Journal of Bone and Mineral Metabolism (2019) 37:161–170
https://doi.org/10.1007/s00774-018-0910-7

ORIGINAL ARTICLE

Does Trabecular Bone Score (TBS) improve the predictive ability of FRAX® for major osteoporotic fractures according to the Japanese Population-Based Osteoporosis (JPOS) cohort study?

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Received: 6 July 2017 / Accepted: 23 January 2018 / Published online: 21 February 2018

Abstract

This study examined whether bone microarchitecture determined by Trabecular Bone Score (TBS) is associated with the risk of major osteoporotic fractures independent of FRAX® in Japanese women. Participants included 1541 women aged ≥ 40 at baseline. Major osteoporotic fractures during a 10-year follow-up period were documented by the Japanese Population-based Osteoporosis Cohort Study. TBS and areal bone mineral density (aBMD) were calculated for the same spinal regions at baseline. To compare the predictive ability of FRAX® model when used alone versus in combination with TBS, Akaike information criterion (AIC), the area under the receiver operating characteristic curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were calculated. We identified 67 events of major osteoporotic fractures. The skeletal sites of the first fracture event were as follows: hip (11), vertebrae (13), radius (42), and humerus (1). The model incorporating FRAX® [1.35 (95% CI 1.09–1.67) for 1 standard deviation (SD) increase] with TBS [1.46 (95% CI 1.08–1.98) for 1 SD decrease] demonstrated better fit compared to a model consisting of FRAX alone (AIC 528.6 vs 532.7). NRI values for classification accuracy showed significant improvements in the FRAX® and TBS model, as compared to FRAX® alone [0.299 (95% CI 0.056-0.541)]. However, there were no significant differences in AUC or IDI between these models. The TBS score is associated with a risk of major osteoporotic fracture independent of FRAX® score obtained with or without BMD values among Japanese women during a 10-year follow-up period.

Keywords Trabecular Bone Score (TBS) · FRAX® · Japanese women · Prospective cohort study · Major osteoporotic fracture

Introduction

The FRAX® fracture risk assessment tool, developed by the World Health Organization (WHO) [1, 2], is important in clinical decision-making in primary care and community health settings. FRAX® tools have been developed for different countries and ethnicities, and are currently available in 52 countries (http://www.shef.ac.uk/FRAX/tool.jsp?lang). FRAX® is used widely for fracture risk assessment, based on clinical risk factors, with or without measurement of femoral neck (FN) areal bone mineral density (aBMD). FRAX® includes only aBMD as a skeletal measurement, and does not incorporate any other measurements of bone strength. It is, however, widely accepted that aBMD alone is not sufficient for the prediction of fracture risk [3].

A recently developed analysis technique, trabecular bone score (TBS), has made it possible to assess spinal

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microarchitecture status using the same X-ray images as those used for measurement of aBMD [4]. TBS is a gray-level texture measurement that can be applied to X-ray images, including dual-energy X-ray absorptiometry (DXA) scans, to quantify local variations in gray level within the images [4, 5]. This technique, although not a direct physical measure of bone microarchitecture, has been reported to correlate with three-dimensional parameters of bone microarchitecture in human cadavers [4]. There is also a significant correlation between spine TBS and compression stiffness of human vertebrae [6]. A prospective cohort study [7] has shown that lower TBS values are associated with a higher risk for vertebral fractures, independent of BMD or other clinical risk factors. Recently, a meta-analysis on prospective population-based cohorts has indicated that TBS is a significant predictor of fracture independent of FRAX® [8].

The purpose of this study was to describe the predictive ability of applying TBS as an adjustment for the Japanese version of FRAX® for the 10-year probability of major osteoporotic fractures among Japanese women using the Japanese Population-Based Osteoporosis (JPOS) Cohort Study.

Materials and methods

Setting and follow-up study

Details of the JPOS study have been described elsewhere [9–11]. This study randomly selected subjects from 5-year age groups (age range, 15-79 years) using resident registrations from seven municipalities within Japan. Of the 4550 women selected, 3985 women (87.6%) completed the baseline survey in 1996. The participants from five municipalities were selected as subjects of the cohort study (Fig. 1). We conducted four follow-up surveys in 1999, 2002, 2006, and 2011 or 2012. Two of the four municipalities were invited to participate in all follow-up surveys, and the other two, in the 15-year follow-up survey in 2011 only. Participants from Miyakojima were included in the first three follow-up surveys; the latest follow-up survey in Miyakojima was the 10-year follow-up survey.

