	−9.8 ± 4.4	−9.6 ± 5.0	0.850
Range of flexion and extension	106.7 ± 17.1	109.7 ± 15.9	100.6 ± 18.4	0.037
ROM of the ankle (°)				
Dorsal flexion	16.6 ± 5.1	17.3 ± 5.1	15.0 ± 4.8	0.070
Plantar flexion	57.9 ± 6.3	59.1 ± 6.1	55.2 ± 6.1	0.014
Instability (0–3; 3 = most unstable)[a]	0.9 ± 0.7	1.0 ± 0.8	0.8 ± 0.7	0.384
Muscles strengths of knee extension (Nm/kg)	2.1 ± 0.5	2.1 ± 0.5	2.1 ± 0.5	0.816
Hallux valgus (1–4; 4 = most severe)[b]	1.9 ± 1.0	2.0 ± 1.1	1.9 ± 0.9	0.867
Limitation of ankle mobility (%)[c]	25.7	25.5	26.1	0.960
Kyphosis (%)[d]	8.6	6.8	15.0	0.350
One-leg standing (s)	8.6 ± 7.7	8.9 ± 7.9	7.8 ± 7.6	0.578
10-m gait test				
Speed (m/s)	0.97 ± 0.2	0.98 ± 0.2	0.95 ± 0.2	0.612
Step length (m)	0.49 ± 0.1	0.50 ± 0.1	0.49 ± 0.1	0.686

Data are mean ± SD (range)

[a] Used 4-point ordinal scale (0 = rigid,1 = normal, 2 = slightly instable, 3 = more than moderately instable)

[b] Manchester scale (1 = no deformity, to 4 = severe deformity)

[c] ROM of talocalcaneal joint (inversion and eversion)

[d] Milne's method was used ("kyphosis" defined as an index greater than 15%)

Table 4 Self-administered questionnaires in non-fallers and fallers

	Total (n = 70)	Non-fallers (n = 47)	Fallers (n = 23)	P value
JKOM				
Total score (25–125; 125 = worst)	46.1 ± 15.9	45.5 ± 16.7	47.6 ± 14.5	0.601
VAS (0–10; 10 = worst)	1.9 ± 2.4	1.7 ± 2.4	2.2 ± 2.4	0.342
Pain (8–40; 40 = worst)	13.8 ± 5.3	13.8 ± 5.9	13.8 ± 4.1	0.985
Limitations of activity (10–50; 50 = worst)	18.6 ± 6.7	18.3 ± 6.9	19.6 ± 6.3	0.449
Restriction of participation (7–35; 35 = worst)	13.9 ± 5.6	13.7 ± 5.7	14.3 ± 5.6	0.679
GDS (0–15; 15 = worst)	4.2 ± 4.0	4.0 ± 4.2	4.8 ± 3.6	0.459
MFES (14–140; 14 = worst)	122.9 ± 24.4	123.3 ± 23.3	122.2 ± 27.1	0.874

Data are means ± SD (range)

JKOM Japanese Knee Osteoarthritis Measure, *VAS* Visual Analogue Scale, *GDS* Geriatric Depression Scale, *MFES* Modified Fall Efficacy Scale

patients fell during the year prior to TKA and another study showed that the annual incidence among elderly women with musculoskeletal pain in lower extremities was 39% [38]. Thus, although TKA may reduce the incidence of falls in patients with OA or RA, elderly people who underwent TKA are considered more likely to fall compared with healthy elderly people.

In the study by Swinkels et al. [14], subjects were surveyed using self-administered questionnaires that included the WOMAC and Activities-specific Balance Confidence (ABC) Scale before and after TKA. However, the results of these questionnaires did not demonstrate any risk factors for postoperative falls. Similarly, the results of the self-administered questionnaires in the present study, including

Table5 Selected risk factors for falls by multivariate analysis

	Odds ratio	95% IC	*P* value
Range of knee flexion (postoperative)[a]	0.277	0.088–0.869	0.028
Range of knee flexion and extension (postoperative)[b]	2.308	0.847–6.289	0.102
Range of ankle plantar flexion[c]	0.594	0.374–0.945	0.028

Variables for multivariate analysis were selected by univariate analysis using a significance level of $P < 0.05$

[a] Knee flexion categorized into 10-degree groups (80–140)

[b] Knee flexion and extension categorized into 10-degree groups (60–135)

[c] Ankle plantar flexion categorized into 5-degree groups (40–70)

the JKOM regarding ADLs, did not show any difference between fallers and non-fallers. The JKOM examines respondents' level of difficulty with daily activities due to pain at the time of the survey, while MFES measures the confidence of respondents in their ability to avoid a fall during ADLs. Nevertheless, considering the results of past studies which demonstrated inaccurate perceptions of postural stability borders among elderly people [39] and greater errors in estimated reach distance in the elderly who fell compared with those who did not fall [40], it is possible that our subjects who fell overestimated their ability to perform activities and selected the answers "no difficulty" or "I can do it" in self-administered questionnaires. Swinkels et al. [14] found that the preoperative GDS score was a risk factor for falls. In our study, although approximately 40% of subjects had either probable or definite depression, there was no difference between fallers and non-fallers. Therefore, no particular relationship between depression and falls was identified in this study.

In the present study, the occurrence of falls was prospectively examined after objectively evaluating the physical function of elderly individuals who underwent TKA. Our results showed significant differences in postoperative range of knee flexion, postoperative range of knee flexion and extension and range of ankle plantar flexion between fallers and non-fallers. Fallers demonstrated lower values in all three parameters. In addition, multivariate analysis showed that postoperative ranges of knee flexion and ankle plantar flexion were risk factors for falls among the elderly who underwent TKA.

Among activities of daily living, the motion in which limited knee flexion is most likely to cause falls is rising from a chair. Itokazu et al. [41] conducted biomechanical analyses of patients who underwent TKA to examine the relationship between knee flexion angle and the motion of rising from a chair, and showed that patients whose range of knee flexion was limited (100° or less) required higher angular velocity of the hip and higher swing velocity to lift the trunk forward than patients whose range of motion was larger. When individuals whose knee flexion is limited attempt to force themselves to rise from chairs by increasing the flexing action of the trunk and hip in order to compensate for limited knee flexion, they may fall forward or, if the center of gravity of their upper bodies does not sufficiently shift forward, lose their balance and fall backwards. These individuals may trip while ascending steps or experience difficulty in lowering their center of gravity while descending steps, leading to loss of balance and falls.

Limited knee flexion also frequently causes falls while walking. In normal walking, it is speculated that people repeat flexion and extension of their knees twice in a gait cycle with a maximum flexion angle of approximately 65° [42], while gait analysis after TKA [43] has revealed that the knee flexion angle of the swing phase is smaller than that of healthy elderly people. Therefore, patients who cannot sufficiently flex their knees while walking may trip over obstacles and fall. Moreover, crouching requires 130° or greater knee flexion [44]. Thus, these motions are difficult for elderly who have undergone TKA and have limited knee flexion, again potentially leading to loss of balance and falls.

Range of ankle plantar flexion is the most important ROM of joints during the push-off phase of the gait cycle and in ensuring the toe-off. Barak et al. [45] conducted a gait analysis of healthy elderly people in their seventies who fell during the past 6 months, and reported that their range of ankle plantar flexion during the push-off phase of the gait cycle was smaller than that of those who did not fall. Furthermore, another study showed that smaller range of ankle plantar flexion during the push-off phase leads to delayed heel-off, which is compensated for by movements including excessive ankle dorsal flexion of the foot and anteversion of the trunk in order to move forward [42]. Such compensation may disturb balance, pushing the body forward and causing falls. The small ranges of both knee flexion and ankle plantar flexion in the fallers in our study suggests that they may have joints with limited ROM throughout their bodies. We speculated that the decrease in ROM of the joints in the lower limbs, in particular, coupled with impaired motor skills, can cause falls.

