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IMPLEMENTATION OF A MODEL DATABASE FOR A NOVEL ULTRASONIC APPROACH TO BONE EVALUATION

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Abstract: Osteoporosis is considered as a major public health problem, second only to cardiovascular diseases. The gold standard for its diagnosis is currently represented by dual energy X-ray absorptiometry (DXA), which, however, suffers from some important drawbacks. In order to overcome such limitations, the use of ultrasound (US) techniques has been proposed. In this paper, a novel approach to the diagnosis of osteoporosis through US scans on lumbar spine and proximal femur is described. The approach relies on the estimation of diagnostic parameters by measuring the degree of similarity between the spectra of the raw radiofrequency (RF) echo signals and reference spectral models of osteoporotic or healthy bones. Reference models are representative of the features of either osteoporotic or healthy bone structures and are matched with subject age, sex, ethnic group and body mass index to take into account variations in bone physiological condition and subject anatomy. In this paper, the methods implemented to build the database of reference models and to estimate diagnostic parameters are presented. The performance of the approach was assessed on a total of 145 Caucasian underweight and normal-weighted women with age in the range from 46 to 55. Performance was assessed through direct comparison with DXA results. The obtained median relative error in the estimation of bone mineral density was as low as 9.1% on women aged 51 to 55 years and 12.0% on women with age in the range from 46 to 50 years. Moreover, for the two groups, the estimation error was lower than 20% for 81% and 78.6% of subjects, respectively. Therefore, the proposed method combines the advantages of the use of US techniques with a remarkable diagnostic accuracy, thus lending itself to the possibility of being used for population mass screenings.

Keywords: osteoporosis; quantitative ultrasound; radiofrequency signal; radiofrequency spectrum analysis.

1. INTRODUCTION

Osteoporosis is considered as a major public health problem, being associated to significant morbidity, mortality and costs, mainly related to osteoporotic fractures. Osteoporosis is thought to affect over 75 million people in Western countries, with an estimated incidence of 10 million new fragility fractures per year worldwide [1]. According to the World Health Organization (WHO), osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [2]. Common sites for osteoporotic fractures are spine, hip, distal forearm and proximal humerus. Fractures in these sites cause pain, deformity, immobility, and difficulty to walk, thus resulting in a significant decay of patients' quality of life. Total direct costs of osteoporosis and related fractures in European countries in 2010 were estimated to amount to € 38.7 billion [2]. These medical expenditures are expected to double by the year 2050 based on demographic projections [1]. Hence, osteoporosis and its complications represent a challenge for health professionals. Much research effort has been put in developing new tools for early osteoporosis diagnosis and deriving prognostic information on the risk of fractures by characterizing skeletal structure.

Currently, the clinical diagnosis of osteoporosis is based on the quantification of bone mineral density (BMD) of spine, proximal femur and, more rarely, peripheral sites, through dual energy X-ray absorptiometry (DXA) [3]. The BMD is the amount of bone mass per unit area (measured in g/cm^2), and is most often described through a T- or Z-score, both of which are expressed as units of standard deviation with respect to a population-averaged mean value [3,4]. The major drawbacks of the use of DXA are ionizing radiation exposure, high costs and the need for specialized personnel. Moreover, the use of BMD as a diagnostic tool is susceptible to a low predictive value on patients' fracture risk. This lack of sensitivity is probably due to the partial information that BMD provides on cancellous bone characteristics, assessing exclusively the mineral quantity. Other factors, such as geometrical characteristics of trabecular microstructure and tissue-intrinsic material properties, which are not encompassed by BMD, may contribute in determining bone strength and its resistance to fracture [5].

