

Trabecular Bone Score—An Emerging Tool in the Management of Osteoporosis

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Abstract

Areal bone mineral density (aBMD) is currently the gold standard for the diagnosis of osteoporosis, however, it has its own pitfalls. Trabecular bone score (TBS), a novel tool in the evaluation of osteoporosis is an indirect indicator of bone microarchitecture. It is a textural index that evaluates pixel gray-level variations in the lumbar spine DXA (dual energy X-ray absorptiometry) image. Both cross-sectional and longitudinal studies have demonstrated that TBS may independently predict fragility fractures. TBS can also be used to adjust FRAX probabilities of fracture, though data available till date doesn't support any additional benefit. TBS also shows an improving trend with anti-osteoporotic treatment; however, the least significant change (LSC) is high that it takes more than 2 years for the change to manifest. TBS is also used in the evaluation of bone strength in cases of secondary osteoporosis. Though TBS predicts fracture risk independently in both genders, with the currently available data, it cannot be recommended as a standalone tool for decision regarding treatment of osteoporosis. TBS can be used as a tool to complement BMD in assessment of bone health. Additional studies are needed to assess its utility in clinical practice.

Keywords: Bone microarchitecture, fragility fracture, osteoporosis, trabecular bone score

INTRODUCTION

Osteoporosis, which is reported to occur in about 25–60% of Indian postmenopausal women, is a common, yet under recognized public health problem.^[1,2] The lifetime risk of osteoporotic fracture is around 40–50% in women and the mortality rate following fragility fractures is as high as 25% in the first year.^[3]

Osteoporosis is a disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk.^[4] Thus the definition itself brings forth the concept that not only bone mass, but also microarchitectural quality is an important determinant of bone strength. However, areal bone mineral density (aBMD) assessment by DXA (dual energy X-ray absorptiometry) being the gold standard for non-invasive diagnosis of osteoporosis doesn't provide information on bone microarchitecture. Also, around 50% individuals with fragility fractures can have aBMD value in the osteopenic/normal range, which suggests that in addition to bone mass, there are other factors that determine bone strength.^[5]

Microarchitecture of the bone can be measured by histomorphometric analysis of the transiliac crest bone

biopsy, quantitative computed tomography (QCT), high-resolution peripheral QCT (HRpQCT), high-resolution magnetic resonance imaging (HRMRI), microcomputed tomography (mCT), and trabecular bone score (TBS). Among these, TBS appears to be a non-invasive, readily available technology that permits efficient and accurate clinical evaluation of skeletal microarchitecture.^[6,7] Moreover, it has minimal radiation exposure and can be retrieved retrospectively through previously available lumbar spine aBMD images.^[8]

A study on cadaveric vertebrae to determine the level of correlation between mCT and TBS showed a good correlation ($0.77 \leq r^2 \leq 0.96$).^[9] In the study by Silva *et al.* TBS positively correlated with LS trabecular volumetric

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Submitted: 21-Mar-2020

Revised: 25-Apr-2020

Accepted: 14-May-2020

Published: 30-Jun-2020

Access this article online

Quick Response Code:



Website:
www.ijem.in

DOI:
10.4103/ijem.IJEM_147_20

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How to cite this article: Rajan R, Cherian KE, Kapoor N, Paul TV. Trabecular bone score—An emerging tool in the management of osteoporosis. Indian J Endocr Metab 2020;24:237-43.

BMD (vBMD) ($r = 0.664$) and cortical thickness ($r = 0.540$) assessed by QCT.^[10]

WHAT IS TRABECULAR BONE SCORE?

