REVIEW

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Trabecular Bone Score: A Noninvasive Analytical Method Based Upon the DXA Image

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ABSTRACT

The trabecular bone score (TBS) is a gray-level textural metric that can be extracted from the two-dimensional lumbar spine dual-energy X-ray absorptiometry (DXA) image. TBS is related to bone microarchitecture and provides skeletal information that is not captured from the standard bone mineral density (BMD) measurement. Based on experimental variograms of the projected DXA image, TBS has the potential to discern differences between DXA scans that show similar BMD measurements. An elevated TBS value correlates with better skeletal microstructure; a low TBS value correlates with weaker skeletal microstructure. Lumbar spine TBS has been evaluated in cross-sectional and longitudinal studies. The following conclusions are based upon publications reviewed in this article: 1) TBS gives lower values in postmenopausal women and in men with previous fragility fractures than their nonfractured counterparts; 2) TBS is complementary to data available by lumbar spine DXA measurements; 3) TBS results are lower in women who have sustained a fragility fracture but in whom DXA does not indicate osteoporosis or even osteopenia; 4) TBS predicts fracture risk as well as lumbar spine BMD measurements in postmenopausal women; 5) efficacious therapies for osteoporosis differ in the extent to which they influence the TBS; 6) TBS is associated with fracture risk in individuals with conditions related to reduced bone mass or bone quality. Based on these data, lumbar spine TBS holds promise as an emerging technology that could well become a valuable clinical tool in the diagnosis of osteoporosis and in fracture risk assessment. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: TRABECULAR BONE SCORE; OSTEOPOROSIS; FRACTURE RISK; BONE MINERAL DENSITY; MICROARCHITECTURE

Introduction

Osteoporosis is a major health concern in virtually all developed countries with up to 9 million new osteoporotic fractures expected annually worldwide.[1–4] The excess mortality rate associated with fragility fractures exceeds 20% in the first year after the fracture.[5,6] In the United States, osteoporosis affects as many as 10 million individuals over the age of 50 years,[7] with 2 million fractures occurring annually.[8] The chance that a woman >50 years of age will suffer an osteoporotic fracture in her lifetime is 40% in the United States.[2] Osteoporosis is also prevalent in men older than 50 years, with 20% suffering an osteoporotic fracture during their lifetime.[9] With the aging world population, these staggering numbers are projected to double over the next 40 to 50 years with 6 million hip fractures expected to occur worldwide by 2050.[1]

Osteoporosis is conceptually defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[10] The operational definition of osteoporosis is made by dual-energy X-ray absorptiometry (DXA), although clinically the presence of a fragility fracture with or without DXA corroboration is commonly used as a diagnostic criterion and an intervention threshold.[11] Although bone mineral density (BMD) measured by DXA is a major determinant of bone strength and fracture risk,[12] most individuals with a fragility fracture will have BMD values in the osteopenic or even normal range.[11,13] This observation means

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that factors other than BMD influence bone strength and fracture risk, including microarchitectural deterioration of bone tissue as implied from the conceptual definition of osteoporosis. Additional skeletal and extra-skeletal factors such as bone geometry, micro-damage, mineralization, bone turnover, age, family history, and fall risk contribute to the overall fracture risk.[14–19]

Assessment of skeletal microstructure can be made by histomorphometric analysis of the transiliac crest bone biopsy. Although valuable and highly informative, the iliac crest bone biopsy is an invasive procedure and primarily a research tool. Moreover, there has always been concern about whether the iliac crest is representative of sites that are truly at risk for fracture such as the spine and the hip. High-resolution noninvasive imaging technologies have been developed to address this issue: High-resolution peripheral quantitative computed tomography (HRpQCT),[20] flat-panel volume CT,[21,22] and magnetic resonance imaging (MRI)[23] have value in the assessment of bone microarchitecture. Although attractive in principle, these technologies are not routinely available. A major challenge, therefore, has been to develop a readily clinically available, noninvasive technology that permits efficient and accurate clinical evaluation of skeletal microstructure. To this end, two-dimensional (2D) X-ray–based images, such as plain radiographs, have been investigated.[24–29]

Over the past several years, the hardware and software components of DXA technology have advanced.[30] Newer generations of DXA systems provide not only accurate and reproducible measurements of BMD but also the opportunity to use high-quality DXA scans in place of standard X-rays to identify vertebral fractures. Semiquantitative and fully quantitative methods to determine the presence of vertebral fracture,[31] as well as indices related to hip geometry,[32,33] can be derived from high-quality DXA images. Bone stiffness assessed by finite element analysis of X-ray images (FEXI), a technique that uses a finite element analysis model applied to 2D gray-level images, can also be extracted from DXA images.[34–36] Finally, the evaluation of bone mineral distribution at the proximal femur in hip DXA scans may be well suited to enhance standard densitometric evaluations as a predictor of hip fracture risk.[37] Taking advantage of high-quality DXA images, and based upon previous studies using 2D X-ray images to estimate bone microarchitecture, the trabecular bone score (TBS) was developed as another approach for assessing skeletal microstructure noninvasively from 2D DXA projection images.[38–40]

Estimation of 3D Indices From a 2D Projected Image

Transforming a 2D projected image into a three-dimensional (3D) structure is a mathematical challenge.[41,42] However, several kinds of texture analysis methods, such as Fourier conversion, fractal analysis, and run-length analysis, have been proposed as indirect measurements of 3D trabecular bone microarchitecture.[41–45] These methods analyze trabecular structures according to different statistical properties of pixels in relation to density, computing a feature strongly related to the 3D parameters of the projected trabecular bone. These techniques provide a global estimate of bone quality, but they are not direct physical measurements of trabecular parameters.[46] Independent of the method used to analyze bone texture, it is important to consider the reproducibility and discriminative capacity of the measurement, sensitivity to changes with disease and treatment, and the incremental improvement in the evaluation of osteoporotic fracture risk over that obtained with current approaches to clinical risk factor assessment, with or without BMD measurement.

What Is the Trabecular Bone Score?

TBS is a textural index that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect index of trabecular microarchitecture. TBS is not a direct physical measurement of bone microarchitecture, but rather an overall score computed by the projection of the 3D structure onto a 2D plane.[46] As is the case for most developing technologies, TBS has undergone refinement from its earliest description[38] to more recent versions.[39,40] With the exception of the study by Pothuaud and colleagues,[38] all the TBS studies available and reviewed here were performed using the more recent versions of the TBS software. The following principles underlie TBS: A dense trabecular microstructure projected onto a plane generates an image containing a large number of pixel value variations of small amplitude. Conversely, a 2D projection of a porous trabecular structure produces an image with a low number of pixel value variations of high amplitude (Fig. 1). A variogram of those projected images, calculated as the sum of the squared gray-level differences between pixels at a specific distance, can estimate a 3D structure from the existing variations on the 2D projected images. TBS is derived from the experimental variograms of 2D projection images. TBS is calculated as the slope of the log-log transform of the 2D variogram, where the slope characterizes the rate of gray-level amplitude variations. A steep variogram slope with a high TBS value is associated with better bone structure, whereas low TBS values indicate worse bone structure. More simply stated, TBS principles could be compared to an aerial view of a forest. An aerial view of the forest cannot discern individual elements of that forest (ie, trees); the DXA image cannot discern the individual elements of its components (trabeculae). Although both of these "low power" views do not have sufficient resolution to identify individual trabeculae (by the spine DXA image) or trees (in the forest aerial view), the areas of missing bone in the trabecular compartment or clearings in the forest are quite clearly noticeable.

Because the DXA image is usually retrievable, even though it might have been obtained years before, TBS can be readily applied to any available DXA image obtained from GE Lunar (Prodigy and iDXA; Madison, WI, USA) and Hologic (Delphi, QDR 4500, and Discovery; Waltham, MA, USA) densitometers.[46] TBS, typically measured at the lumbar spine, is determined using the same region of interest as the BMD measurement, so that vertebrae excluded from the BMD calculation, eg, vertebrae with fractures or osteoarthritis, are also excluded from the TBS analysis. Although the TBS result is given for each vertebra, the TBS value reported represents the average of L_1 to L_4.

