(A, B + 1), (A − 1, B + 1), (A + 1, B), (A − 1, B), (A + 1, B − 1), (A, B − 1), and (A − 1, B − 1), using units of 1 mm.

RF signals at these nine points were acquired and recorded in both the 6-month-old and 3-year-old porcine cartilages, and TOF was measured in each sample using the cross-correlation method and the following three amplitude-related methods (Fig. 3).

Peak amplitude method

The absolute amplitude of each RF signal wave was calculated, and peaks of the RF signal with maximum amplitude values were considered to represent reflection waves from the cartilage surface and cartilage–bone interface.

Peak envelope method

The envelope of each RF signal was calculated using a Hilbert transform [24]. Peaks of the envelope signal were attributed to reflections occurring at the cartilage surface and cartilage–bone interface.

Signal phase method

The analytical signal phase of the RF signal was calculated as previously described [25, 26]. Zero positions closest to envelope peaks were attributed to reflections occurring at the cartilage surface and cartilage–bone interface.

In each method, TOF was defined as the duration (Δt) between peaks or zero positions, corresponding to the travel time of the ultrasound pulse back and forth between the cartilage surface and cartilage–bone interface of the specimen.

Cross-correlation method

The cross-correlation method was performed after the procedures previously described [21], in the following manner. A flat, smooth, stainless steel board was set in the water tank using the same settings as those for RF signal acquisition of the osteochondral sample, and the reflected ultrasound wave signal was acquired (Fig. 4a). A wave set of 1000 sampling data, covering the reflected steel ultrasound wave, was extracted as a reference signal, and the cross-correlation coefficient was calculated at each point of the osteochondral RF signal from the porcine sample (Fig. 4b). Peaks for the absolute value of the cross-correlation coefficient were attributed to reflections occurring at the cartilage surface and cartilage–bone interface. TOF was defined as the duration (Δt) between peaks, as in the amplitude-related methods.

Microscopic optical thickness measurement

For measurement of cartilage thickness, direct optical measurement using microscopy of the cross-section of the

