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## OSTEOPOROSIS: EPIDEMIOLOGY AND AVAILABLE DIAGNOSTIC APPROACHES

*S. Casciaro<sup>1</sup>, M.D. Renna<sup>1</sup>, P. Pisani<sup>1</sup>, A. Greco<sup>2</sup>, F. Conversano<sup>1</sup>, M. Muratore<sup>3</sup>*

<sup>1</sup>National Research Council, Institute of Clinical Physiology, Lecce, Italy; <sup>2</sup>Echolight S.r.l., Lecce, Italy;  
<sup>3</sup>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 is the most common disorder of bone metabolism, with a high rate of diffusion, especially in the elderly population. The main consequence of osteoporosis is bone fragility, with the consequently increased risk of fracture. Vertebral and hip fractures represent one of the most important causes of morbidity and disability and cause also high economic costs for the National Healthcare Systems. The currently accepted "gold standard" method for osteoporosis diagnosis is represented by the evaluation of bone mineral density (BMD) through dual X-ray absorptiometry (DXA). However, DXA presents some considerable limitations such as the exposition to ionizing radiations, employment of bulky devices and high costs of management. This paper gives an overview of the most widely used X-ray based techniques to perform osteoporosis diagnosis and describes the working principles of non-invasive ultrasound (US) based methods for bone densitometry, underlining the corresponding advantages and limitations for their use in the clinical practice. Moreover, the article illustrates the effectiveness of an innovative US technique, directly applicable on the main anatomical reference sites, in terms of diagnostic accuracy and fracture risk prediction. Early diagnosis is the key to resize the impact of osteoporosis on healthcare systems. Therefore, it would be necessary to encourage the widespread use of quick, cheap and non-invasive screening techniques.

**Keywords:** ultrasound; osteoporosis; healthcare costs; early diagnosis; fracture risk.

### 1. INTRODUCTION

Osteoporosis is a widespread systemic disease that causes a reduction in both quality and density of bones, consequently increasing fracture risk. Because of the economic burden caused by osteoporosis fractures, there is a strong need for the assessment of the best practices in prevention and treatment and for their adoption at international level in order to contrast worldwide expansion of the disease.

In this context, ever new findings are emerging to assess the risk of osteoporotic fractures. Presently, there are no satisfactory clinical tools available to evaluate bone quality

independently of bone density, so that in clinical practice the assessment of osteoporosis depends upon the measurement of skeletal mass by bone mineral density (BMD) evaluation [1]. BMD is generally estimated by X-ray based techniques, which involve ionizing radiation exposure and high management costs.

The aim of this paper was to review the currently available techniques for osteoporosis diagnosis and to illustrate also the feasibility of an innovative ultrasound (US) method.

The ultimate goal was to encourage the early diagnosis of osteoporosis by the use of quick, cheap and non-invasive screening techniques.

#### A. Epidemiology and social impact of osteoporosis

Osteoporosis has a significant impact on public health through the increased rates of morbidity, mortality and economic costs associated with bone fractures. The frequency of osteoporotic fractures is in fact rising in many countries. In 1990, there were an estimated 1.7 million hip fractures worldwide [2,3] and by 2050 they could exceed 21 million [3,4]. This is in particular due to the increased longevity of the population and the consequent higher prevalence of chronic diseases, including osteoporosis and the complications due to the fracture risk. In Italy, since 1950, life expectancy at birth has increased by 4 months per year and, currently, is 77.9 years for men and 84.4 years for women [5]. People over 65 years of age represent more than 20% of population in our country, and this demographic trend is also increasing. Then, one in five women and one in seven men are over 65 years of age. Among these, octogenarians are 5% and will exceed 11% in 2045 [5]. Nowadays, in our country there are 137.7 people aged over 65 for every 100 young people under 15 years of age, with some differences between the North (157.9), Center (160.7) and South (106.6) [5].

The epidemiological study ESOP (Epidemiological Study On the Prevalence of Osteoporosis), carried out in 2000 in Italy on 16,000 patients recruited in 83 centers with the collaboration of 1,850 family physicians, has shown that osteoporosis is a disease with a high prevalence in our country, especially among women [6,7]: there are around 4 million of women exposed to a higher fracture risk (in

particular women aged over 75 years), and more than 800,000 men (Table I).

**Table I.** Epidemiology in Europe: osteoporosis prevalence in some European countries. Adapted from [8].

Country	Osteoporosis prevalence
Denmark	41% of women >50 18% of men >50
Germany	6.5 million women and 1.3 million men
Italy	4 million women and 800,000 men
Spain	2 million women >50 (26% of people >50)
Sweden	15% of women >50 8% of men >50

The progressive and constant aging of the population in Italy and, in general, in Europe (Table I) confirms the clinical and public relevance of osteoporosis. Europe's six largest countries spent €31 billion for osteoporotic fracture management in 2010 and these costs are expected to increase to €76.7 billion in 2050 because of the demographic changes [9].

