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COMMENTARY

TBS and bone strength

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Commentary on: Maquer G, Lu Y, Dall'Ara E, Chevalier Y, Krause M, Yang L. *et al.* The initial slope of the variogram, foundation of the trabecular bone score, is not or is poorly associated with vertebral strength. *J Bone Miner Res* 2015.

The recent study from Maquer *et al.*,[1] indicating that the initial slope of the variogram (ISV), foundation of the trabecular bone score (TBS), is not or poorly associated with vertebral strength has generated much interest and leads us to ask a number of questions.

Before focusing on conclusions of this paper and comment on it, a brief summary of where we are with TBS appears necessary.[2–5]

What is the TBS?

TBS is a texture parameter that evaluates pixel gray-level variations in anteroposterior dual energy X-ray absorptiometry (DXA) images of the lumbar spine. It was developed to reflect bone microarchitecture and is currently used in clinical studies for predicting fracture risk. The TBS analyzes local gray-scale variations in two-dimensional (2D) projection images. The method was initially described on three-dimensional (3D) micro-computed tomography (μCT) image and subsequently adapted for DXA images. The software for TBS computation (TBS iNsight, Geneva, Switerzland) can be installed on high-performance DXA machines. TBS and areal bone mineral density (aBMD) are computed in the same region of interest but separately and via different methods. A high TBS value is thought to reflect a microarchitecture associated with good mechanical strength. A low TBS value, in contrast, indicates poor-quality microarchitecture. TBS is thought to reflect the homogeneity of the trabecular microstructure, hence potentially a higher strength, although the respective contribution of trabecular vs cortical compartments to vertebral resistance to failure is not clear, being likely dependent on age. The TBS can currently and easily be obtained in everyday practice on DXA images of the lumbar spine. The reimbursement policy is not yet established in most countries, however. In clinical practice, the TBS may be used in a 'qualitative' manner, that is, for subjects with a normal BMD value and a low TBS value. From a quantitative point of view, the TBS may be used as a modulator of FRAX tool (see below).

What Evidence Do We Have Today That TBS Can be Used for Predicting Fragility Fractures?

Several prospective studies have shown that TBS is an independent predictor of fracture. A meta-analysis including 17 809 persons (both men and women) has been recently published by McCloskey *et al.*[6] The gradient of risk (GR) of TBS for major osteoporotic fracture was 1.44 (95% CI: 1.35–1.53) when adjusted for age and time since baseline and was similar in men and women. The gradient was quite similar for hip fracture: 1.44 (95% confidence interval (CI): 1.28–1.62). Also, the combination of both TBS and aBMD increases the prediction of fracture, as it was well demonstrated in the Manitoba cohort.[7] These findings suggest that TBS and aBMD are two independent predictors of fracture. In the same manner, it has been shown that the correlation between TBS and lumbar spine aBMD is statistically significant but weak ($r \approx 0.3$). When adjusted for FRAX 10-year probability of major osteoporotic fracture, TBS remained a significant, independent predictor for fracture (GR 1.32, 95% CI: 1.24–1.41).[6] Also, the adjustment of FRAX probability for TBS resulted in no change in the GR (1.76, 95% CI: 1.65, 1.87 vs 1.70, 95% CI: 1.60–1.81), although some increase or decrease may be detected according to age.[6] Owing to these findings, it is now possible to include in the FRAX the value of TBS for improving the calculation of the probability of both major and hip fractures.

What Evidence Do We Have Today That TBS Reflects Bone Microarchitecture?

Because of its measurement conditions (images obtained from DXA), the TBS cannot be considered as a true parameter measuring bone microarchitecture. Several *ex vivo* studies investigated the relationship between TBS and micro-architectural parameters. Winzenrieth *et al.*[8] showed that TBS derived from 2D-projection μCT images of human cadaveric vertebrae correlated with several trabecular microarchitecture indices measured by μCT. The levels of correlation were as follows: Conn. D: $r = 0.746$ ($P < 0.001$), trabecular number (Tb.N): $r = 0.637$ ($P < 0.001$), and trabecular separation (Tb.Sp:

$r = 0.430$; $P < 0.001$). The correlation with trabecular thickness was significant but weaker.

In a study from Silva *et al.*,[9] 71 pre- and 44 postmenopausal women were investigated using DXA, quantitative computed tomography (QCT) of the spine and hip and high resolution peripheral computed tomography (HRpQCR) at the radius and tibia. TBS correlated with all QCT indices of volumetric BMD (vBMD), with the strongest association at lumbar spine (LS) trabecular vBMD ($r = 0.664$; $P < 0.001$). TBS correlated with an estimate of cortical thickness at the femoral neck (FN) and total hip (TH) ($r = 0.54$; $P < 0.001$ for both) but not with bone size (cross-sectional area). Correlations between the TBS and microstructural indices at radius and tibia ranged between 0.135 and 0.266 (absolute *r*-values). For example, Tb.N at the radius and tibia explained 4% only of the TBS variance and Tb.Sp 6%. This study indicates that TBS is well correlated to vBMD but poorly to microarchitecture; however, microarchitectural parameters and TBS were not measured at the same site.

