# Estimation of Bone microarchitecture Pattern from AP spine DXA scans using the Trabecular Bone Score (TBS): An added value in clinical routine for the patient. A short review.

D. HANS, R. WINZENRIETH

*Bone and Joint Department, Center of Bone Diseases, Lausanne University Hospital, Lausanne, Switzerland*

## SUMMARY

Hans D., Winzenrieth R.: **Estimation of Bone microarchitecture Pattern from AP spine DXA scans using the Trabecular Bone Score (TBS): An added value in clinical routine for the patient**

Intrinsically it is accepted that defining osteoporosis on the sole basis of bone mineral density (BMD) reached its limit. Indeed, the multifactorial aspect of this disease encourages the current definition of osteoporosis to evolve towards a complex risk model based on Clinical Risk Factor (CRF) and BMD. Considering these CRFs along with BMD in the assessment of fracture risk, increases the sensitivity of screening without sacrificing specificity. Whereas part of the limit of the current use of DXA is currently being addressed by the concomitant use of CRFs it only partially takes into account the information of bone micro-architecture. Therefore, any additional information about micro-architecture would help to reduce the overlap between fracture and non-fracture subjects.

The *trabecular bone score* (TBS) is a novel grey-level texture measurement that is based on the use of experimental variograms of 2D projection images, and is able to differentiate between two 3-dimentional (3D) micro-architectures that exhibit the same bone density, but different trabecular characteristics. TBS measures the mean rate of local variation of grey levels in 2D projection images. The TBS is obtained after re-analysis of a DXA exam, and can be compared with BMD, since both evaluate the same region of bone. An elevated TBS reflects strong, fracture-resistant microarchitecture; a low TBS reflects weak, fracture-prone microarchitecture.

The added value of the TBS in bone mineral densitometry for fracture risk assessment has been documented in cross-sectional, prospective and longitudinal studies. Indeed, TBS has been found: 1) to be lower in post-menopausal women with a past osteoporotic fracture compared with age- and BMD-matched women without fracture; 2) to give an incremental increase in the odds ratio for spine fracture when combined with spine BMD; 3) to be lower in women with (versus without) fractures, irrespective of whether their BMD met the criteria for osteoporosis or osteopenia; 4) to prospectively predict facture as well as spine BMD; 5) recapture around 1/3 of the miss-classified fracture according to the BMD WHO definition of osteoporosis alone; and 6) to react differently according to the type of bone therapy.

The aim of this short review is to report the current clinical studies as well as to position TBS in clinical routine to complement BMD in the light of its current validation.

*Keywords: osteoporosis, fracture risk, bone mineral density, trabecular bone score, bone quality, microarchitecture, clinical risk factors*

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**Address:** Dr. Didier Hans, Center of Bone Diseases – Bone and Joint Department, Lausanne University Hospital, Av. Pierre-Decker 4, 1011 Lausanne, Switzerland, e-mail: didier.hans@ascendys.ch / didier.hans@chuv.ch

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## Bone Microarchitecture: the missing link in clinical routine

The 1993 Consensus Development Conference defined Osteoporosis as "a systemic skeletal disease characterized by a low bone mass and a micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture". Osteoporosis has emerged as a major health concern in almost all industrialized countries [1–3], with up to 9 million new osteoporotic fractures expected each year [4]. The mortality rate associated with hip and spine fractures can exceed 20 % [5,6]. In the United States, osteoporosis affects as many as 4–6 million post-menopausal women [7], with 2 million fractures occurring annually [8]. Up to 10 % of women in their fifties have already experienced an osteoporotic fracture [9]. Other investigators have identified significant osteoporosis risks in men, as well [10,11]. Moreover, given steady increases in the life-spans of both men and women, these numbers have been projected to double over the next 40–50 years [12]. Bone mineral density (BMD), measured by dual x-ray absorptiometry (DXA), has been the gold standard for osteoporosis diagnosis in the absence of established fragility fractures [13] BMD is one of the major determinants of bone strength and fracture risk [14], but there is considerable

overlap (up to 40 %) exists in BMD values between individuals who develop fractures and those who do not [15]. Other factors influence bone strength and fracture risk, including the macro-geometry of cortical bone, the micro-architecture of trabecular bone, bone micro-damage, mineralization, and turnover [16,17].

In recent years, a number of developments have contributed to bone micro-architecture assessment techniques. Among the non-invasive techniques, (peripheral-) quantitative computed tomography (p-QCT, QCT, flat-panel volume CT) [18,19] and magnetic resonance imaging (MRI) [20] allow for the direct or indirect measurement of bone micro-architecture, and both have benefited from significant enhancements in acquisition technology and/or image analysis. Nonetheless, these two techniques remain impractical for the routine screening and clinical management of osteoporosis, due to high costs and patient inconvenience, as well as their availability for such diseases. Histomorphometric assessment of iliac crest bone biopsies remains the gold-standard method for the direct assessment of bone micro-architecture, but this technique is invasive and not directly 3D. A major challenge, therefore, has been to develop some novel technique that allows for the efficient, non-invasive clinical evaluation of bone micro-architecture status. Two-dimensional (2D) X-ray based images, like plain radiographs, have been investigated widely as a more practical alternative for the non-invasive and indirect assessment of bone micro-architecture. Different grey-level features have been explored, including fractal dimension and Fourier analysis, among others [21–26].

