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Accuracy of Quantitative Ultrasound Parameters in the Diagnosis of Osteoporosis

Research Article

Raluca Pais[1*], Remus Campean[2], Siao-Pin Simon[1], Calin R. Bolosiu[3], Laura Muntean[1], Horatiu D. Bolosiu[1]

1 Department of Internal Medicine II and Rheumatology, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca, 400012 Cluj-Napoca, Romania

[2] Department of Statistics, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca, 400012 Cluj-Napoca, Romania

[3] Department of Radiology, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj Napoca, 400012 Cluj-Napoca, Romania

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Abstract: Quantitative ultrasound (QUS) is of increasing interest for evaluation of osteoporosis because, compared with dual-energy X-ray absorptiometry (DXA), it is portable, less expensive, and radiation-free. The aim of our study was to determine the sensitivity, specificity, and cut-off values of quantitative ultrasound parameters in identifying patients with osteoporosis compared to the World Health Organization (WHO) standard definition. We performed a cross-sectional investigational study of 73 subjects, and determined total hip and lumbar spine T-scores by dual-energy X-ray absorptiometry (DXA) (Prodigy Advance Lunar-GE). The QUS parameters (broadband ultrasound attenuation [BUA], speed of sound, bone mineral density, the stiffness index, and QUS T-score) were determined with Sahara Hologic equipment. The AUC was 0.81 (95% CI 0.67 – 0.95, $p<0.05$) for speed of sound (SOS) and 0.76 (95% CI 0.62 – 0.90, $p<0.05$) for BUA for the patients with DXA T-scores $\geq$ -1 DS; the cut-off values were 1542.2 meters per second for SOS and 63.3 dB/MHz for BUA. In patients with DXA T-scores $\leq$ - 2.5 DS, AUC was 0.80 (95% CI 0.70 – 0.90, $p<0.05$) for SOS, and 0.76 (95% CI 0.65 – 0.87, $p<0.05$) for BUA. The cut-off values were 1504.95 meters per second for SOS and 49.5 dB/MHz for BUA. Pearson correlation coefficients were positive and statistically significant (> 50%) for all QUS parameters in both groups, (2-tailed, $p<0.05$). QUS parameters correctly identified normal patients (false negative 34.21% and false positive 2.53%) and those with osteoporosis (false negative 8.55% and false positive 7.82%). The patients with QUS parameters between the cut-off values corresponding to DXA T-scores of -1 SD and - 2.5 SD should be further evaluated by DXA.

Keywords: *Osteoporosis • Quantitative ultrasound • speed of sound • broadband ultrasound attenuation • T-Score • DXA • bone mineral density*

1. Introduction

The definition of osteoporosis according to the World Health Organisation (WHO) is "a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture" [1]. Osteoporosis has a significant impact on public health through the increased rates of morbidity and mortality and economic costs associated with fractures.

Dual-energy X-ray absorptiometry (DXA) is the most widely used technique for osteoporosis screening, and it is still considered the gold standard for that diagnosis.

Quantitative ultrasound technique (QUS) was developed and has been used in clinical practice since the 1990s and is in second position among validated methods for evaluating bone strength, after DXA of the spine and proximal femur [2]. The absence of exposure to ionizing radiation, the portability, the low cost of the machines, and the encouraging results elicited by the

* E-mail: ralu_pais@yahoo.com

first clinical studies are among the most appealing characteristics of quantitative ultrasonography. Several large prospective studies have shown that QUS can predict future fracture risks nearly as well as DXA, but the use of this technique for screening and identifying people with osteoporosis is still controversial. Osteoporosis cannot be defined using QUS, and WHO criteria are not applicable for this technique. The role of ultrasound might be only to identify patients at risk for osteoporosis as a first-line pre-screening tool, but there are no consensus criteria yet.