One of the limitations of this study is its small sample size. However, as a result of the detailed physical examinations and performance tests we conducted on all subjects, sufficient objective data for various indices were obtained and significant risk factors for falls that are characteristic of elderly people who underwent TKA were obtained despite the small number of subjects. Another limitation is that the incidence of falls and physical function were not compared with those of any control group. Direct comparison of many of our examined variables

could not be performed in this study, and we therefore compared our results with those of similar previous studies and characterized the incidence of falls among elderly individuals who had undergone TKA. In the future, this incidence should be compared with that of healthy elderly people or patients with OA or RA who have equivalent levels of physical function. In addition, comparison of physical function and studies on changes in the incidence of falls before and after TKA should also be performed.

In conclusion, this 6-month prospective study of elderly subjects who underwent TKA revealed a fall incidence of 32.9%, higher than that in elderly population in general. Reduced postoperative ranges of knee flexion and ankle plantar flexion were determined to be risk factors for falls among the elderly who underwent TKA. For patients with limited knee flexion, improvement of ROM by exercise therapy and patient education regarding the prevention of falls and fractures are considered necessary.

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ORIGINAL RESEARCH

The Risk of a Second Hip Fracture in Patients after Their First Hip Fracture

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Abstract We investigated the incidence of additional fractures and the rate of prescription of osteoporotic pharmacotherapy after an initial hip fracture. We surveyed female patients aged 65 and over who sustained their first hip fracture between January 1, 2006, and December 31, 2007, treated at 25 hospitals in five geographic areas in Japan. Data for 1 year after the first hip fracture were collected from medical records, and questionnaires were mailed to all patients. In total, 2,663 patients were enrolled, and 335 patients were excluded based on exclusion criteria. The analysis was performed on 2,328 patients. During the 1-year follow-up period 160 fractures occurred in 153 patients and 77 subsequent hip fractures occurred in 77 patients. The incidence of all additional fractures among patients who sustained their first hip fracture was 70 (per 1,000 person-year) and that for second hip fracture was 34. In comparison to the general population, women ≥65 years of age who sustained an initial hip fracture were four times as likely to sustain an additional hip fracture. Antiosteoporosis pharmacotherapy was prescribed for 436 patients (18.7%), while 1,240 patients (53.3%) did not receive any treatment during the 1-year period. Patients who have sustained one hip fracture have a higher risk of a second hip fracture compared to the general population, and most of these women receive no pharmaceutical treatment for osteoporosis.

Keywords Hip fracture · Second hip fracture · Treatment of osteoporosis

Introduction

Hip fractures are a common cause of morbidity and mortality in the elderly and are associated with considerable health expenditures in most industrialized countries. Several studies have suggested a worldwide geographic variation in the incidence of hip fractures, with the highest rates reported for northern European countries and the United States and the lowest rates reported in Africa and some Asian populations [1]. However, epidemiological information regarding the risk of sustaining subsequent hip fractures is limited compared to that of sustaining the first hip fracture as fewer studies have addressed this issue. Overall 1- and 5-year mortality rates after the first hip fracture are 15.9 and 45.4%, while rates after a second hip fracture are 24.1 and 66.5%, respectively [2].

The incidence of hip fractures had been increasing in Europe and the United States until about 10 years ago, when this rate plateaued or decreased [3–5]. Contrast this

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to Japan and other Asian countries, where the incidence of hip fractures has increased steadily from 1986 to 2006 [1, 6]. However, only a few epidemiological studies have been conducted to determine the incidence of sustaining a second hip fracture within the Asian population.

Because of the high risk of sustaining a second hip fracture in patients after their initial hip fracture, pharmacologic intervention is essential. However, reports suggest that pharmacotherapy is not necessarily prescribed adequately in these populations. Cadarette et al. [7] reported an increased proportion of hip-fracture patients treated with osteoporosis drugs; however, the overall proportion remains low, with fewer than one-third of these patients receiving pharmacotherapy. In another report, 9.2% of women and 4.1% of men began therapy after a hip fracture in 2004 [8]. Currently, no data are available concerning the rates of prescription for osteoporosis treatment after a first hip fracture based on an investigation of Asian patients.

The aim of this study was to elucidate the incidence of additional fractures in patients within 1 year after they sustained their first hip fracture. An additional aim was to investigate the frequency of prescription of antiosteoporotic pharmaceuticals in these patients.

Patients and Methods

Study Design and Overview

The present study was designed as a historical, register-based, uncontrolled, follow-up study. This study was approved by the local ethics committee at the Faculty of Medicine, Tottori University (no. 1096), and by each participating hospital. Data on demographics, treatments, and health outcomes during each patient's hospital stay were collected from medical records. Data on patients who were followed after the treatment for 1 year following the fracture were also collected from medical records at each hospital. A voluntary and confidential questionnaire was mailed to patients and/or their family members regarding the patients' health outcomes in the 1-year period after the initial hip fracture. The letter included an informed consent explaining the study purpose, with instructions on how to complete and return the survey.

Five geographic areas in Japan were selected for this study: Niigata, Toyama, Tokyo, Tottori, and Kumamoto. Within each area, four, five, two, nine, and five hospitals (total of 25) participated in the study, respectively. A tally of all female patients who sustained a hip fracture, 65 years or older, injured during the 2-year period from January 1, 2006, to December 31, 2007, and treated in these hospitals was conducted. All hospital data, registered anonymously by number, were sent to Tottori University and compiled.

Data Collection

Medical Record Review

Hip fractures were identified by hospital records with radiographs. Inclusion criteria were female patients 65 years or older who had experienced a hip fracture due to minor trauma for the first time and had been admitted to one of the 25 study hospitals during the study period (January 2006 to December 2007). Patients with pathological fractures or high-impact trauma, such as traffic accidents, were excluded from the enrollment. During the medical records review, all patients were selected according to the above inclusion and exclusion criteria by orthopedists.

Data collected from medical records were patient's age at the time of the first hip fracture, fracture site (right or left), fracture type (neck or trochanter), date of birth, body height, body weight, residence before the fracture, bone mineral density (BMD, percent of young adult mean, YAM), and if osteoporosis medications were taken. The patients' ambulatory ability before the first hip fracture was also recorded, divided into the following six categories: ability to walk without difficulty, ability to walk outside with a walking aid, ability to walk only inside with an aid, inability to walk without support, complete inability to walk, and unknown.

Comorbidities were defined as conditions that patients had before hip-fracture surgery. Main comorbidities included hypertension, heart failure, arrhythmia, diabetes mellitus, respiratory disease, a history of stroke, Parkinson disease, osteoarthritis, rheumatoid arthritis, and dementia. Dementia was defined as patients having fewer than 21 points on the revised version of Hasegawa's Dementia Scale. The presence of cognitive dysfunction was ascertained by a medical records review.

Treatment data included admission and discharge dates, type of surgery (osteosynthesis or arthroplasty), implants used for surgery, rehabilitation protocol, and if osteoporosis treatment was prescribed during the hospital stay. Medical record reviews at the treating hospitals confirmed whether follow-up data were available in the hospital, if the patient was currently alive or dead, the occurrence of new fractures within 1 year after the first hip fracture and treatment for those fractures, and if osteoporosis was treated. Fractures were verified by radiographs.

Questionnaire

A letter was sent from coinvestigators at each hospital to the patients who met the study inclusion criteria. The informed consent and surveys were sent to the billing addresses used at their last hospitalization. Patients and/or

their family members were asked to sign the consent form and complete and return the questionnaire in a self-addressed, stamped envelope if they agreed to participate in the study. The questionnaire inquired if osteoporosis treatment had been prescribed and the occurrence of any new fractures. If the latter was present, the details about the new fracture site, the cause of the fracture, and treatment details were also asked.

Statistical Analysis

Age-specific incidence was calculated based on the number of fractures and observational year. Age- and gender-specific incidences (per 1,000 person-years), reported previously for the general population in Japan, were adopted to compare the risk of hip fracture among patients with a prior hip fracture. Age- and gender-specific incidences (per 1,000 person-years) of hip fracture for the general population in women are 1.9, 8.6, 24.5, and 25.4 in the age groups of 65–74, 75–84, 85–94, and ≥95 years, respectively, and the risk for all women 65 years old or older is 8.3 (data were analyzed based on the study by Hagino et al. [1]).

Continuous variables, including age, body height, body weight, and body mass index (BMI) before surgery, were compared using *t*-tests. Pearson's chi-squared tests or Fisher's exact tests were used to compare the categories/ratios of variables.

