osteomalacia, Paget's disease, Scheuermann's disease, hyperparathyroidism, renal bone disease and malignancy with bone metastasis, were excluded. Information on symptoms associated with vertebral fractures was also collected, including difficulty in bending forward, kyphosis (occiput-to-wall >0 cm and/or gap between the costal margin and iliac crest <3 fingerbreadths), low back pain and height loss more than 2 cm since the age of 25 years. These data were collected from interviews conducted by a trained research assistant.

All subjects were followed annually via telephone interviews using a structured questionnaire for assessment of the clinical outcome of incident fractures, falls, hospitalization, use of anti-osteoporotic medications, living status and functional status. Subjects who commenced anti-osteoporosis medication prior to the occurrence of a primary fracture were excluded. Medical history and incident fractures were verified with the computerized patient information system of the Hospital Authority of the Hong Kong Government. For this study, only non-traumatic incident hip fractures and clinical vertebral fractures were included in the analysis. Hip fractures were defined as having a diagnosis coded as International Classification of Disease, Tenth Revision (ICD-10) S72.0-S72.2 (fracture of the femoral neck, intertrochanteric, trochanteric, or subtrochanteric), and clinical vertebral fractures were identified in subjects who received medical attention from a physician with a diagnosis coded as ICD-10S22.0-S22.1 (fracture of the thoracic vertebra/multiple thoracic vertebrae), S32.0 or S32.7 (fracture of the lumbar vertebra/multiple lumbar vertebrae). Pathological fractures or fractures caused by traffic accidents or falls from standing heights were excluded. The study was approved by the Institutional Review Board of the University of Hong Kong and the Hong Kong West Clusters Hospital of the Hospital Authority.

Japan

The hip and clinical vertebral fracture incidence rates for the Japanese were obtained from previously published data used to develop the Japanese version of FRAX® [24]. The hip fracture incidence rate was based on data from a census study in Tottori Prefecture, Japan, in 1994 [25]. The incidence of vertebral fracture was based on data obtained from the Adult Health Study in Hiroshima, Japan [26]. Participants were followed through biennial medical examination including radiology assessments since the establishment of the study in 1958. A total of 2,613 subjects (763 men and 1,593 women) who attended at least two follow-up examinations in 1994 to 2000 were included in the analysis. An incident morphometric vertebral fracture was diagnosed by lateral and posterior–anterior chest and spinal X-rays using the semi-quantitative assessment [12], in which a decrease of at least 20% in height of any vertebral body from initial reading to the end of the study was defined as a morphometric vertebral fracture. Since the incidence of clinical vertebral fracture was not known in Japan, the ratio of clinical fracture to morphometric fracture incidence was assumed to be the same in Japan as it was for Sweden when the Japanese version of FRAX® was developed, i.e. 30% of morphometric vertebral fractures were assumed as clinical fractures [24, 27].

Sweden

The incidence rates of hip and clinical vertebral fractures for Swedish Caucasians were also obtained from a previously published study by Kanis et al., in which all incident fractures, including hip fractures (1991) and clinical vertebral fractures (1993 and 1994) were identified from files at the Department of Diagnostic Radiology in Malmo, Sweden, for the relevant year. Only vertebral fractures that came to clinical attention were captured, and subjects who previously sustained a fracture of the same type were excluded from analysis. The annual incidences of hip and clinical vertebral fractures were calculated for men and women by age [28].

Statistical analyses

Baseline characteristics of the Chinese subjects are expressed in means±SD for continuous variables and in percentage for categorical variables. Time to incident hip or vertebral fractures was calculated according to the date of X-ray reports or physician's consultations when the diagnosis was made. The average follow-up period for all subjects was 4.0±2.8 (range, 1 to 14) years, with a total follow-up of 14,733 patient-years. Subjects who had received anti-osteoporosis medication after sustaining a fracture during the follow-up period or those who deceased at the time of analysis were analysed up to their time of treatment initiation or last contact time point. Incidence rates were reported as rate per 100,000 person-years. The incidence rates of vertebral and hip fractures were compared to the published data from Japan and Sweden. Vertebral-to-hip fracture ratios were used to demonstrate the proportion of vertebral fractures in relation to hip fractures in different populations.

Results

A total of 4,116 Southern Chinese subjects (2,302 women and 1,810 men) aged 50 or above were included in the analysis. The mean age at baseline was 62±8.2 years for

women and 68±10.3 years for men. Of the women, 37.2% and 63.4% of men were above the age of 65 years. Baseline demographic information and characteristics are shown in Table 1. Of the men, 55.5% and 72.1% of women reported having difficulty bending forward, kyphosis, low back pain and/or height loss >2 cm since the age of 25. However, only 2.7% of men and 5.5% of women reported a history of past clinical vertebral fracture.

Two hundred and sixty-seven subjects had died at the time of analysis (77 women and 190 men), and 353 patients (333 women and 19 men) received anti-osteoporosis medication after sustaining a fracture during the follow-up period. The data for these subjects were analysed up to their last contact time point or time of treatment initiation, respectively. During the follow-up period, 57 clinical vertebral fractures and 34 incident hip fractures were reported (11 vertebral fractures and 10 new hip fractures in men; 46 vertebral fractures and 24 new hip fractures in women). The incidence for vertebral fractures was 194 per 100,000 person-years in men and 508 per 100,000 in women (overall female/male ratio=2.6:1), and the incidence for hip fractures was 176 per 100,000 person-years in men and 265 per 100,000 person-years in women (female/male ratio=1.5:1). Table 2 shows the incidence rates of clinical vertebral and hip fractures according to sex and age groups. Both clinical vertebral and hip fracture incidences increased exponentially with increasing age in both sexes. Men aged 50–55 years had a fracture incidence of 50 per 100,000 person-years for the vertebra and 10 per 100,000 for the hip versus men aged 85 years and above who have a vertebral fracture incidence of 954 per 100,000 person-years and a hip fracture incidence of 477 per 100,000 person-years. Similarly, incidences of vertebral and hip fracture increase from 219 and 16 per 100,000 person-years in women 50 years of age to 2,689 and 1,377 per 100,000 person-years, respectively, at age 85. Overall, men older than 65 years have a vertebral fracture incidence of 299 per 100,000 person-years and hip fracture incidence of 332 per 100,000 person-years, and the overall incidence of vertebral and hip fractures for women older than 65 years were 594 per 100,000 person-years and 379 per 100,000 person-years, respectively.

The fracture incidence of Chinese subjects was compared to those of the Swedish and Japanese populations. The incidence rates of hip fractures in Caucasian men and women rose exponentially with age, whereas the rise was near linear for vertebral fractures. In contrast, for Asian women in Hong Kong and Japan, the incidence rate for vertebral fractures rose exponentially with age, whereas the rise was near linear for hip fractures. In Asian men, both the incidence rates of vertebral and hip fractures rose near linearly with age. The hip fracture incidences in Hong Kong men and women were similar to those of Japan but much lower than those of the Caucasian population in Sweden. For example, the hip fracture rates for Hong Kong men and women aged 65 to 69 years old were only 49% and 33%, respectively, of those of the Caucasian men and women in the same age group. However, the incidence of vertebral fractures in Asian men was similar to that of Caucasian men; and Asian women have a much higher

Table 1 Clinical characteristic of the study population (Mean±SD)

	Men (n=1,810)	Women (n=2,302)
Years of follow-up (mean±SD (range))	3.5±2.9 (1–14)	4.7±2.6 (1–14)
Age (year)	68±10.3 (50–99)	62±8.2 (50–91)
Height (cm)	164.6±6.5	152.7±6.0
Weight (kg)	62.9±10.3	55.3±9.1
Body mass index (kg/m^2)	28.1±8.4	23.7±3.7
Number of postmenopausal women	–	2,229 (96%)
Age at menopause (year)	–	49.5±4.0
Current or history of hormone replacement therapy	–	217 (9.4%)
Difficulty bending forward	185 (10.2%)	365 (15.8%)
Kyphosis	78 (4.3%)	126 (5.5%)
Low back pain	510 (28.2%)	1,336 (58.0%)
Height loss >2 cm since 25 years old	442 (24.4%)	854 (37.1%)
Have at least one of the above symptoms	1,004 (55.5%)	1,660 (72.1%)
History of clinical vertebral fracture	48 (2.7%)	126 (5.5%)
History of hip fracture	24 (1.7%)	31 (1.3%)
Incident clinical vertebral fracture at follow-up	11 (0.6%)	46 (2.0%)
Incident hip fracture at follow-up	10 (0.6%)	24 (1.0%)

Table 2 Incidence (per 100,000 person-years) of hip and clinical vertebral fracture according to sex and age groups

Fracture site and age group	Men	Women	F/M
Hip			
50–54	10	16	1.6
55–59	21	31	1.5
60–64	46	57	1.2
65–69	99	103	1.0
70–74	215	273	1.3
75–79	348	527	1.5
80–84	602	1,059	1.8
85+	477	1,377	2.9
Vertebral			
50–54	50	219	4.4
55–59	111	313	2.8
60–64	165	516	3.1
65–69	95	564	5.9
70–74	226	874	3.9
75–79	450	1,205	2.7
80–84	594	2,119	3.6
85+	954	2,689	2.8

vertebral fracture incidence than Caucasian women (Fig. 1a and b). Among older women aged 80 or above, the incidence of vertebral fracture in Asians almost doubled to that of Swedish Caucasian women.

