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¿Puede la prueba BES ayudar a evaluar el riesgo de fracturas por fragilidad en pacientes con una puntuación T de DEXA normal u osteopénica?

CAN BES TEST HELP IN ASSESSING THE RISK OF FRAGILITY FRACTURES IN PATIENTS WITH NORMAL OR OSTEOPENIC DEXA T-SCORE? HOW TO COMPARE DEXA AND BES TEST IN OSTEOPENIC PATIENTS WITH OR WITHOUT RECENT FRAGILITY FRACTURES

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Can the BES TEST help in assessing the risk of fragility fractures in patients with normal or osteopenic DEXA T-score?

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ABSTRACT

Introduction: osteoporosis is characterized by bone mass reduction and bone micro-architecture damage leading to bone fragility. Dual-X-ray absorptiometry (DEXA), which measures the bone mineral density (BMD), is considered the gold standard for the diagnosis of osteoporosis/ osteopenia. However, BMD is only one among several risk factors for fracture. Consequently, DEXA should be associated with a map of fracture risk (FRAX, DeFRA or FRA-HS). Therefore, the development of other tests capable of measuring the trabecular structure properties (quality), instead of just density of bone are needed.

Methods: the Bone Elastic Structure Test (BES TEST) is a measure of bone elastic response to loads, a CE marked, registered, software. medical device, based on an internationally patented method that uses high definition digital radiographs in the proximal epiphysis of three fingers to investigate the biomechanical functionality of the trabecular structure, in terms of its contribution to bone strength.

Results: the main objective of the study is to assess the reliability and the performance of BES TEST in patients affected by fragility fracture with normal or osteopenic DEXA T-score. Previous data suggest that BES TEST could be a helpful complementary test for completing the fracture risk assessment. Therefore, we conducted a RCT in which 50 female patients, divided in two groups (25 non fractured and 25 recently fractured), underwent a basal lumbar, femoral and femoral-neck DEXA and a basal BES TEST, both of which were repeated after 18-24 months with the addition of spine morphometry.

Conclusion: preliminary data confirm the reliability and reproducibility of both DEXA T-score and BSI T-score. The expected result is the confirmation that BSI, associated to DEXA and FRAX-score or DeFra-score can help in assessing the risk of fragility fractures.

Keywords: BES TEST. Osteoporosis. Osteopenia. Fragility fractures. DEXA.

INTRODUCTION

Osteoporosis (OP) is a condition characterized by bone mass reduction and bone micro-architecture damage. This process leads to bone fragility with consequent high probability of fractures. Dual-X-ray absorptiometry (DEXA), which measures the bone mineral density (BMD), is considered the gold standard for the diagnosis of osteoporosis/ osteopenia. DEXA expresses results in terms of T-score, a statistical value indicating the number of standard deviations below the average of young Caucasian subjects. BMD is commonly measured at lumbar spine, left femur and left femoral neck. Wrist BMD can also be measured when both femurs are not available (because of bilateral prosthesis), while DEXA total body scan is, at the moment, limited to the study of sarcopenia by the measure of muscle mass and fat body mass (1,2).

According with the WHO criteria, four different degrees of bone mineral density can be defined: a) Normal: when the value of BMD results within 1 standard deviation of T-score (T-score ≤ 1); b) Osteopenia: when the value of BMD is between 1 and 2.5 standard deviations below the young adult mean; c) Osteoporosis: when the value of BMD is 2.5 standard deviations below the young adult mean; and d) Severe osteoporosis (or established osteoporosis) when the BMD value is 2.5 standard deviation below the young adult mean and one or more fragility fractures have occurred. Fragility fractures are the consequence of a low-energy trauma, following WHO criteria defined as a fall from one's own height (1,3,4). The correct densitometric diagnosis is due to the lowest T-score found in spine or femur or femoral neck (5,6). However, it is clear that BMD is only one among several risk factors for fracture. For this reason, DEXA should be associated with a map of fracture risk.

