VALUE OF QUANTITATIVE HEEL AND PROXIMAL PHALANGES ULTRASONOGRAPHY VERSUS DUAL X-RAY ABSORPTIOMETRY IN WOMEN AGED 24-80 YEARS

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Abstract

Despite several attempts to establish the role of QUS in clinical practice, issues such as definition of osteoporosis based on QUS, screening strategy and therapy efficacy for patients identified by QUS as having high risk of fracture remain a matter of debate. The present study aimed to evaluate the diagnostic agreement between two QUS techniques (heel QUS and proximal phalanges QUS) and DXA in an unselected population of Romanian women aged 24-80 years, as well as to offer cut-off levels for QUS to distinct between women with or without osteoporosis identified by DXA. In women measured by both DXA and calcaneus QUS (c-QUS), bone mineral density (BMD) moderately correlated with stiffness index (SI) (L1-L4: r=+0.51, p<0.001; femoral neck: r=+0.53, p<0.001; hip: r=+0.57, p<0.001), while in women examined by both DXA and phalanx QUS (ph-QUS), BMD was positively related to amplitude-dependent speed of sound (Ad-SoS) (L1-L4: r=+0.47, p<0.001; femoral neck: r=+0.50, p<0.001; hip: r=+0.38, p<0.001) and ultrasound bone profile index (UBPI) (L1-L4: r=+0.44, p<0.001; femoral neck: r=+0.50, p<0.001; hip: r=+0.38, p<0.001). At a T-score cut-off level of -2.5SD, the high specificity but low sensitivity suggests a low false positive rate of c-QUS as a diagnostic test; still, several patients with the disease may not be correctly diagnosed. At the same cut-off level, ph-QUS showed higher sensitivity and lower specificity. Diagnostic agreement between DXA and QUS was poor, with k-scores ranging from 0.33 to 0.39 for c-QUS and from 0.14 to 0.29 for ph-QUS, respectively. Lowering c-QUS T-score cut-off for lumbar spine osteoporosis screening to -1.5SD and ph-QUS T-score cut-off to -1.9SD, respectively, improved sensitivity and had a minor effect on diagnostic agreement. Regardless of the evaluated site, neither c-QUS nor ph-QUS does represent an adequate predictor of BMD in Romanian women. Changing the diagnostic T-score threshold from -2.5 SD to -1.5 SD and -1.9 SD in subjects examined by c-QUS or ph-QUS, respectively, is followed by improved sensitivity and diagnostic agreement in the identification of patients with vertebral osteoporosis. Cut-off values may allow QUS to be used as a screening tool for spine and femur osteoporosis.

Key words: dual X-ray absorptiometry, quantitative phalanges ultrasonography, quantitative heel ultrasonography, osteoporosis, fracture.

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INTRODUCTION

Osteoporosis is defined as a systemic skeletal disease characterized by reduced bone strength and increased susceptibility to fracture. Bone strength is reflected by both bone density and bone quality (1). Nowadays, the diagnosis of osteoporosis still relies upon the World Health Organization (WHO) osteodensitometry criteria as assessed by dual X-ray absorptiometry (DXA) (2), mainly based on studies that have shown that bone mineral density (BMD) is able to predict 50-70% of femoral neck fracture risk in white postmenopausal women (3).

In comparison to DXA, a relatively expensive and time-consuming method, quantitative ultrasonography (QUS) applied at the calcaneus, radius, tibia or phalanx is easy, portable and less expensive. QUS is known to correlate only moderately with DXA parameters, but may predict fracture independently of BMD (4, 5); moreover, in comparison to clinical risk factors, ultrasound parameters are better predictors of fracture risk assessment in various populations (6, 7). Still, definition of osteoporosis based on QUS data is not possible, thus no equivalency between T- and Z-scores assessed by DXA or QUS, respectively, is to be made. In addition, there is no clear consensus on the screening strategy with QUS in various populations and no clear evidence of treatment efficacy for patients identified by QUS as having high risk of fracture. Studies comparing diagnostic agreement in fracture risk evaluation between DXA and QUS resulted in variable results, according to the region of interest considered, the population study, the reference population and equipment used.

