Diplomarbeit

Pre-screening for Osteoporosis with Quantitative Ultrasound in Postmenopausal Caucasian Women

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Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 01.10.2018 *Bernhard Steiner eh*

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Title: Pre-screening for Osteoporosis with Quantitative Ultrasound in Postmenopausal Caucasian Women

Running Title: QUS Pre-screening for Osteoporosis

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Structured Abstract

Background:

Calcaneal quantitative ultrasound (QUS) is a readily accessible and radiation-free alternative to DXA for assessing BMD. Results obtained from QUS measurement cannot directly be compared to DXA, since these two techniques capture different bone-specific parameters. In order to identify individuals who are likely to have osteoporosis by DXA, device-specific thresholds have to be defined for QUS.

Objective:

This cross-sectional study evaluated the accuracy of QUS to identify postmenopausal women with osteoporosis defined as a T-score of ≤ -2.5 SD by DXA, and to calculate device-specific cutoff values for the QUS device investigated.

Methods:

We assessed BMD at the lumbar spine, bilateral femoral neck and total hip sites with DXA, and QUS parameters of the right and left calcaneus in a cohort of 245 postmenopausal treatment-naive women between the age of 40 and 82. Correlation coefficients of BMD and QUS parameters were calculated. Receiver operating characteristic (ROC) curves were generated and areas under the curves (AUC) evaluated. Cutoff values for QUS were defined.

Results:

Calcaneal QUS' has the ability to identify postmenopausal women with a T-score ≤ -2.5 at the right hip (AUC = 0.887) and left femoral neck (AUC = 0.824). Cutoff values for the QUS T-score of the right (-1.455) and left (-1.480) calcaneus were defined for screening purposes.

Conclusion:

This study provides insights into the comparative performance of QUS with DXA. Considering the diagnostic accuracy of this device in comparison with DXA it can be recommended as a pre-screening tool to reduce the number of DXA screenings.

Capsule summary

- Quantitative Ultrasound as valuable alternative for osteoporosis pre-screening.
- Quantitative Ultrasound cut-off values for "Pegasus".
- Quantitative Ultrasound is low cost and readily accessible compared to DXA.

Zusammenfassung

Hintergrund:

Die Messung des Calcaneus mittels Quantitativem Ultraschall (QUS) ist eine strahlungsfreie und gut verfügbare Alternative gegenüber DXA, für die Messung der Knochendichte. Die Ergebnisse von QUS Messungen sind nicht direkt mit DXA zu vergleichen da unterschiedliche Parameter des Knochens erfasst werden. Um jene Individuen zu identifizieren, bei welchen höchstwahrscheinlich eine Osteoporose nach DXA vorliegt, sind gerätspezifische Cutoff-Werte für QUS zu definieren.

Ziel:

Diese Querschnittstudie untersuchte die Genauigkeit von QUS bei der Identifikation von postmenopausalen Frauen mit Osteoporose, definiert durch einen T-score von ≤ -2.5 SD mittels DXA, und berechnete gerätspezifische Cutoff-Werte für das verwendete QUS-Gerät.

Methoden:

Gemessen wurde mittels DXA die Knochendichte an der Lendenwirbelsäule, bilateral am Femurhals sowie an der totalen Hüfte. Mittels QUS wurden rechter und linker Calcaneus gemessen. Die untersuchte Kohorte bestand aus 245 postmenopausalen unbehandelten Frauen zwischen 40 und 82 Jahren. Korrelationskoeffizienten von Knochendichte und QUS Parametern wurden berechnet. Receiver operating characteristic (ROC) curves wurden berechnet und areas under the curves (AUC) beurteilt. Weiters wurden Cutoff-Werte für QUS berechnet.

Ergebnisse:

Mit QUS des Calcaneus ist es möglich postmenopausale Frauen mit einem T-score von ≤ -2.5 an der rechten Hüfte (AUC = 0.887) und am linken Femurhals (AUC = 0.824) zu identifizieren. Cutoff-Werte für den QUS eigenen T-score des rechten (-1.455) und des linken (-1.48) Calcaneus wurden für die Anwendung bei Pre-Screenings definiert.

Conclusio:

Diese Studie bietet Einblick in die vergleichbare Leistung von QUS mit DXA. In Anbetracht der diagnostischen Genauigkeit dieses Gerätes, im Vergleich mit DXA, kann dieses Werkzeug für ein Pre-Screening, für die Reduktion der Anzahl an DXA Screenings, verwendet werden.

