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ASSESSMENT OF BONE HEALTH

Clinical Application of Spine Trabecular Bone Score (TBS)

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Abstract Trabecular bone score (TBS) is a software program recently approved by the US Food and Drug Administration for post-acquisition processing of lumbar spine dual-energy X-ray absorptiometry images that allows assessment of bone texture as a surrogate for bone microarchitecture. Low TBS values are associated with increased risk of major osteoporotic fracture risk in postmenopausal women and men aged 40 years and older independent of BMD. TBS data can be used to adjust FRAX probability of fracture. As such, TBS data can be useful in osteoporosis treatment initiation decisions. Following treatment initiation, TBS increases are smaller than seen with BMD; at present, there is insufficient evidence that TBS can be used to monitor treatment. TBS may be particularly helpful in fracture risk prediction for those with diabetes mellitus or receiving glucocorticoid therapy, but additional validation of existing observations is needed. In summary, TBS should not be used alone to guide treatment initiation, but can be used with FRAX to estimate fracture probability in postmenopausal women and older men, thereby facilitating treatment initiation decisions.

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Introduction

Osteoporosis is a disease of low bone mass with concomitant deterioration of bone microarchitecture with resultant increased fragility fracture risk [1]. Classically, osteoporosis is diagnosed using dual-energy X-ray absorptiometry (DXA)-measured bone mineral density (BMD). When the BMD measurement is 2.5 standard deviations (SD) or more below the average young normal mean (i.e., a T-score of ≤ -2.5), osteoporosis is diagnosed [2–4]. While low BMD is associated with increased fracture risk (relative risk increases 1.4- to 2.6-fold for every SD reduction in BMD [5, 6]), the majority of "osteoporosis-related" fractures occur in those with a T-score better than -2.5 [1, 7–9]. Obviously, BMD measurement alone is not an ideal approach to identifying those who will subsequently sustain fracture. It is logical that assessment of other skeletal parameters (in addition to BMD) affecting bone strength could potentially improve fracture discrimination capability. Historically, there has been no approach to clinically assessing bone microarchitecture.

Lumbar spine trabecular bone score (TBS) was developed to allow an assessment of skeletal microarchitecture independent of BMD. The US FDA cleared TBS for clinical use in 2012 labeled, in part, as follows: "TBS is derived from the texture of the DEXA image and has been shown to be related to bone microarchitecture and fracture risk." Existing data behind TBS and examples of its potential clinical utility are reviewed here.

TBS Technique

The TBS concept is based on the potential to estimate structure of three-dimensional bone from two-dimensional DXA images [10]. Based upon X-ray absorption, gray-level variations in the DXA image (the so-called bone "texture") are assumed to correlate with whole bone absorption properties according to a mathematical relationship. How this is accomplished is published elsewhere [10, 11]; based on this approach, software has been developed for post-acquisition processing of a DXA image such that a high TBS value (which is a unitless number) reflects a more homogeneously textured bone characterized by low-amplitude fluctuations in photon absorption. By contrast, less well-textured bone is characterized by higher-amplitude fluctuations and produces a lower TBS value (Fig. 1).

TBS depends on DXA image texture, which can be affected by factors unrelated to bone including scan acquisition mode, differences between densitometers and soft tissue composition. Differences between densitometer models have been reported and may potentially relate to image resolution [12]. As such, new installations of TBS software require manufacturer calibration using a specially constructed phantom. The important role of soft tissue composition was highlighted in early studies of TBS in men in comparison with women. The original TBS algorithm was optimized for women and gave lower TBS measurements in men; an unexpected result was that men have lower fracture risk and could, physiologically, be expected to have more intact trabecular structure [13]. It was subsequently clarified that this was caused by greater abdominal adiposity (with resultant greater tissue thickness over the lumbar spine) in men; as a result, the TBS algorithm was modified (version 2.x) to address these technical issues [14]. The clinical performance of this updated algorithm was assessed in the Manitoba BMD cohort using 47,736 women and 4348 men. In this cohort, men had a higher TBS (1.360 ± 0.132) than women (1.318 ± 0.123, $p < 0.001$) consistent with the lower fracture risk observed in males. Fracture prediction in men was improved over the earlier software version for both major osteoporosis-related fractures and hip fracture. However, due to the effect of tissue thickness, the manufacturer recommends that TBS only be performed in those with a BMI of 15–37 kg/m^2.

Given the high prevalence of spinal degenerative changes in older adults, with resultant elevation of the DXA-measured BMD, one would be tempted to assume that TBS would be similarly elevated. However, available data find that TBS may be relatively unaffected by these changes. For example, Kolta et al. [15] correlated lumbar BMD with corresponding radiographs in which lumbar osteoarthritis (OA) was graded 0–4 according to the Kellgren and Lawrence classification. As expected, BMD increased with higher grades of OA, but spine TBS did not differ in those with and without grade 2 or higher lumbar spine OA. Indeed, in this investigation, TBS was not correlated with OA grade. Over 6 years, lumbar spine BMD was unchanged (although there was a significant decrease in hip BMD), while lumbar spine TBS showed a significant decrease over time that was independent of Kellgren–Lawrence grade.

TBS In vitro Evaluation

TBS has been evaluated using human cadaveric lumbar vertebral, femoral neck and distal radius samples in which TBS was compared with micro-CT 3D data [10].

