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Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice:

A consensus report of a European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) Working Group

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Abstract

Trabecular bone score (TBS) is a recently-developed analytical tool that performs novel grey-level texture measurements on lumbar spine dual X-ray absorptiometry (DXA) images, and thereby captures information relating to trabecular microarchitecture. In order for TBS to usefully add to bone mineral density (BMD) and clinical risk factors in osteoporosis risk stratification, it must be independently associated with fracture risk, readily obtainable, and ideally, present a risk which is amenable to osteoporosis treatment. This paper summarizes a review of the scientific literature performed by a Working Group of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis. Low TBS is consistently associated with an increase in both prevalent and incident fractures that is partly independent of both clinical risk factors and areal BMD (aBMD) at the lumbar spine and proximal femur. More recently, TBS has been shown to have predictive value for fracture independent of fracture probabilities using the FRAX® algorithm. Although TBS changes with osteoporosis treatment, the magnitude is less than that of aBMD of the spine, and it is not clear how change in TBS relates to fracture risk reduction. TBS

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may also have a role in the assessment of fracture risk in some causes of secondary osteoporosis (e.g. diabetes, hyperparathyroidism and glucocorticoid-induced osteoporosis). In conclusion, there is a role for TBS in fracture risk assessment in combination with both aBMD and FRAX.

Keywords

osteoporosis; epidemiology; trabecular bone score (TBS); fragility fracture; bone mineral density; FRAX

Introduction

Osteoporosis, fragility fractures and risk assessment

Measurements of bone mineral density (BMD) are a central component of any provision that arises from the definition of osteoporosis, agreed internationally as: a progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. This definition captures the notion that low areal BMD (aBMD) is an important component of fracture risk, but that other bone abnormalities contribute to skeletal fragility. The conceptual description of osteoporosis thus centres both on the assessment of bone mass and quality, specifically bone microstructure. Until recently, there were no satisfactory clinical means to assess bone microstructure non-invasively, so that the operational diagnosis of osteoporosis is based on the measurement of aBMD. Osteoporosis is so-defined as a femoral neck aBMD 2·5 SD or more below the young adult female mean (T-score ≤−2·5) [2, 3]. The same T-score derived at other sites is widely used in clinical practice (e.g. lumbar spine, total hip, distal radius).

A consequence of this operational definition, which identifies the small proportion of the population at highest risk, is that the greater number of individuals above this threshold, although individually at lower risk, contribute the greater number of fractures to the total burden. Indeed, the majority of fragility fractures occur in patients who have an aBMD T-score >−2.5. In other words, the detection rate for these fractures (sensitivity) is low [4], which is why widespread population-based screening is not generally recommended in women at menopause [2, 5]. Thus, factors other than bone mass influence bone strength and fracture risk, including microarchitectural deterioration of bone tissue, as given in the conceptual definition of osteoporosis. Additional skeletal and extra-skeletal factors, such as bone geometry, micro-damage, mineralization, bone turnover, age, and a large range of clinical risk factors, including family history, prior fracture and fall risk, contribute to the overall assessment of fracture risk [6-9]. Several of these additional factors are captured by FRAX®. FRAX estimates the 10-year probability of hip and major osteoporotic fracture based on the individual's risk factor profile [4]. Apart from BMD, FRAX does not capture other skeletal determinants of bone strength that improve upon or are at least partly independent of aBMD [10]. Several such determinants are the subject of clinical research [11-18] using novel imaging techniques, such as Quantitative Computed Tomography (QCT) and high resolution (peripheral) QCT [19, 20], and minimally invasive approaches for probing bone material properties, notably microindentation techniques [21]. Although

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there is evidence of their predictive ability for fracture [22, 23] , none of these modalities appears to reliably outperform aBMD in the prediction of the various types of osteoporotic fractures, and their general lack of availability and validation in the clinical setting means that an adjunctive role alongside DXA-measured aBMD is unlikely to be feasible in most settings in the near future. In contrast, trabecular bone score (TBS) is a novel imaging technique, based on standard DXA images, and appears to constitute an index of bone texture that provides skeletal information additional to the standard aBMD results [24].

Trabecular bone score: definition

TBS has emerged as a novel grey-level texture measurement that uses experimental variograms of 2D projection images, quantifying variation in grey-level texture from one pixel to the adjacent pixels. TBS is not a direct measurement of bone microarchitecture but it is related to 3D bone characteristics such as the trabecular number, the trabecular separation and the connectivity density [25, 26]. An elevated TBS appears to represent strong, fracture-resistant microarchitecture, while a low TBS reflects weak, fracture-prone microarchitecture. As such, there is evidence that TBS can differentiate between two 3-dimensional (3D) microarchitectures that exhibit the same bone density, but different trabecular characteristics. TBS is generally obtained by re-analysis of AP lumbar spine DXA images, which allows direct comparison with aBMD and application to existing datasets. This latter opportunity has led to a rapid rise in published research assessing its potential role in the assessment and management of osteoporosis.

