ISBN 978-92-990073-5-8

3rd Imeko TC13 Symposium on Measurements in Biology and Medicine
"New Frontiers in Biomedical Measurements"
April 17-18, 2014, Lecce, Italy

AN INNOVATIVE ULTRASOUND-BASED METHOD FOR THE IDENTIFICATION OF PATIENTS AT HIGH FRACTURE RISK

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Abstract: The clinical significance of osteoporosis lies in the relevant occurrence of fractures. Osteoporosis affects about 200 million people in the world and is responsible for 8.9 million fractures each year worldwide. Hip fractures are a major public health burden, from both social and economic point of view, since they represent one of the most important causes of morbidity, disability, decreased quality of life and mortality for the elderly population. It has been demonstrated that bone mineral density (BMD) measurements on lumbar spine or proximal femur, standardly evaluated by dual-energy X-ray absorptiometry (DXA) examinations, are the most reliable available tool to predict the general risk of osteoporotic fractures. However, DXA, bearing X-ray related issues, is inadequate for population screening purposes and early diagnosis. In the present work, we present a new ultrasound (US)-based method and evaluate its performance for the prediction of osteoporotic fractures. We enrolled 40 women with recent non-vertebral osteoporotic fractures (frail subjects) and 44 controls without fracture history (non-frail subjects): this sample was used to compare the discriminatory power of the novel US methodology applied on spine with lumbar DXA by building the corresponding Receiver Operating Characteristic (ROC) curves. Obtained results showed that the new proposed US parameter (named Fragility Score, F.S.) is suitable for population screening purposes, since its Area Under the Curve (AUC) was the same of DXA-measured BMD (0.77) but it was coupled with a better sensitivity (83% *vs* 68%) in identifying patients at high risk of osteoporotic fracture.

Keywords: spine; osteoporotic fractures; ultrasound; dual-energy X-ray absorptiometry; fragility score.

1. INTRODUCTION

Osteoporosis is associated with a substantial health care burden through the increased rates of morbidity (especially in terms of pain and disability), mortality (hip and vertebral fractures are associated with high mortality in the 2 years after the event [1]) and economic costs associated with fractures. The frequency of osteoporotic fractures is currently rising in many countries. In Western countries, one in two women and one in five men over the age of 50 years will experience an osteoporotic fracture during their remaining lifetime [2,3]. In 1990, there were 1.7 million hip fractures worldwide and this value is expected to exceed 21 million by 2050 [4]. In this context, attention should be focused on the identification of patients at high risk of fracture rather than the identification of men and women with osteoporosis [5]. Dual-energy X-ray absorptiometry (DXA) is currently the first-choice clinical tool for measuring bone mineral density (BMD) and for making clinical decisions concerning bone fragility [6]. Unfortunately, as other X-ray based techniques, DXA has specific limitations (i.e., use of ionizing radiation, bulky equipments, high costs, limited availability) that hinder its application for population screenings and primary care diagnosis [7]. These limits resulted in the development of an increasing number of radiation-free screening tools for osteoporosis diagnosis and fracture prevention.

Aims of this work is to evaluate the performance of a new US parameter, named "Fragility Score" (F.S.), in the estimation of the general risk of osteoporotic fractures from an abdominal spinal scan.

2. MATERIALS AND METHODS

A. Patient enrolment

The study was conducted at the Operative Unit of Rheumatology of "Galateo" Hospital (San Cesario di Lecce, Lecce, Italy), where 84 Caucasian postmenopausal female patients [50-80 years; BMI (body mass index) ≤ 30 kg/m^2] were enrolled: 40 with a recent non-vertebral osteoporotic fracture and 44 controls without fracture history. The study included only female patients because women account for 71% of all osteoporotic fractures and 75% of all the related costs. In particular, among women, Caucasian account for the majority of osteoporotic fractures (89%) [8].

All the recruited patients underwent two examinations: a spinal DXA and an abdominal US scan of lumbar spine. Each participant gave her informed consent.

