QUANTITATIVE HEEL ULTRASOUND COMPARED WITH DUAL-ENERGY X-RAY ABSORPTIOMETRY IN EVALUATION OF BONE MINERAL DENSITY IN CHRONIC HAEMODIALYSIS PATIENTS

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REZUMAT

Premize: Insuficiența renală cronică (IRC) în stadiu terminal este asociată cu o scădere semnificativă a densității minerale osoase, în comparație cu adulții aparent sănătoși. La ora actuală, standardul de aur al evaluării este absorbțiometria cu raze X (DXA). Aceasta este o metodă scumpă de investigație, ce necesită echipament special, presupune mobilizarea pacienților, precum și expunerea la raze X. Ultrasonografia cantitativă a călcâiului (QUS) este o metodă ieftină, ușor reproductibilă, mobilă, fără expunere la radiații, recunoscută pentru abilitatea de a prezice riscul de fractură, ce identifică persoanele cu densitate minerală diminuată. Studiul de față își propune să studieze abilitatea QUS versus DXA de a identifica situațiile cu densitate minerală osoasă diminuată. **Material și metodă:** Pacienții au fost selectați aleator, din totalul pacienților aflați în evidența activă a Centrului de hemodializă și transplant renal al Spitalului Clinic Județean de Urgență Timișoara. Fiecare pacient a fost evaluat atât prin DXA, cât și prin QUS. Am urmărit corelațiile între parametrii osteodensitometriei ultrasonice și densitatea minerală osoasă măsurată la diferite situsuri prin DXA. Tehnica ROC a fost folosită pentru compararea valorii diagnostice a QUS versus DXA. De asemenea, am identificat valorile prag ale QUI și BUA, cei mai buni 2 parametri de diagnostic, care identifică cu o sensibilitate și specificicate mare demineralizarea, folosind definiția OMS pentru identificarea osteoporozei și osteopeniei. Am utilizat strategia propusă de Societatea națională britanică de studiu al osteoporozei pentru identificarea valorilor optime ale QUI, interval care să permită o sensibilitate și specificitate diagnostică de 90%. **Rezultate:** 131 de pacienți, cu o vârstă medie de 47,7 ani, aflați în program de hemodializă cronică au constituit lotul de studio. BUA s-a corelat cel mai bine cu valorile DMO măsurate la nivelul colului femural. Folosind ariile de sub curbele de diagnostic ROC, observăm o sensibilitate bună, de 76,1% a BUA și QUI în diagnosticul osteopeniei, respectiv o specificitate și mai mare, de 72,5-77,8%. Diagnosticul osteoporozei este și mai bun, la o sensibilitate de 77% cu specificitate de 84%. Valorile prag identificate au fost de 76,1 (pentru osteopenie) și 69,6 (pentru osteoporoză). Calitatea diagnostică se îmbunătățește și mai mult în momentul definirii intervalului de valori ale QUI optim pentru diagnostic. **Concluzii:** Parametrii măsurați prin DXA și QUs se corelează important. Cel mai bun parametru diagnostic măsurat de osteodensitometria ultrasonică este QUI. Valoarea predictivă negativă mare sugerează capacitatea excelentă de screening a metodei în identificarea situațiilor fără demineralizare osoasă. Valorile prag ale QUI identifică cu o sensibilitate mare (60-80%), respectiv cu o specificitate bună (75%), osteopenia, respectiv osteoporoza. Utilizând varianta intervalului (valorile asociate unei sensibilități și specificități de 90%) putem identifica precis marea majoritate a cazurilor cu și fără afecțiune.

Cuvinte cheie: insuficiență renală cronică, osteoporoză, absorbțiometrie cu raze X, ultrasonografie cantitativă

