

A multicentre, retrospective case–control study assessing the role of trabecular bone score (TBS) in menopausal Caucasian women with low areal bone mineral density (BMDa): Analysing the odds of vertebral fracture

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ABSTRACT

Introduction: The trabecular bone score (TBS) is a new parameter that is determined from grey level analysis of DXA images. It relies on the mean thickness and volume fraction of trabecular bone microarchitecture. This was a preliminary case–control study to evaluate the potential diagnostic value of TBS, both alone and combined with bone mineral density (BMDa), in the assessment of vertebral fracture.

Methods: Out of a subject pool of 441 Caucasian, postmenopausal women between the ages of 50 and 80 years, we identified 42 women with osteoporosis-related vertebral fractures, and compared them with 126 age-matched women without any fractures (1 case: 3 controls). Primary outcomes were BMDa and TBS. Inter-group comparisons were undertaken using Student's t-tests and Wilcoxon signed ranks tests for parametric and non-parametric data, respectively. Odds ratios for vertebral fracture were calculated for each incremental one standard deviation decrease in BMDa and TBS, and areas under the receiver operating curve (AUC) calculated and sensitivity analysis was conducted to compare BMDa alone, TBS alone, and the combination of BMDa and TBS. Subgroup analyses were performed specifically for women with osteopenia, and for women with T-score-defined osteoporosis.

Results: Across all subjects ($n = 42, 126$) weight and body mass index were greater and BMDa and TBS both less in women with fractures. The odds of vertebral fracture were 3.20 (95% CI, 2.01–5.08) for each incremental decrease in TBS, 1.95 (1.34–2.84) for BMDa, and 3.62 (2.32–5.65) for BMDa + TBS combined. The AUC was greater for TBS than for BMDa (0.746 vs. 0.662, $p = 0.011$). At iso-specificity (61.9%) or iso-sensitivity (61.9%) for both BMDa and TBS, TBS + BMDa sensitivity or specificity was 19.1% or 16.7% greater than for either BMDa or TBS alone. Among subjects with osteoporosis ($n = 11, 40$) both BMDa ($p = 0.0008$) and TBS ($p = 0.0001$) were lower in subjects with fractures, and both OR and AUC ($p = 0.013$) for BMDa + TBS were greater than for BMDa alone (OR = 4.04 [2.35–6.92] vs. 2.43 [1.49–3.95]; AUC = 0.835 [0.755–0.897] vs. 0.718 [0.627–0.797], $p = 0.013$). Among subjects with osteopenia, TBS was lower in women with fractures ($p = 0.0296$), but BMDa was not ($p = 0.75$). Similarly, the OR for TBS was statistically greater than 1.00 (2.82, 1.27–6.26), but not for BMDa (1.12, 0.56–2.22), as was the AUC ($p = 0.035$), but there was no statistical difference in specificity ($p = 0.357$) or sensitivity ($p = 0.678$).

Conclusions: The trabecular bone score warrants further study as to whether it has any clinical application in osteoporosis detection and the evaluation of fracture risk.

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Introduction

Osteoporosis is a bone disorder that is characterized by a reduction in bone density, relative to 'normal' values, and a change in bony microarchitecture, both of which appear to increase skeletal fragility

and the associated risk of bone fractures [1]. Osteoporosis is especially prevalent in postmenopausal woman. In fact, two out of five women beyond the age of 50 years will experience a vertebral fracture [2], and the actual prevalence of vertebral fracture in these women may even be higher than this, given that many, and perhaps even a majority of these fractures remain asymptomatic or undiagnosed [3].

Bone mineral density (BMDa) is one of the major determinants of bone strength and fracture risk [4] which, in routine clinical practice, typically is measured by means of dual energy X-ray absorptiometry

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(DXA), expressed in g/cm^2 and converted to a T-score. This is the most commonly used classification/diagnostic scheme in published and ongoing research and in clinical practice. However, particularly in clinical practice, this scheme has limitations.