The spine-to-hip fracture ratios also differed between different Asians and Caucasians. Although vertebral fractures occur with a higher incidence earlier in life than hip fractures in both Asians and Caucasians, Asians have a much higher spine-to-hip fracture ratio than Caucasians, meaning vertebral fractures have a higher proportion to hip fractures in Asians than in Caucasians, especially among subjects younger than 65 years (Table 3).

Discussion

Vertebral fractures are the most common type of osteoporotic fractures, and they are well known as an independent predictor of future osteoporotic fractures, including both vertebral and non-vertebral fractures [22]. However, reports about the incidence of vertebral fracture are scant because of the discrepancies in the definition of vertebral fracture and the difficulties in recognizing them clinically. A

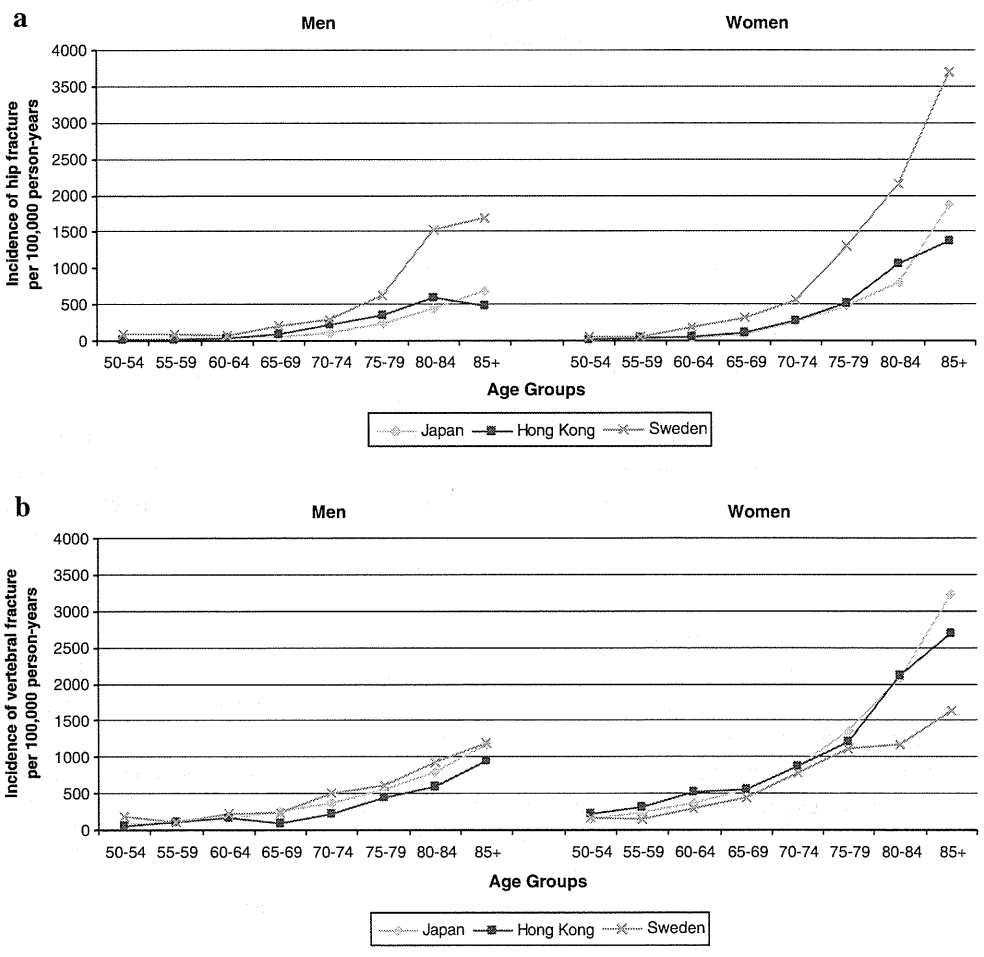

Fig. 1 Age-specific incidence rates (per 100,000 person-years) in Hong Kong compared to Japanese and Swedish Caucasians for hip fracture (**a**) and clinical vertebral fracture (**b**)

Table 3 Age- and sex-specific clinical vertebral-to-hip fracture ratio in Hong Kong compared to Japanese and Swedish Caucasians

	Men			Women		
Age group	Japan [24]	Hong Kong	Sweden [28]	Japan [24]	Hong Kong	Sweden [28]
50–54	3.9	5.0	2.2	N/A[a]	13.7	2.6
55–59	7.1	5.3	1.4	4.7	10.1	2.9
60–64	2.8	3.6	3.2	8.9	9.1	1.6
65–69	4.1	1.0	1.2	6.3	5.5	1.4
70–74	3.5	1.1	1.7	3.4	3.2	1.4
75–79	2.3	1.3	1.0	2.8	2.3	0.8
80–84	1.8	1.0	0.6	2.6	2.0	0.5
85+	1.7	2.0	0.7	1.7	1.1	0.4

[a] Clinical vertebral-to-hip fracture ratio for Japanese women aged 50–54 was not available since the hip fracture incidence for this group was zero

previous study has shown that the postmenopausal women in Hong Kong, Beijing and Taiwan have a similar prevalence of morphometric vertebral fracture as Caucasian women in the USA and Europe (about 25% in all regions), in contrast to the marked worldwide variations in the prevalence of hip fractures [21]. The present study further confirmed that, although the risk of hip fractures in Asians was low, Asian men do have a vertebral fracture risk similar to Caucasian men, and Asian women have an even higher clinical vertebral fracture risk than Caucasian women.

The observed ethnic differences in fracture incidences may be due to the fact that hip fracture risk was affected by fall risk, whereas the risk of vertebral fracture mostly depends on bone strength [13]. Despite the low hip fracture rate in our population, Hong Kong women had a higher prevalence of osteoporosis (bone mineral density T-score≤ -2.5 at any one site in reference to ethnic-specific peak young mean according to the ISCD recommendation) than US Caucasian women (35.8% vs. 20%, respectively) [29, 30] and a similar prevalence of about 6% in Hong Kong and US Caucasian men [31]. In view of the ethnic differences, it is important to obtain accurate information on population fracture risk to characterize the absolute fracture risk of individual subjects. At present, information on the risk of clinical vertebral fracture in Asians is lacking, and the WHO fracture risk assessment algorithms (FRAX®) estimated population-specific absolute major osteoporotic fracture risks based on the assumption that the ratio of hip-to-vertebral fracture is the same as that observed in Swedish populations to provide. However, our study demonstrated the variations of the spine-to-hip fracture ratios between ethnic groups; thus, a fracture prediction model that assumes a universal spine-to-hip fracture ratio may be biased.

Our previous prospective study on Southern Chinese men over 50 years old has shown that the FRAX® algorithm seemed to overestimate the 10-year major osteoporotic fracture risk in subjects with low fracture risk, but underestimated the risk for high-risk groups [29]. Results from the current study raise a concern that a model that presumes a ratio of vertebral fractures to hip fractures in a Swedish population might underestimate the risk of vertebral fractures in Asians, resulting in a general underestimation of the absolute risk of major osteoporotic fracture.

Strengths of this study include the use of a community-based population to investigate the incidence rate of clinical vertebral fractures. All clinical vertebral fractures and hip fractures were confirmed by the medical record. A major limitation of the present study is that the comparisons to incidence rate of clinical vertebral fracture to other ethnic groups were based on published literatures, and the data among Asian countries are scanty. Japan is the only country in Asia that reported the incidence rate on morphometric vertebral fractures based on a radiographic survey in a community-based population. Also, the Japanese data used for comparison came from the early 1990s, and there has been some evidence that hip fracture rates are increasing in Asians [20]. The impact on the change in epidemiology of fracture in Asians has not been evaluated. Another drawback of the present study is that only the incidences of clinical vertebral fractures were reported due to the lack of a common definition of morphometric vertebral fractures in other publications. Furthermore, the sample size and the number of fractures recorded in the men's cohort were small, and this study may have underestimated the fracture rates in the general male population.

In conclusion, this study demonstrated that while the hip fracture incidence in Asians is lower than in Caucasians, the incidence of clinical vertebral fractures was at least as high in Asians as in Caucasians.

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Conflicts of interest None.

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ORIGINAL ARTICLE

JBMR

Height Loss Starting in Middle Age Predicts Increased Mortality in the Elderly

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ABSTRACT

The purpose of this study was to determine the mortality risk among Japanese men and women with height loss starting in middle age, taking into account lifestyle and physical factors. A total of 2498 subjects (755 men and 1743 women) aged 47 to 91 years old underwent physical examinations during the period 1994 to 1995. Those individuals were followed for mortality status through 2003. Mortality risk was estimated using an age-stratified Cox proportional hazards model. In addition to sex, adjustment factors such as radiation dose, lifestyle, and physical factors measured at the baseline—including smoking status, alcohol intake, total cholesterol, blood pressure, and diagnosed diseases—were used for analysis of total mortality and mortality from each cause of death. There were a total of 302 all-cause deaths, 46 coronary heart disease and stroke deaths, 58 respiratory deaths including 45 pneumonia deaths, and 132 cancer deaths during the follow-up period. Participants were followed for 20,787 person-years after baseline. Prior history of vertebral deformity and hip fracture were not associated with mortality risk. However, more than 2 cm of height loss starting in middle age showed a significant association with all-cause mortality among the study participants (HR = 1.76, 95% CI 1.31 to 2.38, $p = 0.0002$), after adjustment was made for sex, attained age, atomic-bomb radiation exposure, and lifestyle and physical factors. Such height loss also was significantly associated with death due to coronary heart disease or stroke (HR = 3.35, 95% CI 1.63 to 6.86, $p = 0.0010$), as well as respiratory-disease death (HR = 2.52, 95% CI 1.25 to 5.22, $p = 0.0130$), but not cancer death. Continuous HL also was associated with all-cause mortality and CHD- or stroke-caused mortality. Association between height loss and mortality was still significant, even after excluding persons with vertebral deformity. Height loss of more than 2 cm starting in middle age was an independent risk factor for cardiovascular and respiratory-disease mortality among the elderly, even after adjusting for potential risk factors. © 2012 American Society for Bone and Mineral Research.

