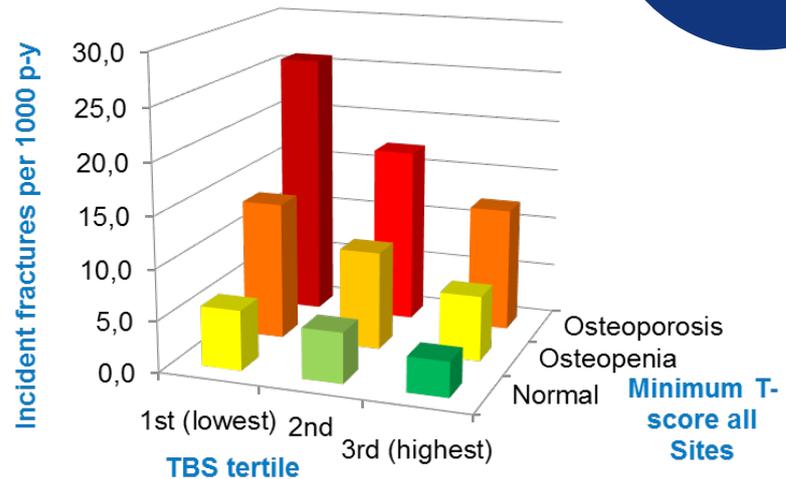


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Why do hips fracture?

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The potential roles of trabecular bone score (TBS) in clinical practice

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Osteoporosis is characterised by low bone mass and a microarchitectural deterioration of bone tissue, resulting in a propensity to fragility fracture. It has been defined operationally as a bone mineral density (BMD) by dual-energy X-ray absorptiometry of 2.5 standard deviations or more below the young adult female mean (T-score ≤ 2.5), measured at the femoral neck, total hip, or lumbar spine⁽¹⁾. DXA BMD presents an amalgam

of contributions from bone size, volumetric density and microarchitecture. This latter aspect has not been easily assessed clinically until recent years, with the advent of novel imaging techniques such as (peripheral) quantitative computed tomography (QCT) and high resolution peripheral QCT. Whilst these modalities yield indices associated with fracture risk partly independently of DXA BMD, they do not reliably outperform BMD in prediction of osteoporotic fractures, and are not as readily available.

Trabecular Bone Score (TBS) assesses bone microarchitecture indirectly through a grey-level texture measurement that uses experimental variograms of 2D projection images, quantifying variation in grey-level between adjacent pixels. This yields information related to 3D bone characteristics such as trabecular number, separation and connectivity⁽²⁾. An elevated TBS arises from more numerous, and connected, and less sparse trabeculae and indicates strong, fracture resistant microarchitecture. The TBS can be obtained from re-analysis of AP lumbar spine DXA images, and thus has the merits of being widely available, subject to the acquisition of the software required. The remainder of this review will provide an overview of the available evidence which informs the potential role of TBS in clinical practice.

TBS and fracture risk

The evidence supporting the use of TBS in clinical practice has been recently reviewed⁽³⁾. The eighteen included studies, of which eleven were cross-sectional and seven prospective, assessed fracture risk using TBS and DXA BMD. Fourteen of these studies assessed women only. In every cross-sectional study significantly increased odds of prior fracture (every fracture type) were found among those patients with low TBS even when adjusted for age, lumbar aBMD, body mass index, and clinical risk factors.

Although helpful, case-control studies do not yield evidence that a modality will be useful in the prediction of incident fractures. The considered prospective studies included a much larger number of individuals, for example a cohort of 29,407 postmenopausal women in the Canadian province of Manitoba⁽⁴⁾. Fracture risk was greatest for individuals in the highest compared to lowest third of TBS across the range of DXA BMD (*Figure 1*). To assess the ability of BMD and TBS to discriminate between those with and without clinical

fractures, Receiver Operating Curves (ROC) and Area Under the Curve (AUC) estimates were performed, where a value for AUC of 1 is perfect (i.e. zero false positives and zero false negatives) and a value for AUC of 0.5 is no better than chance. For a model combining total hip BMD and lumbar spine TBS, the AUC values were 0.73 (95%CI: 0.71, 0.75) and 0.82 (95%CI: 0.79, 0.84) for vertebral and hip fractures respectively. The AUC for femoral neck, total hip and lumbar aBMD were all improved ($p < 0.001$) with the inclusion of TBS.