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1. Introduction

Due to aging societies around the world, osteoporosis and osteoporotic fractures have become a major global burden for health care providers and health care systems. The economic burden of osteoporotic fractures has been highlighted in previous studies. In 2010 Europe's six largest countries expended €31 billion for the treatment of osteoporotic fractures.[1]

The life-time risk for a fragility fracture is approximately 50% for women and 25% for men above the age of 50, likely to rise in the near future due to demographic changes.[2]

Current Austrian practice guidelines, as published recently by the Main Association of Austrian Social Security Institutions, advocate the assessment of fracture risk by using the Fracture Risk Assessment tool FRAX®, which aside from clinical risk factors (CRFs) also takes into account BMD of the femoral neck.[3] However, this approach is limited on the one hand by the availability of DXA devices, and on the other hand by a widespread lack in awareness and perception of osteoporosis not only in the general population but also among healthcare professionals.[4][5][6]

According to the World Health Organization (WHO) osteoporosis has been defined as a bone mineral density (BMD) of -2.5 or more standard deviations below the average value for young healthy individuals, described as a T-score of ≤-2.5 SD, measured with DXA. [7] Based on this definition quantitative ultrasound (QUS) cannot be used as a tool to diagnose osteoporosis per definition, since bone specific parameters as captured by QUS are different from those captured by DXA.

However QUS of the calcaneus has been shown to be a useful means for early diagnosis and pre-screening for osteoporosis.[8][9][10][11] Compared to DXA, which is center bound and emits low doses of ionizing radiation, QUS is transportable, inexpensive, timesaving and radiation free.[4] Previous studies suggest that QUS of the calcaneus could be used as a pre-screening tool to identify patients at high risk for which treatment should be initiated, just as it could limit the number of patients who need a DXA measurement by predicting patients at very low risk. [12][13] As a result of differing measurement techniques and skeletal sites, cut-off values vary between different QUS devices. The purpose of this study was to identify optimal cutoff values for a specific calcaneal QUS device (Pegasus®, Medilink, Mauguio, FR) to identify patients at risk of osteoporosis in postmenopausal women.

2. Material and Methods

2.1 Participants

This cross-sectional study was performed at a private practice specialized in osteoporosis screening ("OG – Ost" Apparategemeinschaft Osteoporose St. Peter, Graz, Austria). Between May and July 2017, postmenopausal Caucasian women, aged 40 to 82 years, who were untreated and had no history of secondary osteoporosis, were invited to have a DXA scan performed together with Calcaneal QUS measurement.

Exclusion criteria were treatments known to affect bone metabolism, except calcium and vitamin D, previous diagnosis of osteoporosis and any case of secondary osteoporosis. Ethical approval for the study protocol was received by the Institutional Review Board of the Medical University of Graz (30-229 ex 17/18).

2.2 Measurements

All DXA measurements were carried out using the same device ("GE Lunar Prodigy Pro", GE Healthcare, Cèdex, FR), with a Least Significant Change (LSC) of 0.021 g/cm^2 at the left total hip and 0.027 g/cm^2 at the right total hip. Values for BMD, T-score and Z-score of the lumbar spine (at least 2 assessable vertebrae), left and right femoral neck and total hip region, as well as trabecular bone structure (TBS) were assessed. Based on the WHO classification a T-score ≤ -2.5 was categorized as osteoporosis, a T-score < -1.0 to > -2.5 as osteopenia, and a T-score > -1 as normal.

QUS measurements were performed on the same day as the DXA measurement, using one single unit of the gel-coupled QUS device ("Pegasus", Medilink, Mauguio, FR). Values measured and calculated by this device include broadband ultrasound attenuation (BUA) (dB/MHz), the speed of sound (SOS) (m/s), QUS T-score equivalent to DXA T-score and QUS Z-score equivalent to DXA Z-score.

A wall mounted standardized stadiometer was used to determine height to the nearest centimeter and body weights were measured using a calibrated digital scale noted to the nearest 0.1 kg. All measurements were performed by one certified well-trained medical technician and results were entered into a password protected anonymized database.