A

B

C

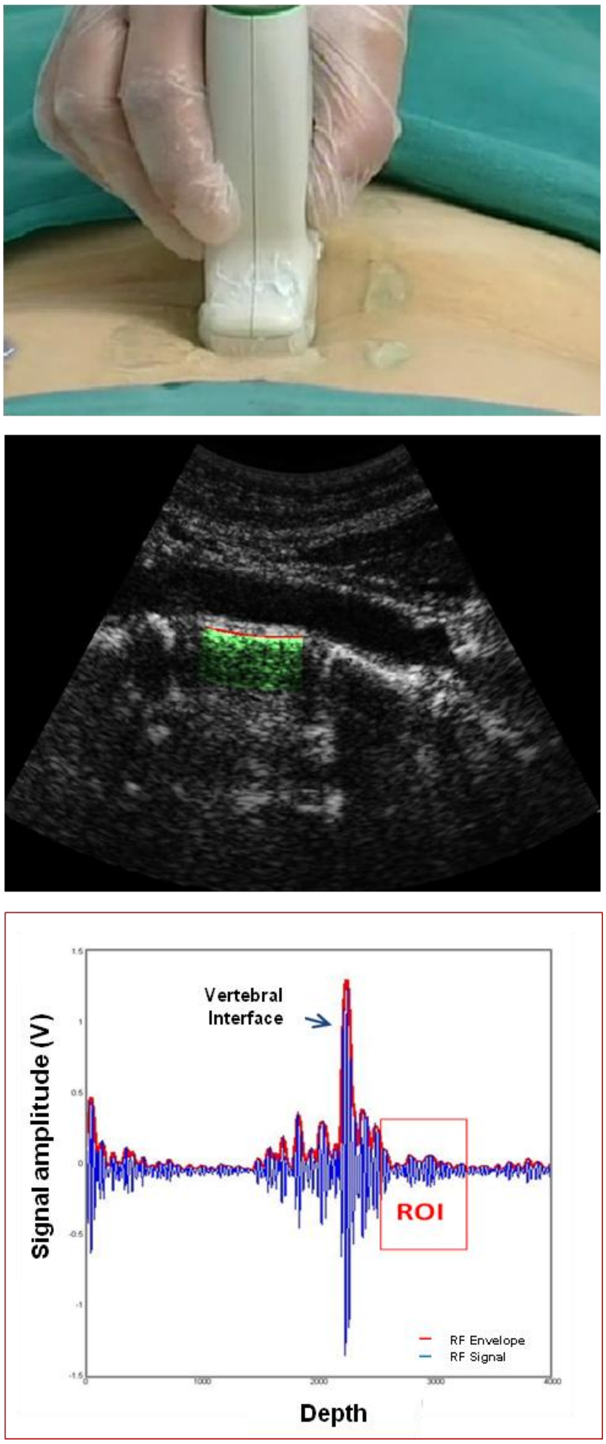

Figure 1. A) US scan of the lumbar vertebrae; **B)** selection of the target bone structure and automatic detection of the region of interest (ROI); **C)** diagnostic evaluations of F.S. value performed on the RF signal corresponding to the selected ROI.

B. DXA measurements

Spinal DXA scans were performed by an Hologic Discovery W scanner (Hologic, Waltham, MA, USA). DXA-calculated spinal BMD was measured over the lumbar vertebrae from L1 to L4 and the mean BMD value was expressed as grams per squared centimeters (g/cm^2).

C. US data acquisition and analysis

Each US spinal scan was carried out by employing a 3.5-MHz convex echographic probe connected with an innovative US device developed in Lecce (Italy) within the ECHOLIGHT Project through a collaboration between CNR-IFC and Echolight srl.

Digitized radiofrequency (RF) signals (40 MS/s, 16 bits) were transferred via USB to a PC and stored in an hard-disk for subsequent analysis [9].

Among US defined parameters, transmitted power was settled to 75% of maximum, Time Gain Compensation (TGC) was linear, mechanical index (MI)=0.4, gain=0 dB.

