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A 3-year follow-up study on bone structure elastic quality

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Abstract. Osteoporosis is called a silent disease because bone fragility manifests itself to the patient only in an advanced state, through fracture and pain. Medical and industry leaders recognize that the current golden standard diagnostic method, densitometry, or Dual Energy X-ray Absorptiometry (DEXA), may not always be sufficient to assess the patient's real risk of fragility fracture [1]. Indeed, pathological alterations affect not only the mineral content (quantity) of the bone, but also its "quality", which can be measured from the elastic properties of the bone internal trabecular structure by means of the Bone Elastic Structure Test, BES TEST®. In this study, the incidence of fragility fractures was assessed after a 3-year follow-up period in the women enrolled for a population study in 2015. The BES TEST® resulted an effective estimator of bone health, and can improve the assessment of the patient's fracture risk map.

Introduction

Osteoporosis is called a silent disease, due to the fact that bone fragility often manifests itself to the patient in an advanced state, through a major fracture (such as that of femur or wrist) or pain due to trabecular micro-fractures (often in the vertebrae).

The current golden standard diagnostic method is the densitometry, or Dual Energy X-ray Absorptiometry (DEXA). The DEXA results are usually expressed in terms of T-score, a statistical value indicating the number of standard deviations below the average value of young Caucasian women. According to WHO [2], there are four general diagnostic categories for women:

• *Normal*. A value of BMD within 1 standard deviation of the young adult reference mean (T-score >= -1).

• *Low bone mass (osteopenia)*. A value of BMD 1 or more standard deviations below the young adult mean, but less than 2.5 standard deviations below this value (-2.5 < T-score < -1).

• *Osteoporosis*. A value of BMD 2.5 or more standard deviations below the young adult mean (T-score <= -2.5).

• *Severe osteoporosis (established osteoporosis)*. A value of BMD 2.5 or more standard deviations below the young adult mean value in the presence of one or more fragility fractures.

However, medical and industry leaders recognize that the DEXA examination may not always be sufficient to assess the patient's real risk of fragility fracture: 62% of fragility fractures that could be prevented fail to be diagnosed in time [1]. Indeed, bone alterations are not usually detected at an early stage by DEXA scans, as they firstly affect the elastic properties of the internal structure of the bone [3]. This translates into a cost of care on health budgets that is far from negligible: in 2010 the EU6 countries (France, Germany, Italy, Spain, Sweden, and UK) spent € 37 billion, and this cost is projected to reach €47 billion by 2030 [4].

The Bone Elastic Structure Test, BES TEST®, is a software medical device for the assessment of the bone micro-architecture elasticity, i.e. its ability to withstand loads. It is registered by the Italian Ministry of Health and has CE mark and ISO 13485 qualification.

The purpose of this study is to investigate the effectiveness of BES TEST® in the identification of patients at risk for incident osteoporotic fractures.

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Methods

BES TEST®

The test is based on an application of the Cell Method, a direct discrete numerical method, effective from the point of view of computation time, memory requirements and accuracy of the results [5, 6]. A radiographic virtual biopsy of the patient, acquired in the proximal phalanges of the non-dominant hand, is converted into a structural model and the response to compressive loads along the orthogonal axes is computed.

The simulation results are synthetized in a numerical score, which combines the elastic response of the reconstructed structure in several directions, purified of the normalized sum of gray tones, indicative of mineralization in the region under examination: the *Bone Structure Index* (*BSI*) summarizes the elastic behavior of the trabecular structure in different directions and, therefore, the ability to withstand the loads of the trabecular part of the bone.

The BES TEST® results are not correlated with the DEXA ones [7], and its precision parameters are in line with the golden standard requirements [8]. The test has shown potential in a variety of fields like rheumatology [9], oncology [10] and nephrology [11], in which clinical trials are currently being carried on. The procedure is schematically represented in Fig.1.