Among the 1984 participants aged 25 years or older at the baseline survey from four regions, 158 were excluded due to their inability to be located, institutionalization, hospitalization, or death (Fig. 1). We attempted to conduct the 15-year follow-up survey in four regions in 2011. However,

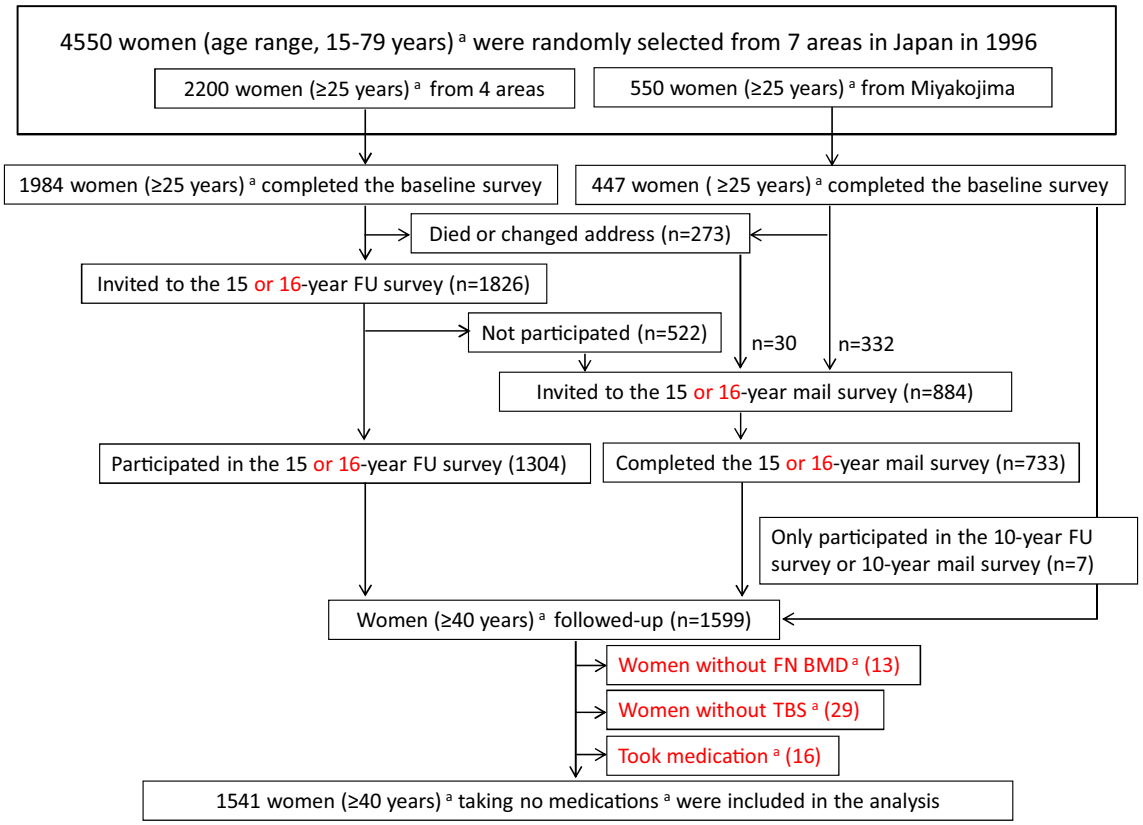

Fig. 1 Subject flow diagram. *FU* follow-up, *FN aBMD* areal bone mineral density at the femoral neck, *TBS* trabecular bone score, *Fx* fracture events. Values in the parentheses represent numbers of subjects. [a]At the baseline survey

the follow-up survey for one of the four regions was postponed until 2012 due to the Great East Japan Earthquake. As a result, a total of 1304 (71.4%) participants among 1826 invited subjects from four regions completed the 15 or 16-year follow-up survey (Fig. 1).

Study population

A questionnaire on osteoporotic fracture events was mailed to women in the four regions who did not participate in the 15 or 16-year follow-up survey (Fig. 1). Mail surveys were also conducted for baseline participants in Miyakojima in 2012 (Fig. 1). Participants were excluded if they did not have FN aBMD measurements or TBS values at baseline, or if they were taking osteoporosis drugs at baseline. From 1599 women aged 40 years or older at baseline whose responses regarding the fracture event (yes/no) were obtained during a period of 10 years from the baseline survey, 1541 were selected for inclusion in the final analysis (Fig. 1).

The study protocol was approved by the Ethics Committee of the Kinki University School of Medicine. Written informed consent regarding all study procedures was obtained from each participant prior to baseline and follow-up studies.

