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Original Article

Clinical Performance of a Highly Portable, Scanning Calcaneal Ultrasonometer

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Abstract. The aim of this study was to establish a normative database, assess precision, and evaluate the ability to identify women with low bone mass and to discriminate women with fracture from those without for a highly portable, scanning calcaneal ultrasonometer: the QUS-2. Fourteen hundred and one Caucasian women were recruited for the study. Among them were 794 healthy women 25–84 years of age evenly distributed per 10-year period to establish a normative database. Of these, 171 aged 25–34 years were defined as the young normal group for the purpose of *T*-score determination. Precision was assessed within 1 day (short-term) and over a 16-week period (long-term) in 79 women aged 25–84 years. Five hundred twenty-eight women ranging from 50 to 84 years of age with or without prevalent fractures of the spine, hip or forearm were measured to compare the QUS-2 with bone mineral density (BMD) of the hip and spine. Mean calcaneal broadband ultrasound attenuation (BUA) was constant in healthy women from 25 to 54 years of age and decreased with increasing age thereafter. Short-term precision, with and without repositioning of the heel, and long-term precision yielded comparable results (BUA SDs of 2.1–2.4 dB/MHz, coefficients of variations (CVs) of 2.5–2.9%). Calcaneal BUA was significantly correlated with BMD of the total hip (TH), femoral neck (FN) and lumbar spine (LS) in 698 women (r = 0.6–0.7, all $p < 0.0001$). A similar relationship was observed for LS BMD compared with either TH or FN BMD ($r = 0.7$, $p < 0.0001$). Prevalence of osteoporosis in our population (WHO criteria) was 20%, 17%, 21%, and 24% for BUA, BMD of the TH, FN and LS, respectively. Age-adjusted values for a 1 SD reduction in calcaneal BUA and TH and FN BMD predicted prevalent fractures of the spine, forearm, and hip with significant ($p < 0.05$) odds ratios of 2.3, 2.0 and 2.1, respectively. Areas under the receiver operating characteristic curves for age-adjusted bone mass values predicting prevalent fracture were 0.62 for BUA, 0.59 for TH BMD, 0.60 for FN BMD, and 0.57 for LS BMD; all statistically equivalent. We conclude that the QUS-2 calcaneal ultrasonometer exhibits reproducible clinical performance that is similar to BMD of the spine and hip in identifying women with low bone mass and discriminating women with fracture from those without.

Keywords: Bone mineral density; Calcaneus; Fracture; Osteoporosis; Ultrasound

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Introduction

Low bone mass has been repeatedly demonstrated to predict subsequent fractures in prospective studies [1]. Marshall's meta-analysis, derived predominantly from studies of older women, has been affirmed in more recent

studies [2–8], and has been extended to younger women [8–10] and men [4,11,12]. Quantitative ultrasound (QUS) devices are rapidly becoming widely used due to their smaller size, portability, freedom from use of ionizing radiation, and lower cost than dual-energy X-ray absorptiometers (DXA), enabling bone mass measurement by primary care providers and in the community.

To date, QUS measurements made by transmitting ultrasonic signals through the calcaneus have proven to be the most clinically useful [13,14]. Two QUS parameters have been widely investigated, broadband ultrasound attenuation (BUA) and speed of sound (SOS). Of these, BUA has been studied more extensively. Low BUA has consistently been associated with fragility fracture risk of the hip, spine, wrist and all nonspine sites collectively in populations aged 55 years or older [5–8,15,16]. Low BUA also predicted fractures of all types (both atraumatic and traumatic) in perimenopausal and early postmenopausal women [17,18], and stress fractures occurring as a result of military training [19]. These data suggest that calcaneal BUA can be used to assess fracture risk.

In the present study, we have evaluated the clinical performance characteristics of the QUS-2, a highly portable, gel-coupled, scanning calcaneal ultrasonometer. The aims of this investigation were (1) to establish a normative database for the QUS-2; (2) to evaluate the short- and long-term precision of the device; (3) to examine the ability of the QUS-2 to identify women with low bone mass and discriminate between women with and without fracture; and (4) to compare the performance of the QUS-2 with DXA measurements of the spine and hip.