2.3 Statistical analysis of the study population

All variables were checked for plausibility to detect outliers in the data set. Assumption of normal distribution was proven with Shapiro Wilk tests ($p>0.05$ normally distributed data assumed) and Q-Q plots. Descriptive statistics were calculated for continuous variables presented as means and standard deviations. To analyse associations of DXA (T-score of L1-L4 including TBS, left and right femoral neck and total hip), with QUS (BUA, SOS, QUS T-score), and body mass index (BMI) Pearson correlation coefficients were computed for normally distributed data, otherwise Spearman coefficient was applied. Receiver operating characteristics (ROC) analysis was used to evaluate the discriminatory ability of QUS to detect postmenopausal women with and without osteoporosis as defined by the gold standard DXA (T-score ≤ -2.5). The area under the curve (AUC) was calculated for available DXA sites with a confidence interval of 95%. Describing the inherent validity of diagnostic tests the AUC is an effective and combined measure of sensitivity and specificity.[14] The sensitivity (%) and the specificity (%) were determined at various cutoffs with DXA T-score ≤ -2.5 of L1-L4, the right and the left femoral neck and total hip combined into one variable to evaluate the overall capability of this QUS device to diagnose osteoporosis in the studied cohort. This was done by combining all cases with at least one DXA T-score ≤ -2.5 into a single variable. SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA) and STATA 12 (StataCorp LP, College Station, TX) was used for statistical analysis. A two-tailed p-value of less than 0.05 was considered as statistically significant.

3. Results

A total of 245 participants was screened for eligibility. Eleven patients had to be excluded due to invalid measurements and a total of 234 cases were included in the final analysis.

The characteristics of the study population are summarized in Table 1. The T-score at the lumbar spine ranged from -4.9 SD to +2.6 SD with a mean of -1 SD ± 1.4 SD. With a mean BMI of 24.98 ± 4.47 kg/m² the population investigated was near the upper threshold of normal weight. Women with osteoporosis had a lower BMI, T-score, BUA and QUS T-score ($p<0.001$) compared to women without osteoporosis. 165 participants were between the ages of 50 to 65. 24 out of the total 32 cases with a DXA T-score ≤ -2.5 were found in this cohort. The mean age of this group was 56.67 and the mean BMI 24.3.

The following bivariate correlations are all significant at the 0.01 level. A moderate positive correlation of DXA and QUS measurements was evident between the T-score of the left hip and QUS T-score at the left calcaneus (*r = 0.515*). There was a weaker correlation between the QUS T-score of the left calcaneus and the T-score of the lumbar spine (*r = 0.397*). QUS T-score of the right calcaneus had slightly lower correlations with the DXA T-score of the right hip (*r = 0.505*) and lumbar spine (*r = 0.404*). A strong positive correlation was noted between the BUA measurements of the right and left calcaneus (*r = 0.834*). Whereas SOS of the left calcaneus moderately correlated with left BUA measurements (*r = 0.541*). There was no significant correlation between SOS and BUA of the right calcaneus. A weak but significant positive correlation was noted between TBS and left (*r = 0.309*) as well as right (*r= 0.333*) BUA. BMI had very weak positive significant correlations with SOS measurements of the right (*r = 0.218*) and left (*r = 0.207*) side.

Since some of the studied variables did not follow a normal distribution non-parametric estimation AUC from the ROC curve were computed. The accuracy of QUS to detect women with osteoporosis at the lumbar spine, the left and right hip and femoral neck is summarized in Table 2 and 3. A better overall performance is associated with an AUC > 0.80. A high diagnostic accuracy was achieved at the right hip between the DXA T-score and the QUS T-score of the right calcaneus (AUC = 0.887). At the right hip no significant difference could be found between the QUS T-score of the right calcaneus and the QUS T-score of the left calcaneus (*p=0.093*). At the left calcaneus results for the left femoral neck (*AUC = 0.823*) outperformed the left hip (*AUC = 0.772*). The diagnostic accuracy at the lumbar spine, paired with calcaneus measurements of the right (*AUC = 0.700*) and left side (*AUC = 0.704*), was slightly lower. When pairing QUS T-scores with the combined findings out of all DXA sites the right (AUC = 0.732) and left (AUC = 0.731) QUS measurements achieved nearly the same AUC. The best AUC for isolated DXA sites was calculated for participants between the ages of 50 to 65 for the right (AUC = 0.956) and for the left (AUC = 0.95) calcaneus when paired with DXA results of the ipsilateral hip.

Table 4 summarizes the performance of QUS to determine postmenopausal women with osteoporosis at suitable cutoff points. A cutoff of -1.455 for the right and -1.48 for the left QUS T-score achieved acceptable specificities to qualify as screening-parameters of osteoporosis. Separate cutoffs were defined for women between the ages of 50 – 65. For the left calcaneus a QUS T-score of -1.325 resulted in 62.5% sensitivity and 83.1% specificity. At the right calcaneus a QUS T-score of -1.305 achieved 54.2% sensitivity and 86% specificity.

