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● *Original Contribution*

AN ADVANCED QUANTITATIVE ECHOSOUND METHODOLOGY FOR FEMORAL NECK DENSITOMETRY

Sergio Casciaro,* Marco Peccarisi,† Paola Pisani,* Roberto Franchini,* Antonio Greco,† Tommaso De Marco,† Antonella Grimaldi,‡ Laura Quarta,‡ Eugenio Quarta,‡ Maruizio Muratore,‡ and Francesco Conversano*

*National Research Council, Institute of Clinical Physiology, Lecce, Italy; †Echolight srl, Lecce, Italy; and ‡Operative Unit of Rheumatology, Galateo Hospital, San Cesario di Lecce, Lecce, Italy

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Abstract—The aim of this paper was to investigate the clinical feasibility and the accuracy in femoral neck densitometry of the Osteoporosis Score (O.S.), an ultrasound (US) parameter for osteoporosis diagnosis that has been recently introduced for lumbar spine applications. A total of 377 female patients (aged 61–70 y) underwent both a femoral dual X-ray absorptiometry (DXA) and an echographic scan of the proximal femur. Recruited patients were sub-divided into a reference database used for ultrasound spectral model construction and a study population for repeatability assessments and accuracy evaluations. Echographic images and radiofrequency signals were analyzed through a fully automatic algorithm that performed a series of combined spectral and statistical analyses, providing as a final output the O.S. value of the femoral neck. Assuming DXA as a gold standard reference, the accuracy of O.S.-based diagnoses resulted 94.7%, with $k = 0.898$ ($p < 0.0001$). Significant correlations were also found between O.S.-estimated bone mineral density and corresponding DXA values, with r^2 up to 0.79 and root mean square error = 5.9–7.4%. The reported accuracy levels, combined with the proven ease of use and very good measurement repeatability, provide the adopted method with a potential for clinical routine application in osteoporosis diagnosis. (E-mail: sergio.casciaro@cnr.it) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Osteoporosis diagnosis, Quantitative Ultrasound, Bone Mineral Density Measurement, Femoral Neck, Bone Densitometry, Radiofrequency Signal Analysis.**

INTRODUCTION

Osteoporosis is a highly prevalent bone disease characterized by a decrease in bone mass accompanied by micro-architectural alterations, resulting in bone fragility and increased fracture risk (Liu et al. 2011). Vertebral and hip fractures are the most frequent, expensive and disabling osteoporotic fractures, leading to reductions in patient quality of life and also causing significant mortality rates (Albanese et al. 2011; Cooper 1997; Ensrud et al. 2000).

According to the operational definition provided by the World Health Organization, osteoporosis is diagnosed when bone mineral density (BMD) measured at lumbar spine or proximal femur is at least 2.5 standard deviations (SDs) lower than the young adult mean (*i.e.,* T-score ≤ -2.5) (Genant et al. 1999; Kanis 1994). Analogously, a patient will be classified as "osteopenic" if $-2.5 <$ T-score < -1.0, or "healthy" if T-score ≥ -1.0. For instance, according to the National Health and Nutrition Examination Survey database, young adult white women (aged in 20–25 y) had an average femoral neck BMD (mean ± SD) of 0.847 ± 0.110 g/cm^2, therefore a generic white woman will be classified as "osteoporotic" if her femoral neck BMD is ≤0.572 g/cm^2, "osteopenic" if her BMD is internal to the range 0.572–0.737 g/cm^2, or "healthy" if BMD ≥0.737 g/cm^2.

Dual X-ray absorptiometry (DXA) currently represents the most common method for osteoporosis diagnosis and it is considered the gold standard reference for BMD assessments (Baim and Leslie 2012; Link 2012; Schnitzer et al. 2012). However, DXA also has some important intrinsic limitations that prevent its use

Address correspondence to: Sergio Casciaro, Consiglio Nazionale delle Ricerche, Istituto di Fisiologia Clinica, c/o Campus Ecotekne (Ed. A7), via per Monteroni, 73100 Lecce, Italy. E-mail: sergio.casciaro@cnr.it

for population mass screenings (*i.e.,* exposure to ionizing radiation with associated risks, high costs, and the need for dedicated structures with certified operators) (Pisani et al. 2013), and this resulted in the development of quantitative ultrasound (QUS) approaches to bone health assessment and osteoporosis diagnosis (Breban et al. 2010; Nayak et al. 2006; Paggiosi et al. 2012; Pais et al. 2010; Schnitzer et al. 2012; Trimpou et al. 2010). In fact, QUS methods have several potential advantages over DXA, including absence of ionizing radiation, lower costs, portable machines and availability in primary care settings without requiring dedicated structures or certified operators.

