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

CLINICAL EVALUATION OF A NOVEL ULTRASOUND-BASED METHODOLOGY FOR OSTEOPOROSIS DIAGNOSIS ON OVERWEIGHT AND OBESE WOMEN

S. Casciaro[1], M. D. Renna[1], F. Conversano[1], G. Soloperto[1], E. Casciaro[1], E. Quarta[2], A. Grimaldi[2] and M. Muratore[2]

[1]National Research Council, Institute of Clinical Physiology, Lecce, Italy,
[2]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: Osteoporosis and overweight/obesity constitute major worldwide public health burdens that are associated with aging**.** The gold standard for osteoporosis diagnosis is currently represented by bone mineral density (BMD) measurement through dual-energy X-ray absorptiometry (DXA). However, DXA cannot be used for early diagnosis through population mass screenings due to ionizing radiation employment. Because of this, generally, only people considered at high risk of fracture (underweight women after the menopause) undergo to osteoporosis screening. In fact, a significant risk factor for fracture is the low body mass index (BMI), while the tendency to overweight or obesity delays osteoporosis onset. Nevertheless, a high proportion of women after the menopause develop intra-abdominal adiposity, which leads to metabolic disorders and osteoporosis. This paper describes the diagnostic accuracy of a novel ultrasound (US)-based method to perform spinal densitometry. The proposed innovative methodology is based on a combined analysis of both echographic images and "raw" radiofrequency US signals. The diagnostic output is represented by the same parameters provided by DXA (BMD, T-score, Z-score). The efficiency of the proposed methodology was evaluated on a cohort of 280 overweight or obese (BMI > 25 kg/m^2) female patients in the age range 45-65 years. For 81.4% of the patients, US diagnosis (osteoporotic, osteopenic, healthy) was the same of the corresponding DXA one, showing the high accuracy of the proposed US technique, especially in the youngest patients (86.4% of correct diagnoses in the age range 45-50 y). A good correlation was also found between the diagnostic parameters provided by both US and DXA methods: all obtained values of Pearson coefficient (r) were within the interval 0.66-0.76 (p<0.001). Then, this new non-ionizing approach to spinal bone densitometry has the potential for being extremely useful for early osteoporosis diagnosis through population mass screenings.

Keywords: ultrasound; spinal bone densitometry; ionizing radiation; osteoporosis diagnosis; obesity; overweight.

1. INTRODUCTION

The frequency of osteoporotic fractures worldwide is rising and, because of the increased longevity of the population, osteoporotic fractures are becoming a major cause of public health burden in terms of mortality, disability and health care costs [1,2]. Early diagnosis of osteoporosis is, therefore, essential for identifying patients that are at high fracture risk and for their timely treatment. The reference indicated by World Health Organization (WHO) for osteoporosis diagnosis is currently represented by the quantitative measurements of bone mineral density (BMD). Such measurements are mainly performed through dual X-ray absorptiometry (DXA) that is considered the gold standard for BMD assessment. Lumbar spine and proximal femur are the most frequently investigated anatomical sites, since it has been demonstrated that BMD measurements on these sites are the most reliable to predict the global fracture risk. Spinal DXA, in particular, is the preferred technique for temporal monitoring of BMD variations.

Several studies indicate that BMD of hip and spine regions is associated with different factors such as body body mass index (BMI) and weight [3,4]. In particular, the Studies of National Osteoporosis Foundation and others suggested that low BMI should be included in the risk assessment tools for evaluation of osteoporosis and osteoporotic fracture risk [4-7]. On the other hand, with increasing overweight and obesity the risk for osteoporosis decreases. A recent study demonstrated that patients with BMI < 25 kg/m^2 had 4.4 times higher age-adjusted risk of osteoporosis than those with BMI ≥ 25 [4]. In general, overweight, male gender, black ethnic background, physical activity, calcium intake and use of diuretics play a relevant and positive role on BMD. However, a greater BMD does not necessarily mean a healthy status of bones [8,9]. In fact, it has been shown that increased BMI may affect DXA determination of BMD, which resulted spuriously high in overweight/obese postmenopausal women. Experimental data suggest that, with respect to X-ray propagation, axial speed of sound (SOS) measured across bones is less affected by soft tissue. Then, the use of ultrasound (US)-based

ISBN 978-92-990073-5-8

methods for evaluating bones of overweight women may be a more appropriate means than DXA [10].

Moreover, DXA cannot be used for early diagnoses through population mass screenings because requires the employment of ionizing radiation [11,12].

