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Review Article

Trabecular bone score for the evaluation of fracture risk: A literature review

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Abstract

Osteoporosis is a chronic disease which constitutes a major social and economic problem, increasing the burden of health's cost worldwide. Despite the fact that the diagnosis of osteoporosis relies on Dual energy X-ray absorptiometry (DXA), important parameters of bone strength include microarchitecture of the trabecular and cortical bone. Trabecular bone score (TBS), is a novel DXA-based technique that incorporates microarchitecture in the fracture risk assessment. In our review, we assessed the current bibliography and found numerous published articles stressing the validity of this technique for the estimation of fracture risk. As shown, TBS can be used to evaluate the risk of osteoporotic fracture in postmenopausal women and men over 50 years of age, with data for men being less extensive, as well as for the management of patients with a wide range of secondary causes of osteoporosis, including diabetes mellitus, rheumatoid arthritis, use of glucocorticoids for a long period etc.

Keywords: Bone Mineral Density, Bone Strength, Fracture risk, Osteoporosis, Trabecular Bone Score

Introduction

Osteoporosis, bone strength and fracture risk

Osteoporosis is a chronic disease that has been shown to affect individuals throughout the world, and has been associated with significant social and economic, both direct and indirect, costs[1]. According to the World Health Organization (WHO) the definition of osteoporosis conceptually refers to a progressive systemic skeletal disease characterized by the combination of low bone mass (reduced bone quantity) and micro-architectural deterioration of bone tissue (impaired bone quality). The combination of these two factors negatively affects bone strength with a consequent increase in bone fragility and risk of fracture[1-4].

Dual energy X-ray absorptiometry (DXA) has been considered the gold standard technique in order to measure bone mineral density (BMD, gr/cm^2) and is currently used for the diagnosis of osteoporosis[5-7]. This signifies that the operational detection of osteoporosis is based on the measurement of areal BDM, defining osteoporosis as a femoral neck/total hip/lumbar spine (L1-L4 or L2-L4) aBMD of 2,5 SD or more below the young adult individuals mean (T-score≤-2,5)[2,3,6,8]. Despite the fact that the measurement of bone density as derived from DXA is a trustworthy interpretation for fracture risk assessment, we are currently as a scientific community facing two concerns: 1) the largest number of individuals with fragility fractures are found to have T-scores over the -2,5 threshold so as to have BMD measurement values in the normal or most commonly osteopenic range[2,3,6-8] and 2) DXA as diagnostic tool is very reliable to access bone quantity but does not provide adequate information regarding bone quality[9]. As a result, the sensitivity of the technique for the assessment of subjects with an imminent fracture risk is acknowledged to be considerably low based on the T-SCORES, and more over, it is widely agreed upon that multiple other factors, apart from BMD, such as bone geometry, microarchitecture of trabecular and cortical bone, bone micro-damage, mineralization and bone turnover, affect bone strength. Other important clinical factors of fracture risk include age,

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history of previous fracture and falls[1,2,3,6,8,10].

In order to evaluate the individual's risk of osteoporotic fracture, multiple attempts have been made to create algorithms. One of the most widely used is FRAX. FRAX was developed by the Collaborating Centre for Metabolic Bone Diseases at Sheffield University, UK, in order to provide estimate of the 10-year probability of major osteoporotic and hip fractures for each individuals separately in numerous countries all over the world[2,10].

One of the most important determinants of bone strength is microarchitecture, whose contribution in bone strength has proven to be vital in recent years. Microarchitecture of the trabecular bone consists mainly of the size, shape, number and connectivity of the trabeculae and a growing number of studies has shown that these parameters are closely related to bone strength. As a result, it is thought that if such data were available for individual patients, the estimation of fracture risk might improve[1,2,10-13]. A new method called trabecular bone score (TBS) is a tool that uses the DXA technology in order to provide estimates of micro-architecture of trabecular bone as well as to provide an BMD-independent estimate of osteoporotic fracture risk[1,6]. Moreover, the incorporation of TBS scores within the FRAX tool is thought to enhance the diagnosis of fracture risk even further[1,2].

