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ORIGINAL RESEARCH

Absolute Fracture-Risk Prediction by a Combination of Calcaneal Quantitative Ultrasound and Bone Mineral Density

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Abstract Quantitative ultrasound measurement (QUS) and bone mineral density (BMD) have each been shown to predict fracture risk in women. The present study examined whether a combination of QUS and BMD could improve the predictive accuracy of fracture risk. This is a population-based prospective study which involved 454 women and 445 men aged 62–89 years. Femoral neck BMD (FNBMD) was measured by DXA and calcaneal QUS was measured as broadband ultrasound attenuation (BUA) by a CUBA sonometer. Fragility fracture was ascertained by X-ray reports during the follow-up period, which took place between mid-1989 and 2009. During the follow-up period (median 13 years, range 11–15), 75 men and 154 women sustained a fragility fracture. In women, the model with FNBMD and BUA had a higher AUC compared to that without BUA (0.73 vs. 0.71 for any fracture, 0.81 vs. 0.77 for hip fracture, and 0.72 vs. 0.70 for vertebral fracture). Reclassification analysis yielded a total net reclassification improvement of 7.3%, 11.1%, and 5.2% for any, hip, and vertebral fractures, respectively. For men, the addition of BUA to FNBMD did not improve the predictive power for any, hip, or vertebral fracture. These results suggest that calcaneal QUS is an independent predictor of fracture risk and that a combination of QUS and BMD measurement could improve the predictive accuracy of fracture risk in elderly women.

Keywords Osteoporosis · Fracture · Ultrasonography · Bone mineral density · CUBA

Osteoporosis, with its consequent increased fracture risk, is increasingly recognized as a major public health concern, due largely to the rapid aging of the population worldwide. The lifetime risk of any fracture is about 44% for women and 30% for men aged over 60 [1]. Fragility fracture is associated with an increased risk of mortality [2, 3], and incurs significant health-care costs [4, 5]. Thus, there is a major need to identify high-risk individuals for earlier preventive intervention. Bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DXA) is currently the standard tool for assessing fracture risk. However, BMD is imperfect in the prediction of fracture risk, with a considerable overlap in BMD distribution between fracture and nonfracture groups [6–8]. This may be related to the fact that bone strength is determined not only by bone density but also by other skeletal properties such as bone elasticity and trabecular microarchitecture.

Quantitative ultrasound (QUS), as measured by broadband ultrasound attenuation (BUA, dB/MHz) and speed of

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sound (SOS, m/s), has been suggested to be reflective of bone structure parameters such as connectivity and spacing of trabeculae [9–11], in addition to bone density. Since its introduction in 1984 [12], various QUS devices have been developed for measuring bone status at different skeletal sites [13–16]. Most studies have focused on the calcaneus because it is easily accessible and rich in trabecular content. Several studies have examined the utility of QUS and its potential role in fracture-risk assessment. Both cross-sectional and prospective studies indicate that QUS at the calcaneus could identify those individuals at risk of fracture as reliably as BMD measured by DXA [17–21]. Moreover, the two modalities (QUS and BMD) do not identify precisely the same people, and in several studies calcaneal QUS was an independent predictor of fracture risk [22–24]. Although there is insufficient evidence to support the use of QUS in place of BMD, a combination of QUS and BMD may improve fracture-risk prediction over BMD alone. So far, few data exist to validate the assumption [24, 25] and no consensus has been reached.

The present study addressed a specific research question: whether a combination of calcaneal QUS and BMD measurements can improve the predictive accuracy of absolute fracture risk in men and women.