Over the past several years, DXA technology has advanced dramatically, in terms of both its hardware and software components [27]. Recent generations of DXA systems provide not only accurate and reproducible measurements of BMD, but also the opportunity to use high-quality DXA scans in place of standard X-rays to confirm and characterize existing vertebral fractures. Hence, Genant's indices of vertebral fracture [28,29] and certain indices related to hip geometry [30,31] can be evaluated directly from high-quality DXA images. More recently, a new application called hip structure/hip strength analysis (HSA) allows us to obtain information related to bone strength of the proximal femur [32,33]. These macroscopic geometrical measurements constitute risk factors that are independent of BMD, and the ability to obtain them from the same DXA examination is an additional advantage. Langton et al. [34] have developed a new technique, called finite element analysis of X-ray images (FEXI), which uses a finite element analysis model applied to DXA grey-level images. This technique permits the evaluation of a new DXA-based measure: 'FEXI stiffness'. Boehm et al. [35] introduced an algorithm to evaluate hip-DXA-scans using quantitative image analysis procedures based upon Minkowski Functionals. This new DXA-based measure considers bone mineral distribution in the proximal femur, instead of just bone mineral density, and may be well-suited to enhance standard densitometric evaluations as a predictor of hip fracture risk.

Clearly, developing a novel technique for the efficient, non-invasive clinical evaluation of bone micro-architecture remains both crucial and challenging. The *trabecular bone score* (TBS) is a novel grey-level texture measurement that is based on the use of experimental variograms of 2D projection images, and is able to differentiate between two 3-dimentional (3D) micro-architectures that exhibit the same bone density, but different trabecular characteristics [36–39].

The aim of this short review is to share the current clinical studies that demonstrate that TBS identifies retrospectively and prospectively those at risk for fractures, regardless of their BMD; and the combination of TBS and BMD potentiates fracture risk detection. From the current level of validation, we will suggest potential use of TBS in clinical routine to complement BMD.

## What is the Trabecular Bone score (TBS)?

TBS development is based upon the following facts:

- A healthy patient has well-structured trabecular bone at the vertebral level. This signifies that his trabecular structure is dense (i.e., high connectivity, high trabecular number, and small spaces between trabeculae). If we project this structure onto a plane, we obtain an image containing a large number of pixel value variations, but the amplitudes of these variations are small.
- Conversely, an osteoporotic patient has an altered trabecular bone structure. This signifies that his trabecular structure is porous (i.e., low connectivity, low trabecular number, and wide spaces between trabeculae). If we project this structure onto a plane, we obtain an image containing a low number of pixel value variations, but the amplitudes of these variations are high.

Consequently, if we can identify a method that differentiates these two types of structure, we can obtain a way to describe a 3D structure from the existing variations in its projected image.

One way to achieve this is to calculate the variogram of the trabecular bone projected image, since it is calculated as the sum of the squared grey level differences between pixels at a specific distance. As such, TBS is a new, grey-level texture measurement that is derived from the exploitation of experimental variograms of 2D projection images. Although a beta version of the concept of TBS has been published previously [36], major improvements have been made and inaccuracies in the process are now corrected and re-explained in more recent studies [37–39]. In brief, TBS is a patented black box algorithm using the variogram after its log-log transformation. TBS is calculated as the slope of the log-log transform of this variogram. This slope characterises the rate of grey level amplitude variations into the trabecular bone. Certain black-box differences render TBS not an H (Hurst parameter) estimator.

TBS can be retrospectively applied to an existing DXA exam, without the need for any further imaging, and can be compared directly with BMD, since both evaluate the same region of bone (in 30 seconds time with neither additional exam nor radiation for the patient – Software TBS iNsight® – Med-Imaps SA, France).

## What does TBS measure?

In previous studies, significant correlations between TBS – as evaluated from simulated 2D-projection µ-CT

images – and standard 3D parameters of bone micro-architecture –evaluated using high-resolution µ-CT reconstructions – in sets of human vertebral bone pieces were identified [36–39]. At 93 µm plane resolution, strong significant correlations have been obtained between TBS and Parfitt's micro-architecture parameters, such as with connectivity density ($0.856 \leq r \leq 0.862$; $p < 0.001$), trabecular number ($0.805 \leq r \leq 0.810$; $p < 0.001$) and trabecular space ($-0.714 \leq r \leq -0.726$; $p < 0.001$) regardless of the X-ray energy used for the projection [38]. Moreover, using multiple linear regression analysis, a significant correlation was found between TBS and the combination of two 3D characteristics of bone microarchitecture: bone volume fraction (BV/TV) and an estimation (given the resolution) of the trabecular thickness (TbTh). It appears that using TBS accurately differentiates between two 3D samples in which the amount of bone is identical, but trabecular characteristics differ, as in the number (TbN) or the estimate of trabecular thickness (TbTh) or separation between trabeculae (TbSp). On the other hand, the effects of image resolution degradation (from 93 to 1 488 µm plane resolution) and noise have been studied [39] using µ-CT images. Significant correlations were obtained between TBS and 3D micro-architecture parameters, regardless of image resolution, up to a certain level. Strong correlations were obtained with ConnD ($0.843 \leq r \leq 0.867$), TbN ($0.764 \leq r \leq 0.805$) and TbSp ($-0.701 \leq r \leq -0.638$), and those up to a resolution of 744 µm. It has been shown that it is possible to estimate bone microarchitecture status derived from DXA imaging using TBS. Indeed, this 3D µ-CT approach has been validated ultimately on DXA images acquisitions with similar level of correlation [37]. The detected correlations between TBS and 3D parameters of bone micro-architecture are mostly independent of any correlation between TBS and BMD.