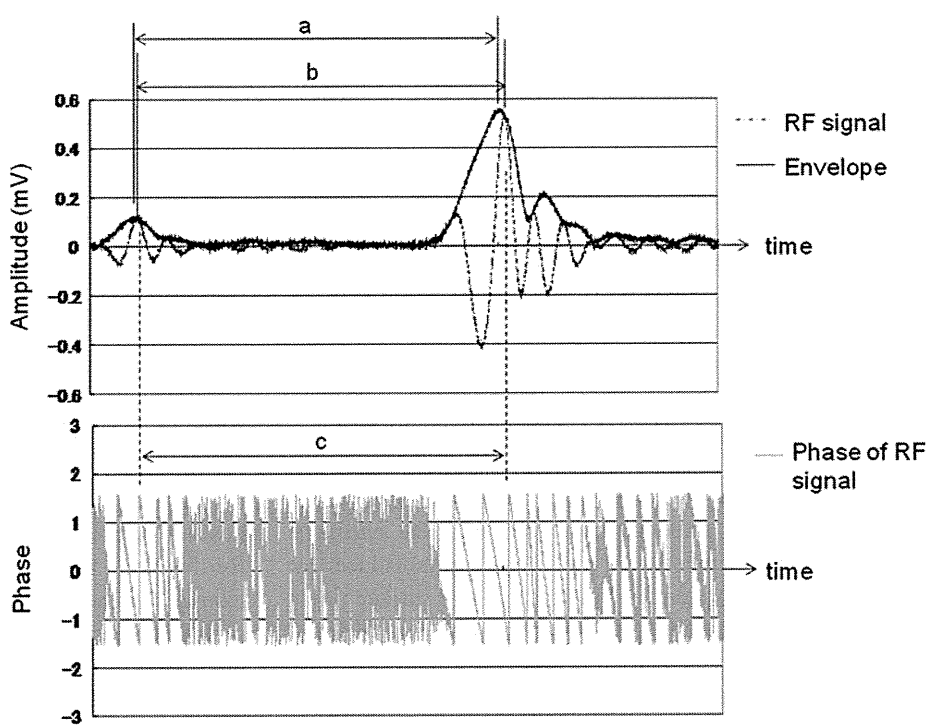

Fig. 3 Graphs show examples of the radiofrequency (*RF*) signal wave, envelope wave, and signal phase calculated from the RF signal. Time of flight measured with amplitude-related methods was defined as the duration between peaks of (**a**) RF signal (peak amplitude method), (**b**) envelope wave (peak envelope method), or (**c**) zero positions closest to the envelope peaks (signal phase method)

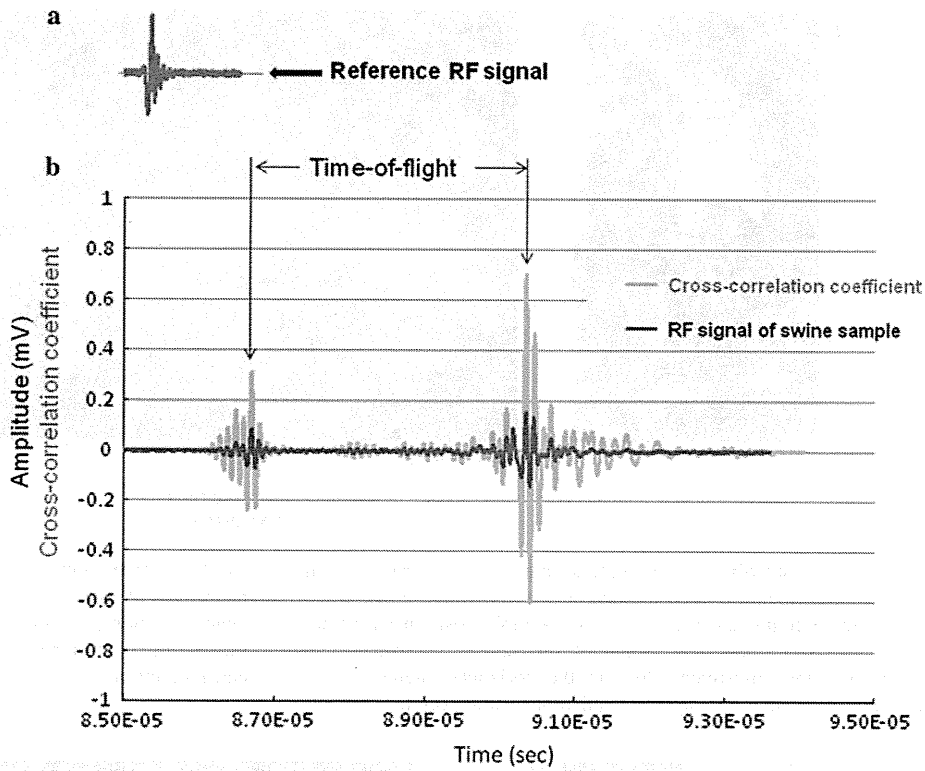

Fig. 4 Graphs showing examples of time-of-flight measurement from peaks of cross-correlation coefficients. **a** Reflected radiofrequency (*RF*) signal wave from a flat metal board was acquired as a reference RF signal. **b** Cross-correlation coefficient was calculated at each point of the osteochondral RF signal from the porcine sample. Time-of-flight measured was defined as the duration between peaks of the absolute value of the cross-correlation coefficient