TBS is a texture index that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect measure of bone microarchitecture. A dense trabecular microstructure projected onto a plane generates an image containing a large number of pixel-to-pixel gray-level variations of small amplitude. Conversely, a 2D projection of a porous trabecular structure produces an image with a low number of pixel-to-pixel gray-level variations, but of higher amplitude. A variogram of these projected images, calculated as the sum of squared gray-level differences between pixels, can estimate a 3D structure from the existing variations on the 2D projected images. TBS is calculated as the slope of the log–log transform of the variogram, where the slope characterizes the rate of gray-level amplitude variations [Figure 1].^[8]

DXA is based on the variation in absorption of X-ray by the different body components and uses high and low energy X-ray photons. Over the past years, DXA components have undergone advancement that information regarding fractures (vertebral fracture analysis), bone stiffness (finite element analysis of X-ray), and mineral distribution at proximal femur (hip structural analysis) can be obtained from the DXA images. TBS is one such advance, which provides an indirect measurement of bone microarchitecture that relates to 3D bone characteristics such as the trabecular number, the trabecular separation, and the connectivity density. High TBS represents strong, fracture-resistant microarchitecture, while a low TBS reflects weak, fracture-prone microarchitecture. A brief comparison of DXA and TBS is provided in Table 1.

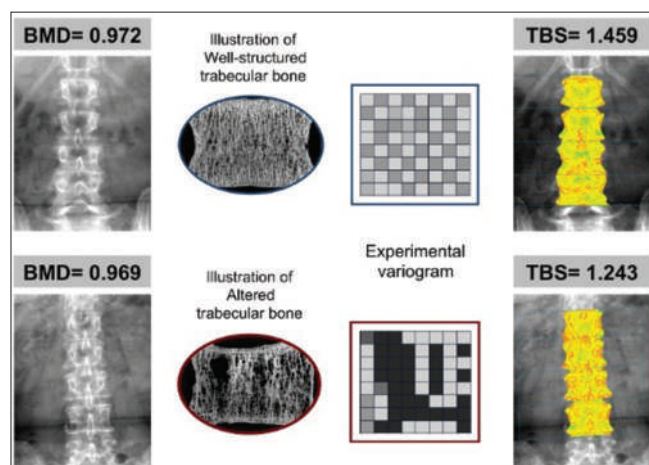


Figure 1: An illustration of the basic TBS principle and relationship to BMD. The upper panel shows BMD and TBS of a 73-year-old woman with BMI of 24.2 kg/m² and the lower panel shows BMD and TBS of a 74-year-old woman with BMI of 24.3 kg/m². The images of the bone architecture and the experimental variogram demonstrate TBS principles: the bone with greater number of trabeculae are associated with high TBS and vice-versa (8)

Currently certain cutoffs [Table 2] are proposed by the working group of TBS users from different countries.^[8]

FACTORS AFFECTING TBS

The current recommendations for the use of TBS in clinical practice are within a BMI range of 15–37 kg/m² in order to mitigate the artifactual effects of extreme variations in tissue thickness.^[11] The original TBS algorithm (version-1) was optimized for women of average body size. Limitations were identified when used in men or extremes of BMI (<15 kg/m², >37 kg/m²). The increase in soft tissue thickness, in both groups, falsely decreases the TBS.^[12] The updated TBS algorithm (version 3, 4) is less affected by BMI, gives higher mean results for men than women. Thus it seems to overcome the residual negative correlation of TBS with body size.^[13] TBS has been shown in various studies to have a negative correlation with advancing age. This is due to the bone microarchitectural changes that occur with aging.^[14,15] The change in TBS with age in both genders is depicted in Figure 2.^[16] Age and puberty have been found to be significant determinants of TBS in children.^[17] A study in Caucasian and African–American population has reported TBS to be less discriminatory with regard to fracture risk in African–Americans.^[18] However, this difference in various ethnic groups needs further validation.

