

A Retrospective Case–Control Study Assessing the Role of Trabecular Bone Score in Postmenopausal Caucasian Women with Osteopenia: Analyzing the Odds of Vertebral Fracture

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Abstract This case–control study assessed whether the trabecular bone score (TBS), determined from gray-level analysis of DXA images, might be of any diagnostic value, either alone or combined with bone mineral density (BMD), in the assessment of vertebral fracture risk among postmenopausal women with osteopenia. Of 243 postmenopausal Caucasian women, 50–80 years old, with BMD T-scores between -1.0 and -2.5 , we identified 81 with osteoporosis-related vertebral fractures and compared them with 162 age-matched controls without fractures. Primary outcomes were BMD and TBS. For BMD, each incremental decrease in BMD was associated with an OR = 1.54 (95% CI = 1.17–2.03), and the AUC was 0.614 (0.550–0.676). For TBS, corresponding values were 2.53 (1.82–3.53) and 0.721 (0.660–0.777). The difference in the AUC for TBS vs. BMD was statistically significant ($p = 0.020$). The OR for (TBS + BMD) was 2.54 (1.86–3.47) and the AUC 0.732 (0.672–0.787). In conclusion, the TBS warrants a closer look to see whether it may be of clinical usefulness in the determination of fracture risk in postmenopausal osteopenic women.

Keywords Osteoporosis · Osteopenia · Bone mineral density · Trabecular bone score · Bone microarchitecture · Vertebral fracture · Case–control

Osteoporosis is a common bone disorder, especially prevalent in postmenopausal women. It is characterized by reduced bone density, relative to ‘normal’ values, and alterations in the normal bony microarchitecture. The primary complication of osteoporosis is bone fractures, which can occur at almost any site, but classically occurs at the hip, vertebral spine, and wrists [1]. For example, roughly 40% of women >50 years old will have a vertebral fracture diagnosed at some time [2], and many more may have undetected fractures [3].

Traditionally, bone mineral density (BMD) has been considered the major determinant of bone strength and fracture risk [4], and it is BMD that is used to diagnose and follow up osteoporosis in routine clinical practice, based on a T-score threshold that has been proposed by the World Health Organization (WHO) [5]. The greatest limitation of BMD measurement is that a considerable degree of overlap exists in BMD values between individuals with and those without subsequent fractures [6]. One potential explanation for this is that BMD is not the only structural determinant of bone strength [7]. Trabecular bone microarchitecture [8, 9], for example, also appears to be a significant bone strength determinant and is complementary to bone density. Another limitation of BMD measurements is that they disproportionately evaluate cortical bone, depending on the skeletal site measured, and cortical bone has a relatively slow rate of turnover relative to trabecular bone [10]. Consequently, one must wait a long time (typically, years) between BMD measurements to be able to detect any meaningful changes, whether the change is related to the

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natural progression of aging or disease, or is the result of treatment [10]. Because of this increased rate of trabecular bone turnover, it is possible that evaluating the microarchitecture of trabecular bone could increase the accuracy and sensitivity of bone quality evaluations in clinical practise.

