Update on trabecular bone score

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ABSTRACT

Trabecular bone score (TBS) is an indirect and noninvasive measure of bone quality. A low TBS indicates degraded bone microarchitecture, predicts osteoporotic fracture, and is partially independent of clinical risk factors and bone mineral density (BMD). There is substantial evidence supporting the use of TBS to assess vertebral, hip, and major osteoporotic fracture risk in postmenopausal women, as well as to assess hip and major osteoporotic fracture risk in men aged > 50 years. TBS complements BMD information and can be used to adjust the FRAX (Fracture Risk Assessment) score to improve risk stratification. While TBS should not be used to monitor antiresorptive therapy, it may be potentially useful for monitoring anabolic therapy. There is also a growing body of evidence indicating that TBS is particularly useful as an adjunct to BMD for fracture risk assessment in conditions associated with increased fracture risk, such as type-2 diabetes, chronic corticosteroid excess, and other conditions wherein BMD readings are often misleading. The interference of abdominal soft tissue thickness (STT) on TBS should also be considered when interpreting these findings because image noise can impact TBS evaluation. A new TBS software version based on an algorithm that accounts for STT rather than BMI seems to correct this technical limitation and is under development. In this paper, we review the current state of TBS, its technical aspects, and its evolving role in the assessment and management of several clinical conditions. Arch Endocrinol Metab. 2022;66(5):694-706

Keywords
Trabecular bone score; dual-energy X-ray absorptiometry; osteoporosis; fracture risk; secondary osteoporosis

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INTRODUCTION

Osteoporosis is a common disease characterized by low bone strength leading to bone fragility and a consequent susceptibility to fractures (1). Bone mineral density (BMD) measurement using dual-energy X-ray absorptiometry (DXA) is the standard tool for the diagnosis of osteoporosis. BMD accounts for 60%-70% of the variation in bone strength (2); additionally, fracture risk increases with decreasing BMD (3). However, most individuals with a fragility fracture are found to have BMD values within the osteopenic or even normal range (4); this indicates that other variables also influence fracture occurrence independent of the BMD. Certain clinical risk factors (CRF), such as older age and personal history of osteoporotic fractures, among others, combined with BMD improves fracture prediction as compared to BMD alone (5).

Additionally, it is important to understand that bone strength is also affected by bone quality, an umbrella term that describes a set of characteristics such as the structural and material properties of the bone, both of which are affected by bone turnover rate. The structural properties of bone include geometry and microarchitecture (trabecular thickness, connectivity, separation and number, and cortical thickness and porosity), whereas the material properties include bone mineral content (crystal size and orientation) and collagen composition, as well as damage accumulation (6).

Investigation of bone microarchitecture and bone remodeling by histomorphometric or micro computed tomography (micro-CT) analysis of the transiliac crest bone biopsy is highly informative (7), but it is an invasive procedure or not widely available. Other noninvasive technologies include high-resolution peripheral

quantitative computed tomography (HR-pQCT) and micro-magnetic resonance imaging (micro-MRI); these methods can assess bone microarchitecture, but their use is limited in clinical settings due to high costs when compared to DXA and serve largely as research tools (8,9). Hence, there is a need to develop noninvasive clinically available techniques to evaluate bone quality. To this end, trabecular bone score (TBS), a texture index derived from a lumbar spine (LS) DXA image, is a novel technique that may be used to improve fracture risk prediction beyond that offered by a combination of BMD and CRFs (10).

TBS – GENERAL PRINCIPLES

TBS is a textural index that evaluates pixel gray-level variations in lumbar spine DXA image providing an indirect parameter of trabecular architecture. It is determined by constructing a variogram of the projected image (containing the region of interest) and computing the sum of the square of gray-level differences between pixels at a specific distance (Figure 1), followed by calculating the slope of the "log-log transform" of this variogram (11). The TBS software (TBS iNsight; Medimaps Group, Geneva, Switzerland) generates results (unitless) for the whole LS (L1 to L4) and each vertebra using the same region of interest as for BMD. Vertebrae excluded from BMD calculation (fractures or osteoarthritis) may also be excluded from the TBS analysis (10). Because the DXA image is usually retrievable, regardless of the timing of obtaining the image, TBS can be readily applied to any available DXA image obtained from a GE Lunar (Prodigy and iDXA; Madison, WI, USA) or Hologic (Delphi, QDR 4500, and Discovery; Waltham, MA, USA) densitometers (12). A low TBS value is associated with a deteriorated bone architecture; conversely, a high TBS value is correlated with a better bone structure (10). The TBS cutoff points are discussed in a subsequent section.

