TBS iNsight
to boost your DXA

The bone quality assessment technique for enhancing identification of fracture risk

Introduction

The World Health Organization defines osteoporosis as a silent disease characterized by low bone mass (bone density) and microarchitectural deterioration of bone tissue leading to increased bone fragility and elevated risk of fracture[1]. Worldwide, osteoporosis affects an estimated 200 million women and causes nearly nine million fractures annually[2, 3]. Globally, one in three women and one in five men over the age of 50 will experience a fracture due to osteoporosis[4, 5] with a subsequent decrease in quality of life and an excess mortality rate for hip fractures >20% in the first year[6]. By 2050, the worldwide incidence of hip fracture in women is projected to increase by 240%; and in men by 310%[7].

Bone densitometry (DXA: dual-energy x-ray absorptiometry) is accurate, painless and readily accessible in most communities. For these reasons, DXA has become well accepted as a standard tool for the assessment of osteoporosis. DXA utilizes x-rays of two distinct energies to provide quantitative information related to bone mineral density (BMD). However, this does not always sufficiently translate into an accurate estimate of future fracture risk.

Moreover, it is now well established that BMD is not the only characteristic of bone that determines its strength and fragility and, therefore other aspects must be considered when deciding upon therapy to prevent new or further osteoporotic fractures[8]. For example, it is well known that over 50% of fractures occur in patients with BMD values that are not classified as "osteoporotic" according to the WHO classification of osteoporosis (figure 1)[9]. This observation implies that factors other than BMD influence bone strength and fracture risk. These factors include bone macro-geometry, bone mineralization, and bone turnover[9, 10]. Another key determinant of bone strength is its micro-architecture, the importance of which has been increasingly appreciated in recent years, on top of the fact it was already implied from the conceptual definition of osteoporosis[10]. This acknowledgement has led to the recognition that evaluating bone micro-architecture might significantly enhance the accuracy of bone strength evaluations and, consequently, also of fracture risk[11, 12].

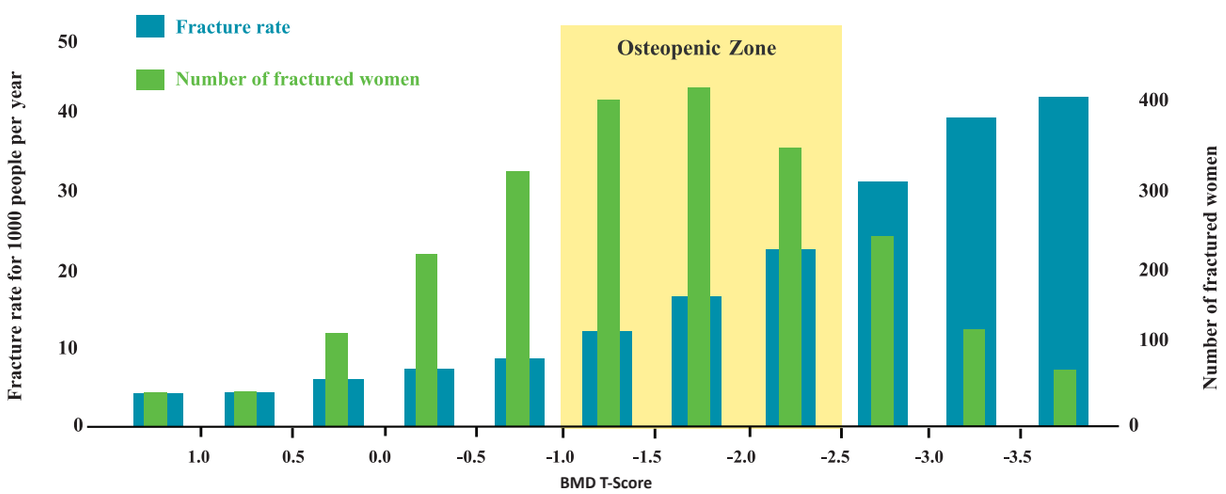

Figure 1: Over 50% of osteoporotic fractures occur in patients who are not classified in the "osteoporosis" category. Source: Siris et al. - The NORA cohort[9]

TBS iNsight: The Tool to Refine Patients' Risk Profile

TBS iNsight™ is a software tool that installs on most existing GE and Hologic DXA scanners. This simple, rapid and reproducible method estimates fracture risk based on a determination of bone texture (an index correlated to bone microarchitecture) [13, 14], in addition to risks determined by DXA based bone mineral density, clinical risk factors and FRAX. The result is expressed as a Trabecular Bone Score (TBS).