However, it is difficult to estimate the total costs of osteoporosis management in a country, because they are based on many assumptions that are not easy to test and depend on a variety of factors, including the age specific fracture risks, the population's size, age and sex distribution, acute hospital care, the cost per fracture, long-term care in the home and the proportion of hip fracture patients requiring nursing home care after fracture, medications, rehabilitation, treatment and loss of working days.

Generally, the majority of costs is attributed to incident fractures and the cost per fracture increases with age, reaching a maximum for individuals older than 74 years (especially women), while pharmacological treatment only represents less than 5% of total [9].

The burden of osteoporosis is described not only in terms of fractures and costs but also in terms of mortality, morbidity and loss in quality of life. The most important long-term impairment is in the ability to walk: up to a third of individuals that suffered a hip fracture can become totally dependent. On the other hand, back pain, kyphosis, and height loss are the major consequences of vertebral fractures, which affect not only physical function but self-esteem, body image, and mood [10].

In this context, the social and economic burden is expected to increase in the future with demographic changes and increasing life expectancy. Attention must be therefore focused on the identification of patients at high risk of fracture rather than the identification of men and women with osteoporosis [11].

Then, the assessment of cheap health technology in the field of osteoporosis could be very useful for an efficient allocation of healthcare resources [12].

## B. X-ray based diagnostic techniques

Early diagnosis of osteoporosis is essential for identifying patients that are at fracture risk and for their timely treatment. Current clinically-available diagnostic methods are mainly based on the use of X-rays. Among the most commonly used techniques, the currently accepted "gold standard" method for osteoporosis diagnosis and fracture risk prediction is represented by the evaluation of BMD through dual X-ray absorptiometry (DXA).

A DXA scanner consists of a mobile X-ray source and a detection system for radiation emerging from the examined bone. The attenuation values of soft tissues are subtracted by an algorithm providing only the attenuation values of bone [13]. These values are compared with standard values in phantoms of known density in order to obtain bone mineral content value (in grams). By dividing bone mineral content by the projected area of the measured site, it is possible to obtain the BMD value (in grams per square centimeter) [14]. DXA can be employed to directly investigate the main anatomical reference sites: proximal femur and vertebral bodies [2].

Quantitative computed tomography (QCT) has also been used to quantify bone mineral content [15]. The main advantage of this technique is that cancellous bone can be examined separately from cortical bone [2]. Starting from the segmentation of an acquired image of a thin bone slice, the QCT diagnostic output is a quantitative measure of volumetric BMD (unlike the two-dimensional BMD provided by DXA). For instance, the cancellous bone of vertebrae is assessed independently of surrounding cortical bone and possible aortic calcifications [15]. QCT can be performed also to peripheral sites of the skeleton (radius, tibia) using smaller, less expensive, dedicated peripheral CT scanners.

Finally, morphometric methods have been developed in order to identify vertebral fractures. Vertebral morphometry is a quantitative method based on the measurement of distinct vertebral dimensions, obtained from conventional spine radiographs or absorptiometric images [16]. By calculating relative changes (or differences) in posterior, middle, and anterior heights of each vertebral body, an automatic software defines vertebral deformities and derives specific indexes that in case indicate the presence of fractures.

In clinical practice, DXA is the most commonly used and validated method for bone densitometry assessment. Unfortunately, all X-ray based techniques have specific limitations (e.g., use of ionizing radiation, large size of the equipment, high costs, limited availability) that hinder their application for population screenings and primary care diagnosis.

## C. US-based diagnostic techniques

DXA provides a measure of BMD, but it has been demonstrated that other structural aspects of the bone are important in determining fracture risk, such as mechanical features and elastic properties [17], which cannot be assessed using densitometric techniques.

Quantitative ultrasound (QUS) techniques for bone structure investigations have been introduced to obtain useful

information regarding the different resistance to loading of the bone tissue in dependence on the trabecular orientation [18]. The usefulness of QUS has been confirmed in predicting osteoporotic fractures of the calcaneus, the distal metaphysis of the phalanx, the radius and the tibia, particularly in elderly women. On the other hand, the effectiveness of these methods in predicting hip fractures resulted inadequate [19].

Actually, commercially-available ultrasonic devices have several advantages: they are much faster, easier to use and more portable than DXA and they are also cheap and radiation-free. However, these techniques have significant limitations, mainly related to their inapplicability on principal anatomical reference sites and poor correlation with DXA [20].