Ascertainment of major osteoporotic fractures

Clinical fractures were defined as fractures that were painful and diagnosed by a medical doctor using radiographic reports. Information on fracture events included fracture location, time of fracture event, situation in which the fracture occurred, and X-ray diagnosis of the fracture (yes or no). Data were obtained via questionnaires that were conducted during trained public health nurse interviews in each follow-up survey of the JPOS study. Additional data were provided by trained staff interviews in mail surveys. A major osteoporotic fracture was defined as a clinical fracture of the hip, vertebra, distal forearm, or proximal humerus that occurred without strong external force (e.g., caused by falls on a flat surface). We did not include fractures that occurred during sport activities. The first fracture that occurred during the 10-year follow-up period was used for analysis in the case of multiple fractures because FRAX® scores estimate the 10-year probabilities of major osteoporotic fractures and hip fractures.

Bone density characteristics and prevalent vertebral fractures at baseline survey

Details of aBMD measurements have been described elsewhere [9, 10]. Briefly, FN and lumbar spine (LS) aBMD were measured by DXA at the baseline survey (QDR4500A, Hologic, Bedford, MA, USA). The in vivo short-term precision (coefficient of variation [CV]) of the aBMD measurements was 1.6 and 1.1%, respectively. Values for LS aBMD were calculated for the first to fourth vertebrae using densitometric software (version 8.16, Hologic Inc., Bedford, MA, USA).

Digital lateral radiographs were used to assess the prevalence of vertebral fractures at baseline. The anterior, posterior, and central heights of each vertebra (T4 to L5) were determined using bone morphometric software (QDR4500A Lateral Image Analyze, Hologic Inc., Bedford, MA, USA). The McCloskey–Kanis criteria were applied in the diagnosis of vertebral fractures [12].

Trabecular Bone Score calculations

Details of TBS calculations have been described elsewhere [4, 5, 7]. Measurements of LS TBS at the baseline survey were obtained via DXA scans using TBS iNsight software (Version 1.9.2., Med-Imaps, Bordeaux, France), under conditions in which the investigator did not know subject outcomes. The CV of the TBS calculations was 1.75% [7].

Body size measurements

Body height and weight at baseline were measured using an automatic scale (TK-11, 868 h, Takei Kagaku, Tokyo, Japan) and used for the calculation of FRAX® scores.

Fracture risk calculation using FRAX®

To calculate FRAX® scores (FRAX® -estimated probability of osteoporotic fracture), the following information about the clinical risk factors for osteoporotic fractures was obtained via baseline survey questionnaires: history of fracture events, disease history, prescribed medications, smoking and drinking habits, and participant's mother's history of fractures that occurred at age ≥ 50 years. Trained public health nurses conducted detailed interviews to confirm each participant response to the questionnaire during follow-up surveys of the JPOS study.

This study used FRAX® Version 3.8 for Japan to calculate the 10-year probabilities of major osteoporotic fractures and hip fractures. The Japanese version of FRAX® was constructed as reported by Fujiwara et al. [13]. Information collected about each participant's mother's history of hip fractures that occurred at age ≥ 50 years was used as familial history of hip fracture. The criterion of "daily alcohol consumption" was substituted for "alcohol intake greater than or equal to three drinks per day", as the information was obtained regarding the frequency of alcohol intake per week, and not the unit size of ethanol intake.

Data on osteoporosis medications during follow-up

Data on medications for osteoporosis was obtained through a questionnaire item, which inquired about medication for osteoporosis (yes/no), and in case of "Yes", it inquired about the type of medicine and prescription period (year and month) in every follow-up survey. The answers to this questionnaire item were inspected and supplemented via interviews by trained public health nurses in each follow-up survey of the JPOS study.

Statistical analysis

The Student's *t* test, or Chi-square test, was used to determine differences in characteristics and TBS values between subjects with or without fracture events. Logistic regression analysis was used to determine the model for prediction of osteoporotic fractures. We used the receiver operating characteristic curve (AUC), using a non-parametric method [14], as the standard measure of the predictive ability of the models. Akaike information criterion (AIC) values were used to examine the fitness of the models to the data [15]. Models with smaller AIC values were considered to fit the data significantly better when the difference in AIC values between the two models was > 1 [16]. Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were used for the supplemental measure of the goodness-of-fit of the models [17, 18].

We conducted a similar analysis in 1457 subjects after excluding subjects with BMI ≥ 30 kg/m^2 ($n = 73$) and those with BMI ≤ 17 kg/m^2 ($n = 11$) because overweight or underweight conditions may influence TBS measurements. Statistical analyses were performed using SPSS (version 14.0 J, SPSS, Tokyo, Japan) or SAS (release 9.30, SAS Institute, Cary, NC, USA).

Results

Osteoporotic fractures during the 10-year follow-up and participant characteristics

The major osteoporotic fracture events were confirmed in 67 subjects (hip, $n = 11$; clinical vertebrae, $n = 13$; forearm, $n = 42$; proximal humerus, $n = 1$) during the 10-year follow-up period (median follow-up time, 10.0 years; total person-years [PY], 15306 PY). The incidence rates of major osteoporotic and hip fracture events were 4.38 women/1000 PY and 0.72 women/1000 PY, respectively.