It requires no additional scan time or additional radiation exposure nor extra work for the technician. Once the standard DXA spine scan is completed, TBS results are displayed automatically within seconds. TBS iNsight enables retrospective analysis of older DXA scans (prior exams must be acquired on the same DXA unit with a valid TBS calibration).

How It Works

TBS is a texture index that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect yet highly correlated evaluation of trabecular microarchitecture [13-15].

Simply stated, TBS principles are based on the fractal property of 2D projected bone microarchitecture[16]. The DXA spine scan does not have sufficient resolution to identify individual trabeculae. However, a dense trabecular microstructure projected onto a plane generates an image containing a large number of pixel-to-pixel gray-level variations of small amplitude, whereas a 2D projection of a porous trabecular structure produces an image with a low number of pixel-to-pixel gray-level variations, but of much higher amplitude. In other words, different bone microstructures will appear differently on the DXA image and that difference is captured through the TBS analysis (figure 2).

A variogram of those projected images, calculated as the sum of the squared gray-level differences between pixels at a specific distance, can estimate a 3D structure from the existing variations on the 2D projected images. TBS is derived from the experimental variograms of 2D projection images. TBS is calculated as the slope of the log-log transform of the variogram, where the slope characterizes the rate of gray-level amplitude variations.

A steep variogram slope with a high TBS value is associated with better bone structure, while low TBS values indicate worse bone structure.

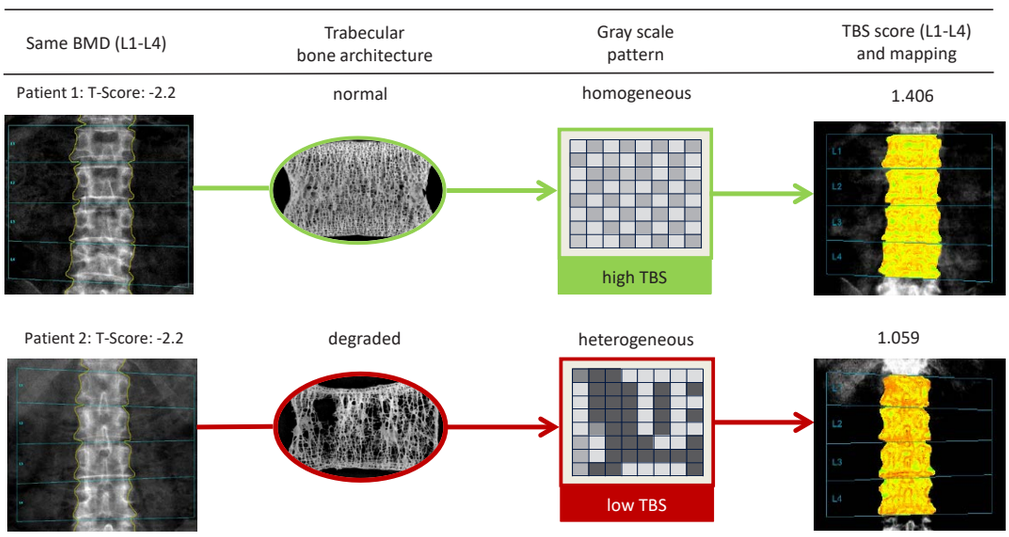

Figure 2: The TBS value is derived from an algorithm that analyzes the spatial organization of pixel intensity which corresponds to the differences in the X-ray absorption power of an osteoporotic bone versus a normal trabecular pattern [19]. Two patients can have similar BMD but could display different structure and subsequently have different fracture risk.

