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Original Article

The ability of calcaneal and multisite quantitative ultrasound variables in the identification of osteoporosis in women and men

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ABSTRACT

Objectives: The aim of this study was to assess the ability of calcaneal and multisite quantitative ultrasound (QUS) parameters in the identification of osteoporosis in women and men.

Patients and methods: A total of 131 women (mean age 53.7±11.9 years; range, 21 to 79 years) and 109 men (mean age 57.8±13.7 years; range, 24 to 85 years) whose bone mineral density (BMD) at the spine and proximal femur was measured between January 2010 and January 2012, using dual-energy X-ray absorptiometry (DXA) were included. Acoustic bone properties were also examined using both a calcaneal and a multisite QUS. The receiver operating characteristic analysis with the calculation of areas under the curve (AUCs) to evaluate the ability of both QUS devices for the identification of osteoporosis. We also calculated a lower and an upper threshold at a specificity of 90% and at a sensitivity of 90%, respectively, for the identification of osteoporosis along with a threshold/cut-off value with the best compromise between sensitivity and specificity.

Results: All calcaneal QUS parameters showed significant AUCs within the range of 0.712 (for Broadband Ultrasound Attenuation [BUA]) and 0.764 (for Speed of Sound [SOS]) in women and ranging from 0.661 (for BUA) to 0.735 (for SOS) in men, while only radial SOS of the multisite QUS demonstrated a significant AUC value of 0.661 for identifying osteoporosis in women. A Quantitative Ultrasound Index T-score of -1.53 for women and -1.68 for men showed sensitivity and specificities around 70%.

Conclusion: Based on the results of this study, all calcaneal QUS parameters in both women and men and possibly radial SOS measurements of the multisite QUS in women may be helpful for the identification of osteoporosis.

Keywords: Calcaneal quantitative ultrasound, diagnostic ability, dual-energy X-ray absorptiometry, multisite quantitative ultrasound, osteoporosis.

Significant mortality and disability are associated with osteoporosis (OP) and related fractures with deaths and lost years of healthy life as defined as disability-adjusted life years having been almost doubled in the last decade across the world.[1] It is well known that decrease in bone mineral density (BMD) is an internationally validated fundamental risk factor for fractures in both females and males, albeit not the sole one.[2] The BMD at a T-score equal to or less than -2.5 standard deviations, defined as OP,[3] is widely used as a case finding strategy for the prevention of hip fractures with other clinical risk factors including the Fracture Risk Assessment Tool (FRAX®) based strategies.[4] Bearing in mind that OP is a treatable disorder with evidence-based pharmacological and/or non-pharmacological options for reducing the risk of fractures, it seems crucial to diagnose OP to prevent fractures associated with OP.[5]

Focusing on fracture risk assessment, the BMD measurement using dual-energy X-ray absorptiometry (DXA) is still considered the gold standard, while the quantitative ultrasound (QUS) has emerged as an alternative to DXA for the prediction of OP-related fracture risk in the late 1990s.[2,6] Among a number of QUS technologies providing acoustic characteristics

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of bone at various skeletal sites including the calcaneus, metatarsal bones, tibia, patella, radius, and phalanges, calcaneus was considered the only validated site for the employment of QUS in OP and the use of validated calcaneal QUS devices was recommended to predict the risk of fractures in both women and men by the International Society for Clinical Densitometry (ISCD).[7] The fracture predictive ability of calcaneal QUS including hip and vertebral fractures as well as other non-spinal fractures similar to the capability of DXA BMD and independently of BMD has been confirmed in a meta-analysis.[8] Recently, multisite QUS has been demonstrated to be a significant predictor of clinical vertebral and non-vertebral fractures as measured at the radius, tibia, and phalanges in only women in a large cohort.[9]

Since the prevention of osteoporotic fractures is the ultimate goal in the management of OP, it is unquestionable that fracture risk prediction is of utmost importance. However, management of OP varies depending on countries. While reimbursement criteria for OP treatment are based on fracture risk in some countries, OP medications are reimbursed based solely on BMD not even considering previous fractures.[10] Therefore, there is still a need for early diagnosis of OP to take preventive measures for fractures. Given the fact that the availability of DXA shows considerable variances in countries, not exceeding 37.5 DXA units per million individuals and being as low as 1.2 DXA units per million in some European countries,[10] other reliable tools may be required for the detection of low bone mass. At this point, QUS offers a valuable option without any exposure to ionizing radiation and with other characteristics such as easiness to use, shorter scanning duration than DXA, portability, ability to investigate structural properties of bone, and wider availability at low costs being also economically advantageous for finding cases with OP or low bone mass.[6,7]

While a previous meta-analysis did neither recommend nor refute calcaneal QUS to exclude or confirm the diagnosis of OP based on DXA BMD due to the heterogeneity of methodology of studies on its diagnostic accuracy,[11] a very recent systematic review indicated the potential usefulness of calcaneal QUS as a prescreening tool for assessing OP providing that a consensus can be reached as to which variable to use as well as device-specific cut-off values for QUS parameters with satisfactory sensitivity and specificity for the detection or elimination of OP.[12]

In the present study, we aimed to evaluate the utility of calcaneal and multisite QUS parameters in the identification of DXA BMD-determined OP in various sites and to provide cut-off values for ruling in or out OP in women and men.