sample was performed. The sample holder with the osteochondral sample was attached to the holding arm of a diamond saw device (Minitom; Struers, Ballerup, Denmark), such that the saw blade was vertical to the top surface of the sample holder and parallel to the x-axis of the sample coordinate. By adjusting the position of the arm with an accuracy of 10 μm, three cut planes were created, each containing three RF signal acquisition points. Cartilage thickness (T_c) was measured using an optical measuring microscope (30× magnification) (MM-400; Nikon, Tokyo, Japan) containing an eyepiece with adjustable crosshairs with an adjustable stage system (MHS 2 × 2; Nikon) as the sample table, which contained two micrometers with a digital recorder for sample position adjustment by parallel movement (x–z plane of the sample coordinate and a micrometer for sample rotation adjustment (θxz) in the horizontal plane (Fig. 5a). With this optical measuring microscope and the stage, the sides of the sample holder, which were parallel to the direction of the ultrasound beam in RF signal acquisition, were aligned parallel to the direction of thickness measurement (z-axis direction of the sample coordinate). The center point of the sample holder, which was concentric with the sample, was identified by measuring the distance from the sides of the sample holder (x-axis direction of the sample coordinate), and then the RF signal acquisition points were identified in a similar manner by measuring the distance from the center point. T_c along the beam direction (z-axis direction) was measured at each RF acquisition point by moving the crosshair pointer from the cartilage surface to the bone-cartilage interface (Fig. 5b). The SOS in cartilage (S_c) at each point was calculated by

$$\mathrm{Sc} = \frac{2\mathrm{Tc}}{\Delta t} \quad (1)$$

To validate the optical thickness measurement, micro-CT scanning (Scan Xmate-E090; Comscantecno, Yokohama, Japan) was performed after thickness measurement. A 1-mm-thick slice sample from each pig was positioned in the cylinder holder (Fig. 6a). To keep the sample moist, the bottom of the cylinder was filled with normal saline, and the top was sealed. The scanning condition for CT was 70 kV and 70 μA, with a slice thickness of 21.8 μm (matrix size, 512 × 512 pixels; pixel width, 21.8 μm × 21.8 μm). The region of interest was large enough to include the entire osteochondral sample. Micro-CT image data were imported to image analysis software (TRIBONE/3DVIEW; Ratoc Engineering System, Tokyo, Japan). Multi-plane reconstruction was performed to acquire a cut surface plane image that included three RF signal acquisition points (Fig. 6b). The center of the sample was identified by measuring the distance from both sides of the sample, and then RF signal acquisition points were identified in a similar manner by measuring the distance from the center point. Thickness of the cartilage according to micro-CT (T_c-CT) was defined as the distance from the RF signal acquisition

