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Added value of trabecular bone score to bone mineral density for prediction of osteoporotic fractures in postmenopausal women: The OPUS study

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ABSTRACT

The objective of this study was to consider whether trabecular bone score (TBS) improves on areal bone mineral density (aBMD) measurement alone for the prediction of incident fractures in postmenopausal women.
Patients and methods: The OPUS study was conducted in ambulatory European women aged above 55 years, recruited in 5 centers followed over 6 years. For the assessment of the performance of TBS, baseline Hologic scans from 3 centers (Kiel, Paris and Sheffield) were available. Follow-up for incident fractures was available for 1007 women (mean age 65.9 ± 6.9 years). We compared the performance of TBS, aBMD, and their combination, by using net reclassification improvement (NRI, primary analysis) and receiver operator characteristic (ROC) c-statistical analysis with ORs and areas under the curves (AUCs) (secondary analyses).
Results: 82 (8.1%) subjects with incident clinical osteoporotic fractures, and 46 (4.6%) with incident radiographic vertebral fractures were recorded over 6 years. Performance of TBS was significantly better than lumbar spine (LS) aBMD for the prediction of incident clinical osteoporotic fractures (NRI = 16.3%, p = 0.007). For radiographic vertebral fractures, TBS and LS aBMD had similar predictive power but the combination of TBS and LS aBMD increased the performance over LS aBMD alone (NRI = 8.6%, p = 0.046) but the prediction is similar to hip and femoral neck aBMD. In non osteoporotic women, TBS predicted incident fragility fractures similarly to LS aBMD.
Conclusions: This prospective study shows that in general population, TBS is a useful tool to improve the performance of lumbar spine aBMD for vertebral osteoporotic fractures.

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture. Whereas low areal bone mineral density (aBMD) is among the strongest risk factors for fracture, a number of clinical studies have demonstrated its limitations in the assessment of the fracture risk. Bone strength does not only depend on the amount of bone mineral in the bone; it also depends on the structural characteristics of the skeleton, including bone size, shape, micro architecture, collagen and crystal properties. Different non-invasive techniques (quantitative computed tomography (p-QCT, QCT) and magnetic resonance imaging (MRI)) have been developed for bone micro-architecture assessment [1–6], to improve the detection of patients at high risk. These techniques remain impractical for routine clinical practice due to high costs and lack of availability.

The trabecular bone score (TBS) is derived from the texture of the DXA image and has been shown to be related to bone mass distribution and fracture risk [7]. It is a texture parameter seemingly recording pixel by gray-level variations in DXA images, obtained after reanalyzing the DXA scan. It can be compared directly with aBMD since both parameters evaluate the same bone region [8,9]. Previous studies in human cadavers demonstrate that TBS positively correlates with 3D bone micro-architecture parameters (in cases with physiological distribution), such as connectivity density and trabecular number, and negatively with trabecular separation [8,10]. In clinical practice, low TBS scores indicate lower bone strength and greater fracture susceptibility. Cross-sectional studies showed that TBS was lower in post-menopausal women with previous osteoporotic fracture compared to those without fracture [11], and was lower in women with fractures irrespective of whether their BMD met the criteria for osteoporosis or osteopenia [12,13]. In these studies, TBS brought an additive value for the discrimination of patients with vertebral fracture when it was combined with lumbar spine aBMD [12,13]. Two retrospective historical cohort studies showed that lumbar

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spine TBS and aBMD predicted major osteoporotic fractures similarly; and that the combination of lumbar spine TBS and aBMD improves fracture risk prediction in non-osteoporotic women [14,15]. Other studies documented the added value of TBS in evaluating fracture risk in patients with secondary causes of osteoporosis (primary hyperparathyroidism and diabetes) [16,17]. Few studies evaluated the ability of TBS to predict incident radiographic vertebral fracture in postmenopausal women. Moreover studies usually tested the performance of TBS using the area under the ROC curve. However, ROC curves should be used for the diagnosis criteria and are not appropriate to judge performance of tools [18]. Reassignment or reclassification analysis has been proposed [19,20].

The objective of this prospective long term study was to analyze how well TBS improves on aBMD measurements alone to predict the risk of incident fractures and radiographic vertebral fractures, using reclassification analysis in a cohort of postmenopausal women.

Patients and methods

Patients

The Osteoporosis and Ultrasound Study (OPUS) is a multicenter prospective study of risk factors for fractures in post menopausal women. Both the rationale and the study design have been described in detail elsewhere [21].

The initial study population consisted of 2409 ambulatory European women aged above 50 years, recruited in 5 European centers from random population samples between 1999 and 2001, and followed for 6 years. This analysis excluded women who had disorders precluding ultrasound and bone mineral density measurements, and also general and cognitive inability that precluded completing questionnaire. Human subject review or ethics committees at each participating institution reviewed and approved the study.