Recently, new QUS techniques to assess the femur and the spine have been also developed. *In vitro* studies have shown a high correlation between QUS measurements and BMD in human femur cadaver specimens [21,22]. Moreover, a QUS device for *in vivo* measurements at the proximal femur has been developed by Barkmann *et al* [23]. This prototype utilizes ultrasonic waves in transmission by using two US transducers that are able to transmit and receive ultrasonic waves. Obtained measurements show a significant correlations with total hip BMD measured by DXA, with  $R^2$  up to 0.72. The main limitation of this study is represented by the restricted sample size. Moreover, for clinical application the device should be smaller and less expensive [23].

To date, only one *in vivo* QUS-based method for measurements at lumbar spine was published [24]: a commercial sonography scanner was used to measure backscattered signals from the lumbar vertebrae. However, the number of subjects was very small (nine), and correlations with BMD were moderate [24].

Currently, the US assessment of osteoporosis is used only as a pre-screening tool, requiring a subsequent diagnosis confirmation by a DXA evaluation.

In this context, our group has developed a new US-based method for osteoporosis diagnosis on the anatomical reference sites based on the exploitation of the radiofrequency (RF) signals acquired during an echographic scan. The innovative RF signal analysis is able to investigate the internal structure of the target bone through an integrate processing including the automatic segmentation of the echographic images and the analytical comparison with reference spectral models [25].

The effectiveness of this technique in osteoporosis diagnosis and fracture risk prediction has been preliminary demonstrated through a clinical validation, as illustrated below.

## 2. MATERIALS AND METHODS

A clinical study was conducted at the Operative Unit of Rheumatology of "Galateo" Hospital (San Cesario di Lecce, Lecce, Italy) with the following two objectives:

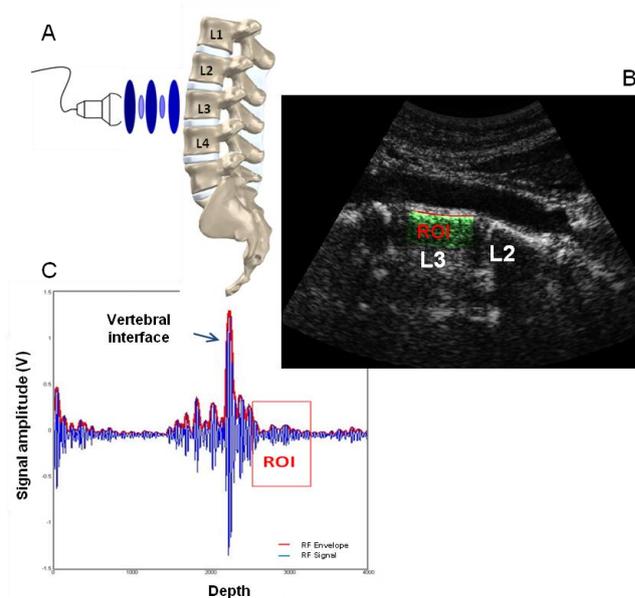
1) to test the diagnostic accuracy of a new custom-developed US-based method to perform spinal densitometry without employing X-rays on a cohort of women in the age

range 45-65 years and with body mass index (BMI) < 25 kg/m<sup>2</sup>, (women with these two characteristics represent the majority of patients that are referred for a spinal DXA [26-30]);

2) to evaluate the performance of this innovative US-based technique for the prediction of osteoporotic fracture risk. For this second aim, 84 female patients (50-80 years; BMI  $\leq$  30 kg/m<sup>2</sup>) were enrolled, 40 with a recent non-vertebral fragility fracture and 44 controls without fracture history.

Medical prescription for a spinal DXA and signed informed consent were required in both cases.

All the patients underwent two examinations: a conventional spinal DXA (Hologic Discovery W scanner, Hologic, Waltham, MA, USA) and an abdominal US scan of lumbar vertebrae, which was performed through a custom echographic device developed in Lecce (Italy) within the ECHOLIGHT Project through a collaboration between CNR-IFC and Echolight srl, equipped with a convex transducer operating at 3.5 MHz. US data were analyzed by an innovative algorithm that processed both echographic images and "raw" RF signals (Fig. 1).



**Figure 1.** Basic principle of the developed US-method: starting from an US scan of the lumbar spine (A), both the echographic images (B) and the corresponding "raw" RF signals (C) are processed by the innovative algorithm that automatically detects the region of interest (ROI).

This algorithm performed a series of spectral and statistical analyses providing a final output represented by two parameters: BMD, as well as DXA, and a new diagnostic parameter named Fragility Score (F.S.).