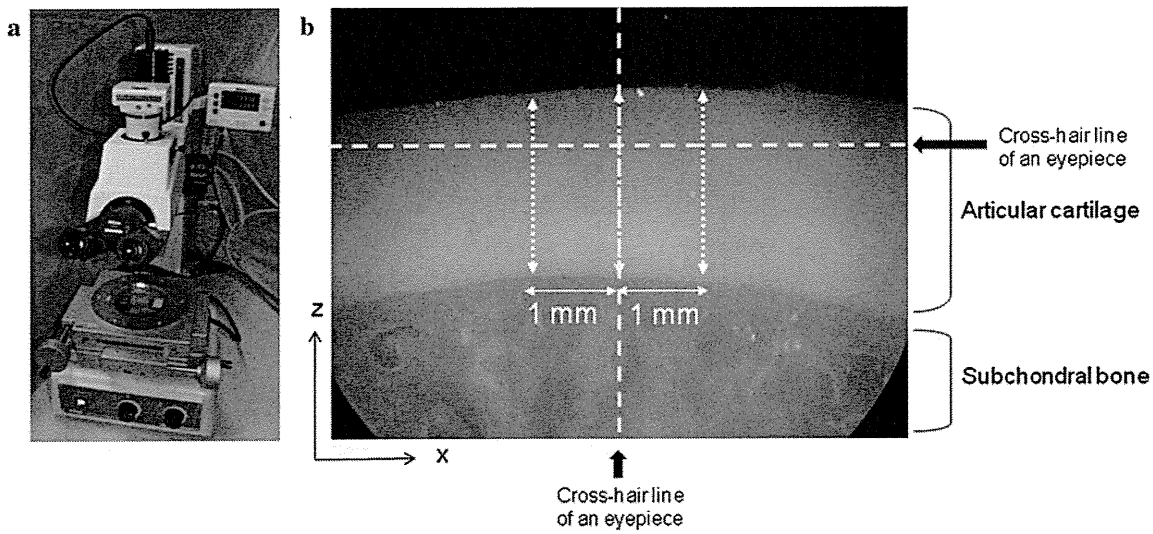

Fig. 5 Image showing (**a**) an optical measuring microscope and (**b**) cartilage thickness measurement using the microscope. **a** The sample table contained micrometers for sample position adjustment by parallel movement (x–z plane of the sample coordinate) and sample rotation adjustment (θxz) in the horizontal plane. **b** After registration of the RF signal acquisition points on the articular cartilage, three cut planes were created, each containing three measurement points. Cartilage thickness was measured along the beam direction (the z-axis direction) at each RF acquisition point by moving the crosshair pointer from the cartilage surface to the bone–cartilage interface

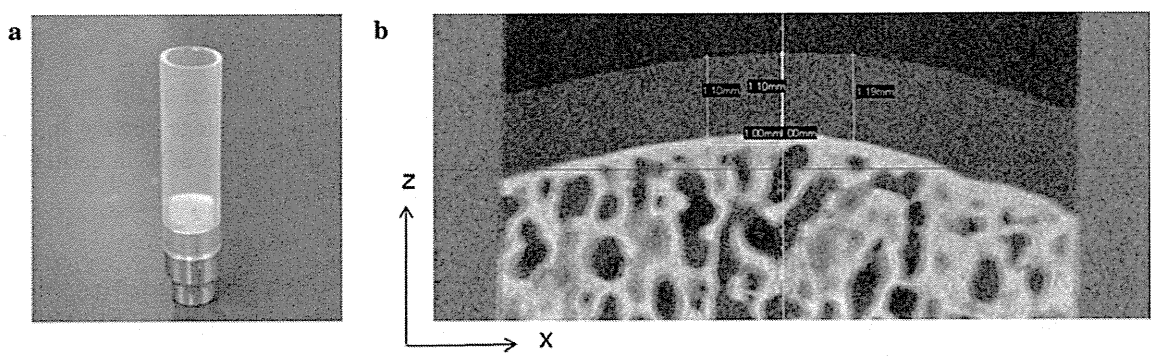

Fig. 6 Image showing (**a**) an osteochondral sample in the cylinder holder and (**b**) cartilage thickness measurement using a micro-CT image

point at the cartilage surface to the cartilage–bone interface parallel to the sides of the sample holder; this distance was measured using the software.

Statistical analysis

Mean and standard deviation (SD) were calculated for S_c and T_c in each sample. To investigate differences between the amplitude-related methods and the cross-correlation method, paired t testing was performed to compare S_c values for each amplitude-related method with that for the cross-correlation method in each sample. To evaluate the accuracy of T_c measurement, Pearson's correlation analysis was used to evaluate correlations between T_c and T_c-CT. Statistical analysis was performed using SPSS Statistics version 17.0 software (SPSS, Chicago, IL, USA), and results were considered significant for values of $p < 0.05$.

Results

In all RF signals at the nine points in each sample, peaks of the reflected ultrasound wave envelopes from the cartilage surface and the cartilage–bone interface were clear enough to be identified. Mean cartilage thickness (T_c) was 2.567 ± 0.084 mm for the 6-month-old pig and 1.161 ± 0.037 mm for the 3-year-old pig. Mean SOSs of cartilage (S_c) from the 9-point measurement by the four TOF methods were 1488 ± 51, 1488 ± 48, 1487 ± 54, and 1466 ± 51 m/s (for peak amplitude, peak envelope, signal phase, and cross-correlation methods, respectively) for the 6-month-old pig, and 1709 ± 107, 1717 ± 104, 1713 ± 105, and 1695 ± 138 m/s, respectively, for the 3-year-old pig (Fig. 7). Paired t testing showed no significant difference between S_c values from the amplitude-related methods and those from the cross-correlation method (6-month-old pig,