TBS Clinical Evaluation

TBS has been used in more than 400 peer-reviewed publications worldwide and on more than 75,000 patients to address several scientific and clinical questions. TBS has repeatedly been proven to be predictive of fragility fractures (current and future) and this largely independently of BMD, clinical risk factor and the FRAX based risk estimates; and, when used in conjunction with any one of these measures, it consistently enhances their accuracy. There is also a growing body of evidence indicating that the TBS has particular advantages over BMD for specific causes of increased fracture risk, like chronic corticosteroid use, type-2 diabetes, chronic kidney disease, primary hyperparathyroidism, patients being treated with anti-aromatase, conditions where BMD readings are often misleading [17, 18].

Some of the key findings have been conveniently summarized in recent review articles published by groups of international bone experts [17, 19-23]. A short list of pivotal studies is reported in table 1. The main points are summarized below:

- TBS is lower in men and postmenopausal women with prevalent vertebral, hip or major osteoporotic fractures compared to controls.
- TBS predicts incident major osteoporotic fractures, spine and hip fractures in women and men independently of both lumbar spine BMD measurements and clinical risk factors; TBS is therefore complementary to these existing approaches. The greatest utility lies in individuals whose BMD levels are in the osteopenic range.
- TBS can be used as an adjustment parameter of the FRAX tool to better predict osteoporotic fractures in conjunction with other clinical risk factors [figure 5]. Added to the FRAX, the TBS's greatest utility lies in individuals whose BMD levels are close to an intervention threshold (up to 25% of the patients will then be impacted).
- From a meta-analysis including 14 prospective cohorts [24], TBS thresholds have been evaluated based on a tertile approach. In the high-risk tertile (TBS < 1.23), gradient of risk for major osteoporotic fracture was more than two times greater than in the low-risk tertile (TBS > 1.31) [figure 4].
- TBS can be used as an aid in the diagnosis of osteoporosis and other medical conditions leading to altered trabecular bone microarchitecture, and ultimately in the assessment of fracture risk. Diseases of interest include diabetes, hyperparathyroidism, HIV, chronic kidney disease or patients under glucocorticoid use or under anti-aromatase treatment [20].
- The short-term reproducibility of TBS measurements has been reported in several studies with values ranging from 1.1% - 2.1% C.V [19];
- Although BMD is more reactive (in amplitude) to the different treatments affecting bone metabolism, the differential effect of these different pharmaceuticals on TBS may have its usefulness in routine clinical practice. As such, TBS may assist physicians in monitoring the response to treatments over time [table 3, figure 6].
- Unlike BMD, TBS results have been demonstrated to be minimally affected by the presence of osteophytes – a common artifact in late postmenopausal patients and those presenting with osteoarthritis [25];
- TBS has been endorsed by many local, national and international medical societies [table 2].