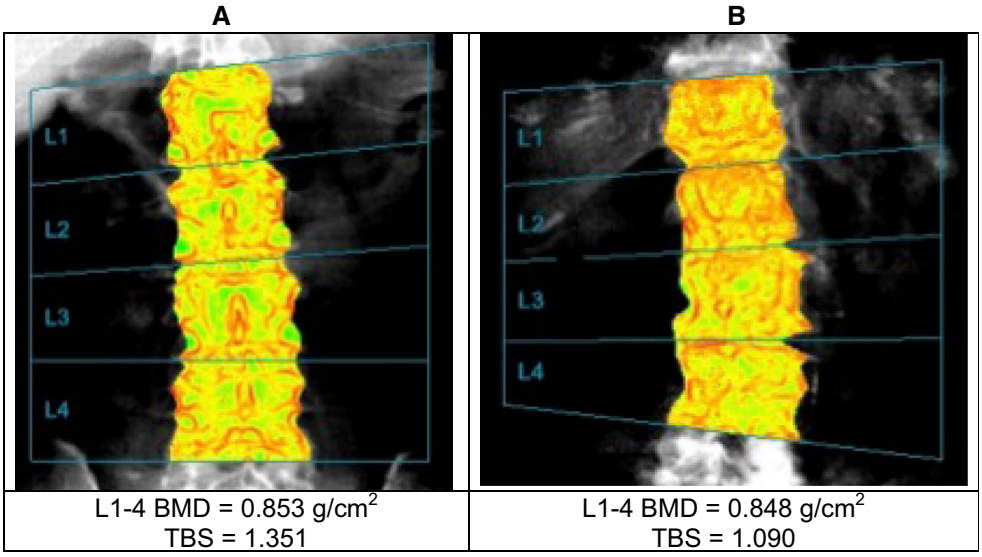

Fig. 1 Example TBS printouts that are (**a**) low and (**b**) normal. The TBS calculation is performed using the same DXA lumbar spine region of interest used for BMD measurement. A low TBS value indicates few gray-level variations of large amplitude and is interpreted as low-quality bone texture. These two postmenopausal women have virtually identical L1-L4 BMD and T-score (−2.8). However, their TBS values are substantially different with **a** being normal and **b** being low

Significant correlations were found, particularly for bone volume fraction, trabecular spacing and trabecular number. A subsequent analysis of 30 human cadaveric vertebrae examined with micro-CT was compared with ex vivo DXA scans of the same samples [16]. Once again, significant correlations were found between TBS and the bone microarchitecture parameters (highest for TBS versus connectivity density, $r = 0.821$). Multivariable regression suggested that TBS was able to differentiate samples of differing microarchitecture despite similar BMD measurements.

Given the inherent limited resolution of DXA images, the question arises of how TBS could evaluate microarchitectural changes in much smaller structures [17]. This has not been entirely clarified; however, it is possible that TBS captures macroscopic skeletal parameters that are correlated with microstructure, thus serving as an indirect proxy measure for skeletal microarchitecture. For example, areal BMD itself was found to correlate with microstructure in the above-noted study, despite not directly measuring microarchitecture. Another possibility is that TBS may directly assess skeletal macroarchitecture degradation (e.g., trabecular network porosity within the limits of DXA image resolution), which, in turn, is coupled with skeletal microarchitecture degradation (below the resolution limits of DXA). A simple analogy to depict such a situation is an iceberg, whereby the visible portion corresponds to the architectural aspects of bone visible to DXA (i.e., image texture), whereas finer microarchitectural details, like the majority of an iceberg, are hidden below the surface. As an iceberg melts (degrades), the visible and submerged components are affected. As noted by others [18], direct evidence that spine TBS measures vertebral trabecular microarchitecture would best be established experimentally in which TBS is derived from cadaveric lumbar spines scanned in situ and then correlated with ex vivo vertebral microarchitecture adjusted for important covariates (age, sex, soft tissue thickness, BMD). Until such time, spine TBS is best considered as an index of bone texture that may serve as an indirect proxy of skeletal microarchitecture.

Regardless of what TBS is truly measuring, its clinical utility requires the capability of assessing fracture risk independently of BMD and other covariates. In this regard, ex vivo vertebral compressive strength of L3 vertebral bodies was compared with TBS of in situ DXA scans [19]. In this small study ($n = 16$), a moderate correlation between TBS and trabecular bone volume was observed ($r = 0.58$) and TBS correlated with vertebral body stiffness ($r = 0.64$). Recently, a micro-CT analysis of transiliac bone biopsies in 80 premenopausal women and 43 men with idiopathic osteoporosis found TBS to independently associated with structural model index (SMI, which reflects the structure's rod- vs. plate-like nature) trabecular number, trabecular spacing and BV/TV [20]. These results led the authors to conclude that TBS was a practical, noninvasive, surrogate technique for assessment of trabecular bone microarchitecture. However, not all ex vivo studies are similarly positive; for example, a study of 62 human lumbar vertebrae scanned with high-resolution peripheral quantitative computed tomography (HR-pQCT) was compared with simulated DXA images to estimate TBS [21]. Although simulated areal BMD predicted failure load and failure stress, simulated TBS was a poor surrogate for vertebral strength. Whether similar results would be seen with the commercial version of the TBS algorithm is uncertain. In summary, ex vivo data generally, but not uniformly, support the premise that TBS is able to serve as a surrogate for bone microarchitecture.

