

ACCURACY OF CLINICAL RISK INDICES AND QUANTITATIVE ULTRASOUND AS SCREENING TOOLS FOR DXA REFERRAL

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Abstract

Background. Dual-energy X-ray absorptiometry (DXA) is the most accurate method to identify subjects with low bone mineral density (BMD), but it is expensive and with limited availability in some communities. Therefore, identification of the subjects at risk for low BMD based on clinical decision rules could be a reasonable alternative to limit DXA referral.

Objectives. To assess the performance of five indices combining different clinical risk factors as a decision rules for DXA referral.

Methods. The study included postmenopausal women referred for DXA scanning by the GPs or hospital-based clinic based on the presence of one or more risk factors for osteoporosis. All patients were evaluated by DXA performed at lumbar spine and total hip (Prodigy Advance Lunar-GE) and QUS (Sahar Hologic). Five osteoporosis risk indices were calculated: OST, ORAI, OSIRIS, OPERA, SCORE.

Results. 140 postmenopausal women were evaluated prospectively. Mean age was 60 ± 9.9 years, mean body mass index (BMI) 27.4 ± 5.3 ; 56% had osteoporosis (T score at lumbar spine or total hip < -2.5). BUA and SOS, correctly identified the osteoporotic subject when compared with DXA T Score ≤ -2.5 at lumbar spine or total hip (AUROC = 0.761, 95% CI 0.684 – 0.838 for BUA and AUROC = 0.771, 95% CI 0.695 – 0.848 for SOS). From the five indices, SCORE and ORAI best identified women at high risk of osteoporosis with a sensitivity of 80.3% for SCORE and 65.6% for ORAI and specificity of 47.8% for SCORE and 58.9% for ORAI.

Conclusion. Both QUS parameters BUA and SOS were accurate to identify patients with osteoporosis. SCORE and ORAI were superior to other clinical risk indices (OST < OSIRIS and OPERA). The ability of the two QUS parameters BUA and SOS to identify the patients with osteoporosis was higher when combined with clinical risk indices but lower than for risk indices alone.

Keywords: DXA, BMD, risk indices, osteoporosis.

ACURATEȚEA INDICILOR DE RISC CLINIC ȘI ECOGRAFIEI CANTITATIVE CA METODE DE SCREENING PENTRU EXAMINAREA DXA

Rezumat

Absortimetria duală cu raze X (DXA) este metoda de elecție pentru depistarea și diagnosticul pacienților cu osteoporoză, dar este o metodă scumpă și cu o disponibilitate limitată în unele comunități. Din aceste motive este importantă identificarea pacienților la risc pentru osteoporoză, pe baza unor algoritmi clinici care să limiteze în acest fel necesarul examinărilor DXA.

Obiective. De a determina performanța a cinci algoritmi clinici care combină diferiți factori de risc pentru osteoporoză, ca metodă de screening care să permită reducerea necesarului de examinări DXA.

Pacienți și Metodă. Femei în postmenopauză adresate pentru examinare DXA, ca urmare a prezenței a unul sau mai mulți factori de risc clinici pentru osteoporoză. Toți pacienții au fost evaluați prin examinare DXA la nivelul coloanei lombare și femurului (Prodigy Advance Lunar-GE) și prin ultrasonometrie calcaneană (Sahara Hologic). Pentru fiecare pacient au fost calculate 5 scoruri de estimare a riscului pentru osteoporoză: Osteoporosis Self Assessment Tool (OST), Osteoporosis Risk Assessment Instrument (ORAI), Simple Calculated Osteoporosis Risk Estimation (SCORE), Osteoporosis Index of Risk (OSIRIS) și Osteoporosis Prescreening Risk Assessment (OPERA).