TBS is a novel gray-level textural measurement obtained from lumbar spine DXA in two-dimensional (2D) experimental (empirical) variograms images[1,2,7,10]. In other words, it measures the quantity of the variations in grey-level texture between adjacent pixels[1,2]. High TBS values appear to represent mechanically adequate bone, with fracture-resistant microarchitecture, whilst a low TBS reflects frail, fracture-prone microarchitecture (low amplitude-scope fluctuations in photon absorption)[2,7]. Consequently, that proves the ability of TBS to distinguish dissimilars in three-dimensional (3D) microarchitecture between areas where in the two-dimensional (2D) images DXA they appear to have similar bone density (BMD) but different trabecular quality[1,2]. TBS, just like aBMD, is an age function variable: at a young age (from the age of 30 to about the age of 45) there are observed small changes in TBS values, but as individual grows older a continuous decrease is noticed, which probably affects women more than men[2].

Additional advantages include fast execution of the technique while the study is not affected by calcifications or osteophytes. There are however a number of studies that debate the usefulness of the technique and for that reason we reviewed the bibliography in order to present authors conclusion concerning this technique[1].

Material and Methods

We reviewed the current published literature concerning studies that correlate TBS with fracture risk and bone strength in patients with osteoporosis. Pubmed (Medline) was used as the reference data base and our search included the terms TBS+Ostoporosis+fracture risk. Our inclusion criteria consisted of original studies, published in the English literature, during the previous 15 years. We excluded case reports or case-series, as well as meta-analyses.

Results

Based in our inclusion and exclusion criteria, we initially retrieved 525 studies and from them we selected 49 to be relevant to our study topic. Most studies assessed the usefulness of TBS in women with postmenopausal osteoporosis. However, numerous studies assessed TBS in patients with secondary osteoporosis due to, for example diabetes mellitus, rheumatoid arthritis, used of glucocorticoids, e.t.c. We will address some of these topics as discuss by the published literatures as well[1].

A) Studies in patients with post-menopausal osteoporosis

In the SWAN study (Study of Women's Health Across the Nation), conducted in USA, Greendale et al., investigated whether TBS may predict fracture risk in early postmenopausal woman. The SWAN study included 891 postmenopausal women of mean age 54.1 years with a total of 141 fractures, of which 9 (6.4%) fractures were recorded prior to visit 7. TBS in those women, adjusted for a number of factors including age, BMI, race and use of medications or calcium/vitamin D supplements was not statistically significantly associated with incident fracture risk either before or after BMD adjustment[14].

The OPUS study (Osteoporosis and Ultrasound Study) was a multi-center prospective study whose objective was to examine whether TBS is additionally useful for the prediction of future fracture in postmenopausal women. The study included 1007 postmenopausal women (mean age 65.9 years) from three European centers, (France, Germany and the UK) who were followed for an average of 6.0 years. In the follow-up period, 82 incident clinical fractures and 46 incident vertebral fractures were reported. TBS was found to have a better performance than lumbar spine BMD alone for the prediction of vertebral fracture. Also, the combination of TBS and lumbar spine aBMD showed better performance than BMD alone[4].

L. Redondo et al., using data from the FRODOS cohort, analyzed data from 2257 postmenopausal women. This study was conducted in order to analyze TBS values and compare them to clinical characteristics, bone mineral density and history of fractures in a cohort of postmenopausal women. They found mean TBS value in L1-L4 to be 1.203±0.121 and 55.3% of the women showed values indicating degraded microarchitecture[15].

Mirzaei A. et al., in a total of 358 women (mean age 61.3±9.5 years) tested for aBMD and TBS, of which 184 were osteopenic and 21 with vertebral fracture. The authors found notable linear relationship (significant correlation) between TBS and spine aBMD and TBS and femoral neck

aBMD. They also found strong relationship between the variables of FRAX and FRAX-TBS in predicting the risk of major osteoporotic and hip fracture. Moreover, the authors reported that the three different models using aBMD, TBS, and combination of aBMD and TBS were similarly predictive of fragility fractures. TBS in this study was not reported to be not clinically useful in postmenopausal women and adding TBS data to aBMD or FRAX has not increased the predictive power for vertebral fracture[16].

