TÜBİTAK

ORIGINAL ARTICLE

Turk J Med Sci
2007; 37 (5): 303-309
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E-mail: medsci@tubitak.gov.tr

Diagnostic Performance of QUS for Identifying Osteoporosis in Postmenopausal Turkish Women

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Aim: The aims of this study were to evaluate the ability of quantitative ultrasound (QUS) to identify osteoporosis in postmenopausal women on the basis of dual-energy X-ray absorptiometry (DXA) T-scores, the best predictor of osteoporotic fractures, and to find a cut-off value for QUS with the optimum sensitivity and specificity, in order to select postmenopausal women for DXA referral.

Materials and Methods: This study included 116 postmenopausal women attending Adnan Menderes University Family Medicine Clinic in Aydin. Bone density was measured at the calcaneus using QUS and at lumbar spine and femoral neck with DXA. Receiver operating characteristic analysis was carried out to determine the best sensitivity and specificity for QUS T-scores for comparison with the gold standard.

Results: Mean age of the group was 57.3 ± 8.4 years. According to DXA measurements, 34.5% of the women were considered osteoporotic and 49.1% osteopenic. There were weak-moderate positive correlations between QUS measurements and DXA T-scores of lumbar spine and femoral neck ($r = 0.231$ and $r = 0.286$, respectively, $P < 0.05$). Using DXA as the gold standard, the cut-off value of QUS T-score was -2.2 with 77.5% sensitivity and 50.0% specificity for osteoporosis. The area under the curve for QUS T-scores in identifying osteoporotic subjects was 0.646 ($P < 0.01$).

Conclusions: In our population, postmenopausal women with QUS T-score ≤ -2.2 are candidates for referral for DXA measurements. QUS can be used for stratifying the population into risk groups for osteoporosis and its use should be encouraged to increase detection of osteoporosis in primary care settings in developing countries.

Key Words: Osteoporosis, quantitative ultrasound, bone mineral density, postmenopausal women

Kantitatif Ultrasonun Postmenopozal Türk Kadınlarında Osteoporoz Tanısındaki Değeri

Amaç: Bu çalışmanın amacı, osteoporotik kırıkları saptamada altın standart olan DXA T-skorları temelinde, kalkaneal kantitatif ultrasonografi (QUS) yönteminin postmenopozal Türk kadınlarında osteoporoz saptamadaki etkinliğini belirlemek ve QUS T-skoru için optimum duyarlılık ve seçicilik sağlayacak bir kestirim değeri saptayarak DXA'dan en çok yarar görecek populasyonu belirlemektir.

Yöntem ve Gereç: Çalışmaya Adnan Menderes Üniversitesi Aile Hekimliği Merkezi'ne başvuran 116 postmenopozal kadın alındı. Achilles Express ultrason cihazı ile katılımcıların önce kalkaneal QUS ölçümleri, ardından Dual Enerji X-ray Absorbsiyometri (DXA) ile lomber ve femoral Kemik Mineral Yoğunluğu (KMY) ölçümleri yapıldı. Altın standart ile karşılaştırmak için en iyi duyarlılık ve özgüllüğü belirlemek amacıyla receiver operator characteristic (ROC) analizi yapıldı.

Bulgular: Grubun yaş ortalaması 57,3 ± 8,4 yıldı. DXA ölçümlerine göre kadınların %34,5'i osteoporotik ve %49,1'i osteopenik olarak değerlendirildi. Lomber ve femoral DXA T-skorları ile QUS T-skorları arasında zayıf-orta pozitif korelasyon tespit edildi (sırasıyla $r = 0,231$ and $r = 0,286$, $P < 0,05$). DXA altın standart olarak alındığında QUS'un, T-skor ≤ -2,2 kesim noktası için osteoporozu saptamadaki duyarlılığı % 77,5, özgüllüğü %50,0 olarak bulundu ve ROC alanı altındaki değer 0,646 olarak saptandı ($P < 0,01$).

Sonuç: QUS T-skorları ≤ -2,2'nin altında olan postmenopozal kadınlar DXA ölçümüne yönlendirilmelidir. QUS ile KMY belirlenerek popülasyonun osteoporoz açısından risk gruplarına bölünmesi ve gerekli olanların DXA'ya yönlendirilmesi sağlanabilir. Gelişmekte olan ülkelerde, birinci basamakta osteoporozun daha çok saptanması amacıyla QUS kullanımı artırılmalıdır.