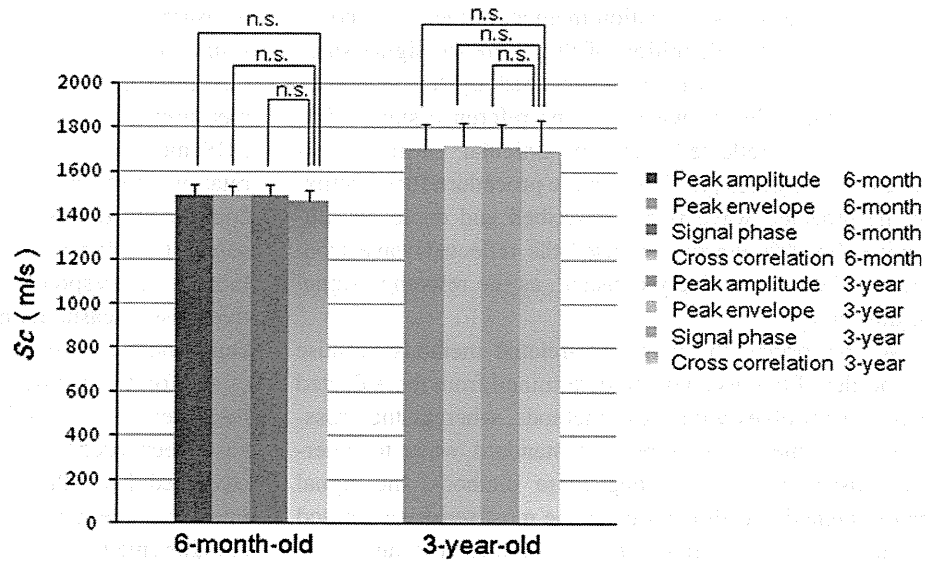

Fig. 7 Graphs showing mean values for speed of sound (S_c). Differences between each S_c value from amplitude-related methods and the cross-correlation method are not significant (*n.s.*)

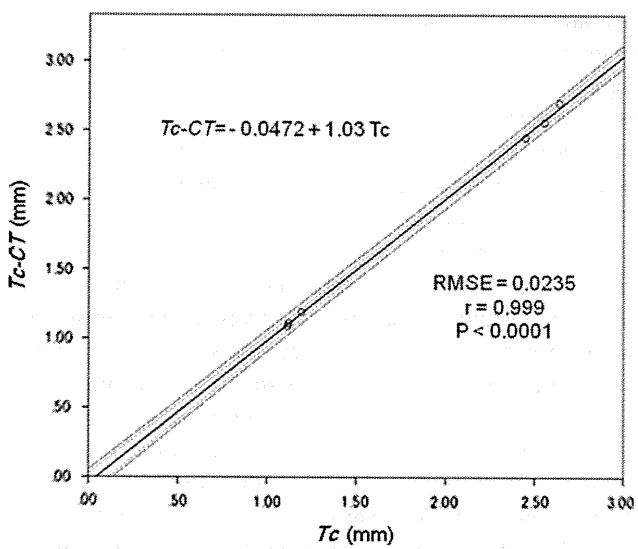

Fig. 8 Correlation between T_c and T_c-CT using samples from a 6-month-old pig and a 3-year-old pig. 95% confidence intervals for the regression (*short dashes*) and population (*long dashes*) are shown

$p = 0.176$, 0.192, 0.227; 3-year-old pig, $p = 0.649$, 0.558, 0.662; peak amplitude, peak envelope, and signal phase methods, respectively), although S_c values tended to be higher from amplitude-related methods than from the cross-correlation method.