Lumbar TBS, like aBMD, is an age dependent variable. Little change in TBS is observed between the ages of 30 and 45 years. Thereafter, a progressive decrease is observed with advancing age [27], which is more marked in women than in men. The percentage decrease with age is similar to that for lumbar spine aBMD, as is the short term reproducibility [25].

This paper reports the findings of a European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) Working Group, which first convened in September 2014 with the aim of comprehensively assessing the evidence supporting the use of TBS in clinical practice. More specifically, this report reviews the potential value of TBS as an independent adjunct to risk assessment using DXA aBMD and/or FRAX in settings such as post-menopausal and secondary osteoporosis, and its potential use in assessment of response to treatment.

Search Strategy

A Medline search for publications with the terms trabecular bone score or TBS was undertaken in September 2014. Published articles in English and French were extracted. Papers in abstract form were not included except where the authors supplied a full copy of the submitted manuscript. A total of 479 papers were identified of which 67 manuscripts were considered relevant and the full publication reviewed. The search was subsequently updated in February 2015 and a total of 73 papers were reviewed.

Does TBS predict osteoporosis-related fracture risk?

To date, eighteen studies assessing fracture risk in post-menopausal women have been published. Of these, eleven were cross-sectional [28-38] and seven prospective, including a meta-analysis [25, 39-44].

Cross-sectional studies

The eleven cross-sectional studies are summarized in Table 1. The studies all were published from 2009 onward to January 2015. Sample sizes ranged from 135 to 3069, with the majority between 150 and 300 subjects. Six of the studies exclusively involved post-menopausal women, while one included only men over 40 years [31], and another both men and women over 50 years who had suffered at least one prior fracture [33]. There was variation in which fractures were assessed and how the fractures were ascertained. For example, five studies used self-report for all fractures, though vertebral fracture assessments (VFA) were used to identify vertebral fractures in three studies. In every study, however, and for every fracture type, there were significantly increased odds of prior fracture among those with low TBS even when adjusted for age, lumbar aBMD, body mass index, and clinical risk factors. Moreover, in one study which reported area (AUC) under receiver operating curves (ROC) as a combined measure of sensitivity and specificity, the AUC for TBS was greater than for aBMD of the spine (0.67 vs. 0.54, $p = 0.035$) but not for hip aBMD for subjects in the non-osteoporotic aBMD range [33]. However, in a further study which reported AUC values, these were similar for total hip BMD and total hip BMD with TBS (0.80 versus 0.81 respectively) [36].

Prospective studies

Cross-sectional studies may not accurately quantify the utility of a measure in the longitudinal prediction of incident fractures. However, data from prospective studies have supported the findings from the cross-sectional investigations. Of the six prospective single studies, one was conducted in France [28], one in the UK, France and Germany [40], three in Canada [25, 43, 54], and one in Japan [41] (Table 2). These cohorts tended to be larger than those in the cross-sectional studies, with the smallest with 560 subjects and the largest over 33,000 post-menopausal women; follow-up ranged from under 5 to over 8 years.

By far the largest published study assessing TBS to date was conducted in the Canadian province of Manitoba [46, 47], comprising 29,407 postmenopausal women (all over 50 years, mean 65.4 years) living in and around the capital city of Winnipeg [25]. At five years of follow-up, there were 1668 incident major osteoporotic fractures, including 439 vertebral fractures and 293 hip fractures. Lumbar spine aBMD and TBS predicted fractures equally well, and the combination of both performed better than either individually. Interestingly, although aBMD-lumbar spine and aBMD-total hip were closely correlated ($r = 0.72$), aBMD-lumbar spine and TBS-lumbar spine were only weakly correlated ($r = 0.32$), with only 10% of the variance in one explained by variance in the other. Similarly weak to moderate correlations between aBMD and TBS have been reported by several others [48-53], and may relate to measurement of different bone properties, or measurement variability. When various models adjusted for age and clinical risk factors were tested for

overall accuracy using receiver operating curves (ROC) and AUC estimates, the model combining aBMD-total hip and TBS-spine performed best, with AUC values for clinical vertebral and hip fractures of 0.73 (95%CI: 0.71, 0.75) and 0.82 (95%CI: 0.79, 0.84), respectively. For femoral neck, total hip and lumbar aBMD, the AUC improved significantly ($p<0.001$) with the inclusion of TBS. Fracture rate increased from highest to lowest third of TBS for subjects across the range of aBMD.