Rezultate. Au fost evaluate prospectiv 140 femei în postmenopauză. Vârsta medie a fost de $60 \pm 9,9$ ani, indexul de masă corporală (IMC) $27,4 \pm 5,3$; 56% pacienți cu osteoporoză pe baza scorului $T < -2.5$ determinat la nivelul coloanei lombare sau șoldului. Cei 2 parametri de ultrasonometrie calcaneană BUA (Broadband Ultrasound Attenuation) și SOS (Speed of Sound) au identificat corect pacienții cu osteoporoză, comparativ cu examinarea DXA (AUROC = 0,761, 95% CI 0,684 – 0,838 pentru BUA și AUROC = 0,771, 95% CI 0,695 – 0,848 pentru SOS). Dintre cei 5 algoritmi clinici utilizați, SCORE și ORAI au avut cea mai bună performanță în identificarea pacienților cu risc crescut de osteoporoză: sensibilitate 80,3% pentru SCORE și 65,6% pentru ORAI ; specificitate 47,8% pentru SCORE și 58,9% pentru ORAI.

Concluzii. Cei 2 parametri de ultrasonografie calcaneană studiați, BUA și SOS, au identificat corect pacienții cu osteoporoză, comparativ cu examinarea standard DXA. SCORE și ORAI au avut o performanță superioară celorlalți algoritmi clinici studiați (OST, OSIRIS și OPERA). Combinarea chestionarelor clinice cu ultrasonometria calcaneană a rezultat într-o mai bună performanță de diagnostic.

Cuvinte cheie: DXA, BMD, scor de risc, osteoporoză .

Osteoporosis, “a systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” [1], is becoming a major health problem worldwide. It affects more than 75 million of people in United States, Europe and Japan and it causes more than 2.3 million fractures annually [2].

It is widely accepted that dual X-ray absorptiometry (DXA) is the current “gold standard” in the diagnosis of osteoporosis and fracture prediction. However DXA it is an expensive and ionizing radiation (albeit at safe levels) method and is, therefore best suited for the accurate diagnosis of osteoporosis rather than for the screening of a large population [3].

Due to high costs and a lack of availability in certain geographical areas, only a small percentage – 20 – 30% of women with osteoporosis are diagnosed using DXA [4].

According to National Osteoporosis Foundation (NOF) recommendation, all postmenopausal women and older men should be evaluated clinically for osteoporosis

risk in order to determine the need for BMD testing [5].

A large number of potential patients “at risk” for low bone mineral density (BMD) can be detected by questionnaire-based methods or the use of quantitative ultrasound scanners.

Comprehensive epidemiological studies have identified clinical risk factors for osteoporosis and these factors have been used to develop risk assessment indices: the Osteoporosis Self Assessment Tool (OST) [6], the Osteoporosis Risk Assessment Instrument (ORAI) [7], the Simple Calculated Osteoporosis Risk Estimation (SCORE) [8], the Osteoporosis Index of Risk (OSIRIS) [9] and the Osteoporosis Prescreening risk Assessment (OPERA) [10]. The purpose of these indices is not to diagnose osteoporosis but to identify those people who are most likely to have a low BMD and need to be referred for DXA measurement.

An alternative approach for mass screening is the quantitative ultrasound (QUS) method. The absence of exposure to ionizing radiation, the portability, the low cost of the machines, and the short time of examination are among the most appealing characteristics of quantitative ultrasonography. QUS can predict future fracture risks nearly as well as DXA, but the use of this technique for screening and identifying people with osteoporosis is still

controversial. Osteoporosis cannot be defined using QUS and WHO criteria are not applicable for this technique. The role of ultrasound might only be to identify patients at risk for osteoporosis as first line pre-screening tools but there are no consensus criteria yet [11].

In this study we intend to examine comparatively and to assess five questionnaires-based systems (OST, ORAI, OSIRIS, OPERA, SCORE) and the QUS parameters – broadband ultrasound attenuation (BUA) and the speed of sound (SOS). The aim of this study is to assess the abilities of these systems as screening tools for DXA and to determine the cut-off levels of above mentioned QUS parameters for identifying low BMD patients.

Methods and statistical analysis

The study population consisted of 140 postmenopausal women referred for DXA scanning by their GPs or from a hospital-based clinic because the presence of one or more risk factors for osteoporosis. There were no general exclusion criteria from the study.