In view of these data, the present cross-sectional study aimed to evaluate the diagnostic agreement between DXA and two QUS techniques (heel QUS and proximal phalanges QUS) in an unselected population of Romanian women aged 24-80 years, as well as to offer cut-off levels for QUS to distinguish between women with or without osteoporosis identified by DXA.

SUBJECTS AND METHODS

Fracture risk evaluation by calcaneus QUS (c-QUS) was carried out on 165 consecutive unselected women aged 55.1 years (range 29-74 years) submitted to the Osteoporosis and Menopause Center at the Endocrinology Clinic Cluj-Napoca. All patients were simultaneously investigated by both quantitative heel ultrasonography on the water-based system Achilles Express (GE, Madison, USA) and DXA of the lumbar spine (L1-L4) and hip using the DPX-NT (GE, Madison, USA) device. The Achilles Express system is of the transmission type, with two ultrasound transducers (transmitter and receiver) positioned on each side of the heel. Both systems were used according to the manufacturer's recommended standard procedures. To ensure uniformity, c-QUS was performed on each subject's left foot. If the subject had a history of fracture or any bone disorder of the left foot, the right

heel was evaluated. Results were expressed as T-score, Z-score and the Stiffness Index (SI), calculated according to the formula: stiffness = (0.67xbroadband ultrasound attenuation)+(0.28xspeed of sound)–420. For quality control, the c-QUS device was calibrated on a weekly basis by using a phantom during the period of screening. The intra-test precision, as evaluated by using the coefficient of variation (CV), was calculated from three repeated scans with repositioning in 10 volunteers. The CV was 1.5% for SI.

Proximal phalanges QUS (ph-QUS, DBM Sonic IGEA, Italy) versus DXA (DPX-NT, GE, Madison, USA) comparative study was carried out in unselected 166 women aged 56.7 years (range 25-78 years) referred to the Osteoporosis and Menopause Center at the Endocrinology Clinic Cluj-Napoca for fracture risk evaluation. The ultrasonography device consists of two probes mounted on an electronic caliper: the emitter probe positioned on the medial surface of the proximal phalanx and the receiver probe positioned on the lateral side of the phalanx. All measurements were undertaken by the same operator and results were expressed as amplitude-dependent speed of sound (Ad-SoS), ultrasound bone profile index (UBPI), T- and Z-scores. Mean coefficient of variation was calculated on 10 patients and was 1%. At the same session, patients were measured by DXA of the lumbar spine and hip and results were expressed as absolute BMD, T- and Z-scores. For quality control, the device was calibrated at least 3-times weekly using two phantoms and precision was calculated from three repeated scans with repositioning and standing up between scans in 10 subjects. CV for lumbar spine was <1% and CV for hip measurements was <2%. For DXA, the diagnostic bone mass threshold for defining osteoporosis was based on the WHO criterion of a T-score of ≤–2.5SD. Osteopenia was defined as a T-score between -1 and -2.5SD. A T-score of ≥-1SD was considered normal.

STATISTICAL ANALYSIS

Data were expressed as mean ± SD. Pearson's simple correlation coefficients were used to describe the associations between two continuous variables. Receiver operator characteristic (ROC) curves were built and the areas under the curve (AUC) were determined. Diagnostic agreement was evaluated by kappa statistics. *P* values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics, DXA results and QUS parameters of the two study groups are presented in Table 1. According to WHO criteria based on BMD measurement, osteoporosis was more frequently encountered in the ph-QUS study group (55.6%) in comparison to the c-QUS study group (39.1%). As expected, an inverse correlation was seen between age and the SI ($r = -0.32$, $p<0.001$, $n=165$) in

Table 1. Baseline characteristics, bone mineral density (BMD), calcaneus (c-) and proximal phalanx quantitative ultrasonography (ph-QUS) data in two groups of 165 and 166 women, respectively. Results are presented as mean±standard deviation. Women in whom ph-QUS was performed were slightly older and had a higher fracture risk as compared to those from the c-QUS study group but differences were not statistically significant