A smaller longitudinal study, conducted in France, was the OFELY (Osteoporose dans les Femmes de Lyon) study involving 560 post-menopausal women of mean age 65.3 years recruited in 2000 and 2001 and followed for a mean 7.8 years [39]. In this cohort there were 112 incident fragility fractures that occurred in 92 women. Adjusted for age and prior fracture, TBS, lumbar spine and total hip aBMD were predictive of fracture occurrence. As with the Manitoba study, the AUC for a combined model of lumbar aBMD and TBS was better than that for either test used alone. TBS appeared to have the discriminative ability only in those women with normal or osteopenic aBMD but not for women in the osteoporotic aBMD range. For example, the incidence of fracture in osteopenic women with a TBS value in the lowest quartile was 25% compared to 13% in osteopenic women with TBS values in the remaining quartiles.

The Japanese Population-Based Osteoporosis Cohort Study (JPOS) prospectively followed 665 Japanese women over the age of 50 years (mean age 64.1 years) for evidence of new morphometric vertebral fractures (VF), over approximately ten years [41]. During follow-up, 92 new vertebral fractures were documented by vertebral fracture assessment (VFA). In contrast to the OFELY study, there was an increased rate of VF from highest to lowest third of TBS score irrespective of BMD; i.e., also in those women in the osteoporotic aBMD range; the combination of aBMD and TBS increased overall performance of VF risk estimation over either used alone.

In the Osteoporosis and Ultrasound Study (OPUS), 1007 post-menopausal women (mean age 65.9 years) were recruited from three European centres, one each in France, Germany and the UK, and followed for an average of 6.0 years [40]. Over those six years, there were 82 incident clinical fractures and 46 incident vertebral fractures identified by radiography. TBS and aBMD at lumbar spine, femoral neck or total hip were similarly predictive of fragility fractures, but the combination of TBS and aBMD performed better than either measure alone, both in osteoporotic and non-osteoporotic women.

Only one longitudinal study on TBS has data for men (Table 2), with 3620 men over age 50 years (mean age 67.6 years) in the Manitoba cohort, followed for an average of 4.5 years and sustaining 183 major osteoporotic fractures [54]. TBS was predictive of hip, vertebral or major fractures. However, predictive power remained significant only for hip fracture when adjusted for FRAX score, osteoporosis treatment, and aBMD. There was some evidence of an interaction between aBMD and TBS such that the relationship between TBS and incident fracture appeared stronger in those with an aBMD T-score < -2.5.

A recent meta-analysis of 14 prospective population-based cohorts comprising 17,809 men and women (59% women) examined fracture risk expressed as a gradient of risk (GR, the

increase in fracture risk/SD difference in TBS). The GR of TBS for hip fracture or other major osteoporotic fracture (clinical spine, distal forearm or proximal humerus fracture) ranged from 1.31 to 1.54 depending on age and fracture outcome with no difference between men and women [42].

These data support the utility of low lumbar TBS as a determinant of fracture risk, at least partly independent of aBMD. The consistency of the predictive value for fracture in international cohorts argues for its clinical use with aBMD.

Is TBS a potential adjunct to FRAX® probability?

FRAX is widely used as a fracture risk assessment tool and the question arises whether TBS might serve as an adjunct to FRAX risk factors in the stratification of fracture risk. For TBS to be considered clinically useful as a FRAX modifier, it should be at least partly independent of lumbar spine aBMD, femoral neck aBMD and FRAX clinical risk factors (CRFs). An assessment of the relationship between CRFs, aBMD and TBS was undertaken in the Manitoba cohort, in which 33,352 women aged 40–100 years (mean 63 years) with baseline DXA measurements of lumbar spine TBS and femoral neck aBMD were studied [43]. Over a mean of 4.7 years follow-up, 1,754 women died and 1,872 sustained one or more major osteoporotic fracture. Lower TBS predicted increased risk of incident fracture (HR/SD decrease: 1.36; 95%CI: 1.30, 1.42, $p<0.001$) and a 32% increase in death rate (HR/SD decrease: 1.32; 95%CI: 1.26, 1.39, $p < 0.001$). Lumbar spine TBS remained a significant predictor of major osteoporotic fracture (HR/SD decrease: 1.18; 95 %CI: 1.12, 1.23) after adjustment for significant clinical risk factors and femoral neck aBMD. Low TBS (10th percentile) increased fracture risk 1.5 to 1.6-fold relative to high TBS (90th percentile), after accounting for competing mortality, across a wide range of ages and femoral neck T-scores.

