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PRELIMINARY CLINICAL VALIDATION OF A NEW ULTRASOUND-BASED METHODOLOGY FOR FEMORAL NECK DENSITOMETRY

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Abstract: Hip fracture has been recognized as the worst consequence of osteoporosis, as it represents one of the most important causes of disability and mortality in elderly people. An accurate knowledge of the osteoporotic fracture risk in asymptomatic individuals through population mass screenings may be the only way to reduce the occurrence of hip fractures. Aim of this study was to perform a preliminary clinical validation of a new ultrasound (US)-based method for bone densitometry directly applicable on femoral neck. A total of 112 female patients were enrolled for this study (61-75 years of age, body mass index (BMI)<40 kg/m^2) and all of them underwent two different diagnostic investigations: a conventional DXA (dual-energy X-ray absorptiometry) of the femoral neck and an US scan of the same bone district, acquiring both echographic images and unfiltered radiofrequency signals. US data were analyzed by a new algorithm that calculated the same diagnostic parameters obtained from DXA examination (BMD, T-score, Z-score). Accuracy of each parameter calculated by this algorithm was then evaluated through a direct comparison with DXA results as a function of both patient age and BMI. For 81.3% of the patients US diagnosis (osteoporotic, osteopenic, healthy) coincided with the corresponding DXA one and this accuracy level was not appreciably influenced by patient age nor by BMI. The illustrated method has the potential to be used for routine population screening programs for early osteoporosis diagnosis and hip fracture prevention.

Keywords: bone densitometry; osteoporosis diagnosis; ultrasound imaging; hip fracture.

1. INTRODUCTION

Osteoporosis is defined as a systemic skeletal disease characterized by a low bone mass and a microarchitectural deterioration of bone tissue, with a subsequent increase in bone fragility and susceptibility to fracture [1]. Hip fracture is a common injury among elderly patients with osteoporosis, requiring expensive interventions and frequently resulting in reduced quality of life, disability and mortality. Hip fracture incidence increases with age, with a 75% occurring in women [2]. The 1-year mortality rates vary from 13% to 36%, depending upon a variety of risk factors (age, comorbidity, pre-fracture functional status, etc.) [3]. In addition, about 50% of fractured patients are unable to recover their independent lifestyle [4]. Therefore, the social and economic costs associated with hip fractures are enormous. In Italy, the cost of treating incident hip fractures and of long-term fracture care in 2010 was equal to € 3,977 million for about 517,000 patients [5].

Considering the increase in life expectancy, the only possible way to reduce the occurrence of hip fractures is represented by the adoption of more effective strategies for early osteoporosis diagnosis and hip fracture prevention through population mass screenings. The use of imaging techniques for osteoporosis diagnosis is of critical importance in identifying individuals at risk for fractures, who would require pharmacotherapy to reduce fracture risk, and also in treatment response monitoring [6]. In fact, there is a large gap between the numbers of women that are treated compared to the proportion of the population that could be eligible for treatment based on fracture risk [5].

Dual-energy X-ray absorptiometry (DXA) of the proximal femur and lumbar spine is currently the state-of-the-art technique to measure bone mineral density (BMD) for osteoporosis diagnosis according to the World Health Organization (WHO) guidelines [7]. In particular, femoral neck BMD is associated with a high gradient of risk for hip fracture [8]; in fact, the WHO fracture risk assessment tool (FRAX), employs the BMD measurements on femoral neck as the reference standard BMD value, which is then integrated with clinical risk factors in order to determine the 10-year fracture probabilities [9].

DXA examination is indicated in women aged 65 years and older, as well as in younger and peri-menopausal women with risk factors for fragility fractures [10]. Men aged 70 years and older and younger men with risk factors for fracture should also undergo DXA. However, DXA cannot be used in primary healthcare for screening purposes because of specific limitations, such as issues related to X-ray employment, high costs, large size of the equipment and limited availability in rural zones [11]. Over the past ten years, quantitative ultrasound (QUS) methods have been

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developed to determine bone quality and the state of skeleton in terms of its structure and elastic properties [12,13]. However, all the commercially-available QUS devices can be applied only to peripheral bone districts (calcaneus, proximal phalanges of the hand, tibial shaft and radius) and their results present poor correlations with femoral neck BMD as measured by DXA. Conversely, interest in US-based methodologies for osteoporosis assessment stems from practical, economic and health safety aspects, since such techniques are less expensive and more portable than DXA and do not employ ionizing radiation. These features suggest a future role for US-based methods as an effective screening tool for osteoporosis diagnosis.

Here we present the preliminary clinical validation of a new US-based methodology for bone densitometry that can be applied directly on femoral neck.