TBS and FRAX

FRAX is a fracture risk assessment tool, which integrates eight clinical risk factors (CRFs: prior fragility fracture, parental hip fracture, smoking, systemic glucocorticoid use, excess alcohol intake, body mass index, rheumatoid arthritis, and other causes of secondary osteoporosis), which, in addition to age and sex, contribute to a 10-year fracture risk estimate independently of BMD⁽⁵⁾. BMD from the femoral neck is an optional input variable when FRAX is used to calculate 10-year fracture probability. FRAX is based on meta-analyses of 12 international cohorts comprising 59,644 individuals and validated in a further 11 cohorts comprising 230,486 individuals worldwide. It is the most widely used and accepted fracture risk assessment tool, incorporated into the majority of fracture risk assessment guidelines internationally. Leslie et al⁽⁶⁾ demonstrated that lumbar spine TBS remained a significant predictor of major osteoporotic fracture after adjustment for significant clinical risk factors and femoral neck aBMD (HR/SD decrease 1.32; 95%CI: 1.12-1.23). Therefore, given the independence of TBS from clinical risk factors and femoral neck BMD for fracture, it could be considered for use as a FRAX modifier.

Data from the Manitoba cohort were used to assess how FRAX probabilities change when

TBS is taken into account⁽⁷⁾, the approach being validated in a meta-analysis of 14 cohorts comprising 17,809 individuals⁽⁸⁾. This work resulted in an algorithm, which adjusts, across a continuous range, the FRAX probability upwards if TBS is low and downwards if TBS is high, the adjustment now available via a link on the FRAX site. An example of this effect of this approach follows: an 80-year-old woman with a femoral neck T score -2, BMI 27kg/m² has a 10-year FRAX probability of major osteoporotic fracture of 16.5%. If her TBS were low at the 10% percentile, her fracture probability would increase to 18%, and conversely with a high TBS at 90% percentile, her fracture probability would reduce to 13.6%. Overall the influence of TBS on the gradient of risk (hazard ratio for new fracture per standard deviation change in FRAX probability) was modest, but varied with age, and taken as a whole, these studies probably best support the use of TBS as an adjunct to FRAX and BMD in deciding treatment decisions where probability lies close to the intervention threshold.

TBS and treatment for osteoporosis

There have been a small number of relatively small studies examining change in TBS with treatment for osteoporosis. These have shown modest increases in TBS with anti-osteoporosis therapy, the magnitude of which are generally lower than changes in aBMD. In the Swiss Horizon trial of 54 post menopausal women treated with zoledronic acid, over 3 years lumbar spine aBMD increased by 9.6% and the TBS by 1.4% on active treatment⁽¹⁰⁾. Notably, whilst the change in aBMD became statistically significant at 6 months, the change in TBS became statistically significant at 24 months. Other studies confirm this pattern, however importantly it is unclear if these changes predict the reduction in risk of future fracture consequent on treatment.

TBS and secondary osteoporosis

There is limited evidence, usually from relatively small studies, that TBS may usefully add to patient assessment in several causes of "secondary osteoporosis", such as type-2 diabetes and primary hyperparathyroidism:

Type-2 diabetes

Patients with type-2 diabetes are at increased risk of fracture, although this is beyond a level explained by a decrease of BMD and is typically at higher BMD than fractures in postmenopausal women. This is thought to be due to a deterioration in bone microarchitecture, and degraded collagen cross-links from glycation and oxidation⁽⁹⁾. Indeed a case-control study demonstrated TBS to be lower in diabetics than to non-diabetics, despite diabetics having greater DXA BMD; TBS was further reduced in diabetics with poor glycaemic control⁽¹⁰⁾. A retrospective subset analysis of the Canadian Manitoba cohort data provided evidence that after adjustment for clinical risk factors, diabetic women were less likely to be in the lowest third of lumbar, femoral neck or total hip aBMD but more likely to be in the lowest third of TBS. Both TBS and measures of aBMD were predictive of incident fracture⁽¹¹⁾.

Primary hyperparathyroidism

Several studies have provided evidence that lumbar spine TBS may be helpful in the management of primary hyperparathyroidism. Reduced TBS was noted in 73 postmenopausal women with this condition compared with 74 age-matched controls⁽¹²⁾. In a further study 92 patients with primary hyperparathyroidism were compared with 98 controls with other conditions consecutively recruited from clinic⁽¹³⁾. Consistent with the previous study, TBS was lower in patients with primary hyperparathyroidism than in controls and was also associated with past vertebral fracture. In this latter study there

was a longitudinal phase in which mean TBS score increased following parathyroid surgery, compared with a non-significant TBS decline in non-surgically treated hyperparathyroidism patients.

Conclusion

Whilst DXA assessment of bone mineral density, ideally at the femoral neck, provides the standard for bone measurement in fracture risk assessment, there is increasing evidence that trabecular bone score usefully adds to current fracture risk prediction strategies. Thus TBS is associated with past and future fracture and predicts incident fracture partly independently of BMD and FRAX probability. The evidence to date suggests adjunctive use of TBS with FRAX/BMD is likely to be of most value in those individuals who are close to an intervention threshold, where further information is required to refine the decision on whether to treat.