Similar results were found in 3620 men from the Manitoba cohort at the age of 50 years or more (mean 67.6 years) [54]. Over a mean follow-up of 4.5 years, 183 men sustained major osteoporotic fractures and 91 clinical vertebral fractures. Lower lumbar spine TBS was observed in fracture versus non-fracture men for all fracture categories, and the AUC for incident fracture discrimination with TBS was significantly better than by chance (major osteoporotic fracture AUC = 0.59, $p<0.001$; hip fracture AUC = 0.67, $p<0.001$; clinical vertebral fracture AUC = 0.57, $p = 0.032$). After adjustment for FRAX without aBMD and osteoporosis treatment, TBS predicted major osteoporotic fracture and hip fracture (but not clinical vertebral fracture), and remained a predictor of hip fracture (but not major osteoporotic fracture) after further adjustment for hip or spine aBMD.

More recently, Manitoba data have been used to derive an adjustment factor to alter FRAX probabilities when accounting for TBS [55]. Data from 33,352 women between the ages of 40 and 100 years in Manitoba were used, including baseline DXA measures of femoral neck aBMD and lumbar spine TBS. Hazard functions for risk of osteoporotic fracture without hip fracture, hip fracture, and death (since risk of death competes with risk of fracture) were used to compute the adjustment factor. Femoral neck aBMD, clinical risk factors and TBS all contributed independent predictive value to the models, and TBS modified the 10-year

probability of fracture outcomes generated from clinical risk factors and aBMD in FRAX-like models. Thus, for example, in an 80-year old women, with a femoral neck T score of −2, and BMI 27kg/m^2, the 10-year probability of major osteoporotic fracture was 16.5%. If her TBS were found to be low (10th percentile), this would increase her fracture probability to 18.0%; conversely if TBS were found to be high (90th percentile), her fracture probability would be reduced to 13.6%.

The validity of the adjustment to FRAX has been explored in a meta-analysis of 14 cohorts (excluding Manitoba), together incorporating 17,809 men and women (59% women) ranging in age from 40 to 90 years (mean age 72 years) [42]. FRAX and TBS both had predictive ability for both major osteoporotic fractures and hip fracture, partly independently of each other. The predictive ability of FRAX was expressed as the gradient of risk (GR; hazard ratio per 1SD change in risk variable in direction of increased risk). Overall, the GR of TBS for major osteoporotic fracture was 1.44 (95%CI: 1.35-1.53) when adjusted for age and time since baseline and was similar in men and women ($p>0.10$). When additionally adjusted for FRAX 10-year probability of major osteoporotic fracture, TBS remained a significant, independent predictor for fracture (GR 1.32, 95%CI: 1.24-1.41). The adjustment of FRAX probability for TBS resulted in a small increase in the GR (1.76, 95%CI: 1.65-1.87 vs. 1.70, 95%CI: 1.60-1.81) suggesting that TBS would have clinical utility, for example, in the reclassification of those close to intervention thresholds.

Is TBS responsive to treatment?

Several relatively small studies have examined treatment-induced changes in TBS [49,50, 53, 56-59] (Table 3). Of these, four were studies of osteoporosis treatment in postmenopausal women, one in both men and women with osteoporosis, and two in the management of breast cancer. One of these compared a specific oestrogen-receptor modifier (tamoxifen) and an aromatase inhibitor (exemestane) in breast cancer patients.

In Manitoba, 534 post-menopausal women treated with a bisphosphonate (86%), raloxifene (10%) or calcitonin (4%), and having more than 75% compliance, were compared with 1,150 untreated women [50]. The mean duration of follow-up was 3.7 years. Women in the treated group were older (mean age 66.1 vs. 62.2 years), had lower scores for aBMD and lumbar TBS, and had a higher prevalence of prior major osteoporotic fracture (15.4 vs. 10.4%) at baseline, consistent with indications for treatment. Over the course of follow-up, spine aBMD and TBS increased in treated women by 1.9% and 0.2%, respectively, whereas in untreated women aBMD and TBS decreased by 0.4% and 0.3% (all statistically significant changes versus baseline). Changes in aBMD and TBS from baseline were only weakly correlated ($r = 0.20$), consistent with the notion that the two indices represent partly independent measures of bone structure.

In the Swiss Horizon trial, 54 post-menopausal women treated with zoledronic acid were compared with 53 on placebo over 36 months of follow-up [52, 53]. The only clinically-meaningful difference in baseline characteristics was a lower lumbar spine T-score in treated women (−2.9 vs. −2.1). Over three years, lumbar spine aBMD and TBS rose significantly, by 9.6% and 1.4%, respectively, in those on active treatment. The spine aBMD T-score also

rose by 1.4% in those on placebo, perhaps due to degenerative disease, whilst TBS declined by 0.5%. The first statistically-significant change from baseline for aBMD was recorded at 6 months, whereas for TBS was at 24 months. Changes in the aBMD and TBS were only weakly correlated (r = 0.20) [52, 53].