PATIENTS AND METHODS

This study included a total of 131 women (mean age 53.7±11.9 years; range, 21 to 79 years) and 109 men (mean age 57.8±13.7 years; range, 24 to 85 years) who were referred to our bone assessment laboratory for DXA BMD measurement at the lumbar spine and proximal femur as the usual practice between January 2010 and January 2012. Among 10 to 15 individuals having DXA BMD measurements, one to three individuals were randomly selected each working day depending on busyness of the schedule of our laboratory to participate in the study and to have additional bone measurements as defined in the study protocol (i.e., calcaneal and multisite QUS measurements in addition to usual DXA BMD measurements). Since our aim was to assess the ability of QUS parameters to predict DXA BMD measurements, but not to evaluate any other factors relevant to OP, there were no exclusion criteria, except for those associated with contraindications to using QUS transducers such as open wounds and physical compromises that would be misleading in the interpretation of QUS results such as upper or lower limb edema, neurological and orthopedic problems affecting the lower limbs as well as unwillingness to participate in the study. A patient information sheet including demographic and clinical characteristics of the participants including menopausal status, physical activity level (as assessed categorically using the International Physical Activity Questionnaire [IPAQ])[13] designated as low, if the participant reported no or some inadequate activity; moderate, if she/he walked for 30 min for ≥5 days in a week or was involved in an activity of at least 600 MET-min/week; and high, if she/he was involved in an activity of at least 3000 MET-min/week), her/his or family history of previous osteoporotic fractures and hip fractures, secondary OP causes such as premature menopause before the age of 45 years, diabetes mellitus (DM), hyperthyroidism, hypogonadism, celiac disease, and chronic liver disease, smoking and alcohol consumption (≥3 units daily), other diseases, particularly rheumatoid arthritis, and medications (i.e., corticosteroids at a dose of 5 mg of prednisolone or equivalent for more than three months, or anti-osteoporotic medications

was completed. A written informed consent was obtained from each patient. The study protocol was approved by the local Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

DXA BMD measurements

The BMD measurements were made at the lumbar spine and the hip using a Hologic QDR-4000 device (Hologic, Waltham, MA, USA). As suggested by the ISCD, BMD of the L1 to L4 vertebrae (two or three vertebrae excluding evidently abnormal or non-assessable vertebra(e) and those differing with a T-score more than 1.0 from the adjacent one), femoral neck, and total femur were included in the data analysis.[14] The OP diagnosis was made according to the World Health Organization criteria.[6] A participant with a T-score ≤-2.5 in any region of interest (ROI) was diagnosed as having OP. Those with a T-score was between -1.0 and -2.5 as the lowest T-score in any ROI were considered osteopenic (or with low bone mass) and normal if the T-score was ≥-1.0 in all ROI.[3] For premenopausal women and for men younger than 50 years, a Z-score of ≤-2.0 was used for defining BMD below the expected range for age, considered having OP and a Z-score of >-2.0 was considered within the expected range for age, considered being normal.[14]

Calcaneal QUS measurements

We used a gel-coupled calcaneal QUS device in this study (Sahara® Clinical Bone Sonometer, Hologic, Waltham, MA, USA) which measures broadband ultrasound attenuation (BUA) (in dB/MHz) and the speed of sound (SOS) (in m/s) and calculates Quantitative Ultrasound Index (QUI) [QUI= (0.41 × BUA) + (0.41 × SOS)-571], a QUI T-score, and estimated heel BMD (eBMD) (in g/cm^2) [eBMD=0.002592× (BUA + SOS) - 3.687]. The stability of QUS parameters was ensured by performing a daily quality control using a phantom provided by the manufacturer. We used the same calcaneal QUS device throughout the study with the same operator conducting measurements who was blind to the study protocol. We measured both heels twice with repositioning of the feet. We calculated the mean of the two calcaneal QUS measurements for each foot and employed the lowest mean value in statistical analyses.

Multisite QUS measurements

We used a multisite QUS device in this study (Sunlight Omnisense® 8000S, Sunlight Medical Inc., Somerset, NJ, USA) which measures axially transmitted SOS (in m/sec) through distal one-third radius at the forearm, mid-shaft tibia at the lower leg, and proximal phalanx III of the finger as well as metatarsal V of the foot with three different handheld probes, one for both the distal radius and mid-shaft tibia, one for the third phalanx, and the other for the fifth metatarsal bone. In the Sunlight Omnisense® 8000S device, two transducers in the handheld probe tangentially scanning the measurement area generate pulsed ultrasound waves at a frequency of 1.25 MHz which are propagated along the bone surfaces and afterwards are detected by two additional transducers in the probe. The SOS values obtained are determined by the duration of the time for the ultrasound waves to move through the emission and the detection.

The SOS measurements were carried out at distal one-third radius and mid-shaft tibia in all participants at both sides. We measured SOS only once due to the time-consuming nature of the multisite measurement. The SOS of the proximal phalanx of the third finger was not obtained in all subjects, as we did not have the specific probe for this site at the beginning of the study. Also, we did not measure the SOS of the fifth metatarsal, as we never had the probe for this site. After applying the ultrasound gel to the skin at the measurement sites, the ultrasound probe was located at a midpoint (determined using a tape measure) along the long axis of bone to be measured. Daily quality control was performed using a phantom as recommended by the manufacturer. The same operator carried out the SOS measurements with the same device throughout the study. Among the both side single measurements of SOS at the three sites, lower values obtained regardless of the dominant side were included in statistical analyses.

Precision of QUS parameters

The short-term precision of the QUS parameters was calculated as the root-mean-square coefficient of variation (RMS CV %) using duplicate measurements of the left heel in the study participants for the Sahara® and using 30 duplicate measurements of left radius SOS, tibial SOS, and phalangeal SOS in a group of individuals comprised of women and men for the Sunlight Omnisense® employing the following formula proposed by Glüer et al.[15] RMS CV %= $\sqrt{\sum CVi^2 / n} \times 100$ (RMS: Root mean square; CV: Coefficient of variation; n: Number of subjects).