Condition	Study	Cohort	Key Findings
Primary osteoporosis	Hans et al. 2011 [26]	29,407 women followed for 4.7 years. Osteoporotic fractures were identified in 1668 women including 439 spine and 293 hip fractures.	- TBS predicts incident fractures as well as lumbar spine BMD, and the combination was superior to either measurement alone ($p<0.001$). - Incremental improvement in the performance of the combination of BMD and TBS remained significant even after adjustment for multiple clinical risk factors.
	Briot et al. 2013 [27]	Subset of 1,007 women aged over 55 recruited in 5 centers over 6 years. 82 subjects had incident clinical osteoporotic fractures and 46 with incident radiographic vertebral fractures.	- Performance of TBS was significantly better than BMD for prediction of incident clinical osteoporotic fractures. - For radiographic vertebral fractures, TBS and BMD had similar predictive power but the combination of TBS and BMD increased the performance over BMD alone.
	Iki et al. 2014 [28]	665 women aged 50 years and older followed over 10 years. 92 women suffered incident vertebral fractures.	- Lower TBS was associated with higher risk of vertebral fracture over 10 years independent of BMD and clinical risk factors (including prevalent vertebral deformity). - TBS could effectively improve fracture risk assessment in clinical settings.
	Leslie et al. 2014 [29]	3620 men aged ≥50 (mean 67.6 years) at the time of baseline DXA were identified from a database. Mean follow up was 4.5 years. 183 (5.1%) men sustain major osteoporotic fractures (MOF), 91 (2.5%) clinical vertebral fractures (CVF), and 46 (1.3%) hip fractures (HF)	- TBS predicted MOF and HF (but not CVF) in models adjusted for FRAX without BMD and osteoporosis treatment. - TBS remained a predictor of HF (but not MOF) after further adjustment for hip BMD or spine BMD.
	McCloskey et al. 2015 [24]	14 prospective population-based cohorts; 17,809 men and women; from 50 years; mean follow-up of 6.7 years. 1109 incident major osteoporotic fractures and 298 hip fractures were recorded.	- TBS predicts osteoporotic fracture independently of BMD and FRAX whatever the type of the fracture and the gender - TBS enhances the fracture risk prediction from the widely used FRAX tool - TBS can be used as an adjustment parameter of FRAX - TBS thresholds obtained are similar for both men and women: low TBS threshold is 1.230 and high TBS threshold is 1.310.
Diabetes	Leslie et al. 2013 [30]	29,407 women 50 years old and older with baseline DXA examinations, among whom 2356 had diagnosed diabetes.	- Diabetes was associated with higher BMD at all sites but lower lumbar spine TBS in unadjusted and adjusted models (all $P < .001$). - Lumbar spine TBS was a BMD-independent predictor of fracture and predicted fractures in those with diabetes (adjusted hazard ratio 1.27, 95% CI 1.10-1.46) and without diabetes (hazard ratio 1.31, 95% CI 1.24-1.38)
	Iki et al. 2017 [31]	1683 men (age, 72.9±5.2 years) were analyzed and classified with type 2 diabetes mellitus (313) or not (1370).	- Fasting plasma glucose, hemoglobin A1c and homeostasis model assessment-insulin resistance levels (HOMA-IR) were significantly and inversely correlated with TBS after adjusting for age, BMI and BMD. - Multivariate linear regression analyses revealed that glycemic indices were significantly associated with increased BMD and decreased TBS, and that HOMA-IR was associated only with TBS.
Glucocorticoid use	Leib and Winzenrieth 2016 [32]	1520 men and women aged 40 years and over including 416 subjects who received GCs (>/=5 mg/day, for >/=3 months) and 1104 sex-, age-, and BMI-matched control subjects.	- GC-treated individuals have a significant deterioration of bone microarchitectural texture as assessed by TBS which is more marked in those with osteoporotic fractures and in men. - TBS seems to be more sensitive than BMD for GC-related fracture detection and should be a good surrogate indicator of bone health in such secondary osteoporosis.
Anti-aromatase treatment	Hong et al. 2017 [33]	321 breast cancer patients under anti-aromatase treatment	- Long-term adjuvant AI treatment negatively influenced bone quality in addition to BMD in patients with breast cancer.

Condition	Study	Cohort	Key Findings
Endocrine disease	Eller-Vainicher et al. 2016 [34]	92 patients with primary hyperparathyroidism (PHPT) (74 females, age 62.1+/-9.7 years) and 98 control subjects	- PHPT patients had significant lower TBS and higher vertebral fractures prevalence (43.5%) than controls. - TBS was associated with vertebral fractures (odds ratio 1.4, 95% CI 1.1-1.9, P=0.02), regardless of BMD, age, BMI and gender.
	Hwangbo et al. 2016 [35]	1376 euthyroid subjects (648 postmenopausal women and 728 men) were recruited from a community-based cohort in Korea	- Higher free thyroxine levels within the normal reference range are associated with deterioration of trabecular microarchitecture in healthy euthyroid postmenopausal women.
Chronic Kidney Disease	Naylor et al. 2017 [36]	1426 participants from the community-based Canadian Multicentre Osteoporosis Study were included, aged 40 years or older (mean age of 67 years). 103 incident fragility fractures were recorded during a 4.7 years follow-up.	- The association between trabecular bone score and fracture was independent of BMD and other clinical risk factors in adults with reduced and normal kidney function.
HIV	Ciullini et al. 2017 [37]	141 HIV-infected patients (87% males, median age 43 years, 94% on stable antiretroviral therapy with undetectable viral load) underwent viro-immunological and bone metabolism biochemical screenings.	- No significant differences were found stratifying vertebral fractures prevalence by BMD, whereas patients with lower TBS showed a higher prevalence of vertebral fractures (p = 0.03). - In multivariate analysis, TBS was the only factor significantly associated to vertebral fractures (OR = 0.56; 95% CI = 0.33-0.96; p = 0.034), with increased fracture risk for lower TBS values.
Osteoarthritis	Kolta et al. 2014 [25]	1,254 postmenopausal women (66.7 ± 7.1 years) including 727 with 6-year follow-up.	- In postmenopausal women, lumbar osteoarthritis leads to an increase in BMD. In contrast, spine TBS is not affected by lumbar osteoarthritis