The greatest limitation of the BMDa measurement is that a large degree of overlap exists in BMDa values between individuals who develop fractures and those who do not [5]. To partially answer this problem the current osteoporosis classification criteria drafted by the World Health Organization (WHO) is currently revised to include clinical risk factors (<http://www.shef.ac.uk/FRAX/>). Additional explanations for this is that BMDa does not capture all of the factors that contribute to bone strength [6]. Among these factors is trabecular bone microarchitecture [7,8], which also appears to be a significant determinant of bone strength and is complementary to bone density. Another limitation of BMDa measurements is that they disproportionately evaluate cortical bone depending on the skeletal site measured, which has a relatively slow rate of turnover [9]. Consequently, one must wait a long time (typically, years) between BMDa measurements to be able to detect any meaningful changes, whether the change is related to the natural progression of ageing or the result of treatment [9]. Conversely, trabecular bone has a much higher rate of turnover (eight times higher than that of cortical bone) [10]. Because of this, evaluation of the microarchitecture of trabecular bone could increase the accuracy and sensitivity of bone quality evaluations in clinical situations. Trabecular bone structure can be assessed using either high-resolution magnetic resonance imaging (HRMR) or multi-slice computed tomography (MSCT) [11], but both techniques are costly, time consuming, and not always available in clinical routine.

The trabecular bone score (TBS) is a novel grey-level texture measurement that is based on the use of experimental variograms of 2D projection images. The TBS is able to differentiate between two 3-dimensional (3D) microarchitectures that exhibit the same bone density, but different trabecular characteristics [12,13]. TBS is not an estimate of fractal dimension [14]. Rather, it measures the mean rate of local variation of grey levels in 2D projection images [14]. This evaluation is constrained by neither the size nor the shape of the region being measured [14]. Hence, 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 re-analysis of a DXA scan, and can be compared with BMDa, since both evaluate the same region of bone. An empirical 3D/2D relationship has been established which expresses the TBS as a function of two 3D bone characteristics: solid volume fraction (f_s) and mean solid thickness (Th) [12–14]. Higher TBS reflects strong, fracture-resistant microarchitecture; a low TBS reflects weak, fracture-prone microarchitecture.

We conducted the current study to test the following two hypotheses: (1) TBS identifies those at risk for vertebral fractures, regardless of their BMDa, and (2) the combination of TBS and BMDa potentiates fracture risk detection. Our main objectives were (1) to estimate and compare the discriminative value of TBS + BMDa versus BMDa alone in the assessment of vertebral fracture risks from an analysis of lumbar spine levels L1–L4 in a population of Caucasian menopausal women with abnormally low BMDa and (2) to estimate and compare these discriminative values in two subsets of women: those with osteoporosis and those with osteopenia.

Materials and methods

Study subjects

We conducted a retrospective, non-random case–control multi-centre study at the Hospital Centre of Libourne, the Mèdoc Radiological Center, and the Lesparre Community Clinic. During the observation period, 441 postmenopausal Caucasian women, between the ages of 50 and 80 years, and with a body mass index (BMI)

between 19 and 33 kg/cm^2 , presented with an abnormally low BMDa (T-score < -1.0) measured by DXA (Prodigy™, General Electric Lunar, Madison, WI) of the lumbar spine, and/or total hip, and/or femoral neck, and were potentially eligible for the survey.

Subjects were classified by fracture status (fracture, no fracture) and by age. For every subject with a fracture (case), three 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 radiography, in accordance with the semi-quantitative classification criteria published by Genant et al. [15], but no evidence of prior osteoporosis-related fracture elsewhere. Conversely, controls could not have any evidence of a low-energy fracture at any bone site, as determined both by history and by appropriate imaging, including a radiographic screen of the spine. Individuals in either group were excluded if they (1) were on any treatment and/or had any illness that would be expected to influence bone metabolism, (2) had undergone any spinal surgery, (3) had any evidence of inflammatory change or arthrosis in the lumbar spine, or (4) they had three or more non-observable lumbar vertebra (13 L1, 5 L2, 3 L3, and 22 L4 were excluded for the BMDa analysis because of significant arthrosis measurements, and 2 L1, 2 L2, 1 L3, and 2 L4 because of fracture). These same excluded vertebrae were also excluded for the TBS analysis so that we were working on the same dataset. Ultimately, 42 women with fractures were deemed eligible to participate in further analysis, for which a total of 126 controls (1 case: 3 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 data base