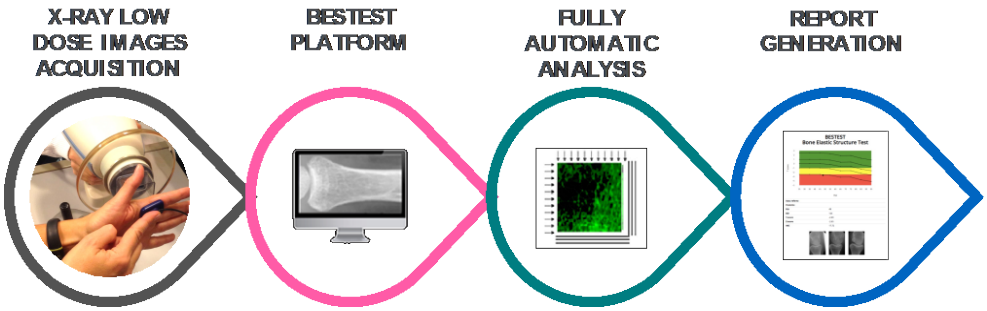

Figure 1. *The BES TEST procedure.*

Analogously to DEXA, the BESTEST results are presented to the doctor also in terms of *BSI_T-score*, which compares the patient's *BSI* with the mean value for young Caucasian women (age 20-45) and measures this difference in number of standard deviations [7].

Given the statistical nature of the T-score parameter, the same guidelines that are normally used in assessing bone density can be used for *BSI_T-score*, with reference to the clinical assessment of bone quality:

- A T *BSI_T-score* = 0 indicates that a patient's *BSI* is equal to the average *BSI* found in young Caucasian women.
- A *BSI_T-score* = -1 or above indicates that a patient's bone quality is normal.
- A T *BSI_T-score* between -1 and -2.5 indicates a first level of bone elasticity deficiency.
- A *BSI_T-score* < -2.5 indicates a second level of bone elastic deficiency.

Population

A population of 351 Caucasian women was enrolled for the BES TEST® population study in 2015 [7], and incidence of fragility fractures has been assessed after a 3-year follow-up period. For the purpose of the present research, two groups were considered (Table1):

- *Non-Fractured*, who had not sustained a fragility fracture in 2015 nor in the following 3 years.
- *Fractured*, who had sustained a fragility fracture at the time of BES TEST® assessment.

The *BSI-Tscore*, *Age,* and the *Bone Mass Index (BMI),* an indirect index of adiposity calculated as the patient's weight in kilograms divided by the square of height in meters, were collected for each subject at the time of the test.

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Table 1. *Population descriptors: Age, BMI and BSI-Tscore Mean (Min – Max) values*

	n	*Age* [years]	*BMI* [kg/m^2]	*BSI-Tscore* [St. Dev.]
Fractured	91	63 (27 – 93)	22.8 (14.7 – 36.3)	- 1.5 (-3.4 – 0.8)
Non-Fractured	75	58 (25 – 84)	23.7 (17.4 – 34.0)	-0.4 (-3.2 – -2.4)

Diagnostic accuracy

True positive (*TP*) is an outcome where the test correctly predicts the positive class. True negative (*TN*), false positive (*FP*) and false negative (*FN*) have analogous definitions.

The *Accuracy* of a diagnostic test is the percentage of correct classifications, giving equal importance to positives and negatives [12]:

$$Accuracy = (TP + TN)/(TP + TN + FP + FN). \quad (1)$$

The *Receiving Operator Characteristic (ROC)* curve is created by plotting at various threshold settings the *True Positives Rate* (*TPR*), or *Sensitivity*, against the *False Positive Rate* (*FPR*), or probability of false alarm, which can be calculated as *(1 − Specificity)*.

Lowering the threshold classifies more items as positive, increasing both *FP* and *TP*. The *Area Under the ROC Curve*, *AUC*, provides an aggregate measure of performance of a diagnostic test across all possible thresholds [13].