The following normal range for TBS values in postmenopausal women has been proposed: TBS $\geq$1.350 is considered to be normal; TBS between 1.200 and 1.350 is considered to be consistent with partially degraded microarchitecture; and TBS $\leq$1.200 defines degraded microarchitecture. These cutoff points were established by a working group of TBS users from different countries,[47] by analogy with the three BMD categories, ie, normal bone mass, osteopenia, and osteoporosis. A normal range for TBS in men has not yet been proposed.

Bone Qualities That Affect TBS

TBS measures the image texture, which correlates with 3D measurements of trabecular microstructure. Studies ex vivo have compared the results of TBS analyses derived from both simulated 2D-projection micro-computed tomography (μCT) images and spine DXA images with standard 3D parameters of bone microarchitecture assessed by high-resolution μCT in specimens of human vertebral bone.[38–40,48] Of note, in all these ex vivo studies, the vertebral bone specimens were used intact, including the superimposed posterior element.[38–40,48] Winzenrieth and colleagues[39] showed that TBS derived from 2D-projection μCT images of human cadaveric vertebrae correlated with trabecular microarchitecture indices by μCT, independent of the image resolution, up to a simulated pixel size of 1023 μm. At 93-μm plane resolution, significant unadjusted correlations were found between TBS from the μCT images and connectivity density (Conn. D: $r^2 = 0.746$; $p < 0.001$), trabecular number (Tb.N: $r^2 = 0.637$; $p < 0.001$), and trabecular separation (Tb.Sp: $r^2 = 0.430$; $p < 0.001$).[39] TBS from the μCT images was also correlated with bone volume fraction (BV/TV) and moderately well correlated with trabecular thickness (Tb.Th).[39] Among human cadaveric vertebral samples that were identical in bone density in g/cm^2, ex vivo TBS analysis derived from spine DXA images of the bone fragments excluding cortical bone showed differences in Tb.N, Tb.Th, and Tb.Sp assessed by μCT of the same bony region.[40] It is unclear, however, why TBS, in this ex vivo study, was negatively correlated with Tb.Th, and whether the associations between TBS and μCT parameters would remain after adjusting for age.

Similarly, Roux and colleagues[48] confirmed that TBS derived from ex vivo DXA images of 16 human L_3 lumbar vertebrae correlated with trabecular microarchitectural parameters assessed by μCT, with the exception of Tb.Th. Moreover, TBS was associated with structural model index (SMI; $r = -0.62$, $p < 0.01$), a topological parameter associated with lumbar vertebral mechanical behavior. TBS was also correlated with vertebral mechanical behavior, but the combination of TBS with areal BMD (aBMD) did not significantly improve the prediction of vertebral mechanical behavior compared with aBMD alone.

Correlations between TBS derived from the DXA images and 3D microarchitecture parameters were also assessed in vivo. Silva and colleagues[49] reported significant correlations between spine TBS and HRpQCT measurements of volumetric densities, cortical thickness, Tb.N, Tb.Sp, and whole bone stiffness at the radius ($r = 0.442$ to 0.507; $p < 0.05$), in 22 postmenopausal women with primary hyperparathyroidism (PHPT). Although TBS was also positively associated with measures of volumetric density, cortical thickness, and whole bone stiffness at the tibia ($r = 0.471$ to 0.619; $p < 0.05$), its correlation with Tb.N and Tb.Sp was significant only after adjusting for body weight ($r = 0.573$ and $r = -0.524$, respectively). Of note, TBS was not associated with Tb.Th or trabecular stiffness in either site evaluated.

In a more recent study, Silva and colleagues[50] evaluated the correlation of TBS with central quantitative computed tomography (QCT) and HRpQCT measures in 115 Chinese-American and

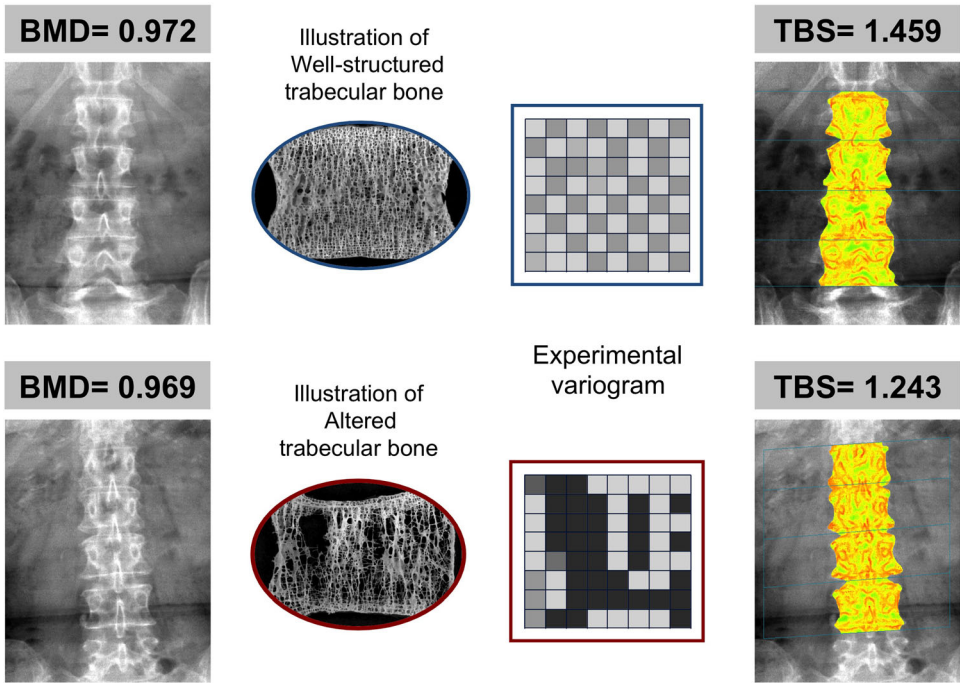

Fig. 1. Representation of the TBS principles and an example where the TBS appears to be independent from BMD. Upper panel shows BMD and TBS images of a 73-year-old woman, with a BMI of 24.2 kg/m^2, lumbar spine BMD of 0.972 g/cm^2, and TBS of 1.459. Lower panel shows BMD and TBS images of a 74-year-old woman, with a BMI of 24.3 kg/m^2, lumbar spine BMD of 0.969 g/cm^2, and TBS of 1.243. Although the images of the bone architecture and the experimental variogram are illustrations and do not represent actual images from these patients' skeleton, they were placed here to demonstrate the TBS principles: more numerous and connected and less sparse trabeculae translate into a high TBS value, whereas a low trabecular number and connectivity and high trabecular separation translate into a low TBS. BMD = bone mineral density; TBS = trabecular bone score.

white women (71 premenopausal and 44 postmenopausal). TBS was correlated with lumbar spine (LS) trabecular volumetric bone mineral density by QCT ($r = 0.664$) and with trabecular and cortical QCT parameters at the femoral neck ($r = 0.346$ to 0.651) and total hip ($r = 0.491$ to 0.643) ($p < 0.001$ for all). TBS and LS aBMD together predicted more of the variance in QCT measures than aBMD alone. TBS was weakly to moderately associated with HRpQCT indices at the radius and tibia ($r = 0.20$ to 0.52), except radial cortical thickness and tibial trabecular thickness.

Age as an Important Factor in TBS

Dufour and colleagues[51] evaluated cross-sectional age-related changes in TBS in a cohort of 5942 white French women, from 45 to 85 years of age with body mass index (BMI) $<40\ kg/m^2$, referred to two clinical centers from January 1997 to December 2008. This "all-comers" approach avoids the problem of defining "healthy subjects" and enrolls a large number of individuals representative of the clinical population. TBS values showed a weak negative correlation with BMI ($r = -0.17$) and weight ($r = -0.14$), and were not correlated with height. A linear decline of 14.5% in L_1 to L_4 TBS was seen between 45 and 85 years of age (6% before 65 years and 8.5% after age 65 years). Similar results were obtained when different regions of interest of the lumbar spine were considered.