Study Design and Methods

Participants and Settings

Participants in the present study were drawn from the Dubbo Osteoporosis Epidemiology Study (DOES), a population-based prospective study of incidence and risk factors for fracture and chronic diseases. Full details of the population and study design have been described previously [26, 27]. Briefly, the DOES project commenced in 1989 in Dubbo, a city of ~32,000 people situated 400 km northwest of Sydney, Australia. The original study population was comprised of 1,581 men and 2,095 women aged ≥60 years, with 98.6% being Caucasian and 1.4% of indigenous Aboriginal background [26]; and recruitment has been continued into younger members of the Dubbo community. However, QUS assessment was not available until 1994. After excluding those with malignant disease and Paget disease of bone, 445 men and 454 women had both QUS and BMD measurements. All participants were aged between 62 and 89 years and had been followed for a median of 13 years (range 11–15) during the period of 1994 to 2009, a total of 8,045 person-years of follow-up. The study was approved by the St. Vincent's Hospital Ethics Committee, and written informed consent was obtained from all participants.

Risk Factor Assessment and Bone Measurement

Anthropometric variables, history of falls, and lifestyle factors (i.e., smoking, dietary calcium intake, physical activity, etc.) were recorded in a structured questionnaire administered by a trained nurse during the interviews with the participants at initial and subsequent visits at 2-year intervals.

BMD was measured at the femoral neck by DXA, using GE Lunar (Madison, WI) DPX-L and later Prodigy densitometers. The radiation dose used was <0.1 μGy and the coefficient of reliability for BMD measurement at our laboratory was 0.95 for the femoral neck. QUS measurements were performed at the calcaneus using a CUBA sonometer (McCue Ultrasonics, Winchester, UK) as in BUA and velocity of sound (VOS), with coefficients of reliability of 0.99 and 0.98, respectively.

Ascertainment of Fracture

The primary outcome of this study was fractures following minimal trauma, e.g., fall from standing height or less. Vertebral fractures were identified on X-rays and associated with clinical symptoms. All incident fracture cases were ascertained during the study period between 1994 and 2009, through X-ray reports from two to three radiology centers within the Dubbo region as previously described [28]. Fractures resulting from major trauma (e.g., motor vehicle accidents) and underlying diseases (e.g., malignant disease and Paget disease) were excluded from the analysis.

Data Analysis

To assess the magnitude of association between fracture risk and QUS or BMD, two separate models were considered in the initial analysis using Cox's proportional hazards regression for each gender. Model I included femoral neck BMD (FNBMD), age, falls, and prior fracture, as previously reported [29]. Model II included BUA, FNBMD, age, falls, and prior fracture. The outcomes of the analyses were presented as hazard ratios (HRs) with their respective 95% confidence intervals (95% CIs) per standard deviation (SD) change in a risk factor. The prognostic performance of each model was assessed by the area under the receiver operating characteristic (ROC) curve (AUC), which reflects the model's ability to discriminate between fracture and nonfracture individuals prospectively [30]. The maximum likelihood ratio test (MLRT) [31] was used to compare the AUCs of different prognostic models. Next, we calculated the 10-year risk of fracture for the base model (model I) and the model with the inclusion of both BUA and FNBMD

Table 1 Characteristics of the study population

	Nonfracture	Any fracture	Hip fracture	Vertebral fracture
Women (*n*)	300	154	33	71
Age (years)	71 (5)	73 (6)***	75 (7)***	73 (5)**
Weight (kg)	68 (13)	65 (11)**	63 (13)*	65 (11)
Height (cm)	160 (9)	159 (7)	158 (6)	158 (7)
BMI (kg/m^2)	26 (5)	25 (4)*	25 (5)	26 (4)
BUA (dB/MHz)	70 (17)	60 (17)***	53 (17)***	62 (16)***
VOS (m/s)	1526 (46)	1512 (37)**	1508 (39)*	1511 (36)*
FNBMD (g/cm^2)	0.80 (0.12)	0.74 (0.11)***	0.70 (0.13)***	0.70 (0.12)***
Falls in last 12 months (%)	23	44***	42*	46***
Prior fracture after age 50 (%)	14	29***	30*	27***
History of smoking (%)	36	33	30	32
Physical activity index (METs/day)	31 (4)	31 (4)	31 (4)	31 (2)
Calcium intake (mg/day)	623 (377)	634 (367)	616 (270)	654 (424)
Men (*n*)	370	75	19	31
Age (years)	73 (5)	74 (6)	75 (7)*	74 (5)
Weight (kg)	79 (13)	74 (11)***	73 (11)*	71 (12)***
Height (cm)	172 (6)	171 (6)	171 (7)	169 (5)*
BMI (kg/m^2)	27 (4)	25 (3)**	25 (3)*	24 (3)**
BUA (dB/MHz)	87 (18)	81 (21)**	80 (24)	77 (22)**
VOS (m/s)	1534 (49)	1523 (44)	1517 (46)	1521 (49)
FNBMD (g/cm^2)	0.92 (0.14)	0.86 (0.17)***	0.78 (0.15)***	0.81 (0.12)***
Falls in last 12 months (%)	12	31***	16	35***
Prior fracture after age 50 (%)	7	19**	21	19**
History of smoking (%)	64	64	42	90**
Physical activity index (METs/day)	33 (6)	34 (6)	37 (9)**	33 (5)
Calcium intake (mg/day)	638 (341)	603 (410)	624 (344)	553 (318)

