Diagnostic value of quantitative ultrasound and Osteoporosis self-assessment tool in comparison with DXA in detecting low bone mineral density in post-menopausal women in Riyadh, Kingdom of Saudi Arabia

Asia Pacific Journal of Multidisciplinary Research
Vol. 3 No. 4, 124-131
November 2015 Part III
P-ISSN 2350-7756
E-ISSN 2350-8442
www.apjmr.com

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Date Received: September 3, 2015; Date Revised: October 6, 2015

Abstract - *The objective of this study was to assess the diagnostic value of quantitative ultrasound (QUS) and Osteoporosis self-assessment tool (OST) compared with Dual Energy x-ray absorptiometry (DXA), and to identify the best cut-off value for determining low bone mineral density (BMD) among postmenopausal women in Riyadh, Saudi Arabia. We conducted a community based cross-sectional study on 224 randomly selected post-menopausal women. Women visited primary heath care centers for answering self-administered questionnaireand screening for low BMD using QUS technique. OST was calculated based on age and weight. DXA scanwas performedforlumbar spine and femur neck at King Khalid University Hospital, Riyadh. Mean age of participants was 58.05(±8.97) years. The prevalence of low BMD at lumbar spine and femur neck was 56% and 28% respectively. The best cut-off value for QUS and OST was ≤-1 and ≤2 respectively. QUS yielded sensitivity and specificity of 73% vs 47% for lumbar spine (area under curve (AUC) 0.56) and 84% vs 43% for femur neck (AUC 0.61). OST yielded sensitivity and specificity of 38% vs 84% for lumbar spine (AUC 0.62) and 48% vs 78% for femur neck (AUC 0.68). On combining the results, sensitivity and specificity were81% vs 41% (AUC 0.61) for lumbar spine and 89% vs 35% for femur neck (AUC 0.68) respectively. QUS and OST separately have limited diagnostic value, however on combining both instruments there is improvement in sensitivity to detect low BMD for both lumbar spine and femur neck.*

Keywords: *diagnostic value***,** *screening tools, quantitative ultrasound, osteoporosis self-assessment tool, DXA*

INTRODUCTION

There is high prevalence of low bone mineral density (BMD) and associated complications among post-menopausal women in the Kingdom of Saudi Arabia (KSA) [1]. *Dual energy x-ray absorptiometry* (DXA), considered as a gold standard technique for diagnosing low BMD, is a highly sensitive and specific test but it is expensive, requires high-tech advanced machine trained technicians, causes exposure to ionized radiations [3]and possible errors in DXA readings can occur because of non-uniform fat distribution[4]. Therefore, various other simpler techniques for screening low BMD have become popular [5, 6]. Quantitative Ultrasound (QUS) is one method recommended for screening low BMD, osteoporosis and fractures, especially in the elderly[7, 8].QUS has the advantage of being portable, inexpensive and radiation-free; however, there may be variations in the readings because of differences in quality of scanners; in selected anatomical site; or in overlying soft tissue as QUS readings are dependent on speed and frequency of sound waves passing through the overlying tissue and bone [8, 9, 10].Previous studies from KSA have utilized QUS in both men and women. El-Desouki and his colleagues measured the correlation between DXA, QUS and Single X-ray absorptiometry (SXA), to determine the role of QUS and SXA as screening tools. He found significant but weak correlation between DXA lumbar spine and QUS of heel and moderate correlation between DXA lumbar spine and SXA forearm[10]. Another study conducted in the eastern province of KSA found 30% and 23% of postmenopausal women and 24% and 12% women of young age suffering from osteopenia and osteoporosis respectively, based on QUS readings [11]. Sadat et al utilized QUS technique to determine Saudi women reference data of stiffness index (SI) for the diagnosis of low BMD and found significant differences between local readings and the standard Middle East and United States reference curve [12]. Despite of QUS utilization in local studies, limited information is available on diagnostic accuracy of QUS among Saudi population.

In addition to QUS, various validated risk assessment tools and criterion are available for screening low BMD and associated fractures. Some common tools are; *Quantitative computed tomography (QCT), Single Photon Absorptiometry (SPA), Digital X-Ray Radiogrammetry(DXR),WHO fracture risk assessment tool (FRAX) and criterions based on simple calculations include Osteoporosis Self-assessment tool (OST), the Osteoporosis Risk Index (ORI), the Simple Calculated Osteoporosis Risk Estimation (SCORE),Weight Criterion and Body Mass Index (BMI)* [13, 14, 15]. Amongst these, OST has been found to be the most convenient, valid, cost-effective and simplest tool for screening high risk women [16, 17]; however, studies from different populations have utilized different cut-off values, showing differences insensitivity and specificity [6, 18]. OST was initially developed for Asian women [19] but was later validated in Caucasians, Chinese and other populations[19, 20]. Comparative studies on QUS and scoring criterion, have found varying results, with some suggesting QUS as a better screening tool [8], whereas, others have found using both tools together have given better accuracy as compared to either of them used alone [21, 22]. In our knowledge, no study from KSA has previously utilized any scoring system to screen low BMD.