TBS In vivo Evaluation

Correlations of HR-pQCT and TBS have been performed but are inherently limited by assessment at different skeletal sites; HR-pQCT is only possible at the distal radius and tibia, while TBS measures only the lumbar spine. Despite this limitation, a study of 22 women with primary hyperparathyroidism found TBS to be correlated with most HR-pQCT indices of trabecular microarchitecture though spine BMD alone showed an even stronger association with trabecular microarchitecture [22]. The same group subsequently found TBS to modestly, but significantly, correlate with most HR-pQCT indices ($r = 0.20$–0.52) in 115 pre- and postmenopausal White and Chinese American women [22]. However, after adjustment for age, ethnicity and BMI, there was no significant residual association between TBS and any of the HR-pQCT indices. Popp et al. [23] studied 72 premenopausal women and found TBS to moderately correlated with trabecular microstructural parameters ($r = -0.43$ to -0.57, $r = 0.42$ to 0.46 for connectivity). Additional adjustments for BMD and other covariates were not performed. The largest study to date ($n = 125$ postmenopausal women) TBS correlated weakly with microarchitectural indices derived from HR-pQCT at the radius ($r = -0.24$ to 0.31) and tibia ($r = -0.16$ to 0.13) [24]. In a recent review of these data [25], it was concluded that TBS explains relatively little of the variance in trabecular microarchitecture in vivo, leaving open the question of what skeletal properties TBS measures that account for its ability to predict fracture risk. In summary, it is less than entirely clear what TBS is measuring; however, the important clinical question is "Does TBS improve fracture risk prediction?"

Clinical Assessment of TBS

In a cross-sectional analysis, TBS was studied in 29,407 women aged 50 years and older. BMD explained only 7–11 % of variation in TBS, while older age, recent glucocorticoid use, prior major fracture, rheumatoid arthritis, chronic obstructive pulmonary disease, high alcohol intake and higher BMI were associated with reduced TBS. These findings were not affected by adjusting for lumbar spine or femoral neck BMD. Multiple studies have found similarly low correlation between lumbar spine TBS and BMD and an age-related reduction in TBS [26–32]. While these studies are international, there has been relatively little evaluation of potential effects of race/ethnicity on TBS [32]. Currently, it is assumed that TBS results are relatively unaffected by race/ethnicity, and this is supported by a recent international meta-analysis which found that mean TBS was similar across cohorts despite large differences in BMD [33].

Multiple cross-sectional studies (Table 1) find TBS to be lower in those with fragility fracture compared with non-fractured controls with an odds ratio (OR) of fracture of approximately 1.5–3 for each standard deviation reduction in TBS [11, 34–38]. The aforementioned studies evaluated women, but relatively comparable findings were reported in men with an OR of fracture per SD decrease of ~1.6 [35]. In summary, cross-sectional data, largely among postmenopausal women, consistently find TBS discriminates those with versus without prior fracture. It appears that this discrimination is independent of other commonly used risk factors including BMD.

A number of longitudinal studies have evaluated the potential for TBS to predict incident fragility fracture (Table 2). The largest studies have been from the Manitoba, Canada BMD database. Initially, in almost 30,000 women aged 50 years and older followed for a mean of 4.7 years, 1668 women sustained one or more major fractures as ascertained from population-based hospitalization and billing records [39]. TBS was lower ($p < 0.001$) in women who sustained fracture than those who did not. Moreover, a gradient of risk across TBS tertiles was observed. Importantly, TBS was independently associated with major osteoporotic fracture following adjustment for multiple clinical risk factors including age, comorbidity score, rheumatoid arthritis, chronic obstructive pulmonary disease, diabetes, substance abuse, BMI, prior osteoporotic fracture, recent corticosteroid use and recent osteoporosis treatment. Similar results were observed in 560 French women followed for a mean of 7.8 years [40]. TBS was retrospectively determined in a large European cohort of postmenopausal women and again was lower in women who sustained fractures than those who did not. [41] Similarly, TBS was lower in Japanese women aged 50 years and older who sustained incident vertebral fractures [42].

Similar to postmenopausal women, the first evaluation of TBS to predict incident fracture in men was performed in the Manitoba BMD database [43]. Fracture data on 3620 men aged 50 years and older were obtained from population-based health services records with a mean follow-up of 4.5 years. Similar to observations in women, the correlation between spine BMD and TBS was relatively low ($r = 0.31$) and much less than the correlation between spine and hip BMD ($r = 0.63$), and TBS was lower in men who sustained major osteoporotic fracture, hip fracture and clinical vertebral fracture. Generally, similar observations were observed in a study of ~2000 community-dwelling Japanese men [42].

In summary, there is consistent clinical evidence that lower TBS is associated with increased fracture risk in multiple studies; however, the effect sizes vary considerably. Overall, the strength of the observed effects is larger in cross-sectional studies and weaker in those that are longitudinal and/or based upon larger populations. This variability does not negate the potential for TBS to provide insights into fracture risk independently of BMD.

Clinical Use of TBS

Use in Fracture Risk Prediction to Assist Treatment Initiation Decisions

It is widely appreciated that BMD alone does not adequately discriminate those who will from those who will not sustain fragility fracture. This recognition led to the development of the WHO FRAX tool that estimates ten-year fracture probability using clinical risk factors with or without femoral neck BMD [44–46]. For TBS to be clinically useful, it must enhance fracture risk estimation beyond that provided by FRAX. To evaluate this possibility, 33,352 women aged 40 years and older (mean 63 years) were studied using the Manitoba database. During 4.7 years of follow-up, 1872 women sustained one or more major osteoporotic fractures; lower TBS was a significant fracture risk factor with an OR for major fracture per TBS SD reduction of 1.36. When additionally adjusted for FRAX clinical risk factors and femoral neck BMD, the OR was slightly attenuated (1.18, 95 % CI 1.12–1.23). Thus, TBS improved the fracture prediction capability of FRAX. Also using the Manitoba BMD cohort, interactions with other risk factors were examined, and ultimately, the ability to adjust the FRAX score based on TBS was incorporated into the FRAX Web site (Fig. 2) [43]. When TBS values are low, the FRAX-estimated risk is increased,