Values are means (SD) unless specified otherwise

BMI Body mass index, *BUA* broadband ultrasound attenuation, *VOS* velocity of sound, *FNBMD* femoral neck bone mineral density, *MET* metabolic equivalent task, *SD* standard deviation

*$P < 0.05$, **$P < 0.01$, *** $P < 0.001$

(model II). Participants were then classified into three risk groups—<18%, 18–29%, >29%—for each model and compared using the reclassification method proposed by Pencina et al. [32]. Net reclassification improvement (NRI) was used to assess any improvement with the inclusion of BUA. This assesses the difference in proportion of those with and those without fracture moving up or down risk category, where Pr stands for probability, as follows [32]:

$$\begin{aligned}\text{NRI} &= [\Pr(\text{up}|\text{cases}) - \Pr(\text{down}|\text{cases})] \\ &- [\Pr(\text{up}|\text{control}) - \Pr(\text{down}|\text{controls})]\end{aligned}$$

The number of categories used was based on previous recommendations for absolute risk assessment [33]. Cut-off values were chosen according to the distribution of fracture risk in the study population (i.e., lower tertile and upper tertile) so as to have a comparable sample size among the three groups. A nomogram based on the resultant model was constructed for predicting 5-year and 10-year any-fracture risks for individual women. All statistical analyses were performed using the R program, version 2.8.1, for Windows [34]

Results

Characteristics of Participants

Of the 899 participants included in the study, 154 women (including 33 with hip fracture and 71 with clinical vertebral fracture) and 75 men (including 19 with hip fracture and 31 with clinical vertebral fracture) had sustained a low-trauma fracture during the follow-up period (median 13 years, range 11–15) (Table 1). Individuals with fracture on average were older, were shorter, had lower body weight, and tended to have falls in the past 12 months or prior fracture after age 50 compared with their nonfractured counterparts. Overall, no significant difference was noted in smoking, physical activity, and calcium intake between the fracture and nonfracture groups.

Both FNBMD and BUA measurements were significantly lower in those with fracture than those without fracture, and the differences were more pronounced in those with hip fracture. VOS measurements were significantly lower among the fracture group than the nonfracture group in women but not in men. However, after adjustment

for age, FNBMD, falls, and prior fracture, VOS was not associated with fracture risk in either sex and, therefore, was not included in further analysis.

Risk Factors for Fracture

In women, lower FNBMD was significantly associated with an increased risk of any, hip, and vertebral fractures (Table 2). The HRs for any fracture per SD decrease in FNBMD were 1.51 (95% CI 1.22–1.86) for any fracture, 2.29 (95% CI 1.44–3.66) for hip fracture, and 1.43 (95% CI 1.05–1.95) for vertebral fracture in the model without BUA (i.e., model I with FNBMD, age, falls, and prior fracture). After inclusion of BUA in model II (i.e., BUA, FNBMD, age, falls, and prior fracture), FNBMD remained an independent predictor of any fracture (HR = 1.26, 95% CI 1.00–1.59) but not with hip or vertebral fracture. BUA, on the other hand, was a consistent predictor of fracture risk regardless of fracture type (HR = 1.47, 95% CI 1.18–1.82; HR = 2.14, 95% CI 1.28–3.56; and HR = 1.37, 95% CI 1.01–1.88 for any, hip, and vertebral fractures, respectively), even after adjustment for FNBMD. Age and falls