The *trabecular bone score* (TBS) is a novel gray-level texture measurement that is based on the analysis of two-dimensional (2D) projection images. The TBS is capable of differentiating between two–three-dimensional (3D) microarchitectures that exhibit the same bone density but different trabecular characteristics [11, 12]. The TBS is not an estimate of fractal dimension [13]. Rather, it measures the mean rate of local variation of gray levels in 2D projection images and is constrained by neither the size nor the shape of the region being measured [13]. Hence, the TBS is a good candidate as a texture measurement for small and/or irregular surfaces of analysis, such as the standard region of measurement defined in DXA images. The TBS is obtained after reanalysis of a DXA exam and can be compared with the BMD, since both evaluate the same region of bone [13]. Based on numerical models of 3D volume of porous materials and 2D simulated projection images [11], we have established a 2D/3D generic mathematical relationship between (i) TBS values, as evaluated from 2D simulated projection images, and (ii) the 3D characteristics of porous material models. As the second step [11], we tested and validated this 2D/3D relationship in a set of 57 human bone reconstructions of different anatomical sites (spine, femoral neck, ultradistal radius), deprived of cortical bone, as well as of posterior elements (in the case of spinal bone reconstructions). This validation has permitted the demonstration of highly significant correlations between (i) TBS values, as evaluated from 2D simulated projection images, and (ii) the standard 3D characteristics of trabecular bone microarchitecture. As the third step [12], we evaluated 2D/3D correlations in a set of complete human vertebrae (including cortical bone and posterior elements), taking into account real, applicable conditions: (i) the assessment of entire bone samples, including cortical bone and posterior elements; (ii) the evaluation of TBS directly from anteroposterior DXA images; and (iii) the determination of 3D characteristics of bone microarchitecture, as evaluated inside vertebral body trabecular bone. This study confirmed significant 2D/3D correlations between the TBS, as evaluated from DXA images, and the 3D characteristics of trabecular bone microarchitecture, independent of BMD, as evaluated from the same DXA images. A low TBS value has been found to be associated with degraded bone microarchitecture, with low connectivity, high trabecular spacing, and a reduced number of trabeculae; conversely, a high TBS value has been found to be associated with good bone microarchitecture, with high connectivity, low

trabecular spacing and an augmented number of trabeculae [11, 12]. Hence, an elevated TBS reflects strong, fracture-resistant microarchitecture; a low TBS reflects weak, fracture-prone microarchitecture.

We conducted the current study to validate TBS for vertebral fracture prediction in patients whose T-score falls in the osteopenia range, between -1.0 and -2.5 , in whom we know there is a considerable degree of overlap between those with fractures and those without. In addition, we wanted to see if there is any additional effect of TBS over and independent of the BMD. Our specific hypotheses were that (i) TBS identifies osteopenic patients with vertebral fractures, irrespective of their BMD; and (ii) TBS has predictive power that is beyond and independent of BMD.

Materials and Methods

Study Subjects

We conducted a retrospective, nonrandom case–control study at the Hospital Centre of Avignon, France. During the observation period, 243 postmenopausal Caucasian women, between 50 and 80 years of age, and having a body mass index (BMI) between 17 and 35 kg/cm², presented with an osteopenic BMD ($-2.5 < \text{T-score} \leq -1.0$) of the lumbar spine and were deemed potentially eligible for the study.

Subjects were classified by fracture status (fracture, no fracture) and by age. For every subject with a vertebral fracture (case), controls were matched for age, ± 3 years. To be fully eligible as a case, the woman had to present with a low-energy vertebral fracture confirmed by X-ray, in accordance with the semiquantitative classification criteria published by Genant et al. [14]. Conversely, controls could not have any evidence of a low-energy fracture at any bone site. Individuals were excluded if they (i) were on any treatment and/or had any illness that would be expected to impact bony metabolism; (ii) had undergone any spinal surgery; (iii) had any evidence of inflammatory change or arthrosis in the lumbar spine; or (iv) had three or more nonobservable lumbar vertebrae. Ultimately, 81 women with fractures were deemed eligible to participate in further analysis, for which a total of 162 controls also were recruited.

This study was conducted in accordance with the current version of the *Declaration of Helsinki* and under the laws and regulations enforced by the Department of Health. In addition, each subject was ensured anonymity, which was maintained by using subject-specific numeric codes, rather than patient names, on all records, including DXA examination files and registration cards.

Construction of the Database

For each subject, the following parameters were determined from patient files and records of the DXA exam: patient age, weight, height, and body mass index (BMI) and vertebral size, fracture status, BMD, bone mineral content (BMC), and projected area, for each vertebra, L1 through L4. Each set of clinical data, DXA measurements, and the TBS were imported into an Excel file.

Bone Mineral Density

Total spine (BMD) was evaluated with the PRODIGY-Lunar densitometer (General Electric) as the mean of the individual measurements for L1–L4, excluding any fractured and/or arthrosed vertebrae. This identification was performed by a clinician who is an expert in DXA scan interpretation.