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

Bone mineral density (BMDa)

Total spine ($\text{BMDa}_{\text{spine}}$) was evaluated as the mean of the individual measurements for L1–L4, excluding any fractured and/or arthrosed vertebrae. This identification was done by a clinician (Marc-Antoine Krieg) who is an expert in DXA scan interpretation.

Trabecular bone score (TBS)

TBS was evaluated in the same regions of measurement as those used for BMDa. $\text{TBS}_{\text{spine}}$ 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 and based upon grey level analysis of DXA images, TBS was evaluated as the slope at the origin of the log–log representation of the experimental variogram.

Consequently, estimates of overall BMDa and TBS were calculated using independent grey level measurements for L1–L4.

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's t-test or the non-parametric Wilcoxon's signed ranks test, depending upon whether or not the parameter being tested exhibited a normal distribution. Anthropometric parameters for which the difference between groups was found to be statistically significant ($p < 0.05$) were entered into a logistical regression model (by 'backward' stepwise analysis). The statistical significance of the TBS cofactor in the obtained logistical regression model provides an account of the significance of the differentiation ability of TBS, independent of the effect of anthropometric parameters. The TBS and BMDa combination model was obtained using logistic regression process. The diagnostic value of each parameter and for the TBS and BMDa combination was further evaluated both by odds ratios (OR)—expressed for each decrease of one 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 were calculated. The test of difference between AUC was performed using a pairwise comparison. Pearson chi-square analysis was conducted to compare the percentage of subjects correctly classified, overall and by the presence or absence of a fracture, using the combination of BMDa and TBS, versus either test used alone. All statistical tests were two-tailed.

Results

Description of the samples

Ultimately, out of the 441 potentially eligible postmenopausal Caucasian women assessed, 42 were deemed to have an osteoporosis-related fracture and to be otherwise eligible for further analysis; an additional 126 women without fractures were recruited from the same sampling frame to serve as controls. The two groups, subjects with and without fractures, were not different in mean age (65.6 vs. 63.5 years, $p = 0.1611$) or height (both 156.9 cm, $p = 0.9634$), but women with fractures were heavier (63.4 vs. 59.7, $p = 0.0145$) and had a higher BMI (25.8 vs. 24.2, $p = 0.0228$) (Table 1). In addition, both BMDa and TBS were less in the fracture group (0.839 vs. 0.906, $p = 0.0017$, and 0.911 vs. 1.053, $p < 0.0001$, respectively).

A comparison of TBS versus BMDa versus TBS plus BMDa

Odds ratios (OR) and areas under the receiving operator curve (AUC) were estimated for TBS, BMDa, and the combination of TBS and BMDa, and compared. For BMDa, each incremental decrease of one standard deviation in BMDa was associated with almost a doubling of the odds (OR = 1.95; 95% confidence interval = 1.34–2.84) of vertebral fracture, and with an AUC of 0.662 (0.585–0.733). Each incremental decrease of one standard deviation in TBS was associated with more than a tripling of the odds (3.20; 2.01–5.08) of vertebral fracture, and an AUC of 0.746 (0.673–0.810). When adjusted for weight, the ORs for BMDa and TBS were 2.48 (1.61–3.83) and 3.81