4. Discussion

With a hip fracture incidence of < 650/100.000 in a population aged 50+, Austria has the third highest rate of hip fractures in the European Union. [15] Especially in people above the age of 85, adequate assessment of osteoporosis is lacking, and the prevalence of osteoporosis is higher than documented diagnosis. [16] DXA-testing is most commonly used in patients who already had experienced their first fragility fracture, in order to initiate osteoporosis treatment. However, prevention of the first fragility fracture should be the primary objective, in order to reduce the burden of disability, increased costs and increased mortality risk inflicted by fragility fractures. However, widespread DXA screening for osteoporosis in the whole population is neither recommended nor accomplishable. [17] To prevent the first fragility fracture, a pre-screening method appears to be useful to identify individuals who are at high risk of osteoporosis and osteoporotic fractures. At the same time, pre-screening with QUS may reduce the number of unnecessary DXA measurements in individuals with high BMD and consequently lower fracture risk. [17] In the present study, QUS of the calcaneus has been shown to be an attractive method for osteoporosis pre-screening because of its portability, low-cost and easy usability. QUS devices like the one investigated in the present study can easily be taken to rural areas or to patients that are homebound, and can be deployed by trained staff in pharmacies or doctor's offices to screen for suspected osteoporosis. [18]

In the population of postmenopausal women investigated in the present study, a significant correlation was found between each DXA site and QUS parameters. Consistent with other studies among older women, the correlation between QUS T-score and DXA T-score of the hip and femoral neck were better than with lumbar spine T-score. [19][17]

Calcaneal QUS' ability to identify women with a DXA T-score of ≤ -2.5 at the right hip (*AUC = 0.887*) excelled in comparison to a T-score ≤ -2.5 at the lumbar spine (*AUC = 0.704*) or left femoral neck (*AUC = 0.824*). Additionally, noteworthy is the very strong AUC of 0.956, for measurements of the right calcaneus and right hip, for participants between the age of 50 and 65, which would indicate an especially high potential use of this device for the pre-screening of hip fractures in women of this age group. The calculated cutoff values sensitivity and specificity were too low for the diagnosis of osteoporosis. Device specific cut-off values with acceptable specificity were defined for the screening of osteoporosis. For the left calcaneus a QUS T-score of -1.48 and for the right calcaneus a QUS T-score of -1.455 were identified. For measurement results below the defined cutoff values additional DXA screening would be advisable, patients above would be considered to be at low risk. The performance of the investigated device is comparable with well studied QUS devices. Boonen et al. did achieve an overall sensitivity of 68% and specificity of 70% (AUC = 0.72) using the Sahara equipment (Hologic) in a community-dwelling population of postmenopausal women (n = 221). [20] Gemalmaz et al. did study a total group of 919, including 87 men, utilizing Achilles Express (GE Lunar) resulting in an overall sensitivity of 73.7% and specificity of 57.4%. [21] Larijani et al. deployed the Achilles (GE Lunar) device investigating a population of 420 postmenopausal women resulting in a total sensitivity of 84.7% and specificity of 50%. [22] Flöter et al. reviewed six articles which compared QUS of the calcaneus to DXA as the gold standard. As in this study author determined thresholds were chosen for QUS T-score. However, with a variability of -1.7 to -2.4 lower as the chosen ones for this device. [23] In these population based studies the crucial point is the determination of a device and population specific cutoff-point, which explains the differences in specificity and sensitivity. Not only the device used but also the population investigated are factors that result in different cutoff-values. This necessity to define specific cutoff values for each device and population is likely to limit QUS usefulness as a screening tool. Our study only included Caucasian postmenopausal untreated women with higher educational background. However, the current results for this device are comparable to results from different populations and other devices. [10] A fact that underlines the potential of QUS as an effective screening tool. This study has several limitations including a possible cohort effect, since all patients were referred to the office for osteoporosis screening a selection bias occurred. Unlike a real life study, which would have had a broad spectrum of patients, this study took place at a private institute thus resulted in a filtered group of participants who are mainly well educated and consists solely out of postmenopausal women above the age of 40.

5. Conclusion

This study provides information on the usefulness of a specific Calcaneal QUS device as an osteoporosis screening tool in postmenopausal women. The comparative performance of the investigated QUS device with DXA was assessed. Due to its low sensitivity, this QUS device cannot be recommended for diagnosis of osteoporosis as defined by the WHO. Like shown for other QUS devices before, the predictive value of the QUS device tested in the prevailing study for BMD is low. [22, 24] However, given the cutoff values specificity of 86.6% at the right and 83.3% at the left calcaneus, this QUS device can be recommended as a pre-screening tool to decide whether DXA measurement should be performed. Future studies in a larger cohort of postmenopausal women representative of the general population are needed to further support these findings.