Anahtar Sözcükler: osteoporoz; kantitatif ultrason; kemik mineral yoğunluğu; postmenopozal kadınlar

Received: March 26, 2007
Accepted: September 14, 2007

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Introduction

Postmenopausal osteoporosis (PMO) is a major health problem that affects millions of women worldwide. PMO and its consequences can be regarded as a major source of mortality, morbidity and medical expenditure in the world. The incidence of osteoporotic fracture in western countries and also in Turkey is constantly increasing due to the increase in life expectancy.

Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is the best predictor of fracture risk, and over the past decade, DXA has emerged as the gold standard to evaluate patients at risk for fragility fractures (1-3). However, DXA is not an optimal tool for population screening because of cost constraints and limited availability (4). Low-cost screening methods in order to select high-risk individuals who are more likely to benefit from DXA testing are needed. In recent years, a new diagnostic test using quantitative ultrasound (QUS) has been developed as an alternative method for non-invasive assessment of skeletal status and fracture risk. Today, QUS is accepted as an attractive reality as it possibly provides early detection of postmenopausal women at high risk of fracture (5). This technique is widely available, radiation-free, portable, relatively inexpensive and more time-saving than DXA (6), and these properties make it suitable for mass screening in primary care. The National Osteoporosis Risk Assessment (NORA) study, enrolling over 200,000 women aged 50 years and older in the U.S., showed that BMD measured with peripheral techniques, including QUS, was predictive of fracture risk after 12 months of follow-up (7). Although results from prospective studies have shown that low QUS was also an independent risk factor for hip and other non-spine fractures (8-11), its accuracy in diagnosing osteoporosis is not clear yet. Therefore, the aims of this study were to evaluate the diagnostic performance of QUS in identifying osteopenia and osteoporosis in postmenopausal women on the basis of DXA T-scores, and to find a cut-off value for QUS in selecting postmenopausal women for DXA referral in our population.

Materials and Methods

Study Population

One hundred twenty-eight consecutive postmenopausal women attending Adnan Menderes University Family Medicine Clinic in Umurlu, Aydin for any medical reason were included in the study. Patients were excluded if they had any of the following: rheumatoid arthritis, other metabolic bone disease, and current or previous usage of bisphosphonates or hormone replacement therapy. Informed consent was obtained from each participant after the general aim of the study was explained. Permission was obtained from the Directorate of Health. In 12 cases, QUS instrument did not work properly due to technical problems, swollen feet or a poor signal. Finally, a total of 116 postmenopausal women were included in the study.

Demographic data was collected by trained nurses using a standard questionnaire with face-to-face interviews. Subjects were weighed on a digital scale (SECA, Hamburg, Germany) without shoes and light clothes; body weight was recorded to the nearest 0.1 kg. Standing height was measured without shoes to the nearest 0.5 cm using a portable wall-mounted stadiometer (SECA). BMI was calculated by using [BMI = weight (kg) / height^2 (m)] formula and women were grouped as normal, overweight and obese according to their BMI values (12). All participants had DXA measurements after completion of the questionnaire and QUS measurement.

Quantitative Ultrasound (QUS) Measurements

The QUS measurements were carried out using Achilles Express ultrasound device (Lunar, Madison, WI, USA) at the left calcaneus. The manufacturer's reference population for stiffness index was used to calculate the T-score. Subjects were classified as normal, osteopenic or osteoporotic based on the QUS T-scores. Although there has been no consensus on the T-score cut-offs and diagnostic categories to be used with QUS, the instrument used commonly in Turkey also accepts the World Health Organization (WHO) criteria as cut-off values.

Daily quality control was carried out for ultrasound systems with acoustic phantoms provided by the manufacturers. All of the QUS measurements were performed by the same technician.

Dual-Energy X-ray Absorptiometry (DXA) Measurements

Bone density was measured using the DEXA-QDR-4000 (Hologic Inc., Waltham, MA, USA) at the lumbar spine [vertebrae L1-L4 (LS)] and the hip [femoral neck (FN)] by trained and certified technicians. The same machine was used on all subjects and quality assurance phantom scans were carried out to check system calibration on a daily basis.