In the first case, BMD obtained by US analysis was evaluated through a direct comparison with corresponding DXA output. While in the case of F.S., the degree of bone fragility is obtained 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).

### 3. RESULTS AND DISCUSSION

#### A. Accuracy in osteoporosis diagnosis

In order to test the diagnostic accuracy of the developed US-based method, each enrolled patient of the first cohort was classified as osteoporotic, osteopenic or healthy according the US-estimated BMD. Each diagnosis was considered “correct” if the relative patient received the same classification from DXA. This happened in 84.9% of the cases. In particular, for each considered 5-year age interval, diagnostic accuracy was in the range 74.1%-90.5% with the maximum in correspondence of the youngest patients (45-50 years) and the minimum in correspondence of the oldest ones (60-65 years) (Table I).

For patients in the same age range, correlation between DXA-measured BMD and US-estimated BMD was also evaluated through Pearson coefficient ( $r$ ): the best correlation ( $r=0.84$ ) was in the age range 45-50 years (Table I), qualitatively reflecting the observed diagnostic accuracy profile.

**Table I.** Diagnostic agreement between US and DXA.

AGE RANGE	N° of patients	US vs DXA	
		Overlapping diagnosis	Correlation coefficient for BMD ( $r$ )
45-50	42	90.5%	0.84
50-55	109	87.2%	0.73
55-60	114	88.6%	0.68
60-65	85	74.1%	0.55
<b>Total</b>	<b>350</b>	<b>84.9%</b>	<b>0.69</b>

The obtained percentage of “correct diagnoses” (84.9%) indicated a good accuracy for the presented US method of osteoporosis diagnosis. Furthermore, it is interesting to observe that maximum agreement between US and DXA diagnoses (90.5%) and the best correlation between US and DXA BMD ( $r=0.84$ ) were found for the youngest considered patients (45-50 years; see Table I). This emphasizes the potential application of the proposed technique for population mass screenings on young individuals.

#### B. Prediction of fracture risk

The performance of the developed technique for the prediction of fracture risk was evaluated in the second group of patients by measuring F.S. for fractured and not-fractured women and comparing this value with DXA discrimination power. The diagnostic parameters derived through both the systems discriminated significantly between the two subgroups of patients: F.S. values found in the fractured patients ( $59.8 \pm 16.5$ ) were significantly higher than the corresponding values found in the control group ( $45.3 \pm 9.7$ ,  $p<0.001$ ) and BMD values of the fractured group ( $0.837 \pm 0.141$  g/cm<sup>2</sup>) were significantly lower than the corresponding values found in non-fractured women ( $0.989 \pm 0.156$  g/cm<sup>2</sup>,  $p<0.001$ ) (Table II).

**Table II.** Comparison between fracture risk assessment derived from US-method (F.S.) and DXA.

PATIENT GROUP	F.S. [adim.]	BMD [g/cm <sup>2</sup> ]	$p$
<b>Fractured</b>	$59.8 \pm 16.5$	$0.837 \pm 0.141$	$p<0.001$
<b>Control</b>	$45.3 \pm 9.7$	$0.989 \pm 0.156$	$p<0.001$

Obtained results demonstrated the good performance of the proposed US approach in the discrimination between fractured and non-fractured patients. The great potential of the method is represented by the direct applicability on vertebrae, since the spine is one of the reference regions for BMD measurements for fracture risk prediction. The high correlation of F.S. to the skeletal fragility and, consequently, to the fracture risk is probably attributable to the accurate RF signal analysis, able to determine the internal characteristics of the investigated bones. On these bases, F.S. can be assumed as a quantitative diagnostic parameter indicating bone quality. Therefore, the proposed US-method has the potential to become an innovative tool for the estimation of osteoporotic fracture risk through early identification of frail patients.

### 4. CONCLUSIONS

Osteoporosis has a significant impact on public health through the increased rates of morbidity, mortality and economic costs associated with fractures. The present work provides data related to epidemiology of osteoporosis, giving special focus on Italy. These data suggest that the frequency of osteoporotic fractures is rising in many countries and especially in Italy due to the increased longevity of the population. In this context, the evaluation of fracture probability is an important component of the management of osteoporotic patients. To this aim, the most common methods for osteoporosis diagnosis and fracture risk assessment are illustrated. In particular, this paper demonstrates the feasibility of a new custom-developed US-based method for osteoporosis assessment that provides information not only related to the mineral content, but also to the structural quality of bone, therefore opening new perspectives regarding direct prediction of fracture risk.

### 5. ACKNOWLEDGEMENTS

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