A multivariate analysis was performed in addition to a univariate analysis. Variables determined during the hospitalization with a significance level of $P < 0.05$, as determined by univariate analysis, were selected for multivariate analysis. Multivariate logistic regression analysis was used to provide adjusted odds ratio (OR) estimates for associations with subsequent fractures.

Statistical analysis was performed using SPSS software (SPSS II for Windows, version 11.0.1J; SPSS, Inc., Tokyo, Japan).

Results

Enrolled Patients and Response Rates for Questionnaires

Two hundred thirty-five patients from the Niigata area, 605 patients from the Toyama area, 216 patients from the Tokyo area, 892 patients from the Tottori area, and 715 patients from the Kumamoto area (in total 2,663 patients) were enrolled. Three hundred thirty-five patients were excluded according to the exclusion criteria: 213 had a fracture before or after the study period, 96 were under 65 years old, and 26 were lacking detailed data regarding the cause of the fracture including a suspicion of pathological fracture. The analysis was then conducted for 2,328 patients (Fig. 1). Fractures occurred on the right side in 1,200 patients and on the left side in 1,128 patients; 1,025 were neck fractures and 1,303 were trochanteric fractures. One thousand eighty-five (46.6%) of 2,328 patients returned their questionnaires. Sixty-one patients died during the follow-up period. Among the remaining patients, 1,076 were followed based on both medical records and patient questionnaires and 887 patients who did not return the patient questionnaires were followed by a medical record review. As a result, 304 were lost to follow-up.

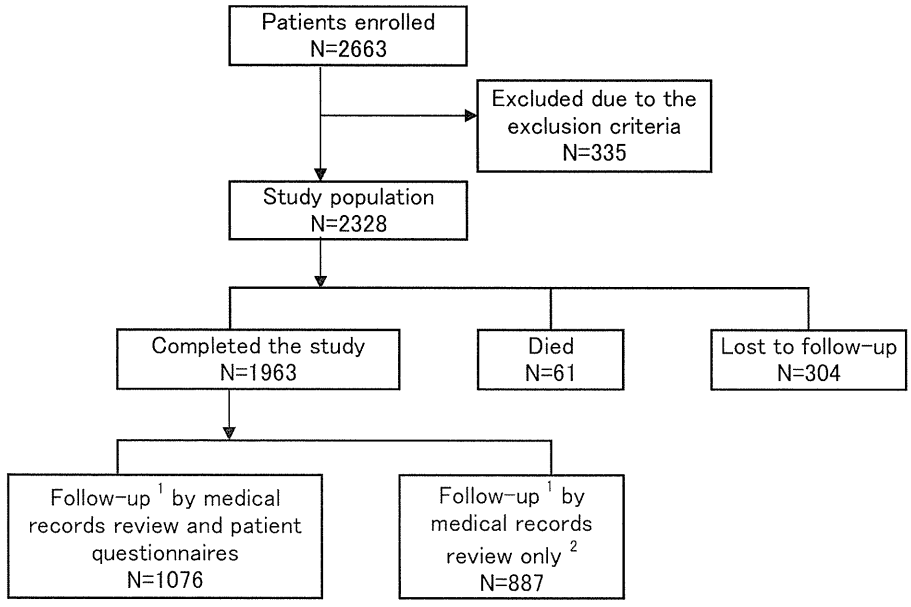

Fig. 1 Patient disposition. *1*, Duration of follow-up 1 year; *2*, patient questionnaires were not returned

Demographics of the Patients

The average age at the time of the initial fracture was 83.6 years (range 65–104). The place of residence, investigated by medical chart records, was the patient's own home in 1,550 patients, a nursing home in 482 patients, a hospital in 190 patients, other in 9 patients, and unknown in 97 patients.

Ambulatory abilities before the first hip fracture according to the medical charts were "Able to walk without difficulty" in 881 patients (37.8%), "Able to walk outside with a walking aid" in 670 patients (28.8%), "Able to walk only inside with aid" in 132 patients (5.7%), "Unable to walk without support" in 329 patients (14.1%), "Unable to walk" in 171 patients (7.3%), and unknown in 145 patients (6.3%).

Regarding comorbidities, hypertension was diagnosed in 1,030 patients, heart failure in 297 patients, arrhythmias in 123 patients, diabetes mellitus in 317 patients, respiratory disease in 148 patients, a history of stroke in 320 patients, Parkinson disease in 87 patients, osteoarthritis in 236 patients, and rheumatoid arthritis in 60 patients. Dementia was diagnosed in 500 patients (21.5%), was not diagnosed in 666 patients (28.6%), and was not examined in 1,139 patients (48.9%). Among those not examined, cognitive dysfunction was present in 472 patients (20.3%).

Osteoporosis was diagnosed before the first hip fracture in 274 patients (11.8%), was not diagnosed in 1,587 patients (68.2%), and status was unknown in 467 patients (20.1%). Antiosteoporosis medication was administered in 185 patients (7.9%). Importantly, no information regarding medications was available in 2,038 patients (87.5%).

BMD was measured in 365 patients (15.7%) before the first hip fracture or during the hospitalization for treatment of the first hip fracture. BMD measurements were performed using dual-energy X-ray absorptiometry of the lumbar spine and hip in 241 patients (66.0%) and of the forearm in 117 patients (32.1%). Radiographic absorptiometry of the metacarpal bone was measured in one patient (0.27%). The mean BMD value (YAM%) was 60.1 ± 15.2%, with a range of 27–127%.

Treatment during Hospitalization for First Hip Fracture

Among 2,328 patients, 2,192 (94.2%) were treated surgically. Among patients with femoral neck fractures treated surgically ($n = 951$), 630 (66.2%) were treated with arthroplasty, including hemiarthroplasty and total arthroplasty. Among patients with trochanteric fractures treated surgically ($n = 1{,}241$), 1,232 (99.3%) were treated with osteosynthesis (cannulated screw or pin 10, sliding hip screw 484, short femoral nail 726, other 12) and 8 (0.6%) were treated with arthroplasty (unknown 1). Postoperative rehabilitation was prescribed for 2,196 patients (94.3%), was not performed in 109 patients (4.7%), and status was unknown in 23 patients (1.0%). Antiosteoporotic pharmacotherapy was administered to 456 patients (19.6%) during their hospitalization. The mean duration of hospitalization was 48.6 ± 53.4 days for neck fractures and 48.0 ± 41.1 days for trochanteric fractures.

Treatment after Discharge from First Hospital Stay

Data regarding treatment after discharge from the first hospital stay were collected from the patient questionnaires and follow-up data, if available, and confirmed by hospital records. During this 1-year period, antiosteoporosis pharmacotherapy was given in 436 patients (18.7%) and 1,240 patients (53.3%) received no treatment. In 24.8% of patients the treatment status was unknown. Only 166 patients (36.4 %) among the 456 receiving antiosteoporosis pharmacotherapy during hospitalization continued treatment during the 1-year follow-up.

Fractures after the First Hip Fracture

During the 1-year follow-up period, 160 fractures occurred in 153 patients (Table 1). Among them, 129 were verified by radiography and confirmed by orthopedic doctors and 24 were self-reported in questionnaires. The average age in this subset of patients at the time of the first fracture was 84.0 years (range 68–98). Sixty-six (43.1%) fractures occurred within 6 months after the first hip fracture and 88 (57.5%) within 8 months (Fig. 2). Among these, 77 hip fractures occurred in 77 patients, 25 clinical vertebral fractures occurred in 25 patients, and 9 forearm fractures occurred in 9 patients within 1 year after the first hip fracture. Among the 77 hip fractures, 67 were verified by radiography and confirmed by orthopedic doctors and 10 were self-reported in questionnaires. Forty (51.9%) hip fractures occurred within 6 months after the first hip fracture and 48 (62.3%) within 8 months (Fig. 2). Subsequent hip fractures occurred on the opposite side in 58 patients (75.3%) and 63.3% were similar in fracture type to the first fracture.