2. METHODS

A. Patients

The study was conducted at the Operative Unit of Rheumatology of "Galateo" Hospital (San Cesario di Lecce, Lecce, Italy) and included a total of 112 consecutive female patients, according to the following inclusion criteria: Caucasian ethnicity, 61-75 years of age, body mass index (BMI) < 40 kg/m^2, absence of important deambulation impairments, medical prescription for a femoral DXA. All the enrolled patients underwent two different investigations: a conventional DXA of the proximal femur and an US scan of the same bone district. The study protocol was approved by the Hospital Ethics Review Board and all patients gave informed consent.

B. DXA Measurements

DXA scans were performed on the proximal femur using a Hologic Discovery W scanner (Hologic, Waltham, MA, USA). In addition to the BMD value, expressed as grams of mineral per area or volume, DXA report provides T-scores and Z-scores. T-score value is defined as the number of standard deviations (SDs) from the peak BMD of young women belonging to the considered ethnicity while Z-score value is the number of SDs from the peak BMD of an age-matched reference population. A T-score of -1 or higher represents a normal value, a T-score in the range from -1 to -2.5 is defined as osteopenia and a T-score of -2.5 or lower is defined as osteoporosis [14,15].

C. Ultrasound Acquisitions

US scans of the femoral neck were performed employing an innovative US device developed in Lecce (Italy) within the ECHOLIGHT Project through a collaboration between CNR-IFC and Echolight srl. The device was equipped with a 3.5-MHz broadband convex transducer and configured to provide both echographic images and unfiltered radiofrequency (RF) signals. Each patient underwent a femoral neck scan that lasted about 40 s and generated 50 frames of RF data, digitized at 40MHz (16 bits), that were stored on a PC hard-disk for offline analysis. Transducer focus and scan depth were each time adjusted in order to have femoral neck interface in the beam focal zone and in the central area of the image. Other acquisition parameters were: echograph power = 75%; mechanical index (MI) = 0.4; gain = 0 dB; linear TGC (time gain compensation).

D. Ultrasound Data Analysis

US data were analyzed by a new algorithm that, through a series of spectral and statistical analyses on both the echographic images and the corresponding unfiltered "raw" RF signals, calculated the same diagnostic parameters obtained from DXA examination (BMD, T-score, Z-score). Accuracy of each parameter calculated by this algorithm was then evaluated through a direct comparison with DXA results as a function of both patient age and BMI. Algorithm working principle is based on a complex patented method [13] that is herein summarized. First, the algorithm automatically identifies femoral interfaces within the sequence of echographic images acquired on the considered patient. After the identification process, the algorithm performs diagnostic parameter calculations on RF signal segments corresponding to a specific region of interest (ROI) internal to the identified femoral neck region. In this process, the algorithm compares RF spectra of the considered patient with reference model spectra of healthy and osteoporotic femoral necks derived from previous US acquisitions on DXA-classified patients. Reference model spectra are in fact taken from a preliminarily built database in which specific models are available for different combinations of patient sex, BMI interval and age range. For each analyzed patient, the algorithm provides as a final output the same diagnostic parameters of a DXA investigation: BMD, T-score and Z-score. In this study, algorithm accuracy was assessed through a direct comparison with DXA results (assumed as a "gold standard" reference) according to the evaluation scheme reported in Fig. 1.

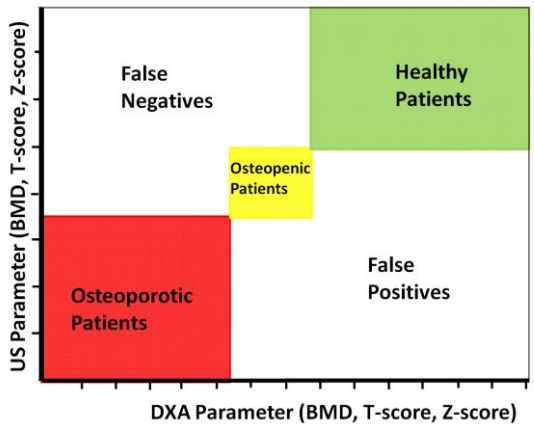

Figure 1. Evaluation scheme adopted for the assessment of US diagnostic accuracy against DXA.

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3. RESULTS

For 81.3% of the studied patients US diagnosis (healthy, osteopenic or osteoporotic) was the same of the corresponding DXA one, as visually emphasized by the graphs reported in Fig. 2, Fig. 3. and Fig. 4.