Subjects and Methods

Reference Range Study

Healthy Caucasian women between the ages of 25 and 84 years were identified through advertisements and by contacting specific groups, e.g., community organizations, senior citizens facilities, or from the existing patient population at that clinical study centers (nine in the US, one in Finland). Women were eligible if they were free of metabolic bone or chronic liver, kidney or endocrine disease, rheumatoid arthritis or disabling osteoarthritis, had never sustained an atraumatic fracture, and if they had not been treated with a bone-active medication for more than 2 of the previous 6 months. This exclusion included calcium in excess of 1500 mg/day on average and vitamin D in excess of 800 IU/day on average. Women using topical estrogens or progestins or oral contraceptives were not excluded. Women were excluded if they had been pregnant within 6 months or if they were breastfeeding within 4 months. Women were also excluded if they had anatomy unsuitable for ultrasound assessment of the calcaneus or any condition that impacted on weight bearing of the lower limbs, including significant bony trauma, calcaneal fracture, sequelae of orthopedic procedures, or immobilization for more than 1 month in the past year. Women aged 25–34 years were eligible to be included in the 'young normal' reference group if they had regular menstrual periods for the previous 5 years. A total of 794 women were recruited with a minimum of 120 women per 10-year interval, enabling the upper and lower limits of the reference intervals to be calculated nonparametrically with 90% confidence. All women in this group had a calcaneal ultrasound scan. Women in the young normal reference group also underwent DXA scanning of the spine and proximal femur.

Reproducibility Study

Seventy-nine women evenly distributed over a 25–84 year age range that met the criteria for the normative range study participated in the reproducibility study at four clinical study centers in the USA and one in Finland. All women in this group underwent triplicate calcaneal ultrasound scans both with and without repositioning between each scan at baseline to assess short-term precision. Long-term reproducibility was assessed by triplicate scans with repositioning obtained for each woman every 2 weeks for a total of nine visits (27 scans) over 16 weeks.

Bone Mass and Fracture Discrimination Study

Five hundred and twenty-eight women aged 50–84 years and the 171 'young normal' women of the normative range study participated in the bone mass and fracture discrimination study at seven clinical study centers in the USA. Similar entry criteria to the normative range study were utilized except that women with a history of atraumatic fracture of the spine, wrist or hip were recruited and women with osteoporosis (determined by DXA of the total hip) were not excluded. All women in this group had a calcaneal ultrasound scan and DXA scans of the lumbar spine, total hip and femoral neck.

All women provided informed consent and the clinical study protocols were approved by the institutional review boards at each clinical study center.

Ultrasound Assessments

BUA (in dB/MHz) of the calcaneus was measured using the QUS-2 calcaneal ultrasonometer (Metra Biosystems [Quidel], Mountain View, CA). The right calcaneus was scanned unless there was clinical justification for scanning the left (e.g., open wound, edema or history of orthopedic surgeries). An aqueous-based gel (Aquasonic 100, Parker Laboratories, Fairfield, NJ) was used as the coupling agent. The QUS-2's transducers are mounted on motorized arms. At the start of a scan, the QUS-2 anatomically locates the region of interest (ROI) by moving the transducers and detecting the acoustic

edges at the back and bottom of the calcaneus. The ROI is a parallelogram beginning 4 mm above the bottom and 8 mm forward from the back acoustic edges. The BUA value for the scan is the average of values determined at a total of 88 points on a 1 mm grid within this parallelogram. The QUS-2 uses a two-step signal processing method. First, the dominant early period, the average period of a selected portion of the first substantial received sound wave cycle, is quantified. Then a mathematical model is used to convert this dominant early period to the corresponding value of BUA. The stronger the low-pass filtering action of the bone, the longer the dominant early period and the higher the value of BUA.