P. Martineau et al., studied for at least 5 years 37,176 subjects from the Manitoba registry with baseline DXA, FRAX-based fracture probability and lumbar spine TBS. 3741 and 1008 non-traumatic major osteoporotic fractures (MOF) and hip fractures (HF), respectively were recorded.

According to the results of this study, women with recent osteoporosis therapy related to significant increased TBS (+1.5%), whilst significant low ($p \leq 0.001$) adjusted baseline TBS was observed in the following subgroups: osteoporotic hip T-score group (-4.0%), prior fracture group (-2.2%), diabetes group (-2.6%), COPD group (-2.8%), high alcohol use group (-2.3%), glucocorticoid use group (-1.5%), RA group (-0.9%) and secondary osteoporosis group (-0.8%). They also observed greater decrease in TBS regarding HRs per SD for fracture prediction in the following: age < 65 prior fracture glucocorticoid use and osteoporosis treatment (MOF p-interaction=0.005). Multiple risk factors for fracture had a significant effect to TBS alone, while TBS-adjusted evaluated and found useful and beneficial for multiple subgroups[17].

Finally, in an another important study, D. Krueger et al., performed a retrospective, non-random case-control study and they used already existent research DXA lumbar spine (LS) images from 429 women with mean age of 71.3 years old in order to perform TBS blinded to fracture status. According to this study the following paradox occurs: 73% all fractures sustained by women were without osteoporosis and 72% of these women had a TBS score below the median. In conclusion, the ability of TBS to evaluate the trabecular pattern and recognize subjects with vertebral or low trauma fracture was found to enhance DXA. In women with a fracture which were diagnosed for osteoporosis solely by BMD alone, TBS was found to identify 66% -77% of these women[5].

B) Studies in men with osteoporosis

E. Leib et al., in a retrospective, non-random case-control study, recruited 521 Caucasian men and after they applied inclusion (for example participants sustained at least one confirmed fracture) and exclusion criteria (for example if they have or have had previously any treatment or illness that may influence bone metabolism) a group of 180 men was studied. This total of 180 men consisted of 45 fractured subjects 63.3±12.6 y and 135 control subjects 62.9±12 y, matched for age and aBMD. They found that the relationship between TBS and BMD and between TBS and BMI was not very strong (weak correlation). The most important finding of this study is that fractured subjects presented a significantly lower TBS in comparison with control individuals, while no disparity existed concerning BMI, height and weight. The conclusion of this study was that TBS as a tool showed a prospective use in men in the future. TBS also showed an important difference between fractured and age- and spine BMD-matched non fractured subjects. The results of this study agreed with those previously reported on for men of other nationalities[18].

W. Leslie et al., performed a study using data from a database, specifically from Province of Manitoba in Canada. 3620 men aged ≥50 (mean 67.6 years) were followed for an average of 4.5 years. During this period, 183 men (5.1%) sustained major osteoporotic fractures (MOF), 91 men (2.5%) clinical vertebral fractures (CVF) and 46 men (1.3%) hip fractures (HF). The authors reported moderate correlation between spine BMD and spine TBS and low correlation between spine and hip BMD. They also found markedly low value spine TBS in fractured compare to non-fractured men for major osteoporotic, hip (both $p<0.001$) and clinical vertebral fracture ($p=0.003$). TBS presented predictive power for major osteoporotic and hip fracture but not for clinical vertebral fracture compared to TBS-FRAX model and continued to be a predictor of hip fracture but not for major osteoporotic fracture after an additional adjustment for hip or spine BMD. The authors concluded that spine TBS predicts MOF and HF fracture apart from the FRAX tool for the first one and FRAX and BMD for the second one. However, the authors noted that more extensive studies with incident fractures are needed in order to confirm these results[6].