Trabecular Bone Score

The TBS was evaluated in the same regions of measurement as those used for BMD using TBS iNsite V1.0 (Med-Imaps). TBS was calculated as the mean value of the individual measurements for vertebrae L1–L4, again excluding any fractured and/or arthrosed vertebrae. In each region of measurement, the TBS was evaluated, based on gray-level analysis of DXA images, as the slope at the origin of the log–log representation of the data plot.

Statistical Analysis

All statistical analyses were performed using MedCalc software (v8.1, <http://www.medcalc.be>). Means and 95% confidence intervals were estimated for each of the two subject groups, women with fractures and women without fractures, matched for age. Between-group differences were identified by means of the parametric Student *t* test or the nonparametric Wilcoxon signed-ranks test, depending on whether or not the parameter being tested exhibited a normal distribution. The diagnostic value of each parameter was further evaluated both by odds ratios (OR)—expressed for each decrease of 1 standard deviation—and by determining the receiving operator curve (ROC) and the area under the ROC (AUC). For both these estimates, OR and AUC, 95% confidence intervals (CI) were calculated. The test for difference between AUC was performed by means of pairwise comparison. An evaluation associating both parameters was conducted based on a logistic regression model associating TBS and BMD. Both parameters were inserted into the logistic regression model, and the model determined and characterized as a new parameter ‘(TBS + BMD)’:

$$(TBS + BMD) = \exp[(b_0 + b_1) \times (BMD + b_2) \times TBS] / [1 + \exp(b_0 + b_1) \times (BMD + b_2) \times TBS]$$

where b_0 , b_1 , and b_2 are the coefficients generated during logistic regression analysis.

Results

Description of Samples

Ultimately, of the 243 potentially eligible postmenopausal Caucasian women assessed, 81 were deemed to have an osteoporosis-related fracture and to be otherwise eligible for further analysis; and an additional 162 women without fractures were recruited from the same sampling frame to serve as controls. Three and two-tenths percent of vertebra (31/972) was excluded from the measurements due to arthrosis. The two groups, subjects with and without fractures, were not different in mean age (64.3 vs. 62.6 years; $p = 0.16$) or height (159.2 vs. 158.6 cm; $p = 0.47$), but women with fractures were heavier (64.3 vs. 58.5; $p = 0.0001$) and had a higher BMI (25.4 vs. 23.3; $p = 0.0001$) (Table 1). In addition, both BMD and TBS were less in the fracture group (0.945 vs. 0.968 [$p < 0.003$] and 0.970 vs. 1.061 [$p < 0.0001$]).

A Comparison of TBS and BMD

ORs and AUCs were estimated for TBS and BMD and compared. For BMD, each incremental decrease of 1 SD in BMD was associated with slightly more than a 50% increase in the odds (OR = 1.54 95% CI = 1.17–2.03) of vertebral fracture, and the AUC for BMD was 0.614 (CI = 0.550–0.676). Meanwhile, each incremental decrease of 1 SD in TBS was associated with considerably more than a doubling of the odds (2.53; 1.82–3.53) of vertebral fracture, and the AUC for TBS was 0.721 (0.660–0.777). When adjusted for weight, the ORs for BMD and TBS were 1.63 (1.20–2.22) and 1.97 (1.31–2.96), respectively. The difference in the AUC for TBS vs. BMD was statistically significant ($p = 0.020$).

Comparison of TBS Plus BMD Versus BMD Alone

ORs and AUCs were estimated for the combination of TBS and BMD, and for BMD alone, and compared. Relative to the corresponding OR and AUC for BMD alone of 1.54 (1.17–2.03) and 0.614 (0.550–0.676), respectively, each incremental decrease of 1 SD in the (TBS + BMD) model (generated by logistic regression analysis) was associated with about a 150% increase in the OR (2.54; 1.86–3.47) of