Table 1. Demographic and clinical characteristics of women and men with and without osteoporosis

	Women									Men								
	With OP (n=49)				Without OP (n=82)					With OP (n=37)				Without OP (n=72)				
Characteristics	n	%	Mean±SD	Range	n	%	Mean±SD	Range	*p*	n	%	Mean±SD	Range	n	%	Mean±SD	Range	*p*
Age (year)			55.6±13.0	26-79			52.6±11.2	21-78	0.165*			55.1±13.7	28-80			59.2±13.7	24-85	0.139*
Weight (kg)			68.8±10.4				70.5±12.9		0.431*			75.6±12.8				79.4±13.6		0.167*
Height (m)			1.6±0.1				1.6±0.1		0.109*			1.7±0.1				1.7±0.1		0.976*
BMI (kg/m^2)			28.3±4.1				28.2±5.0		0.971*			25.8±3.0				27.2±4.3		0.074*
Menopause	39/10	79.6/20.4			57/25	69.5/30.5			0.207**	NA				NA				-
Menopause age (year)			44.3±5.8				46.5±5.6		0.077*	NA				NA				-
Estrogen use (ever)	2/47	4.1/95.9			8/74	9.8/90.2			0.320**	NA				NA				-
History of previous fracture	4/45	8.2/91.8			8/74	9.8/90.2			1.000**	3/34	8.1/91.9			5/67	6.9/93.1			1.000**
Parent with hip fracture	2/47	4.1/95.9			3/79	3.7/96.3			1.000**	0/100	0.0/100.0			1/71	1.4/98.6			1.000**
Current smoking	10/39	20.4/79.6			15/67	18.3/81.7			0.820*	8/29	21.6/78.4			22/50	30.6/69.4			0.372*
Number of cigarettes (day)			9.5±6.3				11.6±8.2		0.381*			15.3±6.4				18.3±10.2		0.324*
Years smoked			19.2±9.2				22.5±8.1		0.266*			19.2±10.2				24.2±14.9		0.260*
Alcohol use	0/49	0.0/100.0			0/82	0.0/100.0			-	0/37	0.0/100.0			3/69	4.2/95.8			0.324*
Secondary OP causes	23/26	46.9/53.1			30/52	36.6/63.4			0.273**	8/29	21.6/78.4			27/45	37.5/62.5			0.129**
Physical activity									0.808**									0.817**
Low	30	61.2			45	54.9				10	27.0			24	33.3			
Moderate	14	28.6			27	32.9				21	56.8			38	52.8			
High	5	10.2			10	12.2				6	16.2			10	13.9			
Diseases																		
Rheumatoid arthritis	3/46	6.1/93.9			11/71	13.4/86.6			0.250**	0/37	0.0/100.0			0/72	0.0/100.0			-
Others rheumatic diseases	4/45	8.2/91.8			4/78	4.9/ 95.1			0.471**	2/35	5.4/94.6			9/63	12.59/87.5			0.327**
Diabetes mellitus	3/46	6.1/93.9			12/70	14.6/85.4			0.166**	2/35	5.4/94.6			19/53	26.4/73.6			0.009**
Thyroid disease	3/46	6.1/93.9			10/72	12.2/87.8			0.369**	2/35	5.4/94.6			0/72	0.0/100.0			0.113**
Pulmonary diseases	5/44	10.2/89.8			3/79	3.7/96.3			0.419**	1/36	2.7/97.3			6/ 66	8.3/91.7			0.419**
Cancer	2/47	4.1/95.9			2/80	2.4/97.6			0.630**	1/36	2.7/97.3			1/ 71	1.4/98.6			1.000**
Renal insufficiency	1/48	2.0/98.0			1/81	1.2/98.8			1.000**	1/36	2.7/97.3			0/72	0.0/100.0			0.339**
Corticosteroid use	15/34	30.6/69.4			19/63	23.2/76.8			0.411**	4/33	10.8/89.2			9/63	12.5/87.5			1.000**
Corticosteroid dose (mg)			12.6±20.3				6.8±6.4		0.316*			6.3±2.5				6.3±3.8		0.715*
Months of corticosteroids			71.5±82.2				59.5±87.0		0.715*			15.8±14.2				23.2±22.4		0.556*
OP medication use	8/41	16.3/83.7			2/80	2.4/97.6			0.006**	0/37	0.0/100.0			0/72	0.0/100.0			-

SD: Standard deviation; BMI: Body mass index; NA: Not applicable; OP: Osteoporosis; * Independent Samples Test; ** Chi-Square test; Yes/No are given for dichotomous data.

Table 2. Area under the ROC curves for osteoporosis in any ROI including lumbar spine, femoral neck, and total hip

	Women (n=131)					Men (n=109)				
				95% CI					95% CI	
QUS variables	Area	SE	*p**	Lower	Upper	Area	SE	*p**	Lower	Upper
QUI	0.747	0.044	<0.001	0.661	0.832	0.720	0.050	<0.001	0.622	0.817
QUI T-score	0.744	0.044	<0.001	0.658	0.830	0.720	0.050	<0.001	0.623	0.817
BUA (dB/MHz)	0.712	0.047	<0.001	0.621	0.804	0.661	0.054	0.006	0.556	0.767
SOS (m/s)	0.764	0.043	<0.001	0.680	0.848	0.735	0.048	<0.001	0.641	0.830
eBMD (g/cm^2)	0.744	0.044	<0.001	0.657	0.830	0.727	0.049	<0.001	0.630	0.824
Radial SOS (m/s)	0.661	0.050	0.002	0.564	0.758	0.448	0.060	0.372	0.330	0.565
Radial SOS T-score	0.673	0.049	0.001	0.576	0.770	0.449	0.059	0.382	0.332	0.565
Tibial SOS (m/s)	0.586	0.050	0.100	0.487	0.665	0.595	0.060	0.107	0.477	0.712
Phalangeal SOS (m/s) #	0.526	0.076	0.728	0.378	0.626	0.492	0.061	0.897	0.371	0.612

ROC: Receiver operating characteristics; ROI: Region of interest; CI: Confidence interval; QUS: Quantitative ultrasound; SE: Standard error; QUI: Quantitative Ultrasound Index; BUA: Broadband ultrasound attenuation; SOS: Speed of sound; eBMD: Estimated heel bone mineral density; * p-value for area under the curve (significance level=0.5); # Measured in broadband ultrasound attenuation.