In a two-year open-label study [59] comparing teriparatide (n = 65) and ibandronate (n = 122), in which the only clinically-significant inter-group difference in baseline characteristics was a higher prevalence of past vertebral fractures in those on teriparatide (90.5 vs. 44.3%), patients on teriparatide had 7.6 and 4.3% increases in lumbar aBMD and TBS (both $p < 0.001$ vs. baseline), whilst only aBMD increased significantly in those on ibandronate (2.9% vs. 0.03%; $p < 0.001$ and 0.086, respectively). In this study, there was no significant correlation between changes in aBMD and TBS ($r^2 = 0.01$). In this report, responsivity was also assessed as the proportion of patients achieving the least significant change in TBS and aBMD. For both treatment modalities lumbar spine BMD was more sensitive than TBS.

In an analysis of a small subset of treated female breast cancer patients in the Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial (n = 19 on exemestane, 17 on tamoxifen) [49], spine aBMD and TBS increased by 1.9 and 3.3% in those on tamoxifen versus a 5.3 and 2.3% decrease in patients given exemestane. The disparate responses to the two drugs are consistent with prior research demonstrating decreased fracture risk in postmenopausal breast cancer patients treated with tamoxifen and the increased risk observed in those on exemestane [60-62]. Changes in TBS and aBMD were again only weakly correlated (r = 0.25) [49].

A double-blind, randomized, placebo-controlled trial evaluated the effect of 8 cycles of adjuvant treatment with zoledronic acid over a 24-month period (4 mg i.v. once every 3 months) compared to placebo on aBMD and TBS in premenopausal women with estrogen receptor and/or progesterone receptor positive breast cancer [57]. Treatment induced increases in both aBMD and TBS which were somewhat greater in percentage terms in the case of aBMD.

A cohort of 390 patients was analysed to evaluate the effect of different treatments (testosterone, risedronate, alendronate, denosumab, teriparatide) on aBMD and TBS [56]. After 24 months, a significant increase in TBS was observed only in the alendronate (+1.4%), denosumab (+2.8%) and teriparatide (+3.6%) groups, whereas aBMD increases in all treated groups. TBS was preserved on calcium and vitamin D, and decreased in the group without any treatment consistent with an epidemiological study showing that lower intakes of milk were associated with lower values for aBMD and TBS [63].

Longitudinal assessment of change represents a number of challenges both for bone densitometry and the evaluation of TBS. The precision of the measurement is critical, both within and between instruments [64]. However, sensitivity to measure changes is also affected by responsiveness, the ratio of responsiveness to precision being an indicator of sensitivity to measure (treatment-induced) changes [65]. At present, treatment induced changes in TBS have not been consistently assessed in this way. Nor has any possible

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contribution of TBS to fracture efficacy been explored, given that the change in aBMD with treatment does not appear to fully explain the magnitude of fracture risk reduction [66;67].

Taken together, these intervention studies suggest that TBS tends to increase with treatments which increase aBMD, but that the magnitude of change of TBS is less marked than that of aBMD. It is currently unclear whether TBS might usefully contribute to the monitoring of treatment effects; and, given that DXA appears more responsive to change, this seems an unlikely outcome. However, these studies do indicate that TBS is potentially amenable to change as a result of pharmacological therapy. Whether this change is predictive of alterations in risk of future fracture, however, is currently not known.

Does TBS have a role in secondary osteoporosis?

Although in many cases, osteoporosis is idiopathic, there are a number of specific causes of bone fragility that result in “secondary osteoporosis”. Evidence is emerging that TBS might provide useful information with regards to bone health in several clinical contexts [68].

Clinical and subclinical hypercortisolism

Glucocorticoid induced osteoporosis (GIO) is common. Patients on long-term glucocorticoids fracture at a higher BMD than postmenopausal women, potentially implying a deleterious effect on bone structure. These effects may be more pronounced at lumbar spine; thus TBS may be well positioned to detect GIO-associated changes in bone structure.

In a cross-sectional study 65, women with systemic sclerosis were matched with 138 women with rheumatoid arthritis and 227 controls [69]. Multivariate analysis showed that a low TBS was independently associated with daily glucocorticoid dose. In a comparison of 34 patients with adrenal tumour and subclinical hypercortisolism [70], 68 patients with a tumour but no subclinical hypercortisolism, and 70 matched controls, both aBMD and TBS were lower in those with subclinical hypercortisolism. In addition, baseline lumbar TBS predicted incident fractures over a mean 40 months of follow-up, independent of patient age, BMI and lumbar aBMD [70].

