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COMPARISON BETWEEN ULTRASOUND FRAGILITY SCORE AND FRAX® FOR THE ASSESSMENT OF OSTEOPOROTIC FRACTURE RISK

A. Greco[1], *P. Pisani*[2], *G. Soloperto*[2], *M.D. Renna*[2], *F. Conversano*[2], *M. Muratore*[3], *and S. Casciaro*[2]

[1]Echolight S.r.l., Lecce, Italy; [2]National Research Council, Institute of Clinical Physiology, Lecce, Italy;
[3]O.U. of Rheumatology, Galateo Hospital, San Cesario di Lecce, ASL-LE, Lecce, Italy.

Mailing address: c/o Campus Universitario Ecotekne (Ed. A7), via per Monteroni, 73100 Lecce, Italy

Abstract: The assessment of osteoporotic fracture risk requires the measurement of bone mineral density (BMD) on reference sites (hip and spine) and the evaluation of clinical risk factors (CRFs) for fracture. The Fracture Risk Assessment algorithm (FRAX®), internationally recognized by official guidelines for osteoporotic patient management, represents a tool for estimating 10-year probability of hip and major fragility fractures by integrating CRFs and femoral neck BMD or T-score, when available. In this work we presented an innovative ultrasound (US)-based method for estimating fracture risk by means of a safe and radiation-free approach. From abdominal ultrasound scans performed on 64 female patients, we defined and quantified a new US diagnostic parameter named Fragility Score (F.S.), which estimates bone fragility. Obtained results showed an high Pearson correlation coefficient between fracture probabilities calculated by FRAX® and F.S. (*r* up to 0.75 in the case of FRAX® estimates including femoral neck BMD and *r*=0.71 in the case of FRAX® estimates based on femoral neck T-score). The present study demonstrated the feasibility of a novel US approach for fracture risk prediction and prevention, directly applicable on spine and independent from BMD measurements and CRF assessments. The proposed methodology could represent a valid alternative to both FRAX® and BMD for early assessment of fracture risk.

Keywords: fracture risk assessment; FRAX®; ultrasound; osteoporosis.

1. INTRODUCTION

The main consequence of osteoporosis is the increased bone fragility, which leads to enhanced fracture risk and huge social and economic costs. The most common method for osteoporosis diagnosis and fracture risk assessment is represented by bone mineral density (BMD) measurement through dual-energy X-ray absorptiometry (DXA). Furthermore, clinical risk factors (CRFs) should also be considered in the evaluation of fracture probability, since it has been demonstrated that the integration of BMD and CRFs predicts fractures better than BMD or CRFs alone [1-3]. An algorithm that integrates such informations has been developed by the World Health Organization (WHO) Collaborating Centre for Metabolic Bone Diseases at Sheffield (UK) [4,5]: according to the International Osteoporosis Foundation (IOF) and the WHO [6,7], the Fracture Risk Assessment tool (FRAX) reliably computes the 10-year probability of fracture at the hip joint or at major fragility fracture sites (spine, hip, forearm and humerus).

Nowadays, DXA is considered the "gold standard" for osteoporosis diagnosis, but unfortunately, as other X-ray based techniques, DXA has specific limitations (i.e., use of ionizing radiation, large size of the equipment, high costs, limited availability) that hinder its application for population screenings and primary care diagnosis. In order to overcome such issues, a new ultrasound (US) methodology performing bone densitometry of spine and proximal femur has been recently developed by our research group [8]. In the present work we introduce a new US-based parameter named Fragility Score(F.S.) that provides an estimate of skeletal fragility and, therefore, of fracture risk. In particular, we investigated the effectiveness of the new methodology in fracture risk assessment by correlating FRAX fracture probability and F.S. values in a group of 64 postmenopausal women.

2. MATERIALS AND METHODS

A. Patient recruitment

The study was conducted at the Operative Unit of Rheumatology of "A. Galateo" Hospital (San Cesario di Lecce, Lecce, Italy), where a total of 64 postmenopausal women of Caucasian ethnicity were included in this study according to the following criteria: 50-80 years, body mass index (BMI) <30 kg/m^2, no deambulation impairments, medical prescription for a vertebral DXA.
All the recruited patients underwent two different diagnostic examinations: 1) a conventional DXA of both lumbar spine and proximal femur; 2) an abdominal US scan of lumbar spine. Each participant gave her informed consent.

B. DXA scans

DXA scans were performed by an Hologic Discovery W scanner (Hologic, Waltham, MA, USA). DXA-calculated BMD, expressed as grams per squared centimeters (g/cm^2),

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was measured over the lumbar vertebrae from L1 to L4, and on the proximal femur. Furthermore, the T-score values, which describe the difference between the BMD of the patient being examined and the mean BMD of a standard young adult population [9], were also recorded at both sites.

C. US acquisitions and data analysis

Ultrasound scans of lumbar spine were performed by employing a 3.5-MHz convex echographic probe connected to an innovative US device developed in Lecce (Italy) within the ECHOLIGHT Project through a collaboration between CNR-IFC and Echolight srl.