A significant linear correlation was seen between T_c and T_c-CT [$r = 0.999$; 95% confidence interval 0.990–0.999; root mean square error (RMSE), 0.0235 mm; $p < 0.0001$] (Fig. 8). The slope was 1.03 with an intercept of 0.0472 mm (not significantly different from 0, $p = 0.154$).

Discussion

Recently, acoustic methods to evaluate articular cartilage degeneration have been widely investigated. An intra-articular probe with a diameter of 1 mm has been developed and applied clinically, and is reportedly capable of detecting changes in acoustic properties of the cartilage due to degeneration [27, 28]. Moreover, an animal study disclosed that acoustic parameters play an important role in the evaluation of surgically repaired cartilage [29].

In addition to ultrasound parameters, such as reflection coefficient, attenuation, backscatter, and roughness index [4, 28, 30], SOS of articular cartilage has been considered a candidate parameter for detecting cartilage degeneration [13] since values depend on the tissue structure and composition [16]. Past animal studies [30, 31] have shown that SOS decreases in chemically induced degenerative articular cartilage. However, since the TOF method could theoretically influence SOS values and no study to date has compared differences in SOS values derived from different TOF methods, we performed SOS measurements for articular cartilage using ultrasound amplitude-related methods for TOF measurement as well as the cross-correlation method and compared the results.

Ultrasound waves are divided into an incident wave and a reflected wave at the border of materials with different acoustic impedance. When the border of materials is to be identified by RF signals, the point with the largest amplitude reflected wave can generally be considered as the border location. However, since the reflected wave is the cumulative wave of all waves returning from the border, simple information on amplitude can potentially cause errors. The cross-correlation method [15, 22] and amplitude-related methods [10, 23] have thus been used in past

studies. In the cross-correlation method, in fact, TOF could be affected by the definition of the reference signal since the border of the tissue is determined by the similarity between the reflected wave and the reference signal. The representative reflected wave of articular cartilage was used in past studies [15, 22], but the procedure for selection of the reflected wave is not described and could be subjective. For this reason, we used the reflected wave from metal, which is relatively constant, as the reference signal in this study.

We performed the amplitude-related methods because the border of tissues could be determined from the reflected waves themselves with these methods, whereas the cross-correlation method required the standard wave to determine tissue borders. Among these methods, the signal phase method was thought to be the most sensitive method for determining the tissue border because the analytical signal phase of the RF signal was calculated through complex transformation in this method. However, the results exhibited almost equal values among amplitude-related methods, and we believe the peak envelope method and the peak amplitude method, which require only very simple procedures, can be used equivalently in this setting.

The results of this study revealed that SOS did not differ significantly between each amplitude-related method and the cross-correlation method in either porcine sample. Although S_c values tended to be highest with the peak envelope method and lowest with the cross-correlation method, differences in mean values between methods were as small as about 1.5% in both samples. Since the cross-correlation method has been considered one of the standard methods of detecting borders by ultrasonography [21], SOS measured by amplitude-related TOF methods could be considered relatively accurate. In fact, SOS values in our study were relatively compatible with a past study (1580 m/s) [15] on cartilage SOS in several species, including porcine cartilage.

Several factors are likely to influence SOS measurement values. Firstly, particularly in amplitude-related TOF measurement methods, sharp peaks of RF signals from the cartilage and cartilage–bone interface are crucial. To achieve this, transmitter ultrasound waves must hit the sample surface or interface as perpendicularly as possible [20]. The cartilage surface must also be as close as possible to the transducer focus. We concentrated on measuring TOF by meeting these conditions in our study. Secondly, accurate registration of points between RF signal acquisition and optical thickness measurement is important. We used a customized assembly in a water tank with an adjustable stage for RF signal acquisition and a cutting device with accurate plane adjustment. In addition, the customized acrylic sample holder that enabled us to detect the direction of the ultrasound beam in microscopic measurement could achieve registration between ultrasound beam direction and microscopic measurement direction. Under these conditions, amplitude-related TOF measurement methods were assumed to be as applicable to SOS measurement in articular cartilage as the cross-correlation method. However, since large variance in SOS could result unless the orthogonal orientation of the ultrasound transducer axis to the cartilage surface and the location correspondence of each of the ultrasonic and thickness measurement points are achieved [20], these conditions could be critical for SOS measurement.