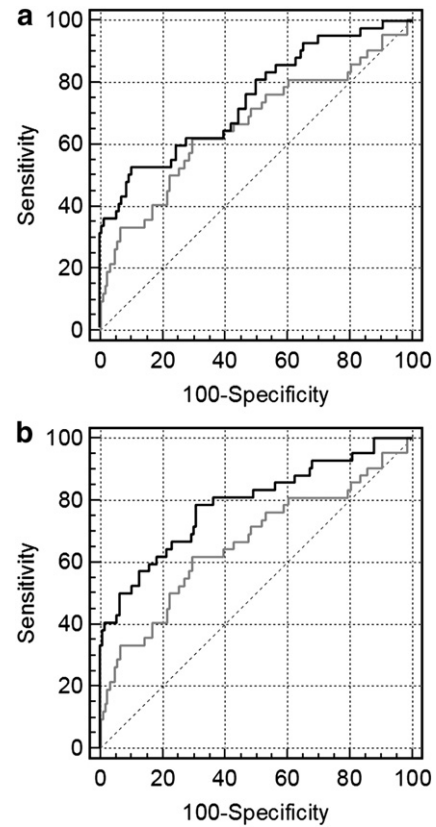


Fig. 1. (a) Area under the receiver operating curves for bone mineral density (BMDa, the grey curve) and trabecular bone score (TBS, the dark curve). (b) Area under the receiver operating curves for bone mineral density (BMDa, the grey curve) and the combined trabecular bone score plus BMDa (TBS + BMDa, the dark curve).

(2.17–6.72), respectively. The AUCs for TBS vs. BMDa were not statistically different ($p = 0.140$) (Fig. 1a). Finally, each incremental decrease of one standard deviation in the combination of TBS and BMDa (TBS + BMDa) was associated with a large increase in the odds (3.62; 2.32–5.65) of vertebral fracture, and an AUC of 0.788 (0.718–0.847). When adjusted for weight, the ORs for BMDa and (TBS + BMDa) were 2.48 (1.61–3.83) and 3.55 (2.24–5.62), respectively. The AUCs for (TBS + BMDa) vs. BMDa were statistically different ($p = 0.006$) (Fig. 1b).

The combination of TBS plus BMDa was compared to both BMDa alone and TBS alone, in terms of the accuracy of classifying patients overall, based on threshold giving the equality of sensitivity and specificity. The combination correctly classified 70.0% of all subjects, versus 61.9% for both BMDa alone and TBS alone ($\chi^2 = 2.45$, $df = 1$, $p = 0.1172$, $n = 168$). With iso-sensitivity of 61.9%, the combination was statistically superior to either BMDa or TBS for overall classification (74.4% vs. 61.9%; $\chi^2 = 6.05$, $df = 1$, $p = 0.0139$, $n = 168$) and for specificity (78.6% vs. 61.9%; $\chi^2 = 8.41$, $df = 1$, $p = 0.0037$, $n = 126$).

Table 1

Characteristics of the subjects.

	Age [years]	Height [cm]	Weight [kg]	BMI [kg/m ²]	BMDa L1–L4 [g/cm ²]	TBS L1–L4 [mm ⁻¹]
Entire sample (n = 168)						
Mean ± SD	64.0 ± 8.2	156.9 ± 6.3	60.6 ± 8.4	24.6 ± 3.1	0.889 ± 0.103	1.017 ± 0.137
Age-matched controls (n = 126)						
Mean ± SD	63.5 ± 8.3	156.9 ± 6.0	59.7 ± 8.1	24.2 ± 2.8	0.906 ± 0.089	1.053 ± 0.102
Fracture subjects (n = 42)						
Mean ± SD	65.6 ± 7.8	156.9 ± 7.2	63.4 ± 8.8	25.8 ± 3.7	0.839 ± 0.126	0.911 ± 0.171
Test of difference, p	0.1611 ^a	0.9634 ^a	0.0145 ^a	0.0228 ^b	0.0017 ^b	<0.0001 ^b

^a Student's t-test.

^b Mann–Whitney test.

Table 2
Characteristics among those subjects with osteopenia.