ABSTRACT

Background: End stage renal disease (ESRD) is associated with reduced bone mineral density (BMD), compared with aged-matched healthy population. Dual-energy X-ray absorbtiometry (DXA) is the standard noninvasive method to asses BMD. It is expensive, it requires special equipment, X-ray exposure, mobility of the patients. Quantitative heel ultrasonography (QUS) is inexpensive, portable, easy to perform, radiation free, being recognized for its screening abilities and risk fracture prediction in normal population. This study intends to assess the ability of QUS versus DXA to determine BMD in a haemodialysed population. **Material and methods:** Patients randomly selected from all patients in the evidence of the Haemodialysis and Renal Transplantation Center of the Clinical Emergency County Hospital Timisoara, have performed DXA and QUS. The correlations between DXA and QUS parameters were evaluated. Receiver operator characteristic curves (ROC) were plotted for BUA, SOS and QUI and used to define cut-off values for best sensitivities and specificities for all parameters. WHO T score diagnosis of osteoporosis and osteopenia were used. We also have used the UK NOS strategy to define the interval of the best QUS diagnostic parameter, to identify with 90% sensitivity and 90% specificity different degrees of bone demineralization. **Results:** 131 patients, mean age 47.7 years, in the haemodialysis prgram, were evaluated. BUA and QUI seemed to be the parameters of choice when considering BMD at cortical level. Areas under ROC for BUA and SOS in diagnosis of osteoporosis and osteopenia, had a sensitivity of 76.1%, respectively a specificity of 72.5%-77.8%. The values for osteoporosis were even better: 77% and 84%. The identified cutoff levels for QUI were 76.1 (osteopenia) and 69.6 (osteoporosis). The diagnostic value of QUS (when reporting QUI) were even higher when we have defined the proper interval. **Conclusions:** DXA and QUS parameters correlate significantly. The best QUS diagnostic parameter is QUI. The high negative predictive value of different cut-off point suggests a very good screening power of QUI in identifying cases without bone demineralization. Cut-off values for QUI associated a high sensitivity (between 60-80%), respectively a specificity of over 75%, for the diagnosis of osteopenia and/or osteoporosis. Using the 90-90 approach, we can identify the precise interval for QUI values, that allows the best diagnosis of bone demineralization.

Key Words: end stage renal disease, osteoprosis, dual-energy X-ray absorbtiometry, quantitative ultrasonography

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INTRODUCTION

Renal osteodystrophy and bone demineralization generally generate significant morbidity and occasionally even mortality in patients with end stage renal disease (ESRD), especially in stage V (of chronic renal supplementation therapy). The current diagnosis algorithm for renal bone disease includes clinical signs, biochemical assays, bone remodeling markers and also

bone radiology. Independently of the type of bone disease, the measurement of bone mineral density (BMD) is important in evaluation the overall mortality and predicts the future fracture risk.[1,2]

Many authors recommend dual-energy X-ray absorbtiometry (DXA) in identifying the cardiovascular risk profile in patients with ESRD, especially in stages IV-V.[1,3,4]

The terms osteopenia and osteoporosis, commonly used in general population, are somehow uncharacteristic for secondary bone demineralization, such as in ESRD.[5] The World Health Organisation diagnostic criteria (1994) should be considered just for the literature citation. According to the American NIH Consensus the new definition for secondary osteoporosis is as follows: "a skeletal disease characterized by alteration of bone strength with increased risk of secondary fracture; bone strength reflects bone mineral density and bone quality".[6] Thus the diagnostic target in secondary cases of osteoporosis is to identify cases with low bone mineral density (BMD), and also decreased bone strength.[7]

DXA is the preferred method for measuring BMD in ESRD patients.[7-12]

There is also a need to measure the cortical bone, the trabecular compartment being sometimes increased in secondary hyperparathyroidism.[3,7,13,14] Median radius and especially femoral neck are the preferred sites for DXA.[3,15] Lumbar spine has to be evaluated especially in postmenopausal women.

Because there are some difficulties in mobilizing the patients, the fear of X-ray overexposure is significant, the cost is relatively high, while the reimbursement of DXA is sometimes difficult, quantitative ultrasonography (QUS) could be an alternative method.[3] There are a lot of favourable reports about the usefulness of QUS in evaluating patients with ESDR.

AIM OF THE STUDY

We have tried to analyze and determine the domains in which QUS can be properly used in the diagnosis of patients with ESRD. Screening or final diagnosis are equally useful in the complex diagnostic algorithm, used in the Center for Haemodialysis and Renal Transplantation of the Clinical Emergency County Hospital in Timisoara.

MATERIAL AND METHOD

The study group was composed of 131 patients, 63 females and 68 males (1:1,079), randomly selected from all patients registered in the chronic haemodialysis center. The patients were between 18 and 70 years old (average 47.776 ± 12.32 years) and were under chronic renal supplementation therapy for 0.2 - 12.32 years (mean 51.488 ± 4.686 months).