Simonelli and colleagues[52] investigated cross-sectional age-related changes in LS TBS in a cohort of non-Hispanic US white women aged 30 and older. Subjects, recruited from three geographically spaced centers, were excluded if they had fractures, were receiving any osteoporosis treatment, or had any illness known to influence bone metabolism. DXA was performed in 619 white US women aged 30 to 90 years using GE-Lunar Prodigy densitometers. With age, there was a significant decrease in TBS values obtained for all lumbar vertebral combinations. L_1 to L_4 TBS decreased by 16.0% between 45 and 90 years of age (versus –2.34 *T*-score for spine BMD). The annual rate of loss in TBS increased after the age of 65 years (from –0.004 to –0.006) and was similar to that obtained for French white women.[51]

In agreement with these reports, a cross-sectional study showed parallel age-related declines in LS BMD and TBS in 29,407 women $\geq$50 years from the Canadian province of Manitoba referred for baseline BMD evaluation.[53] Similarly, El Hage and colleagues[54] showed a negative correlation between L_2 to L_4 TBS and age ($r = -0.39$, $p < 0.001$) in 4907 Lebanese women aged 20 to 90 years.

Precision of TBS

The short-term in vivo precision of BMD and TBS was reported in 30 subjects using two repeat measurements and the root-mean-square coefficient of variation.[51] For the two centers evaluated, precision was 1.1% and 1.35% for BMD and 1.9% and 1.5% for TBS. In 92 individuals with repeat spine DXA scans performed within 28 days (51 same day, 41 different day), interobserver short-term reproducibility (CV) for spine TBS and BMD calculated were 2.1% and 1.7%, respectively.[55] In the OPUS study,[56] the short-term precision calculated after repositioning in 60 patients was 1.44% for TBS and 1.18% for LS BMD. Finally, Popp and colleagues[57] reported in 15 outpatients measured thrice after repositioning a coefficient of variation for spine BMD measurements of 0.90% with a corresponding coefficient of variation of 1.12% for TBS.

TBS as a Risk-Assessment Tool: Cross-sectional Studies

Several cross-sectional studies have shown that TBS is associated with vertebral, femoral neck, and other types of osteoporotic fracture in postmenopausal women.[58–63]

The retrospective case-control study by Pothuaud and colleagues[58] evaluated 135 postmenopausal women from two centers, of whom 45 had radiographically confirmed fractures: 20 vertebral, 5 hip, and 20 other types of osteoporotic fractures. Ninety age- and LS BMD-matched controls were included. LS BMD and TBS were assessed at L_2 to L_4 after exclusion of vertebrae with fractures or osteoarthritis. Women with any fracture had significantly lower TBS values than controls (0.784 ± 0.176 versus 0.899 ± 0.177; $p = 0.0005$). Unadjusted odds ratio (OR) and the area under the receiving operator curve (AUC) for all fractures were 1.95 (95% confidence interval [CI] 1.31–2.89) and 0.685, respectively. For the analyses of vertebral fractures, 60 age- and LS BMD-matched controls were used. TBS was also lower in women with vertebral fracture than in controls (0.747 ± 0.140 versus 0.908 ± 0.178; $p = 0.0004$), with an unadjusted OR and AUC of 2.66 (95% CI 1.46–4.85) and 0.776, respectively.

Another retrospective case-control study evaluated TBS in 243 French white postmenopausal women, aged 50 to 80 years, with osteopenia (BMD *T*-scores between -2.5 and -1.0), and BMI ranging from 17 to $35\ kg/m^2$.[59] Vertebral fractures were assessed on radiographs. A total of 81 patients with vertebral fractures were compared with 162 age-matched ($\pm$3 years) controls without evidence of fracture at any bone site. Mean BMI was significantly lower in controls ($23.3\ kg/m^2$ versus $25.4\ kg/m^2$; $p = 0.0001$). Women with vertebral fractures had lower LS BMD and TBS than controls (0.945 versus $0.968\ g/cm^2$, $p = 0.002$; and 0.970 versus 1.061, $p < 0.0001$, respectively). After adjustment for body weight, the ORs for LS BMD, TBS, and the combination of LS BMD + TBS were 1.63 (95% CI 1.20–2.22), 1.97 (95% CI 1.31–2.96), and 2.04 (95% CI 1.42–2.92), respectively. Although the unadjusted AUC was significantly greater for the combination LS BMD + TBS than for LS BMD alone ($p = 0.005$), the differences in the adjusted AUCs were not reported.

In the study of Rabier and colleagues,[60] 42 patients with vertebral fractures assessed by X-rays were compared with 126 controls without evidence of low-trauma fracture at any bone site. This retrospective, nonrandom case-control study conducted in three centers in France enrolled white postmenopausal women with low BMD (*T*-score < -1.0 at the LS, total hip, and/or femoral neck), aged 50 to 80 years, and BMI values ranging from 19 to $33\ kg/m^2$. Cases and controls were matched for age ($\pm$3 years). LS BMD and TBS were assessed in the same region of interest (ROI), excluding any fractured and/or arthrosed vertebrae. Women with vertebral fractures had a higher BMI than subjects without fracture (25.8 versus $24.2\ kg/m^2$; $p = 0.02$). Both LS BMD and TBS were lower in fractured subjects than in controls (0.839 versus $0.906\ g/cm^2$, $p = 0.002$; and 0.911 versus 1.053, $p < 0.0001$, respectively). After adjusting for body weight, the ORs were 2.48 (95% CI 1.61–3.83) for LS BMD, 3.81 (95% CI 2.17–6.72) for TBS, and 3.55 (95% CI 2.24–5.62) for LS BMD + TBS. Although the AUCs for LS BMD or TBS alone were comparable ($p = 0.140$), the combination of LS BMD and TBS resulted in a greater AUC than LS BMD alone ($p = 0.006$).

The association of spine TBS with femoral neck fracture has also been assessed in a nonrandom case-control study of 191

women, aged 50 to 91 years (mean 66.84 ± 9.45 years), and BMI ranging from 17 to 35 kg/m^2 (mean 26.8 ± 3.3 kg/m^2).[61] Cases were women presenting with an osteoporotic femoral neck fracture ($n = 83$). The control group ($n = 108$), which was not matched for age or BMD with the fracture group, included women without low-energy fractures at any site. Cases were older and had a lower BMI than controls (69.8 versus 64.6 years, $p = 0.0001$; and 26.2 versus 27.2 kg/m^2, $p = 0.03$, respectively). Significantly lower BMD at all sites and spine TBS values were found in women with hip fracture than in those without ($p < 0.0001$). Spine BMD and TBS discriminated fractured from nonfractured subjects equally well (LS BMD: AUC = 0.695 [0.625–0.760] and OR = 2.21 [95% CI 1.56–3.13] versus LS TBS: AUC = 0.668 [0.597–0.734] and OR = 2.05 [95% CI 1.45–2.89]) and independently. BMD at the femoral neck and at the total hip were also associated with fracture (unadjusted ORs and AUCs of 5.86 [95% CI 3.39–10.14] and 0.825; and 6.06 [95% CI 3.55–10.34] and 0.844, respectively). After adjustment for age, the OR for femoral neck fracture remained significant for LS BMD (OR = 1.94 [95% CI 1.35–2.79] and TBS (OR = 1.71 (95% CI 1.15–2.79]).

Krueger and colleagues[62] tested whether the routine use of TBS would improve identification of those at high fracture risk by DXA alone in a retrospective, nonrandom case-control study. The study population comprised 429 white postmenopausal women (mean age of 71.3 years), of whom 158 had a history of low-energy nonvertebral fracture or a prevalent vertebral fracture identified by vertebral fracture assessment (VFA; $n = 91$). The control group constituted 271 age-matched women with no evidence of osteoporotic fracture either by self-report or VFA. The two groups were well matched in age, but the mean BMI was higher in cases than in controls (26.2 versus 25.3 kg/m^2; $p = 0.026$). Age and BMI-adjusted ORs for all fractures and vertebral fractures were 2.46 (95% CI 1.9–3.1) and 2.49 (95% CI 1.9–3.3), respectively, for TBS. Adjusted ORs ranged from 1.36 to 1.63 for LS, hip BMD, or the lowest BMD *T*-score for these fractures. The OR for TBS remained significant after adjustment for LS BMD or the lowest BMD *T*-score. Seventy-three percent of all fractures occurred in nonosteoporotic women, 72% of whom had a TBS below the median. Although such a simplistic approach is not practical for clinical decision-making, these results indicate that TBS assessment may enhance standard DXA measurement.