The aims of this paper are to establish the accuracy of QUS in the diagnosis of osteoporosis on the basis of the correlation between QUS and DXA parameters and then to identify which one of the QUS parameters is the most reliable in discriminating among normal, osteopenic, and osteoporotic patients. We calculated the cut-off values for QUS parameters related to DXA thresholds for osteopenia and osteoporosis.

2. Material and Methods

We performed a cross-sectional investigational study on 73 subjects, including 68 postmenopausal women (mean age 61.37 years) and 5 men (mean age 54.78 years) seen in the Rheumatology Department in Cluj-Napoca, Romania. All subjects were evaluated by dual-energy X-ray absorptiometry (DXA) with a Prodigy Advance Lunar-GE device. DXA measurements at the lumbar spine ($L_2 – L_4$) and total hip were performed by a certified physician. According to WHO criteria [3], the patients were then classified as normal, osteopenic, or osteoporotic by the DXA T-score applied at lumbar spine and total hip.

All patients were consecutively evaluated by QUS of the left calcaneus with Sahara Hologic equipment; the ankle was maintained in 90° flexion to ensure that all the measurements were processed in the correct area, and the transducers were coupled to the skin through a coupling gel. An appropriate phantom test was performed before each QUS measurement. The QUS parameters were broadband ultrasound attenuation (BUA) (dB/MHz) and the speed of sound (SOS) (meters per second) measured in a fixed region of the calcaneus. The composite parameter, quantitative ultrasound index (QUI), was calculated from BUA and SOS as follows:

$$QUI = 0.41 \times (SOS + BUA) – 571$$

The Sahara system software automatically estimates bone mineral density (BMD) from the QUI/stiffness value.

The QUS T-score was obtained similarly to the DXA T-score, that is, by reporting the values calculated in comparison to the standard normal population. The T-score is defined as the difference in patients' results from the mean results obtained in a young adult population, expressed in units of standard deviation of the young adult population. Mathematically, the T-score is defined as:

$T = (P-YA)/SD_{YA}$

P= patients' results

YA = young adults' average value

SD_{YA} = standard deviation of the young adult population

The Sahara system provides age-dependent reference values for Caucasian females in the United States. These reference values come from a large multi-center study, in which Sahara results were obtained for 2208 Caucasian females at nine clinical centers located across the U.S. [4].

The primary aim of our study was to compare the value of QUS parameters in discriminating osteoporosis (as defined by DXA T-scores at the lumbar spine or total hip).

We used descriptive statistical methods to evaluate the central and dispersion tendencies and Q-Q plot and P-P plot diagrams for the quartile and percentiles analysis. The 95% confidence intervals (CI) were calculated for the significant values of the QUS parameters.

Receiver operating characteristic curves (ROC) were constructed by representing the specificity and sensitivity of each QUS parameter at different cut-off values for discriminating osteoporosis. The areas under the curves (AUCs) were computed. Sensitivity was defined as the proportion of subjects with osteoporosis that was classified as such by QUS parameters and specificity as the proportion of subjects without osteoporosis correctly identified by QUS parameters.

For each model parametric correlation coefficients were calculated to indicate the relative importance of each QUS parameter in the model. Reported P values were two-sided. The nominal significance level was set at 0.05. All statistical analyses were performed with SPSS 12.

3. Results

Bone mineral density (BMD) derived from QUS parameters was well correlated with BMD values determined by DXA both at the lumbar spine and total hip (Figures 1 and 2). Similar results were obtained by Boonen et al. in a study involving 221 postmenopausal women, 41 of whom had osteoporosis. The authors noted a significant correlation between QUS- and DXA-determined BMD at the lumbar spine ($R=0.478$, $P<0.001$) [11].

Figure 1. Correlations between QUS BMD and DXA-determined lumbar spine BMD (R = 0.570, P <0.05); R = Pearson correlation coefficient. (QUS = quantitative ultrasound; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry).