We have performed the DXA scan (Hologic Inc, antero-posterior technique, Delphi W device) on the lumbar spine and non-dominant femoral neck. Total BMD CV is 1.0%, ACF = 1.029, BCF = 0.993, TH = 8.076. The femoral neck and the total hip were analyzed separately.

QUS was performed with the Sahara device (Hologic Inc.), using the dry technique, in the non-dominant leg, the device being one of the two validated QUS devices worldwide (ISCD 2007). SOS (speed of sound), BUA (broadband ultrasound attenuation) and also the QUI (combined value of SOS and BUA) were measured for each patient.

Each device was operated by only one technician.

Analysis

We have used the T score for DXA (representing the standard deviation, compared with the normal young adult same sex population). WHO definition for osteoporosis and osteopenia were used.

We have also used the ROC curve to compare the diagnostic value of QUS compared with DXA, trying to identify severe demineralization (so called "osteoporosis" on DXA), and also demineralization (osteopenia in DXA). These cut-offs were used to calculate the sensitivities, specificities, false positive and false negatives, and positive (PPV) and negative predictive value (NPV) of SOS and BUA in diagnosis of bone demineralization.

Finally, we have tried to evaluate the best SOS and BUA cutoff point values in identifying both conditions.

The second part of our study compares the validated data for males and females for QUS parameters with our own.

RESULTS

The distribution of age and length of supplemental therapy in pur study group is presented in Figs. 1, 2.

Because both value series are under the Gauss slope, we consider that the study group is significant for the hemodialysis population from our region.

Table 1 shows the values (mean and SD) for BMD, and the T and Z score at each measurement site.

The relationship between DXA and QUS measurements (Pearson correlation) is demonstrated in Table 2, and also in Figs. 3, 4.

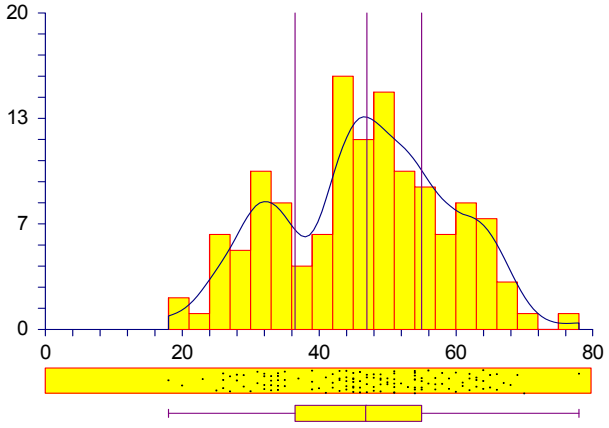

Figure 1. Age distribution in the study group (Gauss curve).

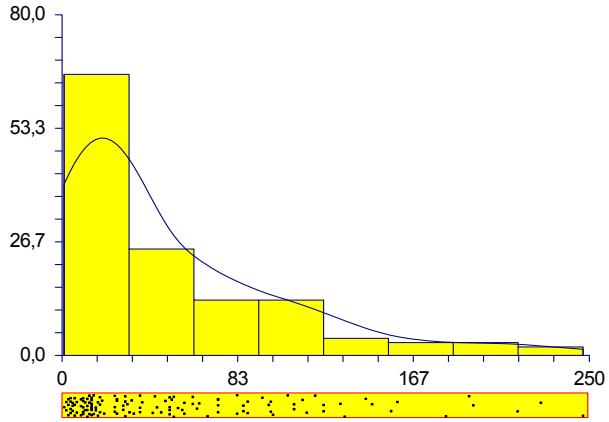

Figure 2. Length of haemodialysis treatment in the study group.

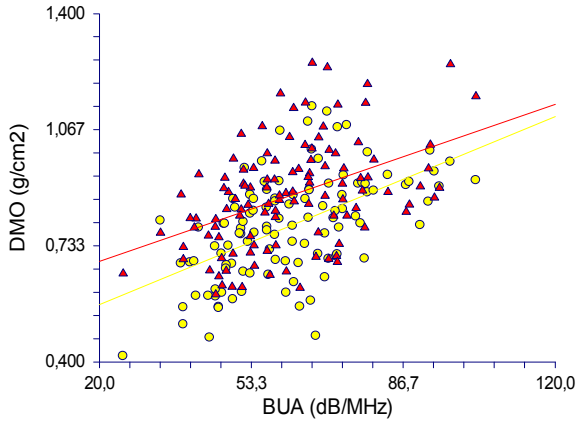

Figure 3. Correlation between femoral neck/lumbar BMD (g/cm^2) versus BUA (dB/MHz).