Statistical analysis

Statistical analysis was performed using the SPSS software version 16.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed in mean and standard deviation (SD) for continuous variables and in number and percentage for categorical data. Based on the normality of the data using the Kolmogorov-Smirnov test, continuous variables were compared using the Student's t-test. Dichotomous variables were compared using the chi-square or Fisher's exact tests, depending on the number of variables in each cell. The receiver operating characteristic (ROC) analysis was used to analyze the ability of calcaneal QUS parameters and SOS at multiple sites to identify participants with DXA-determined OP. Areas under the ROC curves (AUCs) were calculated for each parameter. While ROC analysis was performed for calcaneal QUS (Sahara® device) parameters and radial and tibial SOS using the multisite QUS (Sunlight Omnisense®) in all study participants, the ROC analysis for phalangeal SOS was conducted separately in fewer participants. Specificity and sensitivity of cut-off values for QUS parameters at a level of 90% as the lower threshold

Table 3. Cut-off values for QUI and QUI T-score of the calcaneal QUS and radial SOS and its T-score of the multisite QUS to identify women and men with a high or low likelihood of osteoporosis

	Women (n=131)			Men (n=109)		
QUS $_{\text{variables}}$	Cut-off value	Specificity	Sensitivity	Cut-off value	Specificity	Sensitivity
QUI $_{\text{lower threshold}}$	63.80	0.902	0.184	67.85	0.903	0.169
QUI $_{\text{best compromise}}$	76.75	0.720	0.714	79.55	0.736	0.730
QUI $_{\text{upper threshold}}$	85.1	0.488	0.898	93.0	0.361	0.919
QUI T-score $_{\text{lower threshold}}$	-2.28	0.902	0.184	-2.35	0.903	0.189
QUI T-score $_{\text{best compromise}}$	-1.53	0.720	0.714	-1.68	0.722	0.703
QUI T-score $_{\text{upper threshold}}$	-1.03	0.427	0.898	-0.88	0.375	0.919
Radial SOS $_{\text{lower threshold}}$	3935.5	0.902	0.327	3888.5	0.903	0.162
Radial SOS $_{\text{best compromise}}$	4073.0	0.598	0.592	4073.5	0.472	0.486
Radial SOS $_{\text{upper threshold}}$	4254.0	0.232	0.898	4249.0	0.097	0.919
rSOS T-score $_{\text{lower threshold}}$	-2.35	0.902	0.327	-1.85	0.903	0.108
rSOS T-score $_{\text{best compromise}}$	-0.95	0.585	0.592	-0.25	0.444	0.486
rSOS T-score $_{\text{upper threshold}}$	0.85	0.232	0.898	1.15	0.083	0.919

QUI: Quantitative Ultrasound Index; QUS: Quantitative ultrasound; SOS: Speed of sound; rSOS: Radial SOS.

Table 4. Analysis of Variance and non-parametric tests results for QUS parameters