The incidence of all fractures among patients with a first hip fracture was 70 (per 1,000 person-years), and that for hip fractures was 34. Age-specific incidences for subsequent fractures were highest in the ≥95 year age group; however, the differences between the age groups were small (Table 2). In comparison to the general population, women ≥65 years of age who sustained an initial hip fracture were four times as likely to sustain an additional hip fracture. The rate ratio among those with one hip fracture was as high as 18.6 times in the age group 65–74 years compared to that in the general population (Table 2).

Table 1 Characteristics of patients with subsequent fractures

	All fracture		*P*	Hip fracture		*P*
	(+) $n = 153$	(–) $n = 2,175$		(+) $n = 77$	(–) $n = 2,251$	
Age (years)	84.2 ± 7.0	83.6 ± 7.1	n.s.	84.4 ± 7.3	83.6 ± 7.1	n.s.
Body height (cm)	145.3 ± 7.2	146.7 ± 7.0	n.s.	144.8 ± 7.6	146.6 ± 7.0	n.s.
Body weight (kg)	42.8 ± 8.3	44.3 ± 8.6	0.038	42.2 ± 7.9	44.3 ± 8.6	0.046
Body mass index (kg/m^2)	20.1 ± 3.1	20.6 ± 3.4	n.s.	20.0 ± 3.0	20.6 ± 3.4	n.s.
Comorbid disease						
+	135	1,964		66	2,033	
–	17	159	n.s.	10	166	n.s.
Cognitive dysfunction						
+	70	902		35	937	
–	74	1,117	n.s.	39	1,152	n.s.
Ambulatory abilities before the first hip fracture						
No aid	24	476		12	488	
Dependent	123	1,560	0.049	61	1,622	n.s.
Fracture site (1st hip fracture)						
Right	80	1,120		41	1,159	
Left	73	1,055	n.s.	36	1,092	n.s.
Fracture type						
Neck	69	956		40	985	
Trochanteric	84	1,219	n.s.	37	1,266	n.s.
Surgical procedure						
Osteosynthesis	105	1,446		53	1,498	
Arthroplasty	43	595	n.s.	22	616	n.s.
Pharmacotherapy						
During hospitalization						
+	38	418		13	443	
–	107	1,717	n.s.	58	1,766	n.s.
Posthospitalization						
+	48	388		19	417	
–	103	1,715	<0.001	57	1,761	n.s.

n.s. Nonsignificant

Among patients with subsequent fractures, antiosteoporosis drugs were administered in 24 (15.7%, unknown 123 [80.4%]) before the first hip fracture, 38 (24.8%, unknown 8 [5.2%]) during the hospitalization, and 48 (31.4%, unknown 29 [19.0%]) during the 1-year follow-up period. Among 77 patients with a second hip fracture, antiosteoporosis drugs were administered in 11 (14.3%, unknown 64 [83.1%]) before the first hip fracture, 13 (16.9 %, unknown 6 [7.8%]) during the hospitalization, and 19 (24.7%, unknown 18 [23.4%]) during the 1-year follow-up period.

There were significant differences in body weight between patients with and without subsequent fractures (Table 1). Ambulatory abilities were divided into two categories of "no aid" and "dependent": "no aid" was "to

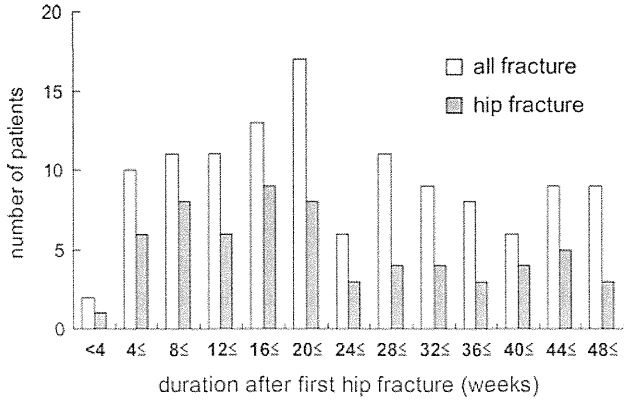

Fig. 2 Number of patients with subsequent fractures in selected time intervals after the first hip fracture

Table 2 Age-specific number and incidence of fractures after the first hip fracture

Age group (years)	*n*	Person (years)	Subsequent fractures						Incidence (per 1,000 person-years)			Rate ratio of hip fractures[a]
			Once	Twice	Total patients	Total fractures	Hip fractures	Clinical vertebral fractures	All fractures	Hip fractures	Clinical vertebral fractures	
65–74	276	275	15	2	17	19	10	3	69.0	36.3	10.9	18.6
75–84	919	906	59	2	61	63	26	15	69.6	28.7	16.6	3.3
85–94	1,025	1,003	62	3	65	68	36	7	67.8	35.9	7.0	1.5
≥95	108	106	10	0	10	10	5		94.8	47.4		1.9
Total	2,328	2,289	146	7	153	160	77	25	69.9	33.6	10.9	4.0

[a] Age- and gender-specific incidences, reported previously for the general population in Japan, were adopted to compare the risk of hip fracture among patients with a first hip fracture

walk without difficulty," "to walk outside with a walking aid," and "to walk only inside with an aid" and "dependent" was "unable to walk without support" and "completely unable to walk." The proportion of patients with subsequent fractures was significantly higher in the "dependent" than in the "no aid" ambulatory group. The proportion of patients with subsequent fractures was significantly higher among patients treated with antiosteoporosis drugs than those without antiosteoporosis drugs during the posthospitalization duration. There was no significant difference between the two groups regarding other factors. A multivariate analysis was performed using variants such as body weight and ambulatory abilities before the first hip fracture, and only body weight was a significant risk factor for subsequent fractures (OR = 0.96, 95% CI 0.928–0.993).

Discussion

This study demonstrated a high risk of subsequent fractures in patients with an initial hip fracture. It also revealed that, after fractures, antiosteoporosis pharmacotherapy was prescribed in only 19.6% of patients during their hospitalization and in only 18.7% during the 1-year follow-up period after discharge from the first hospital stay. The strength of this study is the substantially large number of subjects with a wide age distribution. As a result, the age-specific incidence of a second hip fracture in patients with an initial hip fracture could be calculated.

In retrospective studies, the rate of sustaining a second hip fracture is reported to be 7.5–11.8% [9–12]. In a population-based cohort study, Melton et al. [13] estimated that the recurrence rate for an additional hip fracture was 1% at 1 year after the first fracture in Minnesota in 1943–1977. Another US population-based study showed almost identical data, with a cumulative incidence of a second hip fracture of 2.3–2.5% after 1 year [2, 14], while the cumulative incidence after 5 years varied between 8.2 and 20%. A recent report from Finland showed a higher risk of 5.08% for persons aged 60 years and over within the first year following an initial fracture [15]. These differences may mirror the large variations in the risk of hip fractures and life expectancies in different populations.

Very little data are available on the risk of sustaining a second hip fracture after an initial hip fracture in the Asian population, although there is a large difference in the incidence of fragility fractures between Asians and Caucasians [1]. In a prospective study, Yamanashi et al. [16] reported that the annual incidence of a second hip fracture was 0.038 per person-year during the first year after an initial hip fracture and 0.028 per person-year during the second year. The 1-year incidence rate as determined in our current study (3.40%) is very consistent with their data. The age- and gender-specific incidence rates of sustaining a second hip fracture established in this study indicate that the rate ratio of a second hip fracture compared to the general population in Japan is higher in patients with an initial hip fracture under 75 years of age than that in those 75 years or older. In a Danish study, age- and gender-specific incidence rates (per 1,000 person-years) in women were 40, 51, 62, and 73 in the age groups 60–69, 70–79, 80–89, and ≥90 years, respectively [14]. Although the incidence rates of a second hip fracture in the Japanese and Caucasian populations are thought to be equal [16], there are differences in the population over 70 years of age, possibly due to a lower hip-fracture incidence in the Japanese population compared to that in northern Europe.

In this study, second hip fractures most frequently occurred within 32 weeks after the first hip fracture. The rate of sustaining a second hip fracture in a previous Japanese study tended to rise during the first 8 months after the first hip fracture and then to plateau [16]. A recent nationwide study in Denmark with a large number of hip-fracture patients demonstrated that the risk of a second hip fracture was increased almost 12 times at 1 month and more than doubled at 1 year; however, the risk remained significantly elevated until 15 years of follow-up [14].