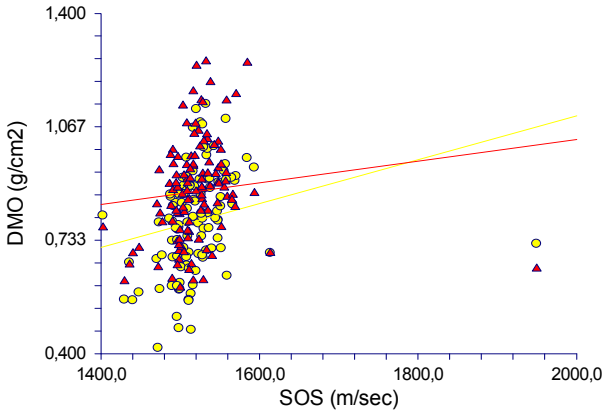

Figure 4. BMD correlation with SOS: comparison between DXA and QUS measurements.

Table 1. Results of DXA and QUS in the study group

	Mean ± SD	**T score ± SD**	**Z score± SD**	**Osteoporosis prevalence (%)**	**Osteopenia prevalence (%)**
DXA femoral neck (g/cm^2)	0,878 ± 0,15104	-1,6707 ± 1,394	-1,1596 ± 1,370	29,01	71,5
DMO total hip (g/cm^2)	0,7905 ± 0,147	-1,446 ± 1,073	-1,148 ± 0,952	15,26	68,70
DMO lumbar (g/cm^2)	0,8542 ± 0,213	-1,506 ± 0,987	-1,108 ± 0,763	16,79	69,46
SOS (dB/MHz)	1520,286 ± 49,62	-1,631 ± 1,017			
BUA (m/sec)	61,865 ± 14,959	-2,163 ± 1,263			
QUI	76,428 ± 16,517	-1,732 ± 1,023			

Table 2. Correlation between DXA and QUS measurements

	Femoral neck	**Total hip**	**Lumbar**	**BUA calcaneus**	**SOS calcaneus**	**QUI**
Femoral neck	-	0,89	0,782	0,613	0,342	0,613
Total hip	0,89	-	0,692	0,5435	0,225	0,502
Lumbar	0,782	0,692	-	0,447	0,117	0,407
BUA calcaneus	0,613	0,543	0,447	-	0,416	0,858
SOS calcaneus	0,342	0,225	0,117	0,416	-	0,503
QUI	0,613	0,502	0,407	0,858	0,503	-

As observed in the literature, the correlation between DXA parameters and QUS measurements are fair, but still it is obvious that these parameters are independent, measuring different things.[16] BUA (r = 0.613/0.447) and QUI (r = 0.613/0.502) seem to be the parameters of choice when considering BMD at cortical level. The correlation between QUS and lumbar spine DXA is rather poor than fair, and can be explained by the effects of spinal osteophytes and aortic calcifications, that can be superimposed when using anteroposterior DXA.

The best correlations between QUS and DXA were observed in the BUA – BMD at femoral neck. As seen in the literature, there is a good-high correlation between QUS parameters and BMD for skeletal sites matched regions-of-interest, in our case femoral neck.[17-19]

The ROC curves were plotted for SOS, BUA and QUI, using first only femoral neck T scores, the standard method to identify low BMD (so called osteoporosis and osteopenia).

The diagnostic values for QUS parameters as compared with femoral neck are listed in Table 3.

Table 3. QUS diagnostic value.

	Osteopenia			Osteoporosis		
	BUA	**SOS**	**QUI**	**BUA**	**SOS**	**QUI**
Sensitivity	**70,79**	77,52	**60,25**	**76,19**	80,95	**76,19**
Specificity	**72,50**	62,50	**77,5**	**83,33**	62,96	**66,48**
PPV	85,13	78,40	77,38	47,05	29,82	25,39
NPV	85,37	50,74	77,71	84,73	94,44	92,42

The area under ROC curves in the diagnostic of osteoporosis and osteopenia are presented in Figures 5 and 6.