FRAX (Fracture Risk Assessment Tool, developed in 2008 by the Centre for Metabolic Bone Diseases of the University of Sheffield. The Italian version was revised in 2013) (7), DeFRA (a software developed by the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases in 2012 and recently revised) and FRA-HS (developed by the Italian Society for General Practitioners

in 2017) (8,9) are currently used alongside DEXA to measure the risk of major fractures. These algorithms are designed to predict the 10-years risk of fracture, based on the most common and severe risk factors for fragility fractures: spine and femoral BMD, smoking, daily alcohol intake (more than 3 units), previous fragility fractures, use of corticosteroids (daily dose), arthritis or chronic inflammatory connective tissues diseases, age at menopause, thinness (when calculated BMI is < 18.5), family history of major osteoporotic fractures. Clearly DEXA can only evaluate BMD, but not bone quality, therefore alterations in the bone micro-architecture are probably the reason of the high number of fragility fractures in patients with osteopenia (10,11).

Given that DEXA alone cannot be a reliable, predictive instrument to avoid fragility fractures, the development of other tests capable of measuring the trabecular structure properties (quality), instead of just density of bone are needed.

TBS (Trabecular Bone Score) is a textural index of bone microarchitecture derived from the DEXA image. It analyses the grey-level variations in the lumbar spine, providing information about the microarchitecture of the trabecular bone (12).

However, TBS is under discussion because of its limitations because it can be applied only to spine DEXA images which are by itself limited because of the common presence of osteophytes and of aortic calcifications (13,14).

Conversely, the Bone Elastic Structure Test (BES TEST) is a measure of bone elastic response to loads. Based on a directly discrete numerical approach (15) the BES TEST analyses low-dose (< 0.005 mSv) planar Rx projection of the proximal epiphysis of the first phalanx in the hand to perform a non-invasive biomechanical evaluation of trabecular bone microarchitecture, by means of engineering simulations of load application, which can quantify the pathological alterations in bone microarchitecture (16). BES TEST is a CE marked, registered, software. medical device, based on an internationally patented method. The BES TEST software processes the radiographic images, transforming them into numerical structural models that are employed to simulate the application of compression loads using the Cell Method approach, highly effective in terms of robustness, computation time, memory requirements, and accuracy of the results (17,18).

The outcomes of the simulations are combined into an index, the Bone Structure Index (BSI), which denotes the trabecular bone structure capability of absorbing loads (19).

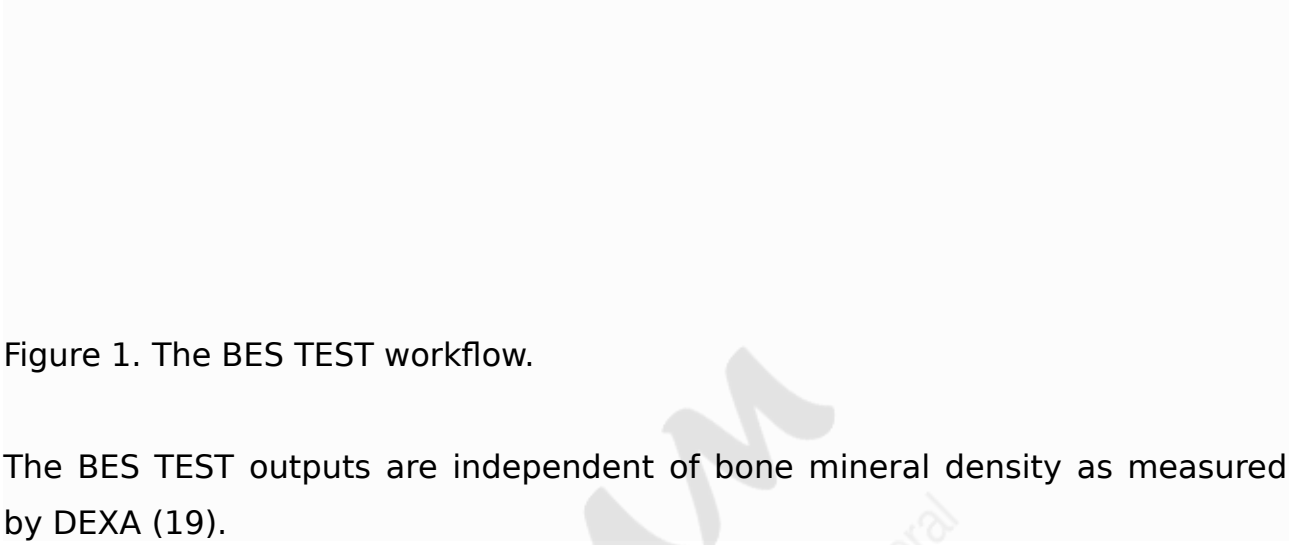

Figure 1. The BES TEST workflow.