It is important to note that TBS does not directly assess bone microarchitecture because DXA lacks the resolution to detect bone trabeculae.

TBS was developed using two-dimensional projections of three-dimensional micro-CT images of human cadaveric bone specimens (13). There were significant correlations between TBS and bone volume fraction, trabecular spacing, and the number of trabeculae obtained using cadaveric vertebra, femoral neck, and distal radius samples. Eventually, the technique was extended to DXA images acquired *ex vivo*

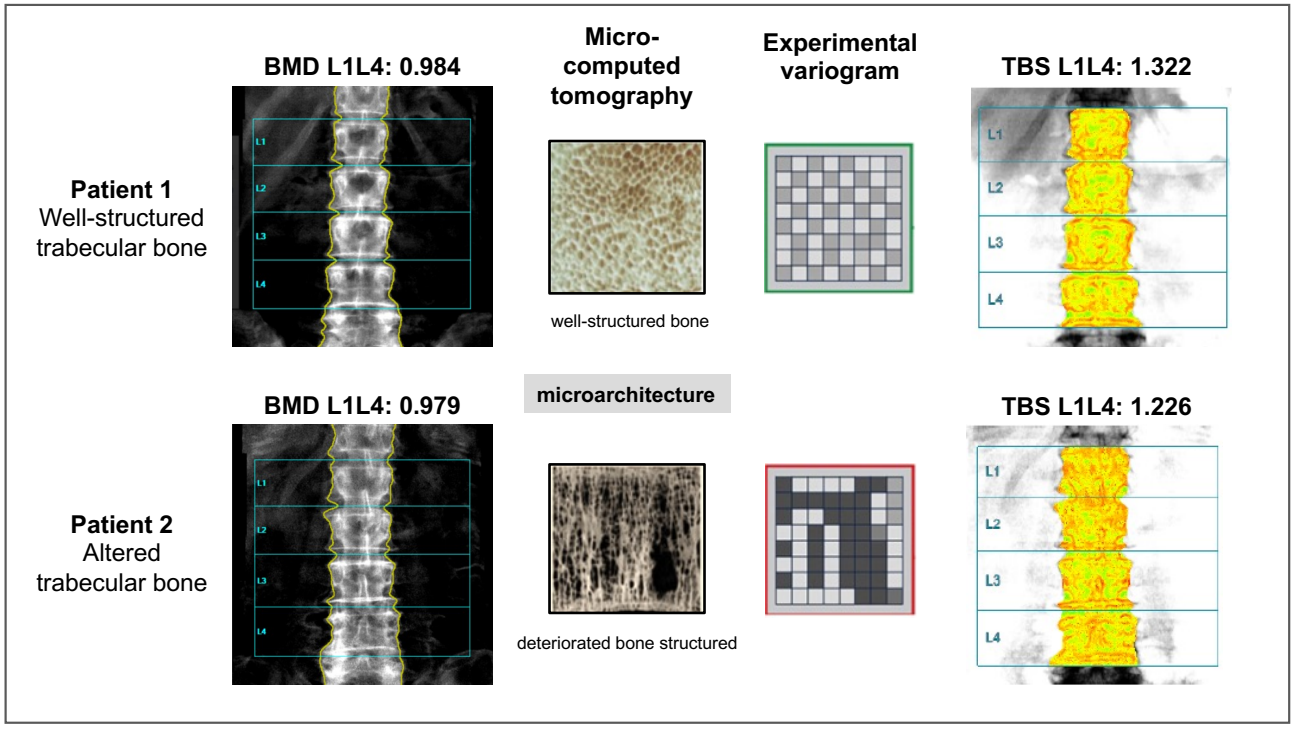

Figure 1. Concept of TBS – the figure presents an example of two different patients with equivalent BMD but different TBS
TBS: Trabecular Bone Score; BMD: Bone Mineral Density.

in cadaveric vertebrae, and significant correlations were found between trabecular indices obtained by micro-CT and TBS; notably, these results were independent of the patient's BMD (14,15).

However, some studies have failed to demonstrate a significant correlation between TBS and microarchitecture parameters (16,17). *In vivo* studies have reported weak to moderate correlations between TBS and microarchitecture (18-20). Nevertheless, irrespective of the structural properties assessed by TBS, its clinical utility derives from its demonstrated ability to predict fractures.

FRACTURE RISK ASSESSMENT

In postmenopausal women, several studies (summarized in Table 1) have consistently supported the ability of TBS to predict isolated vertebral or hip, and major osteoporotic fractures (MOF: clinical spine, hip, forearm, and humerus) independently of BMD and CRF (21-29). On average, every 1-point standard deviation (SD) decline in the TBS leads to a 30%-40% increase in the risk of fragility fractures in postmenopausal women.