J. Schousboe et al., performed a cohort study using data from the Osteoporotic Fractures in Men (MrOS) Study. For this study 5979 men aged 65 years and older were studied for a period from 2000 to 2002. The objectives of this study were to evaluate the link between TBS and incident major osteoporotic and hip fractures in aging men and to assess the utility of the method for fracture prediction either alone or combined to FRAX/BMD. They used proportional hazards models in order to assess the link between this study and incident major osteoporotic and hip fractures. For each standard deviation decrease in TBS, hazard ratios for major osteoporotic fracture were 1.27 and 1.92 respectively and for hip fracture was 1.20 and 1.86 when combined FRAX with BMD and prevalent radiographic vertebral fracture and in subjects with prevalent radiographic vertebral fracture versus in subjects without prevalent radiographic vertebral fracture, respectively. The addition of TBS, prevalent radiographic vertebral fracture status, or both of them to FRAX with BMD and age enhance classification of major osteoporotic fracture cases. The conclusion was that incident major osteoporotic fractures in older men related to TBS and prevalent radiographic vertebral fracture independent of each other and FRAX 10-year fracture risks[19].

K. Holloway et al., performed a longitudinal study in Australia and used data from the Geelong Osteoporosis Study

(GOS). This study attempted to investigate the prediction of major osteoporotic and hip fracture in Australian men and to compare TBS adjusted FRAX score with unadjusted score. The study assessed 591 men aged 40-90 years and follow-up time was 9.5 years. 50 men sustained incident major osteoporotic fractures and 14 hip fractures, all identified radiologically. From all the diagnostic indexes (sensitivity, specificity, positive predictive value, negative predictive value), sensitivity was higher in the TBS-adjusted scores (MOF 4%, hip 78.6%) than the unadjusted scores (MOF 2%, hip 57.1%) and a decrease in specificity (MOF 98.9 vs 99.3%; hip 79.9 vs 83.9%). The authors concluded that the MOF or Hip FRAX adjusted to TBS was not really improving the prediction of these fractures[20].

C) Studies in patients with secondary osteoporosis (diabetes, rheumatic diseases etc.)

TBS (trabecular bone score) and Diabetes-Related Fracture Risk

In a recent review, C. Poiana and C. Capatina among others, report that Diabetes mellitus type 1 as well as type 2, is linked to decreased bone strength and increased fracture risk. However, in type 1 DM BMD is decreased while in type 2 is increased, compared with controls. In patients with type 2 diabetes bone fragility is related to deterioration of bone quality and is not reflected by bone mineral density and bone mass reduction. Moreover, BMD and FRAX are thought to be useful in assessing fracture risk but TBS and TBS-adjusted FRAX may offer a more comprehensive assessment of fracture risk[13].

William D. Leslie et al., in a retrospective cohort study, assessing the usefulness of TBS for the prediction of fracture risk in patients with diabetes, used BMD data from the Manitoba cohort. 29,407 women >50 years were studied for a mean of 4.7 years, among whom 2356 (8,1%) had been diagnosed with diabetes. Concerning the results, 175 women with DM suffered major osteoporotic fractures (7.4%) as opposed to 1493 women without (5.5%) diabetes. TBS was found to be a BMD independent predictor of fracture and predicted fractures in diabetic and non-diabetic patients. When they adjusted TBS to the prediction model, the impact of diabetes on fracture was decreased. The conclusion of this study was that in patients with DM, TBS predicts osteoporotic fractures and had higher predictive power for fracture risk than BMD[21].

F. Baleanu et al., in a cross-sectional analysis of 260 patients from the FRISBEE cohort study, found that patients in the T2D group appeared to had significantly higher BMD of the total hip compared to controls (0.90±0.13 compared to 0.87±0.12, P=0.015). Patients in the T2D group had considerably lower TBS score (mean=1.19±0.17) in comparison to the control group (mean=1.27±0.13) (P=0.005) and also after adjustment of TBS to BMI, it still remained significantly lower in T2D compared with the control group (P=0.02)[22].

TBS (trabecular bone score) in patients with auto-immune diseases of the skeleton

Kwi Young Kang et al., compared TBS between axial spondyloarthritis (SpA)-(axSpA) patients with and without vertebral fractures in order to explore the possible usefulness of TBS in detecting patients with vertebral fractures. 225 patients 20-67 years were recruited between August 2013 and February 2017. 28 of them (11%) had morphometric vertebral fractures. Subjects with vertebral fractures presented TBS mean value 1.30 (0.13) and subjects without vertebral fractures presented TBS mean value of 1.39 (0.11). Also, patients with vertebral fractures had lower femoral neck BMD. In axSpa patients, for the prediction of vertebral fractures, TBS presented greater distinctive ability than BMD at the total hip. In conclusion, the authors report low TBS in axSpA patients with vertebral fractures and conclude that TBS has predictive power for vertebral fractures in patients with axSpA[23].