	Calcaneus QUS (c-QUS) study group	Phalanx QUS (ph-QUS) study group
n	165	166
Age (years)	55.2±10.1	56.7±12.7
BMD L1-L4 (g/cm^2)	0.942±0.152	0.938±0.152
BMD femoral neck (g/cm^2)	0.848±0.133	0.844±0.137
BMD hip (g/cm^2)	0.881±0.137	0.881±0.148
T-score L1-L4 (SD)	-1.98±1.26	-2.01±1.26
T-score femoral neck (SD)	-1.10±0.52	-1.12±1.14
T-score hip (SD)	-1.02±1.1	-1.01±1.18
SI	74±17.2	-
T-score c-QUS	-1.57±1.16	-
Ad-SoS	-	1931.72±106.27
UBPI	-	0.48±0.23
T-score ph-QUS	-	-2.74±1.51
% women with T-score <-2.5 SD by DXA	39.1%	55.6%
% of women with T<-2.5 SD by QUS	20.4%	58.0%

n=number; SI=stiffness index; Ad-SoS=amplitude-dependent speed of sound; UBPI=ultrasound bone profile index; SD=standard deviation.

women examined by c-QUS. Likewise, age was negatively associated with ph-QUS parameters such as Ad-SoS (r=-0.62, p<0.001, n =166) and UBPI (r =-0.68, p<0.001, n =166).

A moderate correlation was found between SI and BMD values, with the highest correlation coefficients for the total hip. The correlation remained highly statistically significant with respect to T-scores (Table 2), although with slightly, not significantly lower Pearson's correlation coefficients, possibly due to different reference populations used by the two equipments. As expected, ph-QUS parameters (Ad-SoS) and UBPI were positively highly correlated (r=+0.92, p<0.001, n=166) and, as shown in Table 2, both correlated moderately with BMD measurements at the lumbar spine and femur.

We further calculated the sensitivity (the % of patients with the disease who test positive) and specificity (the % of patients without the disease who test negative) of c-QUS at the cut-off level of -2.5SD to correctly classify women with or without osteoporosis according to BMD measurement by DXA and WHO

Table 2. Pearson's correlation coefficients between dual X-ray absorptiometry (DXA) and quantitative ultrasonography (QUS) parameters

	SI	T-score c-QUS	Ad-Sos	UBPI	T-score ph-QUS
BMD L1-L4	+0.51[c]	-	+0.47 [c]	+0.44 [c]	+0.47 [c]
n	156		165	165	165
BMD Neck	+0.53 [c]	-	+0.50 [c]	+0.52 [c]	+0.50 [c]
n	133		166	166	166
BMD Hip	+0.57 [c]	-	+0.38 [c]	+0.43 [c]	+0.38 [c]
n	133		166	166	166
T-L1-L4	-	+0.47 [c]	-	-	
n		156			
T-femoral neck	-	+0.51 [c]	-	-	
n		133			
T-hip	-	+0.55 [c]	-	-	
n		133			

[c]p<0.001

BMD=bone mineral density; c-QUS=calcaneus quantitative ultrasonography; ph-QUS=phalanx quantitative ultrasonography; n=number; SI=stiffness index; Ad-SoS=amplitude-dependent speed of sound; UBPI=ultrasound bone profile index; SD=standard deviation.

definition. It resulted that c-QUS had a sensitivity of 43.3% and specificity of 92.3% to diagnose women with lumbar spine osteoporosis and a sensitivity of 66.7% and specificity of 84.4% to diagnose women with total hip osteoporosis according to DXA criteria. The highest sensitivity (83.3%), at a specificity of 84.4%, was observed when c-QUS cut-off levels were applied to diagnose patients with osteoporosis at the femoral neck. The high specificity but low sensitivity of c-QUS as a diagnostic test of osteoporosis suggests that few women without osteoporosis will present T-scores ≤-2.5SD at c-QUS (low false positive rate); however, several patients with the disease may not be correctly diagnosed.