Characteristics of the 1541 women with and without major osteoporotic fracture incidents are shown in Table 1. Women who experienced major osteoporotic fractures had significantly lower TBS values than those without fractures (Table 1). Women who experienced hip fractures were significantly older, lighter, and shorter. Compared to those without fractures, those who experienced hip fractures had significantly lower FN and LS aBMD, a higher frequency of secondary osteoporosis, significantly lower TBS values (1.083 ± 0.774 vs. 1.185 ± 0.117, $p = 0.040$), and higher FRAX® scores (including FN aBMD, 7.0 vs. 1.2%, $p = 0.032$; without FN aBMD: 6.7 vs. 1.5%, $p = 0.011$). Except for the above, there were no statistically significant differences in the distributions of the characteristics or prevalence of clinical risk factors between the two groups.

There were significant inverse correlations between TBS and both age ($r = -0.70$, $p < 0.001$) and FRAX®-estimated probability ($r = -0.59 \sim -0.415$, $p < 0.001$ for all). There were significant positive correlations between TBS and aBMD at both FN and LS (FN: $r = 0.591$, $p < 0.001$; LS: $r = 0.70$, $p < 0.001$). Women with secondary osteoporosis and previous fragility fractures showed significantly lower TBS values than those without (1.139 ± 0.106 vs. 1.187 ± 0.117, $p < 0.001$; 1.108 ± 0.108 vs. 1.191 ± 0.115, $p < 0.001$, respectively).

Comparison of logistic regression models for the use of FRAX® alone versus FRAX® with TBS

Incidence rates of major osteoporotic fracture were classified into TBS tertile groups within three FRAX® score groups (≤ 4.9, 5–9.9, ≥ 10%), as shown in Fig. 2. Without FN aBMD, the incidence rate in the ≥ 10% FRAX® score group with high TBS scores tended to be lower than that in the 5.0-9.9 FRAX® score group with low TBS scores (Fig. 2b).

The predictive abilities of the model including both FRAX® and TBS for major osteoporotic fractures and hip fractures are indicated in Table 2. A decrease in TBS score was significantly associated with an increased risk for major osteoporotic fractures. AUC values for predicting major osteoporotic fractures were not significantly different between models that incorporated both FRAX® and TBS versus those that used FRAX® alone (Model 1 vs. Model 3; Model 2 vs. Model 4, Model 5). AIC values indicated a significantly better fit for the data in models incorporating both FRAX® and TBS compared to models incorporating FRAX® alone (Model 1 vs. Model 3; Model 2 vs. Model 4, Model 5). NRI values showed a significant increase in classification accuracy achieved by models that incorporated both FRAX® and TBS versus those that used FRAX® alone for prediction of major osteoporotic fractures, while IDI values showed no significant increases (Model 1 vs. Model 3; Model 2 vs. Model 4, Model 5). Among 1457 participants with BMI between 17 and 30 kg/m^2, the TBS scores indicated statistical significance in the models shown in Table 2 although AUC values for predicting fractures were not significantly

Table 1 Participant characteristics from the baseline JPOS Study, 1996

Characteristics and clinical risk factors	($N = 1541$)	Subjects with major osteoporotic fracture event ($n = 67$)	Subjects without major osteoporotic fracture event ($n = 1474$)	p value
Age (year), mean (SD)	58.1 (10.6)	64.2 (9.8)	57.8 (10.6)	<0.001
Weight (kg), mean (SD)	54.5 (8.4)	54.1 (8.4)	54.5 (8.4)	0.715
Height (cm), mean (SD)	151 (5.8)	149.2 (6.1)	151.1 (5.8)	0.007
Body mass index (kg/m^2), mean (SD)	23.9 (3.4)	24.3 (3.2)	23.9 (3.5)	0.341
Femoral neck aBMD (g/cm^2), mean (SD)	0.707 (0.121)	0.636 (0.099)	0.710 (0.121)	<0.001
Lumbar spine aBMD (g/cm^2), mean (SD)	0.846 (0.167)	0.769 (0.152)	0.850 (0.166)	<0.001
Current smoking, No. (%)	61 (4.0%)	2 (3.0%)	59 (4.0%)	0.999
Daily drinking, No. (%)	64 (4.2%)	3 (4.5%)	61 (4.1%)	0.755
Secondary osteoporosis[a], No. (%)	89 (5.8%)	8 (11.9%)	81 (5.5%)	0.052
Rheumatoid arthritis No. (%)	11 (0.7%)	0 (0.0%)	11 (0.7%)	0.999
Oral glucocorticoid therapy[b], No. (%)	2 (0.1%)	0 (0.0%)	2 (0.1%)	0.999
Previous fragility fractures[c], No. (%)	139 (9.0%)	9 (13.4%)	130 (8.8%)	0.191
Familial history of hip fracture[d], No. (%)	40 (2.6%)	2 (3.0%)	38 (2.6%)	0.692
Treatment for osteoporosis during follow-up[e], No. (%)	127 (8.0%)	6 (9.0%)	121 (8.2%)	0.819
FRAX® obtained with FN aBMD (%), mean (SD)	6.9 (6.2)	10.8 (8.4)	6.7 (6.0)	<0.001
FRAX® obtained without FN aBMD (%), mean (SD)	7.1 (6.6)	10.8 (8.2)	6.9 (6.5)	<0.001
TBS, mean (SD)	1.184 (0.117)	1.122 (0.098)	1.187 (0.117)	<0.001