Finally, in a cross-sectional study, Lamy and colleagues evaluated 631 women from the OsteoLaus cohort, a Swiss population-based group of 1502 women aged 50 to 80 years.[63] The mean age of the study group was 67.4 ± 6.7 years, with a mean BMI of 26.1 ± 4.6 kg/m^2. Vertebral fractures were assessed by VFA. The prevalence of grade 2 or 3 vertebral fractures, major osteoporotic fractures, and at least 1 osteoporotic fracture were 8.4%, 17%, and 26%, respectively. The age- and BMI-adjusted ORs for vertebral fracture (grades 2 and 3), major osteoporotic fractures, and all osteoporotic fractures were, respectively, 1.8 (95% CI 1.2–2.5), 1.6 (95% CI 1.2–2.1), and 1.3 (95% 1.1–1.6) for each SD decline in LS BMD, and 2.0 (95% CI 1.4–3.0), 1.9 (95% CI 1.4–2.5), and 1.4 (95% CI 1.1–1.7) for each SD decline in TBS. The association between fracture and TBS remained significant after adjusting for LS BMD, with an age-, BMI-, and LS BMD-adjusted OR of 1.7 (95% CI 1.1–2.7) for vertebral fracture, and 1.6 (95% CI 1.2–2.2) for major osteoporotic fractures.

A few abstracts presented at international meetings have assessed the ability of TBS to differentiate between fractured and nonfractured groups of men.[64,65] Leib and colleagues[64] studied 184 men, of whom 46 had sustained a fragility fracture. The average TBS value was lower in the group with fractures than the age- and lumbar spine BMD-matched controls ($p = 0.007$; ΔTBS = –0.062). The OR per standard deviation and the AUC for TBS were 1.60 (95% CI 1.13–2.27) and 0.620 (0.546–0.690), respectively. Similarly, Lorenc and colleagues[65] showed lower TBS values in men who had at least one prevalent vertebral fracture as assessed by VFA ($n = 44$) than in those without fractures ($n = 50$) (0.96 ± 0.15 versus 1.06 ± 0.14; $p = 0.001$). LS BMD also tended to be lower in fractured subjects ($p = 0.07$). TBS, but not LS BMD by DXA, predicted vertebral fracture (AUC = 0.69; 95% CI 0.589–0.783; $p = 0.0004$). The optimal cut-point for TBS was 0.987, giving 60.47% sensitivity and 80% specificity. Subjects with TBS values below this cut-point had ~5 times higher risk for vertebral fracture (OR = 5.7; 95% CI 2.271–14.28) than individuals with TBS values above that threshold.

In summary, these studies show that TBS values are lower in postmenopausal women with a prior osteoporotic fracture compared with individuals without fracture, irrespective of whether the BMD *T*-score is in the osteoporotic or osteopenic range. Similar performance characteristics have been demonstrated in men, but so far the reports are preliminary.[64,65] The ORs reported in the cross-sectional studies of postmenopausal women are summarized in Fig. 2.

TBS as a Risk-Assessment Tool: Prospective Studies

Prospective studies have shown that TBS predicts fracture risk in postmenopausal women (Fig. 3).[55,56,66,67] The Manitoba study[55] included 29,407 women aged ≥50 years, of whom 1668 (5.7%) had incident osteoporotic fractures, including 439 (1.5%) clinical spine and 293 (1.0%) hip fractures during a mean follow-up of 4.7 years. Women with incident major osteoporotic, spine, and hip fractures had significantly lower LS TBS and BMD (all $p < 0.0001$) at baseline than nonfractured subjects. Each SD decline in TBS conferred a 35% greater age-adjusted risk of any major osteoporotic fractures (HR 95% CI 1.29–1.42, AUC 0.63) versus 47% (HR 95% CI 1.39–1.55, AUC 0.64) for LS BMD and 68%

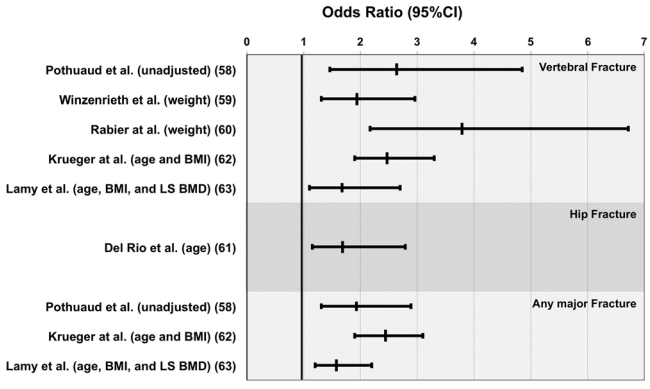

Fig. 2. TBS odds ratios for different types of osteoporotic fractures in cross-sectional studies of postmenopausal women. Markers represent odds ratios (ORs) and error bars (continuous lines) represent 95% confidence intervals (CIs). Studies and respective references as well as the covariate used to adjust the ORs (in parentheses) are indicated in the Y-axis.

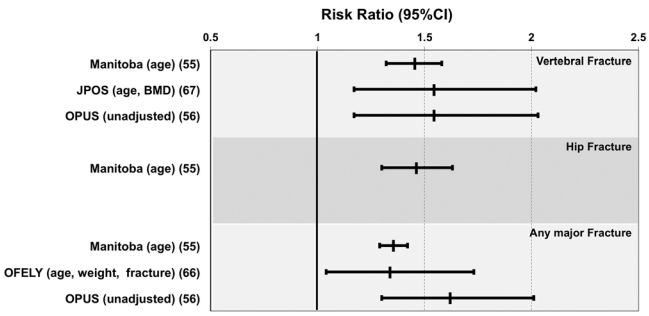

Fig. 3. TBS risk ratios for different types of osteoporotic fractures in prospective studies of postmenopausal women. Markers represent risk ratios and error bars (continuous lines) represent 95% confidence intervals (CIs). Studies and respective references as well as the covariate used to adjust the risk ratio (in parentheses) are indicated in the Y-axis.

(HR 95% CI 1.58–1.78, AUC 0.68) for femoral neck BMD. The combination of any BMD measurement (lumbar spine, femoral neck, or total hip) with LS TBS significantly improved fracture prediction compared with BMD or TBS alone ($p < 0.0001$). The incremental improvement in AUC for BMD alone compared with BMD and TBS combined was statistically significant but small (lumbar spine +0.02, femoral neck +0.01, total hip +0.01). When adjusted for BMD and additional clinical risk factors, each SD decline in TBS conferred a 17% to 20% greater risk of any major osteoporotic fractures. The age-adjusted hazard ratios for lumbar spine TBS to predict clinical vertebral fracture was 1.45 (95% CI 1.32–1.58) and for hip fracture was 1.46 (95% CI 1.30–1.63); adjustment for BMD and additional clinical risk factors attenuated the HRs (vertebral fractures 1.14–1.22, hip fractures 1.25–1.40).

A prospective study of the OFELY cohort of 560 postmenopausal white women showed, over a mean follow-up of 8.0 ± 1.1 years, that women who sustained a fragility fracture ($n = 94$, any site) had lower spine BMD (*T*-score: -1.9 ± 1.2 versus -1.4 ± 1.3, $p < 0.001$) and spine TBS (1.237 ± 0.098 versus 1.284 ± 0.105; $p < 0.001$) than women without incident fracture ($n = 466$).[66] Women with incident fractures were also older and had a lower body weight than women without fractures (70.4 ± 9.4 versus 65.3 ± 7.6 years, $p < 0.001$; and 59.9 ± 9.0 versus 62.0 ± 9.0 kg, $p < 0.05$, respectively). Unadjusted fracture prediction was similar for spine BMD (OR = 1.42; 95% CI 1.17–1.72) and TBS (OR = 1.57; 95% CI 1.25–1.98), but lower than with total hip BMD (OR 2.12; 95% CI 1.62–2.77). The OR for TBS, although attenuated, was still significant for fracture prediction when age, body weight, and prevalent fracture were entered in a multivariate stepwise analysis (OR 1.34; 95% CI 1.04–1.73). Thirty-seven percent of fractures occurred in the lowest quartile of LS TBS, regardless of BMD.