Currently, health practitioners in KSA refer patients for DXA based on presence of risk factors [23]. These risk factors are numerous and may be present due to reasons other than low BMD. DXA is available in some tertiary care Government hospitals, which is not convenient for everyone to visit (especially women, as their mobility is restricted). In addition, referring a large population to Government hospitals increases the burden on the health system. Therefore, it becomes pertinent to measure the diagnostic accuracy of screening tools like QUS and OST so that recommendations can be made regarding their utilization at primary care level in the KSA.

OBJECTIVES

This study aimed to assess the diagnostic value of quantitative ultrasound (QUS) and Osteoporosis self-assessment tool (OST) compared with Dual Energy x-ray absorptiometry (DXA) and to identify the best cut-off value for determining low bone mineral density (BMD) among postmenopausal women in Riyadh, Saudi Arabia.

METHODS

This is a community based cross-sectional study conducted in Riyadh, KSA. Two stage cluster sampling technique was used. In the first stage enrollment of women, questionnaire filling and screening for low BMD using QUS technique (Achilles machine)was done. Riyadh comprises of five administrative areas and each area has several primary health care centers (PHCCs). A complete list of all PHCC was developed and one PHCC was randomly selected from each area, making five PHCCs. The catchment population of PHCC served as cluster. In the second stage, equal number of houses were randomly selected from the catchment area of each PHCC to enroll 400post-menopausal women. The inclusion criteria was women with Saudi nationality and having menopause, where, menopause was defined as “complete cessation of periods for the last 12 months”. Women were excluded if they were suffering from any of the following secondary causes for low BMD; hyperthyroidism, hyperparathyroidism, chronic liver disease or history of intake of oral gluco-corticosteroids or hormonal replacement therapy.

Anthropometric indices including weight and height were measured with an electronic scale [Secca 220-(Hamburg, Germany 2009)].All participants provided written consent prior to questionnaire filling and measurements. The Institutional Review Board, King Saud University, Riyadh, approved the study protocol.

Measurement of BMD using Quantitative ultrasound (QUS) Technique:

The QUS-Achilles machine (Lunar, General Electric, Madison, Wis.) was used to scan the calcaneum of the left foot. The Achilles device is a water-based system, using fluid coupled through transmission in a temperature-controlled water bath (37°C). Study utilized two QUS machines (by the same manufacturer), calibrated every morning according to the manufacturer's instructions using a standardized phantom. Trained female technicians were hired for conducting this screening test. Results were measuredas T-scores.

Dual energy x-ray absorptiometry (DXA):

Women were referred to King Khalid University hospital (KKUH) for DXA scan and blood test. BMD measurement were carried out at the anterio-posterior spine L1-4 and right and left Femur neck (using GE prodigy, Lunar GE, Wisconsin USA). DXA scan for both right and left femur neck was performed and mean of both was taken as single value. All women having T-score <-1.0 SD at lumbar spine or femur neck were diagnosed as low BMD [24]. The quality control procedure using the standardized phantom were carried out each morning according to the manufacturer's protocol. Well-trained technicians performed each scan and special attention was given to proper positioning and avoidance of any type of artefact. All patients had the test performed, processed and finalized for reporting on the same day. The automatic region of interest (ROI) was used in all procedures to calculate the BMD at lumbar spine and femoral neck. As recommended, manual adjustments were made in the ROI for the lumbar spine and femur neck when necessary, for example, in cases of severe scoliosis or femur neck deformity [25].

Blood test for bone profile:

In order to reconfirm that no women is suffering from secondary causes for low BMD ten CCs of blood sample was taken from each participant by a trained phlebotomist. Samples were tested for Calcium, Phosphorus, Alkaline Phosphatase, Vitamin D, T4, TSH and Parathyroid hormone levels. Blood report was sent to each participants file in the respective PHCC.