T-scores were used to categorize BMD values as normal (T-score ≥1.0) or indicating osteopenia (T-score < -1.0 and > -2.5) or osteoporosis (T-score ≤-2.5), as proposed by a working party of the WHO (13). Subjects were classified as having osteoporosis if at least one of the two measurements (lumbar spine or femoral neck) indicated osteoporosis, and as having osteopenia if at least one measurement indicated osteopenia but none indicated osteoporosis.

Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences program (SPSS 13.0). The descriptive data was given as a mean ± standard deviation (SD). Pearson's correlation coefficients were used to examine the association between QUS parameters, BMD and demographic features. Parameters were compared among groups using an analysis of variance (ANOVA). DXA BMD measurement was used as the gold standard. Receiver operating characteristic (ROC) analysis was carried out to determine the best sensitivity and specificity for QUS T-scores to compare to the gold standard and to find the best cut-off values that would give the highest sensitivity. Statistical difference was defined as $P < 0.05$.

Results

Demographics

The study population consisted of 116 participants and the characteristics of the women are shown in Table 1. Mean age was 57.3 ± 8.4 years. The majority of women were married, with low level of education, and overweight or obese. One in four women was multiparous (≥4) and mean parity was 3.4 ± 1.2. Of the total, 19.0% had previous fragility fractures and 14.7% had family history of fragility fractures. Osteoporotic women were older, had greater parity and were less educated than the others.

DXA and QUS Measurements

According to the WHO criteria, 40 women (34.5%) were considered as osteoporotic, 57 (49.1%) as osteopenic, and 19 (16.4%) had normal bone mass using DXA measurement as the gold standard; 32.8% of the subjects (38/116) had a T-score ≤-2.5 at LS and 17.2% (20/116) had a T-score ≤-2.5 at FN. According to QUS T-scores, 55 women (47.4%) were in the osteoporotic group and 57 (49.1%) presented osteopenia. QUS results were compared with DXA results in Table 2. There was

Table 1. Characteristics of the participants.

	Osteoporotic n = 40	Osteopenic n = 57	Normal n = 19	Total n = 116
Age (year)	61.0 ± 8.3	57.4 ± 7.5**	49.4 ± 5.8	57.3 ± 8.4
BMI (kg/m^2)	30.3 ± 5.0	31.5 ± 4.7	30.7 ± 5.2	31.0 ± 4.8
Years of education	2.3 ± 2.6*	4.15 ± 3.3	4.15 ± 3.5	3.6 ± 3.3
Years since menopause	17.9 ± 9.2*	11.7 ± 9.5	8.0 ± 7.0	13.4 ± 9.7
Parity	4.0 ± 1.2*	3.1 ± 1.1	3.0 ± 1.4	3.4 ± 1.2
QUS T-score	-2.8 ± 0.9*	-2.5 ± 1.1**	-2.1 ± 0.8	-2.6 ± 1.0
Spine T-score	-3.1 ± 0.6*	-1.7 ± 0.6**	-0.0 ± 0.6	-1.9 ± 1.2
Femur T-score	-2.2 ± 0.7*	-1.2 ± 0.9**	0.1 ± 0.9	-1.3 ± 1.5

Data is given as mean ± standard deviation
*P < 0.05 compared with the normal and osteopenic groups
**P < 0.05 compared with the normal group

Table 2. Comparison of QUS and DXA results of the participants according to WHO criteria.

DXA	QUS results			Total
	Osteoporosis	Osteopenia	Normal	
Spine				
Osteoporosis	22	16	0	38 (32.8%)
Osteopenia	24	26	3	53 (45.7%)
Normal	9	15	1	25 (21.6%)
Total	55 (47.4%)	57 (49.1%)	4 (3.4%)	116 (100%)
Hip				
Osteoporosis	14	6	0	20 (17.2%)
Osteopenia	26	30	1	57 (49.1%)
Normal	15	21	3	39 (33.6%)
Total	55 (47.4%)	57 (49.1%)	4 (3.4%)	116 (100%)
Spine+hip				
Osteoporosis	24	16	0	40 (34.5%)
Osteopenia	25	29	3	57 (49.1%)
Normal	6	12	1	19 (16.4%)
Total	55 (47.4%)	57 (49.1%)	4 (3.4%)	116 (100%)

moderate-weak correlation between QUS and DXA T-scores (LS T-score r = 0.231; FN T-score r = 0.286; P < 0.05).