In order to overcome the limitations of DXA, non-invasive devices based on quantitative ultrasound (QUS) measurements have been proposed to diagnose osteoporosis and predict the risk of future fractures [4,5]. The main advantage of QUS methods is the absence of ionizing radiation exposure. Moreover, ultrasound (US) devices are portable, have reduced costs, and do not require certified

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operators. Further, apart from osteoporosis, other bone pathological conditions may benefit from US measurements. Indeed, US is appropriate to probe bone biomechanical strength, since US wave characteristics are closely linked to the material and structural properties of the propagation medium [5]. Currently, clinical applications of QUS refer only to peripheral skeletal sites. However, the most relevant sites are the lumbar spine and the proximal femur, since these are the sites experiencing the most severe fractures. Recently, novel QUS techniques to assess femur and spine have been developed [4,6,7]. In particular, an innovative approach to the diagnosis of osteoporosis on central skeletal sites has been developed by our research group [8]. The diagnostic parameters (BMD, T-score and Z-score) are derived from an US scan of either lumbar spine or proximal femur. The approach relies on advanced signal and image processing techniques which are *jointly* applied to both echographic images and raw backscattered radiofrequency (RF) signals. Reference RF spectral models are built to be representative of the features of either osteoporotic or healthy bone structures. They are generated on a training set of RF signals recorded on subjects that were classified as osteoporotic or healthy by preceding DXA examination. Then, the reference models are used to diagnose osteoporosis on subjects whose DXA diagnosis is unknown. Diagnostic parameters are estimated by comparing the spectra of the acquired RF signals to such reference models. Preliminary results have shown that the proposed approach is able to identify osteoporotic patients, accurately estimating diagnostic parameters. Additionally, it could also provide further information including a qualitative characterization of the bone tissue.

In this paper the rationale behind the innovative proposed approach is illustrated, giving special focus to the techniques implemented to build the database of reference osteoporotic and healthy spectral models.

2. THE APPROACH

As highlighted in the previous section, the proposed approach relies on the joint acquisition and processing of echographic images and RF signals from US scans of lumbar vertebrae (from L1 to L4) and proximal femur. Echographic images are processed to automatically detect the regions of interest (ROIs), i.e., matrices of the RF signal corresponding to the echoes of the detected bone structures. Such matrices have T rows and L columns, where L identifies the number of scanning lines crossing the detected bone surface and T is related to the thickness of the bone tissue under investigation. ROIs are typically about 10 mm thick and include exclusively bone structures. Diagnostic parameters (BMD, T-score and Z-score) are then estimated after proper processing of the ROI RF signals involving a comparison with the reference models.

Reference models are created from a training set that includes RF data acquired on subjects whose BMD was known from a DXA investigation performed in the close proximity of the US scan. The term *reference model* refers to a curve encompassing the spectral characteristics distinctive of RF signals of either osteoporotic or healthy subjects. Reference models vary with subject age, sex, ethnic group and body mass index (BMI), in order to account for variations in bone physiological condition and subject anatomy. Regarding BMI, different reference models are generated for underweight and normal-weighted (BMI < 25 kg/m^2), overweight (25 kg/m^2 < BMI < 30 kg/m^2), and obese (BMI > 30 kg/m^2) subjects. Moreover, different models are created for ages ranging from 26 to 85 years, considering intervals of 5 years, according to the literature [9]. For each class of subjects two reference models are generated, one for osteoporotic features and the other for normal ones. Thus, a database of reference models is generated, collecting models matched with different subjects' characteristics.

A. Generation of reference models

The procedure adopted to build reference models is depicted in Fig. 1.