Table 2 Risk factors for fracture in men and women

	Unit	Hazard ratio (95% CI)[a]		
		Any fracture	Hip fracture	Vertebral fracture
Women				
Model I				
Age	+5 years	**1.28 (1.11–1.47)**	**1.40 (1.05–1.86)**	**1.29 (1.05–1.58)**
FNBMD	−0.14 g/cm^2	**1.51 (1.22–1.86)**	**2.29 (1.44–3.66)**	**1.43 (1.05–1.95)**
Falls	Yes	**2.42 (1.75–3.35)**	**4.24 (1.95–9.24)**	**3.31 (2.04–5.38)**
Prior fracture	Yes	**1.82 (1.26–2.64)**	2.05 (0.87–4.81)	**2.07 (1.16–3.68)**
Model II				
Age	+5 years	**1.23 (1.07–1.42)**	**1.32 (1.03–1.77)**	**1.26 (1.02–1.55)**
BUA	–18 dB/MHz	**1.47 (1.18–1.82)**	**2.14 (1.28–3.56)**	**1.37 (1.01–1.88)**
FNBMD	–0.14 g/cm^2	**1.26 (1.00–1.59)**	1.54 (0.91–2.61)	1.23 (0.88–1.73)
Falls	Yes	**2.46 (1.77–3.41)**	**4.02 (1.84–8.79)**	**3.37 (2.06–5.49)**
Prior fracture	Yes	**1.68 (1.16–2.44)**	1.71 (0.72–4.06)	**1.97 (1.10–3.52)**
Model III				
Age	+5 years	**1.29 (1.13–1.50)**	**1.50 (1.11–2.02)**	**1.35 (1.09–1.67)**
VOS	–43 m/s	1.15 (0.95–1.39)	1.47 (0.98–2.20)	1.34 (0.98–1.76)
FNBMD	–0.14 g/cm^2	**1.45 (1.18–1.81)**	**2.17 (1.34–3.50)**	1.36 (0.99–1.87)
Falls	Yes	**2.36 (1.70–3.27)**	**4.21 (1.92–9.23)**	**3.25 (1.99–5.29)**
Prior fracture	Yes	**1.78 (1.23–2.58)**	2.01 (0.85–4.74)	**2.02 (1.13–3.61)**
Men				
Model I				
Age	+5 years	1.06 (0.87–1.29)	1.06 (0.75–1.51)	1.03 (0.78–1.38)
FNBMD	–0.14 g/cm^2	**1.37 (1.08–1.74)**	**3.06 (1.71–5.47)**	**2.03 (1.36–3.03)**
Falls	Yes	**2.99 (1.83–4.90)**	1.74 (0.49–6.12)	**3.60 (1.71–7.55)**
Prior fracture	Yes	**2.43 (1.33–4.44)**	1.83 (0.54–6.17)	2.06 (0.80–5.35)
Model II				
Age	+5 years	1.06 (0.87–1.28)	1.08 (0.75–1.55)	1.04 (0.78–1.38)
BUA	–18 dB/MHz	1.16 (0.91–1.47)	0.87 (0.56–1.34)	1.16 (0.79–1.69)
FNBMD	–0.14 g/cm^2	1.27 (0.98–1.66)	**3.25 (1.76–6.01)**	**1.86 (1.18–2.93)**
Falls	Yes	**3.03 (1.85–4.96)**	1.69 (0.48–5.99)	**3.64 (1.73–7.07)**
Prior fracture	Yes	**2.24 (1.21–4.17)**	1.94 (0.57–6.59)	1.84 (0.68–5.05)
Model III				
Age	+5 years	1.07 (0.89–1.30)	1.07 (0.75–1.52)	1.05 (0.79–1.40)
VOS	–49 m/s	1.16 (0.92–1.47)	1.18 (0.72–1.91)	1.15 (0.80–1.67)
FNBMD	–0.14 g/cm^2	**1.33 (1.04–1.69)**	**2.95 (1.64–5.29)**	**1.97 (1.31–2.96)**
Falls	Yes	**3.02 (1.85–4.95)**	1.78 (0.51–6.29)	**3.61 (1.72–7.60)**
Prior fracture	Yes	**2.31 (1.26–4.24)**	1.76 (0.52–5.93)	1.94 (0.74–5.10)