Bone Mineral Density Assessments

BMD of the lumbar spine (LS), total hip (TH) and femoral neck (FN) was measured by DXA (QDR-1000 and -4500, Hologic, Waltham, MA, or DPX-alpha, -IQ and -L, Lunar, Madison, WI) according to the manufacturers' instructions. The hip DXA scan was performed on the same side (left or right) as the calcaneal ultrasound scan. DXA scans obtained up to 2 months prior to the BUA measurement were permitted. DXA devices were maintained in accordance with the quality assurance protocols established by each clinical study site.

Fracture Assessments

Radiographic reports of women 50 years of age or older were used to confirm existence of an atraumatic fracture of the spine, hip or wrist. Additional radiographs were obtained to confirm fracture if historical records were not readily available. Women without history of atraumatic fracture after age 50 years underwent lateral radiography of the thoracic and lumbar spine using standard techniques. Films were reviewed by a staff radiologist at each clinical study site.

Statistics

Dependence of BUA values on age was assessed by linear and polynomial regression. The age-dependent BUA curve was best fit using trinomial regression. We applied the young normal SD across all age ranges according to the convention adopted by other device manufacturers [20,21]. *T*-scores for BUA and BMD were calculated from the mean and SD of the young normal reference range according to the standard formula: $T\text{-score}_{\text{subject}} = (\text{Bone mass}_{\text{subject}} - \text{Bone mass Mean}_{\text{young normal}}) / \text{Bone mass SD}_{\text{young normal}}$. BUA *T*-scores derived from the 25–34 year-old young normal reference range in this study were used for subsequent analyses. DXA T-scores were calculated from the manufacturer's young normal reference ranges (Hologic [NHANES III for hip] $n = 419$, Lunar $n = 279$). World Health Organization (WHO) criteria were used to classify bone mass values as normal, osteopenic or osteoporotic [22]. Cross-sectional rates of loss of bone mass were determined by linear regression for women between 50 and 84 years of age.

To determine short- and long-term reproducibility, standard deviations (SDs) were calculated by determining the variance for each time point, averaging these variances (all subjects and all clinical study sites), and taking the square root of this mean variance. Percent coefficient of variation (CV) was calculated by dividing this SD by the overall average BUA. Precision was expressed relative to the biological range of BUA values in two ways. Standardized precision (SP) was calculated according to the method of Frost et al. [23] where the BUA precision SD was divided by the SD for the young normal population. Standardized CVs (SCVs) were calculated according to the method of Cheng et al. [24] where $\text{SCV} = \text{CV} / (4 \times \text{SD}_{\text{study population}} / \text{Mean}_{\text{study population}})$ using the total study population.

Student's *t*-tests (independent or paired as appropriate) or analysis of variance (ANOVA) were used to determine statistical significance between various populations. Pairwise comparisons of significant results were conducted using the method of Tukey as modified by Dunnett. Linear regression was used to compare calcaneal BUA, spine BMD and hip BMD values. Receiver operator characteristic (ROC) curve analysis and logistic regression were applied to evaluate the association of QUS-2 and DXA *T*-scores to fracture outcome. Categorical data were also analyzed using chi-square test.

Results

Normative Data

Calcaneal BUA values reached a maximum between 35 and 44 years of age and thereafter decreased in an age-dependent manner (Fig. 1). However, BUA values in the three 10-year intervals, 25–34, 35–44, and 45–54 were not statistically different. A young normal reference range for the QUS-2 was established using BUA values obtained in the 171 women between 25 and 34 years of age (mean 89.0 dB/MHz, SD 12.4 dB/MHz). There were no differences in mean young normal values across the study sites. BMD values in this young normal group were similar to manufacturers' reference ranges as evidenced by the means (SDs) of the *T*-scores: LS BMD 0.13 (1.00), TH BMD 0.22 (0.97), FN BMD 0.26 (1.04). BUA decreased linearly as a function of age from 50 to 84 years ($r = 0.45$, $p < 0.0001$). The rate of decrease, 0.75 dB/MHz/year, corresponds to a loss rate of 0.06 *T*-score units/year or 0.85%/year at age 50 (using fitted mean BUA) and 1.21%/year at age 85. Mean BUA values in each of the three oldest 10-year intervals, 55–64, 65–74, and 75–84, were lower than in each preceding 10-year interval and in each of the three youngest 10-year intervals ($p < 0.05$). *Z*-scores are illustrated in Fig. 1.