Type-2 Diabetes

There is evidence that patients with type-2 diabetes fracture at higher aBMD than postmenopausal women [71]. As such, there is a need for improved approaches to estimate fracture risk in such individuals. Recently, three studies have demonstrated that, although aBMD tends to be higher in type-2 diabetics than non-diabetics, the reverse is true of TBS. In the first paper, a cross-sectional case-control study by Dhaliwal et al., 57 women with type-2 diabetes were compared with 43 women without. TBS was lower and aBMD higher among diabetics ($p = 0.001$ and 0.01, respectively). Moreover, TBS was lower ($p = 0.01$) and aBMD no different in those diabetics with poor glycemic control compared to those with good glycemic control (an A1c above, versus below, 7.5%) [72]. The authors speculated that “abnormal architecture may help explain the paradox of increased fractures at higher aBMD” in these patients, although other mechanisms, such as glycosylation of collagen cross-links, key to the basic nano-structure of bone, have also been postulated [71]. Leslie et al [73] retrospectively analyzed data from 29,407 Canadian women age 50 years or

over, who had undergone a baseline DXA examination, comparing 2356 diagnosed diabetics with the remainder of the cohort. After adjustment for clinical risk factors, diabetic women were found to be more likely to be in the lowest third of lumbar TBS, but less likely to be in the lowest thirds of lumbar, femoral neck or total hip aBMD. Both TBS and measures of aBMD were predictive of incident fracture. Finally, in the Ansung cohort, which included 1229 men and 1529 postmenopausal women (325 men and 370 women with type-2 diabetes) [74], lumbar spine TBS was lower in men and women with diabetes than those without, whereas lumbar spine BMD was higher in men and women with diabetes. Interestingly, TBS was negatively correlated with HbA1c, fasting plasma glucose and fasting insulin. Based on the above studies, TBS may aid fracture risk assessment in patients with type-2 diabetes.

Primary hyperparathyroidism

Several studies provide support for use of lumbar TBS in the management of asymptomatic primary hyperparathyroidism [75-78]. Romagnoli et al [77] noted lower TBS in 73 post-menopausal women with primary hyperparathyroidism (29 of them having a documented vertebral fracture) than in 74 age-matched controls. In a study that included both cross-sectional and longitudinal components, Eller-Vainicher et al [76] compared 92 patients with primary hyperparathyroidism (74 of them post-menopausal females and the remainder males over age 50 years) and 98 controls with other conditions, consecutively recruited from clinic. Again, TBS was lower in patients with primary hyperparathyroidism than in controls, and was statistically significantly associated with vertebral fracture, even after adjustment for age, gender, BMI and lumbar spine aBMD (adjusted OR = 1.4; 95%CI: 1.1-1.9). In the longitudinal phase of the study, 20 primary hyperparathyroidism patients who underwent a parathroidectomy to achieve ‘cure’ were compared at 24 months follow-up with 10 patients treated conservatively. In the surgery group, the mean TBS z-score increased by 1.20 ($p < 0.01$), whilst TBS non-significantly declined in the ten conservatively-treated counterparts [76].

Osteoarthritis

One limitation of spinal aBMD assessment is that the presence of overlying calcifications due to degenerative change can erroneously elevate the resulting measurement. Recent studies have suggested that TBS may be less affected by such artefactual influences [79]. Both points were demonstrated in a recent study by Kolta et al. [80] in which 1254 post-menopausal women in the European OPUS cohort, mean age 67 years, underwent TBS measurement at baseline and again at a mean of six years later. The severity of spinal osteoarthritis was graded according to Kellgren and Lawrence [81]. The investigators found that TBS was no different in women with, versus without, osteoarthritic changes in the spine at baseline, while lumbar spine aBMD measurements averaged 5.7% higher in the former group ($p< 0.003$). Over a mean six years of follow-up, TBS declined by 3.3% ($p < 0.001$), independent of the severity of spinal osteoarthritis. Conversely, though femoral neck and total hip aBMD also decreased over time and were not affected by osteoarthritis grade, there was no net decrease in lumbar aBMD, which was also associated with the grade of spinal arthritis [82].

Currently-published data support a role for the TBS in the assessment of fragility fracture risk in patients with a variety of secondary causes of osteoporosis, including subclinical hypercortisolism, type-2 diabetes, and parathyroid disease. Clearly, prospective cohort studies will be needed to confirm any added utility of TBS in these specific situations over and above its general predictive ability for fracture.