KEY WORDS: HEIGHT LOSS; MORTALITY; VERTEBRAL DEFORMITY; CORONARY HEART DISEASE; RESPIRATORY DISEASE

Introduction

Many studies have shown increased fracture risk[1–3] and mortality[4–8] after clinical vertebral fracture. Even subjects with no clinical fracture and little pain but with vertebral deformity detected by X-ray showed slightly increased mortality.[9] Other studies, however, showed no evidence of increased mortality among elderly with vertebral fracture.[10] Increased mortality after hip fracture was observed in several studies.[7,11,12]

Kyphosis and height loss are thought to result mainly from underlying vertebral fractures, but have not yet gained much clinical interest other than as markers for osteoporosis.[13–18] Height loss, however, not only could be caused by vertebral fracture, but also to some extent by intervertebral disk degeneration that decreases disk height; osteoarthritic conditions of the spine, hip, or knee, various inflammatory and structural/congenital spinal deformities; and weakness of the back muscles.[19,20] Our previous report showed that height loss and vertebral deformity significantly and independently affected quality of life (QOL) in the elderly, and height loss aggravated QOL more significantly than did vertebral deformity in all domains, even with different effect patterns between height loss and vertebral deformity.[21] The mechanism behind such decreased height loss–associated QOL remains uncertain. Recent reports have suggested that hyperkyphotic posture or marked height loss might predict future fracture risk[22] and mortality.[23–25]

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In the present study, we assessed whether height loss starting in middle age affects all-cause and specific-cause mortality, after taking into account vertebral deformity and hip fracture in Japanese men and women.

Materials and Methods

Data source

Study participants comprised cohort members of the Adult Health Study (AHS), which was established to investigate late health effects of radiation exposure among atomic-bomb survivors in Hiroshima and Nagasaki. The original AHS cohort was comprised of about 20,000 atomic-bomb survivors and their controls selected from residents of Hiroshima and Nagasaki, based on the 1950 national census. Since 1958, the AHS cohort members have been followed through biennial health examinations, including physical examinations; measurements of height, body weight, and blood pressure; and chest X-rays. The health study participants were interviewed by nurses to obtain disease histories and lifestyle information, such as smoking status and alcohol intake. Participation rates in the study were around 70% to 80% throughout the follow-up period. Further information about the cohort and details of the health examinations are available elsewhere.[26–28]

Subjects of this study numbered a total of 2498 individuals (755 men and 1743 women) aged 47 to 91 years old, undergoing physical examinations in Hiroshima during the health study's 1994 to 1995 examination cycle (Fig. 1). Measurements of height, using a stadiometer, were available for all subjects at each examination since 1962. Participants were measured without shoes, with their heels, buttocks, and back against an upright board. The participants with hyperkyphosis were instructed to stand straight and stretch the muscles in their backs as much as possible. We defined height loss starting in middle age (HL) as the difference between a participant's average height in their 40s and height measured in 1994 to 1995. We calculated average height based on from two to five measurements at ages in the 40s for each participant. If a participant did not have data on average height in the 40s, we then defined HL as the difference between his or her average height in the 50s and height measured in 1994 to 1995 (those for whom height in their 50s was used: 12.5%). We also defined marked HL as a difference of more than 2 cm based on results from receiver operating characteristic (ROC) analysis for mortality.

The subjects underwent bone mineral density (BMD) measurements at the spine (L1-4, anteroposterior direction) and the total hip using dual X-ray absorptiometry (DXA, QDR-2000 [Hologic Inc, Waltham, MA, USA]) at the time of the examinations in 1994 1995. Morphometric vertebral deformity was diagnosed by lateral and posterior-anterior chest and spinal X-ray examinations. An experienced radiologist diagnosed vertebral deformity using semi-quantitative procedures.[29,30] We defined "prevalent vertebral deformity" as vertebral deformity at thoracic and lumbar vertebrae diagnosed during the 1994 to 1995 examination cycle, that is, prevalent cases in 1994 to 1995. Diagnosis of hip fracture was based on history-taking by a physician. Pathologic fractures or fractures due to traffic accidents or falls from heights were excluded.

The study follow-up of all participants began in the 1994 to 1995 examination cycle. The accumulation of each participant's person-years of risk ended at the date of death, or the date of the last examination before December 2003. Mortality follow-up was conducted through checks of the vital status of cohort members using the Japanese family registration system. We were thus able to completely follow the mortality status of the cohort members.

Statistical Methods

The rates of many diseases increase as some power of age, so a simple linear adjustment factor would undercontrol for age effects. To avoid this bias, we used an age-stratified Cox proportional hazard analysis, whereby people are assigned to an age stratum reflecting their age at baseline according to five-year age intervals. After confirming the assumption that hazard ratios were proportional, we used an age-stratified Cox proportional

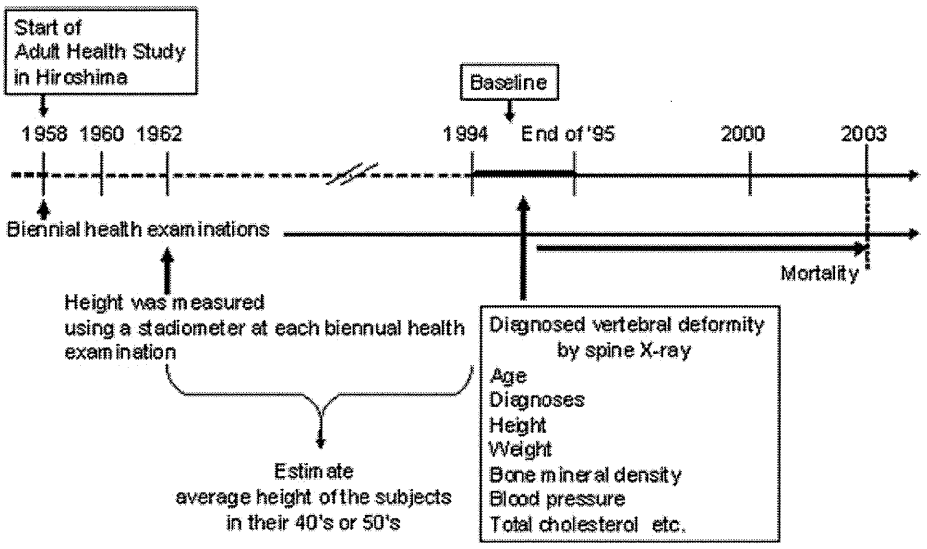

Fig. 1. Timeline of the study.

hazards model to assess the multivariate-adjusted hazard ratio (HR) for mortality. Fitted as categorical variables in the adjustment were assessments obtained at the 1994 to 1995 baseline: prevalent vertebral deformity (yes/no), prevalent hip fracture (yes/no), smoking status (never, current, former smoker, and unknown), alcohol intake (never, current occasional, current often, former drinker, and unknown), preexisting hypertension (yes/no), preexisting hyperlipidemia (yes/no), preexisting diabetes (yes/no), preexisting cardiovascular disease (yes/no), preexisting cancer (yes/no), marked HL (HL $\geq$ 2 cm/HL $<$ 2 cm). Weight, height, body mass index (BMI: calculated as weight in kilograms divided by height in meters squared), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, BMD at baseline, radiation dose, and HL were fitted as continuous variables. For each risk factor, we first evaluated all-cause mortality using an univariate model. We then conducted evaluation with multivariate model, including variables found to be significantly associated with all-cause mortality. We obtained a final model after removing non-significant terms. As a result, we included such variables as sex, preexisting cancer, preexisting cardiovascular disease (CVD), preexisting diabetes, radiation dose, marked HL, smoking status, and alcohol intake in the model. We also evaluated mortalities caused by coronary heart disease (CHD) or stroke, respiratory disease, pneumonia, and cancer. In the same procedure, we analyzed participants excluding 191 participants with prevalent vertebral deformities. We used individual radiation dose estimates on the Radiation Effects Research Foundation's Dosimetry System 2002 (DS02).[31]

For the mortality analysis, we used the PHREG procedure in SAS program (SAS version 9.1, SAS Institute Inc, Cary, NC, USA), with stratification by 5-year intervals of baseline age, for estimation of the parameters and testing. With consideration for parameter distributions, we tested differences between the alive group and the death group using Student's *t*-tests for continuous variables and χ^2 tests for categorical variables. A value of $p < 0.05$ was used for determination of statistical significance.

Ethical considerations

The present study was carried out in accordance with such national regulations as the *Ethical Guidelines Concerning Epidemiological Studies* (Ministry of Education, Culture, Sports, Science and Technology [MEXT], and Ministry of Health, Labour and Welfare [MHLW]). The study was approved by the Research Protocol Committee and the Human Investigation Committee at the Radiation Effects Research Foundation. At the time of the health examinations, informed consent was obtained from the participants. All participants provided written consent for all aspects of the examinations.