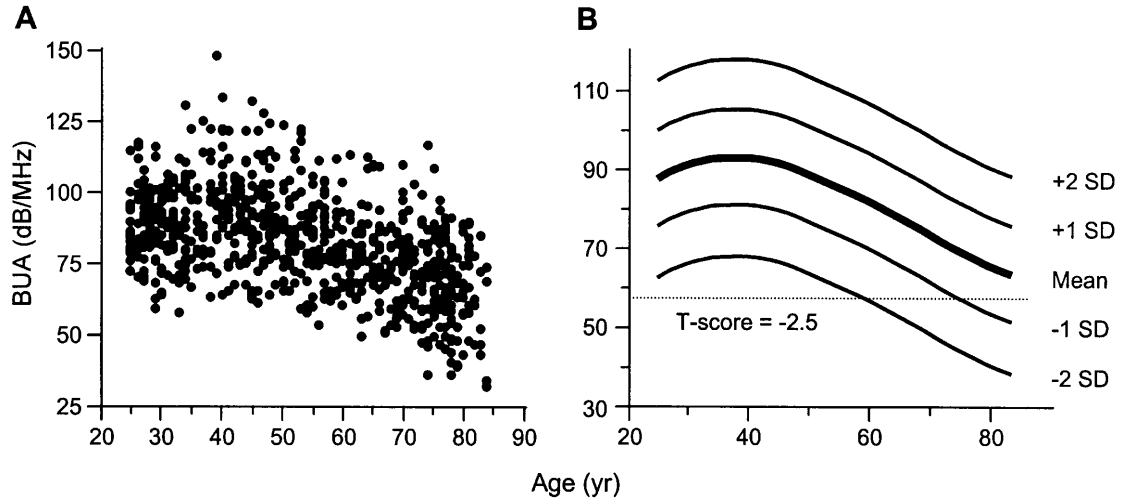

Fig. 1 A. Calcaneal broadband ultrasound attenuation (BUA) in 794 healthy Caucasian women. **B** Mean calcaneal BUA fitted through all data points plotted in **A** and corresponding standard deviations (SDs) determined in the young normal population.

Reproducibility

Short-term calcaneal BUA precision was slightly lower ($p < 0.05$) than the long-term precision (Table 1). Repositioning of the foot had no effect on precision. There was no association between either short- or long-term precision and age or menopausal status. However, variance increased with increasing BUA resulting in a relatively constant CV across the range of BUA values. The short-term (with repositioning) BUA SD for women with osteopenic or osteoporotic *T*-scores (<-1) was 1.6 dB/MHz (2.5% CV), or 0.13 when expressed as a *T*-score SD. By comparison, women with normal *T*-scores ($\geqslant -1$) had a BUA SD of 2.4 dB/MHz (2.6% CV), or a *T*-score SD of 0.19. The same relationship was observed for long-term precision. There were no differences in the average short- or long-term precision obtained at the five clinical study sites.

Comparisons Between Bone Mass Methods

Calcaneal BUA was highly correlated with and TH, FN and LS BMD (r = 0.6 to 0.7, all $p < 0.0001$; Fig. 2).

Table 1. Short- and long-term precision

	BUA (dB/MHz)				CV	SCV
	Mean	SD	Interquartile range	SP	(%)	(%)
Short-term (no repositioning)	83.0	2.1	0.6–2.0	0.17	2.5	2.9
Short-term (with repositioning)	83.2	2.2	0.9–2.3	0.17	2.6	2.9
Long-term (with repositioning)	83.2	2.4	1.5–2.6	0.19	2.9	3.2

BUA, broadband ultrasound attenuation; SP, standardized precision; SCV, standardized coefficient of variance.