At the same cut-off level, it was determined that ph-QUS had 80.7% sensitivity and 53.2% specificity to diagnose women with lumbar spine osteoporosis based on DXA measurements. At the hip, sensitivity was 100% at a specificity of 46.3%, whereas at the femoral neck, a sensitivity of 94.4% at a specificity of 45.9% was obtained. Thus, the sensitivity of the test was higher but the specificity of the measurement, reflecting the false positive rate, was significantly lower in comparison to c-QUS. In order to identify the cut-off level for QUS with the highest sensitivity at an acceptable specificity, receiver operator characteristics (ROC) curves were built (Figs. 1 and 2). As shown in Table 3, with both c-QUS and ph-QUS, the highest area under curve (AUC) was observed when femoral neck was

considered as the region of interest.

In order to determine the diagnostic agreement between c-QUS and DXA at a cut-off level of ≤ -2.5SD we calculated the kappa score (k). A rather fair to poor diagnostic agreement was observed, with k-scores ranging from 0.33 to 0.39 on various skeletal sites and using the WHO criteria (Table 4). Likewise, diagnostic agreement between ph-QUS and DXA at a cut-off level of ≤ -2.5 SD was poor, with k-scores between 0.14 and 0.29. We further sought to determine if changes in T-score cut-off levels according to ROC curves improve diagnostic agreement between DXA and QUS to assess fracture risk. We found out that at a c-QUS T-score cut-off level of -1.47SD, calculation of diagnostic agreement on diagnosis of lumbar spine osteoporosis according to DXA resulted in a k-score of 0.40 (Table 4), a sensitivity of 83.6 % and specificity of 60.2 %. Considering the femoral neck as ROI, at a new c-QUS T-score cut-off level of -2.34SD, the sensitivity increased to 91.7% with a specificity of 81.3%, whereas considering the total hip as ROI, at a c-QUS T-score cut-off level of -2.24SD the sensitivity was 80% at a specificity of 78.1%. However, as shown in Table 4, k-score did not improve significantly (0.38 for femoral neck and 0.33 for total hip).