The relationship between TBS and the incidence of fractures has also been assessed in men over the age of 50 years. Most of the longitudinal publications have reported that TBS can independently predict MOF and hip fractures in this population (28-32) (Table 2). Only a few reports have provided information about vertebral fractures in older men, with mixed results (30,33).

Recently, Greendale and cols. (34) evaluated TBS values and fracture incidence in pre and early postmenopausal women. Minimal trauma but also traumatic fractures were considered in this study (Table 1). For premenopausal women (n = 1,362; mean age = 46.4 years), TBS was related to fracture risk in models adjusted for age, body mass index (BMI), race/ethnicity, and bone active medications. However, TBS was no longer a predictor of fracture incidence after adjusting for LS or femoral neck (FN) BMD. On the other hand, in early postmenopausal women (n = 891; mean age = 54.1 years), TBS was not associated with fracture risk even in models without BMD adjustment, but the power to detect this association was insufficient.

To summarize, so far, the existing literature supports the use of TBS to assess the risk of MOF, vertebral, and hip fractures in postmenopausal women, as well as that of MOF and hip fractures in men over the age of 50 years.

TBS AND FRAX (THE WORLD HEALTH ORGANIZATION (WHO) FRACTURE RISK ASSESSMENT TOOL)

The FRAX tool is an online fracture risk assessment algorithm developed by the Collaborating Center for Metabolic Bone Diseases of the World Health Organization in 2008 to assess the 10-year fracture probability in people aged 40 to 90 years. FRAX contains country-specific prediction models based on underlying fracture risk and mortality for the reference population. Its calculation is based on the most frequently studied CRFs namely age, BMI, history of prior fractures, parental hip fractures, current smoking status, chronic use of glucocorticoids (GC), rheumatoid arthritis, secondary osteoporosis, and alcohol intake; the use of FN-BMD is not mandatory. The algorithm provides the 10-year probability of an individual sustaining a MOF and hip fractures (FN, intertrochanteric, or subtrochanteric) (36).

Several cross-sectional and prospective studies including different populations have consistently shown that TBS may improve FRAX accuracy in postmenopausal women and older men (25,26,28,31,32,37). Data from the Manitoba Study (26), large population-based research comprising > 33,000 people aged 40-99 years followed up over an average of 4.7 years, have been used to derive potential correction factors for calculating a TBS-adjusted FRAX score. In the Manitoba cohort, even after fully adjusting for FRAX risk variables, TBS was found to be an independent predictor of MOF (excluding hip fracture) (hazard ratio/standard deviation (HR/SD): 1.18, 95% confidence intervals, CI: 1.12-1.24), hip fracture (HR/SD: 1.23, 95% CI: 1.09-1.38), and mortality (HR/SD: 1.20, 95% CI 1.14-1.26) (Table 1).

McCloskey and cols. (28) conducted a wide meta-analysis including data from 14 prospective population-based cohorts (using individual-level data from 17,809 men and women) from North America, Asia, Australia, and Europe. They observed that TBS was independently associated with the risk of MOF, and mainly hip fractures at all ages, in both sexes (Tables 1 and 2). Moreover, the incorporation of a TBS adjustment factor allowed for slightly greater risk stratification for both MOF and hip fractures. In short, the combination of TBS with CRFs and BMD enhanced the performance of FRAX to predict MOF and hip fractures compared with using either TBS or FRAX risk variables alone. Similar results have been reported in studies including older Chinese men and Japanese

Table 1. A summary of longitudinal studies evaluating trabecular bone score and fracture risk in women