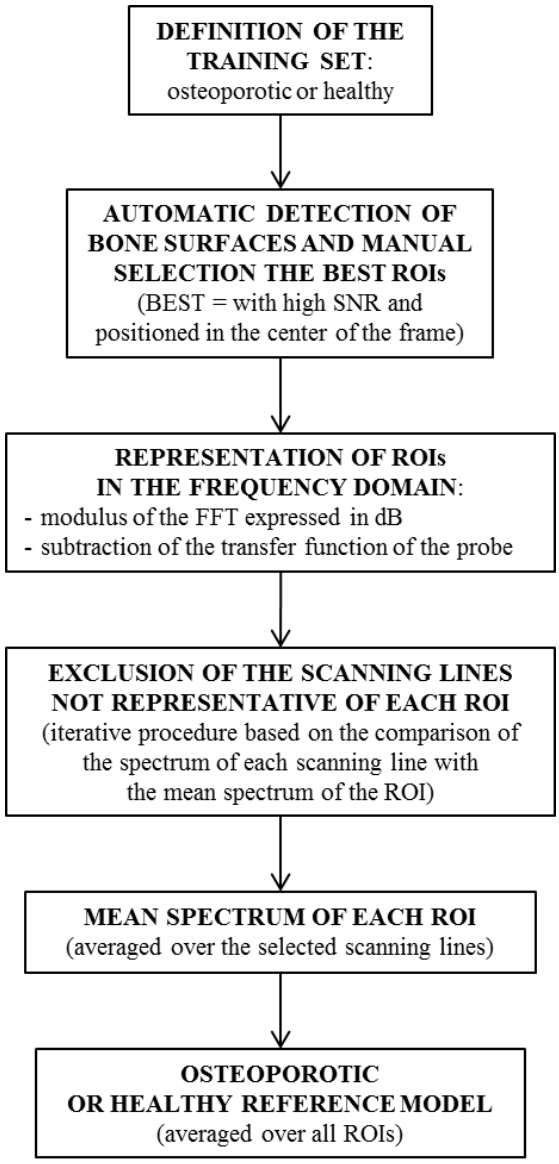

Figure 1. Procedure for the generation of reference spectral models.

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Reference models are typically generated considering three US scans per model. Selection of US scans occurs according to the following criteria. First, only the US scans of those patients that were classified as osteoporotic or healthy by DXA examination are initially selected. Second, each patient used for model generation must have every bone sub-region (i.e., single vertebrae in the case of spine; neck, trochanter and intertrochanter in the case of femur) classified as osteoporotic or healthy by DXA analysis. These two conditions were established to include in the reference models only the distinctive features of osteoporotic and healthy RF signals, thus enhancing the discriminant ability of the approach. Third, US scans with low signal-to-noise ratio (SNR) or from subjects with history of fractures at the considered anatomical site are excluded. Once the training set is established according to the above mentioned criteria, ROIs are automatically detected for each US dataset. Detected ROIs are visually checked by an expert to exclude cases of wrong detection and select the ROIs that are as close as possible to the centre of the image and belong to frames with high SNR. For the sake of notation, let consider that these selection steps (of US datasets and ROIs) lead to a subset of N valid ROIs, each including L_i scanning lines, with $i = 1, \ldots, N$.

Valid ROIs are represented in the frequency domain by computing the modulus (expressed in dB) of the Fast Fourier Transform (FFT) for each line of each ROI. The transfer function of the scanning probe is subtracted to each spectrum, with the purpose of making acquired data independent from the employed echographic probe. Considering the i-th ROI, the mean spectrum, namely $\overline{S}_i$, is computed and is used as initialization step of the following iterative procedure. The correlation coefficient between the mean spectrum $\overline{S}_i$ and the spectrum of each scanning line is computed. Each correlation coefficient, denoted by r_{ij} (the index $i = 1, \ldots, N$ refers to the ROI; the index $j = 1, \ldots, L_i$ refers to the scanning lines in each ROI), is compared to an empirical threshold, denoted by η. If $r_{ij} < \eta$, the j-th scanning line is discarded and the mean spectrum $\overline{S}_i$ of the ROI is updated averaging only the scanning lines such that $r_{ij} > \eta$. For each of the N ROIs, the iterative procedure stops when no scanning lines are discarded, i.e., for all selected lines the following holds: $r_{ij} > \eta$. A ROI is withdrawn if more than 50% of its scanning lines is discarded. Once the iterative procedure has ended for all ROIs, all the resulting mean spectra $\overline{S}_i$ are averaged to build the reference model, which is classified as osteoporotic or healthy according to the DXA diagnosis of the subjects associated to the input US data.