Table 1 Studies of lumbar spine TBS for fracture discrimination (cross-sectional design)

References (source)	Study population	Fractures (prevalent)	Major results
Ayoub et al. [37] (public advertisements, LB)	1000 postmenopausal women aged 45–89 years, mean 61.1 years	164 MOF	OR significant ($p < 0.001$) [unadjusted] OR significant ($p = 0.01$) [BMI, age, L-spine BMD]
Del Rio et al. [65] (medical clinic, Barcelona, ES)	191 women aged 50+years	83 mild or moderate trauma femoral neck	OR per SD 2.05 (1.45–2.89) (unadjusted), 1.71 (1.15–2.79) [age] AUC 0.668 (0.597–0.734)
Krueger et al. [66] (university hospital, Madison, US)	429 women, mean age 71.3 years	158 low-energy non-vertebral or vertebral on VFA	OR any fracture 2.46 (1.9–3.1), vertebral 2.49 (1.9–3.3) [age and BMI]; AUC any fracture 0.74, vertebral 0.73. OR any fracture 2.36 (1.8–3.0), vertebral 2.44 (1.8–3.3) [age, BMI, BMD]
Leib et al. [35] (university hospital, Burlington, USA)	2165 women aged 40+ years	289 low-energy	OR per SD 1.38 (1.22–1.56) [unadjusted], 1.28 (1.13–1.46) [age] AUC 0.598 (0.563–0.633)
Leib et al. [35] (University Hospital, Burlington, USA)	180 men aged 40+years (age- and BMD-matched case–control)	45 low-energy any site	Overall: OR per SD 1.59 (1.09–2.20), AUC 0.614 (0.539–0.685) Vertebral fracture: OR per SD 2.07 (1.14–3.74), AUC 0.695 (0.615–0.767)
Nassar et al. [36] (Fracture Liaison Service in Paris, FR)	362 aged 50+ patients hospitalized after non-vertebral fracture, 51 % hip fracture, 77 % women, mean age 74.3 years	133 vertebral on VFA	Overall: AUC 0.677 (CI unknown) for vertebral fracture. Non-osteoporotic BMD: AUC TBS 0.671 (CI unknown) for vertebral fracture
Pothuaud et al. [11] (university hospitals in Lausanne, CH and Bordeaux, FR)	200 postmenopausal women (case–control)	45 (5 hip, 20 vertebral, 20 other)	OR per SD 1.95 (1.31–2.89) AUC 0.685 (0.599–0.762)
Rabier et al. [34] (hospitals Libourne, Médoc-Lesparre, FR)	168 postmenopausal women (age-matched case–control)	42 osteoporosis-related vertebral	Overall: OR per SD 3.20 (2.01–5.08), AUC 0.746 Osteoporotic: OR per SD 3.36 (1.90–5.92), AUC uncertain. Osteopenic: OR per SD 2.82 (1.27–6.26, AUC 0.716 (0.572–0.833
Touvier et al. [38] (university hospital, Orleans, FR)	255 postmenopausal women, mean age 65 years (range 40–92)	79 fragility fractures	OR 2.25 (1.58–3.29) [age] OR 1.83 (1.24–2.77) [age, hip BMD, height, weight, calcaneus Hurst parameter]
Winzenrieth et al. [67] (hospital in Avignon, FR)	243 postmenopausal women (age-matched case–control) with BMD T-scores between −1 and −2.5	81 vertebral	OR per SD 2.52 (1.82–3.53). AUC 0.721 (0.660–0.777)

OR, odds ratio (95 % confidence interval) per SD decrease [covariate adjustments]; SD, standard deviation; AUC, are under the curve (95 % confidence interval); VFA, vertebral fracture assessment; BMI, body mass index; MOF, major osteoporotic fractures (hip, clinical spine, forearm, humerus)

and conversely, when TBS is high, fracture risk estimates are reduced (Fig. 3). To validate the TBS adjustment, 14 prospective international cohorts (total $n = 17{,}809$, 59 % female, mean age 72 years) were assembled [33]. In this dataset, TBS adjusted for time since baseline and age was significantly associated with major osteoporotic fracture (gradient of risk [GR] per SD 1.44, 95 % CI 1.35–1.53 men and women combined; 1.50, 95 % CI 1.36–1.66 men only and 1.40, 95 % CI 1.30–1.52 women only) and was only slightly attenuated when adjusted for FRAX probability (GR per SD 1.32, 95 % CI 1.24–1.41 men and women combined; 1.35, 95 % CI 1.21–1.49 men only; 1.31, 95 % CI 1.21–1.42 women only). Additionally, for hip fracture and major osteoporotic fracture prediction, incorporation of the TBS adjustment factor derived from the Manitoba cohort improved the GR. Finally, no important between-cohort heterogeneity was found for TBS and its relation to major osteoporotic or hip fracture outcomes. These findings support the use of TBS to adjust FRAX probability.