Results

Characteristics of the participants taken at baseline are shown in Table 1. In men, mean ages $\pm$ 1 standard deviation (SD) in the 1994 to 1995 examination period for the alive group were 61.2 $\pm$ 8.9 years, and 70.3 $\pm$ 9.1 years for the death group, ranging from 47 to 91 years. In women, mean ages were 64.7 $\pm$ 9.1 years and 73.5 $\pm$ 8.9 years, respectively, ranging from 47 to 91 years. Mean age of the "death" group was significantly higher than that of the "alive" group. Mean height loss starting in middle age was 0.83 cm for men and 1.85 cm for women. Figure 2 shows HL distribution by sex. We used $\geq$ 2 cm as the cut-off value through the sensitivity analysis, and compared the death group with the alive group. Twenty-one men and 170 women had prevalent vertebral fracture, and 12 men and 44 women had prior history of hip fracture in the 1994 to 1995 examination period. Prevalence of diseases at baseline is presented in Table 1. The proportion of individuals with cancer and CVD appeared to be higher in the death group than in the alive group in both men and women. The proportion of individuals with hypertension appeared to be higher in the death group than in the alive group in women. Approximately 90% of women were postmenopausal with an average age at menopause of 47.7 years.

Through December 2003, there were 302 all-cause deaths, 46 CHD and stroke deaths, 58 respiratory-disease deaths including 45 pneumonia deaths, and 132 cancer deaths. Mean follow-up was 8.3 years (Table 2). Participants were followed for 20,787 person-years after baseline. The death rate was 14.5 per 1000 person-years.

Multivariate adjustments were made for variables including physical and lifestyle factors, as described in "Methods," which were further adjusted for estimation of mortality risk (Table 3). After these adjustments, mortality hazard ratio for the marked HL was 1.76 (95% CI, 1.31to 2.38), $p = 0.0002$.

Mortality risk also was analyzed for specific causes of death. Adjusted mortality risk results are presented in Table 4. When causes of death were classified, increased mortality risk for marked HL was observed in CHD- or stroke-caused death (HR = 3.35, 95% CI 1.63 to 6.86, $p = 0.0010$) and respiratory disease-caused death (HR = 2.52, 95% CI 1.25 to 5.22, $p = 0.0130$), but not cancer-caused death ($p = 0.3143$). No significant increase in mortality from cancer was observed. With significance, continuous HL also was associated with all-cause mortality (HR = 1.08 per 1 cm HL increase, 95% CI 1.03 to 1.14, $p = 0.0034$) and CHD- or stroke-caused death (HR = 1.11, per 1 cm HL increase, 95% CI 1.00 to 1.23, $p = 0.0465$). Previous history of vertebral deformity and hip fracture were not associated with all-cause mortality risk (Table 4).

The hazard ratios for marked HL were reduced only slightly when the 191 prevalent cases of vertebral deformity were excluded (eg, HR of 1.65, rather than 1.76 for all-cause mortality) (analyses not shown).

Discussion

HL and mortality

This is the first study to show that HL of more than 2 cm increased the risk of all-cause death, CHD- or stroke- and respiratory disease-caused death, but not cancer death, with vertebral fracture assessed simultaneously. Furthermore, the present study showed that HL treated as a continuous variable was

Table 1. Baseline (1994–1995) Characteristics of Study Population by Sex and Vital Status

	Men		Women	
Variable	Alive	Dead	Alive	Dead
Number of subjects	627	128	1569	174
Age (years)	61.2 (8.9)	70.3 (9.1)**	64.7 (9.1)	73.5 (8.9)**
Height (cm)	163.9 (6.0)	161.5 (6.3)**	150.7 (5.7)	147.6 (6.4)**
Weight (kg)	61.4 (8.8)	58.2 (9.2)**	52.8 (8.7)	48.6 (9.3)**
BMI (kg/m^2)	22.8 (2.9)	22.3 (3.0)	23.2 (3.6)	22.3 (3.9)**
height at 40s or 50s (cm)[a]	164.5 (5.8)	162.9 (5.8)**	152.3 (5.2)	150.9 (5.4)**
HL (cm)	0.69 (1.01)	1.50 (1.46)**	1.69 (1.94)	3.34(2.76)**
marked HL (%)	67 (10.7)	42 (32.8)**	556 (35.4)	127 (73.0)**
BMD (g/cm2)				
Spine (L1-4)	0.960 (0.155)	0.972 (0.164)	0.796 (0.154)	0.739 (0.148)**
Total hip	0.739 (0.115)	0.709 (0.109)**	0.626 (0.107)	0.571 (0.093)**
Prevalent hip fracture	7 (1.1%)	5 (3.9%)*	34 (2.2%)	10 (5.8%)**
Prevalent vertebral deformity	15 (2.4%)	6 (4.7%)	138 (8.8%)	32 (18.4%)**
SBP	131.8 (20.3)	136.3 (22.1)*	130.7 (21.1)	136.4 (21.4)**
DBP	80.8 (11.4)	77.3 (15.2)**	77.3 (11.4)	76.4 (12.5)
Total cholesterol	203.2 (34.0)	202.0 (36.7)	221.3 (34.6)	211.1 (42.6)**
Diagnosed disease				
Hypertension	185 (32.9%)	37 (39.0%)	390 (27.7%)	50 (40.7%)**
Hyperlipidemia	44 (7.8%)	6 (6.3%)	194 (13.8%)	15 (12.2%)
Diabetes	96 (15.3%)	28 (21.9%)	162 (10.3%)	23 (13.2%)
CVD	288 (45.9%)	78 (60.9%)**	660 (42.1%)	113 (64.9%)**
Cancer	40 (6.4%)	18 (14.1%)*	153 (9.8%)	33 (19.0%)**
Alcohol intake				
Never	105 (16.7%)	27 (21.1%)	769 (49.0%)	102 (58.6%)*
Current occasional	107 (17.1%)	29 (22.7%)	256(16.3%)	31 (17.8%)
Current often	262 (41.8%)	31 (24.2%)**	113 (7.2%)	9 (5.2%)
Former	14 (2.2%)	8 (6.2%)*	13 (0.8%)	5 (2.9%)*
Unknown	139 (22.2%)	33 (25.8%)	418 (26.7%)	27 (15.5%)**
Smoking status				
Never	88 (15.6%)	9 (11.7%)	920 (64.5%)	67 (58.6%)
Current	210 (33.5%)	42 (32.8%)	104 (6.6%)	11 (6.3%)
Former	167 (26.6%)	35 (27.4%)	47 (3.0%)	6 (3.5%)
Unknown	152 (24.3%)	36 (28.1%)	406 (25.9%)	55 (31.6%)*
Radiation dose (Gy)	0.382 (0.634)	0.432 (0.608)	0.297 (0.514)	0.407 (0.568)

HL, historical height loss starting in middle age; BMI, body mass index; BMD, bone mineral density; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease.

Mean (SD).

With consideration for parameter distributions, we tested difference between death or alive using *t*-test for height, weight, BMI, height at 40s or 50s, marked HL, BMD, SBP, DBP, total cholesterol, radiation dose, using a Wilcoxon test for age, and using χ^2-test for prevalence of hip fracture, prevalence of vertebral deformity, alcohol intake, smoking status, and diagnosed diseases.

[a]Longitudinal data of height are available for all study participants of the cohort since 1962. We defined height loss starting in middle age (HL) as the difference between a participant's average height in his or her 40s and height measured in 1994 to 1995.

*$p < 0.05$.

**$p < 0.01$.

associated with significantly increased risk of all-cause mortality and CHD- or stroke-caused mortality.

Our previous report[21] showed that height loss and vertebral deformity affected QOL significantly and independently in the elderly. Even after excluding individuals with vertebral deformity, height loss was associated with decreased QOL. Furthermore, it is observed that factors other than vertebral deformity, such as intervertebral disk degeneration and osteoarthritic conditions, also caused height loss. In the present study, we observed association between mortality and height loss starting in middle age, but not prevalent vertebral deformity. The presence of certain adverse health conditions, for example poor muscle strength, possibly causing height loss may be implicated.