Bold signifies statistical significance at $P < 0.05$

[a] HR was based on 1 SD decrease of the independent variable

HR Hazard ratio, *FNBMD* femoral neck bone mineral density, *BUA* broadband ultrasound attenuation, *VOS* velocity of sound

were also associated with any, hip, and vertebral fractures, whereas prior fracture was significantly associated with any fracture and vertebral fracture but not hip fracture.

In men (Table 2), low FNBMD was a consistent risk factor for any (HR = 1.37, 95% CI 1.08–1.74), hip (HR = 3.06, 95% CI 1.71–5.47), and vertebral (HR = 2.03, 95% CI 1.36–3.03) fractures in the model without BUA. However, when both FNBMD and BUA were considered in a multivariable model (model II), neither FNBMD (HR = 1.27, 95% CI 0.98–1.66) nor BUA (HR = 1.16, 95% CI 0.91–1.47) was statistically significant as a predictor of any fracture. However, FNBMD was associated with hip (HR = 3.25, 95% CI 1.76–6.01) and vertebral (HR = 1.86, 95% CI 1.18–2.93) fractures, but BUA was not. History of falls was associated with any fracture or vertebral fracture but not hip fracture. Prior fracture was associated with subsequent fracture risk but was only statistically significant for any fracture.

Fracture Discrimination

In order to assess the performance of each model in terms of fracture discrimination, the AUC was computed (Table 3). In women, the AUCs of model I (without BUA) were 0.71 for any fracture, 0.77 for hip fracture, and 0.70 for vertebral fracture. When BUA and FNBMD were considered simultaneously in model II, the AUC values were significantly higher for any fracture (0.73, $P = 0.001$), hip fracture (0.81, $P = 0.003$), and vertebral fracture (0.72, $P = 0.05$) in respect to those without BUA.

In men, no significant difference was noted in the AUCs between the models with and without BUA. AUC values for both models I and II were 0.71 for any fracture and 0.75 for vertebral fracture. Although the AUC of hip fracture in model II (0.78) was slightly higher than that in model I (0.77), the difference was not statistically significant.

Reclassification Analysis

Tables 4 and 5 summarize the reclassification analysis of 10-year fracture risk based on model I (without BUA) and model II (with BUA) in women and men, respectively. Overall, 22% of women and 7% of men were reclassified into different risk categories when BUA was added to the base model (model I). In women, 7.3% (any fracture), 11.1% (hip fracture), and 5.2% (vertebral fracture) of NRI were obtained with the inclusion of BUA; i.e., 1 in 13, 1 in 9, and 1 in 20 were more correctly classified.

In men, a combination of BUA with FNBMD yielded a total NRI of 5.5% and 3.8%, respectively, for hip fracture and vertebral fractures but no improvement was found in any fracture.

Clinical Application of Nomogram

Based on the parameter estimates of model II (BUA, FNBMD, age, falls, and prior fracture), a nomogram for predicting 5-year and 10-year fracture risk in women was constructed (Fig. 1). The clinical application of this nomogram can be illustrated by the following examples: A woman aged 70 years, with no history of falls or prior fracture, FNBMD T-score of −2.5, and BUA of 50 dB/MHz is predicted to have ~13% and ~25% chance of sustaining fragility fracture over 5- and 10-year periods, respectively. However, with the same age, clinical history, and BMD level, a woman with a higher BUA, e.g., 100 dB/MHz, would have a significantly lower risk of fracture (i.e., 4% within 5 years and 10% within 10 years).