Statistical analysis:

Data were analyzed using SPSS Pc+ version 21.0 statistical software and MedCalc software. Descriptive statistics (mean, standard deviation and proportions) were used to describe continuous and categorical variables. DXA and QUS readings were taken as T-scores, which depicts the units of standard deviation from the mean.OST scores were calculated for each women based on age and weight using the formula: (weight in kg – age in years) x 0.2. To get the diagnostic value if any of the screening test was positive, OST scores and QUS T-scores were combined with the help of logistic regression analysis.Sensitivitywas defined as proportion of women with low BMD based on DXA that tested positive on either the QUS or OST, and specificity was defined as proportion of women with low BMD who were negative according to DXA and tested negative on either the QUS or OST. Positive predictive value was defined as proportion of individuals who test positive and truly have the disease and negative predictive value was defined as proportion of individuals who tested negative and truly did not have the disease [26]. MedCalc software was used to develop the Receiver-operating characteristic (ROC) curve, which is a graphical representation of the accuracy of a test and plots a curve for sensitivity against (1-specificity) for all threshold levels. Area under the ROC curve quantifies the diagnostic accuracy of the screening tests, with 0.5 value meaning the test gives no useful information, and 1.0 means a perfect test. Using the Youden index formula, the best cut-off value that yielded maximum value of sensitivity and specificity wasdetermined for QUS and OST to identify low BMD. The 95% confidence intervals and p-value <0.05 were used to report the precision and statistical significance, respectively, of the estimate.

RESULTS

Out of 400, 386post-menopausal women visited the PHCC (10 were excluded because they did not fulfill the inclusion criteria) and 225 (60%) got their DXA scan done from KKUH. We further excluded one woman because her DXA report was missing; hence, final analysis was done on 224 post-menopausal women. Mean age (SD) of the participants was 58(±8.97) years, ranging from 49 to 77 years; mean BMI was 32.22(±5.58) (Table I). Mean age (SD) of the participants was 58 (±8.97) years, ranging from 49 to 77 years; mean BMI was 32.22(±5.58) (Table I). DXA scan found 58% and 28% women suffering from low BMD at lumbar spine and femur neck, respectively (Table I).

Results for different blood indices are given in Table I. Mean levels for Calcium, Phosphorus, Alkaline Phosphatase, T4, TSH and Parathyroid hormone were within normal range. However, mean vitamin D level was 43.13(±26.84) mmol/L, which is considered as deficient. The role of vitamin D in maintaining bone health has remained controversial [27],in this study also there was no significant difference in vitamin D levels between those who had low BMD versus normal BMD (p=0.22).Similarly, 20% of women had fasting blood sugar >7.0 mmol/L, but there was no significant difference in the mean blood sugar levels between the two groups (p=0.10).

Significant, but weak correlation was found between OST scores and QUS T-scores (r=0.20, p<0.01). Correlation between QUS T-scores and DXA lumbar spine was significant but weak[r=0.13 (p=0.02)]. Similar trend was seen between QUS and DXA femur neck [r=0.18 (p=0.007)]. Moderate correlation was found between OST and DXA lumbar spine (r=0.23, p<0.01) and DXA femur neck (r=0.28, p<0.01).

Diagnostic value for QUS T-scores

The best cut-off value determined for QUS for both sites (lumbar spine and femur neck) was T-score≤-1. Validity for QUS using DXA technique as gold standard found 84% sensitivity for femur neck as compared with 73% for lumbar spine, whereas specificity for both sites was 43% and 47% respectively. AUC was 0.62 (p=0.002) for femur neck as compared with 0.56 for lumbar spine (p=0.11) (Table II). Positive and negative predictive values were 66% and 56% for lumbar spine whereas femur neck had 87% and 36% negative and positive predictive value.

Diagnostic value for OST scores

The best –cut-off value for both sites was determined as OST scores ≤2. Results for OST found sensitivity as 38% and 48% for both lumbar spine and femur neck, whereas specificity was 84% for lumbar spine and 78% for femur neck. AUC for lumbar spine and femur neck was 0.61 (p=0.003) and 0.67 respectively (p<0.001). Positive predictive value for lumbar spine and femur neck were 77% vs 46%, whereas negative predictive value were 79% vs 49% respectively (Table III). Figure 1 is showing the ROC curves for QUS T-scores and OST for lumbar spine and femur neck.

Diagnostic value for both QUS T-scores and OST

Both instruments when utilized in combination yielded sensitivity and specificity of 81% and 41% for lumbar spine, and 89% and 35% for femur neck respectively. Positive and negative predictive value for QUS T-scores at lumbar spine were 66% and 60%, whereas, at femur neck it was 35% and 89% respectively (Table IV). By using binary logistic regression, in which the dependent variable is "DXA T-score for lumbar spine" (diseased & normal) and independent variables are QUS T-score and OST score, a new variable was created. From the regression coefficients of the model, probabilities were derived using, logit(p)= (0.645)+ (-0.067)x (QUS T-score) + (-0.090)x(OST score). These probabilities were used to generate the ROC curves. Similarly, a new variable was obtained using "DXA T-score for Femur neck" (diseased & normal) as dependent variable and probabilities were derived using, logit(p)= (-0.756)+ (-0.271)x (QUS T-score) + (-0.143)x(OST score). These probabilities were used to generate the ROC curves, for lumbar spine and femur neck. AUC for lumbar spine was 0.61 (p=0.003) and for femur neck 0.70 (p=0.001).