Wannamethee et al. followed 4213 men measured for height at ages 40 to 59 and again 20 years later, observing 760 deaths occurring after six more years. In the aforementioned study, Wannamethee et al. described how osteoporotic disease complicated by vertebral fractures was not likely to explain

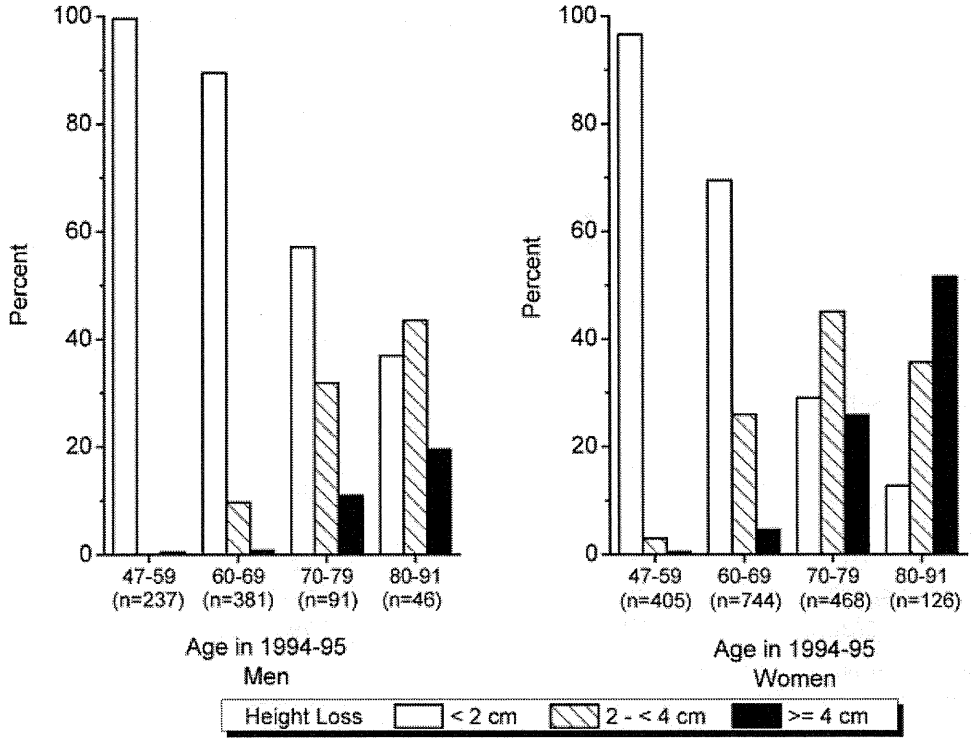

Fig. 2. Percentage of those with height loss starting in middle age, for men and women.

increased mortality risk associated with height loss. Poor muscular strength and low skeletal muscle mass have been linked to bone loss and poor bone structure in men, which could result in height loss.[32] The increased risk of CHD and all-cause mortality associated with height loss may thus reflect poor muscular strength and skeletal muscle mass loss from aging (sarcopenia), both of which have been shown to be predictors of mortality.[33–35] Wannamethee et al. also discussed the idea that height loss might serve as a marker for sarcopenia and frailty.[24] Hyperkyphosis, commonly used as a marker of aging, is frequently observed in the elderly. It is known that hyperkyphosis is associated with restrictive pulmonary disease[36] and poor physical function.[37–39] These findings suggest that hyperkyphosis also might be associated with occurrence of other states of poor health. Some studies have suggested association between kyphosis and mortality.[22,23,25] Recently, Kado et al.[25] conducted a prospective cohort study of 610 older white women who were diagnosed with kyphosis, and assessed mortality rates over an average follow-up of 13.5 years. They concluded that hyperkyphosis predicted increased risk of death independent of prevalent vertebral fractures. In addition, Kado et al.[23] followed 1353 men and women over a period of 4.2 years, with mortality and cause of death confirmed by review of death certificates. They observed that older men and women with hyperkyphotic posture had higher mortality rates.

Table 2. Deaths Observed Between Baseline Examinations in 1994 to 1995 and December 2003

	Men	Women	Total
Number of individuals	755	1743	2498
Number of all-cause deaths	128	174	302
Person-years	6188	14,599	20,787
Mean follow-up period (years)	8.2	8.4	8.3
Death rate (per 1000 person-years)	20.7	11.9	14.5
Number of deaths by cause			
Coronary heart disease and stroke	21	25	46
Respiratory disease	27	31	58
Pneumonia	19	26	45
Cancer	66	66	132

Table 3. Hazard Ratios (HRs) Using Age-Stratified Cox Regression Analysis for All-Cause Mortality[a]

Baseline factor in 1994–1995		Hazard ratio	95% CI
Sex	Women/Men	0.39	0.28–0.53**
Marked HL	Yes/No	1.76	1.31–2.38**
Preexisting cancer	Yes/No	1.55	1.12–2.15**
Preexisting CVD	Yes/No	1.32	1.03–1.71*
Preexisting DM	Yes/No	1.48	1.07–2.05*
Radiation dose	1 Gy increment	1.22	1.01–1.48*
Alcohol habit	Current occasional/ Never	1.14	0.82–1.57
	Current often/Never	0.55	0.36–0.84**
	Former/Never	1.86	1.02–3.39*
	Unknown/Never	0.71	0.51–0.99*

CI, confidence interval; HL, height loss starting in middle age; CVD, cardio vascular disease.

[a]The analysis included all variables in the table simultaneously.

*$p < 0.05$; **$p < 0.01$.

Table 4. Hazard Ratios (HRs) Using Age-Stratified Cox Regression Analysis by Continuous HL, Marked HL, Vertebral Fracture, and Hip Fracture for Mortality

Death	Continuous HL	Marked HL	Prevalent Vertebral Deformity	Prevalent Hip Fracture
All-cause death				
HR	1.08	1.76	1.13	1.26
95% CI	1.03–1.14	1.31–2.38	0.78–1.64	0.72–2.18
p value	0.0034	0.0002	0.5267	0.4183
CHD- or Stroke-caused death				
HR	1.11	3.35	1.89	1.97
95% CI	1.00–1.23	1.63–6.86	0.86–4.16	0.67–5.82
p value	0.0465	0.0010	0.1123	0.2186
Respiratory disease–caused death				
HR	1.10	2.52	1.35	0.71
95% CI	0.99–1.23	1.25–5.22	0.63–2.89	0.17–2.95
p value	0.0684	0.0130	0.4378	0.6316
Cancer-caused death				
HR	1.05	1.26	0.92	1.17
95% CI	0.96–1.15	0.80–1.99	0.48–1.76	0.47–2.92
p value	0.2634	0.3143	0.7944	0.7367

HL, height loss starting in middle age; CHD, coronary heart disease.
Adjusted for sex, radiation dose, preexisting diabetes, preexisting cardiovascular disease, preexisting cancer, smoking status, and alcohol intake.

For CHD mortality, our results are consistent in principle with the results of the two previous studies. Additionally, we observed association between respiratory disease mortality and height loss starting in middle age in both men and women. Furthermore, height loss was associated with mortality even after individuals with vertebral deformity were excluded. The mechanism regarding how height loss might be associated with subsequent mortality is not currently well understood. Resulting height loss could affect normal functioning of the respiratory and gastrointestinal systems,[13] which in turn might lead to early satiety, poor nutritional status, and weight loss.[13] Height loss also appears to be related to sarcopenia,[32] which is defined as the loss of skeletal muscle mass and strength with aging and is associated with weight loss[40–43] and increased mortality.[33–35]

We found increased mortality associated with marked HL due to CHD or stroke and respiratory diseases, but no increased cancer mortality. Kado et al. reported that hyperkyphotic posture was specifically associated with increased rate of death due to atherosclerosis.[23] Browner et al. reported that low bone mass was significantly associated with death from CVD and specifically stroke.[44] Some evidence indicated similar pathophysiological mechanisms underlying both osteoporosis and cardiovascular disease.[45,46] Risk factors such as age, diabetes, hypertension, inflammation, dislipidemia, homocystienemia, and estrogen deficiency are prevalent in both disorders.[44,47]

Osteoporotic fracture and mortality

Bliuc et al.[48] reported that excess mortality was highest immediately after almost all fragility fracture events and then declined. The researchers observed that 30% of all post–hip-fracture deaths occurred in the first six months and 21% in the next 18 months. Other studies reported that increased mortality after hip and vertebral fractures was consistent over the initial five-year period.[4,6,8,11]

In the present study, prevalent morphometric vertebral deformity and prevalence of hip fracture were not associated with increased mortality. Inconsistency between our report and many previous studies can be explained by differences between incidence and prevalence of fracture, because prevalent vertebral deformity and hip fracture in our study included those cases that had developed many years in the past. In addition, in the follow-up period, such differences as whether or not to include morphometric vertebral fracture and adjustment of potential confounders might have resulted in the inconsistency.

Strengths and limitations

One strength of this study is that the investigation was based on measured height using consistent methods throughout biennial health examinations conducted since 1962, thus reducing measurement errors. Since mean height in most age groups has increased recently in many regions around the world, including Japan, height loss would be overestimated in cross-sectional studies, and bias would be significant if recalled height were used.[49] Our study was carried out using measured height at ages 40 to 49 and again some years later in a population-based study of men and women. Second, mortality follow-up has been carried out through checks of the vital status of cohort members using the Japanese family registration system. We were thus able to completely follow mortality of the cohort members.

There are some limitations to our findings. First, baseline data for physical activity and lung function were not available. Second, diagnosis of hip fracture was based on history taking by a physician, not X-ray examination. Furthermore, participants were atomic bomb survivors and thus not representative of the general Japanese population, although we adjusted for

radiation, and there are no indications from earlier studies of this cohort that radiation affected BMD and fracture frequency.[38,48,50]

Conclusion

In conclusion, height loss starting in middle age is considered to be a factor associated with CVD and respiratory-disease mortality, independent of vertebral deformity, in Japanese elderly men and women. Further studies will be needed to elucidate the mechanisms behind such findings. Although the mechanisms are unknown, height loss, regardless of its causes, is a clinically important finding.

Disclosures

All the authors state that they have no conflicts of interest.

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POSITION PAPER

Japanese 2011 guidelines for prevention and treatment of osteoporosis—executive summary

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Abstract
Introduction In 1998, the first Japanese practice guidelines on osteoporosis was published. It has been updated several times, with the most recent being the full-scale 2011 edition and its abridged edition. The present guidelines provide information for the managements of primary osteoporosis in postmenopausal women and men over 50 years old, a summary of the evidence for the treatment of secondary osteoporosis, and a summary of the evidence for the prevention of osteoporosis in younger people.