aBMD areal bone mineral density, *TBS* trabecular bone score

[a]Premature menopause (menopausal age < 45 years), type 1 diabetes mellitus, and hyperthyroidism without medical control for extended periods were included

[b]Oral glucocorticoid therapy which has the potency of prednisolone at 5 mg/day for more than 3 months

[c]Fracture of hip, vertebrae (including asymptomatic fractures), forearm, and proximal humerus, occurring without a strong external force at an age ≥ 20 years and before the baseline survey

[d]Study participant's mother's history of hip fractures that occurred after age 50

[e]Treatment for osteoporosis during follow-up was defined as taking bisphosphonates for six months or more ($n = 17$), vitamin D for two or more years ($n = 33$), hormone replacement therapy ($n = 66$), or selective estrogen receptor modulator ($n = 5$), and 17 participants who were followed by the mail surveys and took medications for osteoporosis

different in models that used both FRAX® and TBS and those that used FRAX® alone (not shown in the table).

For prediction of hip fractures, TBS scores were not significantly associated with an increased risk for fracture (Table 2). Neither IDI nor NRI values showed increases in the accuracy of the combined FRAX® and TBS model, as compared to FRAX® alone, for prediction of hip fractures. Among 1457 participants with BMI between 17 and 30 kg/m^2, the TBS scores for the prediction of hip fractures indicated no significance in either model, similar to those shown in Table 2.

Comparison of models in participants who did not take medications for osteoporosis during the 10-year follow-up period

The risk for fracture among women who did not take medications for osteoporosis during the 10-year follow-up period was investigated. A total of 1414 participants were included during the 10-year follow-up period, after excluding 127 participants who received bisphosphonates for six months or more ($n = 17$), vitamin D for two or more years ($n = 33$), hormone replacement therapy ($n = 66$), and selective estrogen receptor modulator ($n = 5$), and 17 participants who were followed via mail surveys and took medications for osteoporosis. Among these 1414 women, those who experienced fractures at the hip or other major osteoporotic fracture sites had significantly lower TBS values than those without fractures (1.077 ± 0.078 vs. 1.184 ± 0.115, $p = 0.003$, at the hip; 1.123 ± 0.093 vs. 1.186 ± 0.116, $p < 0.001$, at other sites). Those who experienced fractures had significantly higher FRAX® scores than those without fractures at both the hip and major osteoporotic sites ($p < 0.05$ for all).

Results in 1414 participants obtained by a similar analysis, as shown in Table 2, were similar to those in 1541 participants. TBS values were significantly associated with an increased risk for major osteoporotic fractures. OR (95% CI) for 1 standard deviation (SD) decrease in TBS in the same model 3, 4, and 5, as shown in Table 2, using 1414 participants was 1.43 (1.04, 1.96), 1.52 (1.12, 2.07), and 1.44