For the assessment of the predictive value of TBS, baseline Hologic scans from 3 centers (Kiel, Paris and Sheffield) were only available, as TBS was not validated on Lunar Expert technology at the time of this study (these devices were used in the 2 other centers).

Assessment of risk factors

Questionnaire and examinations

Each participant filled in a questionnaire, which was a modified version of the EVOS (European Vertebral Osteoporosis Study) risk factor questionnaire, and validated in English, German and French. Weight and height were measured at baseline, and body mass index (BMI, kg/m^2) was calculated. Prior non-vertebral fractures were those that occurred after the age of 50 years and were identified by self-reporting from the baseline questionnaire.

Bone mineral density

aBMD of the lumbar spine and of the proximal femur (hip and femoral neck FN) was measured by DXA in postero-anterior projection (Hologic QDR-4500; Hologic, Bedford, MA, USA) using standardized procedures and centralized quality control.

Trabecular bone score (TBS)

All TBS measurements were performed in the Bone Diseases Unit at the Cochin Hospital (Paris, France). TBS (TBS iNsight® Software version 1.8, Med-Imaps, Pessac, France) was obtained after re-analysis of DXA lumbar spine (L1–L4) scans. In the current analysis, we used a research version of the commercialized TBS iNsight software which allows for large batched analyses from a work station. The study was conducted without knowledge of incident fractures and independently of the manufacturer. The software uses the AP spine raw image(s) from the densitometer, including the BMD region of interest (ROI) and edge detection, so that the TBS calculation is performed over exactly the same ROI as the BMD measurement. For each region of measurement, TBS was evaluated based upon the gray level analysis of the DXA images as the slope at the origin of the log-log representation of the experimental variogram. TBS was calculated as the mean value of the individual measurements for vertebrae L1–L4. A low TBS value indicates few gray-level variations of large amplitude and is interpreted as a low quality of bone texture (Fig. 1). The short term reproducibility (RMSCV) calculated after repositioning in 60 patients was 1.44% and 1.18%, for TBS and lumbar spine BMD respectively.

Fracture assessment

Self-reports of peripheral fractures were confirmed by written reports of radiographs or other tests. We excluded fractures due to bone metastases or other pathologies. We included incident low trauma fractures (peripheral and clinical vertebral fractures) that occurred without trauma or were caused by a fall from standing height or less; we excluded fractures of the skull, face, hands, and feet.

Vertebral fracture status was determined on lumbar and thoracic spine radiographs performed using a standardized procedure identical in all centers, and a standardized assessment in a central facility in the Berlin centre. Radiographs were performed at baseline and final 6-year visits using the same procedures, and evaluated centrally by two radiologists. The procedure to assess fracture status combined morphometric measurements of vertebral heights and the qualitative interpretation of fracture status: vertebrae with deformities of non-osteoporotic origin (e.g. degenerative changes) or exhibiting potential misleading appearances were not considered as fracture. For both prevalent and incident deformities a decrease of at least 20% of any height or height ratio was required for the diagnosis of fracture.

Statistical analysis

The characteristics of women with and without incident fractures were compared by using chi-square tests or Fisher's exact tests, or t-tests as appropriate.

Risk fracture discriminatory performance of TBS, aBMD, and TBS and aBMD in combination was evaluated as continuous variable using reassignment analysis assessed by net reclassification improvement (NRI) [19,20] as primary analysis. The NRI evaluates the movement of individuals between risk categories from one model to another. First, among those who fracture, one calculates the proportion moving upward from low-risk to high-risk category minus the proportion moving downward from high-risk to low-risk category. Among those who remain free of fracture, the proportion moving upward from low-risk to high-risk category is subtracted from the proportion moving downward from high-risk to low-risk category. Finally, 2 differences are summed; the higher the value, the more appropriate the reassignments. For this analysis, 3 categories of risk were determined using 2 thresholds; one defined based on statistical criteria (Younden's Index) and the other on criteria from established osteoporosis guidelines. The first cut point was determined using the ROC threshold that gave the maximum Younden's Index [22] (equal to the sensitivity plus the specificity minus 1) which corresponded to a sensitivity of 80%, i.e. 10% for 10-year incident osteoporotic fracture probability. This value corresponded to a TBS value of 1.228 for the prediction of incident clinical osteoporotic fracture and to 1.200 for the incident radiographic vertebral fracture. The second cut point was the clinical treatment threshold of 20% for major osteoporotic fractures proposed by the National Osteoporosis Foundation (NOF) for the use of FRAX® [23]; the TBS values were 1.046 and 0.875, respectively. Logistic regression to calculate the OR and 95% CI was used as secondary analysis. We used the C-statistic and 95% CI to evaluate the discrimination of each model. The C-statistic estimates the area under the receiver operator characteristic (ROC) curve (AUC) and indicates the model's ability to distinguish those with and without incident clinical osteoporotic fractures and incident radiographic vertebral fractures. Statistics were performed using Statistical Analysis Software (SAS V9.1, SAS Institute, Cary, NC, USA).