Trabecular bone score measured by different DXA manufacturers showed that, although there was a good correlation ($r = 0.73$; $P < 0.05$) between scanners, there was a significant difference in precision error.^[19] TBS also depends on DXA scan acquisition mode, differences between densitometer manufacturers, and scanner resolution. Krueger *et al.* reported differences in TBS measurements between densitometers, suggesting a need to evaluate TBS thresholds by each model and limiting serial comparisons to scans obtained on the same instrument.^[20] Pencil beam devices are not compatible with TBS software. A certain threshold of image quality has been determined to maintain the correlation between TBS score and quality of trabecular bone assessed (trabecular spacing,

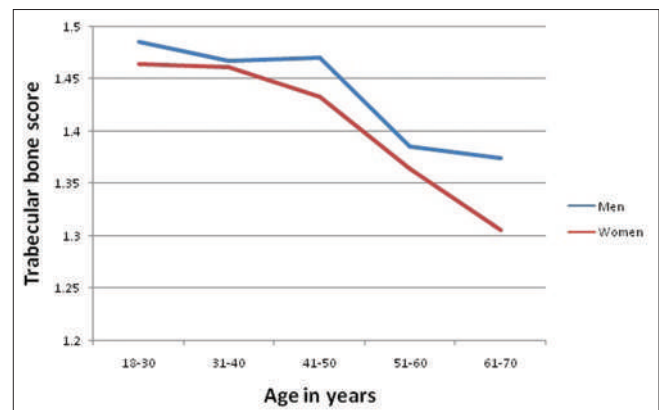


Figure 2: Trabecular bone score (TBS) and age-related changes. The blue and red lines represent the male and female normative TBS curves for age respectively. Adapted from Simonelli *et al.*^[15]

Table 1: Comparison of aBMD and TBS

	aBMD	TBS
Bone site	Total body Lumbar spine Hip Forearm	Lumbar spine
Effective radiation exposure	Adult spine DXA 0.013 mSv Adult hip DXA 0.009 mSv	No additional radiation in addition to DXA
Scan time	10-20 mins	Obtained in less than a minute from spine DXA image
Advantages	More published literature in different ethnicities and disease cohorts	Indirect measure of bone micro-architecture It's a complementary tool to aBMD assessment by DXA Can be obtained retrospectively by re-analysis of DXA images
Disadvantages	No data on microarchitecture Cannot separate cortical and trabecular bone Fracture of spine may give falsely high values	Not widely available Soft tissue interference, syndesmophytes may falsely increase TBS Relatively novel tool, hence cannot be used as a stand-alone tool for diagnosing/treating osteoporosis

Table 2: TBS cut-offs proposed for postmenopausal women

TBS score (no units)	Bone status
>1.350	Normal
1.200 and 1.350	partially degraded bone
≤1.200	degraded bone

trabecular number, and connectivity density). Below a certain threshold, this correlation is lost and hence pencil beam devices are not compatible.

Several studies have shown that TBS is lower in patients with vertebral fractures compared to controls.^[21-33] However, vertebrae with fractures have to be excluded from TBS measurements, just as for BMD.^[34] For example, if one patient has a fracture in L3, TBS will be computed on L1, L2, and L4. However, at least two vertebrae are necessary to compute a TBS value. As per International Society for Clinical Densitometry (ISCD) recommendations, while obtaining TBS, all evaluable vertebrae must be taken into account and those that are affected by local structural change or artifact should be excluded.^[34]

TBS AS A TOOL TO PREDICT FRACTURES

Several cross-sectional studies have looked at how TBS predicted fragility fractures.^[21-27] The findings of these studies are summarized in Table 3. All studies have found that TBS could potentially complement aBMD in predicting fragility fractures. Longitudinal studies have also looked at how TBS predicts incident fractures.^[28-33] The findings of these studies are summarized in Table 4. Most studies that have been summarized were conducted in postmenopausal women. It was found that those with low TBS were associated with 1.5 times higher risk of fracture compared with those with normal TBS. Also, it was found that TBS predicted vertebral as well as major osteoporotic fracture (MOF) with an area under the curve of 0.6–0.7 [Table 4].

HOW DOES TBS MODIFY FRAX (FRACTURE RISK ASSESSMENT TOOL)?