Results

Population

The Age distribution of the population is depicted in Fig.1. The *Fractured* group appears to be slightly older than the *Non-Fractured* one (Student's test p =0.00485).

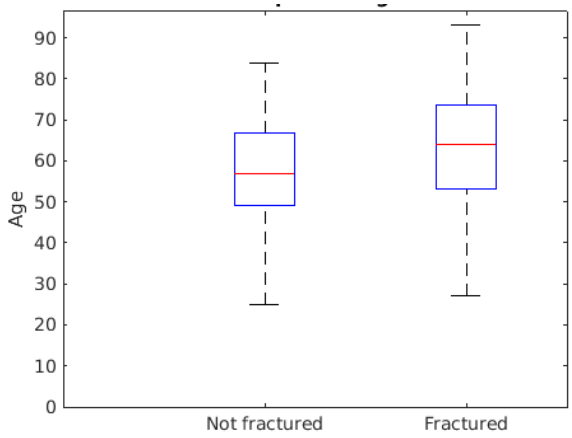

Figure 1. *Box plot of Age distribution.*

The *BMI* distribution for the two groups, classified according to the WHO guidelines, is reported in Table 1. The *BMI* values for the two groups appear to be similar (p = 0.1243).

Table1. *BMI distribution for the two groups, according to the WHO classification.*

BMI	*CLASSIFICATION*	*FRACTURED*	*NON-FRACTURED*
< 18.5	*UNDERWEIGHT*	8%	3%
18.5 – < 25.0	*NORMAL RANGE*	74%	64%
>= 25.0	*OVERWEIGHT*	13%	27%
>= 30.0	*OBESE*	5%	5%

The distribution of *BSI_T-score* in the two groups is shown in Fig.2. The *Non-Fractured* patients are characterized by a median of -0.5 and a first and third quartile of -1.2 and 0.1, respectively, and are very satisfactorily discriminated from the *Fractured* group (p = 3.18e-10).

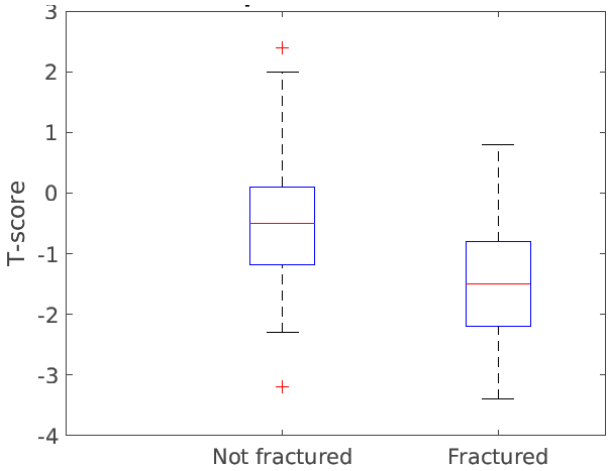

Figure 2. *Box plot of BSI_T-score distribution.*

As shown in Fig.3, no correlation appears to be present between the *BMI* and the *BSI_T-score* values for each of the two groups (R^2 = 0.0032 in the *Fractured* and R^2 = 0.0188 in the *Non-Fractured* group). The fitted ROC curve [14] is plotted in Fig.4, and the *AUC* value is 0.78.