In Fig. 2 an example of reference models (osteoporotic in red continuous line, healthy in black dashed line) for the diagnosis of osteoporosis on lumbar spine is reported. These refer to Caucasian women aged in the range 56-60 with BMI < 25 kg/m^2. Reference models have been generated from RF signals sampled at 40 MHz and spectra have been considered in the band 1–5 MHz. It is worthwhile noting that a more advanced technique for the generation of spectral models is under study. Such technique relies on the automatic identification of the couple models that provide, for each group of subjects, the best estimate of diagnostic parameters on a training set, according to some optimality criteria.

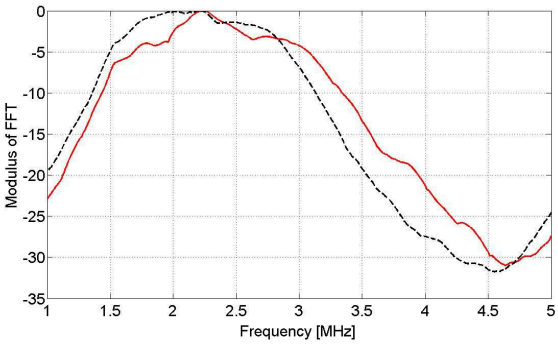

Figure 2. Example of osteoporotic (red continuous line) and healthy (black dashed line) reference models for US scans on spine.

B. Estimation of diagnostic parameters

According to our approach, the diagnostic parameters (BMD, T-score and Z-score) are estimated by comparing the RF spectra extracted from the US dataset of a subject to both the osteoporotic and healthy reference models, matched with respect to anatomical site, age interval, sex, BMI range and ethnic group. The degree of similarity of a RF spectrum to each of the two corresponding reference spectral models is evaluated through the correlation coefficient and is used to diagnose osteoporosis, osteopenia or a normal healthy condition, based on the estimated values of the diagnostic parameters. For each US scan, a combination of the correlation coefficients between the RF spectrum and each of the two reference models is computed. The diagnostic parameters are estimated as a linear function of such a combination. The optimal values of the coefficients of the linear relationship are computed for each group of subjects.

C. Performance assessment

For each US scan, the accuracy of BMD estimate was quantified in terms of relative error, defined as

$$\varepsilon = \frac{\left| BMD_{US} - BMD_{DXA} \right|}{BMD_{DXA}} \cdot 100 \qquad (2)$$

where BMD_{DXA} is the DXA BMD (known a priori) and BMD_{US} is the BMD estimated through the analysis of RF signals, as described in Subsection 2.C.

The performance of the approach was evaluated in terms of accuracy percentage for different values of tolerance of the error $\varepsilon_{\%}$:

$$Acc_{\%}(th) = \frac{1}{N_{TEST}} \sum_{i=1}^{N_{TEST}} 1_{(\varepsilon(i) \le th)}\left(\varepsilon(i)\right) \cdot 100 \qquad (3)$$

where N_{TEST} denotes the number of US scans used to test the approach, $1_E(\cdot)$ is the indicator function of the set E and th is the threshold on error tolerance. In other words, the quantity $Acc_{\%}(th)$ denotes the percentage of subjects such that the

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relative difference between BMD_{US} and BMD_{DXA} is less or equal to *th*.