DISCUSSION

This study reports the diagnostic value of QUS and OST in comparison to DXA in post- menopausal women in Saudi Arabia. Mean bone mineral density measured at lumbar spine and femur neck using DXA scan were similar to earlier findings by El Desouki, 2005 [10]. Low BMD at femur neck is almost double than detected at lumbar spine (58% vs 28%) and these findings are also in support of previous studies [1, 12].

The best cut-off value determined for QUS was similar to the International value, which is T-score≤-1 [28]. Although El Desouki et al recommended to utilize T-score value other than ≤-1, our results don't support his findings. The difference can be explained because of difference in age group. It is recommended that QUS should be used to screen low BMD in postmenopausal age group, however, study by EL Desouki had women aged 20-80 years in his study, which may have affected the results. Having QUS T-score≤-1, the current study showedgood sensitivity and moderate specificity for both lumbar spine and femur neck, however, AUC was 0.56 for lumbar spine and any tool having AUC<0.60 is considered as low in accuracy. We found low PPV for femur neck (36%) as compared to lumbar spine (66%), PPV is directly affected because of prevalence [26], hence having fewer women with low BMD at femur neck (28%) may have affected the PPV value.

The best–cut-off value determined for OST was similar to the International cut-off of ≤2 [18]. OST found

P-ISSN 2350-7756 | E-ISSN 2350-8442 | www.apjmr.com
Asia Pacific Journal of Multidisciplinary Research, Vol. 3, No. 4, November 2015

low sensitivity (38%-47%) but high specificity (78%-84%) for both lumbar spine and femur neck. Although both sensitivity and specificity are important, however, high specificity (false negative) means that we will miss many at risk and only benefit we can achieve is identifying those who do not have low bone density [26]. Therefore, OST alone may not be a good screening tool for chronic conditions like low BMD.

Both instruments when used in combination yielded higher sensitivity of 81% and 89% for lumbar spine and femur neck respectively. Specificity was moderate,41% for lumbar spine and 35% for femur neck. AUC for both, lumbar spine and femur neck >0.60, which is considered adequate. The results of the current study support the results of previous studies, which recommend utilizing both instruments in combination [22, 29]. Both instruments are easy and convenient to use at primary care level. In addition, DXA is expensive [30], one test costs around Saudi Riyal (SR) 500 as compared with QUS, which hardly costs SR 20-25 per test.

The study has certain limitations; first; the postmenopausal status was assessed based on verbal history for menopause status, and no hormonal measurements were conducted, so misclassification of cases could not be ruled out. Second: Diagnostic accuracy was measured separately for lumbar spine and femur neck, whereas, it is better to take the lowest T-score value at any one of the recommended sites (as women may have normal BMD at one site and low at another). This approach may have affected our results.

CONCLUSION

The best cut-off value for QUS and OST among participating Saudi postmenopausal women in the current study was similar to the International values. QUS was found to be a valid tool but only for femur neck, and OST had a good specificity but low sensitivity. On combining both tools, there is improvement in the diagnostic value, hence it is better to utilize both tools in order to screen women with low BMD.

This study was conducted on a limited sample size, which may have affected the results; hence, we recommend larger prospective studies should be conducted. This study was conducted only on postmenopausal women, whereas many elderly males also suffer from low bone mineral density. Therefore, future studies should overcome both of these limitations.

ACKNOWLEDGEMENT

This study was sponsored by “Deanship of Scientific Research, Research Chair Program, King Saud University, Riyadh. We are grateful to Dr. M El Desouki (deceased) for his facilitation and guidance in conduct of this study. We also thank the staff of PHCC and all females who participated in the study for their time and co-operation.