Table 1: Summary of some clinical studies evaluating TBS clinical added value

Recommendation of TBS in guidelines

More than 12 national & international medical societies and working groups have evaluated the role of TBS according to a review of the scientific literature. Table 2 reports the main works currently available in 2018. TBS has also been included in 2 guidelines referring to the management of hyperparathyriodism [22, 23].

TBS in national and international society guidelines			
	Acknowledge TBS as valuable technology	Recommendation to use TBS	Year
US		ISCD [12]	2015
Switzerland		SVGO [38]	2015
France		GRIO [40]	2018
Italy	SIOMMS [39]		2017
UK		NOGG [41]	2017
Germany		DVO [42]	2018
Spain		SEEN [43]	2018
Russia		РАОП and РАЭ [44]	2018
South Africa	NOFSA [45]		2018
Worldwide		IOF/ESCEO [11]/ ISCD [12]	2015

Table 2: Summary of principal recommendations to use TBS

Possible Interpretation of TBS values in overall patient management

The TBS report is generated simultaneously with the standard DXA spine printout. The report (figure 3) shows an overall Trabecular Bone Score, displays the TBS mapping of the spine, and provides age-matched reference values.

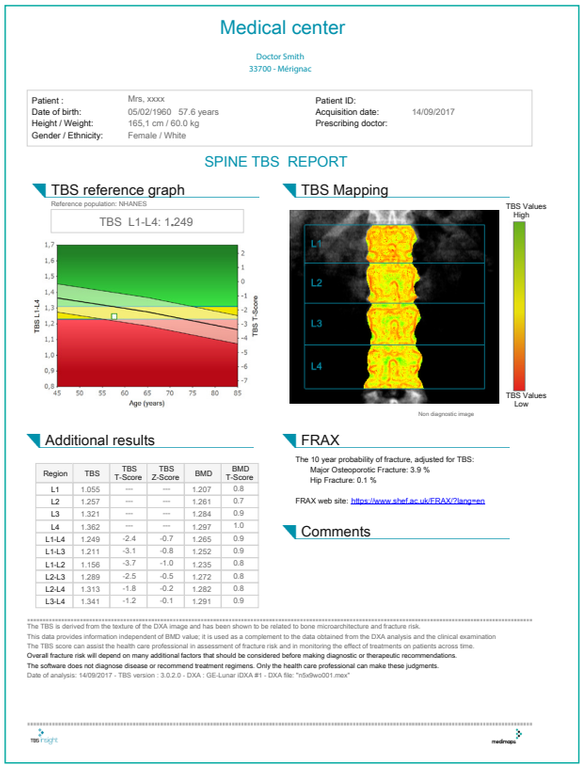

Figure 3: TBS iNsight printout

TBS can be easily combined with BMD T-score as the interpretation table shows in figure 4. This interpretation table is adapted from a meta-analysis [24] and the Manitoba study[26] and provides a class of fracture risk for major osteoporotic fracture which depends on both WHO T-score zone for BMD (normal, osteopenic and osteoporotic) and on TBS thresholds. For example: an osteopenic woman with a -2.2 T-score at the lumbar spine falls into a risk class of major osteoporotic fracture of about 5 to 7 per 1000 women per year. Adding the patient's TBS value (1.180) to the picture, moves her into a superior risk category corresponding to 10 to 14 fractures per 1000 women per year. That is to say, this woman's combined fracture risk is similar to the fracture risk of an osteoporotic woman. This example demonstrates how TBS can be used to better evaluate a patient's risk of fracture and then to improve the overall patient care management.