The BES TEST outputs are independent of bone mineral density as measured by DEXA (19).

Due to the clear evidence of trabecular structure visible in normal plain radiographs, the proximal phalanges of the second, third and fourth fingers are used, as the best evaluable regions for the test (19). The outcomes obtained with BES TEST are then expressed as BSI T-score. As with DEXA, these data are obtained by patients BSI using the average BSI of young Caucasian women aged 22-45 and evaluating the difference in number of SD (20).

Previous experiences suggest that BSI-T-score is able to predict the risk of fractures in the following 3 years and that a value under -1,4 could be the cutoff (19).

Moreover, there is no correlation between BSI and DEXA T-score (20).

For these reasons we performed a RCT to assess the reliability of BES TEST in patients affected by fragility fracture with normal or osteopenic DEXA T-score.

PARTICIPANTS, STUDY DESIGN, MATERIAL AND METHODS

We conducted a trial, approved by the Ethics Committee of Istituti Clinici Scientifici Maugeri, IRCCS, in Pavia (EC2387, Feb. 04 2020). The Helsinki Declaration was followed. Fifty consecutive female outpatients were enrolled and divided into two groups: group A was composed by 25 female patients with no history of recent fragility fractures; group B was composed by 25 female

patients with a recent fragility fracture. Sample size was also approved by the same ethics committee on the base of previous data. All patients underwent a basal lumbar, femoral and femoral-neck DEXA (with densitometer Hologic qdr 4500) and a basal BES TEST, both of which were repeated after 18-24 months with the addition of spine morphometry.

BES TEST performance characteristics: CV intra-operator = 0.06; 95 % CI ± 8 BSI; CV inter-operator = 0.11; 95 % CI = ±10.8 BSI (21), in line with current OP diagnostic standard.

Inclusion criteria were as follows: female patients with lumbar and femoral DEXA T-score < -2,5 SD, aged between 40 and 75 years.

Exclusion criteria were: patients on medication with glucocorticoids or with drugs for osteoporosis.

The trial began in 2020, but it was interrupted due to the COVID pandemic, resulting in 3 patients dropping out. At the moment 44 patients completed the study and the follow-up.

Statistical analysis

A statistical comparison between the groups was conducted using unpaired *t*-Student tests, with $p < 0.05$ considered statistically significant**.**

Currently we are collecting data and studying the final patients. Furthermore, we are contacting all patients to update their situation. We are particularly interested in finding out if a) they had a new fragility fracture in the following year after the second round of BES TEST and DEXA b) they are currently treated with any drugs for osteoporosis c) new facture risks have been identified, d) they have fallen, e) they had been studied with a new DEXA scan and morphometry or other relevant blood or urine tests.

RESULTS: Preliminary data show that at baseline and after 18-24 months no significant difference **was found in** DEXA T-scores between the F and NF groups ($p = 0.09$), while the BSI T-score was significantly different between the F and NF groups ($p = 0.0001$), no significant differences between femoral neck DEXA T-score at baseline and after 18-24 months, no significant differences between femoral DEXA T-score at baseline and after 18-24 months, no

significant difference between spine DEXA T-score at baseline and after 18-24 months.

In group B (fractured) there are no significant differences between BSI-T score at baseline and after 18-24 months, no significant differences between femoral neck DEXA T-score at baseline and after 18-24 months, no significant differences between femoral DEXA T-score at baseline and after 18-24 months, no significant differences between spine DEXA T-score at baseline and after 18-24 months.