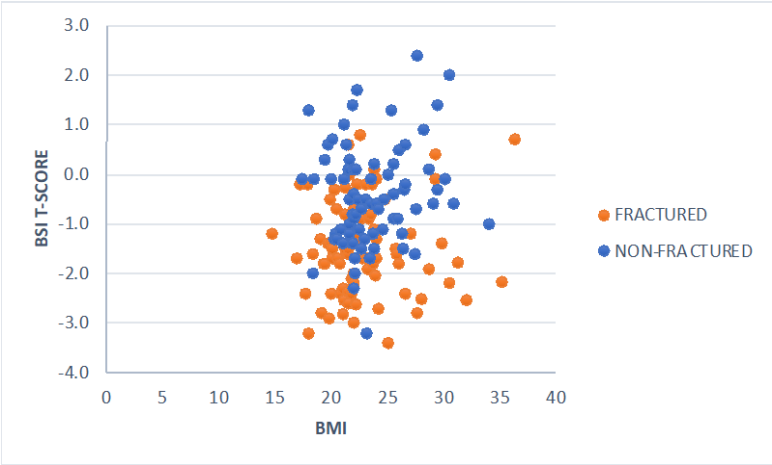

Figure 3. *BSI_T-score vs. BMI distribution in the two groups.*

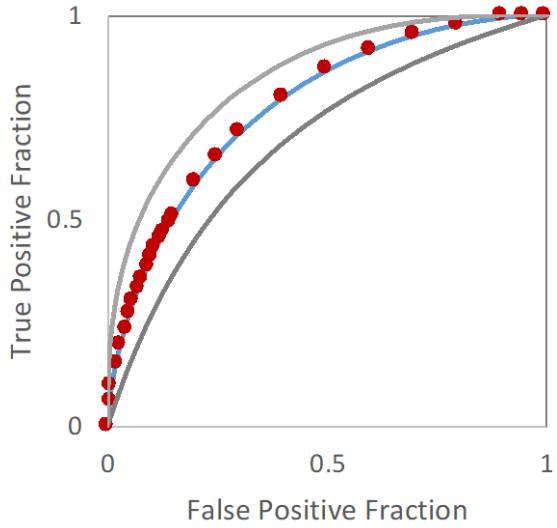

Figure 4. *Red symbols and blue line: Fitted ROC curve for BSI_T-score. Gray lines: 95% confidence interval.*

An optimal threshold value could be identified: the accuracy trend shown in Fig. 5 is characterized by a peak at the *BSI_T-score* = -1.4 cut-off value that maximizes *Accuracy*, corresponding to 78% of correct results, i.e. a diagnostic capacity of the BES TEST® of 0.78. *Accuracy* for the common threshold values of diagnostic significance for fracture risk assessment resulted respectively 53% for a cut-off value of *BSI T-score* =-2.5, and 31% for *BSI T-score* =1.

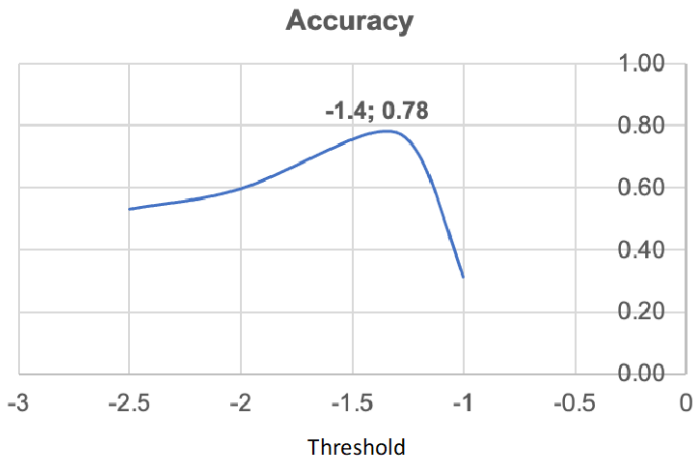

Figure 5. *Accuracy plotted against threshold values.*

Conclusions

The *BSI T-score* resulted an effective predictor for the risk of incident fragility fractures, and an optimal cut-off value for fragility fracture risk was identified.

The results achieved are certainly helpful in the diagnostic and preventive practice: the clinical portrait of a patient who obtained a *BSI T-score* lower than -1.4 should be carefully investigated because there is a high probability of fracturing in the following 3 years.

Given the DEXA reduced ability in assessing the load bearing capability of the internal part of the bone, it appears that BES TEST®, also in association with DEXA, could be helpful in

completing the fracture risk map and reducing the clinical and economic burden of fragility fractures.

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