These findings indicate that the early period of 6 months after the first fracture is a window of opportunity to execute a strategy for fracture prevention.

It has been reported that a previous fracture at any site is an important risk factor for future fractures [17]. Although the risk factors for hip fractures have been well defined in Caucasian subjects, only two epidemiological studies have examined risk factors for hip fractures in Japanese subjects [18, 19]. In the current study, body weight was a risk factor for a second hip fracture; however, age and other comorbidities were not associated with this risk. The study by Yamanashi et al. [16] demonstrated that senile dementia and Parkinson disease are important risk factors for second hip fractures and that prefracture ambulatory ability was similar between the unilateral and bilateral hip-fracture groups. A large cohort Danish study demonstrated that prior fractures, alcoholism, living alone, higher income, and advanced age are risk factors for second hip fractures [14]. Lonnroos et al. [15] found no significant risk of a second hip fracture with multiple comorbidities including dementia, whereas Berry et al. [2] reported a significantly increased risk in patients with a high level of functioning compared to those with moderate functioning. On the other hand, Chapurlat et al. [20] found that walking for exercise, which is an indirect marker for functional status, was a protective predictor. The explanation for these discrepancies might be caused by differences in the definition of comorbidity used in the various studies [14].

It is reported that the vast majority of patients who experience a hip fracture do not take antiosteoporotic therapy after the fracture [7, 8]. Among patients who begin antiresorptive osteoporosis treatment after fracture, the adherence to treatment decreases over time and remains suboptimal [8, 21]. Inadequate treatment after the first hip fracture became evident in the current study. In the current study we also found that patients undergoing osteoporotic therapy were more likely to sustain a new fracture than those not undergoing pharmacotherapy. This is probably due to the fact that more fractures occurred in those with severe osteoporosis; therefore, there was an increased likelihood of prescription of pharmacotherapy. It was not determined if prescribing antiosteoporosis drugs during the 1-year posthospitalization period was effective for fracture risk reduction. It is now known that oral bisphosphonate treatments for 3 years [22] or an annual infusion of zoledronic acid for 1.9 years [23] after repair of a hip fracture is associated with a reduction in the rate of new clinical fractures including hip fracture [22] as well as an improvement in survival [23].

There are some limitations to the current study. First, we estimated the risk of sustaining a second hip fracture based on hospital records from the treating hospital and questionnaires from the patients and calculated rate ratios based on reported age-specific incidence rates derived from a different research method. Because mortality is increased after a hip fracture, this approach underestimates the true incidence and might lead to biased estimates. Although the mortality in this study was much lower than that reported previously, 304 patients were lost to follow-up and their true life span was unknown. Since further follow-up was difficult, this is a limitation of this study; therefore, the true mortality of this study must be interpreted with caution. Second, we included only female patients $\geq$65 years. It is well known that mortality and prognoses are poorer in male versus female patients, and this might affect our results. However, this effect would be limited since the number of female patients with a hip fracture is 3.8 times that of male patients in Japan [24]. Third, we collected data based on admission records and therefore could not fully eliminate patients with additional hip fractures treated at other hospitals. Each rural hospital from where our data originate is the main hospital in its region and has orthopedic specialists. Thus, most patients sustaining fractures visit these hospitals, and the number of patients with an additional hip fracture who are missed would be limited. However, the possible bias introduced by this would underestimate the fracture incidence. A lack of sufficient validation is a potential weakness. Unfortunately, we were not able to further validate our data. Finally, we could not compare the BMD between patients with and without a subsequent hip fracture since BMD was measured in only 314 patients. Although some reports have suggested that BMD between patients with and without an additional hip fracture was similar [10], another study showed that patients with a lower BMD are more likely to sustain an additional hip fracture [20].

In conclusion, the current study discovered a high risk of a subsequent fracture after an initial hip fracture and that the treatment for patients after the first hip fracture is not entirely adequate. Since hip-fracture patients are the most plausible candidates in the prevention of subsequent fractures, prescribing appropriate osteoporosis treatments is essential along with more aggressive interventions for preventing falls.

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Vertebral fracture status and the World Health Organization risk factors for predicting osteoporotic fracture risk in Japan

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ABSTRACT

Introduction: Vertebral fractures are the most common osteoporotic fracture and the prevalence of vertebral fracture is commonly assessed in clinical practice in Japan. The objective of this study was to evaluate potential risk factors for osteoporotic fractures, including morphometric spine fracture status and the WHO risk factors for predicting 4-year fracture risk.

Methods: A population-based community cohort, the Adult Health Study, consisting of 2613 men and women with mean age of 65 enrolled in Hiroshima was followed prospectively for 4 years. The prevalence and incidence of spine fractures were identified from lateral and posterior–anterior spine radiographs using a semiquantitative method. Information on incident nonvertebral fragility fractures (hip, proximal humeral, and forearm) was collected at interviews by trained nurses and physicians during biennial health examinations.

Results: A model, including spine fracture status in addition to the WHO risk factors, appeared to provide greater prognostic information regarding future fracture risk (gradient of risk/standard deviation: GR/SD = 2.73) than a model with the WHO risk factors alone (GR/SD = 2.54). In univariate analyses, age, bone mineral density (BMD), prior clinical fracture, and spine fracture status had the highest gradient of risk. The presence of multiple prevalent spine or non-spine fractures significantly increased fracture risk, but, their contributions to the gradient of risk were similar to those when fracture status was categorized as a binary variable. A model considering those four risk factors yielded GR/SD = 2.67, indicating that it could capture most of the predictive information provided by the model with spine fracture status plus the WHO risk factors.

Conclusion: The use of age, BMD, prior clinical fracture and spine fracture predicted future fracture risk with greater simplicity and higher prognostic accuracy than consideration of the risk factors included in the WHO tool.

Introduction

Prediction of future fracture risk can provide clinicians and patients with important information for their decisions on life style and treatments. Recently, a fracture risk assessment tool (FRAX) was developed by the World Health Organization (WHO) [1]. The WHO fracture risk assessment tool considers clinical risk factors for future fracture, including age, prior clinical fracture, current smoking, alcohol use, parental history of hip fracture, glucocorticoid use, rheumatoid arthritis, and bone mineral density (BMD) in order to assign a 10-year absolute fracture risk [2].

Vertebral fractures are the most common fragility fracture in postmenopausal women with osteoporosis [3–5]. Many studies have demonstrated that prevalent vertebral fractures increased the risk of new vertebral and nonvertebral fractures in postmenopausal women [6–11]. Cauley et al. [12] found that women with a prevalent vertebral fracture at baseline were greater than 4 times more likely to experience an incident vertebral fracture over 15 years of follow-up compared with women without a prevalent vertebral fracture. Furthermore, Siris et al. [13] demonstrated that, at any particular value

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for BMD, spine fracture status increased future vertebral or non-vertebral fragility fracture risk by up to 7-fold.

Vertebral fracture prevalence is higher among Japanese women than Caucasian women [14]. Fujiwara et al. reported that the risk of subsequent vertebral fracture increased 3 times for women with a prevalent vertebral fracture, which is similar to other findings [15]. Since X-ray is recommended to diagnose osteoporosis in Japanese guidelines, prevalent vertebral fracture status is commonly assessed in clinical practice in Japan. However, prevalent vertebral fractures are not identified as a distinct risk factor in the FRAX tool in Japan [16]. Recently, Chen et al. demonstrated the importance of prevalent vertebral fractures for predicting the future fracture risk in the Canadian Multicentre Osteoporosis Study (CaMos) which was one of nine cohorts used for the development and validation of the FRAX tool [17]. The results from CaMos used prevalent vertebral fracture status along with age and BMD to better predict future fracture risk than the WHO risk factors, with greater simplicity for Caucasians in the CaMos adult cohort [17]. Donaldson et al. reported that a combination of radiographic vertebral fracture, femoral neck BMD, and age could predict future vertebral fracture risk as well as the WHO risk factors for Caucasians in the Fracture Intervention Trial (FIT) [18]. Ensrud et al. also reported that simple models based on age and BMD alone or age and fracture history alone predicted 10-year risk of fracture as well as more complex FRAX models in the Study of Osteoporosis Fracture (SOF) [19].