A Report of the Committee for Developing Guidelines for Prevention and Treatment of Osteoporosis: Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research, and Japan Osteoporosis Foundation

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Method The present Executive Summary is primarily based on the content of the 2011 Japanese abridged edition. One of the key changes is revision of the criteria for initiation of pharmacological treatment, along with an introduction of the fracture risk factors used in FRAX®. Key figures and tables were selected from the Japanese abridged edition and a reference list was added.

Result and conclusions The essential points of the Japanese practice guidelines on osteoporosis were translated into English for the first time. It is hoped that the content of the guidelines becomes known throughout the world.

Keywords Criteria for initiation of pharmacological treatment · Diagnosis of osteoporosis · Fracture risk assessment · Prevention of osteoporosis · Secondary osteoporosis · Treatment of osteoporosis

Preamble

In 1998, we published the "Guidelines for (Pharmacological) Treatment of Osteoporosis 1998" under the name of the Working Group for Developing Guidelines for Osteoporosis in the Osteoporosis Research Project supported by the Ministry of Health and Welfare (present-day Ministry of Health, Labor, and Welfare) of Japan. Although they were the first Japanese guidelines for the diagnosis and treatment of osteoporosis and also set a precedent for evidence-based practice guidelines in Japan, there were few effective therapeutic agents for osteoporosis available in Japan at that time. The 1998 edition was updated in 2002.

There has been tremendous change in the field of osteoporosis inside and outside Japan since that update. Addressing osteoporosis has become a more urgent issue also in Japan because of its fast-aging society. Therefore, we published the comprehensive "Guidelines for Prevention and Treatment of Osteoporosis 2006" under the name of the Committee for Developing Guidelines for Prevention and Treatment of Osteoporosis 2006, an ad hoc organization comprising the Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research, and Japan Osteoporosis Foundation. Emphasizing prevention, covering secondary osteoporosis, presenting the criteria for initiation of pharmacological treatment, and grading the recommendation for each therapeutic agent, these guidelines were highly rated in the medical and clinical arenas. Immediately thereafter we published an abridged edition to disseminate the content of the 2006 Guidelines to a greater number of doctors and healthcare professionals.

In late 2011, the 2006 Guidelines and its abridged edition were updated. Key changes are as follows: profile of the research progress on bone quality, revision of the criteria for initiation of pharmacological treatment (associated with the re-examination of the risk factors for fracture and introducing FRAX®), more detailed descriptions about secondary osteoporosis (including new information on the relationship between lifestyle-related diseases and fracture risk), evaluation of new therapeutic agents, and bone metabolic markers covered by public insurance. The present Executive Summary is primarily based on the content of the updated 2011 Japanese abridged edition. Only the most key figures and tables were selected from the Japanese abridged edition and a reference list was added. We hope this Executive Summary contributes to the advancement of medical care for osteoporosis in Asia and the world.

In developing the guidelines, a systematic literature search of MEDLINE, EMBSE, Cochrane Library, and PubMed was conducted. The treatment recommendations in these clinical guidelines were determined by the consensus of the committee. The draft guidelines were available for physician comments at the annual meetings of the Japan Osteoporosis Society in 2010 and 2011.

The funding for all costs to produce the guidelines and this position paper was obtained from the Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research, and Japan Osteoporosis Foundation. All of the authors state they have no conflict of interest related to the guidelines or this position paper.

Definition, epidemiology, and etiology

Definition

The United States National Institutes of Health (NIH) Consensus Development Conference on Osteoporosis Prevention, Diagnosis, and Therapy held in 2000 proposed a new definition of osteoporosis as follows: Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fractures. Further, it was stated that bone strength reflects the integration of two main features: bone mineral density (BMD), which accounts for almost 70 % of bone strength, and bone quality, which accounts for the remaining 30 %.

Risk factors for fractures vary among individuals, and include presence or absence of fragility fractures, family history, lifestyle factors, as well as BMD. Therefore, in clinical practice, the risk of fracture should be comprehensively evaluated based on these clinical risk factors for each individual.

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Recently, some algorithms have been developed to quantitatively estimate an individual's fracture risk by integrating multiple risk factors (see "Risk factors for fracture" for FRAX®).

Epidemiology

The estimated number of osteoporotic patients aged 40 or over in Japan is 12,800,000 (3,000,000 men and 9,800,000 women), based on the result of a survey of the prevalence of osteoporosis (diagnosed with BMD at the lumbar vertebrae or proximal femur) stratified by age in the general population (Fig. 1) [1] and the population structure stratified by age groups in 2005. Furthermore, the estimated annual incidence of osteoporosis, based on the BMD at the lumbar vertebrae in the population aged between 40 and 79 years, is 0.6 % in men and 2.3 % in women.

The estimated incidence of proximal femoral fractures due to osteoporosis in Japan was 148,100 (31,300 men and 116,800 women) in 2007 [2]. A follow-up study targeting a rural population revealed that the 10-year cumulative incidence of vertebral fractures was 5.1 and 14 % for men and women in their 60s, respectively, and 10.8 and 22.2 % among men and women in their 70s, respectively [3]. However, a long-term trend shows that a later year of birth is associated with a lower incidence of vertebral fractures.

The incidence of proximal femoral fractures was found to be higher in western Japan than in eastern Japan. As compared to reports from Western countries, the incidence of proximal femoral fractures is lower and that of vertebral fractures is similar or higher in Japan.

Etiology

From middle-age onward, BMD decreases and bone quality deteriorates with advancing age, resulting in loss of bone strength. Especially in women, BMD decreases sharply in the perimenopausal period and for several years thereafter. In addition to this natural course, genetic factors, nutritional deficiency since childhood and puberty, lack of exercise, and unhealthy lifestyle also cause loss of bone strength. Primary osteoporosis is the clinical condition in which these factors have caused a significant loss of bone strength.

Bone remodeling consists of bone resorption by osteoclasts and bone formation by osteoblasts, a mechanism to maintain bone strength. If bone resorption increases with advancing age and menopause and exceeds the rate of bone formation, BMD will begin to decrease. Low BMD is caused by activation of osteoclasts due to estrogen deficiency associated with menopause, and by inadequate secondary mineralization, microarchitecture deterioration, and a decrease in capacity for absorbing calcium associated with advancing age, among other factors (Fig. 2).

Inadequate secondary mineralization and microarchitecture deterioration result in deterioration of bone quality, which is, however, also affected by the cell function of synthesizing bone matrix, conditions surrounding bone matrix (i.e., levels of oxidation and glycation), and levels of vitamins D and K. When oxidative stress and glycation increase in association with aging and lifestyle-related diseases, the non-enzymatic (nonphysiological) cross-links (see "Prevention of falls") increase between collagen molecules in the bone matrix, resulting in a loss of bone strength (Fig. 2).

Prognosis

Fractures associated with osteoporosis, in particular proximal femoral fractures, lead to impairment in mobility and vital functions and an increase in mortality. The relative risk of overall mortality is high in older women with a low BMD and vertebral deformity, and the greater the number of vertebral fractures, the higher the risk of mortality. Decreased BMD at the proximal femur increases the long-

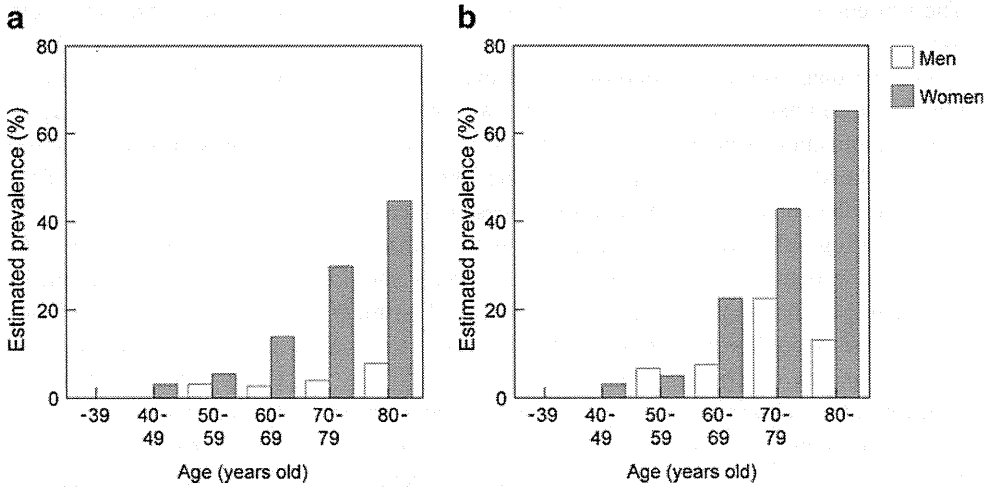

Fig. 1 Estimated prevalence of osteoporosis in Japan. Osteoporosis was diagnosed from BMD at vertebrae L_{2-4} (**a**) and proximal femur (**b**). Data from Yoshimura [1] (Copyright© 2009 Springer Science + Business Media BV)

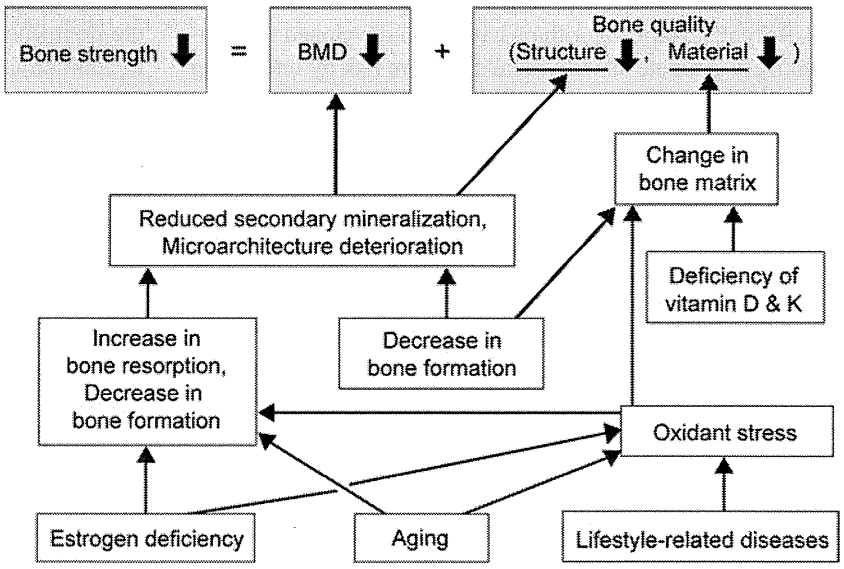

Fig. 2 Factors causing deterioration of bone strength

term mortality risk, regardless of the presence or absence of vertebral fracture.