As for the measurement of cartilage thickness, direct measurement [13, 23] and the needle probe method [23] have been used. In the needle probe method, a needle is advanced from the cartilage surface, and cartilage–bone interfaces are detected by the load–displacement curve. Another method that uses ultrasound is the in-situ calibration method [15, 17], in which cartilage is compressed by a mechanical testing machine and cartilage thickness is calculated from displacement of the compression probe and the temporal shift in the reflected ultrasound wave. We adopted optical measurement as the simplest and most direct method in this study.

The crucial point in cartilage thickness measurement for calculating SOS is whether the cartilage–bone interface can be identified. At the cartilage–bone interface, the material properties of articular cartilage change rapidly [23], and ultrasound reflection should occur. Whether the optical border corresponds to a material property border should thus have been confirmed. The results showed that thicknesses determined by optical measurement and micro-CT measurement corresponded well to each other. Since the resolution of micro-CT was as small as 21.8 μm × 21.8 μm × 21.8 μm, we believe that optical thickness measurement of articular cartilage was very accurate in our setting. The difference in cartilage thickness between the 6-month-old pig (2.6 mm) and the 3-year-old pig (1.2 mm) seemed compatible with a past animal study [32], which showed that the thickness of rat articular cartilage decreased significantly during maturation.

Several factors could have affected S_c differences between the 6-month-old pig (1466–1488 m/s) and the 3-year-old pig (1695–1717 m/s), such as composition [12, 17], material properties [12, 18], and orientation of collagen fibrils [19]. These factors might have caused the changes in acoustic properties with age, as also observed in a study using rat articular cartilage [32], in which apparent integrated backscatter of RF signals was significantly smaller in 5-week-old rats than in 11-week-old rats. Bhatnagar et al. [33] showed that thickness and cellularity of articular cartilage decreased as pigs aged. Our results were compatible with that report on cartilage thickness differences at different ages, and differences in the

proportion of cellularity and matrix of articular cartilage could have affected the differences in SOS in our study. Further studies are needed to investigate the effects of age on SOS using a larger number of animal or human samples.

Since SOS in human cartilage reportedly displays relatively similar values (1580 m/s [15], 1658 m/s [13], 1892 m/s [14]) to the present results, we believe that measurement of SOS in human cartilage in vitro using amplitude-related methods as well as the cross-correlation method is feasible when a wave is clearly reflected from cartilage. In fact, the amplitude-related methods could be beneficial in that they do not require the standard wave and thus can be considered to be very objective. Our results also suggest that the method of TOF measurement should be considered and described in a study measuring SOS in living tissue, such as articular cartilage.

Conclusion

SOS of articular cartilage of the porcine femoral condyles was measured using the amplitude-related methods and the cross-correlation method. Although there was no significant difference between them, the SOS values measured by the cross-correlation method tended to be smaller than the results measured by the amplitude-related methods. These results suggest that the amplitude-related methods of TOF measurement and the cross-correlation method are equivalently applicable to articular cartilage SOS measurement when a wave is clearly reflected from cartilage. TOF methods should thus be considered in studies on SOS measurement.