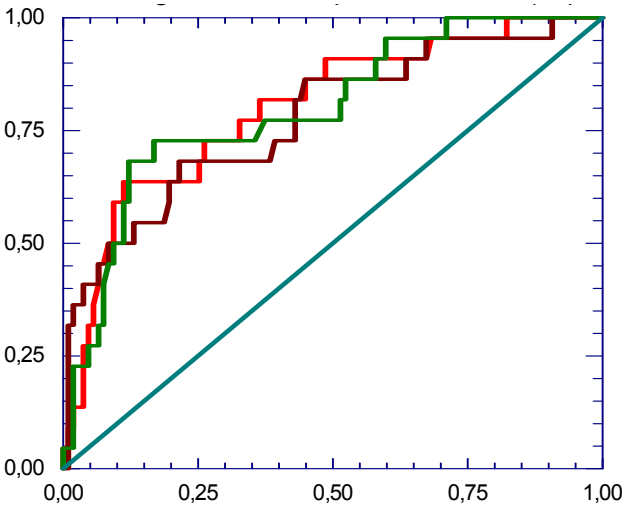

Figure 5. ROC curves for QUS parameters in diagnostic of osteoporosis.

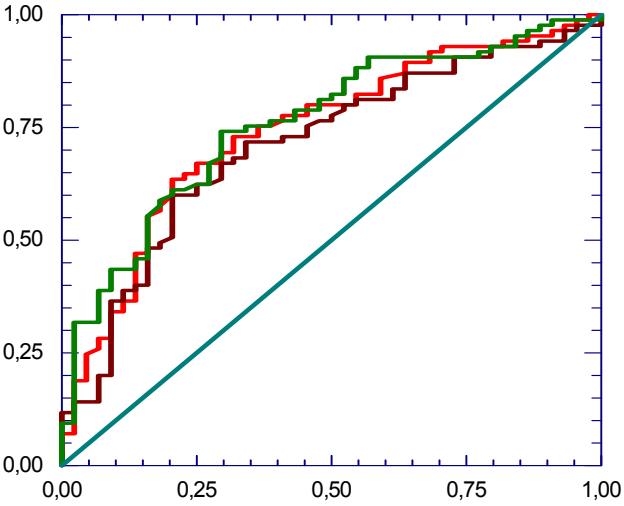

Figure 6. ROC curves for BUA,SOS,QUI in diagnostic of osteopenia.

The analysis of the area under ROC curve (AUC) shows very good results, presented in Table 4.

Table 4. AUC for QUS paramether as compared with femoral neck BMD.

	Osteoporosis	**Osteopenia**
BUA	0,800 ± 0,0535	0,741 ± 0,0456
SOS	0,7767 ± 0,059	0,710 ± 0,0475
QUI	0,798 ± 0,053	0,7586 ± 0,0435

BUA seems to be the best parameter to use in the diagnosis of bone demineralization. The optimal cut-off points for QUS parameters were calculated, considerind the positive diagnostice power. These values are presented in Table 5.

In terms of the diagnosis of severe demineralization, BUA values lower than 53,10 dB/MHz identify with good sensibility and specificity the osteoporotic cases.

The high negative predicted value, seen in BUA but also in QUI (94% and 95%), shows the potential of the method to screen the patients and safely identify the cases without severe bone demineralization.

In respect to osteopenia, the high positive predictive value for BUA (especially), but also for QUI, can identify sure enough cases with low mineral density.

The low NPV decrease the value for screening in osteopenic patients, but if we observe decreased BUA, below 65.10 dB/MHz and/or low QUI values (below 80.4) surely there is a degree of bone loss, with poor cardiovascular prognosis.

We have proceeded to the same algorithm in comparing QUS with total hip and lumbar spine DXA.

Table 5. Optimal cut-off points for QUS parameters (compared with femoral neck DXA).