Each patient underwent a sagittal scan of lumbar spine (Fig. 1A) moving the probe back and forth from L1 to L4 lumbar vertebrae. Scan depth and transducer focus were each time calibrated in order to localize vertebral interface in US focal region. The scan time was about one minute and 100 frames of RF data were acquired.

D. US data analysis

Ultrasound data were analyzed by an innovative algorithm that processed both echographic images (Fig. 1B) and RF signals (Fig. 1C), providing as final output a new parameter named Fragility Score (F.S.), which represents an estimate of skeletal fragility and, therefore, of fracture risk.

Fragility Score is obtained by an algorithm that compares the spectral characteristics of the acquired RF signals with the appropriate models of "frail" and "non-frail" bone structures, previously obtained from data collected on fractured and non-fractured patients.

E. Statistics

Accuracy of F.S. in the identification of subjects prone to fractures was assessed by calculating Receiver Operating Characteristics (ROC) curve and the corresponding area under the curve (AUC): in particular, AUC was calculated for both DXA-measured BMD and US-based F.S. Then, the discrimination power of F.S. was compared with that of DXA-measured BMD. Finally, Youden's indexes [10] have been evaluated and the related cut-off points were calculated [11].

Statistical significance of obtained data was evaluated using unpaired two-sided Student t-test. All these statistical analysis were performed in Excel (Microsoft Corporation, Redmond Washington, U.S.).

3. RESULTS

For each considered patient group, Table I summarizes the average patient characteristics, including in particular mean values and corresponding standard deviations of DXA-measured BMD and US-based F.S., together with the statistical significance of the differences between the two groups.

Table I. Descriptive data of the participants and comparison between US-based F.S. values and DXA-estimated BMD for fractured and non-fractured patients.

	Fracture Group	*Control group*	*p*
	Mean ± SD	**Mean ± SD**	
Age (years)	65.0 ± 8.2	65.7 ± 7.5	*n.s.*
BMI (kg/m^2)	24.34 ± 2.28	24.71 ± 2.66	*n.s.*
BMD (g/cm^2)	0.837 ± 0.141	0.989 ± 0.156	*p<0.001*
F.S.	59.8 ± 16.5	45.3 ± 9.7	*p<0.001*

Women in the fracture group had the same age and BMI (65.0 ± 8.2 years, BMI 24.34 ± 2.28) of non-fractured patients (65.7 ± 7.5 years, BMI 24.71 ± 2.66).

BMD discriminated significantly between fractured and non-fractured women: as expected, BMD values of the fractured group (0.837 ± 0.141 g/cm^2) were significantly lower than the corresponding values found in the control group (0.989 ± 0.156 g/cm^2, $p<0.001$); also F.S. values found in patients with fragility fractures (59.8 ± 16.5) were significantly higher than the corresponding values found in non-fractured women (45.3 ± 9.7, $p<0.001$).

In order to investigate and visualize the accuracy of our novel US-based method in the identification of frail patients, AUC values for BMD and F.S. were also calculated.

As shown in Fig. 2, the comparison between the AUC values indicated that BMD (AUC=0.77) discriminated between "frail" and "non-frail" subjects with good accuracy, as well as F.S. (AUC=0.77). The best cut-off value evaluated for F.S. provided a greater sensitivity with respect to BMD: 83% *vs* 68%.

4. DISCUSSION

The overall public health impact of a single fracture includes the high risk of subsequent fractures. Indeed, a systematic analysis of existing studies showed that history of prior fracture at any site is an important risk factor for future fractures [8,12]. For this reason, the study was conducted on frail patients and the "Fragility Score" (F.S.) parameter was designed to estimate the skeletal fragility.

In this preliminary study it has been evaluated F.S. ability in the estimation of the general risk of osteoporotic fractures from an abdominal spinal scan. Clinical tests conducted on a group of 84 patients revealed that effectiveness of F.S. in fracture discrimination is analogous to that of DXA. F.S. values found in patients with fragility fracture history were significantly higher than the corresponding values found in non-fractured women.