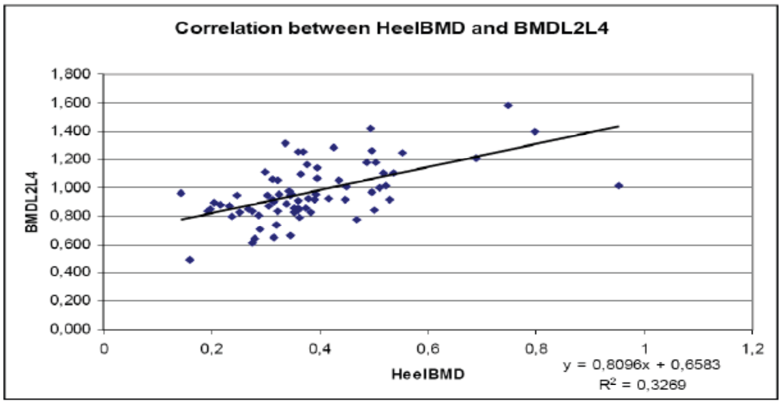
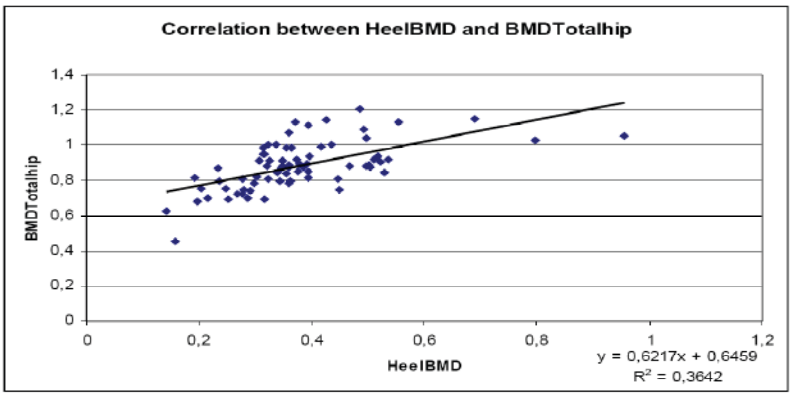


Figure 2. Correlations between QUS BMD and DXA-total hip BMD (R = 0.603, P <0.05); R = Pearson correlation coefficient. (QUS = quantitative ultrasound; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry).



All QUS parameters correctly identified the patients without osteoporosis when compared with DXA T-scores at the lumbar spine (AUC 0.767, 95% CI [0.627 – 0.907] for BUA and AUC = 0.816, 95% CI [0.676 – 0.956] for SOS) or total hip (AUC = 0.769, 95% CI [0.626 – 0.912] for BUA and AUC = 0,831, 95% CI [0.722 – 0.939] for SOS), (Figure 3). (AUC = area under the curve; CI = confidence interval; BUA = broadband ultrasound attenuation; SOS = speed of sound).

Also QUS parameters were positively correlated with either DXA T-score at lumbar spine (AUC = 0.762, 95% CI [0.652 – 0.872] for BUA, and AUC = 0.802, 95% CI [0.700 – 0.905] for SOS) and total hip (AUC = 0.990, 95% CI [0.969 – 1.012] for BUA, and AUC = 0.971, 95% CI [0.929 – 1.013] for SOS) for osteoporotic patients (Figure 4). (AUC = area under the curve; CI = confidence interval).

The AUC values for all QUS parameters corresponding to a DXA T-score of -1 and -2.5 are summarized in Table 1. We calculated the cut-off values for QUS parameters corresponding to DXA T-score of -1 and -2.5, to discriminate between the normal and osteoporotic patients. The results are shown in Table 2.

This means that the patients with BUA values greater than 63.3 and SOS greater than 1542.2 were normal (sensitivity 60%, specificity 82.5% for BUA and 87.3% for SOS), whereas those with BUA less than 49.85 and SOS less than 1504.95 were osteoporotic (sensitivity 90% and specificity 46% for both parameters). Also, the patients with QUS T-scores greater than -0.75 were normal (sensitivity 50%, specificity 86%), whereas those with a QUS T-score less than -2.15 were osteoporotic (sensitivity 90% and specificity 48%).