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Table 1

Descriptive Characteristics and Results of DXA and QUS Measurements of the Study Population

	Women			Women without osteoporosis			Women with osteoporosis		
Characteristic	**N**	**Mean or %**	**SD**	**N**	**Mean or %**	**SD**	**N**	**Mean or %**	**SD**
Age	234	59,75	8,476	202	59,2	8,3	32	62	8,4
40 – 49	15	6.4%		15	6.4%		0	0%	
50 – 59	123	52.1%		106	45.3%		17	7.3%	
60 – 69	58	24.6%		49	20.9%		8	3.4%	
70 – 82	40	16.7%		32	13.7%		7	3%	
Body mass (kg)	236	66,4	11,6	202	67,6	11,4	32	58,1	9,7
BMI (kg/m²)	236	24,9	4,4	202	25,4	4,3	32	22,3	3,3
DXA T-score level	234								
Normal	106	45.3%							
Osteopenia	96	41%							
Osteoporosis	32	13.7%							
DXA									
T-score L1-L4	234	-1	1,4	198	-0,7	1,1	32	-3,2	0,6
T-score Hip (l)	233	-0,83	1,1	195	-0,7	1,1	32	-1,9	0,8
T-score Hip (r)	229	-0,8	1,1	192	-0,6	1,1	31	-1,9	0,9
TBS	231	1,3	0,1	195	1,3	0,1	32	1,2	0,1
QUS									
BUA (l)	232	67,8	7,46	198	68,5	7,4	32	63	6,6
QUS T-score (l)	231	-0,5	1,16	197	-0,4	1,1	32	-1,3	1,0
SOS (l)	232	1417,3	27,38	198	1419,2	27,1	32	1405,2	27,1
BUA (r)	230	68,4	6,77	197	69	6,6	31	64,3	6,2
QUS T-score (r)	230	-0,39	1,05	197	-0,3	1	31	-1	0,99
SOS (r)	230	1439,1	192,769	197	1431,8	123,6	31	1486,9	427,4

Table 2

Receiver Operating Characteristics AUC to identify DXA T-Score ≤-2,5 at the right calcaneus

	AUC	SD	p Value	Lower - Upper Cutoff (95% CI)	
at the right femoral neck: 7 positive 221 negative (n=228)					
BUA (r)	,770	,057	,015	,658	,882
QUS T-score (r)	,736	,071	,033	,596	,876
SOS (r)	,619	,134	,283	,357	,882
at the right hip: 10 positive 219 negative (n=229)					
BUA (r)	,885	,034	,000	,819	,951
QUS T-score (r)	,887	,033	,000	,822	,952
SOS (r)	,714	,088	,022	,541	,886
at the lumbar spine: 31 positive 197 negative (n=228)					
BUA (r)	,708	,049	,000	,611	,805
QUS T-score (r)	,700	,050	,000	,603	,798
SOS (r)	,602	,051	,069	,503	,701

Table 3

Receiver Operating Characteristics AUC to identify DXA T-Score ≤-2,5 at the left calcaneus

	AUC	SD	p Value	Lower - Upper Cutoff (95% CI)	
at the left femoral neck: 11 positive 220 negative (n=231)					
BUA (l)	,810	,054	,001	,703	,916
QUS T-score (l)	,824	,053	,000	,720	,929
SOS (l)	,717	,078	,015	,564	,871
at the left hip: 14 positive 217 negative (n=231)					
BUA (l)	,758	,058	,001	,644	,871
QUS T-score (l)	,772	,057	,001	,660	,884
SOS (l)	,698	,062	,013	,578	,819
at the lumbar spine: 32 positive 197 negative (n=229)					
BUA (l)	,698	,048	,000	,603	,793
QUS T-score (l)	,704	,048	,000	,609	,799
SOS (l)	,621	,048	,028	,528	,714

Table 4

Sensitivity and Specificity at suitable Cutoffs to Identify DXA T-score ≤ -2.5

	Cutoff	Sensitivity (%)	Specificity (%)
QUS T-score (r)			
	-0.125	78.5	48.9
	-0.780	69.2	68.8
	-1.455	41.0	86.6
QUS T-score (l)			
	-0.235	79.5	44.6
	-0.800	66.7	67.2
	-1.480	51.3	83.3