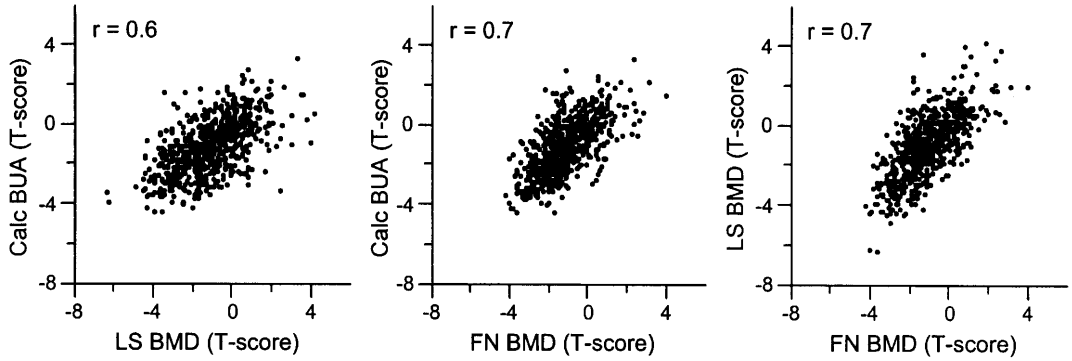

Fig. 2. Correlations between T-scores derived from calcaneal (Calc) BUA, lumbar spine (LS) bone mineral density (BMD), and femoral neck (FN) BMD in 698 women aged 25–84 years; all $p < 0.0001$.

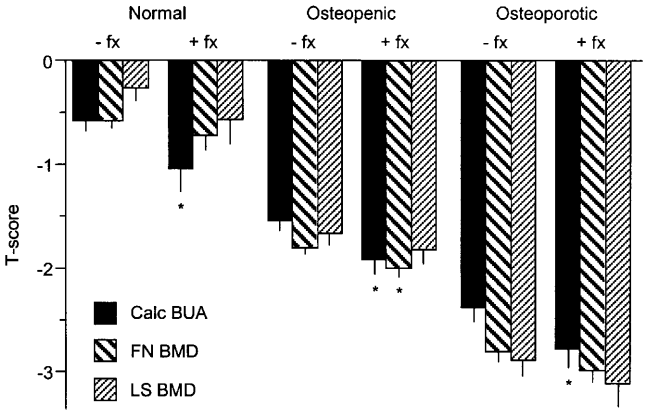

Fig. 3. Mean *T*-scores (± SEM) for calcaneal BUA (*black bars*), femoral neck (FN) BMD (*coarse slashed bars*), and lumbar spine (LS) BMD (*fine slashed bars*) for women in the bone mass and fracture discrimination study group classified according to WHO criteria on the basis of their total hip (TH) BMD. In each TH BMD WHO category, mean *T*-scores are shown for women with or without fractures of the spine, wrist or hip (± fx); * $p < 0.05$ for comparison between fracture and nonfracture within each TH BMD WHO category.

When women were classified as normal, osteopenic or osteoporotic according to their TH BMD, mean *T*-scores in each group were similar using all measurement methods (Fig. 3). Concordance in classification between methods when each method was used to classify every other is illustrated in Fig. 4. The prevalence of osteopenia and osteoporosis in the study population was comparable when using all methods (Table 2).

Fracture Discrimination

One hundred and forty-seven women of the 528 participating in the bone mass and fracture discrimination study had sustained an atraumatic fracture of the spine, hip or wrist. Of these, 116 women had prevalent spine fractures, 10 women had hip fractures, and 21 women had Colles' fractures. Within each WHO classification (by TH BMD) mean calcaneal BUA *T*-scores were significantly lower in women with fractures than in women without ($p < 0.05$; Figure 3). Differences were also observed for TH BMD in women classified as osteoporotic or osteopenic, for FN BMD in women classified as osteopenic, but not for LS BMD for women of any classification.