Of those patients with a negative QUS test, about 90% had no osteoporosis (negative predictive value, NPV = 93.33% for BUA and 95.45% for SOS), whereas only one third of patients with positive QUS test had osteoporosis (positive predictive value, PPV = 19.35% for BUA and 21.88% for SOS).

All QUS parameters were more closely correlated with DXA T-scores at the total hip than lumbar spine. The Pearson correlation coefficients of QUS parameters and DXA T-Score are shown in Table 3.

Figure 3. Receiver operating characteristic curves (ROC) analysis for QUS parameters, BUA and SOS related to DXA T score ≥ -1 either at lumbar spine or total hip. (P<0.05) (QUS = quantitative ultrasound; BUA = broadband ultrasound attenuation; SOS = speed of sound; DXA = dual-energy X-ray absorptiometry).

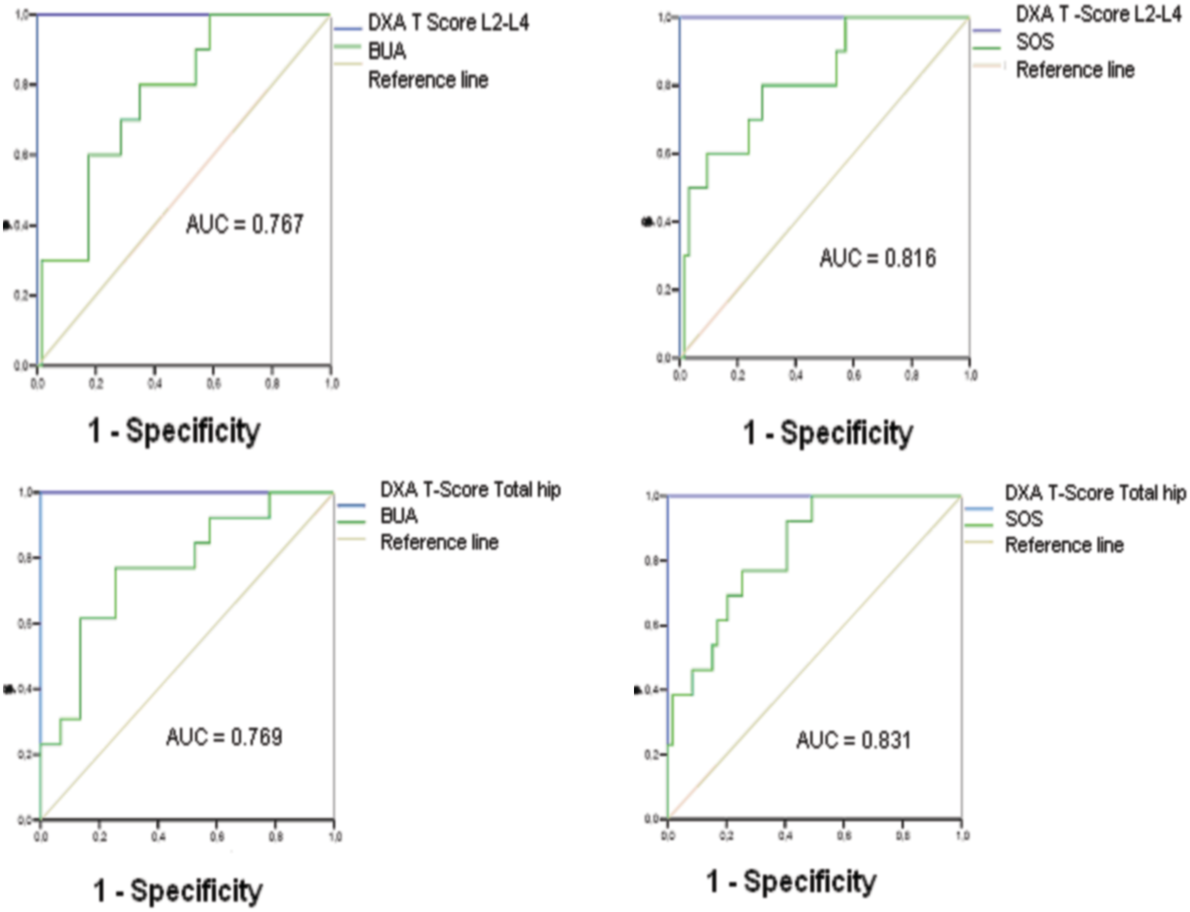


Table 1. AUC values and 95% CI for QUS parameters related to DXA T-score for normal and osteoporotic patients. (P<0.05).

	DXA T-score L2 – L4		DXA T-score Total Hip	