In another study conducted by Iki and colleagues,[67] 665 women (mean age 64.1 ± 8.1 years) were evaluated for incident vertebral fractures on VFA over a mean follow-up of 8.3 years. At follow-up, 140 incident vertebral fractures were diagnosed in 92 women. Women with vertebral fracture had lower LS BMD (0.729 ± 0.126 g/cm^2) and TBS (1.132 ± 0.110) than those without fractures (BMD 0.814 ± 0.141 g/cm^2, TBS 1.200 ± 0.095; both $p < 0.0001$). The TBS difference was substantially attenuated after adjusting for confounding variables but remained significant (1.175 versus 1.193, $p = 0.0386$). Unadjusted odds ratios of vertebral fracture for each SD decrease in LS BMD and TBS were, respectively, 1.69 (95% CI 1.39–2.05) and 1.98 (95% CI 1.56–2.51). The AUCs of LS BMD, TBS, and LS BMD + TBS were 0.673, 0.682, and 0.700, respectively. TBS remained a predictor of vertebral fracture after adjusting for age and LS BMD (OR = 1.54; 95% CI 1.17–2.02). The combination of spine TBS and spine aBMD was not significantly better than using BMD alone. When patients were classified into TBS tertile groups, higher incidence rate of vertebral fracture was observed in lower TBS groups in each BMD stratum.

Finally, Briot and colleagues[56] investigated the added value of TBS to BMD for prediction of fractures in 1007 postmenopausal women aged >50 years from three European centers of the Osteoporosis and Ultrasound Study (OPUS). Over the mean follow-up of 6 years, incident low-trauma fractures, assessed by self-report, and incident vertebral fractures, assessed by thoracic and lumbar spine radiographs, were detected in 82 (8.1%) and 46 (4.6%) women, respectively. Compared with subjects without fractures, women with incident fractures were older and had a lower TBS and BMD at all sites (LS, total hip, and femoral neck). The fracture discriminatory performance of TBS, BMD, and the combination of both was evaluated using reassignment analysis assessed by net reclassification improvement (NRI). For prediction of incident clinical osteoporotic fractures, performance of TBS was significantly better than LS BMD (NRI = 16.3%, $p = 0.007$), but similar to total hip BMD (NRI = 13.1%, $p = 0.08$) and femoral neck BMD (NRI = 9.5%, $p = 0.215$). The combination of TBS with LS BMD was not different from LS BMD alone (NRI = 10.5%, $p = 0.105$). For prediction of vertebral fractures, the combination of TBS and LS BMD increased the performance over LS BMD alone (NRI = 8.6%, $p = 0.046$), but the performance of TBS did not differ from BMD at LS, total hip, or femoral neck. Similarly, TBS and BMD at the LS, total hip, or femoral neck, either alone or in combination, predicted clinical osteoporotic and vertebral fractures equally well. The unadjusted OR for TBS was 1.62 (95% CI 1.30–2.01) for clinical osteoporotic fracture, and 1.54 (95% CI 1.17–2.03) for vertebral fracture. For both types of fractures, the AUC for TBS was similar to BMD and to the combinations of TBS with BMD at any site.

Changes in TBS With Treatment of Osteoporosis

Several studies have investigated the effects of treatment on spine TBS.[57,68–72] Although a number of these studies have been published as full-length papers,[57,68,69] data available in abstracts[70–72] are also reviewed here.

Krieg and colleagues[68] investigated the effects of antiresorptive agents (86% bisphosphonates, 10% raloxifene, and 4% calcitonin) on TBS in a retrospectively defined cohort of women aged 50 years and older. The study group comprised 534 women newly initiating treatment with high adherence (defined as a medication possession ratio >75%) and 1150 untreated women followed for a mean period of 3.7 years. Relative to baseline, similar significant decreases in mean spine BMD (-0.36 ± 0.05%/year) and spine TBS (-0.31 ± 0.06%/year) were evident among nontreated subjects (both $p < 0.001$). Treated women experienced a mean increase in BMD of $+1.86 \pm 1.8$%/year ($p < 0.002$), whereas TBS improved by only $+0.2 \pm 1.9$%/year ($p < 0.001$). An independent study showed similar effects on TBS in women treated with zoledronic acid ($n = 54$) over 3 years compared with placebo-treated subjects ($n = 53$).[57] Relative to baseline, patients treated with zoledronic acid had a significant increase

in LS BMD at months 12, 24, and 36 (+4.96%, +7.88%, and +9.58%, respectively; $p < 0.0001$ for all). Patients treated with zoledronic acid also had an increase in TBS at month 24 (+1.11%; $p < 0.05$) and month 36 (1.41%; $p < 0.04$), whereas in placebo-treated subjects, TBS was not different from baseline at any time point. In treated patients, 35% of patients achieved a TBS increase above the LSC.

Kalder and colleagues[69] performed an analysis of a small substudy of the randomized Tamoxifene Exemestane Adjuvant Multinational (TEAM) trial to determine the effects of exemestane (EXE) and tamoxifene (TAM) on LS BMD and TBS in postmenopausal women with hormone-sensitive primary breast cancer. In all, 36 women were randomized to receive TAM ($n = 17$) or EXE ($n = 19$). Although patients receiving TAM had a mean increase from baseline in LS BMD of +1.0, +1.5, and +1.9%, patients receiving EXE showed a mean decrease of –2.3, –3.6, and –5.3% at 6-, 12-, and 24-month treatment, respectively. Similarly, TBS increased by +2.2%, +3.5%, and +3.3% in TAM-treated subjects, whereas it decreased by –0.9%, –1.7%, and –2.3% in EXE-treated women at months 6, 12, and 24, respectively. Changes in TBS from baseline were different between EXE and TAM at months 6 ($p < 0.05$), 12 ($p < 0.007$), and 24 ($p < 0.006$). No correlations between changes in TBS and BMD were seen during the follow-up.

The effects of strontium ranelate (SrRan) and alendronate on TBS were evaluated in a post hoc analysis performed in 79 women with postmenopausal osteoporosis of 189 included in a double-blind, double-dummy, randomized study.[70] Women were randomized to either SrRan 2 g/day or alendronate 70 mg/week for 2 years. TBS and BMD parameters were assessed in the LS after 12 and 24 months of treatment. Over 1 and 2 years, LS BMD increased significantly by 5.6% and 9.0% in the SrRan group and by 5.2% and 7.6%, respectively, in the alendronate group. LS TBS increased by 2.3% ($p < 0.001$) and 3.1% ($p < 0.001$) in the SrRan group, but the change in the alendronate group was not significant (0.5% and 1.0%, respectively). There was a significant between-group difference with SrRan showing larger TBS increases than alendronate ($p = 0.04$ and $p = 0.03$).

The effects of teriparatide on LS BMD and TBS were investigated in postmenopausal women with osteoporosis.[71] In this open-label, multicenter study, 82 women were treated with teriparatide for 2 years. LS BMD increased by +7.6% ($p < 0.001$) and spine TBS increased by +4.3% ($p < 0.001$). At 2 years, there was no correlation between the changes in BMD and TBS from baseline.

Finally, McClung and colleagues[72] explored the effects of denosumab (DMAb) on TBS over a 36-month period in women from the FREEDOM trial with DXA scans eligible for TBS evaluation. In FREEDOM, a 3-year, randomized, double-blind trial, women with postmenopausal osteoporosis received placebo or 60 mg DMAb every 6 months. A subset of women was enrolled in a DXA substudy, where LS DXA scans were obtained at baseline, 12, 24, and 36 months, and TBS was retrospectively calculated in a blinded-to-treatment manner. A total of 285 women (128 placebo, 157 DMAb; mean age 73 years) had an evaluable TBS value at baseline and ≥ 1 post-baseline visit. Mean LS BMD *T*-score was –2.79, and mean LS TBS was 1.200. Among DMAb-treated subjects, LS BMD compared with TBS increased by +5.7% versus 1.4% (month 12), +7.8% versus +1.9% (month 24), and +9.8% versus +2.4% (month 36), respectively. TBS change was largely unrelated to BMD change, either absolute or percent change (all $r^2 < 0.06$).