Study	Study population and place of research	Mean age (years)	Mean follow-up time (years)	Outcome (number of fractures)	Adjustments	HR or OR per SD decrease in TBS (95% CI)
Hans and cols., 2011 (21)	29,407 women aged ≥ 50 years (Canada)	65.4	4.7	MOF by Fx codes in health service records (n = 1,668)	Age, LS-BMD, and a combination of clinical risk factors*	HR = 1.17 (1.09-1.25)
				Clinical vertebral Fx (n = 439)		HR = 1.14 (1.03-1.26)
				Hip Fx (n = 293)		HR = 1.47 (1.30-1.67)
Boutroy and cols., 2013 (22)	560 postmenopausal Caucasian women (France)	66.2	7.8	Fragility Fx at any site (except head, toes. and fingers), confirmed by radiographs (n = 94)	Age, weight, and prevalent fracture at baseline	OR = 1.34 (1.04-1.73)
Briot and cols., 2013 (23)	1,007 postmenopausal Caucasian women aged >55 years (Europe)	65.9	6.0	Clinical self-reported osteoporotic Fx, confirmed by radiographs (n = 82)	None	OR = 1.62 (1.30-2.01)
				Vertebral Fx by radiographs (n = 46)		OR = 1.54 (1.17-2.03)
Iki and cols., 2014 (24)	665 women aged ≥ 50 years (Japan)	64.1	8.3	Vertebral Fx by VFA (n = 92)	Age, LS-BMD, and prevalent vertebral deformity	OR = 1.52 (1.16-2.00)
Leslie and cols., 2014 (25)	33,352 women aged 40-100 years (Canada)	63.2	4.7	MOF by Fx codes in health service records (n = 1,872)	Age, time since baseline, clinical risk factors**, and LS-BMD/Age, time since baseline, clinical risk factors**, and femoral neck BMD	HR = 1.17 (1.11-1.23)/ HR = 1.18 (1.12-1.23)
				Death (1,754)		HR = 1.26 (1.19-1.32)/ HR = 1.20 (1.14–1.26)
McCloskey and cols., 2015 (26)	33,352 women aged 40-100 years (Canada)	63.2	4.7	MOF (excluding hip) by Fx codes in health service records (n = 1,639)	Age, time since baseline, femoral neck BMD, and clinical risk factors***	HR = 1.18 (1.12-1.24)
				Hip Fx (306)		HR = 1.23 (1.09-1.38)
				Death (1,754)		HR = 1.20 (1.14-1.26)
Popp and cols., 2016 (27)	556 postmenopausal elderly women (Switzerland)	76.1	2.7	Clinical fragility Fx (n = 52: 20 forearms, 10 vertebral, 9 humeral, 6 hip, 3 ankle, 2 pelvis, 1 clavicular, and 1 elbow)	Age, BMI, and lowest BMD	HR = 1.87 (1.38-2.54)
McCloskey and cols., 2016 (28)	17,809 individuals (10,507 women); a meta-analysis of 14 international population-based cohorts (North America, Asia, Australia, and Europe)	72	6.1	MOF (n = 1,109)	Age, time since baseline, and FRAX score (with BMD)	HR = 1.31 (1.21-1.42)
				Hip Fx (n = 298)		HR = 1.29 (1.09-1.52)
Su and cols., 2017 (29)	1,950 community-dwelling women aged ≥ 65 years (Hong Kong)	72.5	8.8	MOF (n = 215)	FRAX score (with BMD)	HR = 1.32 (1.13-1.54)
Tamaki and cols., 2019 (35)	1,541 women aged ≥ 40 years (Japan)	58.1	10	MOF by interviews or mail surveys (n = 67)	FRAX score (with BMD)	OR = 1.46 (1.08-1.98)
				Hip Fx (n = 11)	FRAX score (with BMD)	OR = 1.73 (0.82-3.65)
Greendale and cols., 2020 (34)	1,362 premenopausal women (United States)	46.4	22	Any type of Fx (except face, skull, toes, and fingers) detected by self-reported questionnaire – 75% confirmed by medical reports (n = 292, 111 minimal trauma)	Age, race/ethnicity, BMI, bone active medications, LS BMD	HR = 0.95 (0.79-1.14)
	891 early postmenopausal women (United States)	54.1		Any type of Fx (n = 141, 60 minimal trauma)		HR = 1.03 (0.79-1.33)

BMD: bone mineral density; BMI: body mass index; FRAX: The WHO Fracture Risk Assessment tool; Fx: fracture; HR: hazard ratio; LS: lumbar spine; MOF: major osteoporotic fracture (hip, clinical spine, forearm, and humerus); OR: odds ratio; TBS: trabecular bone score.

* Clinical risk factors: ambulatory diagnostic groups comorbidity score, rheumatoid arthritis, chronic obstructive pulmonary disease, diabetes, substance abuse, body mass index, prior osteoporotic fracture, systemic corticosteroid use in the last year, and osteoporosis treatment in the last year.

** Clinical risk factors: secondary osteoporosis, rheumatoid arthritis, chronic obstructive pulmonary disease (smoking proxy), high alcohol use, body mass index, previous fracture, and glucocorticoid use > 90 days.

*** Clinical risk factors: secondary osteoporosis, rheumatoid arthritis, smoking, alcohol use, body mass index, previous fracture, and glucocorticoids.