Table 2 Studies of lumbar spine TBS for fracture prediction (longitudinal design)

References (source)	Study population	Fractures (incident)	Major results
Boutroy et al. [40] (OFELY, FR)	560 postmenopausal women age range 31–89 years	94 with 112 fragility fractures (35 wrist, 32 vertebral, 16 tibia, 8 hip, 7 rib, 6 humerus, 3 metatarsal, 2 scaphoid, 1 scapula, 1 elbow, and 1 patella)	OR AUC 0.63 (0.57–0.68), 1.57 (1.25–1.98) [unadjusted] OR not significant with total hip BMD; not significant with age, prevalent fracture, lumbar spine BMD.
Briot et al. [41] (OPUS, European centers Kiel, Paris and Sheffield)	1007 women aged 55+ years, mean age 65.9 years	82 clinical osteoporotic (80 with TBS), 46 radiographic vertebral	Clinical osteoporotic: AUC 0.62 (0.56–0.69), OR 1.62 (1.30–2.01), [unadjusted] Radiographic vertebral: AUC 0.63 (0.54–0.72), OR 1.54 (1.17–2.03) [unadjusted]
Hans et al. [39] (CA)	29,407 women aged 50 + y, mean age 65.4 y	1668 one or more MOF (including 439 vertebral and 293 hip)	Any MOF: AUC 0.63 (0.61–0.64), HR 1.35 (1.20–1.42) [unadjusted], HR 1.20 (1.14–1.26) [multiple clinical risk factors and femur neck BMD] Vertebral: AUC 0.66 (0.64–0.69), HR 1.45 (1.32–1.58) [unadjusted], HR 1.22 (1.10–1.34) [multiple clinical risk factors and femur neck BMD] Hip: AUC 0.68 (0.65–0.71). HR 1.46 (1.30–1.63) [unadjusted], HR 1.28 (1.13–1.46) [multiple clinical risk factors and femur neck BMD]
Iki et al. [68] (JPOS, JA)	665 women aged 50+ years, mean age 64.1 years	92 with incident vertebral fracture by VFA	OR AUC 0.682 (0.662–0.773), 1.98 (1.56–2.51) [unadjusted], OR 1.52 (1.16-2.00) [age, prevalent vertebral deformity, spine BMD adjusted]
Iki et al. [30, 42] (JPOS, JA)	2012 community-dwelling men age 65+, mean age 73 years	22 MOF (by interviews or mail and telephone surveys)	AUC 0.669 (0.548–0.790), OR 1.89 (1.28–2.81) [unadjusted]
Leslie et al. [13] (CA)	3620 women aged 50+ years, mean age 67.6 years	183 one or more MOF (including 91 clinical vertebral and 46 hip)	Any MOF: AUC 0.59 (0.55–0.63), HR 1.22 (1.05–1.41) [clinical FRAX score & osteoporosis treatment], HR 1.12 (0.96–1.30) [above + hip BMD]. Hip: AUC 0.67 (0.59–0.75), HR 1.60 (1.21–2.11) [clinical FRAX score and osteoporosis treatment], HR 1.36 (1.01–1.83) [above + hip BMD. Vertebral: AUC 0.57 (0.51–0.63), HR 1.12 (0.91–1.38) [clinical FRAX score and osteoporosis treatment], HR 1.09 (0.88–1.34) [above + hip BMD]
Leslie et al. [13] (CA)	33,352 women aged 40–100 y. mean age 63 y	1872 one or more MOF, 1754 deaths	MOF: HR 1.36 (1.30–1.42) [time since baseline and age], HR 1.18 (1.12–1.23) [clinical risk factors and femoral neck BMD]. Death: HR 1.32 (1.26–1.39) [time since baseline and age], HR 1.20 (1.14–1.26) [clinical risk factors and femoral neck BMD].
McCloskey et al. [33] (CA)	33,352 women aged 40–100 years	1754 deaths, 1639 one or more MOF excluding hip, 306 women 1 or more hip	Death HR 1.20 (1.14–1.26), MOF excluding hip HR 1.18 (1.12–1.24), hip 1.23 (1.09–1.38) [all FRAX risk variables]
McCloskey et al. [33] (14 international cohorts)	17,809 (41 % men and 59 % women), mean age 72 y	1109 one or more MOF including 298 hip	MOF HR 1.44 (1.35–1.53) [age and time since baseline], HR 1.32 (1.24–1.41) [FRAX MOF probability]. Hip HR 1.44 (1.28–1.62) [age and time since baseline], HR 1.28 (1.13–1.45) [FRAX hip probability]
Popp et al. [70] (SEMOF, CH)	556 women mean age 76.1 y	52 clinical fragility (20 forearm, 6 hip, 10 vertebral, 9 humerus, 2 pelvis, 3 ankle, 1 clavicle, 1 elbow)	AUC 0.69 (0.62–0.77), HR 2.01 (1.54–2.63) [age and BMI], 1.66 (1.25–2.22) [above + femoral neck BMD]

Table 2 continued

References (source)	Study population	Fractures (incident)	Major results
Schousboe et al. [69] (MrOS, US)	5979 men aged 65+ years	448 one or more MOF including 181 hip	MOF 1.27 (1.17–1.39) and hip 1.20 (1.05–1.39) [FRAX with BMD and prevalent vertebral fracture]

HR, hazard ratio (95 % confidence interval) per SD decrease [covariate adjustments]; SD, standard deviation; AUC, are under the curve (95 % confidence interval); BMI, body mass index; MOF, major osteoporotic fractures (hip, clinical spine, forearm, humerus)

It is important for clinicians to appreciate the significant interaction observed between TBS, fracture risk and age. TBS exerts a stronger effect on fracture risk in younger women but a weaker effect among older women (Fig. 4). The reasons for this waning effect of TBS with age are uncertain, but could well reflect the multifactorial nature of fractures being that it is influenced by not only by bone strength, but also to a large extent, by falls risk. Falls become increasingly common in older adults and as such likely play a greater role in determining overall fracture risk (especially for hip fracture) than does low bone strength, whereas in younger individuals, falls are less frequent and measures of skeletal strength may be of greater importance. This interaction was incorporated into the final models developed for predicting TBS-adjusted fracture probability [43]. In summary, TBS allows adjustment for FRAX-estimated fracture risk. For which patients does this adjustment affect treatment decisions?