Digitized radiofrequency (RF) signal (40 MS/s, 16 bit/s) was transferred via USB to a PC and stored in an hard-disk for subsequent analysis.

Scan depth and transducer focus were adjusted for every US acquisition in order to have vertebral interfaces located in the US focal region, leaving constant the other US scanner operating parameters: signal power=75%, mechanical index (MI)=0.4, gain=0 dB, linear time gain compensation (TGC). Each patient underwent a sagittal scan of lumbar spine (Fig. 1.A), moving the probe back and forth from L1 to L4. Each patient acquisition lasted for about one minute and 100 frames of RF data were acquired.

US data were analyzed by a novel algorithm that processed both the echographic images and the corresponding RF signals, providing as final output a new US diagnostic parameter named Fragility Score (F.S.), which represents an estimation of skeletal fragility and, consequently, of fracture risk. Specifically, F.S. evaluates the degree of bone fragility through the comparison with spectral models coming from previous acquisitions on "frail" and "non-frail" reference patients. F.S. is expressed as dimensionless number, ranging from 0 to 100.

D. Fracture Risk Assessment tool (FRAX®)

FRAX tool (available at www.shef.ac.uk/FRAX) is a computer-based fracture risk algorithm developed in order to estimate the 10-year probability of hip and other major osteoporotic fractures [2]. The fracture risk evaluation is based on the presence of CRFs associated with fracture. Therefore, patients are subjected to the FRAX questionnaire, which includes questions on validated CRFs: age, sex, weight, height, prior fragility fracture, parental history of hip fracture, long-term use (e.g. for 3 months or more) of oral glucocorticoids, rheumatoid arthritis, current cigarette smoking and alcohol consumption. Fracture probability is then computed by an algorithm that integrates these CRFs with DXA-measured femoral neck BMD/T-score, when available. Three methods have been implemented to derive the FRAX index from the WHO tool: A) leaving blank the BMD field; B) providing as input the value of femoral neck BMD; C) typing the T-score value as read on the DXA report.

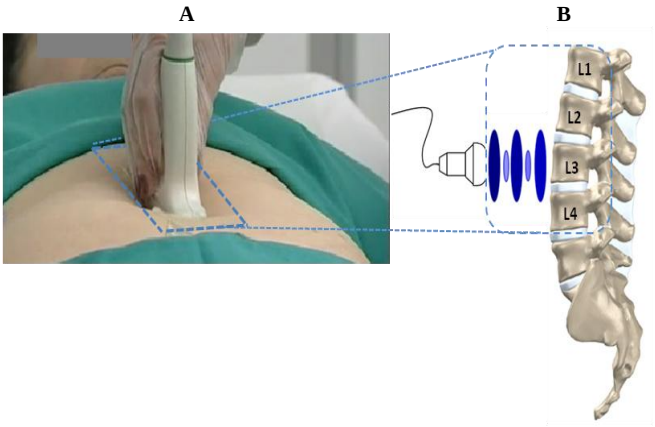

Figure 1. A) US scan of spine (from L1 to L4 lumbar vertebrae). **B)** Scheme of the ultrasound technique based on the reflection of US waves.

E. Statistical Analysis

Pearson coefficient (r) was used to assess the correlation between the 4 available parameters (lumbar BMD, femoral neck BMD, femoral neck T-score and F.S.) and FRAX calculated indexes.

Unpaired two-sided Student t-test was used to calculate statistical significance of obtained data. All statistical analysis was performed in EXCEL (Microsoft Corporation, Redmond, WA, USA).

3. RESULTS

The obtained correlation values of FRAX indexes with lumbar BMD, femoral neck BMD, femoral neck T-score and F.S (see par. 2.E) for each of the three described ways of calculating FRAX fracture probabilities are reported in Tables I-III.

Table I shows the obtained results for the case "A" (i.e., no DXA parameters included in FRAX calculations). All the considered parameters have a very low correlation with both FRAX indexes (r <0.37, $p<0.001$).

When femoral neck BMD was included in the FRAX calculation (case "B", Table II), the highest correlation was found, as expected, between femoral neck BMD and FRAX output (r = -0.84; $p<0.001$) regarding both major and hip fractures probability values. In this case, the correlation between FRAX indexes and F.S. values was also high. In particular, we found r = 0.69 and r = 0.75 ($p<0.001$) for the correlation with the probability of a main osteoporotic or only hip fracture, respectively.

Finally, by calculating FRAX indexes using the femoral neck T-score value (case "C", Table III), the correlation between this specific DXA parameter and FRAX indexes was high (r = 0.85 and r = 0.74 for FRAX® estimates based on femoral neck BMD and on femoral neck T-score, respectively; $p<0.001$) as well as the correlation between FRAX indexes and F.S. values (r = 0.71; $p<0.001$) referring to both major or hip fracture prediction.