In general, the impact of osteoporosis therapy on TBS is smaller in magnitude than on BMD (Fig. 4; not a head-to-head comparison). This is not surprising because one would expect a greater improvement in BMD, particularly with antiresorptive therapy, resulting from increased mineralization and filling in of the remodeling space than improvement in trabecular microstructure as estimated by TBS. Similarly, although these studies cannot be formally compared, the data show greater changes on TBS with teriparatide and SrRan than with antiresorptive therapy. This observation might be explained by previous findings of maintenance of bone microarchitecture attributable to antiresorptive therapy rather than a major improvement in microarchitecture, as expected with teriparatide. SrRan might give more impressive results by TBS by virtue of how it intercalates into the bone crystal per se. In general, 30% to 60% of actively treated individuals for 2 or 3 years did show a TBS gain above the LSC. Conversely, at least 20% to 33% of patients in the placebo group showed a TBS loss exceeding the LSC. The role of TBS for monitoring treated or untreated osteoporosis is unclear. Further research is needed to determine whether a treatment-related increase in TBS provides an index of antifracture effectiveness.

Can TBS Be Useful in Other Conditions Associated With Reduced Bone Mass or Quality?

The evaluation of bone microarchitecture in addition to BMD is of interest in a number of conditions associated with increased fracture risk. In cases of long-term glucocorticoid (GC) therapy, for example, the increase in fracture risk is largely independent of BMD by DXA,[73] which could be related to alterations in bone microstructure as described by histomorphometric parameters. Type 2 diabetes is another example in which the fracture risk is increased despite BMD values by DXA that are higher than in nondiabetic individuals.[74,75] Several studies have evaluated TBS in individuals with conditions or diseases related to increased fracture risk.[49,76–82] TBS was associated with fragility fracture in subjects with diabetes,[76] rheumatoid arthritis,[77] primary

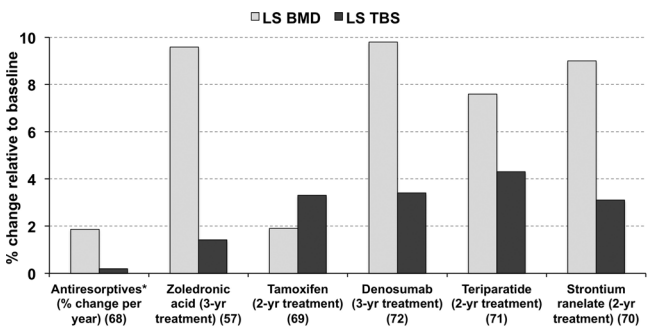

Fig. 4. Percent change from baseline in LS BMD and TBS with different osteoporosis treatment in different studies (not a head-to-head comparison). The percent change for the antiresorptive agents is reported per year, whereas the percent changes for the other therapies are reported after 2 or 3 years of treatment as indicated. References are shown in parentheses in the X-axis. *Antiresorptive agents represent a cluster of bisphosphonates (86%), raloxifene (10%), and calcitonin (4%).[68]

hyperparathyroidism,[78,79] and adrenal incidentaloma.[80] Data reported in abstracts also showed that TBS is related to fractures in individuals on long-term GC therapy[81] and chronic kidney disease.[82] Evidence for these conclusions is presented below.

The ability of LS TBS to account for increased fracture risk in diabetes mellitus was evaluated in a retrospective cohort study from a large clinical DXA registry in the province of Manitoba, Canada.[76] Of the 29,407 women aged ≥50 years with baseline DXA examinations, 2356 (8.1%) had diabetes mellitus (type 1 and type 2 diabetes mellitus could not be distinguished in the data sources, so that the definition for diabetes mellitus included is inclusive). Compared with nondiabetic subjects, BMD at all sites was higher, whereas LS TBS was lower in diabetic individuals in unadjusted and adjusted models (all $p < 0.001$). The adjusted odds ratio (aOR) for a skeletal measurement in the lowest versus highest tertile associated with diabetes status was less than 1 for BMD (all $p < 0.001$) but was increased for LS TBS (aOR = 2.61; 95% CI 2.30–2.97). During a mean follow-up of 4.7 years, major osteoporotic fractures were identified in 175 (7.4%) women with diabetes and 1493 (5.5%) women without diabetes ($p < 0.001$). LS TBS was a BMD-independent predictor of fracture, and predicted fractures in those with diabetes (adjusted HR = 1.27; 95% CI 1.10–1.46) as well as those without diabetes (HR = 1.31; 95% CI 1.24–1.38). Diabetes was associated with a 49% increase in the risk for major osteoporotic fracture (HR 95% CI 1.27–1.74) after covariate adjustment. When lumbar spine TBS was included in the model, the diabetes effect (Wald statistic) decreased (from 23.6 to 13.6), whereas inclusion of lumbar spine BMD increased this value (to 32.0), indicating that lumbar spine TBS captured a larger portion of the diabetes-associated fracture risk than BMD.

Breban and colleagues[77] studied the combination of LS TBS and BMD for vertebral fracture risk detection in a cross-sectional study of women with rheumatoid arthritis (RA). The study population comprised 185 women aged 56 ± 14 years, with RA for 15.5 ± 9.9 years, among whom 112 (60.5%) were receiving glucocorticoids (mean dose of 6.4 ± 4.3 mg/day equivalent to prednisone) and 33 (17.8%) had detected vertebral fractures (grade ≥ 1). The correlation between spine TBS and BMD measurements ranged from 0.53 to 0.58 (all $p < 0.0001$). BMD *T*-scores were significantly lower in patients with versus without vertebral fracture. Similarly, TBS was lower among patients with vertebral fracture than in nonfractured individuals ($p = 0.0001$). The AUCs were 0.704, 0.621, 0.727, and 0.719 for TBS, LS BMD, femoral neck BMD, and total hip BMD, respectively (differences not significant). Combinations of BMD and TBS gave slightly higher AUCs (range 0.703 to 0.730), but the study was underpowered to assess incremental change.

Three independent studies have assessed TBS in primary hyperparathyroidism (PHPT).[49,78,79] A cross-sectional study assessed TBS from spine DXA images in relation to HRpQCT indices and bone stiffness at the distal radius and tibia in 22 postmenopausal women with PHPT.[49] TBS was significantly correlated with whole bone stiffness and all HRpQCT indices, except for Tb.Th, and trabecular stiffness at the radius. At the tibia, significant correlations were observed between TBS and volumetric densities, cortical thickness, and whole bone stiffness. Correlation between TBS and indices of trabecular microarchitecture, except Tb.Th, became significant after adjusting for body weight.

Romagnoli and colleagues[78] studied 73 white postmenopausal women with PHPT and 74 age-matched healthy women. Patients and controls did not differ in age, years since menopause, BMI, 25(OH)D serum levels, or creatinine clearance. Mean spine TBS values were significantly reduced in PHPT (1.19 ± 0.10) compared with controls (1.24 ± 0.09, $p < 0.01$), as was total hip BMD ($p < 0.01$) and 1/3 radius BMD ($p < 0.0001$). LS BMD and FN BMD were similar between the groups. In the PHPT group, 29 subjects with vertebral fracture assessed by spine X-rays (24 Grade 1, 4 Grade 2, 1 Grade 3) had TBS values significantly lower than in the 44 without fracture (1.14 ± 0.10 versus 1.22 ± 0.10, respectively; $p < 0.01$). Mean TBS values were not significantly different between patients with ($n = 18$) and without ($n = 55$) nonvertebral fractures (1.16 ± 0.09 versus 1.20 ± 0.11). The ROC curve analysis showed that TBS was associated with vertebral fracture (AUC: 0.716; 95% CI 0.590–0.841; $p = 0.002$), as was years since menopause (AUC: 0.717; 95% CI 0.595–0.840; $p = 0.002$). TBS < 1.2 showed good performance in identifying prevalent vertebral fracture (sensitivity 80% and specificity 60%), but the study was limited by the small number of fracture cases.