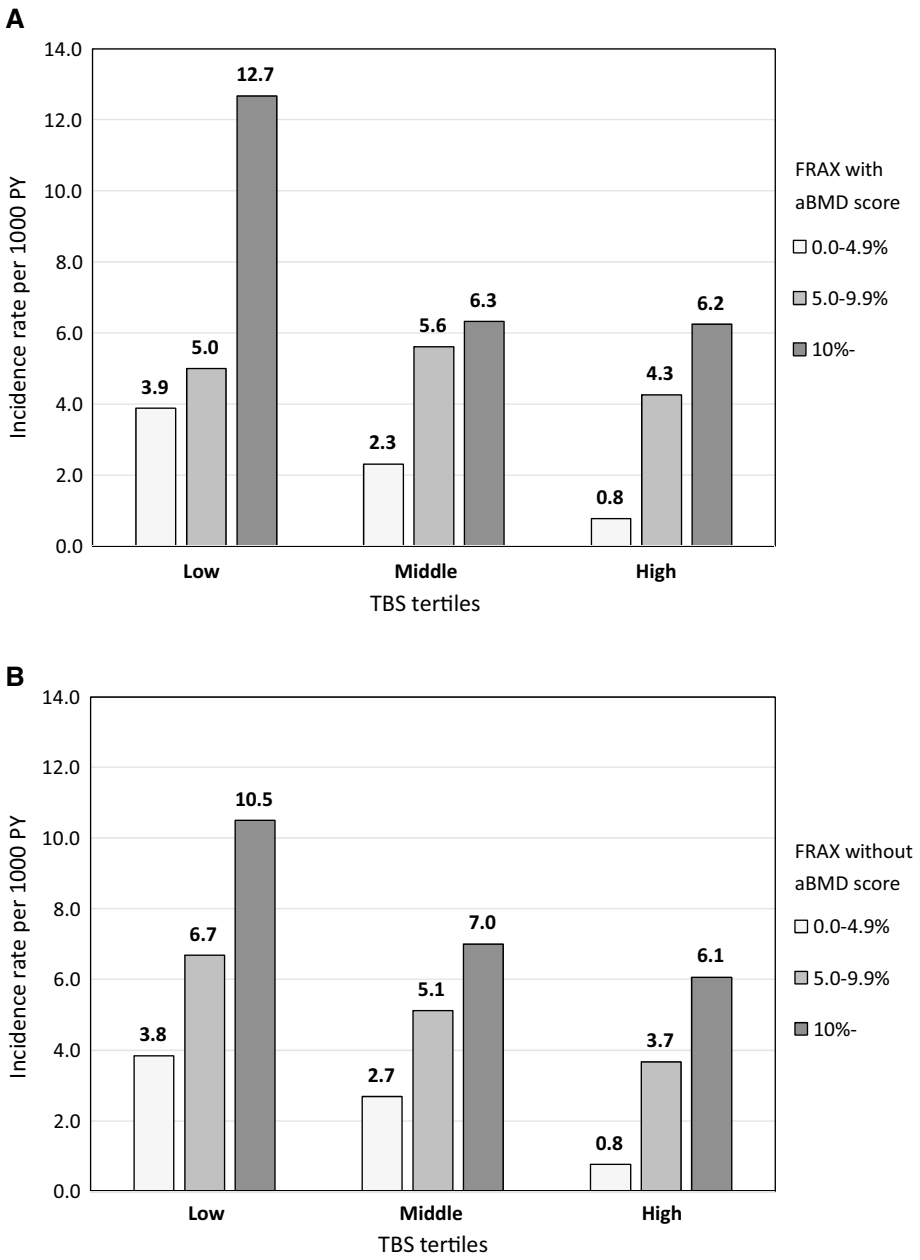

Fig. 2 Incidence rates for major osteoporotic fractures are classified into TBS tertile groups within three FRAX® score groups (≤ 4.9, 5–9.9, ≥ 10%). **a** FRAX® score obtained with areal bone mineral density (aBMD) at the femoral neck (FN). **b** FRAX® score obtained without FN aBMD. *PY* person-years, *TBS* Trabecular Bone Score

(1.01, 2.05), respectively. Regarding the comparison of the predictive ability of models using FRAX® alone and of those using both FRAX® and TBS with AUC, AIC, IDI, and NRI, the findings were quite similar to those shown in Table 2.

Discussion

The present study found that TBS can improve the predictive ability of the Japanese version of FRAX® for major osteoporotic fractures (hip, vertebra, distal forearm, or proximal humerus) in Japanese women. The strengths of this study include the random selection of women from geographically different areas of Japan and the relatively high follow-up rate regarding osteoporotic fracture incidents during the 10-year follow-up period. This study is the first to report that TBS could improve the predictive ability of FRAX® for major osteoporotic fractures in Japanese women.

A meta-analysis derived from 17,800 men and women in 14 prospective population-based cohort studies indicated that the gradient of risk (GR) for the FRAX® probability of major osteoporotic fractures resulted in a small increase when adjusted for TBS (GR, 1.70 vs. 1.76) [8]. In the meta-analysis, there were no statistically significant differences in GRs of TBS and FRAX® probabilities between men and women. However, our findings gave only better AIC and a

Table 2 Predictive ability for osteoporotic fracture incidents according to the receiver operative characteristics and reclassification analyses during the Japanese Population-Based Osteoporosis Cohort Study ($N = 1541$)