Conclusions

In recent years, there has been increasing interest in the use of TBS, a surrogate of bone microarchitecture, for risk stratification in osteoporosis. The present assessment of the existing literature indicates that low lumbar spine TBS is associated with both a history of fracture and the incidence of new fracture. The effect is independent of aBMD and of sufficient magnitude to enhance risk stratification with aBMD. The effect is also partly independent of FRAX with likely greatest utility for those individuals who lie close to an intervention threshold. TBS increases with treatment for osteoporosis, but the magnitude of this change is smaller than that with bone mineral density; the relationship between change in TBS and magnitude of fracture risk reduction remains to be elucidated. There have been a number of smaller investigations, which have suggested that TBS may play a role in specific causes of increased fracture risk, such as glucocorticoid excess, hyperparathyroidism and type-2 diabetes.

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Table 1

Cross-sectional case control studies that examine TBS and fracture risk

First Author	Year Published	Location	Subjects	Outcome(s)	TBS OR/SD decrease	TBS 95% CI	BMD OR/SD decrease	BMD 95% CI	Adjustments
Pothuaud [34]	2009	Switzerland France	135 PM females 45 cases with Fx 90 BMD-matched controls	vertebral Fx hip Fx MOF	2.66 NR 1.95 se	1.46, 4.85 NR 1.31, 2.89	NR NR NR	NR NR NR	none none none
Winzenrieth [38]	2010	France	243 PM females 81 cases with vertebral Fx 162 age-matched controls	vertebral Fx	1.97	1.31, 2.96	1.63	1.20, 2.22	weight
Rabier [35]	2010	France	168 PM females 42 cases vertebral Fx 126 age-matched controls	vertebral Fx	3.81	2.17, 6.72	2.48	1.61, 3.83	weight
Lamy [30]	2012	Switzerland	631 PM women 164 with Fx (53 VF, 107 MOF) 467 controls	all Fx (self-report) vertebral Fx (VFA) MOF	1.4 2.0 1.9	1.1, 1.7 1.4, 3.0 1.4, 2.5	1.3 1.8 1.6	1.1, 1.6 1.2, 2.5 1.2, 2.1	age, BMI age, BMI age, BMI
Del Rio [28]	2013	Spain	191 PM women 83 cases with Fx 108 non-matched controls	femoral neck Fx (self-report)	1.71	1.15, 2.79	1.94	1.35, 2.79	age
Vasic [37]	2013	Serbia Bulgaria Ukrain Romania	1031 women 271 with Fx	MOF	1.27	1.07, 1.51	NR	NR	age, LS BMD
Leib [32]	2014	USA	2165 women 289 cases with Fx 1876 non-matched controls	all Fx (self-report)	1.28	1.13,1.46	NR	NR	age, LS BMD, weight, smoking, maternal history of hip fracture
Krueger [29]	2014	USA	429 PM women 158 cases with Fx (91 vertebral Fx) 271 age-matched controls	fracture (self-report) vertebral Fx (VFA)	2.46 2.49	1.9, 3.1 1.9, 3.3	1.36 1.36	1.2, 1.6 1.1, 1.7	age, BMI
Leib [31]	2014	USA	180 men 45 cases with Fx 135 age/LS-BMD matched controls	low-energy Fx (self-report)	1.55	1.09, 2.20	NR	NR	age, LS BMD
Nassar [33]	2014	France	280 women, 82 men > age 50	vertebral Fx (VFA) vs. Non-vertebral Fx AUC TBS > AUC BMD	NR NR	NR NR	NR NR	NR NR	NR NR

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First Author	Year Published	Location	Subjects	Outcome(s)	TBS OR/SD decrease	TBS 95% CI	BMD OR/SD decrease	BMD 95% CI	Adjustments
			133 vertebral Fx, 186 hip Fx 133 vertebral Fx, 186 hip Fx 176 non- vertebral Fx, non-hip Fx	(0.67 vs. 0.54, p = 0.04)					
			255 women, 40-92 years						Age
Touvier [36]	2015	France	79 fragility fracture 176 controls	Fragility fracture (orthopedic clinic)	2.25	1.58, 3.29	1.70	1.18, 2.54	

PM = postmenopusal, Fx = fracture; MOF = major osteoporotic fracture; NR = not recorded