	Variable values							
			Between groups				95% CI (Mean difference)	
QUS variables	Bone status	Mean±SD	for χ^2	*p*	Multiple comparisons	*p*	Lower	Upper
A) In women with osteoporosis or low bone mass (osteopenia) or those with 'normal' bones								
QUI Sahara®			16.777	<0.001*				
OP	49	71.3±11.3			"OP" vs. "OPN"	0.003†	-15.17	-2.67
OPN	45	80.2±11.5			"OP " vs. "NML"	<0.001†	-22.50	-9.32
NML	37	87.2±15.7			"OPN" vs. "NML"	0.039†	-13.71	-0.28
QUI T-score Sahara®			16.846	<0.001*				
OP	49	-1.85±0.64			"OP" vs. "OPN"	0.004†	-0.64	-0.14
OPN	45	-1.36±0.65			"OP " vs. "NML"	<0.001†	-1.28	-0.53
NML	37	-0.94±0.89			"OPN" vs. "NML"	0.029†	0.14	0.84
BUA Sahara®			18.308	<0.001**				
OP	49	57.1±11.1			"OP" vs. "OPN"	0.001‡	-	-
OPN	45	63.7±10.1			"OP " vs. "NML"	<0.001‡	-	-
NML	37	69.2±14.3			"OPN" vs. "NML"	0.119‡	-	
SOS Sahara®			18.465	<0.001*				
OP	49	1508.8±17.8			"OP" vs. "OPN"	0.003†	-24.36	-4.23
OPN	45	1523.1±19.1			"OP " vs. "NML"	<0.001†	-37.65	-16.41
NML	37	1535.9±25.2			"OPN" vs. "NML"	0.017†	-23.56	-1.92
eBMD Sahara®			16.507	<0.001*				
OP	49	0.375±0.072			"OP" vs. "OPN"	0.004†	-0.093	-0.015
OPN	45	0.429±0.072			"OP " vs. "NML"	<0.001†	-0.141	-0.058
NML	37	0.475±0.099			"OPN" vs. "NML"	0.030†	-0.088	-0.004
Radial SOS Sunlight Omnisense®			5.429	0.005*				
OP	49	4042.7±162.2			"OP" vs. "OPN"	0.139†	-137.4	14.7
OPN	45	4104.0±152.4			"OP " vs. "NML"	0.004†	-190.5	-30.0
NML	37	4152.9±149.6			"OPN" vs. "NML"	0.334†	-130.7	32.8
Tibial SOS Sunlight Omnisense®			3.540	0.032*				
OP		3726.0±129.3			"OP" vs. "OPN"	0.948†	-75.95	58.26
OPN	45	3734.9±156.2			"OP " vs. "NML"	0.037†	-145.31	-3.74
NML	37	3800.6±121.3			"OPN" vs. "NML"	0.082†	-137.81	6.45
Phalangeal SOS Sunlight Omnisense®			0.438	0.647*				
OP	28	3952.0±243.3			"OP" vs. "OPN"	NA	-	-
OPN	45	3939.8±230.3			"OP " vs. "NML"	NA	-	-
NML	37	4015.4±256.7			"OPN" vs. "NML"	NA	-	-
B) In men with osteoporosis or low bone mass (osteopenia) or those with 'normal' bones								
QUI Sahara®			14.680	0.001**				
OP	37	77.2±10.8			"OP" vs. "OPN"	0.001##	-	-
OPN	36	87.5±13.9			"OP " vs. "NML"	0.001##	-	-
NML	36	87.1±16.8			"OPN" vs. "NML"	0.366##	-	-
QUI T-score Sahara®			14.869	0.001**				
OP	37	-1.82±0.63			"OP" vs. "OPN"	0.001##	-	-
OPN	36	-1.20±0.83			"OP " vs. "NML"	0.001##	-	-
NML	36	-1.22±0.99			"OPN" vs. "NML"	0.309##	-	-
BUA Sahara®			7.845	0.020**				
OP	37	65.7±10.7			"OP" vs. "OPN"	0.013##	-	-
OPN	36	73.2±10.9			"OP " vs. "NML"	0.026##	-	-
NML	36	70.8±16.9			"OPN" vs. "NML"	0.456##	-	-
SOS Sahara®			17.023	<0.001**				
OP	37	1513.8±16.4			"OP" vs. "OPN"	0.001##	-	-
OPN	36	1532.2±23.5			"OP " vs. "NML"	<0.001##	-	-
NML	36	1533.4±26.1			"OPN" vs. "NML"	0.244##	-	-
eBMD Sahara®			15.537	<0.001**				
OP	37	0.410±0.067			"OP" vs. "OPN"	0.001##	-	-
OPN	36	0.477±0.088			"OP " vs. "NML"	0.001##	-	-
NML	36	0.474±0.106			"OPN" vs. "NML"	0.366##	-	-
Radial SOS Sunlight Omnisense®			0.043	0.958*				
OP	37	4052.2±228.9			"OP" vs. "OPN"	NA	-	-
OPN	36	4061.6±131.6			"OP " vs. "NML"	NA	-	-
NML	36	4063.3±146.8			"OPN" vs. "NML"	NA	-	-
Tibial SOS Sunlight Omnisense®			1.507	0.226*				
OP	37	3846.8±113.4			"OP" vs. "OPN"	NA	-	-
OPN	36	3886.1±104.4			"OP " vs. "NML"	NA	-	-
NML	36	3884.2±109.8			"OPN" vs. "NML"	NA	-	-
Phalangeal SOS Sunlight Omnisense®			0.050	0.952*				
OP	32	3958.3±162.7			"OP" vs. "OPN"	NA	-	-
OPN	31	3944.9±169.1			"OP " vs. "NML"	NA	-	-
NML	32	3951.3±174.3			"OPN" vs. "NML"	NA	-	-

ANOVA: Analysis of Variance; QUS: Quantitative ultrasound; QUI: Quantitative Ultrasound Index; SD: Standard deviation; OP: Osteoporosis; OPN: Osteopenia; NML: Normal; BUA: Broadband ultrasound attenuation; SOS: Speed of sound; eBMD: Estimated heel bone mineral density; NA: Not applicable; p values for * ANOVA test; ** Kruskal-Wallis test, † Tukey test; ‡ Mann-Whitney U test.

and as the upper threshold, respectively, as suggested by Krieg et al.[7] to identify individuals with a high or low likelihood of OP and cut-off values showing the best compromise between specificity and sensitivity were identified using the coordinate points of the ROC curve. Homogeneity of variances was tested for all variables. The analysis of variance (ANOVA) was used to compare differences in QUS parameters in women and men with DXA-determined OP or low bone mass (osteopenia) or those with normal bones (identification of bone status was described in the DXA BMD measurements section). The Tukey's honestly significant difference (HSD) post-hoc test was used to evaluate significant differences between the mean values of the groups. For those variables which did not have equal variances, non-parametric tests were employed. Correlation between BMD at various ROIs and QUS parameters was tested using the Pearson correlation coefficients. A p value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the demographic and clinical characteristics of the study participants. There was no significant difference in the demographic and clinical characteristics of women and men with or without OP, except for the presence of DM (the percentage of men with DM being significantly higher in men without OP than those with OP) and OP medication use (significantly higher percentage of women with OP having been using OP medications than those without).

The OP discriminative ability of QUS parameters expressed as AUCs derived from the ROC curves are shown in Table 2, with the highest significant AUC for calcaneal QUS SOS in women (0.764) and men (0.735) and with multisite QUS radial SOS only in women (0.673).

Lower and upper thresholds/cut-off values at ≥90% specificity and at ≥90% sensitivity, respectively, for QUI and QUI T-score of the calcaneal QUS and radial SOS and its T-score as measured using the multisite QUS and cut-off values showing the best compromise between specificity and sensitivity are shown in Table 3.

Table 4 shows the means of QUS parameters in women and men, respectively, with OP, osteopenia, and normal bones as well as ANOVA and non-parametric tests results showing the significance of mean differences between those with OP and osteopenia, OP and normal bones, and osteopenia and normal bones.