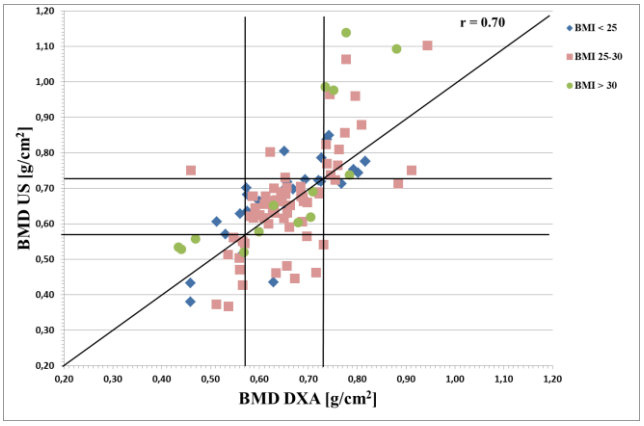

Figure 2. US-measured BMD against the corresponding DXA values for all the studied patients. (p<0.001; please refer to the evaluation scheme in Fig. 1 to identify correctly diagnosed patients, false negatives and false positives)

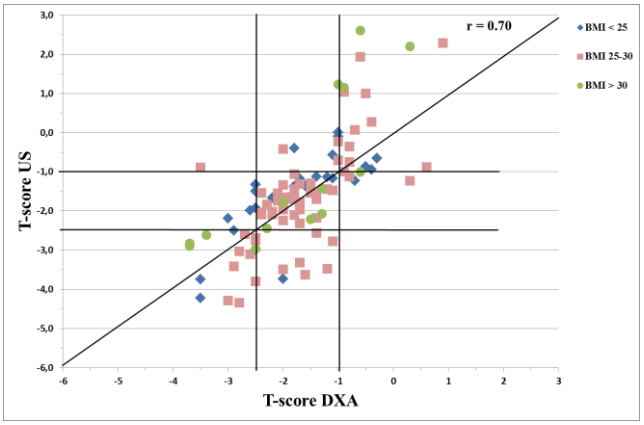

Figure 3. US-measured T-score values against the corresponding DXA values for all the studied patients. (p<0.001; evaluation scheme illustrated in Fig. 1)

Figure 4. US-measured Z-score values against the corresponding DXA values for all the studied patients (p<0.001).

Pearson correlation coefficient (r) between DXA and US measurements was evaluated for each diagnostic parameter, obtaining r=0.70 for BMD, r=0.70 for T-score and r=0.72 for Z-score. In addition, analyzing the correlation values for each group of patients having age in the same range, we found maximum correlation for the diagnostic parameters measured on patients with age in the range 71-75 yr, while minimum correlation was found for the diagnostic values measured on patients having age in the range 61-65 yr, as reported in Table 1. Similar correlation values were obtained for the diagnostic parameters measured on patients with BMI in the same range (<25 Kg/m^2, 25-30 Kg/m^2 and >30 Kg/m^2), indicating that the accuracy level for each diagnostic parameter was not significantly influenced by BMI nor by patient age. In fact, the observed differences in the correlation values as a function of age range (Table 1) are a consequence of the sample size, since r decreases for larger number of analyzed patients, although the correlation is still statically significant (p<0.01).

Age range	N° patients	Pearson coefficient (r) between DXA and US		
		BMD	T-score	Z-score
61-65	31	0.78	0.75	0.78
66-70	66	0.65	0.66	0.65
71-75	15	0.8	0.8	0.79

Table 1. Pearson correlation coefficient (r) between DXA and US measurements for each diagnostic parameter as a function of age range.

4. DISCUSSION

DXA of the hip for osteoporosis diagnosis is a relatively expensive procedure requiring a large equipment and implying the exposure to ionizing radiation. In the last years, many efforts have been dedicated to research and development of less expensive, safe, and portable techniques that can predict hip fracture. In this context, QUS methods have been investigated for osteoporosis screening purposes [16-18], but the currently QUS devices available for the clinical routine are all applied to peripheral anatomical sites (*e.g.*, calcaneus), instead of referring to lumbar spine or to femur, which are the most critical and valuable diagnostic sites. [19]. Therefore, QUS methods cannot yet be used to actually replace the gold-standard DXA test for osteoporosis diagnosis and they are not recommended to monitor treatment response [6,19]. To date, the widely accepted physician opinion is that QUS methods can be actually useful only as a preliminary test for hip fracture risk to be followed by a DXA confirmation.

The present study demonstrated the feasibility of a novel US approach for osteoporosis diagnosis directly applicable to femoral neck. Assuming DXA as the gold standard reference, US-based identification of osteoporotic, osteopenic and healthy patients resulted correct in 81.3% of the analyzed cases (n=112). In particular, each considered diagnostic parameter obtained from US-measurements showed a good correlation with the corresponding DXA values. In addition, the accuracy level for each diagnostic

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parameter was not appreciably influenced by patient age nor by BMI (BMD, T-score, Z-score).

5. CONCLUSION

We presented a novel US-based approach for bone densitometry directly applicable on femoral neck, showing an accuracy level comparable with the gold-standard DXA technique, in terms of both diagnosis agreement and correlation of single parameter values. Thanks to the observed accuracy levels, combined with the absence of ionizing radiation, the proposed method has the potential to be effectively used for population mass screenings aimed at early osteoporosis diagnosis and hip fracture prevention.

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