One SD reduction in calcaneal BUA, TH BMD and FN BMD, adjusted for age, was a predictor of all fractures (odds ratios 2.0–2.3, $p < 0.05$; Table 3).

Table 2. Prevalence of osteopenia and osteoporosis by WHO criteria [22] in the bone mass discrimination study population according to each method's *T*-score

	Calc BUA	TH BMD	FN BMD	LS BMD
All (*n*)	528	528	526	526
Osteopenic (%)	44.7	44.9	50.0	37.5
Osteoporotic (%)	20.5	17.2	21.5	24.1
50–64 years (*n*)	186	186	184	186
Osteopenic (%)	34.9	37.1	40.2	37.1
Osteoporotic (%)	9.1	8.6	11.4	15.6
65–84 years (*n*)	335	335	335	333
Osteopenic (%)	49.3	49.9	55.5	36.9
Osteoporotic (%)	27.2	22.4	27.5	29.4

Calc, calcaneal; TH, total hip; FN, femoral neck; LS, lumbar spine; BMD, bone mineral density.

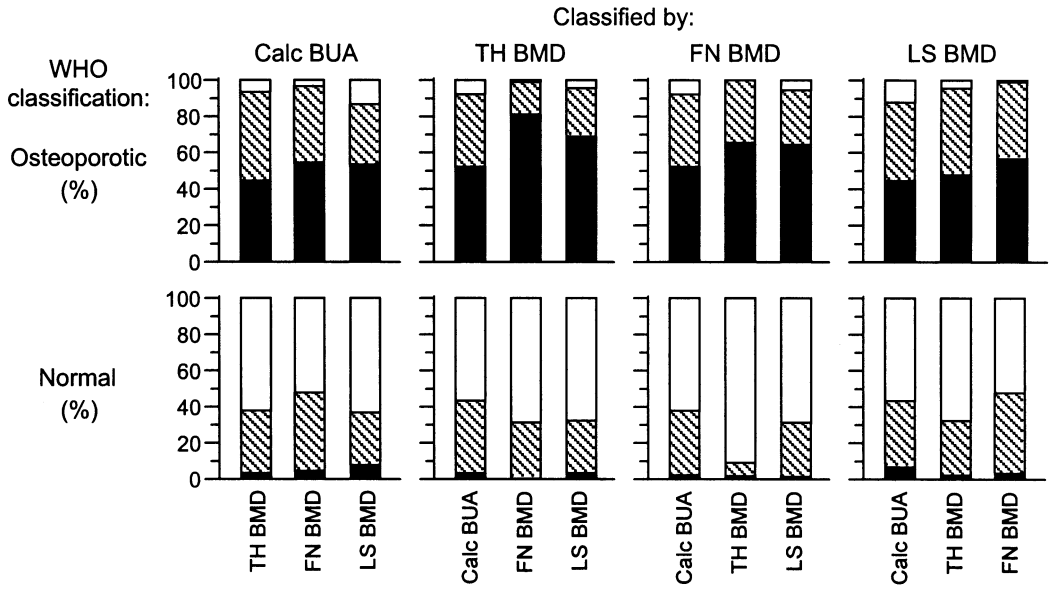

Fig. 4. Concordance of *T*-score classification (by all bone mass methods) for women in the bone mass and fracture discrimination study group classified as osteoporotic or normal according to WHO criteria; osteoporotic (*black bars*), osteopenic (*slashed bars*), normal (*white bars*).

Table 3. Odds ratios (95% confidence intervals [CI]) for association of 1 SD reduction in bone mass level (adjusted for age) with fracture risk

	Odds ratio (95% CI)
All fractures	
Calc BUA	2.35 (1.51–3.65)
TH BMD	1.96 (1.30–2.96)
FN BMD	2.10 (1.29–3.40)
LS BMD	1.26 (0.85–1.89)
Spine fractures only	
Calc BUA	2.68 (1.63–4.41)
TH BMD	2.01 (1.27–3.16)
FN BMD	2.09 (1.23–3.55)
LS BMD	1.61 (1.02–2.54)