Correlation between BMD at various ROIs and QUS parameters in the all study participants (women and men combined) is shown in Table 5. While all calcaneal QUS parameters showed statistically significant correlations with DXA BMD at different ROIs with r values ranging from 0.305 to 0.422, among multisite QUS parameters, only tibial SOS showed significant correlations with DXA BMD measurements at all ROIs and radial SOS demonstrated a significant correlation with only L1-L4 BMD. When the same analysis was made separately for women and men, the difference was that radial SOS was also significantly correlated with femoral neck BMD (r=0.181, p=0.038)

Table 5. Pearson correlation coefficients between DXA BMD measurements and QUS parameters

	L1-L4 BMD	Femoral neck BMD	Total hip BMD	Radial SOS	Tibial SOS	Phalangeal SOS
QUI	0.409 p<0.001	0.350 p<0.001	0.412 p<0.001	0.138 p=0.033	0.164 p=0.011	0.074 p=0.359
BUA	0.364 p<0.001	0.305 p<0.001	0.363 p<0.001	0.087 p=0.182	0.171 p=0.008	0.072 p=0.376
SOS	0.422 p<0.001	0.358 p<0.001	0.411 p<0.001	0.169 p=0.009	0.155 p=0.016	0.085 p=0.295
eBMD	0.416 p<0.001	0.352 p<0.001	0.413 p<0.001	0.136 p=0.035	0.167 p=0.010	0.074 p=0.358
Radial SOS	0.159 p=0.014	0.065 p=0.319	0.050 p=0.438		0.161 p=0.012	0.346 p<0.001
Tibial SOS	0.238 p<0.001	0.259 p<0.001	0.248 p<0.001			0.219 p=0.006
Phalangeal	0.034 p=0.675	0.026 p=0.747	-0.17 p=0.830			

DXA: Dual-energy X-ray absorptiometry; BMD: Bone mineral density; QUS: Quantitative ultrasound; SOS: Speed of sound; QUI: Quantitative Ultrasound Index; BUA: Broadband ultrasound attenuation; eBMD: Estimated heel BMD.

and tibial SOS did not show a significant correlation with total hip BMD (r=0.079, p=0.368) in women. In men, the BUA did not show a significant correlation with femoral neck BMD (r=0.101, p=0.294) and none of the multisite QUS parameters showed a significant correlation with DXA BMD at any ROI (separate data for women and men are not tabulated).

In addition, short-term *in vivo* precision of QUS parameters expressed as RMS CV % was found to be 3.53 for QUI, 4.33 for BUA, 0.36 for SOS, and 2.96 for eBMD for the Sahara® duplicate measurements and 0.69 for radial SOS, 0.65 for tibial SOS, and 1.29 for phalangeal SOS for the Sunlight Omnisense® duplicate measurements.

DISCUSSION

The results of the present study demonstrated the ability of calcaneal QUS parameters for identifying OP in both sexes with significant AUCs within the range of 0.712 (for BUA) and 0.764 (for SOS) in women and ranging from 0.661 (for BUA) to 0.735 (for SOS) in men. Consistent with our findings, the majority of studies using the same QUS device demonstrated similar AUCs varying from 0.697 to 0.797 for BUA, 0.735 to 0.792 for SOS, and 0.720 or 0.780 for QUI for the identification of OP at either spine or hip in postmenopausal women.[16-19] Lower or higher AUC values were reported in some studies which ranged between 0.662 and 0.678 for various QUS parameters for the discrimination of femoral neck OP or as 0.830 for QUI for OP at any site.[20,21] In men, while Adler et al.[22] demonstrated an AUC of 0.688 for QUI T-score for the identification of a central DXA T-score of ≤-2.0, lower than that in this study (for the identification of a DXA T-score of ≤-2.5), other studies evaluating the same QUS device used in this study in Chinese men reported AUC values between 0.762 and 0.800 for QUI or its T-score for the identification of OP either at the spine or hip.[23,24] Considering the results of these studies (albeit not based on head-to-head comparisons) as well as in ours, OP discrimination performance of calcaneal QUS seems to be slightly better in women than in men, one possible reason for which may be the difference in the rate of age-related changes in trabecular connectivity having been found more noticeable in women than in men, a feature that can be captured by QUS.[25,26] With regard to the OP identification ability of multisite QUS parameters, only radial SOS and its T-score demonstrated significant AUC values of 0.661 and 0.673 and solely in women in our study. The reason why radial SOS showed a significant OP discriminatory ability only in women, but not in men, can be attributed to sex-specific differences in the pattern of bone loss during ageing, which tended to result in more cortical porosity at the radius in women (particularly in their sixth decade) than in men with ageing, detectable by QUS SOS.[27,28] The better ability of calcaneal QUS for OP identification than that of the multisite QUS as found in our study is also supported by a number of studies. Cook et al.[29] found AUCs of 0.677 for distal radius, 0.582 for mid-shaft tibia, and 0.678 for phalangeal SOS which was lower than that of calcaneal BUA (0.766) of a different device for the identification of a T-score of ≤-2.5 at either spine or hip in postmenopausal women. Cepollaro et al.[30] demonstrated a significantly better OP discriminatory ability of stiffness index of a different calcaneal QUS device than amplitude-dependent speed of sound (AD-SOS) of a phalangeal QUS in corticosteroid-induced OP. Reported AUCs in two studies using the same device varied from 0.659 to 0.721 for radial SOS and from 0.604 to 0.709 for phalangeal SOS for the discrimination of OP at the hip or either at the spine or hip in women.[31,32] The discrepancy in the OP identification performance of the two devices can be explained by the different technology of each device and the measurement sites. Calcaneal QUS using transverse transmission through trabeculae measures mainly trabecular bone with a thin cortical layer. However, multisite QUS uses a cortical axial transmission technique at the radius and tibia and measures mainly the cortical bone.[6,7] Calcaneal QUS parameters are associated with the nature of trabeculae relevant to connectivity as well as BMD, all of which contributing to bone strength.[26] On the other hand, multisite QUS parameters at the radius and tibia are associated mainly with cortical bone characteristics, including density and porosity.[28] Bone loss occurs in an increased rate in the decade following menopause in women with the disproportionate loss of trabecular bone, followed by slower and similar losses of trabecular and cortical bone later in life and bone loss in men mimics this slow phase.[33] Therefore, it is not surprising that calcaneal QUS can detect these OP-associated changes at the calcaneus in women with a mean age of 53.7±12.0 and men with a mean age of 57.8±13.8, while multisite QUS cannot.