All subjects were assessed by DXA at lumbar spine and total hip (Prodigy Advance Lunar-GE) and then classified as normal, osteopenic or osteoporotic according to WHO criteria [1]. All patients were consecutively evaluated by QUS of the left calcaneus using the Sahara Hologic equipment. The ankle was maintained in 90°

flexion to ensure that all the measurements were processed in the correct area and the transducers were coupled to the skin through a coupling gel. Appropriate phantom test was performed before each QUS measurement. The QUS parameters were broadband ultrasound attenuation (BUA) (dB/MHz) and the speed of sound (SOS) (m/s) measured in a fixed region of the calcaneus. Each subject completed a questionnaire designed to give information on patient's life-style and historical risk factors for osteoporosis (smoking habits, alcohol consumption, antecedents of fracture after 45 years, maternal history of fracture, prior estrogen or glucocorticoids use, rheumatoid arthritis and secondary causes of osteoporosis). Then five osteoporosis risk indices were calculated: OST, ORAI, OSIRIS, OPERA, SCORE. The number of points recommended by the developers of the respective decision rules was used to select women at risk for low BMD, presumably addressed for DXA referral (Table 1).

The ability of risk indices and QUS parameters to distinguish between osteoporotic and non-osteoporotic patients was evaluated using receiver operating characteristic (ROC) curve analysis. ROC curves were plotted for each model to determine the area under the ROC curve (AUROC) and the sensitivity (probability that a test result will be positive when the disease is present) and specificity (probability that a test result will be negative when the

Table 1. Calculation of evaluated indices.

Factor	Score
OST – Selection cut-point: Score < 2	
Age	
Body weight	
ORAI – Selection cut-point: Score > 9	
Age > 75	+ 15
Age 65-74	+ 9
Age 55-64	+ 5
Body weight < 60 kg	+ 9
Body weight 60-70 kg	+ 3
Estrogen therapy	+ 2 if not currently estrogen user
OSIRIS– Selection cut-point: Score > 1	
Body weight (kg)	+ 0.2 x body weight
Age (years)	- 0.2 x age
History of low impact fractures	- 2
Estrogen therapy	+ 2
OPERA– Selection cut-point: Score > 2	
Age ≥ 65 years	1
Weight < 57 kg	1
History of minimal trauma	1
Early menopause (before age of 45 years)	1
Steroid use > 6 month (> 5 mg/day)	1
SCORE – Selection cut-point: Score ≥ 6	
Race other than black	+ 5
Rheumatoid arthritis	+ 4
Non-traumatic fracture after age 45 years	+ 4 per fracture up to maximum 12
Age	+ 3 for each decade
Estrogen therapy	+ 1 if never
Weight	- 1 for each 4.5 kg

disease is not present). From the ROC curves we computed the optimum cut-off of QUS parameters, corresponding to the maximum sum of sensitivity and specificity to distinguish between osteoporotic and non-osteoporotic patients. For each model parametric correlation coefficients were calculated to indicate the relative importance of each risk indices in the model. Reported P values are two-sided. All statistical analyses were performed using the SPSS 12 software.

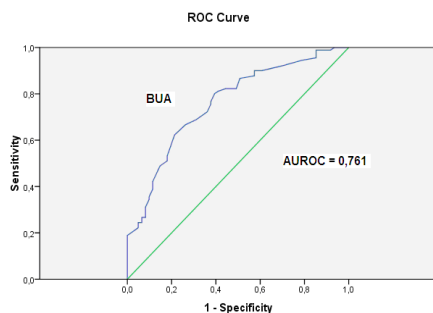
Results

A total of 140 postmenopausal women were evaluated prospectively. The demographic and clinical characteristics of the patients are summarized in table 2.

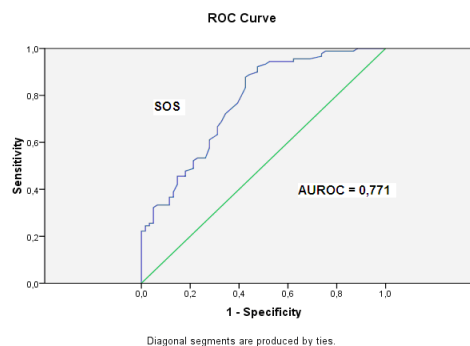
Table 2. Summary of demographics, risk factors for osteoporosis and bone mineral density (BMD) status in the study cohort.