It was acknowledged by the authors of the WHO tool [20] that a prior clinical vertebral fracture was an especially strong risk factor. It was also acknowledged that a fracture detected as a radiographic observation alone (a morphometric vertebral fracture) should be counted as a previous fracture [20]. However, most of the epidemiology studies from which this tool was developed did not include spine imaging, and so spine fracture status information was not available for study or for inclusion in the tool.

The objective of this analysis was to evaluate and compare potential risk factors, including morphometric vertebral fracture status and the WHO fracture risk factors for predicting 4-year fracture risk in a Japanese population-based cohort which was also used for the development and validation of the FRAX tool. Furthermore, because spine fracture status is an important determinant of future fracture risk, we hypothesized that consideration of morphometric vertebral fracture status would lead to a simple risk prediction tool.

Subjects and methods

Study participants and population

The study subjects were a total of 2613 Adult Health Study (AHS) subjects aged 47 to 95 years old who underwent physical examinations in Hiroshima in the 1994–95 examination cycle. The AHS was established in 1958 to document the late health effects of radiation exposure among atomic-bomb survivors in Hiroshima and Nagasaki. The initial AHS cohort consisted of about 15,000 survivors and approximately 5000 controls, all of whom were selected from residents of Hiroshima and Nagasaki on the basis of a questionnaire included in Japan's 1950 national census and survey of atomic-bomb survivors. AHS subjects have been followed through biennial medical examinations since 1 July 1958. The participation rate has been around 70% throughout this period. The details of the cohort have been previously described [21]. All participants provided written informed consent for BMD measurement, spine X-ray examination, and all other health examinations.

Bone mineral density

BMD at the spine (L2–L4, antero–posterior direction) and proximal femur were measured at each biennial health examination using dual X-ray absorptiometry (DXA, QDR-2000; Hologic Inc, Waltham, MA, USA). An anthropomorphic spine phantom was scanned daily to calibrate the instrument. Precision of the DXA was monitored over the study period using the anthropomorphic phantom, and fluctuation was found to be less than 1%.

Clinical risk factor measurement

Measurements of height and weight were made at each examination. Participants completed an extensive interviewer-administered questionnaire to assess for osteoporosis and fracture-related risk factors at baseline. All clinical risk factors were derived from the baseline interview. Subject responses were coded to indicate if they were current cigarette smokers, if they had used systemic glucocorticoid therapy, if they had sustained a prior clinical fracture, and if they were currently drinking alcohol. Information on glucocorticoid use and dosage was confirmed by a pharmacist to check medicine that the participants bring their medicine to their appointment. About 80% of the participants bring medicine. Diagnoses of rheumatoid arthritis were made by a physician based on interview of symptoms, health examination, and laboratory data. Parental history of hip fracture was unavailable in this study. Because there is no association between radiation dose and BMD, or vertebral and hip fracture incidence [14,15], we did not take account of radiation dose in the analyses.

Fracture diagnosis

Vertebral fracture was determined by semiquantitative assessment of T4–L4 vertebrae [22]. Incident vertebral fractures were diagnosed based on clinical reading of lateral thoracic and lumbar spine X-ray images by a radiologist at the health examinations. However, 7.7% (201 of 2613) subjects were evaluated by thoracic spine radiographs only because they refused to undergo lumbar spine X-ray twice. New vertebral fracture was defined as a decrease of at least 20% in height of any vertebral body. Information about nonvertebral fragility fractures (hip, forearm/wrist, humerus, and other) was collected at interview by trained nurses and physicians during the biennial health examinations. The WHO risk fracture assessment tool predicts the risk for hip fractures and of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture). In our study, the risk of any fragility fracture refers to the risk of a participant experiencing either an incident vertebral fracture detected by spine radiography and/or a nonvertebral fragility fracture.

Statistical analysis

A series of logistic regression analyses were performed to determine the importance of vertebral fracture status and the WHO risk factors for predicting the 4-year risk of any future vertebral or nonvertebral fragility fracture. Although the WHO fracture risk assessment tool provides a 10-year fracture risk, it is stated that, in individuals with low mortality, the one-year probability is up to 10% of the 10-year probability [1]. To test the significance of vertebral fracture status on the prediction of future fracture risk, a logistic regression model including the WHO risk factors only was compared with models including the WHO risk factors plus vertebral fracture status (yes/no). To pool the data from the genders, the models included the interaction effects of risk factors with gender at the 10% level of significance. As there were no statistically significant interactions, the relationship between all the risk factors and incident fracture risk was statistically consistent between the two genders. The performance of each model was assessed as the gradient of risk (GR), i.e., the increase in fracture risk per standard deviation (GR/SD); this assessment was used in the development of the WHO fracture risk tool [23].

After finding an improvement for the fracture risk prediction by adding the vertebral fracture status to the WHO risk factors, further analyses were conducted to determine the predictive ability of sequential addition of the most important WHO risk factors and vertebral fracture status. To do this, a series of univariate analyses were conducted to investigate the association between each of individual risk factors (age, BMD, prior fragility fractures, number of non-spine fracture, spine fracture status, number of spine fractures, current smoking, alcohol use, glucocorticoid use, and rheumatoid arthritis) and future fracture risk. The gradient of fracture risk was examined in different models by sequential addition of the most important risk factors determined from the univariate analyses. Four-year absolute fracture risk was estimated using the logistic regression model including the risk factors age, BMD T-score, spine fracture (yes/no), and prior fragility fractures (yes/no). All analyses are reported for pooled data using SAS version 8.2 (SAS Institute, Cary, NC, USA).

Results

Subject characteristics

In the Hiroshima cohort, 2613 subjects had spine radiographs both at baseline and 4 years later. The average observation period was 3.8 ± 0.8 (mean ± 1 standard deviation) years. The mean age of the sample population was 63.2 years for men (n = 794) and 65.9 years for women (n = 1819). Compared to men, women had significantly lower BMD values, a higher rate of prevalent morphometric vertebral fracture, and a higher proportion with prior clinical fracture (Table 1). Two hundred fifteen subjects experienced at least one incident vertebral fracture while seventy-five subjects had multiple incident vertebral fractures. Seventy-nine subjects experienced at least one nonvertebral fragility fracture (32 hip, 35 forearm/wrist, and 16 humerus). Two hundred eighty-one subjects experienced either an incident vertebral fracture and/or a nonvertebral fragility fracture during the follow-up period.

Comparison of models considering WHO risk factors alone versus WHO risk factors plus spine fracture status

Table 2 shows the performance characteristics of the model expressed as GR/SD change in the risk indicator. The GR for the WHO risk factors was 2.54 when lumbar spine BMD was used in the prediction model and 2.57 when femoral neck BMD was used. Inclusion of the vertebral fracture (yes/no) in the lumbar spine BMD model and femoral neck BMD model increased the GR to 2.73 and 2.77, respectively.

Table 1
Baseline demographics of the study population[a].

	Women (N = 1819)	Men (N = 794)	Total (N = 2613)
Age (years)[b]	65.9 ± 0.23	63.2 ± 0.35	65.1 ± 0.19
Prevalent morphometric vertebral fracture(s) (% yes)[b]	10.3	3.3	8.2
Prior clinical fracture (% yes)[b]	17.5	12.1	15.8
Lumbar spine BMD (g/cm^2)[b]	0.79 ± 0.004 (N = 1815)	0.96 ± 0.006 (N = 791)	0.84 ± 0.003 (N = 2606)
Femoral neck BMD (g/cm^2)[b]	0.62 ± 0.003 (N = 1804)	0.73 ± 0.004 (N = 792)	0.65 ± 0.002 (N = 2596)
Prior glucocorticoid use (% yes)	2.9	2.4	2.8
Current smoking (% yes)[b]	6.8	32.6	14.6
Alcohol use (% yes)[b]	6.9	39.2	16.7
Rheumatoid arthritis (% yes)	1.0	0.6	0.9

[a] Values are mean ± standard error (SE) unless otherwise stated.
[b] $P<0.01$ between women and men.

Table 2
Comparison of predictive ability of WHO clinical risk factors for new osteoporotic fracture.