	> -1	< - 2.5	> - 1	< - 2.5
BUA				
AUC	0.767	0.762	0.769	0.990
95% CI	0.627 – 0.907	0.652 – 0.872	0.626 – 0.912	0.969 – 1.012
SOS				
AUC	0.816	0.802	0.831	0.971
95% CI	0.676 – 0.956	0.700 – 0.905	0.722 – 0.939	0.929 – 1.013
Heel BMD				
AUC	0.806	0.800	0.809	0.995
95% CI	0.672 – 0.939	0.699 – 0.902	0.689 – 0.929	0.981 – 1.010
QUI Index				
AUC	0.804	0.800	0.809	0.995
95% CI	0.670 – 0.938	0.698 – 0.902	0.689 – 0.929	0.981 – 1.010
QUS T-Score				
AUC	0.813	0.807	0.812	0.993
95% CI	0.684 – 0.942	0.707 – 0.907	0.691 – 0.934	0.974 – 1.011

(AUC = area under the curve; CI = confidence interval; QUS = quantitative ultrasound; DXA = dual-energy X-ray absorptiometry; BUA = broadband ultrasound attenuation; SOS = speed of sound; BMD = bone mineral density; QUI = quantitative ultrasound index)

Figure 4. Receiver operating characteristic (ROC) curves for the diagnosis of osteoporosis by the QUS indices, BUA and SOS. The WHO criteria, DXA T-score ≤ -2.5 for eitherlumbar spine or total hip were used.