In summary, an elevated TBS reflects strong, fracture-resistant microarchitecture; a low TBS reflects weak, fracture-prone microarchitecture. TBS is therefore not a physical measurement but rather an index of the trabecular pattern of the measured bone.

## Does TBS discriminate osteoporotic fractured subjects from controls?

The added value of the TBS in bone mineral densitometry for fracture risk assessment has been documented in several cross-sectional studies [40,44]. Indeed, TBS has been found: 1) to be lower in post-menopausal women with a past osteoporotic fracture compared with age- and BMD-matched women without fracture [40]; 2) to give an incremental increase in the odds ratio for spine fracture when combined with spine BMD [41–44]; and 3) to be lower in women with (versus without) fractures, irrespective of whether their BMD met the criteria for osteoporosis or osteopenia [41–44].

In the first multi-centric study [40], consisting of 45 women with major osteoporotic fractures and 155 women matched for age and spine BMD without a fracture (all BMD zone considered), total spine TBS was significantly lower between those with and without fractures, when one considered: 1) all types of fractures combined (OR = 1.95 [1.31–2.89] per SD decrease [95% CI]; p = 0.0005) and 2) vertebral fractures alone (OR = 2.66 [1.46–4.85]; p = 0.0004). Such results were very encouraging for TBS since the discriminatory effect was independent of site matched BMD thus suggesting the added value of TBS over the BMD. The added effect has been further demonstrated by several other studies [41–44]. In the study of Rabier et al. [41], 42 women with osteoporosis-related vertebral fractures were compared with 126 age-matched women without any fractures (1 : 3). All subjects had a low bone density (T-score ≤ –1).The odds of vertebral fracture were 3.20 [2.01–5.08] for each incremental decrease in TBS, 1.95 [1.34–2.84] for BMD, and 3.62 [2.32–5.65] for BMD + TBS combined. The AUC (area under the curve) was significantly greater for TBS than for BMD (0.746 vs. 0.662, p = 0.011). At iso-specificity (61.9 %) or -sensitivity (61.9 %) for both BMD and TBS, TBS + BMD sensitivity or specificity was 19.1 % or 16.7 % greater than for either BMD or TBS alone. Among subjects with osteoporosis (n = 117, 31 fractured subjects) both BMD (p = 0.0008) and TBS (p = 0.0001) were lower in subjects with fractures, and both OR and AUC (p = 0.013) for BMD + TBS were greater than for BMD alone (OR = 4.04 [2.35–6.92] vs. 2.43 [1.49–3.95] and AUC = 0.835 [0.755–0.897] vs. 0.718 [0.627–0.797] respectively). Among subjects with osteopenia (n = 51, 11 fractured subjects), TBS was lower in women with fractures (p = 0.0296) while no difference was obtained for BMD (p = 0.75). Similarly, the OR for TBS was statistically greater than 1.00 (2.82 [1.27–6.26]), but not for BMD (1.12 [0.56–2.22]), as was the AUC (p = 0.035), but there was no statistical difference in specificity (p = 0.357) or sensitivity (p = 0.678). In another study, Winzenrieth et al. [42] assessed whether the trabecular bone score (TBS), determined from grey level analysis of DXA images, might be of any diagnostic value, either alone or combined with bone mineral density (BMD), in the assessment of vertebral fracture risk among post-menopausal women with osteopenia. Out of 243 post-menopausal Caucasian women, 50–80 years old, with BMD T-scores between –1.0 and –2.5, we identified 81 with osteoporosis-related vertebral fractures, and compared them with 162 age-matched controls without fractures (1 : 2). Primary outcomes were BMD and TBS. For BMD, each incremental decrease in BMD was associated with an OR = 1.54 [1.17–2.03], and the AUC was 0.614 [0.550–0.676]. For TBS, corresponding values were 2.53 [1.82–3.53] and 0.721 [0.660–0.777]. The difference in the AUC between TBS and BMD was statistically significant (p = 0.020). The OR for (TBS + BMD) was 2.54 [1.86–3.47] and 0.732 [0.672–0.787] for the AUC. Furthermore, another group evaluated the ability of spine TBS to diagnose hip fracture [43]. The study group consisted of 83 hip fractured subjects (age = 69.8 ± 8.2 years, BMI = 26.2 ± 3.4 kg/m$^2$, Hip T-score = –2.4 ± 0.6, 41 % with Hip T-score ≤ –2.5) and 108 control subjects (age = 64.9 ± 9.8 years, BMI = 27.2 ± 3.2 kg/m$^2$, Hip T-score = –1.2 ± 1.1). Significant lower spine BMD and spine TBS were found in fractured than in non-fractured women (p < .0001). Spine BMD and TBS diagnosed fractures equally well (AUC = 0.69 [0.62–0.76], OR = 2.20 [1.56–3.13] and AUC = .67 [0.60–0.73], OR = 2.05 [1.45–2.89] for BMD at spine and TBS respectively) and independently. After adjustment for age, BMD and TBS re-

mained significant for femoral neck fracture diagnosis (OR = 1.94 [1.35–2.79] and 1.71 [1.15–2.55] respectively). In multivariate analysis, using backward analysis, Spine BMD and TBS remained significant co-factors (p = 0.001 and p = 0.007 respectively) to explain hip neck fracture whereas, age, BMI and weight were excluded (p > 0.1). BMD + TBS model was associated with more than doubling of the odds 2.39 [1.70–3.37] for hip neck fracture.