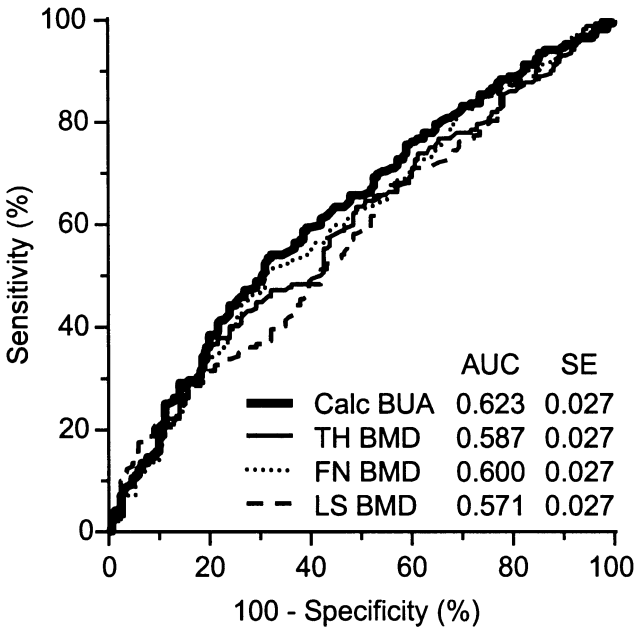

Fig. 5. Receiver operating characteristic (ROC) curves comparing *T*-scores for women in the bone mass and fracture discrimination study group with fractures of the spine, wrist or hip versus those without fracture for BUA (*thick line*), TH BMD (*thin line*), FN BMD (*dotted line*), and LS BMD (*dashed line*); areas under the ROC curves (AUC; standard error [SE]) were statistically equivalent.

Excluding women with fractures of the lumbar vertebrae did not improve the predictive ability of LS BMD. When the analyses were restricted to fractures of individual skeletal sites, no method was able to predict the small number of hip or Colles' fractures. All methods were predictors of spine fractures (Table 3). Calcaneal BUA remained the only predictor of spine fractures in multiple logistic regression models that included each of the BMD sites. When the same analyses were made for all fractures, calcaneal BUA failed to reach significance ($p = 0.06$ or 0.07 depending on BMD site).

ROC curves for discriminating women with fracture from those without were constructed for each method after adjustment for age (Fig. 5). Areas under the ROC curves (AUCs) ranged from 0.57 for LS BMD to 0.62 for calcaneal BUA. AUCs were equivalent for all methods. Sensitivity, specificity, and positive and negative predictive values were computed at discrete *T*-score cut-points determined for each method (Table 4).

Discussion

There were several aims of this study. We established a normative database for the QUS-2 calcaneal ultrasonometer. We demonstrated that the QUS-2 is a precise and reproducible technique for assessing bone mass in Caucasian women. Using the WHO criteria for the QUS-2 device, *T*-score classifications were similar to those ascertained by hip and spine BMD measurements. We found that this portable ultrasound device can discriminate between patients with and without fractures in a manner similar to determinations made by hip bone density. Finally, we demonstrated that the prevalence of osteoporosis and osteopenia provided by the QUS-2 is similar to that provided by axial DXA assessments. Therefore, the QUS-2 is a reliable tool that will allow clinicians to classify and assess bone mass and fracture risk in women.

Although this study did not involve direct comparison with other ultrasound devices, we utilized a study design similar to previous protocols, which examined many ultrasound devices, both wet and dry [25]. The QUS-2 uses BUA as its primary outcome while some other devices use SOS or a calculated parameter derived from BUA and SOS variously called 'stiffness', 'quantitative ultrasound index', or 'estimated BMD'. BUA precision expressed relative to the biological range of data in this and other studies conducted with the QUS-2 appeared comparable to or better than data reported for other devices that use BUA, SOS, or a calculated index as the measurement parameter [23–27]. The good performance by the QUS-2 with BUA may reflect an advantage of its scanning design to locate an anatomically defined ROI.