Roux *et al.*[10] studied 16 L3 fresh vertebrae from 16 elderly human donors (7 men and 9 women). The specimens were studied with DXA (anteroposterior aBMD and lateral aBMD) and μCT (voxel size 35 μm, Tb.BV/TV, Tb.Th, degree of anisotropy (DA) and structure model index (SMI). TBS was significantly correlated with two microarchitectural parameters: Tb.BV/TV ($r = 0.58$, $P = 0.02$) and SMI ($r = -0.62$, $P = 0.01$) but not with Tb.Th.

What Evidence Do We Have That TBS Reflects Bone Strength?

Because of its interest in the assessment of fracture risk, the TBS, as it has been well demonstrated for aBMD, should be related to bone strength. Very few studies are available about this issue.[1,10]

Roux *et al.*[10] in the study reported above did not find any relationship between the TBS and failure load but a significant relationship between the TBS and bone stiffness ($r = 0.64$, $P < 0.01$). Also, addition of TBS to aBMD did not significantly improve prediction of vertebral strength compared with aBMD alone. Limitations of the study were the small number of specimens, the study population (elderly subjects with low bone mass) and the loading mode (uniaxial, while most osteoporotic fractures are anterior wedge). Consequently to further appreciate the relationship between TBS and bone strength, Maquer *et al.*[1] performed an impressive biomechanical study including a higher number of human vertebrae ($n = 62$) with a larger range of age and several types of analyses for covering a wide range of loading scenarios. Three types of specimens/configuration of tests were performed: 1) 'full vertebra' via intervertebral discs to mimic the *in vivo* situation, 2) 'vertebral body' that corresponds to the classical endplate embedding and 3) 'vertebral section' (ball joint to induce anterior wedge failure). HRpQCT scans acquired prior testing were used to simulate anterior-posterior DXA from which aBMD and the ISV were evaluated. The aBMD correlated significantly with failure load F_{exp} ($0.587 < r^2 < 0.694$, $P < 0.05$) and apparent failure stress σ_{exp} ($0.47 < r^2 < 0.570$, $P < 0.05$). By contrast, the authors found that, unlike aBMD, ISV did not significantly correlate with F_{exp} and σ_{exp}, except for the 'vertebral body' case ($r^2 = 0.396$, $P = 0.028$). Using the 'vertebra section model', ISV explained only 6.4% of σ_{exp} ($P = 0.037$), and it brought no significant improvement compared with aBMD alone. The authors concluded that ISV, a replica of TBS, is a poor surrogate for vertebral strength no matter the testing set up, which supports the prior observations and raises *a fortiori* the question of the deterministic factors underlying the statistical relationship between TBS and vertebral fracture risk.

Although the manuscript by Maquer *et al.*[1] reports a well-done mechanical study, with a rigourous discussion and valuable appendices, it raises several comments:

1. As indicated in the paper, the authors calculated the ISV but did not measure the TBS. Although ISV and TBS are based on the same textural principles, they are not rigorously equivalent. Despite the high level of correlation between the two parameters ($r^2 = 0.745$), this finding indicates that about 25% of variance in the TBS is not explained by the ISV.
2. Although, the two parameters measured in the present study (F_{exp} and σ_{exp}) are obviously relevant, other parameters such as elastic properties and work to failure are also of interest. Indeed, Fyrhies and Vashishth[11] showed a strong correlation between stiffness and failure load in isolated vertebral cancellous bone on five specimens.
3. Similarly, biomechanical studies represent an indirect approach to what happens *in vivo* when a spinal fracture occurs. It is reasonable to think that the ligamentous structures but also muscle and subcutaneous fat (which are not included by definition in these studies) are factors to be taken into consideration, although these factors are not captured by the TBS.

Beyond these minor reserves, the study from Maquer *et al.* provides new and useful insights on the signification of the TBS. It highlights that the TBS has not revealed all its mysteries. Other studies are mandatory to solve the question 'how could TBS be predictive of fracture if it is not related to bone strength? Is there a role for cortical bone in TBS? For all these reasons perhaps it would be more useful to rename the TBS as 'texture bone score' instead of 'trabecular bone score'.

Conflict of Interest

BC has participated to one meeting organized by Medimaps during the ASBMR congress in 2013 at Minneapolis. VB declares no conflict of interest.

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