Table 2. A summary of longitudinal studies evaluating trabecular bone score and fracture risk in men

Study	Study population and place of research	Mean age (years)	Mean follow-up (years)	Outcome (number of subjects)	Adjustments	HR or OR per SD decrease in TBS (95% CI)
Leslie and cols., 2014 (30)	3,620 men aged ≥ 50 years (Canada)	67.6	4.5	MOF by Fx codes in health service records (n = 183)	Clinical FRAX score, osteoporosis treatment, and LS-BMD	HR = 1.08 (0.92-1.26)
				Clinical vertebral Fx (n = 91)		HR = 1.02 (0.81-1.27)
				Hip Fx (n = 46)		HR = 1.44 (1.07-1.94)
Iki and cols., 2015 (31)	1,805 community-dwelling men aged ≥ 65 years (Japan)	73	4.5 (median)	MOF by interviews or mail and telephone surveys (n = 22)	FRAX score (with BMD)	OR = 1.76 (1.16-2.67)
McCloskey and cols., 2016 (28)	17,809 individuals (7,302 men); a meta-analysis of 14 international population-based cohorts (North America, Asia, Australia, and Europe)	72	6.1	MOF (n = 1,109)	Age, time since baseline, and FRAX score (with BMD)	HR = 1.35 (1.21-1.49)
				Hip Fx (n = 298)		HR = 1.27 (1.06-1.53)
Schousboe and cols., 2016 (32)	5,863 community-dwelling men aged ≥ 65 years (United States)	73.7	10	MOF by mail surveys and confirmed by radiographs (n = 448)	FRAX score (with BMD) and prevalent radiographic vertebral Fx	HR = 1.27 (1.17-1.39)
				Hip Fx (n = 181)		HR = 1.20 (1.05-1.39)
Schousboe and cols., 2017 (33)	5,831 community-dwelling men aged ≥ 65 years (United States)	73.7	11.5	Clinical vertebral Fx (n = 202)	Age and LS-BMD	OR = 1.19 (1.02-1.38)
	4,309 community-dwelling men aged ≥ 65 years	Not described	4.6	Radiographic vertebral Fx (n = 196)		OR = 1.11 (0.94-1.30)
Su and cols., 2017 (29)	1,923 community-dwelling men aged ≥ 65 years (Hong Kong)	72.3	9.9	MOF (n = 126)	FRAX score (with BMD)	HR = 1.38 (1.15-1.65)

BMD: bone mineral density; FRAX: The WHO Fracture Risk Assessment tool; Fx: fracture; HR: hazard ratio; LS: lumbar spine; MOF: major osteoporotic fracture (hip, clinical spine, forearm, and humerus); OR: odds ratio; TBS: trabecular bone score.

women (29,35). In contrast, Holloway and cols. (38), in a longitudinal study involving 591 Australian men aged 40-90 years, concluded that fracture prediction using FRAX was not substantially improved by TBS adjustment. Furthermore, Martineau and cols. have shown that the clinical impact of TBS-adjusted FRAX was greater in individuals close to the FRAX-based therapeutic intervention threshold, whereas the TBS adjustment was unlikely to reclassify someone with a very low unadjusted FRAX score into a high-risk (39). Also, it was reported that the utility of TBS-adjusted FRAX was greatest in postmenopausal women under 65 years old, owing to the significant interaction between TBS and age.

Finally, a small study suggested that the adjustment of FRAX by TBS may be useful when there is a discordance between LS and FN BMD, particularly in patients with no history of osteoporotic fractures (40).

APPLICATION OF TBS IN GUIDING CLINICAL DECISIONS

Recommendations from the International Society of Clinical Densitometry (ISCD) and the European Society for Clinical and Economic Aspects of Osteoporosis – Osteoarthritis, and Musculoskeletal Diseases (ESCEO) support the use of TBS to assess fracture risk in postmenopausal women and men over the age of 50 years (37,41). Additionally, TBS was proposed to be evaluated in postmenopausal women with type 2 diabetes (T2D) to predict MOF (42).

However, there is no consensus about TBS cutoff points. Cormier proposed that TBS values ≥ 1.350 should be considered normal, while a TBS = 1.200-1.350 is consistent with "partially degraded" bone, and TBS ≤ 1.200 indicates "degraded" bone in postmenopausal women (43). In this regard, McCloskey

and cols. (28) published an interesting study that related TBS thresholds with fracture risk (low, intermediary, and high-risk groups). The two threshold values are 1.230 and 1.310, with no differences between the sexes. Individuals in the lower two tertiles, i.e., with high (TBS < 1.230) or intermediate risk (TBS = 1.230-1.310), present the highest risk for MOF compared with the lowest risk tertile (TBS > 1.310). For the Latin American population, the manufacturer proposed different TBS values (published as abstract (44) for women and unpublished data for men) for both men and women that are higher than those proposed by McCloskey and Cormier. For men, the thresholds are 1.258 and 1.338, while for women 1.267 and 1.347. TBS tertiles reported for Brazilian elderly women are similar to those proposed for Latin American women (45).