Table 1 Characteristics of the sample

	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)	BMD, L1–L4 (g/cm ²)	T-score	TBS, L1–L4 (mm ⁻¹)
Overall population (<i>n</i> = 243)							
Mean ± SD	63.1 ± 7.7	159.0 ± 6.0	60.5 ± 7.9	24.0 ± 3.0	0.960 ± 0.054	-1.7 ± 0.4	1.031 ± 0.114
Control population (<i>n</i> = 162)							
Mean ± SD	62.6 ± 7.5	158.6 ± 5.9	58.5 ± 6.7	23.3 ± 2.5	0.968 ± 0.052	-1.6 ± 0.4	1.061 ± 0.094
Fracture population (<i>n</i> = 81)							
Mean ± SD	64.3 ± 7.8	159.2 ± 6.2	64.3 ± 8.5	25.4 ± 3.5	0.945 ± 0.055	-1.8 ± 0.4	0.970 ± 0.118
Test for difference <i>p</i>	0.1604 ^b	0.4687 ^a	<0.0001 ^b	<0.0001 ^b	0.0022 ^a	0.0019 ^a	<0.0001 ^b

^a Student's *t*-test, ^b non-parametric Wilcoxon's signed-ranks test

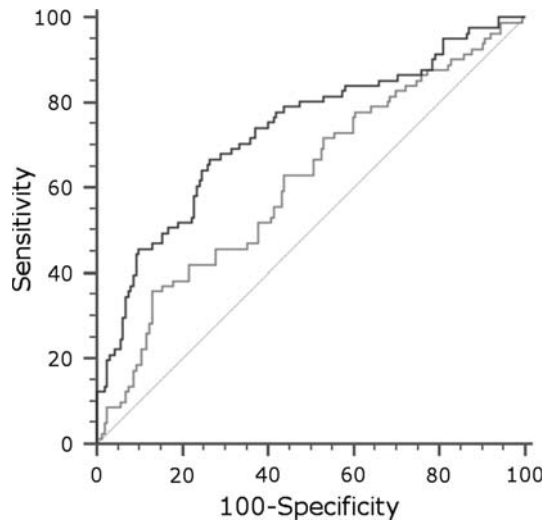


Fig. 1 Area under the receiver operating curves for bone mineral density (BMD; gray curve) and the logistic regression model (TBS + BMD; black curve) determined by the results of the logistic regression analysis, taking TBS and BMD as input parameters

vertebral fracture, and the AUC for the combination was 0.732 (0.672–0.787). When adjusted for weight, the ORs for BMD and for (TBS + BMD) were 1.63 (1.20–2.22) and 2.04 (1.42–2.92), respectively. The difference in the AUC for (TBS + BMD) vs. BMD was statistically significant ($p = 0.005$) (Fig. 1).

Discussion

In previous papers, we presented empirical evidence that suggests that the TBS may have value in the identification of women over 50 who have an increased risk of fractures [11–13]. In the first of these studies [11], we sought to determine the level of correlation between the 3D characteristics of trabecular bone microarchitecture, as evaluated using μ CT reconstruction, and TBS, as evaluated using 2D projection images derived directly from 3D micro-computed tomography (μ CT) reconstruction. Analyses were performed using sets of human cadaver bone samples from

different anatomical sites (lumbar spine, femoral neck, and ultradistal radius). Correlation analyses established significant relationships between the TBS and two 3D characteristics of bone microarchitecture: *bone volume fraction* and *mean bone thickness*. In particular, TBS allows for differentiation between two 3D microarchitectures that exhibit the same amount of bone but different trabecular characteristics, thereby demonstrating the existence of a robust and generic relationship that takes into consideration the simplified model of a 2D projection image. In another experimental study using vertebrae from human cadavers, we also established and validated the 2D/3D generic mathematical relationship between TBS, as assessed by DXA, and the same two parameters—bone volume fraction and mean solid thickness—as assessed by μ CT, thereby validating the mathematical conversion that is necessary for the process of using TBS data gleaned directly from DXA images [12]. In the latter study, conducted under real, applicable conditions, we identified significant direct correlations between the TBS and the 3D standard characteristics of trabecular bone microarchitecture: $r = 0.87$ ($p < 0.0001$) between TBS and connD (density of connectivity); $r = 0.82$ ($p < 0.0001$) between TBS and TbN (trabecular number); and $r = -0.72$ ($p < 0.0001$) between TBS and TbSp (trabecular spacing). Such results established direct correlations between TBS and 3D standard characteristics of bone microarchitecture, independent of real conditions, taking into consideration cortical bone and posterior elements in the DXA image. As the next step, we applied this newly developed TBS in the direct evaluation of clinical DXA images.