	Age [years]	Height [cm]	Weight [kg]	BMI [kg/m ²]	BMDa L1–L4 [g/cm ²]	TBS L1–L4 [mm ⁻¹]
Entire sample (n = 51)						
Mean ± SD	60.4 ± 8.0	159.3 ± 5.1	62.5 ± 8.6	24.6 ± 3.1	0.957 ± 0.067	1.037 ± 0.133
Age-matched controls (n = 40)						
Mean ± SD	60.2 ± 8.1	159.1 ± 5.0	61.3 ± 8.2	24.2 ± 2.7	0.958 ± 0.067	1.065 ± 0.100
Fracture subjects (n = 11)						
Mean ± SD	61.2 ± 8.2	160.0 ± 5.9	66.6 ± 9.0	26.1 ± 4.0	0.951 ± 0.071	0.932 ± 0.185
Test of difference, p	0.7042 ^a	0.6092 ^a	0.0690 ^a	0.0606 ^a	0.7545 ^a	0.0296 ^b

^a Student's t-test.
^b Mann–Whitney test.

With iso-specificity of 61.9%, the combination was not significantly superior to either BMDa or TBS for overall classification (66.7% vs. 61.9%; $\chi^2 = 0.84$, df = 1, $p = 0.3585$, $n = 168$) or for sensitivity (81.0% vs. 61.9%; $\chi^2 = 3.76$, df = 1, $p = 0.0526$, $n = 42$).

Subgroup analyses for women with osteopenia

Fifty-one of the 168 women (30.4%) in the study, 11 of the 42 (26.2%) in the fracture group, and 40 of the 126 (31.7%) in the control group ($\chi^2 = 2.22$, df = 1, $p = 0.1363$) were found to have a T-value between -1.0 and -2.50, so that they were considered to have osteopenia, according to DXA data. The two groups did not differ in mean age (61.2 vs. 60.2 years, $p = 0.7042$), mean height (160.0 vs. 159.1 cm, $p = 0.6092$), mean weight (66.6 vs. 61.3 kg, $p = 0.0690$), BMI (26.1 vs. 24.2, $p = 0.0606$), or BMDa (0.951 vs. 0.958, $p = 0.7545$), but did differ in TBS (0.932 vs. 1.065, $p = 0.0296$) (Table 2). Similarly, the odds ratio for fracture for each incremental decline of one standard deviation in BMDa was not statistically different from 1.12 (0.56–2.22), but a statistical difference from one was identified for TBS (OR = 2.82, 1.27–6.26), and the AUC for the TBS was statistically higher than for BMDa (0.716, 0.572–0.833 vs. 0.511, 0.367–0.654; $p = 0.035$).

Based on the threshold giving equality of sensitivity and specificity, the overall classification accuracy of TBS was slightly higher, but not significantly, than BMDa (60.8% vs. 54.9%; $\chi^2 = 0.36$, df = 1, $p = 0.5463$, $n = 51$). With a sensitivity of 54.9%, TBS was higher but not statistically superior to BMDa for overall classification (63% vs. 54.9%; $\chi^2 = 0.69$, df = 1, $p = 0.406$) or for specificity (65% vs. 54.9%; $\chi^2 = 0.85$, df = 1, $p = 0.357$). With iso-specificity of 54.9%, TBS was higher but not statistically superior to BMDa for overall classification (60.8% vs. 54.9%; $\chi^2 = 0.36$, df = 1, $p = 0.546$), or for sensitivity (63.6% vs. 54.9%; $\chi^2 = 0.17$, df = 1, $p = 0.678$).

Subgroup analyses for women with osteoporosis

Also among the 168 subjects, there were 117 (69.6%) who met the T-score criteria for osteoporosis, with a T-score less than -2.5: 31 of the 42 (73.8%) in the fracture group and 86 of the 126 (68.3%) in the control group ($\chi^2 = 0.45$, df = 1, $p = 0.5019$). Again, there were no inter-group differences in mean age (67.1 vs. 65.0 years, $p = 0.2139$),

height (both 155.8 cm, $p = 0.9998$), weight (62.2 vs. 59.0 kg, $p = 0.0610$), or BMI (25.7 vs. 24.3, $p = 0.0865$), but the groups did differ in both BMDa (0.799 vs. 0.882, $p = 0.0008$) and TBS (0.903 vs. 1.047, $p < 0.0001$) (Table 3). The odds ratio for fracture was 2.43 (1.49–3.95) for each incremental decrease in BMDa, 3.36 (1.90–5.92) for each incremental decrease in TBS, and 4.04 (2.35–6.92) for each incremental decrease in (TBS + BMDa). The AUC again was statistically higher for (TBS + BMDa) (0.835, 0.755–0.897, vs. 0.718, 0.627–0.797; $p = 0.013$).