FRAX adjusted for TBS is an algorithm derived from the online FRAX calculation tool to adjust probability of fracture from clinical risk factors, aBMD and TBS. A meta-analysis by McCloskey *et al.* found that though TBS predicted fracture risk independently, addition of TBS to FRAX didn't improve the fracture prediction significantly (area under the ROC curve for FRAX + aBMD Vs FRAX + aBMD + TBS - 0.74 vs. 0.79).^[33]

Similarly in another study by Mirzaei *et al.*, it was found that addition of TBS to FRAX didn't make any difference to the fracture prediction (area under the ROC curve for FRAX + aBMD vs. FRAX + aBMD + TBS - 0.765 vs. 0.781, $P = 0.19$).^[35] Holloway *et al.* also noted that addition of TBS didn't improve the fracture prediction by FRAX (area under ROC curve for MOF : FRAX + aBMD vs. FRAX + aBMD + TBS - 0.740 vs. 0.738).^[36]

UTILITY OF TBS IN PATIENTS WITH DIABETES MELLITUS

Glucose tolerance and aBMD are negatively affected by advancing age and quite often they coexist. Assessments of bone quantity based on aBMD underestimates the risk of fracture in patients with type 2 diabetes mellitus (T2DM),^[37] suggesting that bone fragility in these patients is caused by poor bone quality.^[38] A study by Yamamoto *et al.* found that in T2DM, low TBS significantly correlated with vertebral fractures irrespective of BMD in both genders.^[39] Similarly in a study by Lin *et al.*, it was found that TBS had a higher AUC for detecting vertebral fractures as compared to aBMD in T2DM.^[40] Thus, bone microarchitectural deterioration by TBS may be a better clinical indicator of poor bone health in T2DM compared to aBMD.^[41] However, further studies would be needed to confirm this finding.

A study on patients with type 1 diabetes mellitus (T1DM) looked at the TBS values in T1DM ($n = 119$) and controls ($n = 68$) and

Table 3: List of cross-sectional studies that looked at the utility of TBS to predict fragility fractures

References	Study population Study design	Fragility fractures (prevalent)	Results OR for TBS per SD decrease and AUC to predict fractures with 95% CI
Pothuaud <i>et al.</i> 2009 ^[21]	Postmenopausal women ($n=200$ - cases 45, controls 155) Retrospective case-control	45 (all sites)	OR per SD 1.95 (1.31-2.89), AUC 0.685 (0.599-0.762)
Winzenreith <i>et al.</i> 2010 ^[22]	Postmenopausal women with T score between -2.5 and -1 ($n=243$ - cases 81, controls 162) Retrospective case-control	81 (vertebral)	OR per SD 2.52 (1.82-3.53), AUC 0.721 (0.660-0.777)
Rabier <i>et al.</i> 2010 ^[23]	Postmenopausal women with T score <-1 ($n=168$ - cases 42, controls 126) Retrospective case control	42 (vertebral)	OR per SD 3.20 (2.01-5.08), AUC 0.746
Del Rio <i>et al.</i> 2012 ^[24]	Postmenopausal women >50 years ($n=191$ - cases 83, controls 108) Retrospective case-control	83 (femur)	OR per SD 2.05 (1.45-2.89), AUC 0.668 (0.597-0.734)
Krueger <i>et al.</i> 2014 ^[25]	Postmenopausal women ($n=429$ - cases 158, controls 271) Retrospective case-control	158 (vertebral on VFA/fragility non vertebral fracture)	Any fracture:, OR per SD 2.46 (1.9-3.1), AUC 0.74, Vertebral fracture:, OR per SD 2.49 (1.9-3.3), AUC 0.73
Choi <i>et al.</i> 2017 ^[26]	Postmenopausal women with rheumatoid arthritis ($n=279$) Cross-sectional study	34 (vertebral)	OR per SD 2.86 (1.34-6.09)
Kim <i>et al.</i> 2019 ^[27]	Postmenopausal women with polymyalgia rheumatic ($n=212$ - cases 106, controls 106) Case-control study	45 (vertebral)- 31 in cases, 14 in controls	AUC 0.759 (0.601-0.918)