Our thresholds/cut-off values for a QUI value of ≤63.8 as the lower threshold for a high likelihood of OP and a QUI value of >85.3 as the upper threshold for a low likelihood of OP in women seem to be slightly higher than those indicated as ≤59 and >83 for Sahara® QUI[34] and our upper threshold seems to

be slightly lower than that suggested by Lippuner et al.[21] as a QUI value of 94. A QUI value of 76.8 and 79.5 and its T-score, -1.53 and -1.68, in women and men, respectively, showed an acceptable sensitivity and specificity compromise around 70 to 74% to rule in and to rule out OP in our study. The values for women were very similar to those demonstrated by Boonen et al.[18] as ≤73.9 and -1.61 for identifying OP at the spine or hip with a sensitivity and specificity 67.6% and 67.9%, respectively as well as to those of Ikeda et al.[17] (-1.58 for SOS and -1.52 for BUA with a sensitivity and specificity around 65 and 69%) comparable to the composite parameter derived from BUA and SOS, that is QUI, in our study. The case for radial SOS and its T-score for the identification of OP was different, which showed unsatisfactory sensitivity and specificity in both women and men. The suggested upper and lower radial SOS T-scores for the diagnosis of OP in women by other investigators for the same multisite QUS device were different from those of ours with an upper threshold T-score of -0.30 with a sensitivity of 96%[32] (vs. 0.85 with a sensitivity of 90% in our study) and -2.6[35] (vs. -2.35 in our study); but, at the expense of overestimation of OP with lower values than -0.30 (with a specificity of 32%),[32] as was the case in our study showing a lower specificity. We can reach the same conclusion by Damilakis et al.[31] who highlighted the negligible percentage of women with OP at the spine or femoral neck (1%) for radial SOS and failure of phalangeal SOS to identify women with OP with adequate certainty with the same QUS device used in this study.

The better ability of calcaneal SOS to reflect bone status was also supported by significant differences in all calcaneal QUS parameters without any exceptions in women with osteoporotic, osteopenic, and normal bones. On the contrary, among multisite QUS parameters, radial and tibial SOS values were found significantly different in those with osteoporotic and normal bones, not showing a significant difference between women with OP versus ostopenia or women with ostopenia or normal bones. Phalangeal SOS values did not show a statistically significant difference according to bone status. All QUS values in women with OP were lower than those in any age group found in normative data studies including Spanish,[36] Greek,[37] and Portuguese (except for BUA being lower in women ≥70 years)[38] populations, as assessed using the Sahara® Clinical Bone Sonometer. In men, while all calcaneal QUS values, with the exception of BUA, significantly differed between those with OP and ostopenia as well as between those with OP and normal bones, they failed to differ between those with osteopenia and normal bones. The case for BUA values, not showing any difference between those with OP or osteopenia and normal bones, can be explained by similar BUA values in men with osteopenia and normal bones. It may be also speculated that BUA is not that sensitive to bone properties in men based on the data of a study, where BUA values obtained using a different QUS device were not found to be significantly different in non-osteoporotic men with fractures than those with fractures contrary to the situation in women, where it was found to be significantly different in any fracture group than non-osteoporotic women without fractures.[39] As for multisite QUS parameters, while radial and tibial SOS values significantly differed between osteoporotic and normal women, none of the SOS values demonstrated any significant difference across various bone stata in men. This situation can be explained by the findings of a very recent study which demonstrated more dramatic trabecular number decrease and trabecular separation increases in the distal radii of osteoporotic women than those in men with OP. Furthermore, men with OP were found to have better bone morphological features than healthy women at the tibia.[40] A high frequency device, such as the one we used, which has the ability of transmitting the cortical shell[28] seems to have detected unfavorable bone features in women with OP. It is also interesting to note that the mean radial and phalangeal SOS values in women with OP and radial SOS values in men with OP were all higher than those of the age group of 60-69 of healthy women and men with phalangeal SOS values being higher in men than those of the age group of 30-39 years in a North American reference population as measured using the same device.[41,42] Furthermore, the mean radial SOS values in women with OP (4042.7 m/s) in our study showed a similarity to those of the age group of 25.1-40 years (4041.5 m/s) who had the highest means in a Mexican female population[43] and our mean SOS values of the multisite QUS in women and men with OP resembled those with a T-score -1.0 or 0.0 in a Canadian population.[44] With all these data, we consider that our sample population might have stronger bones than those in other countries based on multisite QUS SOS values and with less likelihood of fractures. However, the concrete data reflect that age-standardized annual hip fracture incidence in women is much higher in our population than that in the US, Mexico, or Canada and our country is coded as the high-risk group for hip fractures, while the other countries are coded as having the medium risk.[45] This has an important implication that multisite