Commercially available QUS devices are presently usable only on peripheral bone districts, such as the calcaneus, and numerous studies focused on evaluating their diagnostic effectiveness compared to DXA measurements on the axial reference sites (lumbar spine and proximal femur) obtained contradictory results (Breban et al. 2010; Dane et al. 2008; El Maghraoui et al. 2009; Iida et al. 2010; Kwok et al. 2012; Liu et al. 2012; Moayyeri et al. 2012; Schnitzer et al. 2012; Stewart et al. 2006; Trimpou et al. 2010). However, work in this field is ongoing and interesting experimental results are being continuously published, including, for instance, encouraging multi-site measurements of apparent integrated backscatter (AIB) and the integrated reflection coefficient (Karjalainen et al. 2012); extended clinical validations of calcaneal measurements of AIB and spectral centroid shift (Jiang et al. 2014); and improvements of precision in the measurement of speed of sound (SOS) at the heel (Daugschies et al. 2015).

Nevertheless, despite the number of available papers, the International Society for Clinical Densitometry (ISCD) has restricted the actual diagnostic usefulness of QUS methods to validated calcaneal devices used on people aged 65 and older, only in combination with clinical risk factor assessment and only in order to identify those patients at very low risk of fractures who therefore do not require further investigations (ISCD 2013).

As a consequence, clinical routine management of osteoporosis is based on the combined evaluation of axial DXA outcomes and clinical risk factors (*i.e.,* previous fragility fracture, parent with a fractured hip, smoking, use of glucocorticoids, rheumatoid arthritis, causes of secondary osteoporosis, alcohol abuse) (Ferrari et al. 2012), resulting in high rates of under-diagnosis and under-treatment—it was estimated that approximately 75% of osteoporotic patients are not diagnosed and thus never receive appropriate treatment (Curtis and Safford 2012; Nguyen et al. 2004; van den Bergh et al. 2012). In fact, the best osteoporosis treatment would be the prevention of the disease, and of subsequent fractures, through a very early diagnosis, ideally when the patient presents a BMD reduction still in the osteopenic range, before becoming osteoporotic. In most cases, this condition can be effectively managed by targeted corrections to lifestyle habits (*e.g.,* increasing physical exercise, reducing alcohol consumption, *etc.*). Otherwise, a good therapy for osteoporosis should inhibit bone resorption and/or stimulate bone formation—an effective osteoporosis treatment significantly reduces fracture rate by 40–70% in a few months. The most commonly used therapeutic agents include estrogens, selective estrogen receptor modulators, bisphosphonates, agents derived from the parathyroid hormone, strontium ranelate and denosumab (Muratore et al. 2014).

To improve this situation, attention has recently been turned to the investigation of ultrasound (US) approaches for osteoporosis diagnosis directly applicable on lumbar spine and/or proximal femur (Barkmann et al. 2010; Conversano et al. 2015; Karjalainen et al. 2012). In particular, the femur has become the target of many experimental works focused on the translation of peripheral QUS measurement to the proximal femur (Barkmann et al. 2007, 2008a, 2008b, 2010; Dencks et al. 2008; Grimal et al. 2013; Haiat et al. 2005; Karjalainen et al. 2012; Padilla et al. 2008). The most significant clinical results were obtained by Barkmann et al. (2010), employing a "through transmission" US approach for measuring SOS and broadband ultrasound attenuation (BUA), and by Karjalainen et al. (2012), who used a backscatter approach to measure AIB and integrated reflection coefficient.

In this context, a different US methodology for osteoporosis diagnosis on lumbar spine has been recently introduced by our research group, together with a novel diagnostic parameter, the Osteoporosis Score (O.S.) (Conversano et al. 2015). The basic idea underlying this approach is that unfiltered radiofrequency (RF) signals, acquired during an echographic scan of the investigated bone district, can be employed to assess the bone health status through advanced comparisons with previously derived reference spectral models of healthy and osteoporotic bones. Moreover, the implemented RF signal analysis method is natively integrated with echographic imaging, which is needed for both the identification of the region of interest (ROI) for diagnostic calculations and the simultaneous acquisition of several RF signals for each frame, in order to provide a solid and reliable statistical basis for subsequent spectral analyses. This close integration in the processing of echographic images and "raw" unfiltered RF signals has been recently defined as the "echosound approach" (Casciaro et al. 2015).

The aim of the present work was to extend the application of this new methodology to the femoral neck, investigating its clinical feasibility and diagnostic