In this work, we presented a clinical evaluation of a new US-based method for osteoporosis diagnosis on a cohort of overweight and obese female patients.

2. MATERIALS AND METHODS

A. Study population

The study was conducted at the Operative Unit of Rheumatology of "Galateo" Hospital (San Cesario di Lecce, Lecce, Italy). A cohort of 280 female patients was recruited according to the following criteria: 45-65 years, BMI > 25 kg/m^2, absence of significant deambulation impairments, medical prescription for a spinal DXA, signed informed consent. The considered age range was established since it includes the majority of women that are referred for a spinal DXA [13,14]. In the total cohort of patients, the smallest group was represented by women aged in the range 45-50 y since overweight/obese patients, especially before the menopause, rarely undergo osteoporosis screening.

B. Data acquisition

All the enrolled patients underwent two examinations: a conventional spinal DXA and an abdominal US scan of lumbar spine. Spinal DXA scans were performed using a Hologic Discovery W scanner (Hologic, Waltham, MA, USA) measuring BMD over the lumbar vertebrae L1-L4. Abdominal US scans of lumbar spine were performed employing an innovative US device developed in Lecce (Italy) within the ECHOLIGHT Project through a collaboration between CNR-IFC and Echolight srl, which was equipped with a 3.5-MHz broadband convex transducer (Fig. 1) and configured to provide both echographic images and unfiltered radiofrequency (RF) signals. The scan lasted about 1 minute and generated 100 frames of RF data (frame-rate ~1.5 fps) that were acquired and stored in a PC hard-disk for subsequent offline analysis [15].

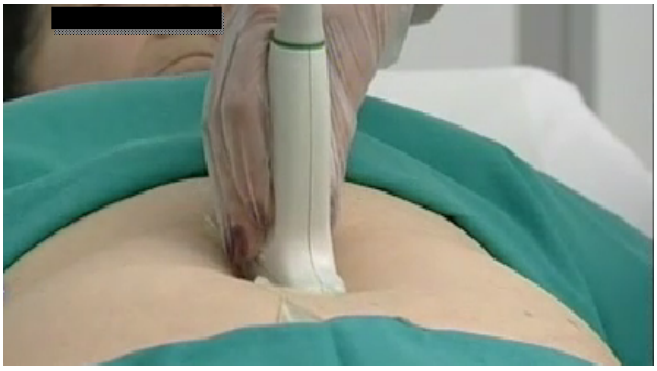

Figure 1. Abdominal US scan of lumbar spine.

C. US Data analysis

A new fully automatic algorithm was developed to analyze US data calculating the same diagnostic parameters provided by DXA (BMD, T-score, Z-score). Starting from the data acquired during the mentioned US scan of lumbar spine, for each considered patient the algorithm:

i) processed both echographic images and corresponding "raw" RF signals;

ii) performed a series of spectral and statistical analyses on the detected regions of interest;

iii) provided the diagnostic output (BMD, T-score, Z-score) through detailed comparisons with reference model spectra of healthy and osteoporotic vertebrae derived from previous US acquisitions on DXA-classified patients.

Diagnostic accuracy of obtained results was evaluated through a direct comparison with corresponding DXA output. Each enrolled patient was classified in one of the three diagnostic categories (osteoporotic, osteopenic, healthy) by DXA and US-based analysis. For each considered age range, patients that received the same classification from both DXA and US system were identified as "correct diagnoses". An explanatory scheme of the method used for the comparison of US and DXA diagnoses is showed in Fig. 2.

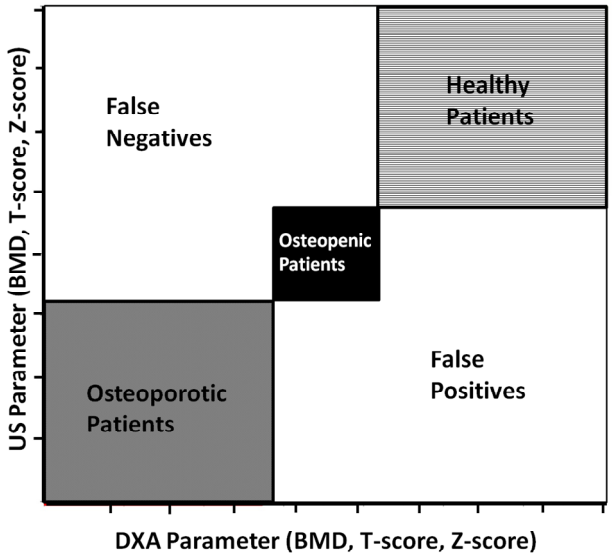

Figure 2. Scheme adopted for the comparison of US and DXA diagnoses.