Demographics	
Mean age (years)	60 ± 9.9 years
Mean age of menopause onset (years)	46.1 ± 6.7 years
Mean body mass index (BMI) (kg/m ²)	27.4 ± 5.3
Risk factors for Osteoporosis	
Smoking (%)	22.52%
History of low impact fracture (%)	29.8%
Prior glucocorticoids use (%)	12.58%
Rheumatoid arthritis (%)	4.64%
BMD status	
Mean BMD L2-L4	0.965 ± 0.184
Mean BMD total hip	0.880 ± 0.137
T Score ≤ -2.5 (total hip or L2-L4) (%)	56.29%

Both QUS parameters, BUA and SOS, correctly identified the osteoporotic subject when compared with DXA T Score ≤ -2.5 at lumbar spine or total hip (AUROC = 0.761, 95% CI 0.684 – 0.838 for BUA and AUROC = 0.771, 95% CI 0.695 – 0.848 for SOS) (Figure 1).



a)



b)

Figure 1. Receiver operating characteristic curves analysis for QUS parameters, BUA (a) and SOS (b) related to DXA T score ≤ -2.5 either at lumbar spine or total hip (p<0.05).

Corresponding to DXA T Score of -2.5, the calculated cut-off values capable to discriminate between normal and osteoporotic patients were 49 dB/MHz for BUA (sensitivity = 81%, specificity = 59%), respectively 1495 m/s for SOS (sensitivity = 93%, specificity = 50%).

According to the WHO criteria - DXA T Score ≤ -2.5, applied either at the lumbar spine or total hip, 56.29% (n = 78) of subjects had osteoporosis, while only 33.77 were classified as such using BUA at a cut-off value of 49 dB/MHz, respectively 22.52% with SOS at a cut-off value of 1495 m/s (Figure 2).

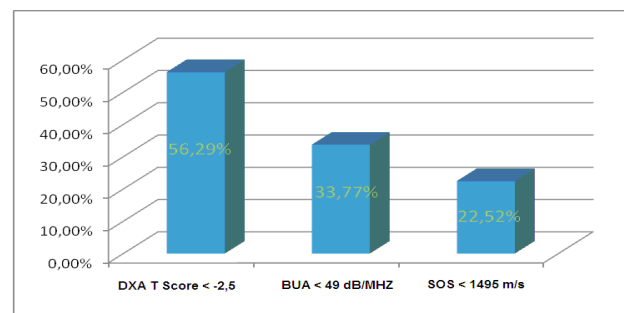


Figure 2. The percentage of patients with osteoporosis using DXA T Score < -2.5, BUA < 49 dB/MHz and SOS < 1495 m/s.

Of the five risk indices that we considered in this study (OST, ORAI, OSIRIS, OPERA, SCORE), at the cut-point recommended by their developers, the AUROC values and 95% CI for each approach to select women at high risk for low BMD, corresponding to a DXA T Score ≤ -2.5, are presented in table 3.

Table 3. AUROC values of the five risk indices to identify postmenopausal women at high risk of osteoporosis in relation to DXA T Score ≤ -2.5.

	AUROC Curve	95% CI
OST	0.309	0.225 – 0.393
ORAI	0.668	0.581 – 0.754
OSIRIS	0.325	0.240 – 0.410
OPERA	0.530	0.435 – 0.626
SCORE	0.661	0.575 – 0.747

The AUROC curves for identifying women with osteoporosis are plotted in the figure 3.

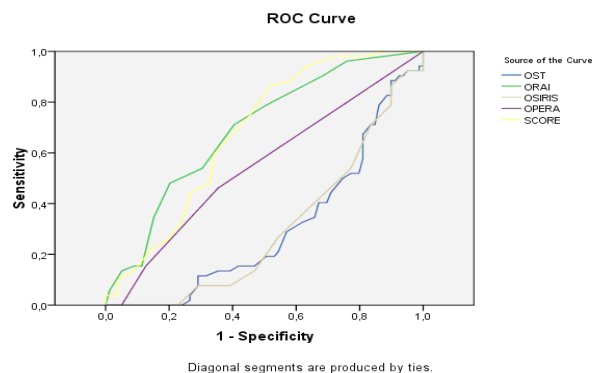


Figure 3. ROC curves for the five risk indices at the cut-point value recommended by their developers to identify subject with osteoporosis (DXA T Score ≤ -2.5).