D. Data collection

US scans of either lumbar spine or proximal femur were performed at the department of Rheumatology of the Galateo Hospital in San Cesario, Lecce (Italy). RF signals were acquired employing a 3.5-MHz convex echographic probe connected to an innovative US device developed in Lecce within the ECHOLIGHT Project through a collaboration between CNR-IFC and Echolight srl. The sampling frequency of RF signals is 40 MHz, with 16-bit resolution. Patients were enrolled according to the following inclusion criteria: Caucasian ethnicity, female sex, age in the range 46-55 years and BMI < 25 kg/m^2. Data were grouped in two classes according to age: a group included N_{TEST} = 42 subjects with age in the range 46-50 years; the other group included N_{TEST} = 103 subjects with age in the range 51-55 years. Different reference models were considered for the two groups of age. Subjects underwent also a DXA examination (Hologic Discovery, Bedford, MA, USA) in the same anatomical sites. The resulting DXA BMD was considered to assess the accuracy of BMD estimated through US according to eq. (2) and eq. (3).

3. RESULTS

Results are summarized in Table I, where the mean m_ε of estimation error ε, its standard deviation, namely σ_ε, and the median error, namely $\tilde{\varepsilon}$, are reported. Moreover, the accuracy for a tolerance on the error of 20%, denoted by $Acc_{\%}(20\%)$, is reported.

The group of subjects with age in the range from 46 to 50 years was characterized by mean BMD_{DXA} = 0.870 ± 0.110 g/cm^2. The mean BMD estimated by the proposed approach for all the subjects in this group was BMD_{US} = 0.868 ± 0.128 g/cm^2, which is quite a good result. With respect to BMD estimation error in Eq. (2), the mean relative error m_ε returned by the proposed approach on BMD estimate was equal to 12.2%, whereas the median error $\tilde{\varepsilon}$ was 12.0%, as shown in Table I. Moreover, for 34 subjects out of 42 (81.0%) the relative error ε in Eq. (2) was lower than 20%.

As regards the group of subjects with age in the range from 51 to 55 years, the mean DXA BMD was BMD_{DXA} = 0.872 ± 0.119 g/cm^2, averaged over all the 103 subjects in the group. Also for these subjects, the proposed approach showed a notable ability to estimate the BMD, since the average BMD estimated was BMD_{US} = 0.872 ± 0.096 g/cm^2. Moreover, the mean relative estimation error m_ε was equal to 9.3% and the median error $\tilde{\varepsilon}$ was 9.1%, as reported in Table I. The estimation error was lower than 20% for 81 subject out of 103 (78.6%), as shown in Table I.

For both groups it is worthwhile noting that the median error, which is a more robust index of centrality being less sensitive of outliers, was quite low. Considering jointly the two groups of subjects, the median error returned by the approach was 9.5%.

Table I. Mean m_ε, standard deviation σ_ε, and median $\tilde{\varepsilon}$ of the BMD estimation error (2) and accuracy $Acc_{\%}(20\%)$ for a tolerance on the error of 20%.

	46-50 yrs BMI < 25 kg/m^2 (N_{TEST} = 42)	**51-55 yrs BMI < 25 kg/m^2 (N_{TEST} = 103)**
m_ε	12.2%	12.0%
σ_ε	8.5%	9.3%
$\tilde{\varepsilon}$	12.0%	9.1%
$Acc_{\%}(20\%)$	81%	78.6%

4. CONCLUSION

In this paper, a novel approach to the diagnosis of osteoporosis through US scans on central skeletal sites was described. The proposed approach relies on the analysis of raw RF echo signals. Diagnostic parameters are estimated by comparing the RF signal with reference spectral models of osteoporotic or healthy bones. The methods developed to build the database of reference models and to derive diagnostic parameters were presented in this paper. The performance of the approach was assessed through comparison with DXA. Obtained results showed that the proposed approach is able to provide an accurate estimate of BMD. In particular, the algorithm returned a median error in BMD estimation as low as 9.1% on women aged 51 to 55 years and 12.0% on women with age in the range from 46 to 50 years. Thus, the adopted method proved to be very promising, since it combines the advantages of the use of US techniques with a remarkable diagnostic accuracy. It has the potential to be used for population mass screenings in order to anticipate the osteoporosis diagnosis.

5. ACKNOWLEDGMENTS

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