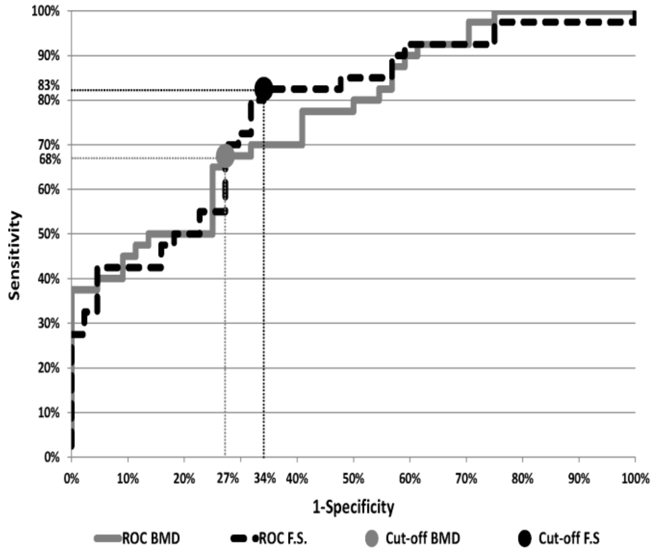

Figure 2. ROC curve calculated for BMD (continuous curve) e for F.S. value (dotted curve).

These evidences indicate that this innovative non-ionizing device could become extremely useful for the early identification of patients at high risk of osteoporotic fracture through the discrimination between "frail" and "non-frail" patients. Moreover, the evidence that sensitivity value associated to the "best cut-off" for F.S. was higher than the corresponding one for BMD (83% vs 68%) implies that the proposed approach is more suitable for population screening purposes.

Quantitative Ultrasound (QUS) devices currently in use are generally applied to peripheral anatomical sites, instead of referring to central sites (lumbar spine and femur), which are more commonly involved by osteoporotic fractures and, at the same time, are the most valuable diagnostic sites. QUS measurements at the calcaneus are used to estimate the osteoporotic fracture risk in elderly people. Recently, a good performance for hip fracture discrimination was assessed using FemUS device, directly applicable on femur [13]. On the other hand, only one *in vivo* study was published involving US application on spine (using a commercial sonographic scanner), but it was realized in order to only measure backscattered signals from lumbar vertebrae and not to evaluate fracture risk on this site [13, 7]. Accordingly, taking into account these findings, the presented approach represents the first US-based device for fracture risk estimation that is directly applicable on spine.

It has been demonstrated that DXA-measured BMD on central sites (lumbar spine and proximal femur) is the most reliable available method to predict the global fracture risk. In this work it has been shown that US-based F.S. has the same discriminatory power of DXA. Therefore the new US-method has the potential to estimate fracture risk on reference sites as well as DXA.

In this context, the fracture risk discrimination power of a non-ionizing device could represent a useful tool in the prevention of primary or secondary fractures, potentially addressed to the whole population without contraindications related to the use of X-ray.

5. CONCLUSIONS

A better management of osteoporosis would require novel treatment options, screening methods for early diagnosis and more accurate tools for fracture risk prediction. In order to alleviate the public and private burden of osteoporotic fractures, assessment and reduction of individual risk is crucial. In this context, we developed a new US approach to evaluate bone fragility overcoming radiation-related issues. A novel US-based diagnostic parameter, F.S., was therefore introduced, showing better sensitivity in identifying patients at high risk of osteoporotic fracture with respect to DXA-measured BMD.

This methodology has the potential to become an innovative tool for the estimation of osteoporotic fracture risk through early identification of "frail" patients by a safe US spinal scan.

6. ACKNOWLEDGMENT

This work was partially funded by FESR P.O. Apulia Region 2007-2013 – Action 1.2.4 (grant n. 3Q5AX31: ECHOLIGHT Project).