DISCUSSION

The BES TEST does not measure bone quantity but evaluates the elastic structural integrity and biomechanical competence of bone, offering insight into functional bone strength. By focusing on trabecular bone elasticity, bone alterations can be monitored in weeks, BES TEST complements densitometry as a low-dose monitoring tool for bone follow-up (20), in rheumatology (22), oncology (23), nephrology (24) and rare diseases (25).

Evidence from a small study applying the test to both hand and foot showed similar trends across anatomical sites, indicating sensitivity to whole-body physiological changes and supporting the idea that skeletal fragility reflects a systemic condition rather than a site-specific one (La valutazione della bone elastic structure (Bestest™) in segmenti scheletrici sottoposti a diverso carico- oral presentation at SIOMMMS National conference 2022, abstract not published).

This concept is further supported by literature showing strong correlations between hand bone measurements and fracture-relevant skeletal sites: bone mineral density assessed at peripheral hand bones correlates with femoral neck DXA values, and quantitative ultrasound measurements at the finger phalanges can effectively assess fracture risk and detect age-related bone changes with diagnostic sensitivity comparable to lumbar densitometry (26-28).

In a previous experience (20) 351 consecutive Caucasian women were enrolled for a population study and they were contacted after a 3-year follow-up period to study the incidence of fragility fractures, 166 out of 351 did answer to the contact.

Ninety-one out of 351 were fractured, while 75 were non-fractured. The fractured patients were slightly older than the non-fractured (Student's test $p = 0.00485$). BMI (bone mass index) of both groups was similar ($p = 0.1243$) while no correlation between BMI and BSI-T-score was found in both group.

The average BSI T-score was -1,5 (-3,4-0,8) in fractured patients and -0,4 (-3,2—2,4) in non-fractured patients. These data suggested that BSI T-score can predict the risk of fractures in the following 3 years and that the patients with a value under -1,4 should be carefully investigated (20).

In 2020, we published the first pilot study comparing BES TEST to DEXA. We enrolled 9 patients under the age of 74 years, with a recent fragility fracture despite a normal or osteopenic femoral neck T-score at DEXA evaluation (group A). Contrary group B comprised by volunteer female patients who had undergone DEXA and BESTEST evaluations in 2015 during the Trieste NEXT 2015 event (Ethics Committee of the University of Trieste approval No 66 of 11.11.2015). All patients of both groups were analysed following the cited BES TEST method and results were presented as mean±SD. A comparison between the groups was performed using an unpaired *t*-test. A p value < 0.05 was considered statistically significant.

In that second paper (22) we confirmed that there is no correlation between BSI and DEXA T-score. Moreover, the fractured patients showed a BSI T-score significantly lower than DEXA femoral neck T-score. In contrast the patients non-fractured had a normal BSI T-score and an osteopenic DEXA femoral neck T-score (22). Indeed, the risk of fracture in those patients can be better evaluated by adding FRAX or DeFRA algorithms (28).

CONCLUSION

The clinical recommendations at time, suggest the treatments also of non-fractured osteoporotic patients only if FRAX o DeFRA show an important risk of fracture in order to avoid overtreatment and the consequent increase of possible side effects (29,30).

As a high number of fragility fractures occur in patients with normal or osteopenic DEXA T-score, the reason is probably the limited ability of DEXA to distinguish and measure bone quality. This phenomenon is often evident in patients affected by secondary osteoporosis (for instance: patients under

chronic treatment with glucocorticoids). Preliminary data of our trial confirm the reliability and reproducibility of both DEXA T-score and BSI *t*-score. The expected result is the confirmation that BSI, associated to DEXA and FRAX-score or DeFra-score can help in assessing the risk of fragility fractures.
BES TEST should be better studied to demonstrate a quick change in course of pharmacological therapy, overall in chronic inflammatory diseases as rheumatoid arthritis. In this case the addition of inflammation and glucocorticoid therapy can quickly induce bone fragility that DEXA alone is not able to show. Therefore BES TEST could be significantly added: it could help in tailoring pharmacological treatments and, if needed, rehabilitation exercises to prevent the risk of falls.

Limitations

The small simple size is a clear limitation. A further trial involving a greater number of patients is needed.

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