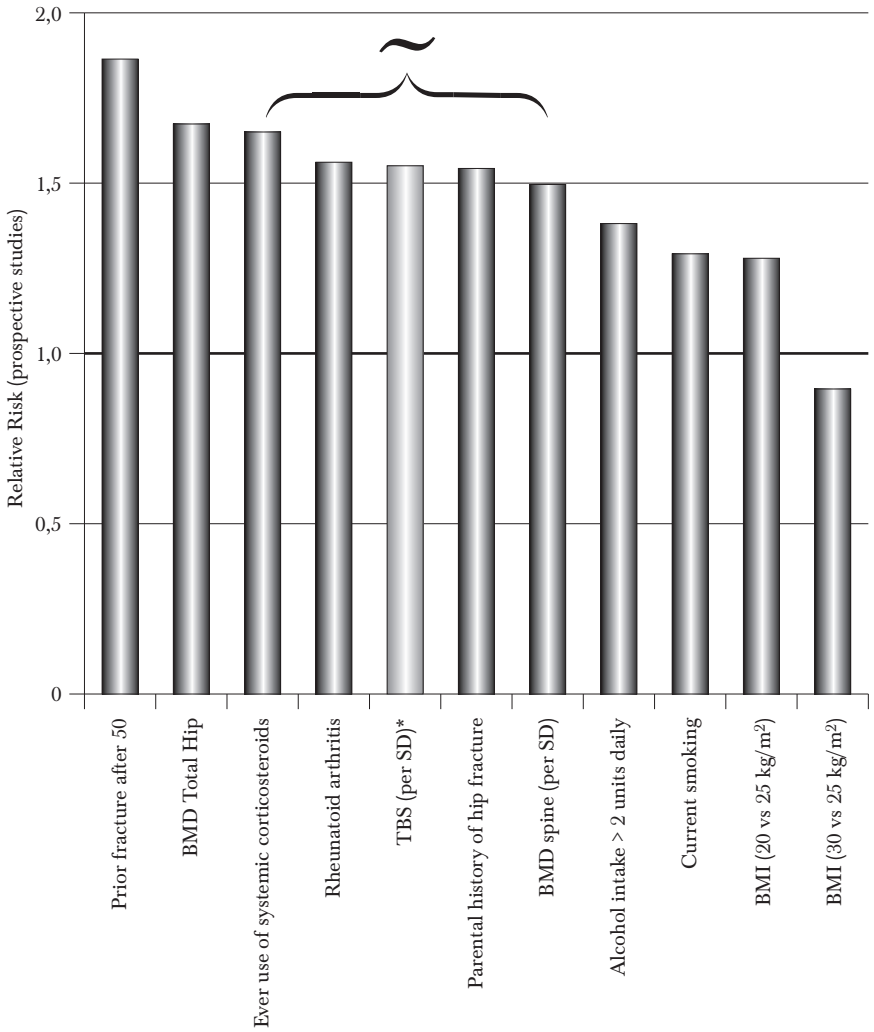
Finally in a more recent study, Colson et al [44] studied the ability of spine TBS to diagnose vertebral fracture in a population of osteopenic subjects on a new generation bone densitometer. Their study groups were consisted of 29 fractured subjects (age = 70.3 ± 8.4 years, BMI = 25.1 ± 3.9 kg/m$^2$) and 87 control subjects (age = 68.5 ± 6.5 years, BMI = 23.3 ± 3.4 kg/m$^2$) matched for age (p = 0.240). A weak correlation was obtained between TBS and BMD and between TBS and BMI (r = 0,241 and r = –0,305, respectively, p < 0.01). The average value of TBS and BMI between the control and fractured group were significantly different (p = 0.002; TBS = 0.070 and p = 0.02; IMC = 1.7 kg/m$^2$ respectively), whereas no difference between groups was obtained for BMD (p = 0,490; ΔDMO = –0.02 g/cm$^2$). The OR per standard deviation and the AUC were OR = 1.98 [1.25–3.12] and 0.68 [0.589–0.765] for TBS, respectively. After BMI adjustment, TBS remains significant (OR = 1.77 [1.10–2.83]). Their study further confirmed the potential of TBS to discriminate healthy from fractured osteopenic subjects using new generation bone densitometer image (iDXA, GE Healthcare Lunar – USA).

All these studies showed the established potential of TBS to discriminate healthy from osteoporotic fractured subjects at hip, spine and all major skeletal sites irrespectively of the level of BMD and independently of the BMD itself.

