

Advanced DXA Using TBS iNsight™



A New Bone Structure Assessment Technique Enhances Identification of Fracture Risk

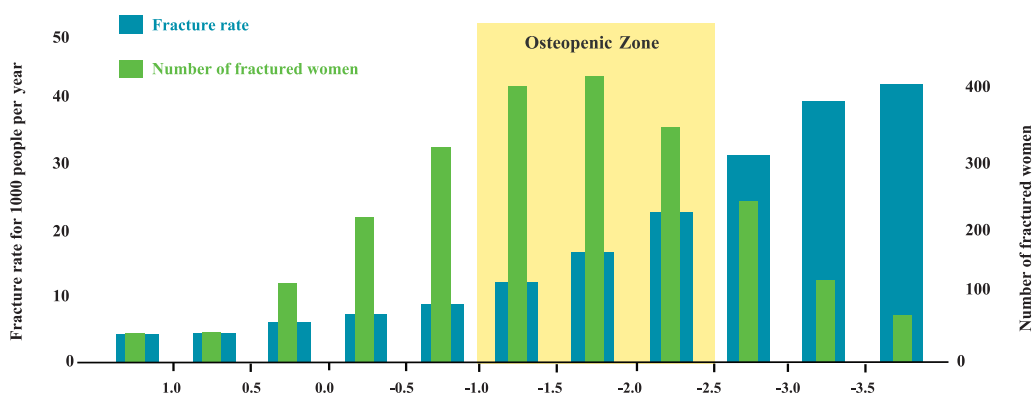
Introduction

The World Health Organization defines osteoporosis as a silent disease characterized by low bone mass (bone density) and a 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) 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. Bone densitometry utilizes x-rays of two distinct energies to provide quantitative information related to bone density. This data has been shown to be correlated to fracture risk.

Although bone mineral density (BMD) measured by DXA is a major determinant of bone strength and fracture risk, it is well known that over 50% of fractures occur in patients with DXA values that are not classified as “osteoporotic” (Figure 1).⁸ This observation means that factors other than BMD influence bone strength and fracture risk, including microarchitectural deterioration of bone tissue as implied from the conceptual definition of osteoporosis. Additional skeletal and extra skeletal factors such as bone geometry, micro damage, mineralization, bone turnover, age, family history, and fall risk contribute to the overall fracture risk.⁹



Source: Siris et al. Arch Intern Med. 2004; 164:1108-1112 – The NORA cohort

Figure 1: Over 50% of osteoporotic fractures occur in patients who are not classified in the “osteoporosis” category.

TBS iNsiGht: A New Tool to Identify Patients at Increased Risk of Fracture

TBS iNsiGht™ is a software tool that installs on existing DXA scanners. It is a simple, rapid and reproducible method that estimates fracture risk based on a determination of bone texture (an index correlated to bone microarchitecture),^{10,11} in addition to risks determined by DXA bone mineral density and clinical risk factors. The result is expressed as a Trabecular Bone Score (TBS).

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. Simply stated, TBS principles could be compared to an aerial view of a forest. An aerial view of a forest cannot discern individual elements of that forest (i.e., trees); the DXA image cannot discern the individual elements of its components (trabeculae). Although both of these 'low power' views do not have sufficient resolution to identify individual trabeculae (by the spine DXA image) or trees (in the forest aerial view), the areas of missing bone in the trabecular compartment or clearings in the forest are clearly noticeable (Figure 2).¹²

Applying this principle to the specifics of TBS, 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. Conversely, 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 (Figure 3).

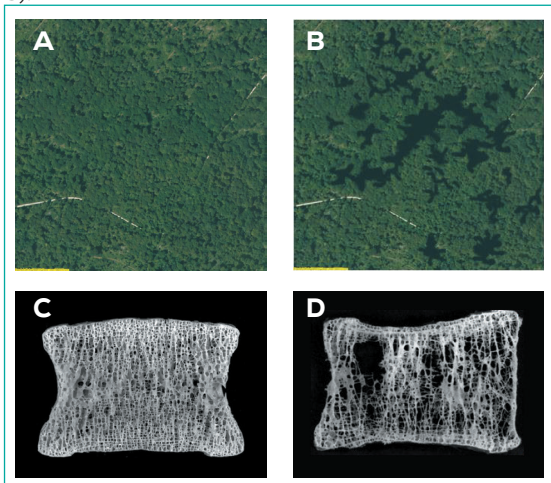


Figure 2: Areas of a compact forest (A) and one with open clearings (B) is analogous to the patterns observed in highly dense (C) and porous (D) bone.

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.

TBS iNsiGht integrates seamlessly with existing Hologic scanners (Table 1). The exam, performed at the same time as DXA, requires no additional scan time or additional radiation exposure. 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). This feature has made possible the accumulation of a large library of data evaluating the performance of TBS on patients who have had previous DXA studies.

TBS Clinical Evaluation

TBS has been evaluated in more than 100 peer-reviewed publications worldwide and on more than 75,000 patients. Some of the key findings have been conveniently summarized in recent review articles published by a group of international bone experts.^{12,13}

Table 1: DXA Units Compatible with TBS iNsiGht

Hologic:

- Horizon™ (A,C,W,Ci,Wi)
- Discovery™ (A,C,W,Ci,Wi)
- Delphi™ (A,C,W,SL)
- QDR 4500™ (A,C,W,SL)
- Explorer not supported