Pearson coefficient (r) was used to assess the correlation between BMD, T-score and Z-score values calculated by both diagnostic methodologies.

3. RESULTS

For 81.4% of the considered cases, US diagnosis was the same of the corresponding DXA one. In particular, diagnostic accuracy showed the following behaviour as function of patient age range: accuracy was 86.4% in 45-50 y, 82.4% in 50-55 y, 83.7% in 55-60 y and 76.7% in 60-65 y (Table I).

ISBN 978-92-990073-5-8

Table I. Diagnostic agreement between US and DXA.

AGE RANGE	N° of patients	US *vs* DXA overlapping diagnosis
45-50	22	86.4%
50-55	74	82.4%
55-60	98	83.7%
60-65	86	76.7%
Total	**280**	**81.4%**

For each group of patients, Table II shows the average values of BMD calculated with both diagnostic methodologies, together with the percentage difference between these two values.

Table II. Comparison between BMD values calculated with DXA and US.

AGE RANGE	BMD DXA* (g/cm^2)	BMD US* (g/cm^2)	Difference* (%)
45-50	0.947±0.090	0.968±0.159	1.92±11.27
50-55	0.935±0.150	0.959±0.266	1.56±19.82
55-60	0.879±0.132	0.897±0.225	1.55±17.11
60-65	0.903±0.158	0.929±0.288	2.19±24.96
Total	**0.905±0.145**	**0.929±0.254**	**1.78±24.85**

*Average value ± standard deviation

For patients in the same age range, Pearson correlation coefficient (*r*) between DXA and US measurements was also evaluated for the diagnostic parameters (BMD, T-score and Z-score): all the obtained values of *r* were very good reflecting the observed diagnostic accuracy trend in dependence of age with the best correlation (r=0.77, p<0.001) found in the youngest considered patients (45-50 years), while the poorest correlation (r=0.66, p<0.001) was again found in correspondence of the oldest ones (60-65 years) (Table III).

Table III. Pearson correlation coefficient (r) between DXA and US measurements for BMD, T-score and Z-score.

AGE RANGE	N° of patients	BMD	T-score	Z-score
45-50	22	0.76	0.76	0.74
50-55	74	0.76	0.76	0.75
55-60	98	0.73	0.74	0.74
60-65	86	0.66	0.67	0.66
Total	**280**	**0.72**	**0.71**	**0.72**

Fig. 3 shows the scatterplots relative to Pearson correlation coefficient for BMD, T-score and Z-score for each age range of patients and the total value of *r*.