In 2022, Kalkwarf and cols. (46) presented a robust reference range for the pediatric population using the new TBS software (pre-release version 4.0) and determined its predictive value for bone fragility in childhood and adolescence.

While a low TBS is associated with a greater risk of fracture, a threshold value to initiate treatment has not been determined yet; therefore, the ISCD has recommended against the use of TBS as a single parameter to guide treatment decisions (37). The ISCD suggestion was to adjust FRAX probabilities using TBS values to assist in treatment decisions (37).

Another important issue regarding TBS is its reproducibility, which is critical for its use in disease progression and therapeutic monitoring. This can be ensured by precision assessment and calculation of the least significant change (LSC), which determines when a difference in the measurement is statistically significant or within the range of error of the test. ISCD recommends a conservative estimate of 5.8% for TBS-LSC as the threshold to consider the use of TBS to monitor changes in individual patients on osteoporosis medications unless the individual site performed their own health service LSC (47).

Approved bisphosphonates, whether administered orally or parenterally, reduce bone remodeling, increase BMD, and reduce fracture risk, but are not known to alter the bone structure. There is a very good consistency across the studies that patients treated with oral bisphosphonates (alendronate, risedronate, and ibandronate) or zoledronic acid for two or more years show minimal, non-significant changes in TBS (37,48-50). Therefore, TBS is not an appropriate measure to follow-up on the progress in patients on bisphosphonates; likewise, the ISCD does not recommend TBS to monitor bisphosphonate therapy (47). Although a study described that the increase in the TBS with denosumab was greater than that obtained with bisphosphonates, the results were insufficient to support the use of TBS for routine monitoring of these patients (51). In general, the literature suggests that TBS should not be used for monitoring patients taking antiresorptive drugs for periods up to three years (47).

Nevertheless, TBS can be potentially useful for monitoring anabolic therapy. Anabolic drugs (teriparatide and abaloparatide) can increase the mean TBS when used over 2-3 years. However, the response may not be uniform; the rate of change beyond the LSC is estimated to be about 52% over 24 weeks for abaloparatide and probably less for teriparatide (50,52,53). Although a change in TBS alone is not recommended to ascertain a good response to an anabolic agent, TBS monitoring in these patients may offer additional information beyond BMD and bone turnover markers (47). Data regarding the potency of romosozumab based on the TBS is lacking. In a recent small study, 10 patients treated with romosozumab for six months had a modest increase in TBS (2.53%; p = 0.04), that did not reach the LSC (5.8%) (54).

TBS AND FRACTURE RISK PREDICTION IN PATIENTS WITH DIABETES AND SECONDARY OSTEOPOROSIS

A growing number of studies have assessed TBS in various conditions known to increase the risk of fragility fractures (10) and many of them have corroborated the ability of TBS to predict such fractures in patients with secondary osteoporosis (55,56). Figure 2 presents a list of some of these pathologies.

In general, compared to control subjects, TBS was reported to be lower in patients with diabetes (42,57-59), primary hyperparathyroidism (60-64), acromegaly (65-68), anorexia nervosa (69,70), hypercortisolism (71-73), primary aldosteronism (especially in women) (74), with prolonged GC exposure (75-84), rheumatoid arthritis and rheumatic disease (85-87), aromatase inhibition (88), kidney transplant recipients (89), as well as in patients on hemodialysis (90,91). In differentiated thyroid carcinomas, TBS was found to be lower in patients receiving long-term suppressive doses of thyroid-stimulating hormone than in patients

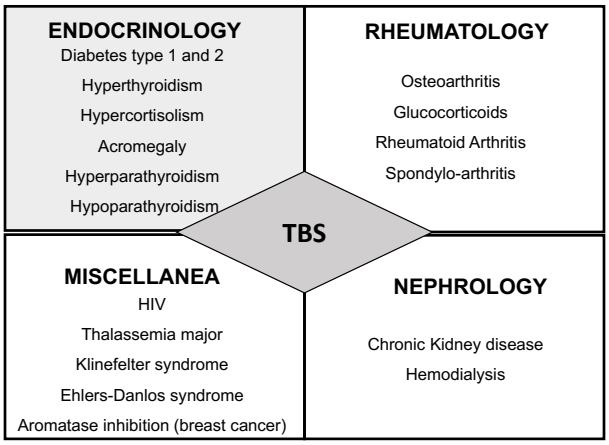

Figure 2. A list of special conditions (causing secondary osteoporosis) known to increase fracture risk in which TBS has been demonstrated to add some clinical value

TBS: Trabecular Bone Score.

receiving shorter-term therapy (92-94). Some other studies also evaluated TBS in thalassemia major (95,96), Human Immunodeficiency virus-acquired immunodeficiency syndrome (HIV-AIDS) (97,98), Klinefelter syndrome (99), Ehlers-Danlos syndrome (100), Down syndrome (101), and short stature (102).