The combination of TBS plus BMDa was compared to both BMDa alone and TBS alone, in terms of the accuracy of classifying patients overall, based on the threshold giving equality of sensitivity and specificity. The combination correctly classified 73.0% of all subjects, versus 64.2% for both BMDa alone and TBS alone ($\chi^2 = 2.10$, df = 1, $p = 0.1470$, $n = 117$). With an iso-sensitivity of 64.2%, the combination was statistically superior to both BMDa and TBS for overall classification (76.1% vs. 64.2%; $\chi^2 = 3.96$, df = 1, $p = 0.0467$) and for specificity (80.2% vs. 64.2%; $\chi^2 = 5.48$, df = 1, $p = 0.0192$). With an iso-specificity of 64.2%, the combination was not statistically superior to either BMDa or TBS for overall classification (71.4% vs. 64.2%; $\chi^2 = 1.39$, df = 1, $p = 0.2386$), but was superior in terms of sensitivity (90.3% vs. 64.2%; $\chi^2 = 6.01$, df = 1, $p = 0.0142$).

Discussion

Albeit in just a small, retrospective, case–control study, there already is previously-presented empirical evidence that the trabecular bone score (TBS) may be of clinical benefit distinguishing between postmenopausal women with and without fractures, be they hip fractures, vertebral fractures, or other [14]. In the current study, we specifically evaluated the potential diagnostic value of TBS alone, and of the combination of TBS and BMDa, in the differentiation of postmenopausal women with versus those without vertebral fractures. We then proceeded to determine if there is a difference in benefit between women with osteopenia, defined as a T-score between -1.0 and -2.5, and women with osteoporosis, strictly defined as a T-score less than -2.5. What we found is that, in the lumbar spine, the TBS appears to discriminate between postmenopausal Caucasian women with a vertebral fracture and those with no fractures, independent of the BMDa in the same region of interest.

Table 3
Characteristics among those subjects with osteoporosis.

	Age [years]	Height [cm]	Weight [kg]	BMI [kg/m ²]	BMDa L1–L4 [g/cm ²]	TBS L1–L4 [mm ⁻¹]
Entire sample (n = 117)						
Mean ± SD	65.6 ± 7.9	155.8 ± 6.4	59.9 ± 8.2	24.7 ± 3.2	0.860 ± 0.103	1.009 ± 0.139
Age-matched controls (n = 86)						
Mean ± SD	65.0 ± 8.0	155.8 ± 6.1	59.0 ± 8.0	24.3 ± 2.9	0.882 ± 0.088	1.047 ± 0.103
Fracture subjects (n = 31)						
Mean ± SD	67.1 ± 7.2	155.8 ± 7.4	62.2 ± 8.6	25.7 ± 3.6	0.799 ± 0.117	0.903 ± 0.169
Test of difference, p	0.2139 ^a	0.9998 ^a	0.0610 ^a	0.0865 ^b	0.0008 ^a	<0.0001 ^b

^a Student's t-test.
^b Mann–Whitney test.