Table 4. Sensitivity, specificity and positive and negative predictive value (PV+ or –) for fractures of the spine, wrist or hip at various *T*-score cut-points determined for each bone mass method

	Calc BUA				TH BMD				LS BMD				FN BMD			
Cut-point	–1	–1.5	–2	–2.5	–1	–1.5	–2	–2.5	–1	–1.5	–2	–2.5	–1	–1.5	–2	–2.5
Sensitivity (%)	79	67	47	28	73	55	39	20	67	58	47	31	84	69	44	28
Specificity (%)	39	54	69	83	42	58	73	86	38	50	65	75	29	49	66	83
PV+ (%)	33	36	37	39	33	34	35	35	30	31	35	32	31	34	34	39
PV– (%)	83	81	77	75	80	77	75	74	75	75	76	74	82	80	75	75

It should also be noted that the precision we observed for the QUS-2 in this study represents the aggregate performance obtained at five centers with multiple operators. Precision was even better in a single-center, 200-subject study [24].

There were several weaknesses of this study. The axial measurements were performed on both Hologic and Lunar densitometers, resulting in the use of different databases for the determination of osteoporosis and osteopenia as provided by the manufacturer. Furthermore, rather than deriving *T*-scores for these devices from standardized BMD values and using our younger population, we utilized the manufacturers' *T*-scores. These are the normative reference points commonly used in clinical practice. Despite the potential for large discrepancies in the results, results of the QUS-2 and axial DXA were remarkably similar, both in our young normal reference population and in the older at-risk population. We confirmed this similarity by comparing results for standardized spine and hip BMD *T*-scores derived from our young normal reference population with *T*-scores derived from a set of common, widely accepted reference data (data not shown). Second, the study population we utilized was healthy and Caucasian. While we were able to determine the prevalence of osteoporosis and osteopenia in Caucasian women and the ability of the QUS-2 to discriminate between women with and without fractures in this group, this study does not provide data in men or women of other ethnicities. Neither does it apply to women who are older than 85 years and who are frequently more frail. In addition, we excluded patients on glucocorticoids, who may have significant differences in ultrasound measurements versus axial assessment [28]. Third, this was a cross-sectional study design that examined the QUS-2's ability to discriminate between women with and without fractures. Although a prospective study design would have been more desirable, many cross-sectional studies have demonstrated fracture risk estimates (relative risks or odds ratios) that are comparable to prospective studies conducted in the same cohorts [4,29–32]. Future prospective studies will be needed to confirm these cross-sectional results for the QUS-2 and demonstrate its ability to predict fracture.

Many studies have shown that the WHO criteria result in different *T*-scores with different devices including axial DXA or quantitative computed tomography (QCT), peripheral forearm devices, heel ultrasound devices, and ultrasound devices that examine other peripheral bones [33–46]. Miller and colleagues [45,47,48] have consistently urged the establishment of a standardized database on all available devices both to reduce *T*-score discrepancies and link a common bone mass value to risk. This would not only provide more uniform *T*-score classifications, but should also improve fracture prediction. While we were not able to approach that goal, we did obtain data from two manufacturers' DXA devices and compared them with this new peripheral unit. New devices will continually become available, and it appears reasonable to compare new devices to axial devices in routine use.

In this study, we identified a small set of patients with coexisting fractures and normal total hip bone density. The QUS-2 was the only device that was able to discriminate between fracture and nonfracture in this unusual group. It may be that the quality of bone, as assessed by ultrasound, is significantly different than the quantity of bone mass, as assessed by standard bone mineral densitometry or DXA techniques. Because the heel is rich in trabecular bone, which experiences more rapid turnover than cortical bone, other assessments of trabecular bone (e.g., QCT) may be needed to examine this subset of patients.

In summary, we found that the QUS-2 calcaneal ultrasonometer is a precise, reliable and reproducible method for the classification of Caucasian women with osteoporosis and osteopenia. Furthermore, it is able to discriminate between fracture and nonfracture status to a degree that is similar to DXA measures of the hip and spine.

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