To explore this question, the net reclassification improvement (NRI) due to the use of the TBS-adjusted FRAX probability was evaluated in 34,316 women aged 40–100 years [47]. During mean follow-up of 8.7 years, 3503 women sustained an incident major osteoporotic fracture including 945 with incident hip fracture. Reclassification was assessed using FRAX-based intervention criteria under three national clinical practice guidelines (Osteoporosis Canada, US National Osteoporosis Foundation [NOF], and UK National Osteoporosis Guidelines Group [NOGG]). Overall, the proportion of women reclassified using the TBS-adjusted FRAX probability was small, <5 %. However, for those close to an intervention threshold, reclassification rates were much higher; for example, the addition of TBS reclassified 17.5 % of women who had a FRAX-estimated major osteoporotic fracture risk of 20 % ± 5 %. The NRI was significantly improved for guidelines from Osteoporosis Canada, US NOF and UK NOGG (all $p < 0.05$). Overall, these data are consistent with a small but significant improvement in fracture risk assessment using TBS-adjusted FRAX probability. However, almost all of the benefits in terms of risk recategorization were seen in individuals close to the intervention threshold. Thus, it is for individuals who are close to an intervention cutpoint that TBS may have the greatest clinical utility.

In summary, TBS should not be used alone to make treatment recommendations, but it can be used to adjust FRAX probability and guide treatment initiation. For those individuals close to the intervention threshold, inclusion of TBS will have a greater impact upon such decisions.

Assistance in Not Initiating Pharmacologic Therapy

The current US National Osteoporosis Foundation Guidelines recommend therapy for those with a BMD T-score of −2.5 or worse. However, some people, particularly relatively young individuals, will have a low FRAX-estimated fracture risk. Anecdotally, some clinicians are electing to not initiate therapy in such individuals. While not evidence based, it is logical that knowledge of TBS would assist in such decisions. As an example, consider a small (95 pounds, 4′ 11″ tall) 55-year-old White female who could well be expected to have a low BMD T-score simply based upon small bone size since DXA is a two-dimensional areal technology and does not consider the effect of the third dimension, i.e., bone depth. Nonetheless, if her T-score was −2.5, she could receive a recommendation to receive therapy, but a high TBS value may reassure the clinician that observation, rather than pharmacologic therapy, is appropriate. In this regard, there is no international consensus regarding what constitutes "high" or "low" TBS values. However, the manufacturer has offered the following guidance regarding TBS values: ≥1.350 = normal, between 1.350 and 1.200 = partially degraded and ≤1.200 = degraded architecture.

Is TBS Useful in Select Patient Populations?

It is possible that TBS may be particularly helpful in fracture prediction in patients with certain diseases. For example, TBS may have value in those with diabetes mellitus (DM) type 2 where fracture risk is paradoxically increased despite higher BMD, leading to underestimation of fracture risk from the FRAX algorithm [48, 49]. In a study of 29,407 women aged 50 years and older (2356 with