	Predictors	OR	AUC	AIC	IDI	NRI	IDI	NRI
Major osteoporotic fracture								
Model 1	FRAX® with FN aBMD	1.56 (1.30, 1.85)	0.681 (0.622, 0.740)	532.7	Reference	Reference		
Model 2	FRAX® without FN aBMD	1.51 (1.26, 1.81)	0.667 (0.606, 0.728)	536.3			Reference	Reference
Model 3	*Model*	1.50 (1.27, 1.76)	0.681 (0.622, 0.741)	528.6	0.002 (− 0.003, 0.007)	29.9 (5.6, 54.1)		
	FRAX® with FN aBMD	1.35 (1.09, 1.67)						
	TBS	1.46 (1.08, 1.98)						
Model 4	*Model*	1.49 (1.25, 1.78)	0.677 (0.617, 0.737)	530.3			0.004 (− 0.001, 0.009)	30.3 (6.0, 54.5)
	FRAX® without FN aBMD	1.30 (1.04, 1.61)						
	TBS	1.53 (1.14, 2.06)						
Model 5	*Model*	1.53 (1.28, 1.82)	0.675 (0.617, 0.734)	531.8			0.003 (− 0.001, 0.010)	25.0 (0.6, 49.3)
	FRAX® without FN aBMD	1.26 (0.997, 1.59)						
	LS aBMD	1.14 (0.79, 1.63)						
	TBS	1.44 (1.02, 2.03)						
Hip fracture								
Model 1	FRAX® with FN aBMD	1.81 (1.46, 2.26)	0.891 (0.833, 0.949)	111.1	Reference	Reference		
Model 2	FRAX® without FN aBMD	1.89 (1.47, 2.42)	0.874 (0.802, 0.947)	115.5			Reference	Reference
Model 3	*Model*	1.33 (1.12, 1.58)	0.856 (0.778, 0.934)	111.0 − 0.001 (− 0.009, 0.006)	37.5 (− 21.6, 96.5)			
	FRAX® with FN aBMD	1.69 (1.33, 2.14)						
	TBS	1.73 (0.82, 3.65)						
Model 4	*Model*	1.33 (1.14, 1.56)	0.844 (0.748, 0.940)	114.8			0.004 (− 0.0002, 0.008)	54.9 (− 2.2, 111.9)
	FRAX® without FN aBMD	1.73 (1.31, 2.27)						
	TBS	1.84 (0.88, 3.82)						

Table 2 (continued)

	Predictors	OR	AUC	AIC	IDI	NRI	IDI	NRI
Model 5	*Model*	1.40 (1.20, 1.62)	0.847 (0.759, 0.935)	115.9			0.008 (− 0.004, 0.020)	55.2 (− 1.8, 112.3)
	FRAX® without FN aBMD	1.60 (1.16, 2.20)						
	LS aBMD	1.56 (0.61, 3.98)						
	TBS	1.52 (0.63, 3.63)						

The numbers of major osteoporotic fractures and hip fractures were 67 and 11, respectively

FN femoral neck, *aBMD* areal bone mineral density, *TBS* trabecular bone score, *LS* lumbar spine, *AUC* area under the receiver operating characteristic curve; represented with the estimate and 95% confidence interval in parentheses, *AIC* Akaike information criterion, *IDI* integrated discrimination improvement, *NRI* net reclassification improvement, *OR* odds ratio of osteoporotic facture incident; estimated for each SD increase in FRAX® score (models 1, 2), and estimated for each SD decrease in LS aBMD and TBS, SD increase in FRAX® score, and SD increase in the estimated risk from multivariate models (Models 3, 4, and 5)

significant increase of NRI values of the model incorporating FRAX® with TBS than FRAX® alone, while there were no significant differences in AUC or IDI between those models. In another previous study regarding the predictive ability of FRAX® with TBS in a cohort study with Japanese men, IDI and NRI indicated significant improvements in the model using FRAX® and TBS compared to FRAX® alone [19]. The above findings in Japanese studies corresponded with those from a cohort study with Chinese men and women [20]. Significantly increased values of AUC, IDI, and NRI in the model with TBS-adjusted FRAX® compared to FRAX® alone were indicated only in men but not in women [20]. The authors wrote that those gender differences could be explained by lower BMD values and higher tendency to fall in women than in men [20]. Moreover, in our findings, the most frequent fracture site was forearm, where over 60% of all major osteoporotic fractures occurred; the number of clinical vertebral fracture was relatively small, approximately 20% of all fractures. On the other hand, in the cohort study with Japanese men, the most frequent type of fracture was the clinical vertebral fracture, with over 50% of 23 major osteoporotic fractures [19]. Most fractures of the hip and upper extremities including the distal forearm were reported to occur because of a fall [21].