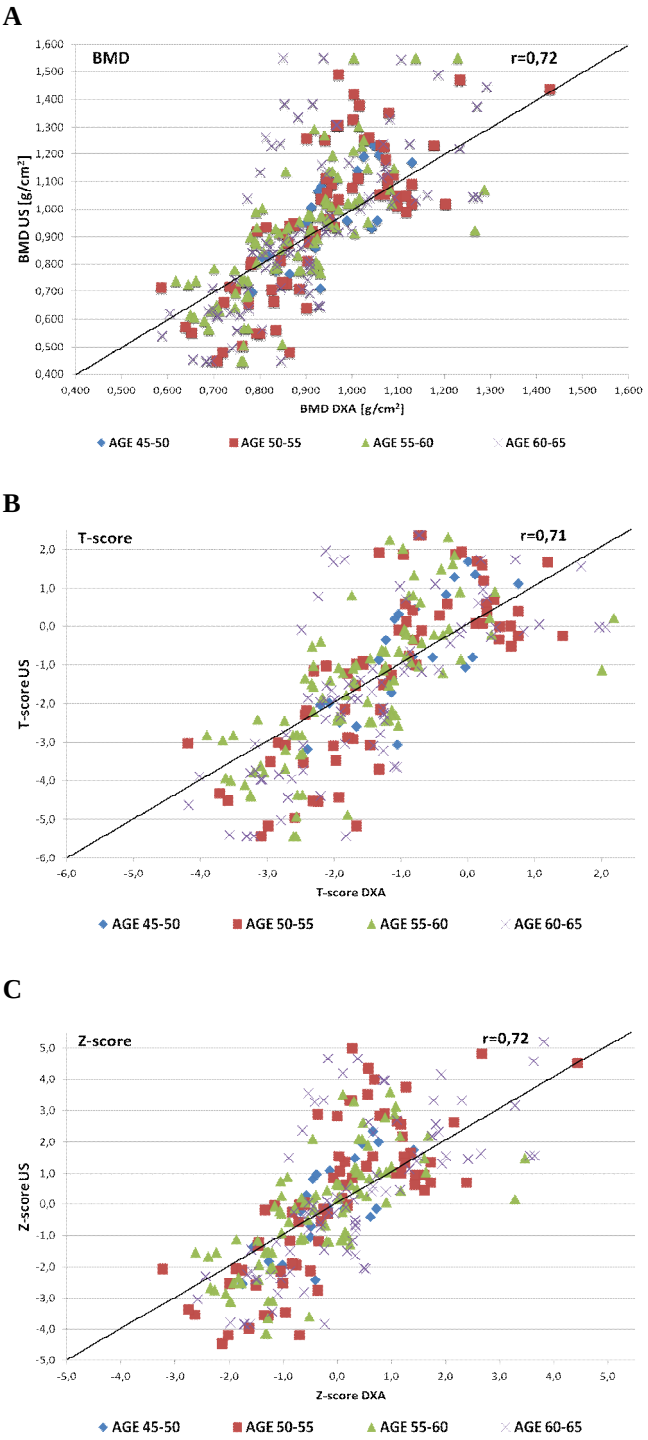

Figure 3. Comparison of BMD (**A**), T-score (**B**) and Z-score (**C**) values measured by US and the corresponding DXA.

4. DISCUSSION

The presented clinical evaluation demonstrated the effectiveness of a new US-based technique for osteoporosis diagnosis on lumbar spine on overweight/obese patients that, generally in clinical practice, are not referred for osteoporosis assessment [4-7].

The peculiarity of our method is represented by the analysis of RF signals acquired during an echographic scan of the lumbar spine to determine the internal bone

ISBN 978-92-990073-5-8

architecture. The target bone can be classified as osteoporotic or healthy through detailed comparisons with reference database containing specific spectra model of healthy and osteoporotic vertebrae for each different age range of patients [15].

US-based identification of osteoporotic, osteopenic and healthy patients evaluated assuming DXA as the gold standard reference, was promising (81.4%) for a future increase in the diffusion of US-based assessment of osteoporosis. The result is even more encouraging if we take into account the applicability of the suggested technique on the same DXA reference site, in fact lower accuracy levels are often reported for other quantitative US-based methodologies relative to peripheral sites (radius, tibia, calcaneus, phalanges) [16].

Moreover, it is important to note the effectiveness of our US method on obese patients never evaluated on clinical reference sites by other quantitative ultrasound devices. In fact, only another US method for BMD evaluation on a reference site (femur) has been developed, but it is not used to assess osteoporosis on obese patients because of positioning [17].

In general, for what concerns the age range (45-65 years), the enrolled women cohort includes the majority of patient that are referred for a spinal DXA, since younger women usually do not undergo osteoporosis controls. It is interesting to observe that maximum agreement between US and DXA diagnoses (86.4%) was found for the youngest considered patients (45-50 years; see Table I), emphasizing the potential of the proposed technique to be applied for population mass screenings on young individuals. On the other hand, minimum values of diagnostic agreement (76.7%) and BMD correlation (r=0.67) were always found for the oldest considered patients (60-65 years; see Table I and Table III). The lower diagnostic agreement in correspondence of these patients is not necessarily due to a lower accuracy of the adopted US methodology, but could be at least partially attributable to a decreased reliability of spinal DXA. It is in fact known [13,14] that, with increasing patient age, spinal degenerations (e.g. calcifications) may affect the accuracy of spinal DXA measurements and for this reason, in clinical practice, the preferred site for osteoporosis evaluation in elderly people is represented by proximal femur and not by lumbar spine.

5. CONCLUSIONS

The proposed method could represent a new valuable future alternative for bone densitometry, providing a diagnostic accuracy comparable to DXA without using X-rays. The application of the presented US-based methodology in clinical practice could make fracture prevention more accurate and effective. In conclusion, this innovative and safe technique is a potentially powerful tool to perform extended screenings for osteoporosis diagnosis in younger population, especially for those categories of patients such as overweight and obese women that currently are not referred for osteoporosis assessment.

6. ACKNOWLEDGEMENTS

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] C. Cooper, G. Campion, L. J. Melton 3rd, “Hip fractures in the elderly: a world-wide projection,” Osteoporosis International, vol. 2, no.6, pp. 285-289, 1992.