From the five indices, SCORE and ORAI best identified women at high risk of osteoporosis with a sensitivity of 80.3% for SCORE and 65.6% for ORAI and specificity of 47.8% for SCORE and 58.9% for ORAI.

The other two indices, OST and OSIRIS proved to have a low sensitivity (24.6% respectively 29.5%) in identifying women with low BMD when compared with DXA T Score ≤ -2.5 , but a good specificity (52.2% respectively 46.7%). The Pearson correlation coefficients for those two indices were 0.383 ($p < 0.01$) respectively 0.321 ($p < 0.05$). In our analysis, the OPERA risk index, having an AUROC of 0.530, 95% CI 0.435 – 0.626, could not distinguish the osteoporotic from non-osteoporotic subjects.

We then analyzed the ability of BUA and SOS in combination with the risk indices to identify those subjects most likely to have a low BMD as determined by DXA T Score ≤ -2.5 (Figure 4). The ability of the two QUS parameters BUA and SOS to identify the patients with osteoporosis was higher when combined with clinical risk indices but lower than for risk indices alone.

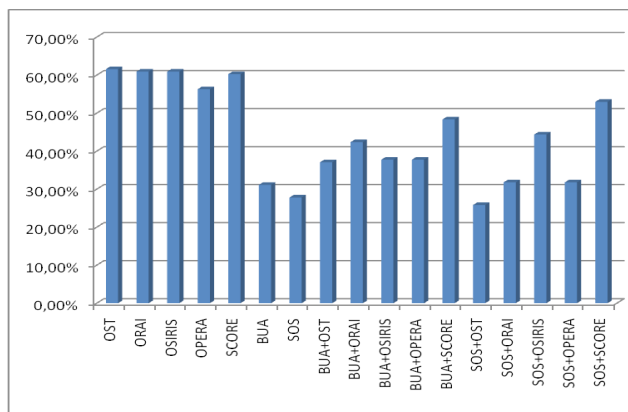


Figure 4. The ability of risk indices and QUS parameters BUA and SOS alone and in combination to identify subjects with low BMD.

Discussion

This study comparatively examined the accuracy of five questionnaires screening system (OST, ORAI, SCORE, OPERA and OSIRIS), alone and combined with QUS parameters as pre-screening tool for DXA. The aim was not necessarily to replace DXA examination, but to explore various strategies which could restricted the use of DXA for those patients defined as having “high risk” for osteoporosis by alternative methods.

Several studies evaluated the usefulness of QUS parameters as a pre-screening tool for osteoporosis in an attempt to reduce the use of DXA, especially in those countries where the availability of DXA is limited. At a cutoff of 49 dB/MHz for BUA (sensitivity = 81%, specificity = 59%), respectively 1495 m/s for SOS, both QUS parameters had 81% and respectively 93% sensitivity to identify women with osteoporosis. Similar results were obtained by Dubois et al [14] in 217 women, using a Sahara Hologic device [15], with a cut-off value of 58 dB/MHz for BUA and 1533 m/s for SOS. Similarly, Falgarone et al [16] found a cut-off value of 71.7 dB/MHz and 50.8 dB/MHz for BUA and 1551.5 m/s, respectively 1544.8 m/s for SOS (Sahara Hologic) in 106 postmenopausal women.

Additionally, our study has demonstrated the validity of the SCORE and ORAI indices as a means of assisting physicians in making decisions regarding BMD testing. These results are concordant with those previously published [12], AUROC = 0.720 for SCORE and respectively 0.664 for ORAI, for a DXA T score of -2.5 . The validity of ORAI as prescreening tool for DXA was also confirmed in a large study including 644 postmenopausal women, with a sensitivity 92.5 (85.7–96.7) and specificity 38.7 (34.5–42.9) [13].

In our study both SCORE and ORAI were superior to OST and OSIRIS to identify patients at risk for osteoporosis. One recent systematic review [15] comparing OST with alternative tests for selecting postmenopausal women for DXA, demonstrated that for the lumbar spine, ORAI was slightly more accurate than OST (summary estimate of odds ratio: 1.02–1.17). Also SCORE had a marginally higher specificity than OST (58% vs. 52%) with respect to femoral neck T score ≤ -2.5 , whereas sensitivities were similar (89% vs. 87%). The difference in accuracy was even less for femoral neck T score ≤ -2.0 .