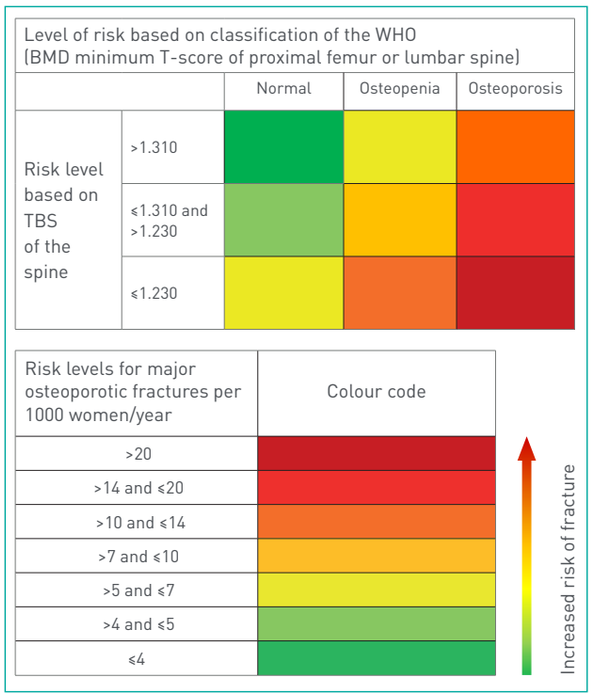

Figure 4: TBS iNsight risk stratification based on TBS and BMD adapted from Hans et al.[26] and McClovsky et al. [24]

Improve fracture prediction with TBS-adjusted FRAX

TBS can be used easily as a FRAX modifier (figure 5). As recommended by the ISCD[12] and IOF/ESCEO[11], TBS can be used in association with FRAX and BMD to adjust FRAX-probability of fracture in postmenopausal women and older men [12]. The FRAX tool is based on individual patient models that integrate the risks associated with clinical risk factors as well as BMD at the femoral neck.

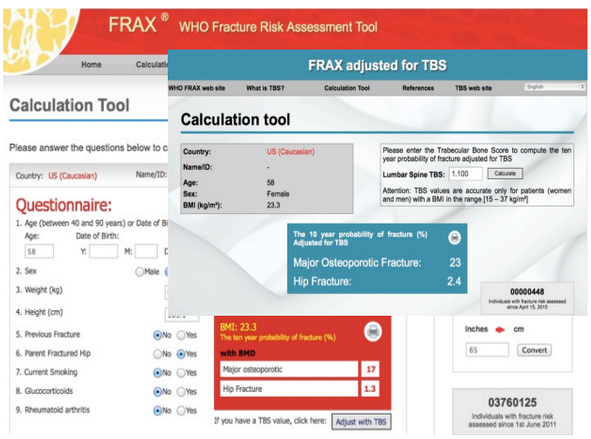

Figure 5: FRAX adjusted for TBS

Models for adjusting fracture probability from FRAX to account for TBS were derived in large population-based cohorts [46] and cross-validated in a meta-analysis including 17,809 men and women from 14 prospective population-based cohorts [24]. Authors found that for both hip fracture and major osteoporotic fracture, incorporation of the TBS-adjustment factor resulted in an improvement in the gradient of risk.

Other independent studies reported an improved fracture prediction using TBS-adjusted FRAX in primary or secondary osteoporosis [47- 49].

Use of TBS to Monitor Treatment: Review of Selected Studies

The TBS parameter, as being influenced by trabecular pattern, might also be influenced by treatments known to impact bone microarchitecture. TBS has been used in various pharmaceutical trials designed to evaluate the effect of osteoporosis treatments, either antiresorptive (slow down bone destruction) or anabolic agents (aimed at rebuilding bone). Bisphosphonates (alendronate, zoledronate, etc.) and denosumab belong to the antiresorptive category, while teriparatide is classified as an anabolic agent. These studies, summarized in table 3, compared the effect of drugs either against placebo or against another reference drug.