As shown in Fig. 2b, without FN aBMD, the incidence rate of major osteoporotic fractures in the ≥ 10% FRAX® score group with high TBS scores (6.1/1000PY) was lower than that in the 5.0–9.9% FRAX® score group with low TBS scores (6.7/1000PY). These findings suggest that FRAX® scores, when calculated without TBS scores, may result in misclassification of low-risk women into a high-risk category. TBS may thus contribute to more accurate fracture risk assessment. NRI results suggest a significant increase among individuals who were correctly reclassified according to the reference model. However, there were no significant changes in AUC values between models using both TBS and FRAX® and those using FRAX® alone. Therefore, we acknowledge that discordant findings, in which only NRI results indicated significance, might be due to random chance or differences in calibration between the models. There were no significant increases in IDI values, which express the new model's improvement in average sensitivity without sacrificing average specificity. However, it is very difficult for a new model that includes an additional variable to yield significant AUC changes, as is typically the case [22]. TBS values have been reported to be associated with clinical risk factors, such as prior major fractures and recent glucocorticoid use [23].

The findings of this study indicate no significance results for the use of TBS for predicting hip fractures, though a meta-analysis reported models incorporating both TBS and FRAX® to be predictive of hip fractures induced a small increase of the GR [8]. Potential reasons for this discrepancy may be that a relatively small number of hip fracture events occurred in the current study [24].

The present study has several limitations. First, fracture events were self-reported, and not confirmed with data from medical records. Self-reported fractures have, however, been reported to be relatively accurate for forearm fractures, as well as vertebral and hip fractures [25, 26].

Second, the use of the patient's mother's history of hip fractures after age 50 for the familial history of hip fracture may have caused underestimation of the FRAX®-estimated probability. This potential underestimation would likely be low, as the incidence of hip fractures in men aged ≥ 50 years was approximately 70% lower than that of women in 1998 [27]. The substitution of "daily alcohol consumption" for "alcohol intake greater than or equal to three units per day" is believed to have little effect on our results, as the

percentage of women drinking more than three units per day would be very low. The percentage of Japanese women aged ≥ 40 years who consumed alcohol regularly was reported to be 6.7% in 1996 [28].

Third, the proportion of participants who were prescribed osteoporosis medications during follow-up was low. We acknowledge that we may have underestimated this figure, and the accuracy of this data could have been improved if we could verify the prescription data in the medication records of participants not only in the 15 or 16-year follow-up survey in 2011 and 2012, but also in the other follow-up surveys.

Finally, it is possible that false negatives may have occurred regarding the diagnosis of prior asymptomatic vertebral fractures, as X-ray absorptiometry was used during the baseline survey instead of conventional radiographic methods. Previous reports have indicated that there is relatively good agreement ($\kappa = 0.75$) between these two diagnostic methods [29].

This study found that combining TBS with the Japanese version of FRAX® may improve risk classification for prediction of major osteoporotic fractures among Japanese women, based on a sample that was randomly selected from geographically different areas of Japan during a 10-year longitudinal study. These findings suggest that combining TBS and FRAX® may be useful for screening and determining thresholds for therapeutic intervention in Japanese women.

Acknowledgements This study was conducted by the JPOS Study Group, consisting of Hideo Yoneshima (the head representative of the Study Group, ex-chairman of the Board of Directors, Medical Corporation Shuuwakai), Fumiaki Marumo (Chairman of the Study Group, Professor Emeritus, Tokyo Medical and Dental University), Toshihisa Matsuzaki (Co-Chairman of the Study Group, Institute of Comprehensive Community Care), Tomoharu Matsukura (Kanazawa University), Takashi Yamagami (Hokuriku Health Service Association), and Yoshiko Kagawa (the former president of Kagawa Nutrition University), along with the authors of this manuscript. Financial support for the baseline survey was provided by the Japan Milk Promotion Board and the Japan Dairy Council. Follow-up surveys were supported by Grants-in-Aid for Scientific Research (B #10470114, 1998–2000; B #14370147, 2002–2003; B #18390201, 2006-2008; C#18590619, 2006-9; B# 23390180, 2011-13; and C#23590824, 2011-13) from the Japanese Society for the Promotion of Science; a grant (2000–2002) from the Research Society for Metabolic Bone Diseases, Japan; and a Grand-in-Aid to study Milk Nutrition (2006) from the Japan Dairy Association. The authors wish to express special thanks to the personnel of the health departments of Miyako-jima City, Sanuki City, and Nishi-Aizu Town for their excellent support of the study. Finally, the authors would like to express their thanks to personnel from SRL, Tokyo, Japan; Toyo Medic, Osaka, Japan; and Toyukai Medical Corporation, Tokyo, Japan, for their technical assistance with the surveys.

Compliance with ethical standards

Conflict of interest Renaud Winzenrieth was a senior scientist at Medimaps at the time of the study. Junko Tamaki, Masayuki Iki, Yuho Sato, Etsuko Kajita, Sadanobu Kagamimori declare that they have no conflict of interest.

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