## Does TBS predict osteoporotic fractures?

In addition of the discriminatory ability, the added value of the TBS in bone mineral densitometry for fracture risk assessment has been documented in prospective studies [45,46]. Indeed from the Manitoba study [45] out of 29,407 women ≥ 50 years, Osteoporotic fractures were identified in 1,668 (5.7 %) women including 439 (1.5 %) spine and 293 (1.0 %) hip fractures (mean follow-up 4.7 years). Significantly lower spine TBS and BMD were identified in women with major osteoporotic, spine and hip fractures (all p < .0001). Spine TBS and BMD predicted fractures equally well, and the combination was superior to either measurement alone (p < 0.001). For each SD decline in total hip BMD there was a 67 % increase in the age-adjusted hazard of any major osteoporotic fractures, versus 47 % with the lumbar spine BMD and 35 % with lumbar spine TBS. The combined model for total hip BMD and lumbar spine TBS showed a significant (76 % increase in the age-adjusted hazard) improvement in fracture prediction compared with models based upon either BMD or TBS alone (p < 0.0001). The same pattern was seen for models combining lumbar spine BMD and lumbar spine TBS, with the combined model again superior to either BMD or TBS alone (p < 0.0001). Women were stratified according to lumbar spine TBS (tertiles) and lumbar spine BMD category (normal, osteopenia, osteoporosis). A consistent trend of lower fracture rates with higher TBS scores, overall and for specific levels of BMD, was seen for the lumbar spine, total hip, femoral neck and minimum T-score (all p < 0.05). For all women combined, OR for fracture for the lowest TBS tertile compared with the middle tertile was 1.57 [1.46–1.68] and for the lowest TBS tertile compared with the highest tertile was 2.88 [2.74–3.01]. Within the osteopenia

Fig. 1
Average Relative risk of major osteoporotic fractures per standard deviation or presence/non presence for major clinical risk factors (from meta-analysis). TBS displayed similar predictive value than the most common major CRF.



subgroup (whether defined from minimum T-score or individual BMD sites), the OR for fracture for the lowest TBS tertile compared with the highest tertile was consistently greater than 2. The authors concluded that spine TBS predicts osteoporotic fractures and provides information that is independent of spine and hip BMD. Combining the TBS trabecular texture index with BMD incrementally improves fracture prediction in postmenopausal women.

Such findings have been confirmed by another independent study [46]. The aim of their study was to assess the ability of TBS to predict incident fracture and improve the classification of fracture prospectively in the OFELY study. TBS was assessed in 564 postmenopausal women (66 ± 8 years old) from the OFELY cohort, who had a spine DXA scan between year 2000 and 2001. During a mean follow up of 7.8 ± 1.3 years, 94 women sustained a fragility fracture. At the time of baseline DXA scan, women with incident fracture were significantly older (70 ± 9 vs 65 ± 8 yrs), had a lower spine BMD (T-score: –1.9 ± 1.2 vs –1.3 ± 1.3, $p < 0.001$) and spine TBS (–3.1 %, $p < 0.001$) than women without incident fracture. The magnitude of fracture prediction was similar for spine BMD (OR = 1.6 [1.2–2.0]) and TBS (OR = 1.7 [1.3–2.1]). The authors concluded that spine BMD and TBS predicted fractures equally well and that combining the osteopenic T-score and the lowest TBS helped defining a subset of osteopenic women at higher risk of fracture.

## Does TBS improve fracture classification?

In both previous prospective studies, the authors studied the impact of TBS measurements subsequent to WHO BMD classification. In both studies, significant improvement has been reported. Indeed, in the Manitoba study [45], a sequential approach to risk reclassification using BMD followed by TBS was explored. Out of 321 (19 %) major osteoporotic fractures in women with normal lumbar spine BMD, 93 (30 %) occurred in the lowest TBS tertile, and 203 (63 %) in the lowest two tertiles. In addition, 635 (38 %) major osteoporotic fractures were identified in patients who had lumbar spine BMD in the osteopenic range, among whom 272 (43 %) had TBS in the lowest tertile and 501 (79 %) in the lowest two tertiles. Only 899 of 7,157 (12.6 %) of women with lumbar spine BMD in the osteoporotic range had TBS in the highest tertile and only 51 of 712 (7.2 %) of the fracture subjects had TBS in the highest tertile. TBS would have correctly reclassified 43 % of the fracture subjects found in the osteopenic BMD range (vs 30.5 % of non-fractured subjects) and 29 % in the normal BMD range (vs 20.2 % of non-fractured subjects). Overall, 365 (38 %) fracture subjects misclassified by lumbar spine BMD as non-osteoporotic according to the WHO definition were in the lowest TBS tertile suggesting poor microarchitecture. Similar results are found when using the minimum of the hip or spine T-scores for WHO classification instead of the lumbar spine alone. In the Ofely study [46] when using the WHO classification, 38 % of the fractures occurred in osteoporotic (fracture rate = 29 %), 47 % in osteopenic (fracture rate = 16 %) and 15 % in women with T-score > –1 (fracture rate = 9 %). By classifying their population in tertiles of TBS, they found that 47 % of the fractures occurred in the lowest tertile of TBS (fracture rate = 23 %) and 39 % of the fracture that occurred in osteopenic women were in the lowest tertile of TBS. Using similar approach (two steps classification process using T-score and TBS) and selecting subjects into the lowest tertile of TBS, Del Rio et al. [43], in a case-control study concerning subjects with and without femoral neck fracture and using TBS and BMD assessed at spine, correctly reclassified 25 % the overall fractured subjects for a cost of 13 % over-diagnosed control subjects.