	Osteopenia			Osteoporosis		
	BUA	**SOS**	**QUI**	**BUA**	**SOS**	**QUI**
Sensitivity	**72,72**	60,72	64,77	**76,19**	75,0	80,0
Specificity	**70,73**	73,17	73,17	**76,85**	60,55	66,9
PPV	84,21	81,53	83,33	39,02	23,21	30,7
NPV	54,71	45,31	47,61	94,31	90,4	94,8
Cut-off	**65,10**	**1516,3**	**76,10**	**53,10**	**1509,6**	**69,60**
AUC	**79,57**	**75,89**	**80,4**	**81,01**	**75,26**	**81,41**

The parameters for total hip were similar to those observed when compared with the femoral neck. AUC were even better than in the pre-mentioned analysis. (Figs. 7, 8)

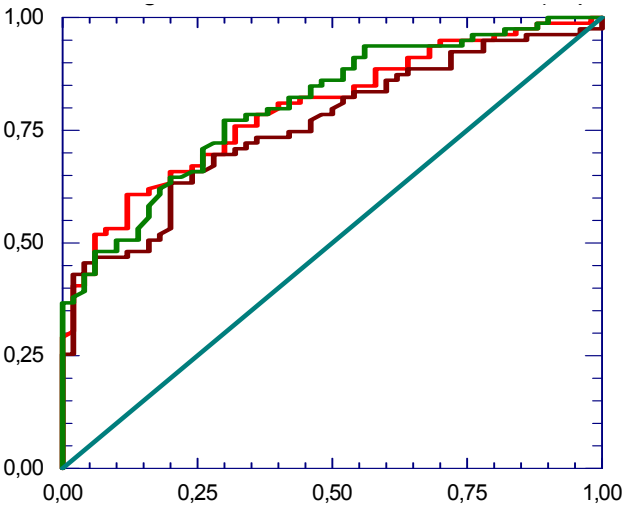

Figure 7. QUS versus DXA total hip – bone demineralisation.

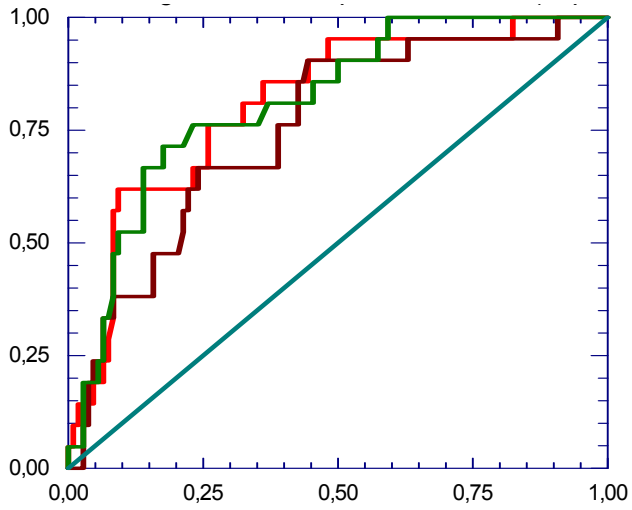

Figure 8. QUS versus DXA total hip – severe demineralization.

The best ROC curve identifies QUI as the best parameter in evaluating and screening of the haemodialised population.

During the analysis of the lumbar spine DXA measurements, we have observed a high prevalence of bone demineralization at this site. Despite some data in the literature that trabecular bone could be increased in secondary hyperparathyroidism, our data showed similar demineralization as compared with total hip, and smaller compared with the isolated nondominant femoral neck.[19]

Table 6 presents the diagnostic power and diagnostic cut-off points for all the three QUS parameters.

As seen before, QUI is the best parameter to be used, with lower values than the identified cut-off, having an excellent NPV, associated with an excellent PNN, helping to evidence osteopenia. That means that lower QUI identify osteopenic patients, and they don't need any further investigations, regarding the lumbar spine.

Severe demineralization is not directly identified (low PPV), but a QUI greater than 67.5 excludes the possibility of osteoporosis (NPV = 93.20).

Our findings are very similar to the literature, which identifies QUS as a very good method for screening different levels of bone demineralization, when considered at different sites.[7]

Currently, the UK National Osteoporosis Society proposes a different method to compare two totally different methods of evaluation bone mineral density, respectively bone demineralization.[20,21]

They have defined upper and lower values for osteodensitometric parameters, with 90% sensitivity (upper threshold) and 90% specificity (lower threshold) for identifying patients with central DXA T-score of - 2.5 or lower at the hip or spine. This leads to a low rate, under 10%, of false positive and falls negative diagnosis.[16] For our device, the validated upper and lower threshold, for QUI, are 83, respectively 59.[21]

We have used the same strategy, in order to describe the best QUI values in identifying osteopenic and osteoporotic patients.