OR: Odds ratio. AUC: Area under curve

Table 4: List of longitudinal studies that assessed the utility of TBS in detecting incident fragility fractures

References	Study population, mean follow up (years)	Fragility fractures (Incident)	Results
Hans <i>et al.</i> 2011 Manitoba study ^[28]	Women >50 years old, $n=29,407$, 4.7 years	1668- MOF (vertebral 439, hip 293)	MOF: AUC 0.63 (0.61-0.64), HR 1.35 (1.20-1.42), Vertebral: AUC 0.66 (0.64-0.69), HR 1.22 (1.10-1.34), Hip: AUC 0.68 (0.65-0.71), HR 1.46 (1.13-1.46)
Boutroy <i>et al.</i> 2013 OFELY study ^[29]	Postmenopausal women, $n=560$, 7.8±1.3 years	112 (vertebral 32, hip 8, wrist 35, others 37)	OR 1.57 (1.25-1.98), AUC 0.63 (0.57-0.68), 35% fractures in osteopenic women- however was within lowest quartile of TBS
Briot <i>et al.</i> 2013 OPUS study ^[30]	Women >55 years of age, $n=1007$, 6 years	82 clinical fractures, 46 radiological vertebral	Clinical fracture: AUC 0.62 (0.56-0.69), OR 1.62 (1.3-2.01), Radiographic vertebral: AUC 0.63 (0.54-0.72), OR 1.54 (1.17-2.03)
Iki <i>et al.</i> 2015 JPOS study ^[31]	Women >50 years of age, $n=665$, 10 years	92 vertebral fracture by VFA	OR 1.98 (1.56-2.51), AUC 0.682 (0.662-0.773)
Popp <i>et al.</i> 2016 ^[32]	Women with mean age 76 years, $n=556$, 2.7 years	52 clinical fragility	HR 2.01 (1.54-2.63), AUC 0.69 (0.62-0.77)
McCloskey <i>et al.</i> 2015 ^[33]	Men and women with a mean age of 72 years $n=17809$, 6.7 years	1109 (298 hip fracture)	OR for MOF 1.44 (1.35-1.53)

MOF: Major osteoporotic fracture, AUC: Area under curve

didn't find any significant difference (1.357 vs. 1.389, $P=0.075$). However, in those with prevalent fractures ($n=24$), TBS was significantly lower as compared to those without (1.309 vs. 1.370, $P=0.04$). Considering the scarce data available, more studies are needed to reach a definite conclusion.^[42]

IMPACT OF DEGENERATIVE SPINE DISEASE ON TBS

In older men, aBMD measured at the lumbar spine shows an apparent increase with advancing age.^[43] This apparent increase is often attributed to degenerative changes of the spine. Hence there is a need for other methods to assess bone quality in those with degenerative changes of the spine. Anderson *et al.* found that TBS was less affected by degenerative changes compared to aBMD. TBS in those with and without degenerative changes

was 1.219 and 1.196, however the corresponding BMD was 1.317 g/cm² and 1.198 g/cm².^[44] Similarly in a study by Buehring *et al.*, it was found that in patients with rheumatoid arthritis ($n=143$), about 20% had vertebral fractures in the presence of normal lumbar spine aBMD. However, their TBS was low correlating with poor bone microarchitecture.^[45]

EFFECT OF HYPERPARATHYROIDISM ON TBS

Patients with primary hyperparathyroidism (PHPT) (asymptomatic) usually show low bone strength that is often under estimated by aBMD measurement. Torres *et al.* found that a higher number of subjects with PHPT showed microarchitectural deterioration by TBS, compared to osteoporosis as assessed by aBMD (51.7% vs. 37.5%).