Discussion

Although low BMD is a robust risk factor for fracture, more than 50% of women and 70% of men with a fracture

Table 3 Fracture discrimination of models I and II as measured by area under the receiver operating characteristic curve (AUC) in men and women

	AUC (95% CI)		
	Any fracture	Hip fracture	Vertebral fracture
Women			
Model I (FNBMD + age + falls + prior fracture)	0.71 (0.66–0.76)	0.77 (0.69–0.86)	0.70 (0.62–0.77)
Model II (model I + BUA)	0.73 (0.68–0.78)	0.81 (0.73–0.88)	0.72 (0.65–0.79)
*P**	0.001	0.003	0.05
Men			
Model I (FNBMD + age + falls + prior fracture)	0.71 (0.64–0.78)	0.77 (0.67–0.87)	0.75 (0.66–0.83)
Model II (model I + BUA)	0.71 (0.64–0.77)	0.78 (0.67–0.88)	0.75 (0.66–0.84)
*P**	0.12	0.70	0.28

FNBMD Femoral neck bone mineral density, *BUA* broadband ultrasound attenuation

* *P* value of maximum likelihood ratio tests between models I and II with level of significance <0.05

Table 4 Comparison of 10-year predicted risk of fracture between model II and model I for women

Model I[b]	Model II[a]			NRI (%)
	<18%	18–29%	>29%	
Any fracture				
Fracture				2.59
<18%	18	6	0	
18–29%	7	30	10	
>29%	0	5	78	
Nonfracture				4.67
<18%	115	11	0	
18–29%	24	49	17	
>29%	0	18	66	
Total				7.26
Hip fracture				
Fracture				12.12
<18%	18	2	0	
18–29%	0	4	2	
>29%	0	0	7	
Nonfracture				−1.00
<18%	274	7	0	
18–29%	6	3	3	
>29%	1	0	6	
Total				11.12
Vertebral fracture				
Fracture	32	4	0	2.82
<18%	0	10	3	
18–29%	0	5	17	
>29%				
Nonfracture				1.33
<18%	210	8	0	
18–29%	13	44	5	
>29%	0	2	18	
Total				5.15

FNBMD Femoral neck bone mineral density, *BUA* broadband ultrasound attenuation, *NRI* net reclassification improvement

[a] Model II: BUA and FNBMD combined after adjusted for age, falls and prior fracture

[b] Model I: FNBMD alone after adjusted for age, falls and prior fracture

Table 5 Comparison of 10-year predicted risk of fracture between model II and model I for men

Model I[b]	Model II[a]			NRI (%)
	<18%	18–29%	>29%	
Any fracture				
Fracture				–1.33
<18%	41	2	0	
18–29%	1	14	1	
>29%	0	3	13	
Nonfracture				–0.54
<18%	296	10	0	
18–29%	6	21	4	
>29%	0	6	27	
Total				−1.87
Hip fracture				
Fracture	15	0	0	5.26
<18%	0	1	1	
18–29%	0	0	2	
>29%				
Nonfracture				0.27
<18%	363	0	0	
18–29%	1	4	0	
>29%	0	0	2	
Total				5.53
Vertebral fracture				
Fracture				3.22
<18%	21	1	0	
18–29%	1	2	1	
>29%	0	0	5	
Nonfracture				0.54
<18%	343	3	0	
18–29%	2	14	0	
>29%	0	3	5	
Total				3.76

FNBMD Femoral neck bone mineral density, *BUA* broadband ultrasound attenuation, *NRI* net reclassification improvement

[a] Model II: BUA and FNBMD combined after adjusted for age, falls and prior fracture

[b] Model I: FNBMD alone after adjusted for age, falls and prior fracture

do not have BMD in the osteoporotic ranges [35]. With the evidence that QUS may provide additional information to bone density for fracture-risk assessment, it was postulated that a combination of BMD and BUA could improve the prognosis of fracture. The present result is consistent with such a hypothesis for women.