Moreover, among postmenopausal Caucasian women with T-scores less than -1.0 , combining TBS and BMDa of the lumbar spine appears to improve discrimination between those with and without vertebral fractures, and the combination is more specific ($+16.7\%$; $p=0.0037$) and more sensitive ($+19.1\%$; $p=0.0526$) than BMDa used alone (61.9%). Sub-analysis restricted to women with T-scores less than -2.5 continue to suggest some added benefit of the combination of TBS and BMDa, producing a gain of 16.0% in specificity ($p=0.0192$), and a gain of 26.1% in sensitivity ($p=0.0142$). In addition, 8.7% more vertebral fractures are detected with TBS vs. BMDa in women whose T-score places them in the osteopenic range, though further, larger studies are necessary to confirm this apparent advantage of TBS. Finally, when assessing all-comers, those who are osteopenic and those who are osteoporotic, the combination of BMDa and TBS appears to be statistically better than either test used alone, in terms of correctly classifying subjects by overall degree of osteoporosis. In addition, it approaches being statistically superior in terms of classifying fracture status. However, we lacked the statistical power to prove any superiority when sub-grouping subjects into just those with osteopenia.

TBS has several redeeming qualities. These potential advantages include combining an evaluation of bone microarchitecture with one of bone mineral density in the determination of bone fracture risk, thereby adding a second component of fracture risk to the evaluation. TBS also utilizes a 2D image to evaluate trabecular bone microarchitecture, whether it be from standard radiographs or from DXA images, and 2-D images tend to be relatively inexpensive, convenient, and associated with a low dose of irradiation. The problem traditionally has been mathematically transforming 2D into 3D projections to allow for such an evaluation [16], since the 3D microarchitecture of tissue and other objects is not directly measurable in 2D projection-based images. In the trabecular bone score (TBS), however, we have found a way to use the 2D images obtained during DXA to generate a measure of bone microarchitecture, calculated using an established empirical 3D/2D relationship, and two 3D bone characteristics: the solid volume fraction, fs , and the mean solid thickness, Th [12–13]. Indeed in this last study, conducted under real, applicable conditions, we identified significant direct correlations between 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.

Having already been shown to be of benefit in the evaluation of all osteoporosis fractures [14], this novel empirical measurement, the TBS, also appears to be at least as specific as, and probably more sensitive to change than BMDa, in terms of evaluating the risk of vertebral fractures.

Several other imaging techniques have been assessed as potential tools with which to evaluate trabecular bone microarchitecture [7,17], but none of these has emerged as sufficiently efficient for routine clinical use. In the meantime, DXA technology has developed, in terms of both its hardware and software components [18], which allows us to utilize high-quality DXA scans in place of standard radiographs to evaluate certain bone characteristics beyond BMDa. In terms of the currently proposed measure, this means that evaluations of BMDa and TBS can be done at the same time, potentially saving both time and money. In a previous version of TBS software, a manual, operator-dependent intervention was required, consisting of preparing DXA grey level and ROI images. Consequently, the time currently required for TBS analysis, including this manual pre-processing step, has been on the order of 15 min per patient, taking into account spine analyses. Some major developments have been made in this later version to

remove this pre-processing step, and to run automatically the analysis process directly from the DXA scan files, thereby reducing the time required to calculate a TBS to about 2–5 s, a duration that certainly seems compatible with the real-time evaluation of TBS in clinical practice.

Though we consider our results promising, our study certainly has limitations that warrant caution by anyone interpreting them. To begin with, our study was case–control and retrospective. Hence, we cannot directly imply a causative association between reduced TBS and osteoporosis-related fracture. To achieve this end, prospective, longitudinal studies are necessary. Second, our study was relatively small—too small, for example, for us to have much confidence in either of our subgroup analyses, assessing the value of TBS, alone or with BMDa, in women specifically with osteopenia, as defined by T-score.

These limitations aside, we feel that the trabecular bone score (TBS) certainly warrants a closer look to see whether or not it may be of clinical usefulness in the detection and management of osteoporosis, and the evaluation of future fracture risk. For example, it would be of interest to test a case finding strategy using spine BMDa, then TBS to identify subjects at the highest risk of fracture, especially within the osteopenic zone. This also could be applied to osteoporotic patients of young age to decide on a treatment strategy, if needed.

Disclosure/conflict of interest

B. Rabier and R. Winzenrieth are both Scientific Employee of Medimaps SA, Bordeaux, France. D. Hans, TBS Patent co-ownership.

There is neither conflict of interest nor disclosure for the other co-authors.

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