Furthermore, our study demonstrated that the accuracy of QUS parameters to identify women at risk for osteoporosis is considerably increased when combined with clinical risk factors. These results might be explained by the low sensitivity of risk indices in identifying osteoporosis as presented above, combined with the high sensitivity of QUS parameters, BUA and SOS, which resulted in a moderate sensitivity of the two methods combined.

In conclusion, an algorithm based on QUS parameters, BUA and SOS, combined with clinical questionnaires might be a pre-screening alternative to DXA, but larger validation studies are needed.

References

1. Kanis J.A., Burlet N., Cooper C., Delmas P.D., Reginster J.Y., Borgstrom F., Rizzoli R., European guidance for the diagnosis and management of osteoporosis in postmenopausal women, *Osteoporos Int.*, 2008, 19, 399-428
2. WHO (2003) Prevention and management of osteoporosis. Report of a WHO study Group (ref type: report). World Health Organisation, Geneve, Technical Report series 919:1-165
3. Cook RB, Collins D, Tucker J, Zioupos P, Comparison of questionnaire and quantitative ultrasound techniques as screening tools for DXA, *Osteoporos Int*, 2005, 16: 1565-1575
4. IOF 2000. How fragile is her future? IOF Report
5. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of Osteoporosis. 2008
6. Rud B, Hilden J, Hyldstrup L, Hrobjartsson A, The Osteoporosis Self-Assessment Tool versus alternative tests for selecting postmenopausal women for bone mineral density assessment: a comparative systematic review of accuracy, *Osteoporosis Int*, 2009, 20: 599-607
7. Cadarette SM, Jaglal SB, Kreiger N, McIsaac WJ, Darlington GA, Tu JV. Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry. *CMAJ* 2000; 162:1289-1294
8. Ben Sendrine W, Devogelaer JP, Kaufman JM, Goemaere S, Depresseux G, Zegels B, Deroisy R, Reginster JY, Evaluation of the Simple Osteoporosis Risk Estimation (SCORE) in a sample of white women from Belgium, *Bone* 2001, 29: 374-380
9. Ben Sedrine W, Chevallier T, Zegels B, et al. Development and assessment of the Osteoporosis Index of Risk (OSIRIS) to facilitate selection of women for bone densitometry. *Gynecol Endocr* 2002; 16:245-250
10. Salaffi F, Siveri F, Stancati A, Grassi W, Development and validation of the osteoporosis prescreening risk assessment (OPERA) tool to facilitate identification of women likely to have low bone density, *Clin Rheumatol*, 2005, 24:203-211
11. Krieg MA, Barkmann R, Gonnelli S, Stewart A, Bauer D, Del Rio Barquero L, Kaufman JJ, Lorenc R, Miller PD, Olszynski WP, Poiana C, Schott AM, Lewiecki EM, Hans D, Quantitative Ultrasound in the Management of Osteoporosis: The 2007 ISCD Official Positions, *J Clin Densitometry*, 2008, 11: 163-187
12. Cook RB, Collins D, Tucker J, Zioupos P, Comparison of questionnaire and quantitative ultrasound techniques as screening tools for DXA, *Osteoporos Int*, 2005, 16: 1565-1575
13. Cadarette SM, McIsaac WJ, Hawker GA, Jaakkimainen L, Culbert A, Zarifa G, et al, The validity of decision rules for selecting women with primary osteoporosis for bone mineral density testing, *Osteoporos Int*, 2004, 15: 361-366
14. Dubois E.F., Van den Bergh J.P., Smals A.G., Van de Meerendonk C.W., Zwinderman A.H., Schweitzer D.H., Comparison of quantitative ultrasound parameters with dual energy x-ray absorptiometry in pre- and postmenopausal women, *Neth J Med.*, 2001, 58, 62-70
15. Rud B, Hilden J, Hyldstrup L, Hrobjartsson A, The Osteoporosis Self-Assessment Tool versus alternative tests for selecting postmenopausal women for bone mineral density assessment: a comparative systematic review of accuracy, *Osteoporos Int*, 2009, 20: 599-607