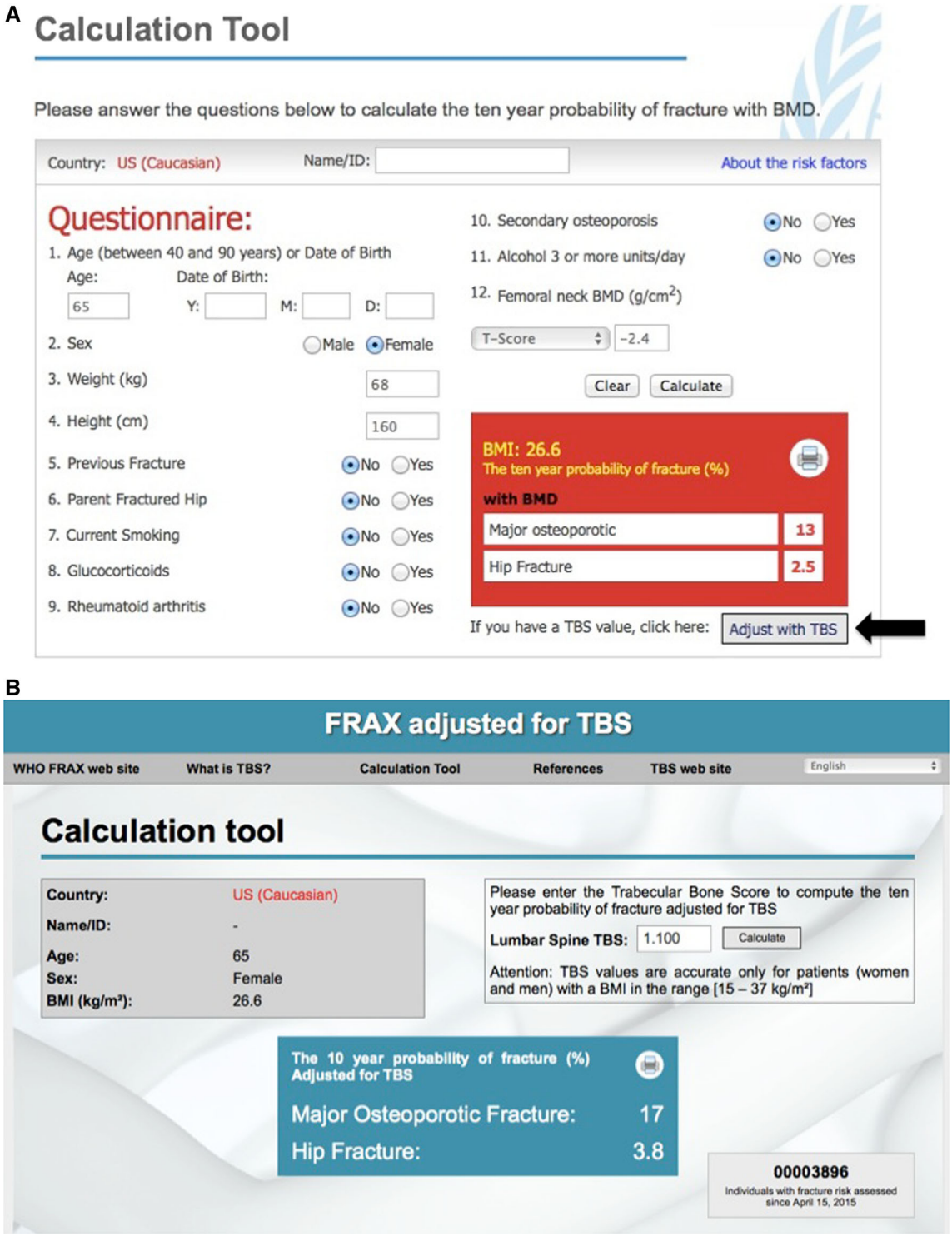

Fig. 2 **a** Example FRAX® screenshot using the US Caucasian tool. In this example, the 10-year probability for major osteoporotic and hip fracture is 13 and 2.5 %, respectively, in a woman aged 65 years, weight 68 kg, height 160 cm, femoral neck T-score −2.4 and no additional clinical risk factors. The *arrow* indicates button for entering TBS if these results are available. **b**. Example screenshot for adjusting FRAX® probability using TBS data. Assuming a reduced TBS measurement of 1.100, the 10-year probability for major osteoporotic fracture increases from 13 to 17 %, and for hip fracture from 2.5 to 3.8 %

previously diagnosed DM predominantly type 2), DM was associated with higher BMD but lower TBS in unadjusted and adjusted models. [50] TBS predicted incident major osteoporotic fractures in those with DM (adjusted OR 1.27, 95 % CI 1.10–1.46) and those without DM (HR 1.31, 95 % CI 1.24–1.38). It was concluded that lumbar spine TBS

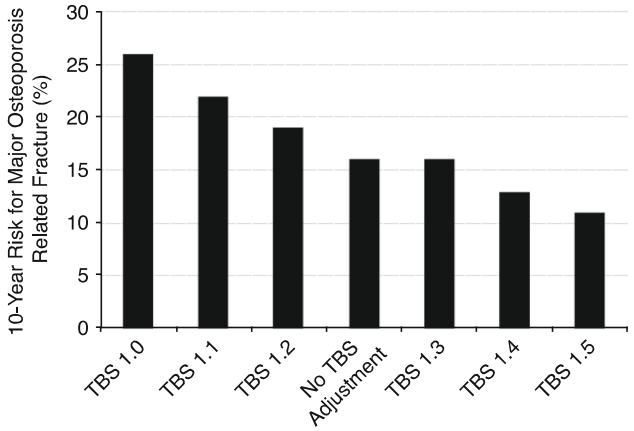

Fig. 3 Effect of TBS on Major Osteoporotic Fracture Risk Estimation. In this example, a 54-year-old White female with a BMI of 24 kg/m^2, a maternal history of hip fracture and a femoral neck femoral neck T-score of −2.4 has a 10-year major osteoporotic fracture risk of 16 % using the US Caucasian tool with no TBS adjustment. As shown here, TBS increases the major osteoporotic fracture risk, whereas higher TBS reduces the risk as shown

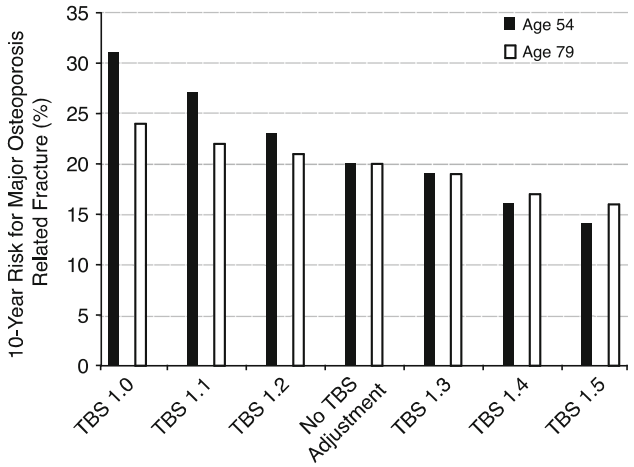

Fig. 4 Effect of age on the TBS Adjustment to Major Osteoporotic Fracture Risk Estimation. In this example, two patients with the same femoral neck T-score (−2.4) and same 20 % FRAX-estimated 10-year risk for major osteoporosis-related fracture are considered. The effect of TBS adjustment for a 54-year-old White female with rheumatoid arthritis and a maternal history of hip fracture and a 79-year-old White female with tobacco use is depicted here. For the younger woman, reduction in the TBS value increases the 10-year risk up to 31 %, while for the older woman, the increase is only up to 24 %

captures a larger proportion of the DM-associated fracture risk than does BMD. No other studies have assessed TBS for prediction of fractures in type 2 DM. TBS does discriminate prevalent radiographic vertebral fractures; TBS was lower in diabetic women with vertebral fracture than those without vertebral fractures (1.072 ± 0.15 versus 1.159 ± 0.15, $p = 0.006$) [51]. A small cross-sectional study of 57 women with type 2 DM found higher TBS in those with good glycemic control (defined as HgbA1C ≤ 7.5 %) compared to those with poor glycemic control (mean 1.254 ± 0.148 versus 1.166 ± 0.094, $p = 0.01$) [52].