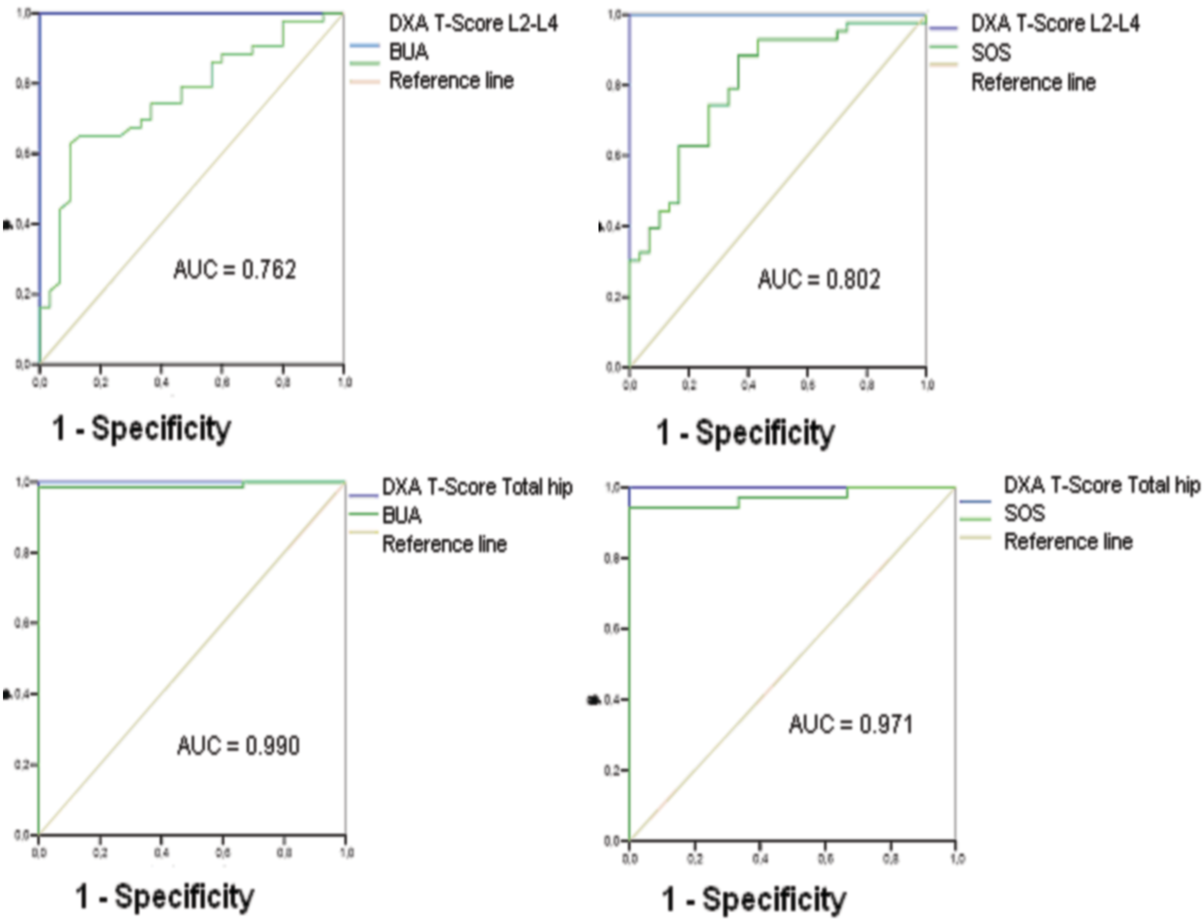


Table 2. Cut-off values for QUS parameters related to DXA T-Score of -1 and -2.5.

DXA T-score	-1			-2.5		
	Cut-off value	Sensitivity	Specificity	Cut-off value	Sensitivity	Specificity
BUA	63.3	60 %	82.5 %	49.85	90 %	46 %
SOS	1542.2	60 %	87.3 %	1504.95	90 %	46 %
QUI	89.5	60 %	85.7 %	66.75	90 %	48 %
Heel BMD	0.489	60 %	85.7 %	0.346	90 %	48 %
QUS T-Score	- 0.75	50 %	86 %	- 2.15	90 %	48 %

(QUS = quantitative ultrasound; DXA = dual-energy X-ray absorptiometry; BUA = broadband ultrasound attenuation; SOS = speed of sound; QUI = quantitative ultrasound index; BMD = bone mineral density)

4. Discussion

Dual-energy X-ray absorptiometry (DXA) is widely accepted as the gold standard for the diagnosis of and risk prediction for osteoporosis. Because DXA is an expensive and ionizing technique, it is best suited for the precise and accurate diagnosis of osteoporosis rather than for screening purposes. This has resulted in an increasing interest in developing reliable pre-screening tools for osteoporosis such as questionnaire-based methods or the use of quantitative ultrasound (QUS) scanners [5]. In the last decades, a large number of studies have focused on the use of QUS technique in the management of osteoporosis. QUS has the benefits of reduced costs in comparison to DXA, and it is a portable and radiation-free system with shorter investigation times than DXA; therefore, it is a more efficient tool for screening large populations [6].

Table 3. Correlations coefficients between QUS parameters and DXA T–score at lumbar spine and total hip.