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Table I: Pearson correlation coefficient (*r*) and related significance (*p*) between FRAX indexes (evaluated without including DXA parameters in the calculation) and US-based F.S., lumbar BMD, femoral neck BMD and T-score.

FRAX INDEXES (NO DXA Parameters)				
	Major Fracture Risk		Hip Fracture Risk	
	Pearson Coeff.	p (sign.)	Pearson Coeff.	p (sign.)
F.S.	0.37	<0.001	0.33	<0.001
BMD_L1-L4	-0.09	<0.001	-0.03	<0.001
BMD_NECK	-0.26	<0.001	-0.18	<0.001
T-Score NECK	-0.26	<0.001	-0.18	<0.001

Table II: Pearson correlation coefficient (*r*)-and related significance (*p*)-between FRAX indexes (evaluated by including also femoral neck BMD in the calculation) and US-based F.S., lumbar BMD, femoral neck BMD and femoral neck T-score.

FRAX INDEXES (with FEMORAL NECK BMD)				
	Major Fracture Risk		Hip Fracture Risk	
	Pearson Coeff.	p (sign.)	Pearson Coeff.	p (sign.)
F.S.	0.69	<0.001	0.75	<0.001
BMD_L1-L4	-0.60	<0.001	-0.69	<0.001
BMD_NECK	-0.84	<0.001	-0.84	<0.001
T-Score NECK	-0.72	<0.001	-0.75	<0.001

Table III: Pearson correlation coefficient (*r*)-and related statistical significance (*p*)-between FRAX indexes (evaluated by including also femoral neck T-score in the calculation) and US-based F.S., lumbar BMD, femoral neck BMD and femoral neck T-score.

FRAX INDEXES (with FEMORAL NECK T-SCORE)				
	Major Fracture Risk		Hip Fracture Risk	
	Pearson Coeff.	p (sign.)	Pearson Coeff.	p (sign.)
F.S.	0.71	<0.001	0.71	<0.001
BMD_L1-L4	-0.63	<0.001	-0.70	<0.001
BMD_NECK	-0.85	<0.001	-0.74	<0.001
T-Score NECK	**-0.74**	<0.001	**-0.74**	<0.001

4. DISCUSSION

Osteoporosis is a skeletal disorder characterized by compromised bone strength, which predisposes individuals to an increased risk of fracture. Evaluation of fracture probability is an important component of the management of osteoporotic patients. Currently, BMD measurements by DXA is the only method to reliably predict main osteoporotic fractures. It is well established that BMD is inversely related to fracture risk [10].

In the present work, we confirmed the existence of an appreciable and statistically significant negative correlation between FRAX indexes and DXA-measured BMD or T-score on the femoral neck: in fact all the obtained values of *r* were within the range from -0.60 to -0.85 ($p<0.001$). Moreover, it is known that fracture risk at any site approximately increases by approximately a factor of 1.5-2 for each SD decrease in BMD at the hip or spine [10,11].

Starting from this assessed correlation, we demonstrated that FRAX-derived fracture probabilities are highly correlated, with the same trend, also with both DXA parameters of femoral neck and with the new US parameter F.S.. Therefore, F.S. could be able to estimate the general risk of osteoporotic fractures by a simple abdominal US scan of lumbar spine.

Notably, when including T-score in the FRAX calculation, the correlation between FRAX indexes and T-score or F.S. values was similar ($r = 0.74$ vs $r = 0.71$ respectively).

In addition, it need to be considered that, although all official guidelines for osteoporosis patient management recognize FRAX as a reliable tool for estimating fracture probability, it has a number of limitations. In fact, FRAX only allows the inclusion of femoral neck BMD but not BMD values measured at other sites. Moreover, FRAX does not take into account the number or the dose-response effect for some of previous fractures, and it may also underestimate the actual risk because it does not distinguish between traumatic and non-traumatic vertebral fractures [10].

The fact that the presented US parameter F.S. correlated with FRAX as well as DXA independently from risk factors, opens new perspectives for the early identification of frail patients. Furthermore, this method has important features, such as safety, absence of ionizing radiation, rapidity, easy to use and affordability of the cost, which could enable its use as a screening tool for fracture prediction. Specifically, the non ionizing radiation used allows extended early assessment of osteoporosis and fracture risk also to those portion of the population to whom standard methods are not currently prescribed (women below 65 years, pre-menopausal; men without explicit CRF). On the contrary, by using this innovative US-based method, fracture risk could be estimated on the entire population, including women men, children, independently from age, BMD and risk factors and allowing a safe and early diagnosis.

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5. CONCLUSION

A new US-based method that evaluates a bone fragility diagnostic parameter (named F.S.) from a safe lumbar scan has been developed. Accuracy of F.S. in fracture risk prediction was comparable to those of DXA-BMD and FRAX®, without requiring X-ray investigations nor CRF records, for which clinicians have to rely on patient answers.

In summary, these preliminary results open a valid perspective for possible population mass screenings and early assessment of fracture risk for better osteoporosis management.

6. ACKNOWLEDGMENT

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