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Table 2

Prospective cohort studies that have examined lumbar TBS and fracture risk

First author, ref number	Year Published	Location	Subjects	Outcome	Follow-up [years]	Lumbar spine TBS HR or RR/SD*	95% CI	Lumbar spine BMD HR or RR /SD*	95% CI	Total hip BMD HR or RR/SD*	95% CI	Adjustments
Hans [25]	2011	Canada	29,407 PM women 5.7% OP Fx (1.5% clinical VFx; 1.0% hip Fx	clinical VF hip Fx MOF	4.7	1.45 1.46 1.35	1.32, 1.58 1.30, 1.63 1.29, 1.42	1.72 1.31 1.47	1.55, 1.91 1.16, 1.48 1.39, 1.55	1.75 2.55 1.67	1.58, 1.96 2.22, 2.93 1.58, 1.76	age age age
Boutroy [39]	2013	France	OLEFY cohort 560 PM women 94 with Fx at any site	clinical VF radiographic VF fragility Fx	8	1.34	1.04, 1.73	1.3	1.06, 1.58	1.99	1.52, 2.62	age, weight
Briot [40]	2013	France UK Germany	OPUS cohort 1007 PM women 8.1% with OP Fx; 4.6% with VF	radiographic VF clinical OP Fx	6	1.54 1.62 OR per SD decrease	1.17, 2.03 1.30, 2.01	1.75 1.47 OR per SD decrease	1.25, 2.48 1.16, 1.89	1.73 1.65 OR per SD decrease	1.26, 2.38 1.30, 2.11	none
Iki [41]	2014	Japan	665 PM women 92 with VF	VF (VFA)	8.3	1.54 OR per SD decrease	1.17, 2.02	1.27 OR per SD decrease	1.02, 1.59	NR	NR	age, LS BMD
Leslie [54]	2014a	Canada	3620 men > 50 (mean age 67.6) 183 MOF (91 VF, 46 hip Fx)	MOF hip Fx VF	4.5	1.22 1.6 1.12	1.60, 1.41 1.21, 2.11 0.91, 1.38	1.14 1.29 1.26	1.02, 1.28 1.03, 1.60 1.09, 1.47	1.66 2.84 1.2	1.40, 1.98 1.95, 4.12 0.95, 1.51	FRAX score, treatment
Leslie [43]	2014b	Canada	33,352 women 40-100 years	MOF Death		1.36 1.32	1.30,1.42 1.26,1.39	NR		NR		Time since baseline and age
McCloskey [42]	2015	Multinational	17809 men & women 298 with hip 1109 with MOF	MOF hip Fx Men MOF Men hip Fx Women MOF Women hip Fx	6.7	1.32 1.28 1.35 1.27 1.31 1.29	1.24, 1.41 1.13, 1.45 1.21, 1.49 1.06, 1.53 1.21, 1.42 1.09, 1.52	NR		NR		FRAX score, time since baseline and age

*Hazard ratio or relative risk per SD decrease in predictor unless otherwise stated

PM = postmenopusal, Fx = fracture; MOF = major osteoporotic fracture; VFx = vertebral fracture;NR = not recorded

Table 3

Treatment related changes in lumbar TBS

First author	Year Published	Location	Study design	Subjects	TBS change/yr	Versus baseline	Versus other Rx	BMD change/yr	Versus baseline	Versus other Rx
Krieg [50]	2013	Canada	Case-control	534 PM women on standard OP Rx 1150 untreated	0.20% −0.30%	p < 0.001 p < 0.001	p < 0.001	1.90% −0.40%	p < 0.002 p < 0.001	p < 0.001
Popp [53]	2013	Switzerland	RCT	54 PM women on zoledronate 53 on placebo	0.50% −0.20%	p < 0.001 p < 0.001	p < 0.001	3.20% 0.50%	p < 0.001 p < 0.001	p < 0.001
Senn [59]	2014	Switzerland	Open-Label	65 PM women on teriparatide 122 PM women on ibandronate	2.20% 0.20%	p < 0.001 p = 0.86	p < 0.001	3.80% 1.50%	p < 0.001 p < 0.001	p < 0.001
Kalder [49]	2014	Germany	RCT substudy	17 PM women on tamoxifen 19 PM women on exemestane	1.70% −1.20%	p < 0.06 p < 0.05	p < 0.001	1.00% −2.70%	NS p < 0.002	p < 0.001
Petranova [58]	2014	Bulgaria	Observational	36 PM women on denosumab no controls	1.70%	p < 0.05	NA			
Kalder [57]	2015	Germany	RCT	34 women with breast cancer on zoledronate 36 women with breast cancer on placebo	2.41% −0.52%	p<0.006	p=0.003	2.17% −5.02%	p<0.001	p<0.005
Di Gregorio [56]	2015	Spain	Open-Label	67 untreated 87 men and women on calcium and vitamin D 88 men and women on Alendronate 36 men on Testosterone 39 men and women on Risedronate 43 men and women on Denosumab 30 men and women on Teriparatide	−1.55% 0.65% 0.70% 0.90% 0.70% 1.40% 1.80%	p<0.05 NS p<0.05 NS NS p<0.01 p<0.01	NA NA NA NA NA NA	0.25% 0.80% 2.05% 2.20% 2.40% 4.40% 4.40%	NS NS p<0.001 p<0.001 p<0.001 p<0.001 p<0.001	NA NA NA NA NA NA

PM = postmenopusal; NA = not applicable