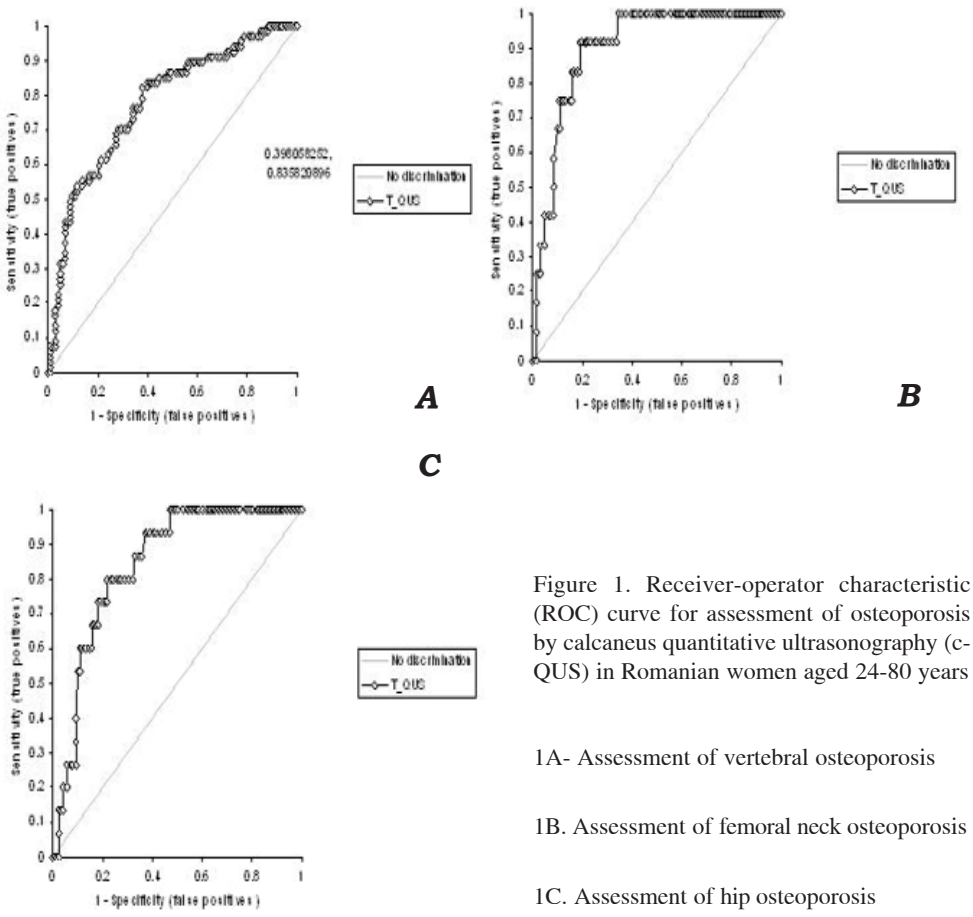

Figure 1. Receiver-operator characteristic (ROC) curve for assessment of osteoporosis by calcaneus quantitative ultrasonography (c-QUS) in Romanian women aged 24-80 years

1A- Assessment of vertebral osteoporosis

1B. Assessment of femoral neck osteoporosis

1C. Assessment of hip osteoporosis

Table 3. Cut-off levels and area under the curve (AUC) as resulted from receiver operator characteristic (ROC) curves for both calcaneus quantitative ultrasonography (c-QUS) and proximal phalanx quantitative ultrasonography (ph-QUS)

	Cut-offs	AUC	95% CI from AUC	SE	p
c-QUS T-score ≤-2.5SD					
L1-L4	≤-1.47SD	0.776	0.704-0.848	0.036	<0.001
Femoral Neck	≤-2.34SD	0.901	0.838-0.965	0.032	<0.001
Total Hip	≤-2.24SD	0.843	0.764-0.923	0.040	<0.001
ph-QUS T-score	≤-2.5SD				
L1-L4	≤-1.91SD	0.718	0.642-0.794	0.038	<0.001
Femoral Neck	≤-3.19SD	0.804	0.709-0.899	0.048	<0.001
Total Hip	≤-2.69SD	0.795	0.709-0.882	0.044	<0.001

n = number; SI = stiffness index; Ad-SoS = amplitude-dependent speed of sound; UBPI = ultrasound bone profile index; SD = standard deviation.

With respect to ph-QUS, considering cut-off levels according to ROC curves (L1-L4: -1.91SD, femoral neck: -3.19SD, hip:-2.69SD), sensitivity and k-scores for the diagnosis of lumbar spine osteoporosis increased (sensitivity 94.7%, specificity 45.9%) but did not change when the hip (sensitivity 94.1%, specificity 52.3%) or femoral neck (sensitivity 83.3%, specificity 66.9%) were considered (Table 4).

DISCUSSION

Our study aimed to compare X-ray-based measurements at the lumbar spine and hip with ultrasonographic measurements at two different skeletal sites, the heel and proximal phalanges. All ultrasound techniques are increasingly employed in clinical practice, however comparisons have led to different conclusions, and data on Romanian subjects are missing. It has been shown that ethnic background and lifestyle factors may influence both bone ultrasonography (8, 9) and BMD measurements, however the influence of these factors on the diagnostic agreement between the two tests remains unclear.

Although ultrasound propagation through bone is, in part, dependent upon bone density, in our study correlation coefficients between SI and BMD were modest. Correlation coefficients between phalanx ultrasound parameters (Ad-SoS, UBPI) and BMD were also modest. This data are in line with previous studies, reporting low to moderate correlations between heel QUS and DXA (10, 11, 12, 13, 14, 15) or hand QUS and DXA (16). One important influential factor explaining differences is that, in contrast to DXA, not only density but also qualitative properties of bone have a major impact on QUS parameters (11). Moreover, in our study, ultrasound and X-ray

determinations, respectively, were performed on different skeletal sites; it has been shown that correlation coefficients between QUS and DXA are significantly higher when the same skeletal site is examined, for example the calcaneus (17).