TABLE VI. Diagnostic characteristic of QUS – compared with limbar spine DXA

	Osteopenia			Osteoporosis		
	BUA	**SOS**	**QUI**	**BUA**	**SOS**	**QUI**
Sensitivity	**72,82**	60,10	68,68	**81,08**	70,27	75
Specificity	**62,12**	53,96	63,10	**51,08**	65,21	73,39
PPV	82,71	76,44	82,23	40,0	44,82	32,55
NPV	47,91	35,23	82,07	87,03	84,5	93,02
Cut-off	**66,10**	**1529,9**	**80,90**	**64,00**	**1511,10**	**67,5**
AUC	**0,737**	**0,61**	**0,741**	**0,756**	**0,692**	**0,80**

Because in our own study, QUI was the best diagnostic tool among QUS parameters, we have used it for further investigations. The values selected (for each clinical situation and each DXA site) are presented in Table 7.

Table 7. Upper and lower QUI values

	Value for 90% sensitivity	Value for 90% specificity	Cut-off value
T < -1 femoral neck	93,90	65,50	74,40
T < -2,5 femoral neck	76,90	61,40	69,60
T < -1 total hip	93,90	67,20	76,10
T < -2,5 total hip	76,50	59,20	69,60
T < -1 lumbar spine	94,50	69,70	80,90
T < -2,5 lumbar spine	85,70	62,20	67,50

We can observe that the widest limits are related to lumbar spine evaluation, respectively the femoral neck compartment seems to be a more precise one.

We can also say that between these identified limits we can find almost all patients with different degrees of demineralization.[22]

Only 10% of cases are falsely identified with having osteoporosis/osteopenia, respective 10% of cases with the disease are misled with this diagnostic approach. (Fig. 9)

The 90%-90% strategy is superior to the one of cut-off values, because the number of cases that we have to investigate further decrease dramatically.

The QUI values between 93.9 and 67.2 help to identify bone demineralization with a sensitivity and specificity higher that 90%. Values between 76.9 and 61.4 represesnt the range for osteoporotic patients, regardless of the DXA sites where osteoporosis is diagnosed.

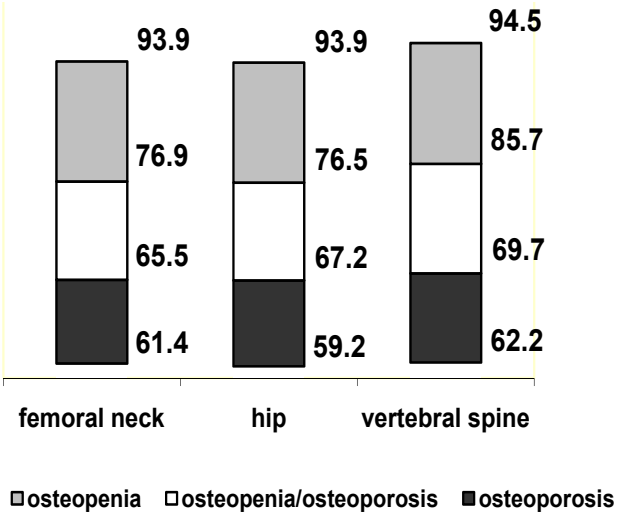

Figure 9. The QUI range of suspect values in diagnosing bone demineralization in different sites.

CONCLUSIONS

QUS is considered a low cost, rapid, highly reproducible and well accepted osteodensitometric option. As seen before, in cases with secondary osteoporosis, bone strength is the parameter to be discussed.[5] QUS parameters, BUA and SOS are associated with overall bone strength, respectively bone density, bone architecture, bone turnover and bone mineralization.[23-25]

Discordant results when comparing QUS and DXA results are occuring because usually the same T-score approach is used. The approach to identify the cut-off values, the best QUS parameter, and also the high risk interval, reduces the difference between the two.

QUS can be used at least for screening bone mineral density in haemodialised patients.[7,26,27] When we are using the 90%-90% method we could significantly reduce the number of necessary DXA scans for correct diagnosis.

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