In a recent study [15], using TBS iNsite beta version (Med-Imaps), 42 postmenopausal women with osteoporosis-related vertebral fractures (31 with osteoporosis confirmed by DXA and 11 with osteopenia) were compared with 126 age-matched women without any fractures. What we found was that the combination of BMD + TBS was better than either test alone, in terms of correctly classifying patients overall ($\chi^2 = 2.45$, $df = 1$, $p = 0.1172$), and tended toward being superior in terms of classifying by

fracture status ($\chi^2 = 3.76$, $df = 1$, $p = 0.0526$). The combination also was statistically more specific than either test used alone ($\chi^2 = 8.41$, $df = 1$, $p = 0.0037$). Unfortunately, this earlier study lacked the numbers to identify any similar, statistically significant relationships in that segment of the postmenopausal population for whom the combination might have the greatest utility, those whose BMD falls in the osteopenia range.

The current study was intended to address this issue of how valuable the TBS is in women whose BMD falls in the osteopenia, rather than the osteoporosis range. Consequently, we only analyzed postmenopausal women whose T-score fell between -1.0 and -2.5 and included in our analysis 81 such women with fractures and 162 age-matched osteopenic controls, versus the 11 and 40 osteopenic subjects recruited in the fracture and nonfracture groups in the previous study. The larger sample sizes used in the current study provided increased statistical power to detect whether the combination of modalities is better than either one used alone.

What we found is that both the OR and the AUC were higher for TBS than for BMD (0.721 vs. 0.614), with the difference in AUC statistically significant ($p = 0.020$); moreover, for the combination of TBS and BMD versus BMD alone (0.732 vs. 0.614), there also was a difference that was statistically significant ($p = 0.005$).

Two previous retrospective case-control studies [13, 15] have permitted demonstration of the added value of the TBS against BMD, independent of the BMD threshold. In the first study [13], it was demonstrated that the added value of the TBS is in differentiating between subjects with and subjects without fractures in the overlap area (BMD-matched subgroups) with no BMD-based threshold: $OR(TBS) = 1.95(1.31-2.89)$ for all types of osteoporotic fractures (45 fracture subjects compared to 90 BMD-matched control subjects) and $OR(TBS) = 2.66(1.46-4.85)$ for vertebral fractures (20 fracture subjects compared to 60 BMD-matched control subjects). In the second study [15], the added value of the TBS was established in a population with low BMD scores (T-score ≤ -1.0), incorporating both osteopenia and osteoporosis densitometric areas: $OR(TBS) = 3.20(2.01-5.08)$ for vertebral fractures (42 fracture subjects compared to 126 age-matched control subjects). Benefiting from the results of these first two case-control studies, we designed the present and a third case-control study in the osteopenia area, because it is in patients who fall in the osteopenia range that the potential use of the TBS, as a complement to BMD, makes more clinical sense. The results found in this group were in the same order as previously, with $OR(TBS) = 2.53(1.82-3.53)$ for vertebral fractures (81 fracture subjects compared to 162 control subjects). Hence, this set of three retrospective case-control studies has demonstrated the

potential added value of the TBS over BMD alone, independent of the BMD threshold.

Our study is not without limitations, however, the most relevant being that it was case-control and retrospective. Hence, we cannot directly imply any causative association between reduced TBS and osteoporosis-related fracture. We were not comparing the various tests (BMD, TBS, or combined BMD + TBS) in terms of their ability to predict fracture risk, which is what clinicians ultimately want to do; rather, as the nature of our statistics indicates, we merely were assessing which test option was better at identifying individuals who already had a fracture. To achieve the former end, prospective, longitudinal studies are necessary. Nonetheless, the studies we have reported so far, albeit all case-control and retrospective, have been consistent in their findings; and this suggests to us that such prospective, longitudinal studies to assess the value and added value of the TBS in the assessment of fracture risk are indeed warranted.

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