According to a survey on quality of life (QOL), patients with osteoporosis score lower on factors related to posture/body shape and falls/psychological in a self-assessment of QOL than persons in the general population who have undergone an osteoporosis screening.

Low BMD is strongly related to the Certification of Needed Long-Term Care for the public nursing-care insurance system in Japan. That is, osteoporosis or low BMD is one of the most significant factors for becoming fragile/immobilized or even becoming bedridden or institutionalized. Therefore, prevention of osteoporotic fractures is likely to prevent reduced mobility or immobilization.

Diagnosis

Diagnostic procedures

The procedures for diagnosis of osteoporosis are shown in Fig. 3 [4].

For the diagnosis of osteoporosis, a medical interview, physical examination, diagnostic imaging, and blood and urine examinations (including measurement of bone metabolic markers) should be conducted first. Then, bone assessment must be conducted with bone mass measurement and spinal radiography. Based on this information, diseases causing low bone mass or secondary osteoporosis should be excluded, and then an accurate diagnosis of primary osteoporosis should be made based on the diagnostic criteria (see "Diagnostic criteria for primary osteoporosis").

Information obtained in the diagnostic process about factors that could contribute to osteoporosis and the risk factors for fractures (e.g., family history, prevalent fractures, and bone metabolic markers) should be used to evaluate the severity of osteoporosis and the fracture risk. This information will also be useful to provide guidance about lifestyle modification and to select the optimal therapeutic strategy.

Clinical presentation

In the absence of a fracture, osteoporosis is nearly asymptomatic. However, patients with osteoporosis are predisposed to the development of fractures due to loss of bone strength, and the occurrence of fractures will severely impair their QOL (Fig. 4). Osteoporotic fracture is also called fragility fracture.

Proximal femoral fractures directly lead to decreases in the activities of daily living (ADL) and can lead to patients being bedridden, resulting in poor prognosis.

The estimated prevalence of vertebral fractures in Japanese in their early 70s is 25 % and is 43 % in person over 80 years old. The occurrence of vertebral fractures often leads to subsequent vertebral fractures. Since a vertebral deformity persists after the fracture heals, accumulation of vertebral fractures in multiple sites causes kyphosis (round back). Progressive kyphosis leads to deterioration of QOL due to significantly limited ADL and lumbar backache, and can cause functional declines or disorders of the digestive, respiratory, and cardiac systems.

Some lifestyle-related diseases which cause atherosclerosis such as diabetes mellitus (DM), hypertension, dyslipidemia, and chronic kidney diseases (CKD) have attracted attention in relation to osteoporosis. In particular, DM and CKD predispose patients to osteoporosis, and increase their fracture risk (see "Prevention of falls"). The possibility of hidden osteoporosis always should be considered during medical care of patients with lifestyle-related diseases.

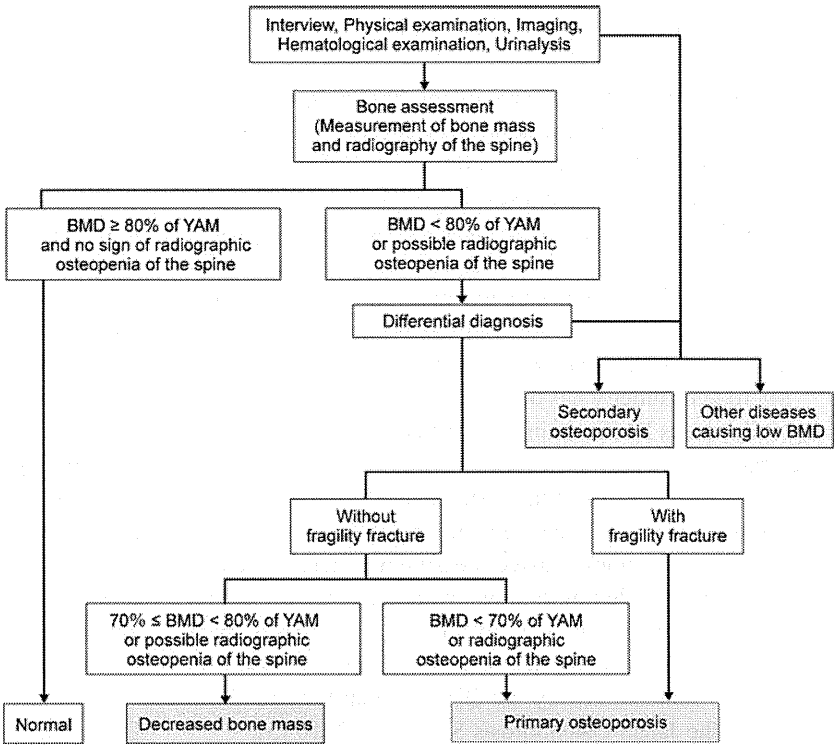

Fig. 3 Procedure for the diagnosis of osteoporosis. *YAM* young adult mean (20 to 44 years of age). Adapted from Orimo [4] (Copyright© 2001 Springer Science + Business Media BV)

Medical interview and physical examination

The objectives of the medical interview and physical examination are to assess the presence and symptoms of osteoporotic fractures, risk factors for osteoporosis and fractures, and to obtain information for the differential diagnosis.

Family history of proximal femoral fractures (in either or both parents), loss of height (4 cm or more relative to the height at 25 years of age), current smoking, and excessive alcohol consumption (3 units/day or more, 1 unit=8–10 g ethanol) are particularly important risk factors for osteoporotic fractures. Therefore, taking a careful history including these factors is needed. History of glucocorticoids use, rheumatoid arthritis, and lifestyle-related diseases such as diabetes mellitus are important information for the differential diagnosis.

In regard to the physical findings, a rounded back, fewer than 20 teeth, and a value of less than −4 on the Female Osteoporosis Self-Assessment Tool for Asians are key factors that strongly suggest osteoporosis.

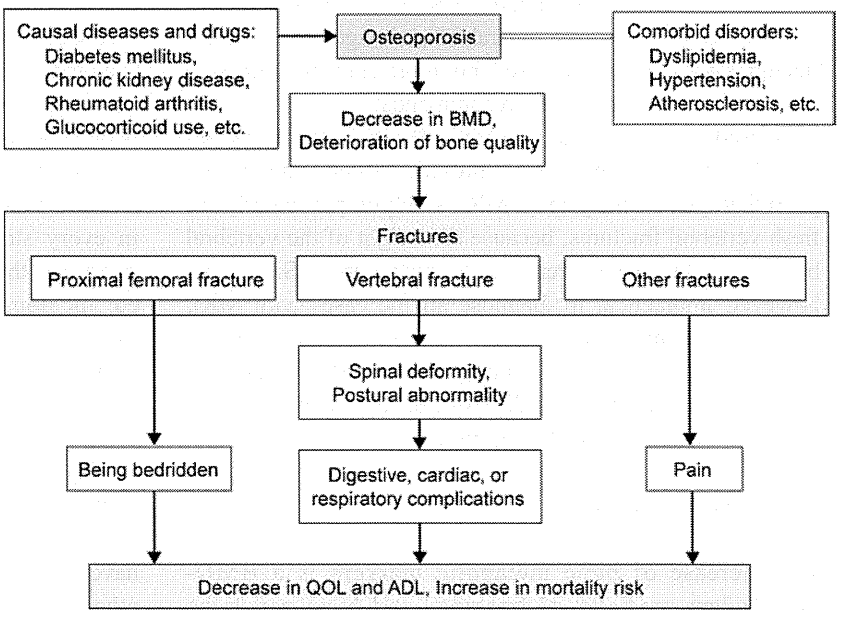

Fig. 4 Clinical presentation and prognosis of osteoporosis

Bone assessment

It is recommended that BMDs of the lumbar spine and/or proximal femur are measured by dual-energy X-ray absorptiometry (DXA). When there is a fracture or deformity in the lumbar vertebrae that increases the influence of an artifact on spine BMD, the data of lumbar spine should not be used. If the measurement at either of these sites is not successful (because of bilateral hip surgery, multiple fractures of the lumbar vertebra, severe vertebral deformity, or excessive obesity, etc.), another choice is forearm bone.