A threshold level of -2.5SD for the QUS T-score to discriminate between women with or without osteoporosis resulted in high specificity but low sensitivity of heel ultrasonography. In this case, most of healthy women will be correctly excluded from further investigations by QUS, but several women with the disease may be inadequately diagnosed. Lowering the cut-off level is accompanied by a higher sensitivity but a lower specificity of the test. With respect to ph-QUS, at a cut-off T-score, ≤-2.5 SD sensitivity was good, especially at the femur, but specificity was low, resulting in a high false positive rate. There is no consensus on what cut-off values to use with QUS to diagnose osteoporosis. To establish the highest sensitivity at an acceptable specificity, ROC curves were built and new T-score cut-off values were calculated from these curves. It was observed that for both ph-QUS and c-QUS,

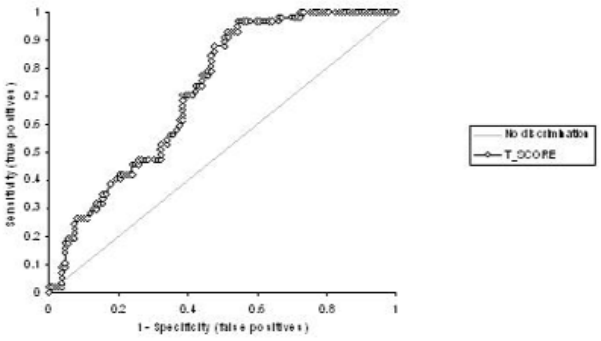

Figure 2A. Receiver-operator characteristic (ROC) curve for assessment of vertebral osteoporosis by proximal phalanx ultrasonography (ph-QUS) in Romanian women aged 24-80 years.

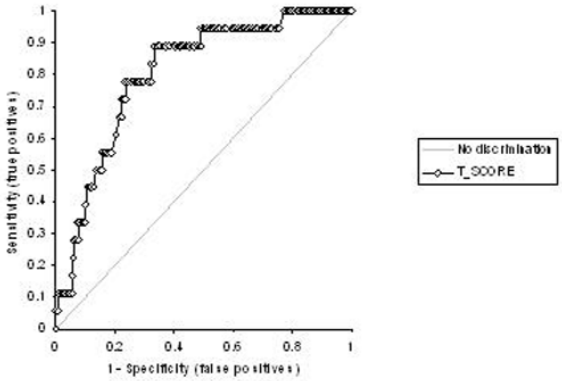

Figure 2B. Receiver-operator characteristic (ROC) curve for assessment of femoral neck osteoporosis by proximal phalanx ultrasonography (ph-QUS) in Romanian women aged 24-80 years.

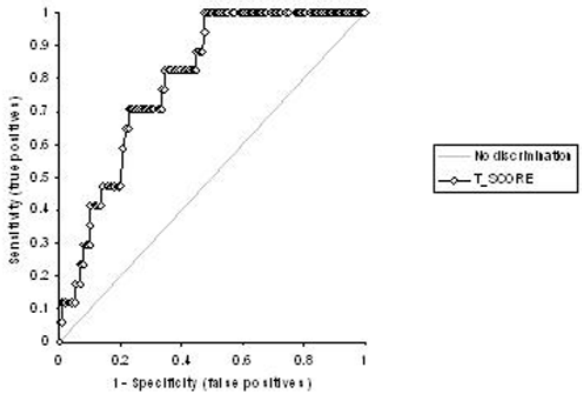

Figure 2C. Receiver-operator characteristic (ROC) curve for assessment of hip osteoporosis by proximal phalanx ultrasonography (ph-QUS) in Romanian women aged 24-80 years.

Table 4. Kappa (χ) statistics, positive predictive value (PPV) and negative predictive value (NPV) for dual X-ray absorptiometry (DXA) T-score of ≤-2.5SD and quantitative ultrasonography (QUS) T-scores of ≤-2.5SD to reflect diagnostic agreement between DXA, c-QUS and ph-QUS respectively. The T -score was recalculated for new c-QUS and ph-QUS T-score cut-offs, as obtained by receiver-operator characteristivc (ROC) curves

	c-QUS T-score			
	≤-2.5SD	≤-2.34SD	≤-2.24SD	≤-1.47SD
Kappa (χ)				
L1-L4	0.39			0.40
Neck	0.38	0.38		
Hip	0.33		0.33	
PPV				
L1-L4	80.5%	-	-	57.7%
Neck	32.2%	31.4%	-	-
Hip	32.2%	-	30%	-
NPV				
L1-L4	71.6%	-	-	84.7%
Neck	98.1%	99%	-	-
Hip	95%	-	97%	-

c-QUS = calcaneus quantitative ultrasonography; ph-QUS = phalanx quantitative ultrasonography; SD = standard deviation.