		QUS T-Score	QUI	Heel BMD	BUA	SOS	DXA T-Score L2L4	DXA T-Score total hip
DXA T-Score L2-L4	Pearson Correlation	,585(**)	,579(**)	,580(**)	,533(**)	,570(**)	1	,696(**)
	Sig. (2-tailed)	,000	,000	,000	,000	,000	.	,000
	N	73	73	73	73	73	73	72
DXA T-score total hip	Pearson Correlation	,626(**)	,620(**)	,620(**)	,588(**)	,597(**)	,696(**)	1
	Sig. (2-tailed)	,000	,000	,000	,000	,000	,000	.
	N	72	72	72	72	72	72	72

*** Correlation is significant at the 0.01 level (2-tailed).*
(QUS = quantitative ultrasound; QUI = quantitative ultrasound index; BMD = bone mineral density; BUA = broadband ultrasound attenuation; SOS = speed of sound; DXA = dual-energy X-ray absorptiometry; Sig. = significant; N = not significant

Most of the studies have confirmed that QUS is nearly as useful as DXA to predict the fracture risk. Khaw et al. demonstrated in the European Prospective Investigation into Cancer (EPIC) – Norfolk study that QUS parameters were important risk factors for fractures (relative risk 3.53, 95% CI: 1.64– 7.62; p=0.001 for every decrease of 20 dB/MHz in BUA or 2.18, 95% CI: 1.19–3.99; p=0.01 for every decrease of 40 meters per second in SOS) [7]. In the Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk (SEMOF) study of 7,609 women (mean age 75.2 years) and the Epidemiology of Osteoporosis (EPIDOS) study of 5,662 elderly women (mean age 80.4 years), each decrease of one standard deviation in calcaneal QUS variables corresponded to an approximately 2-fold increase in the hip fracture risk, suggesting that calcaneal QUS was useful for predicting hip fracture risk [8,9].

However, there are limits in the use of quantitative ultrasound as a first-line diagnostic tool in clinical practice, and up until now there have been no consensus diagnostic criteria for osteoporosis with this technique. The WHO's operational definition for osteoporosis was derived in the context of DXA and has typically been applied to DXA; direct application of this definition to QUS is not advisable [10].

Several studies have evaluated the usefulness of QUS parameters as a pre-screening tool for osteoporosis in an attempt to reduce the use of DXA, especially in those countries where the availability of DXA is limited.

In our study we found that both BUA and SOS were statistically significant when correlated with DXA T-scores of -1 and -2.5 and thus are both able to distinguish between normal and osteoporotic patients, with a negative predictive value of about 90% and a positive predictive value of 20%. Similar results were obtained by Boonen et al. in a comparative study of QUS and DXA in 221 postmenopausal women [11].

As recommended by the position paper of the International Osteoporosis Foundation (IOF) on the diagnosis of osteoporosis [12], we determined the cut-off values of the QUS indices to accurately identify the subjects diagnosed by BMD at the spine or total hip according to WHO criteria by the ROC analysis. We obtained a cut-off value of 63.3 dB/MHz for BUA and 1542.2 meters per second for SOS corresponding to a DXA T-score > -1 (49.85 dB/MHz for BUA and 1504.95 m/s for SOS, respectively, for a DXA T-score < -2.5).

Similarly, in the Japanese Population-Based Osteoporosis (JPOS) study, Ikeda et al, using a Sahara Hologic device, found cut-off levels for a diagnosis of osteoporosis of 53.1 dB/MHz for BUA and 1517.7 meters per second for SOS [13]. Another study that compared the diagnostic value of BUA of the calcaneus and bone densities of the femoral neck and the lumbar spine in 17 normal women and 41 women with osteoporosis established a cut-off value of 63 dB/MHz for BUA, which was similar to our results, with a sensitivity of 76%[14].