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Conflict of interest Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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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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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

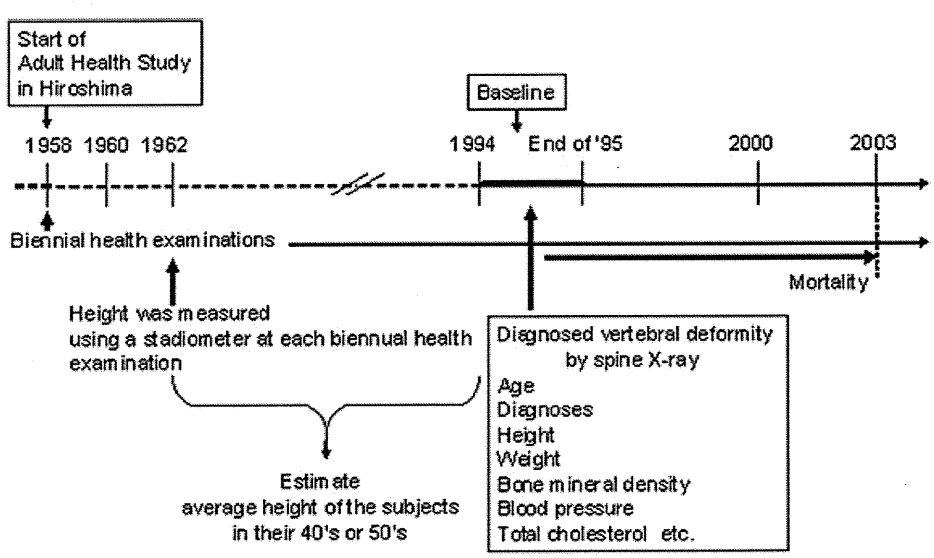

Fig. 1. Timeline of the study.

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 ± 8.9 years, and 70.3 ± 9.1 years for the death group, ranging from 47 to 91 years. In women, mean ages were 64.7 ± 9.1 years and 73.5 ± 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

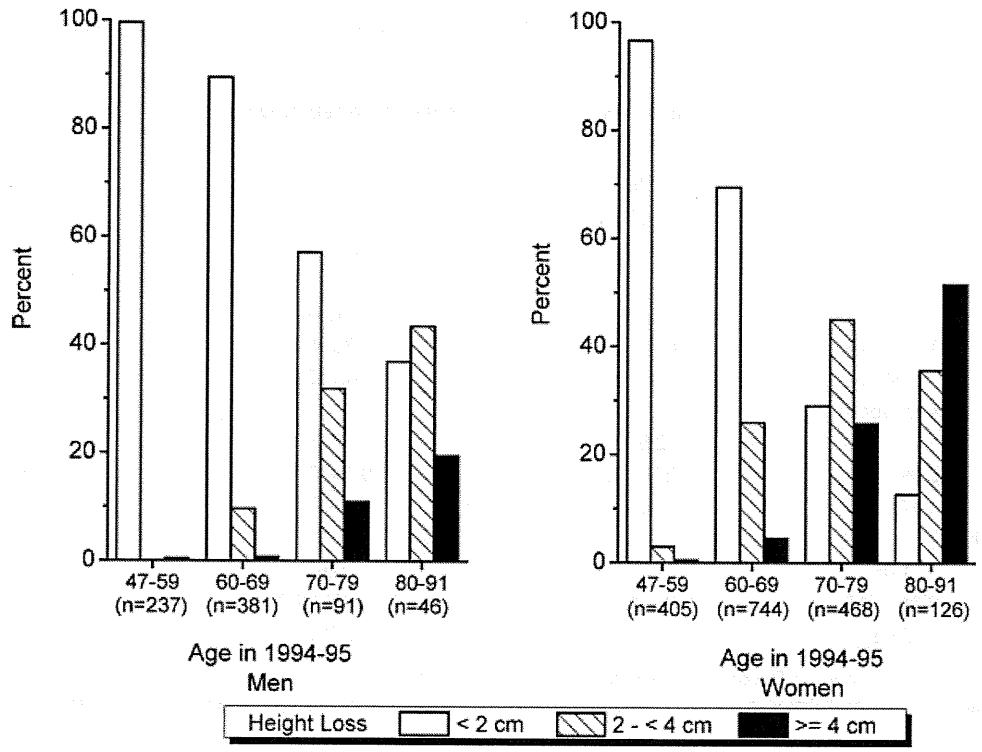

Fig. 2. Percentage of those with height loss starting in middle age, for men and women.

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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