L. Wildberger et al., in a retrospective study reported results from two cohorts of spondyloarthritis (SpA) male patients, one from Switzerland (Lausanne) and the other from Bulgaria (Sofia). According to the study findings, no statistically significant difference was observed for the mean TBS between the overall population (1.26±0.13) and the SpA men with (1.21±0.12) and without (1.33±0.11) syndesmophytes (P=0.001 and 0.06 before and after adjustment for BMI). However, authors found statistically significant differences for the mean BMD T-score between the general population and the SpA men. They also found that BMD (spine and hip) and TBS values were lower in SpA men with and without syndesmophytes versus to overall population, with the exception of men with syndesmophytes and regular spine BMD. From this result they concluded that syndesmophytes can not affect TBS[24].

S. Breban et al., assessed 185 women with RA (mean disease duration of 15.5±9.9 years) aged 56.0±13.5 years, with the aim of evaluate bone mineral density (BMD), trabecular bone score (TBS) and their combination in order to detect rheumatoid arthritis (RA) patients with vertebral fractures (VFs). They also used DXA to evaluate lumbar spine, total hip, and femoral neck BMD and performed Vertebral Fracture Assessment (VFA) to evaluate VFs from T4 to L4. Patients with VF presented significantly lower TBS and T-score values compared to patients without VF. The threshold of 1.173 for TBS had the best sensitivity (63%) and specificity (74%). In order to predict the presence of VF in RA patients, TBS was found superior than lumbar spine BMD and similar to femoral neck BMD[25].

C. Richards et al., in a cohort of patients from the Manitoba Bone Mineral Density, with diagnosis codes for ankylosing spondylitis, assessed whether TBS would predict osteoporotic fracture in patients with AS. A group of 188 subjects diagnosed with AS was studied. Patients who sustained incident MOF had lower TBS values (1.278±0.126 versus 1.178±0.136, p<0.001). The measurement of TBS

alone and the combination of FRAX-MOF-BMD predicted major osteoporotic fracture (p=0.003) and clinical spine fracture (p=0.019) in 19 and 7 patients, respectively. Also, unadjusted models for the TBS showed predictive power of all fracture (N=27) (p=0.02). They concluded that TBS as an independent parameter showed predictive ability for major osteoporotic and clinical spine fracture in patients with AS[26].

E-Ling Lai et al., in a single-center retrospective study, aimed to assess whether TBS identified existing vertebral fractures (VF) more accurately than BMD in systemic lupus erythematosus (SLE) patients. 147 Chinese patients >20 years were enrolled. SLE patients with vertebral fracture presented prevalence at a rate of 19% and significantly lower BMD, T-score, TBS, and TBS T-score values. TBS exhibited higher positive predictive value and negative predictive value than lumbar spine and left femur BMD for prevalent vertebral fractures in SLE. The conclusion of this study was that in SLE patients with degraded microarchitecture and prevalent vertebral fractures, TBS is an additional parameter for assessing vertebral fracture prevalence[27].

TBS (trabecular bone score) and glucocorticoid-Related Fracture Risk

Mei-Hua Chuang et al., retrospectively reviewed medicals records of 46 female patients from a regional hospital in southern Taiwan in order to evaluate the predictive value of TBS and FRAX-adjusted-TBS (T-FRAX) compared with bone mineral density (BMD) and FRAX alone. patients were separated in two groups: one group (N=30) under glucocorticoid-treatment and a control group (N=16) . All adult female (40 to 89 years old) patients had undergone DXA twice within a 12- to 24-month interval. Analysis of covariance was conducted to compare the outcomes between the two groups of patients, adjusting for age and baseline values. According to the results, in the glucocorticoid group they found a significant lower adjusted mean of TBS (P=0.035) and a significant higher adjusted mean of T-FRAX for major osteoporotic fracture (P=0.006) while for the adjusted means for BMD and FRAX significant differences were noticed[28].