The potential utility of TBS for assessing fracture risk in individuals with exogenous or endogenous excess glucocorticoid exposure has been explored. In a cross-sectional and longitudinal assessment of 102 patients with adrenal incidentalomas and 70 matched controls, TBS was lower in those with subclinical hypercortisolism (Z score −3.184 ± 1.211) than adrenal incidentalomas without subclinical hypercortisolism (−1.704 ± 1.541, $p < 0.001$) and controls (−1.189 ± 0.991, $p < 0.0001$). Exogenous glucocorticoid therapy results in lower TBS measurements in older women compared to those who are glucocorticoid naïve (mean 1.011 ± 0.152 vs 1.132 ± 0.136, $p < 0.001$) [53]. In a large clinical dataset, 416 glucocorticoid-treated (prednisone dose ≥5 mg per day for ≥3 months) men and women aged 40 years and older were matched with 1104 control subjects [54]. Mean TBS was significantly lower in glucocorticoid-treated patients than in controls (1.267 vs 1.298, $p < 0.001$). Among glucocorticoid-treated patients, those with fracture ($N = 68$) compared to those without fracture ($N = 348$) had significantly lower mean TBS (1.222 ± 0.131 versus 1.276 ± 0.134, $p < 0.05$). Interestingly, BMD at the spine, total femur and femoral neck were not useful for fracture discrimination in this study population.

TBS may prove to be of clinical value in other patient populations. For example, in patients with primary hyperparathyroidism, TBS is significantly lower and was associated with prevalent vertebral fracture [55, 56]. TBS also appears to be adversely affected by thalassemia major [57] and anorexia nervosa [58].

In summary, it is likely that TBS will provide additional information in the clinical assessment of fracture risk in patients with diabetes, in those with endogenous or exogenous glucocorticoid exposure and potentially in other conditions. However, further studies are needed to validate the positive results noted to this point.

Can TBS be Useful in Monitoring Osteoporosis Therapies?

Ideally, osteoporosis treatment should improve both bone density and architecture. As such, it is plausible that TBS could facilitate monitoring of pharmacologic therapy. Several studies have evaluated this possibility. Overall, these studies find a small but significant increase in TBS with medical therapies, although the magnitude of TBS change is often considerably less than that observed in BMD. For example, in 534 women who initiated anti-resorptive therapy (86 % bisphosphonate), over 3.7 years,

the annual spine BMD increased ($p < 0.001$) by 1.9 % annually, while TBS increased ($p < 0.001$) by 0.2 % per year [59]. Smaller studies with zoledronate and denosumab have reported similar observations [60, 61]. Such observations are physiologically reasonable as anti-resorptive therapy seems unlikely to alter bone microarchitecture. However, it is plausible that a greater TBS effect would be observed with bone anabolic agents. Consistent with this, a non-randomized comparison of 2 years of treatment with teriparatide ($N = 65$) or ibandronate ($N = 122$) found a 2.9 % TBS increase, 2.9 % with the former and 0.3 % with the latter ($p < 0.0001$), though this was less than the increase in lumbar spine BMD (7.6 vs 4.3 %, $p < 0.0001$). Similarly, in a non-randomized study of 390 patients (including 72 men), 24 months of therapy produced significant increases in BMD and TBS with alendronate (4.1/1.4 %), denosumab (8.8/2.8 %) and teriparatide (8.8/3.6 %) [62].

In summary, treatment-related changes in TBS are statistically significant in groups of subjects, but the magnitude of increase is considerably smaller than seen with BMD. It should be noted that most of these studies are limited by small sample sizes. Furthermore, such small TBS increases would likely be difficult to detect in an individual patient based upon measurement precision that is similar to or slightly worse than BMD [63]. Moreover, to this point, no studies have documented that TBS change on therapy is related to anti-fracture efficacy. It is possible that more potent bone anabolic agents will produce a greater TBS change and also provide evidence that TBS changes are associated with anti-fracture efficacy, but this hypothesis currently awaits supporting data. Given the current state of knowledge, the International Society for Clinical Densitometry (ISCD) has recommended against the use of TBS for monitoring bisphosphonate therapy [64].

Conclusion

Low TBS is associated with increased risk of vertebral, major osteoporotic and hip fracture risk in postmenopausal women and with increased major osteoporotic and hip fracture risk in men aged 50 years and older. TBS can be used to adjust the FRAX-estimated probability of fracture in postmenopausal women and older men and thereby assist with decisions regarding pharmacologic treatment initiation. TBS should not be used alone to determine treatment recommendations. Current data are not adequate to support the use of TBS for monitoring bisphosphonate treatment. TBS may ultimately be shown to have benefit in certain patient populations including those with DM, glucocorticoid excess and hyperparathyroidism, but existing data require further validation.

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Compliance with ethical standards

Conflicts of interest Neil Binkley has received research grants from Amgen, Eli Lilly, GE Healthcare, Merck and Opko Ireland and serves as a consultant or on advisory boards for Amgen, Astellas, Bristol-Myers Squibb, Eli Lilly and Merck. William D. Leslie (all fees paid to facility) has received speaker honorarium from Amgen, Eli Lilly, and Novartis and research grants from Amgen.

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