ROC Analysis

Using ROC analysis, we identified the cut-off value that can be used as an optimal agreement between QUS and DXA. Using DXA as the gold standard, the cut-off value of QUS T-score was -2.2 with 77.5% sensitivity and 50.0% specificity for osteoporosis. The probability of women with a positive test result having osteoporosis, expressed as positive predictive value (PPV), was 44.9%, and probability of women with a negative test result not having osteoporosis, expressed as negative predictive value (NPV), was 80.9%. The chance of a positive test in the women who had osteoporosis, expressed as positive likelihood ratio (+ LR), was 1.55 times the chance of a positive result if the women did not have the disease. These results are shown in Table 3.

The sensitivity of QUS using DXA as the gold standard for osteopenia was 78.4% and specificity 52.6%, with a cut-off point -1.94. PPV and NPV are also shown in Table 3.

Table 3. Use of QUS parameters to predict osteoporosis or osteopenia defined by DXA.

Characteristics	Osteoporosis	Osteopenia
Sensitivity (95% CI)	77.5 (61.5-89.1)	78.4 (68.8-86.1)
Specificity (95% CI)	50.0 (38.3-61.7)	52.6 (28.9-75.5)
PPV	44.9	89.4
NPV	80.9	32.3
LR +	1.55	1.65
LR -	0.45	0.41

CI: Confidence interval
PPV: Positive predictive value
NPV: Negative predictive value
LR: Likelihood ratio.

The ROC curves for QUS T-score using the DXA T-scores as the standard method to diagnose osteoporosis and osteopenia are shown in Figures 1 and 2, respectively. The area under the curve (AUC) for QUS T-scores in identifying osteoporotic subjects was 0.646 (P < 0.01) and for identifying both osteoporotic and osteopenic subjects was 0.678 (P < 0.01).

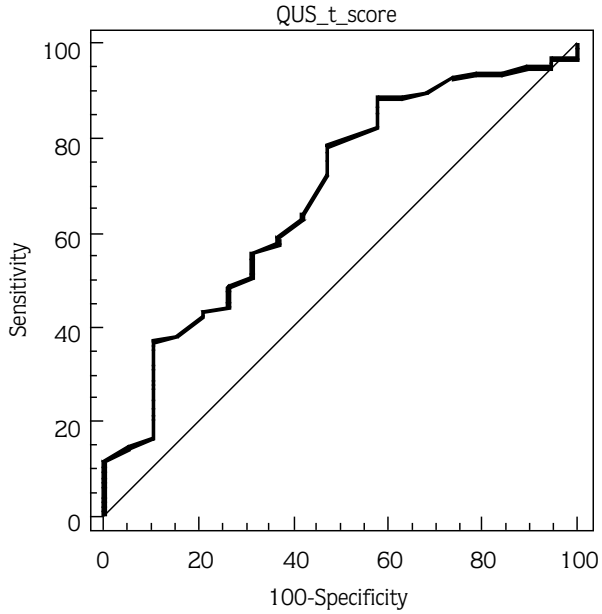

Figure 1. ROC curves for QUS T-score in diagnosing osteoporosis using DXA as the standard.

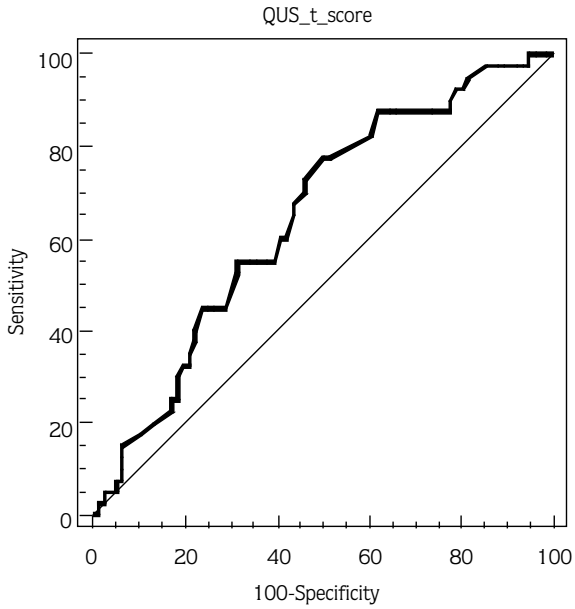

Figure 2. ROC curves for QUS T-score in diagnosing osteopenia using DXA as the standard.