Pooled results are represented in figure 6.

Interestingly, the various efficacious therapies for osteoporosis differ in the extent to which they influence the TBS, with bisphosphonates exerting very little effect, but other drugs like PTH / PTH analog generally increasing TBS in the range of one to two percent per year. These findings seem to be consistent with the mechanism of action of the molecules. Indeed, one would not expect to see an improvement of the micro-structure with a bisphosphonate (and so TBS) while the degree of mineralization would increase and thus also BMD.

These primary studies start to show the interest of evaluating both BMD and TBS during treatment monitoring.

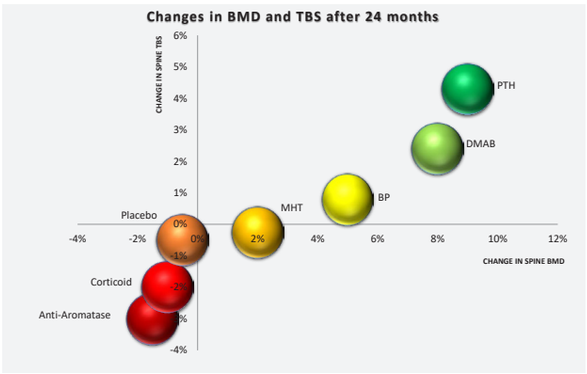

Figure 6: Graphical representation of the change in TBS & BMD over a standardized 24-month period (data pooled from the above referenced studies). Note: This figure is not a head to head study comparison but it is summary of different studies that can not be compared directly. MHT = menopausal hormone therapy, BP = bisphosphonates, DMAB = denosumab, PTH = parathyroid hormone.

Taken together, these studies suggest that TBS tends to increase with treatments that increase BMD. The magnitude of TBS increase is usually less marked than BMD changes. In contrast, the magnitude of the decrease in TBS without treatment is very similar to that of BMD. It seems clinically relevant to consider that an increase of surrogate markers of both bone quantity (BMD) and quality (TBS) would be reassuring to monitor effects of treatments.

Study	Study population	Treatment	BMD variation through the study	TBS variation through the study
Mc Clung et al 2017 [50]	157 postmenopausal women 128 postmenopausal women	Denosumab Placebo	+ 9.8 % 0.0 % at 3 years	+2.4 % -0.7 % at 3 years
Leslie et al 2017 [51]	5083 women 3961 women	Biphosphonates Controls	+ 3.4 % -1.7% per year	-0.2 % -1.2 % per year
Petranova et al 2014 [52]	30 postmenopausal women 30 postmenopausal women	Denosumab + GC Denosumab w/o GC	+ 5.8 % + 6.1 % at 1 year	+5.0 % + 0.3 % at 1 year
Di Gregorio et al 2015 [53]	67 men and women 87 men and women 88 men and women 36 men and women 39 men and women 43 men and women 30 men and women	Naive Ca Vit D Alendronate Testosterone Risendronate Denosumab Teriparatide	+ 0.5 % ns + 1.6 % ns + 4.1 % + 4.4 % + 4.8 % + 8.8 % + 8.8 % at 2 year	- 3.1 % + 1.3 % ns + 1.4 % + 1.8 % ns + 1.4 % ns + 2.8 % + 3.6 % at 2 year
Senn et al 2014 [54]	65 postmenopausal women 122 postmenopausal women	Teriparatide Ibendronate	+ 7.6 % + 2.9 % at 2 years	+ 4.3 % + 0.3 % at 2 years
Krieg et al 2013 [55]	534 postmenopausal women 1150 postmenopausal women	Anti-resorptive Controls	+ 1.9 % -0.4 % per year	+ 0.2 % -0.3 % per year
Popp et al 2013 [56]	54 postmenopausal women 53 postmenopausal women	Zolendronate Placebo	+ 9.6 % + 1.4 % at 3 years	+ 1.4 % -0.5 % at 3 years
Petranova et al 2016 [57]	71 postmenopausal women	Denosumab	+ 8.9 % at 3 years	+ 4.3 % at 3 years
Bilezikian et al 2017 [58]	29 postmenopausal women 25 postmenopausal women 24 postmenopausal women 31 postmenopausal women 29 postmenopausal women	Abaloaratide 20 µg Abaloparatide 40 µg Abaloparatide 80 µg Teriparatide Placebo		+ 2.3 % + 3.1 % + 4.2 % + 2.2 % - 1.1 % ns at 0.5 years
Saag et al 2016 [59]	53 patients under GC 56 patients under GC	Alendronate + GC Teriparatide + GC	+5.5 % + 10.3 % at 3 years	ns + 3.7 % at 3 years
Kalder et al 2015 [60]	34 breast cancer patients 36 breast cancer patients	Zolendronate +AI Placebo + AI	+3.1 % - 6.4 % at 2 years	+ 2.4 % - 2.2 % at 2 years
Prasad et al 2016 [61]	breast cancer patients breast cancer patients	Risendronate + AI Placebo + AI	+ 2.3 % - 1.7 % at 2 years	- 1.3 % - 2.3 % at 2 years
Rodriguez-Sanz et al 2016 [62]	81 breast cancer patients 23 breast cancer patients	Biphosphonates + AI No bisphosphonates + AI	+ 5.0 % - 2.4 % at 5 years	-0.3 % - 3.2 % at 5 years
Librizzi et al 2016 [63]	45 liver transplanted patients 44 liver transplanted patients	Risendronate Controls	+ 4.8 % + 3.4 % at 1 year	- 1.2 % ns - 1.0 % ns at 1 year
Watts et al 2017 [64]	14 patients with AFF prior BP treatment	Teriparatide	+ 6.1% (ns) at 2 years	+ 1.8 % (ns) at 2 years