Using a Sahara Hologic device, Dubois et al. [15] found a cut-off value of 58 dB/MHz for BUA and 1533 meters per second for SOS in 217 women. Similarly, in 106 postmenopausal women Falgarone et al. [16] found cut-off values of 71.7 dB/MHz and 50.8 dB/MHz for BUA and 1551.5 meters per second and 1544.8 meters per second for SOS (Sahara Hologic).

In a 7-year follow-up study, SOS, BUA, and stiffness determined with a LUNAR Achilles device were positively correlated with BMD in all regions (lumbar spine and total hip) measured with DXA both at the start and at 7 years of follow-up. Changes in SOS, BUA, and stiffness were positively correlated with changes in BMD in all regions except proximal radius when measured with DXA. In this study, osteoporosis was found in 70% of cases by QUS and in 56% by DXA at baseline, and at 7 years follow-up in 74% of cases with QUS and in 65% with DXA. The sensitivity of QUS and DXA as the gold standard ranged from 76% to 84% during the 7-year follow-up period, and the specificity from 36% to 57% [17].

Damilakis et al. [18] determined the optimum T-score threshold for BUA and SOS in 453 women aged 20 to 79 years. In their study a T-score threshold of −1.3 for BUA and −1.5 for SOS provided optimum discrimination with use of the Ubis QUS device for determining the presence of osteoporosis. Sensitivity of BUA for the optimum threshold was 68%, and specificity was 83%; sensitivity of SOS for the optimum threshold was 63%, with a specificity of 79%. Therefore, in the study by Damilakis et al. the accuracy of measurements by BUA was greater than that by SOS, which is similar to our findings.

Regarding the determination of QUS T-scores with the Sahara Hologic device, the cut-off values in the medical literature [19] range from –1.2 in men [20] to -1.7 and -2.5 in postmenopausal women [21,22]. In our study, the QUS T-score thresholds were -0.75 for a DXA T-score of -1 and -2.15 for a DXA T-score of -2.5. In the SEMOF study performed with a Sahara Hologic device, Hans et al. [23] found cut-off values of T-score for the QUI index of -1 and -2.2 determining, respectively, the low- and high-risk subjects in relation with hip DXA osteoporotic model. The analyses of AUCs in our study have shown that the diagnosis of osteoporosis by the QUS indices appeared to be more relevant for the diagnosis by the total hip BMD than by the spine BMD. These results are concordant with those obtained in the Japanese Population-Based Osteoporosis Study (JPOS) [13].

Also, in our study, analysis of AUCs have shown that BUA identified osteoporotic patients more accurately than SOS; this appears to be logical, since detection by BUA remains constant until menopause and decreases after that, whereas SOS decreases constantly with age. In the EPIC-Norfolk cohort, [24] the age-related decline in BUA was 0.39 dB/MHz per year up until age 55 and 0 .85 dB/MHz per year thereafter. In contrast, the decline in the effectiveness of BUA in men before and after the age of 55 was no different: -0.13 and -0.12 dB/MHz annually.

Another interesting finding of our study was that the percentage of osteoporotic subjects was greater with use of the DXA T-score at total hip than at lumbar spine. This could be explained by the fact that with advanced age, after an initial loss of trabecular bone (better represented in the vertebras), there is an important loss of cortical bone, which is predominant in the proximal femur. Also, in the subjects of advanced age, the DXA T–score at lumbar spine can be altered due to the presence of osteofites.

The main weakness of our study was the small sample size of the population.

However, our results are concordant with those of most of the other studies comparing QUS and DXA. QUS can be a reliable method to identify persons with osteoporosis, and it can be an alternative to DXA, but with several limitations. In our study, the direct QUS parameters, BUA and SOS, correctly identified normal and osteoporotic patients at established cut-off values for both parameters. Those patients with QUS values between the cut-off points needed to be further evaluated by DXA, because they could be normal, osteopenic, or osteoporotic. Further population studies and studies comparing of different QUS devices are needed to validate the cut-off values of ultrasound parameters in the diagnosis of osteoporosis.

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