While there is an improvement in the classification of fractured subjects, none of these studies worked on optimal thresholds and did not report the sensitivity and specificity. Further analyses are thus needed to really appreciate the level of clinical significance.

## Does TBS react to treatment?

As today very few studies have investigated the effect of treatment on spine TBS [47–49]. Theoretically, the TBS parameter, been influenced by the trabecular pattern, should be also influenced by treatments known to have effect on bone micro-architecture. From the conceptual point of few the reported precision [45] of TBS is sufficient to monitor such potential effect. Indeed the short-term reproducibilities are 2.1 % and 1.7 % for spine TBS and BMD respectively in 92 individuals with repeat spine DXA scans performed within 28 days and the normal "TBS bone loss" approximately 0.25 % per year [47]. Practically, Krieg et al. [48] investigated the effects of Antiresorptive Agents on Bone Micro-Architecture Assessed by Trabecular Bone Score in Women Age 50 and Older. It is known that antiresorptive agents such as bisphosphonates induce a rapid increase of BMD during the 1st year of treatment and a partial maintenance of bone architecture. From the BMD database for Province of Manitoba, Canada, they have selected women age > 50 with paired baseline and follow up spine DXA examinations who had not received any prior HRT or other antiresorptive drug. Women were divided in two subgroups: 1) those not receiving any HRT or antiresorptive drug during follow up (= non users) and 2) those receiving non-HRT antiresorptive drug during follow up (= users) with high adherence (medication possession ratio > 75 %) from a provincial pharmacy database system. Effects of antiresorptive treatment for users and non-users on TBS and BMD at baseline and during mean 3.7 years follow-up were compared. Results were expressed % change per year. A total of 1,150 non-users and 534 users met the inclusion criteria. At baseline, users and non-users had a mean age and BMI of (62.2 ± 7.9 vs 66.1 ± 8.0 years) and (26.3 ± 4.7 vs 24.7 ± 4.0 kg/m$^2$) respectively. Antiresorptive drugs received by users were bisphosphonates (86 %), raloxifen (10 %) and calcitonin (4 %). Significant differences in BMD change and TBS change were seen between users and non-users during follow-up ($p < 0.0001$). Significant decreases in mean BMD and TBS (–0.36 ± 0.05 % per year; –0.31 ± 0.06 % per year) were seen for non-users compared with baseline ($p < 0.001$). A significant increase in mean BMD was seen for users compared with baseline (+1.86 ± 0.14 % per year, $p < 0.0018$). TBS of users also increased compared with baseline (+0.20 ± 0.08 % per year, $p < 0.001$), but more slowly than BMD. In conclusion, they observed a significant

increase in spine BMD and a positive maintenance of bone micro-architecture from TBS with antiresorptive treatment, whereas the treatment naïve group lost both density and micro-architecture.

Two other pilot studies (data not published yet – in house data) reported the effect of strontium ranelate (Sr) and Parathyroid Hormone (PTH) Spine TBS and BMD. The first study is based on 24 women under strontium ranelate (correction for atomic number has not been performed). After 24 months follow-up, the mean Spine BMD and TBS parameters increased by 13 % and 5 % respectively the TBS measurements. No significant correlation between delta BMD and TBS was seen, demonstrating an independent effect of the strontium of both BMD and microarchitecture. The second study is based on 24 women under PTH. However since we have different follow-up period we have standardized the delta change of BMD and TBS per year. In average we observed a significant increase of Spine BMD of 5.4 % per year and of 2.2 % per year for Spine TBS. Again the Correlation between delta BMD and TBS was not significant (R2 = 4 %) suggesting that PTH is acting differently on BMD and TBS.

Maury et al. [49] reported a surgical treatment. Indeed they have studied the evolution of BMD and TBS parameters assessment at spine in patients with primary hyperparathyroidism (PHPT) before and one year after parathyroidectomy. PHPT is a very common endocrinopathy which is often diagnosed during a biological exploration in osteoporotic patients and is considered as a frequent cause of secondary osteoporosis. They have reported a longitudinal study on 29 PHPT Caucasian postmenopausal women with mean age and BMI of 62.1 ± 10.4 years and 25.5 ± 6.5 kg/m$^2$ respectively who were all operated on. Before PTX, all patients had a measurement of serum total and ionized calcium, phosphate, PTH, C-telopeptide of type 1 collagen (CTX), as well of 24-hour urine calcium and phosphate reabsorption rate (TRP). BMD and TBS were evaluated at AP Spine (L1-L4) with DXA Prodigy (GE-Lunar), QDR 4501 (Hologic), and TBS iNsight® (Med-Imaps) within 6 months before PTX, and one year after PTX. Both DXA were cross-calibrated using a custom-made phantom. Correlations (Spearman rank test) were evaluated between pre-surgery BMD or TBS or their difference during the study period, and biological variables independently of each other. Differences between pre-PTX and post PTX values were assessed with the Wilcoxon rank test for paired data. Before PTX, BMD and TBS were tightly correlated ($p < 0.0001$), TBS explaining 45 % of BMD. Before PTX, neither BMD nor TBS was correlated with any of the biological parameters. After PTX, BMD and TBS increased by 4.7 ± 5.4 % and 1.6 ± 4 % respectively, without correlation between BMD gain and TBS gain. Pre-PTX serum total calcium was correlated ($p = 0.035$) with the BMD gain one year post-PTX. No other correlation was found between pre-PTX biological parameters and the post-PTX change in BMD or TBS. Their study was the first to report data on changes in spine BMD and bone microarchitecture assessed both by DXA in PHPT women after PTX. Consistent with previously published data, spine BMD increased after PTX, while TBS increased more slightly. This last result is consistent with what was published when iliac crest biopsies were analyzed longitudinally post-PTX, i.e. an increased in trabecular thickness and trabecular space.