	Model	GR/SD (95% CI)
Lumbar spine BMD	WHO clinical risk factors alone	2.54 (2.20–2.97)
	WHO clinical risk factors + spine fractures (yes/no)	2.73 (2.36–3.21)
Femoral neck BMD	WHO clinical risk factors alone	2.57 (2.22–3.01)
	WHO clinical risk factors + spine fractures (yes/no)	2.77 (2.39–3.26)

Univariate analyses for 4-year risk of new fractures

In univariate analyses, BMD provided the highest GR, followed by age, spine fracture status, and prior clinical fracture. Other risk factors provided relatively lower GRs. Further analyses showed that the gradient of risk for number of vertebral fractures and number of non-vertebral fractures was 1.53 (1.37, 1.66) and 1.29 (1.18, 1.42), respectively. However, their contributions to the gradient of risk were similar to those when fracture status was categorized as a binary variable (yes/no). The presence of multiple prevalent vertebral fractures significantly increased fracture risk 15-fold while the presence of single prevalent vertebral fracture was associated with a 4-fold increase in fracture risk. The presence of multiple non-vertebral fractures significantly increased fracture risk 7-fold while the presence of single non-prevalent vertebral fracture was associated with a 2-fold increase in fracture risk. The risk of incident fragility fractures increased with an increasing number of vertebral fractures as well as an increasing number of non-vertebral fractures. As the results were similar in men and women, multivariable analyses were performed on the combined set of men and women (data not shown).

Multivariable analyses for 4-year risk of new fractures

The performance characteristics of models with sequential addition of the most important risk factors are shown in Tables 3–4, expressed as GR/SD change in the risk indicator. For fracture prediction, a model that included age, lumbar spine BMD, presence or absence of spine fracture, and prior clinical fracture had a GR of 2.67. After those four risk factors were included in the model, the increment in the GR/SD by adding the four additional risk factors described in the WHO risk assessment tool was 0.06. Similarly, a model that included age, femoral neck BMD, presence or absence of spine fracture, and prior clinical fracture had a GR of 2.71. After those four risk factors were included in the model, the increment in the GR/SD by adding the four additional risk factors described in the WHO risk assessment tool was 0.06.

Absolute risk of fracture based on age, BMD T-score, spine fracture status, and prior clinical fracture

The 4-year absolute risk of incident fragility fracture in the Hiroshima cohort based on age, femoral neck T-score, spine fracture (yes/no), and prior clinical fracture (yes/no) is shown for women (Table 5) and men (Table 6). Results for lumbar spine BMD were similar to results for femoral neck BMD (data not shown). The fracture risk increased in both men and women with increasing age, more negative T-score, and presence of spine fracture.

Discussion

In this cohort of a Japanese population, we found that consideration of spine fracture status along with the WHO risk factors provided additional information compared with considering the WHO risk factors alone. In univariate analysis, we found that spine fracture

Table 3
GR/SD change in risk score for different models using lumbar spine BMD.

Model	Age	LS BMD	Spine fracture (yes/no)	Prior Clin Fx	Current smoking	Prior GC use	RA	Alcohol use	GR/SD (95% CI)
1	•								1.93 (1.68–2.24)
2	•	•							2.33 (2.02–2.72)
3	•	•	•						2.49 (2.15–2.91)
4	•	•	•	•					2.67 (2.31–3.13)
5	•	•	•	•	•				2.67 (2.31–3.14)
6	•	•	•	•	•	•			2.67 (2.31–3.14)
7	•	•	•	•	•	•	•		2.70 (2.33–3.17)
8	•	•	•	•	•	•	•	•	2.73 (2.36–3.21)

"•" Indicates that the factor is included in a model.
GR = gradient of risk; SD = standard deviation; LS BMD = Lu bone mineral density; Clin = clinical; Fx = fracture; GC = glucocorticoid; RA = rheumatoid arthritis; CI = confidence interval.

Table 4
GR/SD change in risk score for different models using femoral neck BMD.

Model	Age	FN BMD	Spine fracture (yes/no)	Prior Clin Fx	Current smoking	Prior GC use	RA	Alcohol use	GR/SD (95% CI)
1	•								1.93 (1.68–2.24)
2	•	•							2.34 (2.03–2.73)
3	•	•	•						2.50 (2.16–2.93)
4	•	•	•	•					2.71 (2.33–3.17)
5	•	•	•	•	•				2.71 (2.34–3.18)
6	•	•	•	•	•	•			2.71 (2.33–3.17)
7	•	•	•	•	•	•	•		2.71 (2.36–3.22)
8	•	•	•	•	•	•	•	•	2.77 (2.39–3.26)

"•" Indicates that the factor is included in a model.
GR = gradient of risk; SD = standard deviation; FN BMD = femoral neck bone mineral density; Clin = clinical; Fx = fracture; GC = glucocorticoid; RA = rheumatoid arthritis; CI = confidence interval.

status was one of the most significant predictors of 4-year fracture risk. In addition, we assessed models for predicting future fracture risk by sequentially adding the most important risk factors, and found that a model including age, BMD, presence or absence of spine fracture, and prior clinical fracture provided almost as much information as the WHO risk factors plus the spine fracture status could provide. Moreover, we found that this model provided more prognostic information than consideration of the WHO risk factors alone.

Table 5
Four-year risk of incident fragility fracture in the Hiroshima population of women based on age, femoral neck T-score, spine fracture (no/yes) and prior clinical fracture (no/yes).

Femoral neck T-score	Spine fracture	Prior clinical fracture	Age (years)							
			50	55	60	65	70	75	80	85
−1	No	No	3.6	4.5	5.5	6.7	8.2	10.0	12.1	14.6
		Yes	7.6	9.3	11.3	13.6	16.4	19.6	23.2	27.2
	Yes	No	9.9	12.0	14.4	17.3	20.6	24.4	28.5	33.1
		Yes	19.9	22.9	26.9	31.4	36.2	41.3	46.6	52.0
−1.5	No	No	4.3	5.2	6.4	7.8	9.6	11.6	14.0	16.8
		Yes	8.9	10.8	13.0	15.7	18.8	22.3	26.2	30.6
	Yes	No	11.4	13.8	16.6	19.8	23.4	27.5	32.0	36.9
		Yes	22.0	25.9	30.3	35.0	40.1	45.4	50.8	56.1
−2	No	No	5.0	6.1	7.5	9.1	11.1	13.4	16.1	19.2
		Yes	10.3	12.5	15.0	18.0	21.4	25.3	29.6	34.2
	Yes	No	13.2	15.9	19.0	22.5	26.5	30.9	35.7	40.8
		Yes	25.0	29.2	33.9	38.9	44.1	49.5	54.9	60.1
−2.5	No	No	5.8	7.1	8.7	10.6	12.8	15.4	18.4	21.9
		Yes	11.9	14.4	17.3	20.6	24.3	28.5	33.1	38.0
	Yes	No	15.2	18.2	21.6	25.5	29.8	34.5	39.6	44.8
		Yes	28.2	32.8	37.7	42.9	48.2	53.6	58.9	64.0
−3	No	No	6.8	8.3	10.1	12.2	14.8	17.7	21.1	24.9
		Yes	13.8	16.5	19.7	23.4	27.5	32.0	36.9	42.0
	Yes	No	17.5	20.8	24.6	28.8	33.4	38.4	43.6	48.9
		Yes	31.6	36.5	41.6	46.9	52.3	57.7	62.8	67.7
−3.5	No	No	7.9	9.7	11.7	14.1	17.0	20.2	23.9	28.1
		Yes	15.9	19.0	22.5	26.5	30.9	35.7	40.8	46.1
	Yes	No	20.0	23.6	27.8	32.3	37.2	42.3	47.7	53.1
		Yes	35.3	40.4	45.7	51.1	56.4	61.6	66.6	71.2
−4	No	No	9.2	11.2	13.5	16.3	19.4	23.0	27.1	31.5
		Yes	18.2	21.6	25.5	29.8	34.5	39.5	44.8	50.2
	Yes	No	22.7	26.7	31.2	36.0	41.1	46.4	51.8	57.1
		Yes	39.2	44.4	49.8	55.2	60.4	65.4	70.2	74.5

Table 6
Four-year risk of incident fragility fracture in the Hiroshima population of men based on age, femoral neck t-score, spine fracture (no/yes) and prior clinical fracture (no/yes).