In a cross-sectional study, Florez et al., saught to determine the potential usefulness of TBS for fracture risk assessment in glucocorticoid (GC)-treated patients compared with sole BMD assessment. 127 patients (63% women), mean age 62 years, receiving GC treatment (prednisolone dose: 14.5 mg), for various autoimmune diseases for a median 47.7 months were enrolled. Patients with vertebral fractures and with any fragility fracture had degraded microarchitecture considerably more often than densitometric osteoporosis (OP); 76% vs 38% and 69% vs 36%, respectively. Fracture discrimination for vertebral fractures, using TBS and BMD sensitivity, specificity, positive predictive value, and negative predictive value were 0.76, 0.53, 0.25 and 0.92, and 0.38, 0.72, 0.22 and 0.85, respectively. BMD and TBS combined, had the effect of increasing specificity for VF and for any fragility fracture to 0.89 and to 0.9, respectively. Also, TBS presented better efficiency than BMD to distinguish between patients with fracture, especially VFs vertebral. The results suggested that TBS performed better than BMD to discriminate fracture risk assessment in GC-treated patients[29].

M. Paggiosi et al., carried out a cross-sectional observational study, to compare the diagnostic utility of three parameters (lumbar spine BMD, TBS, and LS-BMD in combination with TBS (LS-BMD+TBS) in order to discriminate between healthy women and glucocorticoid treated women, and glucocorticoid-naïve women with recent fractures. In this study, 484 older women (ages 55-79 years) were recruited and evaluated in 3 subgroups: one subgroup consist of 64 women had received prednisolone ≥5 mg/day for a period more than 3 months, another group consist of 46 women sustained a recent fracture (distal forearm, proximal humerus, vertebra, proximal femur) and finally a subgroup of 279 were healthy women. Women who received glucocorticoid treat presented lower TBS Z-scores than glucocorticoid-naïve women (-0.80 versus 0) but their LS-BMD Z-scores were nearly similar (-0.13 versus 0). Also, women who sustained relatively new fractures presented lower LS-BMD (-0.34 to -1.38) and TBS (-0.38 to -1.04) values than healthy women. TBS alone and the combination of LS-BMD and TBS but not LS-BMD alone was able to discriminate between glucocorticoid-treated and glucocorticoid-naïve women. They concluded that TBS could be a utility method for an additional study of osteoporosis due to glucocorticoids[30].

Limitations of TBS

As shown in numerous studies, TBS presents also a number of limitations, including image noise that may affect the variogram[31], or technical problems related to the modalities (e.g., aging X-ray tubes, sensor deficiencies) causing exogenous noise. Also, the use of TBS in patients with BMI, below 15 kg/m^2 and over 35 kg/m^2 has not been approved[32].

Numerous studies have demonstrated the ability of TBS to distinguish fractures in a substantial number of postmenopausal women but studies exclusively for men are minimal. Also, when using GE-Lunar machines, women appear to have higher TBS values than men. This fact is unexpected and contradicts the results by histomorphometry and HRpQCT of a more conserved trabecular microarchitecture in aging men than in women.

One of the most important clinical limitations is the absence of a threshold that determines which TBS value is normal and which is abnormal. It is necessary to carry out an extensive population-based studies in order to ascertain the optimal health ranges across age and sex as the proposed TBS ranges until now relate to postmenopausal women only[31].

Conclusion

The need for a more accurate tool in fracture risk assessment, beyond BMD and T-score by DXA, has led to an attempt to incorporate a surrogate of trabecular micro-architectural integrity such as the Trabecular Bone Score (TBS). TBS is completely non-invasive, does not require additional patient visits or examinations and has been shown in many studies to be effective either used alone or in combination with others clinical tools such as the FRAX tool. It can be used to evaluate the risk of osteoporotic fracture in postmenopausal women and men over 50 years of age. However, the data for men are less substantial. Studies have also shown the usefulness of TBS in evaluating and treating patients with a wide range of secondary causes of osteoporosis, including Cushing's syndrome, hyperparathyroidism, type 2 diabetes, chronic kidney disease and patients receiving glucocorticoids for a long period. Finally, as a clinical tool, it is very promising however more research is needed in order to conclude as to its actual validity in multiple clinical settings.

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