[2] S. R. Cummings and L. J.Melton, “Epidemiology and outcomes of osteoporotic fractures,” Lancet, vol. 359, no. 9319, pp. 1761-1767, 2002.

[3] G. E. Beranger, D. F. Pisani, J. Castel, M. Djedaini, S. Battaglia, J. Amiaud, F. Boukhechba, G. Ailhaud, J. F. Michiels, D. Heymann, S. Luquet, E. Z. Amri, “Oxytocin reverses ovariectomy-induced osteopenia and body fat gain,” Endocrinology, 2014 [Epub ahead of print].

[4] M. R. Salamat, A. H. Salamat, I. Abedi, M. Janghorbani, “Relationship between Weight, Body Mass Index, and Bone Mineral Density in Men Referred for Dual-Energy X-Ray Absorptiometry Scan in Isfahan, Iran,” Journal of Osteoporosis, vol. 2013, id: 205963, pp. 1-7, 2013.

[5] A. Szklarska and A. Lipowicz, “BMI, hypertension and low bone mineral density in adult men and women,” Homo, vol. 63, no. 4, pp. 282-291, 2012.

[6] A. L. Utz, E. A. Lawson, M. Misra, D. Mickley, S. Gleysteen, D. B. Herzog, A. Klibanski, K. K. Miller, “Peptide YY (PYY) levels and bone mineral density (BMD) in women with anorexia nervosa,” Bone, vol. 43, no.1, pp. 135-139, 2008.

[7] C. De Laet, J. A. Kanis, A. Oden, H. Johanson, O. Johnell, P. Delmas, J. A. Eisman, H. Kroger, S. Fujiwara, P. Garnero, E. V. McCloskey, D. Mellstrom, L. J. Melton 3rd, P. J. Meunier, H. A. Pols, J. Reeve, A. Silman, A. Tenenhouse, “Body mass index as a predictor of fracture risk: a meta-analysis,” Osteoporosis International, vol. 16, no.11, pp. 1330-1338, 2005.

[8] K. S. Sarkis, M. Pinheiro Mde, V. L. Szejnfeld, L. A. Martini, “High bone density and bone health,” Endocrinología y Nutrición, vol. 59, no. 3, pp. 207-214, 2012.

[9] R. K. Marwaha, N. Tandon, Y. Gupta, K. Bhadra, A. Narang, K. Mani, A. Mithal, S. Kukreja, “The prevalence of and risk factors for radiographic vertebral fractures in older Indian women and men: Delhi Vertebral Osteoporosis Study (DeVOS),” Archives of Osteoporosis, vol. 7, no.1-2, pp. 201-207, 2012.

[10] M. Steinschneider, P. Hagag, M.J. Rapoport, M. Weiss, “Discordant effect of body mass index on bone mineral density and speed of sound,” BMC Musculoskeletal Disorders, vol. 4, no.15, pp.1-6, 2003.

[11] M. Brambilla, A. De Mauri, L. Leva, A. Carriero, E. Picano, “Cumulative radiation dose from medical imaging in chronic adult patients,” American Journal of Medicine, vol. 126, no. 6, pp. 480-486, 2013.

[12] E. Picano and M. Matucci-Cerinic, “Unnecessary radiation exposure from medical imaging in the rheumatology patient,” Rheumatology (Oxford), vol. 50, no. 9, pp. 1537-1539, 2011.

[13] K. Chanchairujira, C. B. Chung, J. Y. Kim, O. Papakonstantinou, M. H. Lee, P. Clopton, D. Resnick, “Intervertebral disk calcification of the spine in an elderly population: radiographic prevalence, location, and

ISBN 978-92-990073-5-8

distribution and correlation with spinal degeneration," Radiology, vol. 230, no. 2, pp. 499-503, 2004.

[14] T. Rand, G. Seidl, F. Kainberger, A. Resch, K. Hittmair, B. Schneider, C. C. Glüer, H. Imhof, "Impact of spinal degenerative changes on the evaluation of bone mineral density with dual energy X-ray absorptiometry (DXA)," Calcified Tissue International, vol. 60, no. 5, pp. 430-433, 1997.

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

[16] 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, n. 11, pp. 398-410, 2013.

[17] R. Barkmann, S. Dencks, P. Laugier, F. Padilla, K. Brixen, J. Ryg, A. Seekamp, L. Mahlke, A. Bremer, M. Heller, C.C. Glüer, "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.