Table 3: Summary of clinical studies using TBS to monitor treatments. NA = not assessed, AI = Anti-Aromatase, GC = Glucocorticoid. All changes reported in the table are significant unless "ns"= non significant is specified.

Summary

Trabecular bone score (TBS) is a grey-level textural measurement derived from lumbar spine dual-energy X-ray absorptiometry (DXA) images. It is related to bone microarchitecture that provides skeletal information complementary to that obtained from standard bone mineral density (BMD) measurement.

This summary paper documents a unique way to assess bone texture, a surrogate of bone microarchitecture and subsequently bone strength that not only predicts future fracture risk: it does so independent of BMD, clinical risk factors and the FRAX tool. It also enhances the accuracy of these tools when added as a supplementary test. Moreover, it demonstrates diagnostic accuracy for both primary and secondary osteoporosis and in both females and males, and appears sensitive to change over time that are the result either of effective treatment (with TBS increasing) or continued bone loss in the absence of effective treatment (with TBS decreasing). In some scenarios — for example in patients with type 2 diabetes or disorders associated with increased extraneous calcification around the spine, like degenerative spine disease or ankylosing spondylitis — it almost outperforms even the gold standard diagnostic measure for osteoporosis: DXA measured BMD.

Practically, TBS as an adjustment parameter of FRAX enables physicians to benefit from a more accurate evaluation of fracture risk with no change in the existing workflow.

Using FRAX Adjusted for TBS allows physicians to

- Integrate TBS easily in daily clinical practice
- Enhance fracture predictability using FRAX
- Refine individual fracture risk assessment
- Tighten selection of patients in need of therapeutic treatment.

TBS iNsight is therefore a useful tool to enhance fracture risk prediction in clinical settings in conjunction with BMD and clinical risk factors.

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Medimaps Group Headquarter:
18 chemin des Aulx,
CH-1228 Plan-les-Ouates
(Geneva) - Switzerland
Tel. +41 22 884 8644

Affiliate France: Med-Imaps
Espace France
4 voie Romaine
33610, Canéjan
Tel. +33 55 611 2101

Affiliate USA: Medimaps Group USA:
913N Market Street, Suite 200
Wilmington, DE 19801
Tel. +1 302 416 3063

contact@medimapsgroup.com
www.medimapsgroup.com

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