Our result is consistent with previous observations [22–24, 36–38], in which BUA measurement was significantly lower in individuals with fracture. In women, after adjustment for FNBMD and relevant covariates, BUA measurement remained significantly associated with fracture risk, suggesting that calcaneal BUA is an independent predictor of fracture risk, as found previously [17, 25]. In men, a combination of BUA and FNBMD did not enhance the predictive value of fracture, which is consistent with a report by the Osteoporotic Fractures in Men Study (MrOS) [39], suggesting that BUA provides little or no additional prognostic information in fracture-risk assessment in men.

The gender difference in association between QUS and fracture risk could be related to the higher bone mass and

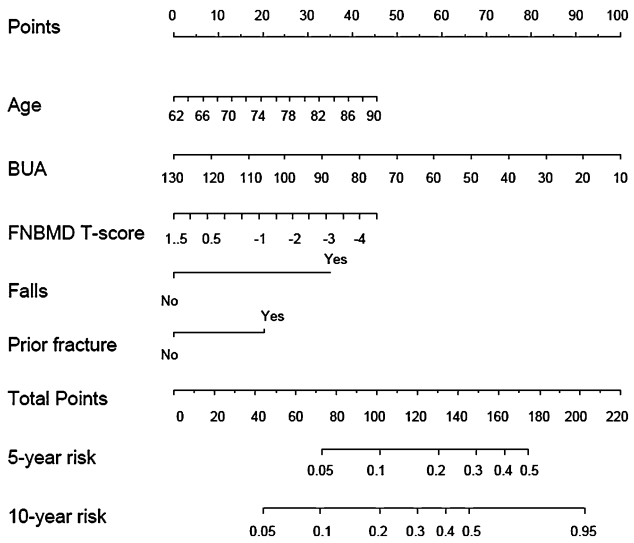

Fig. 1 Nomogram for women in predicting 5-year and 10-year probability of any fracture based on age, BUA, BMD T-score, number of falls during the previous 12 months, and prior fracture after the age of 50. Instruction for usage: Mark the age of an individual on the *Age* axis and draw a vertical line to the *Points* axis to determine how many points toward the probability of fracture the individual receives for her age value. Repeat the process for each additional risk factor. Sum the points of the risk factors. Locate the final sum on the *Total Points* axis. Draw a vertical line down to the 5-year or 10-year risk line to find the individual's probability of sustaining a fracture within the next 5 or 10 years, respectively

lower fracture risk in men. Furthermore, there are relatively fewer fracture cases in men, which affects the power to detect a modest independent effect. Also, it has previously been reported that foot size affects the QUS measurement as a result of the variation in the regions of interest being measured [40], and in vitro studies have shown a significant effect of bone thickness on BUA measurement [41]. Since men have larger foot sizes than women, this may, in part, contribute to the lower fracture predictive ability of calcaneal BUA in men. Another possible explanation for the poor fracture predictive value in men could be unique age-related changes in bone geometry. Although both men and women undergo structural changes in their bone, men also exhibit bone remodeling patterns, in the tibia and femur at least, that could compensate for the loss of bone material properties with aging [42]. Nevertheless, further studies are required to examine the gender-related difference in fracture-risk prediction by QUS.

Our finding that VOS was poorly associated with fracture risk is consistent with a previous finding using a similar model of a CUBA machine [24] and could be partly due to the technical design of the device. However, previous studies on vertebral and human calcaneal bone suggested that the velocity of ultrasound does not correlate as well as BUA with trabecular thickness in the calcaneus [43]. This may explain why VOS's performance was inferior to that of BUA in the prediction of fracture risk.