The overall results are encouraging but clearly need further evaluation from double blind placebo control studies. The advantage for TBS is that it can be retrospectively assessed. As such, most of the past and current large clinical trials can be investigated to demonstrate the effect of different drugs affecting bone metabolism on spine TBS.

## Can TBS be useful in secondary osteoporosis?

Secondary osteoporosis may arise either as a result of the effects of underlying disease or as a result of the treatment of such diseases (e.g. with glucocorticoids). In fact, most of the time, secondary osteoporosis is a result of combinations of risk factors and chronic diseases associated with their treatment. The impact of these risk factors, treatments and diseases on bone density is usually well documented while studies demonstrating the impact on bone microarchitecture are patchier. Nevertheless it is hypothesized that such impact on bone microarchitecture would be more important than on BMD alone. For example, long term glucocorticoids (GCs) therapy induces a rapid bone loss and increases the fracture risk independently of BMD [50]. Such mechanism could be related to bone microarchitecture alteration as described by histomorphometric parameters.

Colson et al. [51] studied the trabecular bone microarchitecture alteration in Glucocorticoids Treated Women in Clinical Routine. TBS and BMD of AP spine were evaluated in 136 women, 45 to 80 years old, receiving GCs (≥ 5 mg/day, for 1 year and over). They showed that GCs-treated patients were characterized by a 4 % decrease of TBS ($p < 0.0001$) compared with the aged-matched normal values while no change in BMD was observed ($p = 0.49$). Similar results were found even at 5 mg/d of GCs (–3.5 % of TBS, $p = 0.0012$). This microarchitecture degradation was confirmed whatever the level of BMD. Indeed, TBS decreased by 5.7 % ($p < 0.0001$) and 2.9 % ($p < 0.003$) in osteoporotic (according to WHO criteria) and osteopenic women, respectively. Furthermore these findings were even more marked when fracture status and number were taken into account. They observed a decrease of 3.4 % of TBS for the non-fractured GCs-patients ($p = 0.0001$), 6.2 % ($p = 0.0007$) for OVF (≥ grade 2), 4.6 %, ($p < 0.035$) for one OPF and 7.8 % ($p < 0.002$) for 2 OPFs and over. Moreover the age-adjusted Odd Ratio (OR) for TBS is 1.60 [1.04–2.47] for OPF and 1.62 [1.02–2.59] for OVF, whereas no significant OR were found for BMD (1.47 [0.96–2.26] and 1.56 [0.97–2.51], for OPF and OVF, respectively).They concluded that GCs-treated women have a significant deterioration of bone microarchitecture as assessed by TBS which worsen with the presence, the type and number of fracture, and thus independently of the BMD level. TBS method seems to be a good surrogate non-invasive technique in assessing vertebral microarchitecture in clinical routine for GCs-treated patients.

Breban et al. [52] studied the combination of TBS and BMD for vertebral fracture risk detection in a rheumatoid arthritis (RA) population treated (CS) or not (NCS) with glucocorticoids. They had 140 women aged 55.9 ± 14.0

years, with RA since 15.2 ± 10.2 years; 94 were receiving glucocorticoids (mean dose of 6.7 ± 4.7 mg/day) and 129 a disease modifying drug. Vertebral fractures from T4 to L4 were evaluated using Vertebral Fracture Assessment (VFA) software on DXA device. The mean spine and hip T-scores were –0.9 ± 1.4 and –1.6 ± 1.0, and –0.8 ± 1.5 and –1.5 ± 1.1, in patients with and without CS respectively. There was no difference in BMD between both groups, but TBS was 1.19 ± 0.11 and 1.23 ± 0.09 in CS and NCS groups respectively (p = 0.03). In the whole population, AUC in the vertebral fracture risk prediction was higher in the TBS model (0.736) compared to the BMD model (0.670 for spine BMD; 0.705 for hip BMD; 0.708 for femoral neck BMD). They have calculated a threshold of TBS (1.173) which corresponds to the best sensitivity (75 %) and specificity (66 %) according to ROC curves. Among patients without osteoporosis (n = 97), 13 had vertebral fractures and 8 of them had a TBS lower than 1.173. They have concluded that TBS provides additional information compared to BMD alone in vertebral fracture risk assessment, in RA population, with or without glucocorticoids.