at a sensitivity of about 85-95%, the ultrasonography T-score cut-off value to be considered for the diagnosis of vertebral osteoporosis was much lower, of about -1.5 SD for c-QUS and about -1.9 SD for ph-QUS. The graphic presentation of the ROC curve and the AUC showed a higher value of QUS to identify patients with femoral neck low bone mass and predict hip fracture risk. Calculated T-score QUS cut-offs to diagnose hip osteoporosis at a sensitivity of 80-95% were quite different, dependent on the equipment used, of -2.3SD for c-QUS and -3.2SD for ph-QUS.

However, the diagnostic agreement by kappa analysis among both c-QUS and ph-QUS and DXA in classifying women as osteoporotic was generally poor. Several causes may be involved such as differences in error sources between the two techniques (i.e. ultrasound and X-ray) or the fact that the appendicular or axial skeletons are differently subjected to genetic or environmental influences. The variable representation of cortical and trabecular bone in selected regions of interest has also to be taken into account (18). In addition, one of the main problems with quantitative sonography is the lack of standardization of different devices, so measurements of the same patients with sonographic equipments from different manufacturers yield different results (18). Our study confirms the modest ultrasonography and DXA diagnostic agreement obtained in various study populations. As reported by others, heel or phalanx QUS shows poor agreement with bone status scanned by DXA in population-based studies (15, 19, 20) or other populations such as patients with inflammatory bowel disease (21) and renal transplant recipients (22).

Surprisingly, changes in T-score cut-offs according to ROC analysis had no major effects on diagnostic agreement, possibly due to small changes in the number of true positive and true negative patients or to the fact that false positive and false negative cases are not taken into consideration in kappa statistics. However, it can be said that the new T-score cut-offs offer the balance of best fit between sensitivity-specificity-positive predictive value and negative predictive value, even though diagnostic agreement remains fair too poor.

Osteoporosis treatment based on QUS results is not possible. In the future, the combination between BMD and the recently developed WHO fracture risk assessment tool (FRAX) may be of use to determine intervention thresholds (23); however no data regarding the pattern of fracture clinical risk factors (CRFs) specific to our country are available to date. On the other hand, FRAX does not include QUS and the role of QUS in the assessment of 10-year probability of fracture is not clear. In a recent study, a hip screening tool that combines CRFs and heel QUS to determine the 10-years probability of hip fractures in elderly women was evaluated, the authors suggesting that SI may be of interest to assess hip fracture probability in elderly women, especially when access to DXA is limited (24).

CONCLUSIONS

The present study compared the performance of QUS at the heel and proximal

phalanx with DXA in terms of their discriminatory ability to identify women with osteoporosis according to WHO criteria. Poor diagnostic agreement between methods suggests that T-scores resulted by QUS and DXA are not interchangeable and WHO criteria in the diagnosis of osteoporosis are applicable exclusively to BMD measurements.

Regardless of the evaluated site, neither c-QUS nor ph-QUS represents an adequate predictor of BMD in women. Changing the diagnostic T-score threshold from -2.5SD to -1.5SD or -1.9SD in subjects examined by c-QUS or ph-QUS, respectively, is followed by improved sensitivity and diagnostic agreement in the identification of patients with vertebral osteoporosis. In such instances, a secondary scan using DXA is required in women with c-QUS T-score ≤-1.5SD and women with ph-QUS T-score ≤-1.9SD, before therapy with anti-fracture agents is started. Cut-off values may allow quantitative ultrasonography to be used as a screening tool for osteoporosis in the spine and femur and helps to prevent unnecessary DXA examinations.

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