7. REFERENCES

[1] M. Hiligsmann, J. A. Kanis , J.Compston, C. Cooper, B. Flamion, P. Bergmann, J.-J. Body, S. Boonen, O. Bruyere, J.-P. Devogelaer, S. Goemaere, J.-M. Kaufman, S. Rozenberg, J.-Y. Reginster, "Health Technology Assessment in Osteoporosis," Calcified Tissue International, vol 93, no. 1, pp. 1–14, 2013.

[2] M. Hiligsmann, O. Bruyere, O. Ethgen, H. J. Gathon, J. Y. Reginster, "Lifetime Absolute Risk of Hip and Other Osteoporotic Fracture in Belgian Women," Bone, vol. 43, no. 6, pp. 991–994, 2008.

[3] J. A. Kanis, O. Johnell, A. Oden, I. Sembo, J. I Redlund, A. Dawson, C. De Laet, B. Jonsson, "Long-term risk of osteoporotic fracture in Malmo," Osteoporosis International, vol.11, no. 8, pp.669–674, 2000.

[4] S. R. Cummings and L. J. Melton, "Epidemiology and Outcomes of Osteoporotic Fractures," Lancet, vol. 359, no. 9319, pp.1761-1767, 2002.

[5] J. A. Kanis, D. Black, C. Cooper, P. Dargent, B. Dawson-Hughes, C. De Laet, P. Delmas, J. Eisman, O. Johnell, B. Jonsson, L. Melton, A. Oden, S. Papapoulos, H. Pols, R. Rizzoli, A. Silman, A. Tenenhouse, "A New Approach to the Development of Assessment Guidelines for Osteoporosis," Osteoporosis International, vol. 13, no. 7, pp. 527-536, 2002.

[6] K.Imai,"Recent methods for assessing osteoporosis and fracture risk. Recent Patents on Endocrine, Metabolic & Immune Drug Discovery, vol.8 no. 1, pp.48-59, 2014.

[7] P. Pisani, M. D. Renna, F. Conversano, E. Casciaro, M. Muratore, E. Quarta, M. Di Paola, S. Casciaro, "Screening and Early Diagnosis of Osteoporosis through X-ray and Ultrasound Based Techniques," World Journal of Radiology, vol. 5, no. 11, pp. 398-410, November 2013.

[8] J. A. Cauley, "Public Health Impact of Osteoporosis," Journals of Gerontology, vol. 68, no. 1, pp. 1243–125, 2013.

[9] F. Conversano, E. Casciaro, R. Franchini, G. Soloperto, A. Greco, S. Casciaro, E. Quarta, L. Quarta, M. Muratore, "A New Ultrasonic Method for Lumbar Spine Densitometry," Proc. of IEEE International Ultrasound Symposium (IUS), pp. 1809-1812, 2013.

[10] W.J. Youden, "Index for rating diagnostic tests," Cancer, vol 3, no. 1, pp. 32-35, 1950.

[11] G.D'Arrigo, F. Provenzano, C. Torino, C. Zoccali, G. Tripepi, "I test diagnostici e l'analisi della curva ROC," Giornale Italiano di Nefrologia; vol.28, no. 6, pp. 642-647, 2011.

[12] C. M. Klotzbuecher, P. D. Ross, P. B. Landsman, T. A. Abbott 3rd, M. Berger, "Patients with Prior Fractures Have an Increased Risk of Future Fractures: A Summary of the Literature and Statistical Synthesis," Journal of Bone and Mineral Research, vol 15, no. 4, pp. 721–739, 2000.

[13] R. Barkmann, S. Dencks, P. Laugier, F. Padilla, K. Brixen, J. Ryg, A. Seekamp, L. Mahlke, A. Bremer, M. Heller, C. C Gler, "Femur Ultrasound (FemUS) - First Clinical Results on Hip Fracture Discrimination and Estimation of Femoral BMD," Osteoporosis International, vol 21, no. 6, pp. 969–976, 2010.