Microdensitometry has been developed in Japan to radiologically assess BMD, mainly of cortical bone in the second metacarpal.

The speed of sound and broadband ultrasound attenuation through bone are measured with quantitative ultrasound (QUS). This is a non-invasive measurement technique and may provide reliable information on bone quality along with the BMD. However, it is easily affected by measurement conditions, among other factors. The parameters used in QUS were standardized by the QUS Standardization Committee of the Japan Osteoporosis Society in 2010 [5].

Fracture evaluation

Radiography of the thoracic and lumbar vertebrae are essential for assessment of fracture, deformity, or change in the vertebrae, and for exclusion of other similar disorders that present with lower back pain, round back, or low bone mass. In the Japanese diagnostic criteria, the presence of fragility fractures alone confirms the diagnosis of osteoporosis (see "Diagnostic criteria for primary osteoporosis"). Since most of the prevalent fragility fractures, however, are vertebral fractures, usually without pain, radiography is fundamental for their proper diagnosis. Either semiquantitative assessment or quantitative morphometry is used. The lateral DXA images for vertebral fracture assessment can be used, but more clinical experience in Japan is needed to make a recommendation.

If used during the early period after a fracture has occurred (within 2 weeks), MRI provides a better diagnostic yield than plain radiography. MRI is helpful particularly for fresh vertebral fractures, because the height of the vertebral body often does not decrease in the early period. Since it is, however, impractical to diagnose all the cases with MRI, MRI is recommended when it is necessary to distinguish osteoporotic fractures including non-vertebral fractures from those caused by other diseases, or for a detailed examination regarding complicating diseases.

Bone metabolic markers

The increase of bone metabolic markers is a BMD-independent predictor of fractures, and bone metabolic markers are one of the indices of fracture risk. There are two types of bone metabolic markers: bone resorption markers and bone formation markers. Examinations of blood or urine for these bone metabolic markers easily provide information on the bone metabolic state (Fig. 5) [6].

Bone metabolic markers are useful particularly for the following situations. (1) The patient has little understanding of the need for treatment. (2) The patient is scheduled to receive pharmacotherapy. (3) It is difficult to decide what drug to choose. (4) You want to adopt an appropriate treatment for the patient's pathological condition. Bone metabolic markers are also useful for evaluation of the response to treatment. Thus, it is recommended to measure them at the time of diagnosis if possible.

Among bone metabolic markers, undercarboxylated osteocalcin (ucOC) can be used as an index of vitamin K deficiency in the bones.

When the values of bone resorption markers are abnormally high, the presence of other metabolic bone diseases is suspected.

Differential diagnosis

The targets of differentiation from primary osteoporosis are secondary osteoporosis and other bone-related diseases. Secondary osteoporosis is caused by other diseases or treatments, but its clinical state can seem similar to that of primary osteoporosis, while other bone-related diseases display a clinical state that is different from that of primary osteoporosis. Some instances of secondary osteoporosis and other bone-related diseases are critical or require immediate medical attention. Further, most types of secondary osteoporosis require a therapeutic strategy different from that for primary osteoporosis, and the appropriate treatment of the causative diseases may lead to a dramatic improvement in secondary osteoporosis. Therefore, the differential diagnosis is an extremely important process, despite the prevalence of secondary osteoporosis being low. The probability of secondary osteoporosis is relatively high among premenopausal women and men.

Information for the differential diagnosis can be obtained in every step of the diagnostic process. In the medical interview, thorough medical and surgical histories are needed, including current medications. Radiography may be useful for exclusion of osteomalacia and bone metastases of malignant tumors. Various causative states of secondary osteoporosis may be suspected by the results of blood and urine examinations, for example, hypercalcemia, hypocalcemia, elevated alkaline phosphatase level, and proteinuria.

It is usually considered that patients who visit specialized medical institutes, such as university hospitals, are likely to have secondary osteoporosis due to endocrine diseases and others.

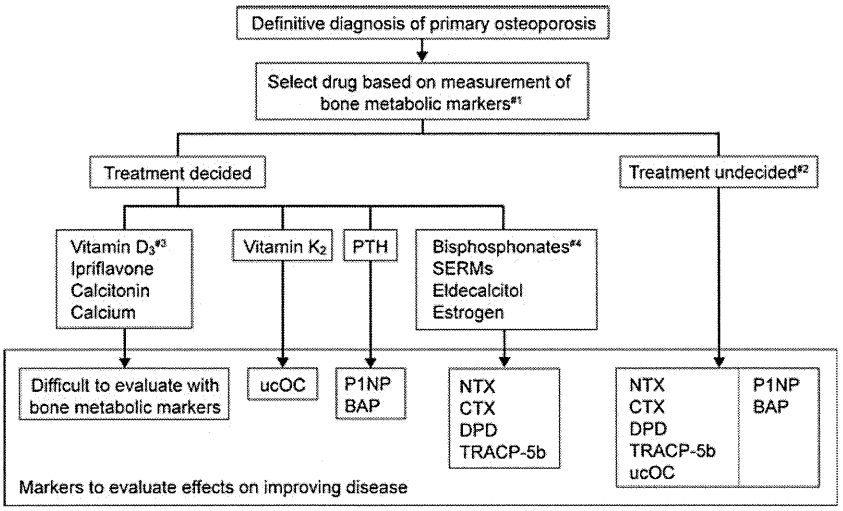

Fig. 5 Measurement of bone metabolic markers in drug treatment of osteoporosis. #1: in patients taking bisphosphonates, measure after stopping drug for at least 6 months, and in patients taking other osteoporosis drugs, measure after stopping drug for at least 1 month. #2: measure one type each of a resorption marker and formation marker. #3: excluding eldecalcitol. #4: in patients expected to be on long-term bisphosphonate therapy, measure bone resorption markers and BAP or P1NP. Nishizawa [6] (Copyright© 2012 Springer Science + Business Media BV)

Diagnostic criteria for primary osteoporosis

After excluding both the presence of other diseases characterized by low bone mass and the possibility of secondary osteoporosis, primary osteoporosis should be diagnosed by a two-step approach: (1) presence or absence of fragility fractures and (2) BMD or assessment of osteopenia on spinal radiography (Fig. 6) [4].

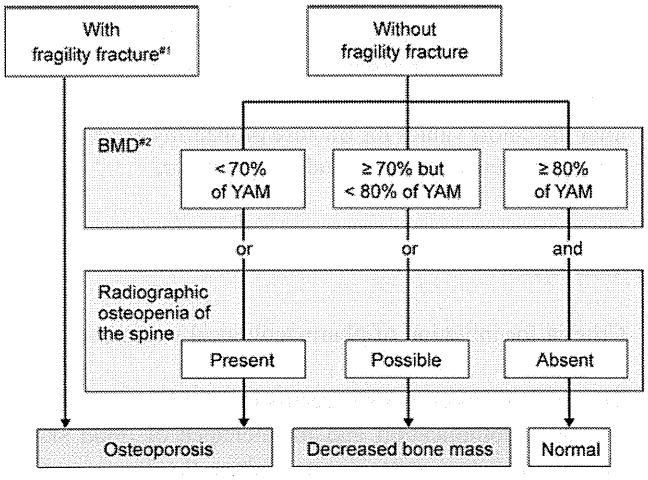

Fig. 6 Diagnostic criteria for primary osteoporosis (updated in 2000). Primary osteoporosis is diagnosed according to these criteria in the absence of diseases causing low bone mass or secondary osteoporosis. #1: fragility fracture is a nontraumatic bone fracture that is caused by slight external force to a bone with low BMD (BMD less then 80 % of YAM). Sites of fracture include the spine, proximal femur, and the distal end of the radius. #2: BMD usually refers to lumbar BMD. However, when the measurement is inappropriate for reasons such as spinal deformity, the proximal femur BMD should be used. When measurement at those sites is difficult, BMD of the radius, second metacarpal bone, or calcaneus will be used. Revision of additional T-scores is under consideration. Adapted from Orimo [4] (Copyright © 2001 Springer Science + Business Media BV)

Primary osteoporosis is diagnosed on the presence of any fragility fractures (defined as a nontraumatic bone fracture caused by slight external force to a bone with low bone mass, which correlates to a BMD<80 % of young adult mean (YAM) or radiographic osteopenia of the spine) at sites including spine, proximal femur, and the distal end of radius. If there is no fragility fracture, the BMD level is used to diagnose the patient as "normal", "decreased bone mass", or "osteoporosis". Evaluation of osteopenia based on spinal radiography should be used as supplementary means, and quantitative bone densitometry is preferable for bone assessment.

The T-score to YAM of BMD, not the percentage, is used as diagnostic criteria internationally. A T-score of −1.5 represents a value of −1.5 standard deviation of the YAM and is approximately equivalent to 80 % of the YAM in Japan. A T-score of −2.5 is approximately equivalent to 70 % of the YAM. Internationally, the proximal femur is considered to be the standard measurement site for BMD.

Risk factors

Risk factors for fracture

Major risk factors for osteoporotic fractures are female gender, advanced age, low BMD, and prevalent fractures. In addition, many other factors affect fracture risk directly or indirectly. Although a poor intake of calcium increases fracture risk via low BMD, other risk factors for fractures such as age, prevalent fracture, family history of fractures, smoking, and drinking are independent of BMD. Low body weight also is a BMD-independent risk factor, but only for proximal femoral fractures.