Femoral neck T-score	Spine fracture	Prior clinical fracture	Age (years)							
			50	55	60	65	70	75	80	85
−1	No	No	4.2	4.3	4.5	4.6	4.8	5.0	5.2	5.3
		Yes	5.3	5.5	5.7	5.9	6.1	6.4	6.6	6.8
	Yes	No	17.5	18.0	18.6	19.2	19.8	20.4	21.0	21.6
		Yes	21.6	22.2	22.9	23.6	24.2	24.9	25.7	26.4
−1.5	No	No	4.9	5.1	5.3	5.5	5.7	5.9	6.1	6.3
		Yes	6.3	6.6	6.8	7.0	7.3	7.5	7.8	8.1
	Yes	No	20.3	20.9	21.5	22.2	22.8	23.5	24.2	24.9
		Yes	24.8	25.5	26.3	27.0	27.8	28.5	29.3	30.1
−2	No	No	5.9	6.1	6.3	6.5	6.8	7.0	7.3	7.5
		Yes	7.5	7.8	8.0	8.3	8.6	8.9	9.2	9.6
	Yes	No	23.4	24.1	24.8	25.5	26.2	27.0	27.7	28.5
		Yes	28.4	29.2	30.0	30.8	31.6	32.4	33.2	34.1
−2.5	No	No	7.0	7.2	7.5	7.8	8.0	8.3	8.6	8.9
		Yes	8.9	9.2	9.5	9.8	10.2	10.5	10.9	11.3
	Yes	No	26.9	27.6	28.4	29.1	29.9	30.7	31.5	32.4
		Yes	32.3	33.1	34.0	34.8	35.7	36.5	37.4	38.3
−3	No	No	8.3	8.6	8.9	9.2	9.5	9.8	10.2	10.5
		Yes	10.5	10.8	11.2	11.6	12.0	12.4	12.8	13.2
	Yes	No	30.6	31.4	32.2	33.1	33.9	34.8	35.6	36.5
		Yes	36.4	37.3	38.2	39.1	40.0	40.9	41.8	42.7
−3.5	No	No	9.8	10.1	10.5	10.8	11.2	11.6	12.0	12.4
		Yes	12.3	12.7	13.2	13.6	14.1	14.5	15.0	15.5
	Yes	No	34.6	35.5	36.4	37.2	38.1	39.0	39.9	40.8
		Yes	40.7	41.7	42.6	43.5	44.4	45.4	46.3	47.3
−4	No	No	11.5	11.9	12.3	12.7	13.1	13.6	14.0	14.5
		Yes	14.4	14.9	15.4	15.9	16.4	16.9	17.5	18.0
	Yes	No	38.9	39.8	40.7	41.6	42.5	43.5	44.4	45.3
		Yes	45.2	46.2	47.1	48.1	49.0	50.0	50.9	51.8

Our results are consistent with the findings in Caucasians from the CaMos cohort that showed a model considering age, BMD, and spine fracture status captured almost all of the predictive information provided by a model considering spine fracture status plus the WHO risk factors and provided greater predictive information than a model considering the WHO risk factors alone [17]. Similar findings have been reported in FIT where a combination of baseline radiographic vertebral fracture, femoral neck BMD, and age is the strongest predictor of future vertebral fracture [18]. Furthermore, baseline vertebral fracture status plus age and femoral neck BMD predicted incident radiographic vertebral fracture significantly better than FRAX with femoral neck BMD. The results of FIT indicate that once femoral neck BMD and age are known, the eight additional risk factors in FRAX do not significantly improve the prediction of vertebral fracture. Our findings are also consistent with reported findings in SOF where a simple model based on age and fracture history alone predicted 10-year risk of fracture as well as more complex FRAX models [19].

FRAX represents a major advance in the field of osteoporosis for several reasons. The tool is based on data collected from cohorts in the United States, Europe, Australia, and Asia and is applicable to both the developed and the developing world. Modeling techniques incorporated into the FRAX tool take into account country-specific fracture and death rates. Its aim to move forward risk assessment from a strategy based on BMD alone to an approach based on the absolute risk of fracture is appealing because absolute risk classification systems overcome several of the drawbacks posed by relative risk classification systems and may be more intuitive to both clinicians and patients [24]. However, despite those merits, findings from this study in a Japanese population suggest that one of the most important risk factors for predicting future risk – prevalent vertebral fracture detected by spine radiography – was not considered in the development and validation for the FRAX tool. In the absence of knowledge about prevalent spine fracture status, assessments based on the WHO risk factors may under- or over-estimate the true risk of an individual experiencing an incident fracture. This is similar to the experience of Siris et al. [13] who observed that in the absence of knowledge about spine fracture status, assessments based on BMD alone may under- or overestimate the true fracture risk.

The present analysis demonstrates that age, BMD, presence or absence of spine fracture, and prior clinical fracture were the most important risk factors for predicting future fracture in this population-based cohort. Consideration of those four risk factors alone provided greater predictive capacity than the risk factors included in the WHO tool. Furthermore, consideration of age, BMD, presence or absence of spine fracture, and prior clinical fracture was sufficient, and little more useful risk prediction was obtained by consideration of the other risk factors in the WHO model.

An advantage of including only four variables in the assessment of future fracture risk is that predicted absolute fracture risk can be reported in simple tables such as Table 5 for women and Table 6 for men. Those tables highlight the prognostic significance of spine fracture status. For example, in a 55-year old woman having a lumbar spine T-score of −1 and without a prior clinical fracture, fracture risk was 4.3% for subjects with no spine fractures and was 11.4% for subjects with spine fractures. For those patients with age or BMD between the intervals provided in the tables, the risk is intermediate. Practitioners assessing patients similar to those in our study for osteoporosis can therefore use age, BMD, presence or absence of spine fracture, and prior clinical fracture to predict 4-year fracture risk using the tables.

Several differences between these analyses and those performed to develop the WHO fracture risk assessment tool bear mentioning. Information on parental history of hip fracture was not available. However, according to a large meta-analysis [25], a parental history of fracture was slightly associated with risk of hip and fragility fracture. Furthermore, Plujim et al. demonstrated that family history of hip fracture was not associated with fragility fracture [26]. Our analyses included only one cohort of patients, whereas nine cohorts were used to develop the WHO fracture risk assessment tool [1]. Our results might not be as generalizable. In addition, the subjects in the Hiroshima cohort consist of atomic-bomb survivors and their controls, who may differ from the general population in Japan. However, our previous studies demonstrated no effects of atomic-bomb radiation on bone mineral density, or spine and hip fracture incidence [14,15], so our findings may be relevant to the Japanese population.

In this study, prevalent vertebral fracture status was assessed semi-quantitatively via lateral spine radiography, a widely used gold standard for identifying vertebral fractures. The prevalence of vertebral fracture is commonly assessed in clinical practice in Japan. Because there are several practical considerations including cost, radiation exposure and patient inconvenience that might preclude obtaining spine radiographs in all patients with low bone mass or osteoporosis, vertebral fracture assessment is not part of osteoporosis treatment guidelines outside of Japan. While our analysis did not use data generated by this approach, lateral spine imaging performed by DXA – vertebral fracture analysis or VFA – at the time of BMD testing in women found to have low bone mass or osteoporosis may provide a practical solution to routine imaging of the spine in clinical practice. VFA involves substantially less radiation exposure and cost, and is less subject to issues of parallax distortion, although it historically has generated images of lower resolution compared with lateral spine radiography. Ongoing refinements in this technology include improvements in resolution. VFA and routine lateral spine radiographs have shown good agreement for identifying vertebral fractures by semi-quantitative assessment.

Our study therefore demonstrates that the use of prevalent vertebral fracture status along with age, BMD, and prior clinical fracture has the capacity to predict future fracture risk at least as well as or better than the risk factors included in the WHO tool [1] but with greater simplicity. Our findings provide the degree to which spine fracture burden offers future fracture risk prediction, show the importance of having such information as part of the routine evaluation for osteoporosis, and provide a practical approach for utilizing this information in Japan.

Disclosures

The authors state that they have no conflicts of interest.

Conflict of interest

Fujiwara S: None.
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