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Table 1: Characteristics and blood indices of women participating in the study (n=224)

Characteristic	***Mean (SD)***
Age (years)	56.05(±8.97)
Height (in cm)	153.75(±5.15)
Weight (in kg)	76.49 (±14.39)
BMI	32.22(±5.58)
BMD (g/cm^2)	
Lumbar spine	0.998 (±0.16)
Femur neck	0.962 (±0.17)
Prevalence of low BMD	
Lumbar spine(T score<-1)	131(58.5%)
Femur neck (T-score<-1)	63(28%)
T-scores	
Lumbar spine	-1.32 (±1.3)
Femur neck	-0.22(±1.7)
Calcaneum bone	-1.13(±1.28)
OST scores	4.07(±3.8)
Frequency of positive history of fractures on minor fall/ injury	24(11.4%)
Blood Indices	
Calcium (mmol/L)	2.31(±0.50)
Phosphorus (mmol/L)	1.28(±0.35)
Alkaline Phosphatase (µ/L)	100.72(±33.8)
Vitamin D (nmol/L)	43.13(±26.84)
T4 (mIU/L)	14.21(±1.76)
TSH (mIU/L)	2.91(±1.99)
Parathyroid Hormone (pmol/L)	4.82(±1.78)
Fasting Blood sugar (mmol/L)	6.27(±1.88)

SD Standard Deviation; BMI Body Mass Index; DXA Dual Energy X-Ray Absorptiometry; QUS Quantitative Ultrasound; OST Osteoporosis Self-Assessment Tool

Table 2: Validity of Quantitative ultrasound in comparison to DXA to diagnose low bone mineral density at lumbar spine. FN false negative; FP false positive. Sensitivity= 96/131=73% , specificity=44/93=47%; positive predictive value=66% and negative predictive value=56%

QUS	Bone mineral density at lumbar spine using DXA		Total
	T-score<-1	*T*-score ≥-1	
≤-1 (high risk)	96 (73.3%)	49 (52.7%)(FP)	145
>-1 (low risk)	35 (26.7%)(FN)	44 (47.3%)	79
Total	131	93	224

Validity of Quantitative ultrasound in comparison to DXA to diagnose low bone mineral density at femur neck. FN false negative; FP false positive. Sensitivity= 53/63=84%, specificity=69/161=45%; positive predictive value=36% and negative predictive value=84%

QUS	Bone mineral density at femur neck using DXA		Total
	T-score<-1	T-score ≥-1	
≤-1 (high risk)	53 (84.1%)	92(57.1%)(FP)	145
>-1 (low risk)	10 (15.9%)(FN)	69 (42.9%)	79
Total	63	161	224

Table 3: Validity of the Osteoporosis Self-Assessment tool in comparison to DXA to diagnose low bone mineral density at lumbar spine. FN false negative; FP false positive. Sensitivity= 81/131=38% , specificity=78/93=84%; positive predictive value=71% and negative predictive value=51%

OST	Bone mineral density at lumbar spine using DXA		Total
	T-score<-1	*T*-score ≥-1	
≤2 (high risk)	50 (38.2%)	15 (16.1%)(FP)	65
>2 (low risk)	81 (61.8%)(FN)	78 (83.9%)	159
Total	131	93	224

Validity of the Osteoporosis Self-Assessment tool in comparison to DXA to diagnose low bone mineral density at femur neck. FN false negative; FP false positive. Sensitivity= 30/63=48% , specificity=126/161=78%; positive predictive value=46% and negative predictive value=79%

OST	Bone mineral density at femur neck using DXA		Total
	T-score<-1	*T*-score ≥-1	
≤2 (high risk)	30 (47.6%)	35 (21.7%)(FP)	65
>2 (low risk)	33 (52.4%)(FN)	126 (78.3%)	159
Total	63	161	224

Table 4: Validity of the Quantitative Ultrasound and Osteoporosis Self-Assessment tool in comparison to DXA to diagnose low bone mineral density at lumbar spine. FN false negative; FP false positive. Sensitivity=106/131=81%, specificity=38/93=41%; positive predictive value=66% and negative predictive value=60%

Screened Using QUS and OST	Bone mineral density at lumbar spine using DXA		Total
	T-score<-1	*T*-score ≥-1	
At risk	106(80.9%)	55(59.1%)(FP)	161
Normal	25 (19.1%)(FN)	38(40.9)	63
Total	131	93	224
Validity of the Quantitative Ultrasound and Osteoporosis Self-Assessment tool in comparison to DXA to diagnose low bone mineral density at femur neck. FN false negative; FP false positive. Sensitivity=56/63=89%, specificity=56/105=35%, positive predictive value=35% and negative predictive value=89%			
Screened Using QUS and OST	Bone mineral density at femur neck using DXA		Total
	T-score<-1	*T*-score ≥-1	
At risk	56(88.8%)	105(65.2%)(FP)	161
Normal	7(11.2%)(FN)	56(34.7%)	63
Total	63	161	224

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Conflict of interest/ Disclosures: All authors declare "No competing financial interest exists"