Finally, a prospective observational study of 92 patients with PHPT (74 females, aged 62.7 ± 10.1 years) and 98 control subjects investigated the association of vertebral fracture and TBS.[79] Among patients with PHPT, 20 subjects who underwent parathyroidectomy were compared with 10 conservatively treated cases after 24 months. Vertebral fractures were assessed by radiographs, using the semiquantitative (SQ) visual assessment as described by Genant and colleagues,[83] by two trained physicians, blinded to the BMD results and clinical history. At baseline, patients had lower TBS values (*Z*-score of −2.39 ± 1.79) and higher prevalence of vertebral fracture (43.5%) than controls (*Z*-score of −0.98 ± 1.07 and 8.2%, respectively, both $p < 0.0001$). BMD was also lower in cases than in controls in all sites measured. TBS was associated with vertebral fracture (OR = 1.4; 95% CI 1.1–1.9; $p = 0.02$), independent of LS BMD, age, BMI, and sex. Although TBS improved in surgically treated patients at month 24, it remained stable in conservatively treated subjects. Of note, PHPT patients included in this study tended to have a more active disease, uncommonly seen now, with a high prevalence of vertebral fracture (43.5%) and nephrolithiasis (47.8%). Despite this, the finding that TBS was associated with vertebral fracture is congruent with the study by Romagnoli and colleagues,[78] which included a more typical cohort of primary hyperparathyroidism subjects.

TBS was also studied in patients with adrenal incidentaloma (AI) and subclinical hypercortisolism (SH).[80] In total, 102 patients with AI (34 with SH) and 70 matched controls were evaluated. In patients, vertebral deformities were assessed by radiograph by two trained physicians, independently, using the SQ visual assessment. BMD at the LS and femoral sites, as well as TBS were reported as *Z*-scores. Patients with SH had lower LS BMD (−0.31 ± 1.17), total femur BMD (−0.29 ± 0.91), and TBS (−3.18 ± 1.21) than patients without SH (0.31 ± 1.42, $p < 0.03$; 0.19 ± 0.97, $p < 0.01$; −1.70 ± 1.54, $p < 0.0001$, respectively) or controls (0.42 ± 1.52, $p < 0.02$; 0.14 ± 0.76, $p < 0.02$; and −1.19 ± 0.99, $p < 0.0001$, respectively). After adjustment for age, BMI, and sex, the presence of fracture was associated with low TBS alone, as defined by a TBS *Z*-score <−1.5 (OR = 4.8; 95% CI 1.85–12.42; $p < 0.001$), and with the cluster low TBS plus low LS BMD, defined by a BMD *Z*-score <0.0 (OR = 4.37; 95% CI 1.71–11.4; $p < 0.002$). Among 40 patients followed for 24 months, TBS predicted the occurrence of a new fracture (OR = 11.2; 95% CI 1.71–71.41; $p < 0.012$) regardless of LS BMD, BMI, and age.

The study of TBS in individuals with chronic kidney disease (CKD) is of interest because this population has an increased risk of fracture, and reliable methods to identify patients with CKD at

high risk for fracture are lacking. Leib and colleagues[82] studied 47 non-Hispanic US white women with CKD (grade not reported) and 94 healthy women (73% postmenopausal) from a single institution, who underwent DXA testing. Mean age (55.9 ± 13.3 versus 55.5 ± 13.5 years) and BMI (26.4 ± 4.7 versus 26.3 ± 4.6 kg/m^2) were similar between the groups. Correlations between spine TBS and BMD and TBS and BMI were 0.48 ($p < 0.0001$) and 0.08 ($p = 0.4$), respectively. Compared with controls, subjects with CKD had a significantly lower LS TBS ($p < 0.0001$), whereas the difference in LS BMD between the groups was of borderline significance ($p = 0.054$). CKD subjects with a prior fracture (number of fractures not reported) had a significantly lower TBS ($p = 0.034$) than subjects without fracture, whereas no difference was seen for BMD ($p = 0.46$). In subjects with CKD, each SD decrease in TBS was associated with 2.5-fold increase in the risk of fracture (unadjusted OR = 2.5; 95% CI 1.02–6.15; AUC = 0.756; 0.609–0.870). The TBS OR adjusted for maternal history of hip fracture remained significant for fracture prediction (OR = 4.67; 95% CI 1.29–16.85), but age- or BMI-adjusted ORs were not reported.

Colson and colleagues[81] studied the impact of long-term GC therapy on TBS in women treated with GCs ($\geq$5 mg/day) for 1 or more years. LS BMD and TBS were evaluated in 136 women, from 45 to 80 years old. GC-treated patients had a 4% decrease in TBS ($p < 0.0001$) compared with the age-matched normal values, whereas no change in BMD was observed ($p = 0.49$). Similar results were found even among those taking 5 mg/day of GC (–3.5% of TBS, $p = 0.0012$). Reduction in TBS was seen in both osteoporotic and osteopenic women, with a decline in TBS of –5.7% ($p < 0.0001$) and –2.9% ($p < 0.003$), respectively. These findings were more evident when fracture status and number of fractures were taken into account. There was a 3.4% decline in TBS for the nonfractured GC-treated patients ($p = 0.0001$), 6.2% ($p = 0.0007$) for vertebral fracture (grade 2 or greater), 4.6% ($p < 0.035$) for one osteoporotic peripheral fracture, and 7.8% ($p < 0.002$) for two or more osteoporotic peripheral fractures. Moreover, the age-adjusted OR for TBS was 1.60 (95% CI 1.04–2.47) for osteoporotic peripheral fracture and 1.62 (95% CI 1.02–2.59) for vertebral fracture, whereas no significant association between fracture risk and BMD was found (OR = 1.47; 95% CI 0.96–2.26 and OR = 1.56; 95% CI 0.97–2.51, respectively]. Larger studies are needed to compare the relative abilities of TBS and BMD assessing fracture risk in the context of GC therapy.

Is TBS Affected by Degenerative Vertebral Osteoarthritis?

Vertebral osteoarthritis (OA) is a common feature in the elderly.[84] These osteoarthritic changes can confound DXA spine measurements and, to a lesser extent, hip measurements. In this setting, DXA BMD measurements are artifactually elevated.[85]

Dufour and colleagues[51] investigated the effect of spine OA on TBS in a subgroup of 390 women aged 50 to 88.5 years in a cross-sectional study designed to evaluate age-related changes in TBS in a cohort of white French women. Subjects were allocated to two groups according to the presence or absence of OA exclusively at the L_4 vertebral level, in accordance with the International Society for Clinical Densitometry (ISCD) definition. The 141 cases with OA at L_4 and 249 control subjects without OA did not differ in age (66.0 ± 8.3 versus 64.1 ± 6.9 years) or BMI ($25.2.8 \pm 3.5$ versus $24.5.8 \pm 3.4$ kg/m^2). The severity of OA was defined by the differences between L_3 and L_4, expressed in standard deviations of *T*-score. There was no significant difference between cases and controls for BMD and TBS at L_1 to L_3 (mean difference between groups of 0% for BMD and 3.6% for TBS). At L_4 vertebral level, BMD was significantly greater in cases than in controls (+19%), whereas no significant difference in TBS was found between the groups (–3.2% in cases versus controls, p = NS). Although the severity of OA was significantly correlated with BMD ($r = 0.503$, $p < 0.001$), it did not correlate with TBS ($r = -0.067$, $p = 0.426$).

These results suggest that OA and its severity have little effect on TBS but markedly influence the LS BMD measurement. Although these observations suggest that TBS may have utility in assessing bone texture even in the presence of OA, additional studies are necessary to confirm these findings. To date, there are no studies that have investigated the potential impact of vertebral fracture on TBS.

Can TBS Be Comparable to a Major Clinical Risk Factor?