QUS SOS may not reflect DXA BMD which is the strongest predictor of fractures.[5] In accordance with this notion, despite relatively high and significant correlations between all calcaneal QUS parameters and DXA BMD at all ROIs in the entire study population, the Pearson correlation coefficients were low and not significant between multisite QUS parameters and BMD measures in this study, except for the tibial SOS. Regarding calcaneal QUS, our results were in line with the literature indicating correlation coefficients of between 0.480 and 0.530 in women and 0.400 and 0.430 for various Sahara® QUS parameters in men aged 55 years or older[46] and QUI with lumbar spine BMD with an r values of 0.478 ($p<0.001$).[18] On the other hand, mostly significant but lower correlations between the multisite QUS SOS and DXA BMD values have also been addressed in other studies of multisite QUS in which correlation coefficients (R values) for radial SOS and L1-L4, total hip or femoral neck BMD ranged from 0.215 to 0.295, those for tibial SOS ranged from 0.127 (for total hip, $p=0.070$) to 0.275, and for phalangeal SOS from 0.173 to 0.340 in postmenopausal women or in a combined group of women and men.[29,32,47] Significantly weak correlations between the multisite QUS parameters and axial DXA BMD may be the reason why multisite QUS parameters failed to detect OP at various axial ROIs in a similar way to calcaneal QUS. The reason why we were not able to find a significant correlation between phalangeal SOS and DXA BMD at any site can be attributable to the higher risk of improper positioning of the QUS probe due to greater anatomical variations in the phalanges of individuals, also relevant to other sites with unfavorable influences on accuracy of the SOS measurements.[47] The inferior reproducibility of phalangeal SOS than those of radial or tibial SOS may have contributed to this finding. Regarding the precision of multisite QUS parameters in our study, while the precision error of radial SOS were similar to that found by Knapp et al.[35] using the same formula (0.61), those for tibial and phalangeal SOS were higher than those found by the aforementioned study (0.43 and 0.72, respectively). The short term *in vivo* precision for calcaneal QUS parameters in our study ranging from 0.36 (for SOS) to 4.33 (for BUA) were comparable to those found in another study using the same calcaneal QUS device ranging from 0.36 (for SOS) to 4.88 for BUA.[36]

One of the limitations of this study is its relatively small sample size. However, various meaningful results comparable to the studies with much larger sample sizes[17,19,32,48] may provide a justification for its validity.

Furthermore, this study included young men and women under the age of 30 years. Thus, it can be argued that they may not have captured the true peak acoustic bone parameters. Calcaneal QUS parameters showed a different trend in this aspect varying across countries, while all calcaneal QUS parameters showed the highest values in the age group of ≤29 years in both sexes in two studies,[36,38] another study showed lower QUS parameters in the age group of 26-29 than those at 30-33 years.[37] However, normative data studies indicated lower values for radial and tibial SOS in women and men aged ≤29[41,42] or ≤25 years.[43] Due to the number of very few young women (n=6: one at the age of 21 and others between 25 and 29) and men (n=3: at the ages of 24, 28, and 29), we consider that their QUS parameters did not affect the results.

In addition, it can be speculated that the inclusion of a heterogeneous population with various diseases and particularly those using corticosteroids may have affected the results. However, we believe that the results may not lead to selection bias, since no statistically differences existed between women and men with OP and those without in terms of diseases the participants had or the status of corticosteroid use, except for DM which was more prevalent in men without OP, but only in about one forth. Although we cannot say whether this influenced the results or not, the paradoxical influence of type 2 DM on BMD characterized by an increase is well-known.[49] With regard to corticosteroid use, a study did not find any alterations in calcaneal QUS parameters in those with corticosteroid-induced or postmenopausal OP.[30] It is also important to note that in the European Male Ageing study, the exclusion of corticosteroid users or those being treated for DM was reported not to have influenced the results including the calcaneal QUS.[50] Nevertheless, the generalizability of the results may be still limited due to the diversity of the study sample.

Another limitation can be that we only measured the intra-observer precision error, but not the inter-observer precision error of the QUS measurement which would be significant, since QUS measurements would have been made by different operators in the real-world setting.

Finally, we were unable to measure the multisite QUS SOS more than once at the same side. Sievänen et al.[28] suggested three consistent consecutive measurements and an additional one in the presence of an outliner to obtain a valid multisite QUS SOS value. However, we attempted to compensate this drawback by including the lowest SOS value obtained in any of the sides.

Nonetheless, there are some strengths to this study. First, this study is one of the few studies[16,29,30,32] with head-to-head comparisons of different QUS technologies for the identification of OP in both women and men (not meaning fracture prediction) in a real clinical setting. We believe our results provide additional evidence on calcaneal QUS in women[12] in terms of its utility in the identification of OP with the established cut-off values and offer data on multisite QUS in women and men. However, the findings of this study failed to go beyond the conclusions of the very recent systematic review indicating the lack of a specific threshold below and above which we could be quite certain that an individual did or did not have OP.[12]

In conclusion, based on the results of this study, we suggest that calcaneal QUS parameters, particularly SOS, can identify both women and men with OP with fair AUCs, their identification ability being higher in women than in men. Only radial SOS of the multisite QUS seems to have an OP identification capability only in women with a relatively poor, but significant AUC. A QUI T-score of -1.53 for women and -1.68 for men with an acceptable sensitivity and specificity around 70% (but not with quite certainty) can be suggested for determining the risk of OP. Calcaneal QUS parameters are more dependent on DXA BMD than the multisite QUS measurements as reflected by significant differences in individuals with osteoporotic, osteopenic, or normal bones, higher correlation coefficients and higher shared variance with DXA BMD.

In circumstances where the availability of DXA is limited, calcaneal QUS in both women and men and possibly radial SOS measurements of the multisite QUS in women may help the identification of OP. However, further prospective studies with larger sample sizes are still needed to determine the utility of QUS with specific thresholds for the identification of OP.

Declaration of conflicting interests

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