Key Points:

- Trabecular bone score (TBS) is obtained from re-analysis of lumbar spine dual-energy X-ray absorptiometry (DXA) images and yields information related to bone microarchitecture
- Low lumbar spine TBS is associated with both a history of fracture and the incidence of new fracture, independent of DXA BMD
- The available evidence supports the use of TBS in fracture risk assessment, as an adjunct to BMD and FRAX
- The clinical utility of TBS is likely to be greatest in those individuals close to an intervention threshold based on FRAX/ BMD

References

1. World Health Organisation. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis (1994). WHO Geneva
2. Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, McCloskey EV, Kanis JA, Bilezikian JP (2014) Trabecular bone score: a noninvasive analytical method based upon the DXA image. *J Bone Miner Res* 29 (3):518-530. doi:10.1002/jbmr.2176
3. Harvey NC, Gluer CC, Binkley N, McCloskey EV, Brandi ML, Cooper C, Kendler D, Lamy O, Laslop A, Camargos BM, Reginster JY, Rizzoli R, Kanis JA (2015) Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. *Bone* 78:216-224. doi:10.1016/j.bone.2015.05.016
4. Hans D, Goertzen AL, Krieg MA, Leslie WD (2011) Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. *J Bone Miner Res* 26 (11):2762-2769. doi:10.1002/jbmr.499
5. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, Burckhardt P, Cooper C, Christiansen C, Cummings S, Eisman JA, Fujiwara S, Gluer C, Goltzman D, Hans D, Krieg MA, La Croix A, McCloskey E, Mellstrom D, Melton LJ, 3rd, Pols H, Reeve J, Sanders K, Schott AM, Silman A, Torgerson D, van Staa T, Watts NB, Yoshimura N (2007) The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 18 (8):1033-1046. doi:10.1007/s00198-007-0343-y
6. Leslie WD, Johansson H, Kanis JA, Lamy O, Oden A, McCloskey EV, Hans D (2014) Lumbar spine texture enhances 10-year fracture probability assessment. *Osteoporos Int* 25 (9):2271-2277. doi:10.1007/s00198-014-2761-y
7. McCloskey EV, Oden A, Harvey NC, Leslie WD, Hans D, Johansson H, Kanis JA (2015) Adjusting fracture probability by trabecular bone score. *Calcif Tissue Int* 96 (6):500-509. doi:10.1007/s00223-015-9980-x
8. McCloskey EV, Oden A, Harvey NC, Leslie WD, Hans D, Johansson H, Barkmann R, Boutroy S, Brown J, Chapurlat R, Elders PJ, Fujita Y, Gluer CC, Goltzman D, Iki M, Karlsson M, Kindmark A, Kotowicz M, Kurumatani N, Kwok T, Lamy O, Leung J, Lippuner K, Ljunggren O, Lorentzon M, Mellstrom D, Merlijn T, Oei L, Ohlsson C, Pasco JA, Rivadeneira F, Rosengren B, Sornay-Rendu E, Szulc P, Tamaki J, Kanis JA (2015) A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. *J Bone Miner Res*. doi:10.1002/jbmr.2734
9. Saito M, Kida Y, Kato S, Marumo K (2014) Diabetes, collagen, and bone quality. *Current osteoporosis reports* 12 (2):181-188. doi:10.1007/s11914-014-0202-7
10. Dhaliwal R, Cibula D, Ghosh C, Weinstock RS, Moses AM (2014) Bone quality assessment in type 2 diabetes mellitus. *Osteoporos Int* 25 (7):1969-1973. doi:10.1007/s00198-014-2704-7
11. Leslie WD, Aubry-Rozier B, Lamy O, Hans D (2013) TBS (trabecular bone score) and diabetes-related fracture risk. *J Clin Endocrinol Metab* 98 (2):602-609. doi:10.1210/jc.2012-3118
12. Romagnoli E, Cipriani C, Nofroni I, Castro C, Angelozzi M, Scarpello A, Pepe J, Diacinti D, Piemonte S, Carnevale V, Minisola S (2013) "Trabecular Bone Score" (TBS): an indirect measure of bone micro-architecture in postmenopausal patients with primary hyperparathyroidism. *Bone* 53 (1):154-159. doi:10.1016/j.bone.2012.11.041
13. Eller-Vainicher C, Filopanti M, Palmieri S, Ulivieri FM, Morelli V, Zhukouskaya VV, Cairolì E, Pino R, Naccarato A, Verga U, Scillitani A, Beck-Peccoz P, Chiodini I (2013) Bone quality, as measured by trabecular bone score, in patients with primary hyperparathyroidism. *Eur J Endocrinol* 169 (2):155-162. doi:10.1530/eje-13-0305