In this section, we delve deeper into the role of TBS in the assessment of bone health in patients with diabetes mellitus and those on long-term GC exposure.

DIABETES

Previous studies have robustly shown the association between diabetes and bone fragility, and it is well-known that the skeleton is affected by both type 1 and 2 diabetes mellitus, leading to an increased risk of fractures (56,103). Interestingly, there is a paradoxical relationship between type 2 diabetes (T2D), BMD, and fractures (61). Compared to the general population, patients with T2D are at an increased risk for fragility fractures at all skeletal sites (104-106) despite having comparable or even higher BMD values measured by DXA (107,108). In other words, BMD may underestimate fracture risk in T2D (109). Alterations in skeletal properties or bone quality are possible explanations for this T2D-related skeletal fragility (110), and TBS could be useful for fracture risk assessment in these patients (59).

In 2013, Leslie and cols. (42) were the first to examine the association between TBS and the incidence of fractures in 29,407 women above the age of 50 years from the province of Manitoba, Canada, including 2,356 with diabetes (mostly T2D). Interestingly, compared to controls, women with diabetes had higher baseline BMD at all sites, but lower TBS, even after adjusting for multiple confounding variables. Furthermore, over a mean of 4.7 years of follow-up, the incidence of MOF was greater in women with diabetes (7.4%, n = 175) than in non-diabetics (5.5%, n = 1,493; $p < 0.001$). They reported that TBS predicted MOF independently of BMD in women with diabetes (HR: 1.27, 95% CI: 1.10-1.46), similar to those without diabetes (HR: 1.31, 95% CI: 1.24-1.38). Other studies have also confirmed that despite greater BMD values, those with T2D have lower TBS than controls (55,58). Another study found a greater prevalence of morphometric vertebral fractures in postmenopausal women with T2D (34.3%) than in controls (18.7%, $p = 0.01$) (111). Vertebral fractures were associated with lower values of TBS (area under the curve, AUC: 0.69; $p < 0.0001$) and FN-BMD (AUC: 0.63; $p < 0.004$).

A recent meta-analysis of 40,508 individuals (35,546 women and 4962 men; 4,269 patients with diabetes) showed that, overall, T2D was associated with decreased TBS (more pronounced in women) (61). However, there was evidence of substantial heterogeneity among studies – most of them used unadjusted TBS values, and only a few adjusted for parameters that may directly affect TBS, such as age, BMI, LS-BMD, and the TBS software (56,61).

In summary, the relationship between T2D and TBS is mixed. Several studies (42,57,112-117), but not all (58,111), have shown that TBS is lower in patients with diabetes, especially in those with poor glycemic control, disease complications, and/or longer duration of disease. This discrepancy could also be attributed to the differences in sample size, duration of diabetes, HbA1c levels, and multifactorial pathophysiology of bone fragility in diabetes, which demands further investigation (45,57,59,61). Recently, our research group reported that the effect of abdominal soft tissue thickness (STT) should be considered when interpreting TBS in patients with T2D in whom increased abdominal adiposity may artifactually reduce TBS values (45).

Another study examined TBS in 119 patients with type 1 diabetes (T1D) (59 males, 60 premenopausal females; mean age = 43.4 years) and 68 matched healthy controls and found that TBS was comparable in T1D patients and non-diabetic controls, but was lower in T1D patients with existing clinical fractures

(n = 24) than in controls (118). Using a multivariate model, TBS (p = 0.049) and HbA1c (p = 0.036) were found to be independently associated with prevalent fractures in T1D patients. A few other studies have examined the differences in TBS between T1D patients and healthy controls and have reported heterogeneous results (119-121).

LONG-TERM GC EXPOSURE

It is well known that prolonged GC exposure is associated with increased fracture risk and a significant age-adjusted decrease in TBS, but not in LS-BMD (75,76). Two independent studies have shown that TBS differentiated subjects according to chronic GC exposure. Paggiosi and cols. studied 484 women (aged 55-79 years), allocated into 3 groups: 64 taking prednisolone ≥ 5 mg/day for > 3 months, 141 who had sustained a recent MOF, and 279 healthy women (75). Compared to healthy women, those with a recent fracture had lower age-adjusted LS-BMD and TBS Z-scores. In contrast, women on GC had comparable age-adjusted LS BMD but lower adjusted TBS Z-scores (p < 0.001) than healthy controls. TBS (AUC = 0.721), but not LS BMD (AUC = 0.572), was able to discriminate between GC-treated and GC-NAÏVE women.