Maury et al. [53] assessed BMD and TBS parameters at spine in patients with anorexia nervosa (AN). They conducted a cross-sectional study on 73 AN young women with mean age and BMI of 21.3 ± 7.1 years and 15.8 ± 2.2 kg/m$^2$ respectively and 74 healthy young women with mean age and BMI of 21.3 ± 7.1 years and 21.6 ± 2.5 kg/m$^2$ respectively. Volumetric BMD (vBMD) and TBS were evaluated at AP Spine (L1-L4) with DXA Prodigy (GE-Lunar). Physical activity, the type of amenorrhea, the type of AN (restrictive rAN or binge-eating/purging bAN) effects on vBMD and TBS were assessed using group comparison. For AN subjects, TBS values and clinical variables were evaluated according to the presence or absence of low BMD defined as a Z-score ≤ –2 at lumbar spine. They obtained significant lower vBMD, TBS, weight, BMI, Fat Mass (FM) and Lean Mass (LM) in the AN group compared with the control group. For AN subjects, vBMD and TBS showed significant correlations (p < .05) with AN severity (weight; r = .27 – .59) while FM and LM were only correlated with TBS (r = .30 and r = .56 respectively). They also found that those who practice physical activities (49 %) have significantly higher vBMD (p = .011) while no significant difference was obtained for TBS. In addition, they found that those who suffer from restrictive AN (70 %) have significant lower TBS (worse microarchitecture; p = .027) and weight (p = .026) than the binge-eating AN subjects, while vBMD did not show significant difference (p = .91). Finally, they have shown that subjects with low BMD (Z-score ≤ –2) had significant lower TBS, weight, lower weight ever and LM than the others (p < .05). Their results were consistent with the literature for vBMD and clinical variables. They concluded that TBS, as a microarchitecture parameter, could be a good surrogate marker used to evaluate severity and AN type.

## Is TBS affected by spine osteo-arthrosis?

Spinal osteo-arthrosis (OA) is a common disease in elderly people [54]. In later life, spine measurements are confounded by osteo-arthrosis whereas the hip is much less affected by these changes. It is well known that OA artificially increased DXA BMD measurement proportionally to its severity [55].

Effects of OA on TBS were evaluated by Winzenrieth et al. [56] in a cross-sectional study on 390 Caucasian subjects. Study group was composed of 141 cases presenting arthrosis (according to ISCD definition) only at L4 vertebra with mean age and BMI of 66.0 ± 8.3 years and 25.2.8 ± 3.5 kg/m$^2$ respectively and 249 control subjects free of arthrosis with mean age and BMI of 64.1 ± 6.9 years and 24.5.8 ± 3.4 kg/m$^2$ respectively. Cases were stratified using severity of arthrosis defined by the differences between L3 and L4 expressed in standard deviation of T-score (severity ranges between 1 to 3.5 T-score). In order to validate control and case groups, a comparison between BMD and TBS data of these groups at L1-L3 was done. In addition, TBS values of control subject were compared with French TBS normative data at L1-L4 [47]. BMD and TBS were evaluated at AP Spine (L1-L4) with DXA Prodigy (GE-Lunar) and TBS iNsight® (Med-Imaps). They found no significant differences between case and control groups for BMD and TBS at L1-L3. At L4 vertebral level, differences between case and control groups for BMD was significantly higher with an increase of 19 % in comparison with the control group value whereas no significant difference was obtained for TBS. They obtained a significant correlation between BMD a nd the severity of arthrosis (r = 0.503, p < 0.001) while no correlation was obtained for TBS (r = –0.067, p = 0.426).

This study had shown that OA and its severity had no significant effects on TBS whereas a stronger effect was obtained for BMD measurement. Thus, TBS could be used to assess bone microarchitecture even if in presence of OA.

## Can TBS be comparable to a major clinical risk factor (CRF)?

To really have an added value a clinical risk factor must be partially or totally independent of BMD and be predictable of osteoporotic fracture. Furthermore ideally you would like a CRF to be reversible (with / without treatment) and when possible quantifiable (e.g. the duration and dose of glucocorticoid). As today there is many recognized major clinical risk factors, the most important being previous fracture, family history of hip fracture, ever use systemic corticosteroids, current smoking, more than 2 unit per day of alcohol, rheumatoid arthritis, multiple fall …

Out of these factors many of them are in fact indirect surrogate factor of bone quality (e.g. independent of BMD), some of them are reversible but very few are quantifiable (mostly yes/no).

From the current studies, it has been demonstrated that TBS predict fracture independently of BMD (e.g. related to bone quality and trabecular pattern) and independently of the major CRF, is reversible under certain treatments, quantifiable. In addition in term of predictive power, TBS is very much comparable to most of the major CRF (*Fig 1*) and thus could be used as one of them.

## In conclusion

The Trabecular Bone Score is an indicator of the quality/pattern of the bone microarchitecture that wasn't availab-

le until now in clinical routine with no extra radiation for the patient. Therefore, TBS holds promise as a low-cost and easily applied adjunct to BMD testing in the assessment of fracture risk and identification of patient potentially misclassified by BMD alone. As such it more accurate in defining individual risk profile and thus selecting the most appropriate cost effectiveness solution for our patient. As today, while waiting for optimum clinical thresholds for TBS as well as official guidelines/endorsement of medical societies, it is scientifically proven that TBS can be used as an additional major Clinical risk factor. As such it should be easily integrated in current medical guidelines. However, current investigations of further use of TBS are underway and should be debated very soon.

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