The AUC for TBS performed better than the combination of femoral, hip, and spine BMD for prevalent fractures (0.714 vs. 0.679). Thus TBS may be a useful tool to identify increased fracture risk in patients with PHPT when under-diagnosed by aBMD.^[46]

How TBS Predicts Fractures in Glucocorticoid Induced Osteoporosis (GIO)?

Vertebral fractures are the most common fractures associated with glucocorticoid (GC) treatment and the risk of vertebral fracture increases within 3 months after initiation of treatment and peaks at 12 months.^[47] In a study by Florez *et al.*, the utility of TBS was compared with aBMD to assess fracture risk in GC treated patients. It was found that the prevalence of vertebral fractures was more among those with degraded microarchitecture (low TBS) compared to those with osteoporosis (76% vs. 38%). Thus TBS may be a better discriminant tool compared to aBMD for fracture assessment in GC treated patients.^[48]

TBS AS A TOOL TO MONITOR TREATMENT RESPONSE

The LSC for TBS is estimated to be about 5.4%.^[49] aBMD has a better LSC compared to TBS. With pharmacologic treatment studies for 1.5–2 years, the lumbar spine aBMD changes were consistently greater than TBS changes, with 4.1%–8.8% increase of LS aBMD versus 1.4%–3.6% increase of TBS.^[49] This suggests a longer time interval required to achieve a statistically significant change with TBS than with LS aBMD.

A recent study from southern India found that TBS didn't show any significant decline (over a period of 3 years) following yearly Zoledronic acid infusion in the cohort studied. Thus bisphosphonates lead to preservation of bone mass in contrast to the normal decline in bone mass with advancing age.^[6] A review of the best available evidence at the 2019 ISCD Position Development Conference concluded that the role of TBS in monitoring anti-resorptive therapy is unclear and that TBS is potentially useful for monitoring anabolic therapy.^[50] In another study done to assess bone health in recipients of allogeneic stem cell transplant, it was found that TBS measurements provided similar information as the lumbar spine aBMD and did not differ significantly between cases and controls.^[7]

TBS IN CLINICAL PRACTICE

Although TBS predicts fracture risk independently in both genders, it cannot be recommended as a standalone tool for decision regarding treatment of osteoporosis. It can be used along with aBMD in assessing risk for fragility fractures. The LSC of TBS is high and hence it takes more than 2 years of anti-resorptive therapy for the change to reflect in TBS. Hence, though TBS changes with treatment, at present there is not enough evidence to recommend it as a tool to monitor response to anti-resorptive treatment. It may be useful to assess risk of

fracture in patients with T2DM, hyperparathyroidism, and degenerative spine disorders as described before.^[51]

Despite its utility in clinical practice, there are certain limitations in the use of TBS. DXA and derived parameters including TBS are subject to the deleterious effects of image noise. Winzenrieth *et al.* has reported that the effect of adding noise to DXA images resulted in a reduction in TBS.^[9] It is well established that variations in soft-tissue density can result in significant errors in aBMD measurements and a similar effect is present with TBS, with increases in soft-tissue thickness overlying the spine resulting in lower TBS values.^[12] Being a relatively novel tool, its availability as well as lack of normative data also adds to its limitations.

CONCLUSION

TBS is a textural index from spine DXA images that predicts the risk of fracture independent of aBMD and clinical risk factors. TBS is associated with incident vertebral, hip and major osteoporotic fractures in postmenopausal women and in men greater than 50 years of age. TBS may be used to adjust FRAX probabilities of fracture, though data available till date doesn't support any additional benefit. Although TBS improves on various anti-osteoporotic treatments, these changes are usually smaller than improvements in LS aBMD and many times do not exceed the least significant change. However, TBS may play a role in the evaluation of fracture risk in diverse conditions, such as T2DM or PHPT. Thus, TBS is an emerging technology and future work will add to the existing data, confirming and extending its clinical utility.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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