Leib and Winzenrieth also assessed TBS, BMD, and osteoporotic fractures in 416 individuals (mean age = 63.4 years; 72 males) taking prednisone ≥ 5 mg/day for ≥ 3 months and compared them to 1,104 sex-, age-, and BMI-matched controls (76). Prevalent osteoporotic fractures were present in 16.3% of cases and 13.1% of GC-naïve subjects (p = 0.12). Also, TBS and BMD Z-scores at the hip sites, but not LS-BMD, were lower in the GC group. In the GC-naïve subjects, both TBS and LS-BMD were able to differentiate between patients with and without fractures. In contrast, in the GC group, TBS (but not LS-BMD) was able to distinguish between fractured and non-fractured individuals. Using a multivariate model, the authors showed that each point decrease in SD of TBS conferred a 51% greater risk of prevalent fracture (95% CI: 1.23-1.86).

In 2019, Florez and cols. (79) published a study including 127 subjects (mean age = 62 years; 63% females) treated with GC for different autoimmune diseases that led to osteoporosis over a mean period of 47.7 months. About 28% of these patients had some type of fracture and 17% of them had prevalent vertebral fractures. While the BMD T-score was used to establish the diagnosis of osteoporosis in 29% of cases, 52% of the study population had degraded microarchitecture as measured by TBS. Another study evaluated 627 patients with asthma being treated with GC and an equal number of non-asthmatic controls (122). TBS values were lower in those with asthma compared to control subjects (1.320 versus 1.360, respectively; p = 0.001), whereas LS-BMD was similar between the two groups.

IMPACT OF HETEROTOPIC OSSIFICATION AND ABDOMINAL STT ON TBS

There is evidence that TBS is less affected by the presence of heterotopic ossifications that may typically overestimate LS-BMD. Data from some studies suggest that neither osteoarthritic changes in elderly women nor lumbar syndesmophytes in men with spondyloarthritis influenced TBS results (123-125). The presence of a vertebral fracture also seems to have less impact on TBS, whereas falsely elevate measured BMD (126). In contrast, White and cols. found that vertebral exclusion, as per ISCD recommendations, generally, tends to lower TBS (but not always) and may result in relevant changes in calculated fracture risk using FRAX (127). Until more data is available, vertebrae excluded from BMD calculation (fractures or osteoarthritis) should also be excluded from the TBS analysis (10).

In contrast, similar to what occurs in BMD measurement (128), TBS analysis may be affected by the amount of local soft tissue, which leads to X-ray attenuation, degrading the image texture. Excess abdominal soft tissue may artificially reduce TBS values due to deleterious effects of image noise (129), particularly in subjects with T2D in whom increased abdominal adiposity may artifactually reduce TBS values.

To address this issue, the current TBS algorithm adjusts for BMI as a surrogate marker for regional STT (10). The manufacturer recommends that TBS only be performed in patients with a BMI of 15-37 kg/m^2; TBS has not been validated in patients with BMIs outside of this range. However, even with a BMI of 15-37 kg/m^2, the use of BMI to adjust the TBS calculation is not perfect because it cannot distinguish patients with higher central adiposity from those with a more peripheral fat accumulation (130). Hence,

BMI adjustment only indirectly addresses soft tissue interference on the lumbar spine scan area used for TBS analysis, while measuring local STT accounts for this issue directly (131). Recently, our study group showed that in women with T2D, glucose intolerance, and normal glucose metabolism, higher HbA1c levels were associated with greater BMD, higher abdominal STT, and lower TBS values (45). However, after adjusting for local adiposity, TBS differences among groups disappeared, except in the subgroup of women with higher HbA1c levels and longer disease duration. These results indicate that the effect of abdominal STT should be considered when interpreting TBS results obtained from the current commercially available TBS software version, particularly in patients with T2D. A new TBS software version is under development which is based on an algorithm that takes into account STT rather than BMI, seems to correct this technical limitation (131).

In conclusion, this review elaborates on the potential applicability of TBS in clinical practice. This textural index is readily available from spine DXA images and is associated with vertebral and non-vertebral fractures in postmenopausal women and older men. TBS appears to reflect qualitative aspects of skeletal structures that are partially independent of CRFs and DXA BMD measurement, being included as a risk factor in the FRAX tool. However, it should not be used alone to guide clinical decisions, and some limitations, such as the lack of a well-established cutoff point and image noise interference, must be acknowledged. Finally, TBS seems to have a role in anabolic drug response but may not be useful for monitoring antiresorptive therapy.

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