The Manitoba study[53] evaluated conditions associated with baseline lumbar spine TBS in 29,407 women aged $\geq$50 years. This cohort included 1213 with recent glucocorticoid use (>3 months in the prior year), 3988 with prior major fracture, 995 with rheumatoid arthritis, 2239 with chronic obstructive pulmonary disease, and 681 with diagnosed alcohol abuse. After adjustment for age and bone-preserving treatment, reduced lumbar spine TBS (lowest versus highest tertile) was associated with recent glucocorticoid use (OR = 1.79; 95% CI 1.52–2.12), prior major fracture (OR = 2.07; 95% CI 1.88–2.28), rheumatoid arthritis (OR = 1.30; 95% CI 1.09–1.55), chronic obstructive pulmonary disease (OR = 2.63; 95% CI 2.32–2.99), alcohol or other substance abuse, a proxy for high alcohol intake (OR = 2.17; 95% CI 1.76–2.69), and higher BMI (OR per 5 kg/m^2 = 1.46; 95% CI 1.41–1.50). These associations were largely unaffected by further adjustment for lumbar spine BMD or femoral neck BMD. The negative correlation between lumbar spine TBS and BMI ($r = -0.15$, $p < 0.001$) was surprising because BMD measurements showed a positive correlation with BMI ($r = 0.29$ for lumbar spine, $r = 0.29$ for femoral neck, both $p < 0.001$). This may reflect technical difficulties in performing TBS texture analysis in obese subjects. Indeed, a large amount of soft tissue overlying the region of interest may lower the apparent TBS. Alternatively, TBS may actually capture alterations in bone structure in obese individuals. Further analyses are required to better assess the accuracy of TBS in obese individuals and how this impacts on fracture prediction.

Although TBS was associated with many of the risk factors that are predictive of osteoporotic fractures[53] and preliminary data have shown that TBS predicts osteoporotic fractures independent of BMD and major clinical risk factors,[86] further work is needed to determine whether LS TBS (along with other risk factors) can enhance fracture risk assessment in clinical practice.

Can TBS Enhance Fracture Prediction From FRAX?

The fracture risk assessment system (FRAX), developed by the WHO Collaborating Centre for Metabolic Bone Diseases, allows for the estimation of the 10-year probability of hip and major osteoporotic fracture based on the individual's risk factor

profile.[87] Preliminary data have shown an incremental improvement in fracture prediction when LS TBS is used in combination with FRAX.[88,89] The study of Leslie and colleagues,[88] which included 42,170 women aged ≥ 50 years from the Province of Manitoba, Canada, found that lower LS TBS and higher FRAX probabilities were found in fracture versus nonfracture women (all $p < 0.001$). FRAX probabilities were calculated with BMD. Cox proportional hazards models including competing mortality were developed for time to first fracture based upon TBS (continuous or tertiles), osteoporosis medication use, and FRAX probability. Two-way interactions between TBS and FRAX risk factors were tested. A preliminary method to adjust FRAX probability was conducted based upon LS TBS tertile. When used to reclassify fracture risk, this approach gave a significant increase in integrated discrimination index for major osteoporotic fracture (+1.3%, $p < 0.001$) and hip fracture (+1.3%, $p < 0.001$), with net reclassification improvement of +4.6% for major osteoporotic fracture ($p < 0.001$). There was an age interaction with larger TBS effects in younger than older women age for major osteoporotic fracture ($p < 0.001$) and hip fracture ($p = 0.002$).

Using a similar approach, Lamy and colleagues[89] evaluated 911 women from the OsteoLaus cohort (mean age 65.2 ± 7.9 years and mean BMI 25.7 ± 4.4 kg/m^2). There was a significant increase in integrated discrimination index of +2.5% ($p < 0.001$), with a net reclassification improvement of +7.6% ($p < 0.001$) for vertebral fracture when TBS is used in combination with FRAX to reclassify the fracture risk.

If these preliminary results are validated in other prospective cohorts, LS TBS could become clinically useful for enhancing fracture prediction from FRAX.

Technical Limitations

As TBS is computed from DXA images, some of the limitations of the TBS measurement are inherent in the acquisition process, such as image noise, which contributes to degradation in resolution. The effects of image noise on TBS have been evaluated.[39] It was found that noise addition reduced TBS mean values, irrespective of the pixel size considered. This effect was linked to the way noise affects the experimental variogram used to calculate the TBS; ie, an additional noise mostly modifies the points at the origin by increasing the variance of the first points; hence, it lowers the slope at the origin of the variogram. These results suggest that any noise from DXA can impact the TBS evaluation, and that if the image noise increases beyond the "normal" noise range, attributable to technical problems such as X-ray tube aging or sensor deficiencies, the TBS may be impacted to a point that values are no longer interpretable.

Additionally, because both bone tissue and soft tissue absorb X-rays, and the texture of the DXA images depends on the tissues that are absorbing the X-rays, the amount of soft tissue and the way it is evaluated and taken into account during the DXA acquisition can interfere with the TBS analysis. Increased soft tissue thickness may have the same effect on TBS as noise, ie, a TBS value reduction. This phenomenon has been evaluated ex vivo and confirmed by in vivo studies. One way to attenuate this problem in vivo is by adjusting the TBS according to the patient's BMI. The adjustment in TBS for BMI is optimized when BMI ranges from 15 to 35 kg/m^2, so that the assessment of TBS is not validated in subjects with a BMI beyond these limits. The use of BMI, however, is limited because it can overestimate adiposity in subjects with a high lean body mass and underestimate adiposity in subjects with low lean body mass. This would lead to TBS overestimation in the first case and an underestimation in the second case. Furthermore, higher BMI does not distinguish abdominal weight accumulation (which would directly affect TBS derived from LS DXA) from weight accumulation at other sites, and this is known to differ according to sex and ancestry.

Finally, TBS results may not be comparable across different DXA machines. This limitation could theoretically be addressed. TBS includes a cross-calibration process utilizing a gray-level TBS phantom. This helps to ensure that a patient will have the same TBS when scanned on different DXA devices of the same model, and, through use of the same reference curve, on different DXA models. Although the TBS calibration process compensates for most of the technical differences that exist between DXA devices of different manufacturers and/or models, some nonlinearities can still affect the way bone texture is perceived among DXA devices. For example, different image resolutions generated by distinct densitometers affect the TBS calculation.[39] In addition, because TBS value is derived from a DXA image and thus depends on the quality of the DXA acquisition, TBS has clinical utility only when DXA is performed with quality-control safeguards (see ISCD guidelines). There is no phantom equivalent for TBS standardization yet, but this advance would be welcome.

Clinical Limitations

Although results from clinical studies have confirmed the fracture-discriminating ability of TBS in a substantial number of postmenopausal women, data in men are still preliminary. TBS appears to be lower in men than in women, when the DXA image is obtained from the GE-Lunar instrument. This observation, evident on the GE-Lunar instrument only, is surprising given the previous findings by histomorphometry and HRpQCT of a more preserved trabecular microarchitecture in aging men than in women.[90,91] More work in this area is clearly needed.

Another potential limitation for the use of TBS in the clinical practice is the lack of a well-established TBS cut-off point that defines normal and abnormal TBS values. The TBS reference range that has been proposed so far applies to postmenopausal women only, and a large population study would be required to determine the optimal health ranges across age and sex. Additionally, as note above, the use of TBS in subjects with BMI below 15 kg/m^2 and over 35 kg/m^2 has not been validated.

Finally, although TBS is highly correlated with μCT indices of trabecular microarchitecture in ex vivo studies, studies in vivo have shown moderate correlations. Moreover, the lack of association between TBS and trabecular thickness indicate that TBS may not fully capture some aspects of trabecular microstructure assessed by higher-resolution imaging modalities.

Summary of TBS as a Clinical Tool

This review illustrates the potential utility of TBS as a clinical tool. This gray-level textural measurement provides an indirect estimate of bone microarchitecture from spine DXA images. It decreases with age and appears to reflect qualitative aspects of skeletal structure that are complementary to BMD. TBS has the major clinical advantage of being readily available from DXA images and of being associated with vertebral and nonvertebral

fractures in several cross-sectional and prospective studies involving a large number of postmenopausal women. Data in men, although much less extensive, reveal similar findings. The association of TBS with fragility fracture was confirmed among individuals with conditions related to bone loss. TBS may improve fracture discrimination over DXA alone, but it remains to be seen whether osteoporosis treatment-related increase in TBS estimates antifracture effectiveness. Finally, preliminary data suggest that TBS might become clinically useful for enhancing fracture prediction from FRAX.

TBS is an emerging technology with promise. It is likely that future work will add to the encouraging repository of data, confirming and extending its clinical utility.

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