Discussion

We aimed to evaluate the diagnostic performance of QUS in identifying osteopenia and osteoporosis in postmenopausal women on the basis of DXA T-scores and also to find a cut-off value for QUS for selecting postmenopausal women for DXA referral in our population.

We found that 34.5% of the postmenopausal women had osteoporosis and 49.1% osteopenia according to DXA T-scores, and these results are concordant with other European studies (14-15).

It has been reported that calcaneal QUS may have a useful role in identifying PMO, and that osteoporotic individuals had lower calcaneal T-scores compared to normals (16,17,18). In the present study, calcaneal QUS T-score values were significantly lower in women with osteoporosis than in their normal counterparts.

Several studies have reported various correlations (r = 0.34-0.87) between QUS values and DXA measurements of LS and FN (18-21). In this study, we found a weak correlation between QUS values and femoral and spinal DXA measurements. Even though these correlations are statistically significant, they are not enough to be predictive.

A screening device may be considered as an effective method when it minimizes the number of false negatives while limiting referral to a second level, like DXA. Therefore, it is indispensable to identify the QUS values below which further referral is necessary (5). In this regard, ROC analysis was performed and QUS T-score of -2.2 was selected as a cut-off point, for an optimal use of calcaneal QUS as a first-step screening tool that could identify the majority of subjects with DXA T-score ≤-2.5, while restricting the number of subjects to be referred for a further DXA examination. In other words, QUS T-score ≤-2.2 identifies a sub-group with osteoporosis in whom further assessment may be justified. In the same way, a cut-off value of QUS T-score is calculated as -1.94 for identifying osteopenic subjects. Peripheral measures, for example QUS, may be used as the first step in diagnosis. If the results indicate a woman is at high risk of osteoporosis, she could then be referred for DXA for definitive diagnosis. Data from a large cohort study, EPIDOS, suggest that such a sequential approach has similar sensitivity to using DXA alone, but requires fewer bone density examinations (22). In a very recent study, it was found that a sequential diagnostic approach, which uses QUS followed by DXA for women with low QUS values, prevents a similar number of hip fractures as does

testing all women with DXA alone, but it reduces the total number of women treated and total costs (23).

In ROC analysis, the AUCs were not large enough to predict osteoporosis and osteopenia as defined by DXA. In our study, sensitivity for predicting DXA-defined osteoporosis was high for QUS T-scores (77.5%), whereas specificity was low (50.0%). A recent study reported that, relative to DXA, QUS was more specific (83%) than 11 risk factors alone (42%) (24). NPV was also high for QUS as a predictor of DXA-defined osteoporosis versus osteopenia. This indicates that a woman with DXA-defined osteoporosis is unlikely to have a QUS result in the osteopenic range.

In the present study, QUS identified about 78.4% of subjects with osteopenia (sensitivity) and about 52.6% of subjects without osteopenia (specificity). Only about 89.4% of subjects with a positive QUS test had osteopenia (PPV). Of the subjects with a negative QUS test, about 32.3% had no osteopenia (NPV). PPV is high for osteopenia and we can suppose that QUS is much more useful for screening for postmenopausal women with osteopenia who are at risk of developing osteoporosis if no intervention is done.

In our study, positive likelihood ratio (+ LR) for the cut-off point of -2.2 was 1.55, meaning that osteoporosis was 1.55 times more likely to occur in an osteoporotic woman than in the others. In the studies held in Thailand and Spain, + LRs were 4.73 and 5.98, respectively, for QUS of calcaneus in predicting osteoporosis (25-26). A high + LR and low – LR close to zero show that the test provides useful information.

The limitation of this study is the small sample size. However, we calculated a cut-off point together with QUS T-score for our postmenopausal female population, and we will take this cut-off into account with other known risk factors for osteoporosis when considering women for DXA referral.

Our study shows that QUS can be used for stratifying the population into risk groups for osteoporosis and that women with QUS T-score ≤-2.2 are candidates for referral for DXA measurements. QUS can be used in any place of convenience for population screening, such as primary care settings, and its use in developing countries should be encouraged to increase detection of osteoporosis.

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