The strength of association between FNBMD and fracture risk was, in general, reduced by incorporation of BUA into the model. This finding is consistent with previous studies [24, 25, 37, 44], suggesting that BMD and BUA are not totally independent of each other. Indeed, the correlations between FNBMD and BUA in this study were 0.40 and 0.51 for men and women, respectively. Theoretically, it is possible that BMD and BUA measure some common bone properties as both bone density and trabecular microarchitecture are determinants of QUS measurements [37].

Nevertheless, it seems that BUA measurement can enhance the accuracy of fracture discrimination in women. With the incorporation of BUA into the predictive model, the AUC was increased by 2% for both any and vertebral fractures and by 4% for hip fracture. However, the AUC does not indicate whether the improvement was in sensitivity or specificity. Using reclassification analysis, we were able to demonstrate that the improvement in fracture prediction included both sensitivity and specificity, particularly in the prediction of hip-fracture cases.

Our finding in reclassification is consistent with that of the EPIC-Norfolk study (European Prospective Investigation into Cancer) [24], in which 17% of the participants were reassigned to adjacent risk groups with BUA added to the BMD-based model.

However, reclassification analysis, like other risk grouping methods, depends on the particular cut-off thresholds used. Ideally, the cut-off value chosen gives the best combination of sensitivity (probability of correct classification among fracture cases) and specificity (probability of correct classification among nonfracture cases), which takes into consideration the predictive values as well as cost-effectiveness [32]. Since no established threshold for fracture risk is currently available, the cut-offs chosen here (i.e., 18% and 29%) were based on the distribution of fracture incidence in our study population and the estimated fracture risk as computed by the two models considered. Substitution of another threshold previously recommended [33] did not have any significant impact on the outcome; e.g., a similar NRI of $\sim$7.7% was obtained for any fracture when the cut-off threshold was changed to 10% and 20%.

The primary goal of a prognostic model is to assist individuals and clinicians with treatment decisions. Since fracture is a multifactorial event, each individual is likely to have his or her own unique risk profile. Thus, for the purpose of clinical application, fracture risk should be assessed individually. The conventional risk categorizations are based on groups of individuals and, therefore, are not ideal for individualized risk assessment [45, 46]. The use of a nomogram to utilize all predictive variables in

continuous scales is more accurate and clinically relevant than the risk stratification systems for individualized fracture-risk assessment. Currently, the Garvan Fracture Risk calculator and FRAX (Fracture Risk Assessment Tool) are the two most widely used models for individualizing fracture risk. They are based on BMD and various clinical risk factors to predict short-term fracture risk for each individual [47]. Although FRAX and the Garvan Fracture Risk calculator are both useful and valid tools for identifying patients at high risk of fracture, there remains room for improvement [48]. This study and previous findings [24] suggest that the addition of BUA to BMD could add information to that provided by BMD and, thus, enhance the accuracy of distinguishing high-risk women from those of lower risk. At present, therapeutic treatment is mainly recommended for those with BMD T-score < -2.5. However, as mentioned above, two women, both with BMD T-score at –2.5, would not necessarily require the same treatment when their BUA levels were taken into account. In fact, therapeutic treatment is likely to be unwarranted for the woman with high BUA despite her low BMD level. However, due to the low numbers of hip and vertebral fracture cases, application of the present nomogram is limited to any fracture and only in women. Further, validation in a larger population is required before implementation in the clinical setting. Nevertheless, our results in the reclassification analysis suggest that inclusion of BUA in a prognostic model, such as nomogram, could increase the reliability of the model and help to select more appropriate patients for therapeutic intervention.

The strengths of this study included its long duration of follow-up and population-based and prospective design, thus helping to minimize potential biases commonly found in cross-sectional studies. The present findings should, however, be interpreted within the context of a number of potential limitations. Since the study population was mainly of Caucasian background aged above 60 years, its findings may not be readily generalizable to other populations, especially those in younger age groups.

Conclusions

In summary, the present results indicate that calcaneal BUA measurement is independently associated with fracture risk in women but not in men. Our results also show that, in women, a combination of BUA and BMD could enhance the accuracy of fracture prediction and that the potential role of QUS in fracture-risk assessment deserves further attention.

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