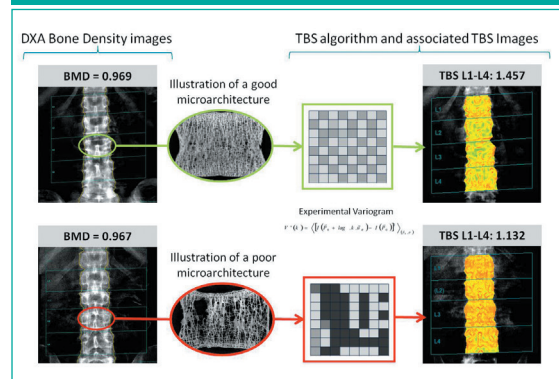


Figure 3: The TBS value is derived by an algorithm that analyzes the spatial organization of pixel intensity which in turn corresponds to the differences in the X-ray absorption power of an osteoporotic bone versus a normal trabecular pattern.¹²

- The short-term reproducibility of TBS determinations has been reported in several studies with values ranging from 1.1% - 1.9% C.V.;¹²
- TBS gives lower values in postmenopausal women and in men with previous fragility fractures than their non-fractured counterparts;
- TBS results have been demonstrated to be unaffected by the presence of osteophytes – a common artifact in late postmenopausal patients and those presenting with osteoarthritis;¹⁴
- TBS is complementary to data available by lumbar spine DXA measurements;
- TBS results are lower in women who have sustained a fragility fracture, but in whom DXA does not indicate osteoporosis or even osteopenia;
- TBS predicts fracture risk as well as lumbar spine BMD measurements in postmenopausal women;
- TBS can assist physicians in monitoring the response to treatments over time;
- TBS is associated with fracture risk in individuals with conditions related to reduced bone mass or bone quality.¹³

A summary of pivotal studies used in this review appears in Table 2.

Journal	Article Title	Authors	Cohort	Key Findings
Journal Bone and Mineral Research 2011	Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: The Manitoba Study	Hans D, Goertzen AL, Krieg MA, Leslie WD	29,407 women followed for 4.7 years TBS values were retrospectively analyzed	<ol style="list-style-type: none"> 1. TBS predicts fractures as well as lumbar spine BMD, and the combination was superior to either measurement alone ($p < 0.001$). 2. Incremental improvement in the performance of the combination of BMD and TBS remained significant even after adjustment for multiple clinical risk factors.
Journal of Bone Mineral Research 2014	Trabecular bone score (TBS) predicts vertebral fracture over 10 years independently of bone density in Japanese women: The Japanese Population-based Osteoporosis (JPOS) Cohort Study	Iki M, Tamaki J, Kadowaki E, Sato Y, Dongmei N, Winzenrieth R, Kagamimori S, Kagawa Y, Yoneshima H	665 women followed over 10 years All patients: VFA+ DXA+TBS	<ol style="list-style-type: none"> 1. Lower TBS was associated with higher risk of vertebral fracture over 10 years independent of BMD and clinical risk factors (including prevalent vertebral deformity). 2. TBS could effectively improve fracture risk assessment in clinical settings.
Bone 2013	Added value of trabecular bone score to bone mineral density for prediction of osteoporotic fractures in post menopausal women: The OPUS Study	Briot K, Paternotte S, Kolta S, Eastell R, Reid DM, Felsenberg D, Glüer C, Roux C	Subset of 1,007 women over age 55 originally recruited in 5 centers over 6 years with subsequent incident fractures	<ol style="list-style-type: none"> 1. Performance of TBS was significantly better than LS BMD for prediction of incident clinical osteoporotic fractures. 2. For radiographic vertebral fractures, TBS and LS BMD had similar predictive power but the combination of TBS and LS BMD increased the performance over LS BMD alone.
Osteoporosis International 2014	TBS result is not affected by lumbar spine osteoarthritis	Kolta S, Briot K, Fechtenbaum J, Paternotte S, Armbrrecht G, Felsenberg D, Glüer C, Eastell R, Roux C	1,254 postmenopausal women (66.7 ± 7.1 years) including 727 with 6-year follow-up	<ol style="list-style-type: none"> 1. In postmenopausal women, lumbar osteoarthritis leads to an increase in LS BMD. In contrast, spine TBS is not affected by lumbar osteoarthritis.
Journal of Bone and Mineral Research 2015	A meta-analysis of trabecular bone score in fracture risk prediction and its interaction with FRAX	McCloskey E, Odén A, Harvey N, Leslie W, Hans D, Johansson H, Barkmann R, Boutroy S, Brown J, Chapurlat R, Elders P, Fujita Y, Glüer C, Goltzman D, Iki M, Karlsson M, Kindmark A, Kotowicz M, Kurumatani N, Kwok T, Lamy O, Leung J, Lippuner K, Ljunggren Ö, Lorentzon M, Mellström D, Merlijn T, Oei L, Ohlsson C, Pasco J, Rivadeneira F, Rosengren B, Sornay-Rendu E, Szulc P, Tamaki J, Kanis J	14 prospective population-based cohorts; 17,809 men and women; from 50 years; mean follow-up of 6.7 years.	<ol style="list-style-type: none"> 1. TBS predicts osteoporotic fracture independently of BMD and FRAX® whatever the type of the fracture and the gender 2. TBS enhances the fracture risk prediction from the widely used FRAX tool 3. TBS can be used as an adjustment parameter of FRAX 4. TBS thresholds obtained are similar for both men and women: low TBS threshold is 1.230 and high TBS threshold is 1.310.
Bone 2015	Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice	Harvey NC, Glüer CC, Binkley N, McCloskey EV, Brandi M-L, Cooper C, Kendler D, Lamy O, Laslop A, Camargos BM, Reginster J-Y, Rizzoli R, Kanis JA	Review of TBS literature - several cohorts	A consensus report of a European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) Working Group
Journal of Clinical Densitometry 2015	Fracture Risk Prediction by Non-BMD DXA Measures: the 2015 ISCD Official Positions Part 2: Trabecular Bone Score	Barbara C. Silva, Susan B. Broy, Stephanie Boutroy, John T. Schousboe, John A. Shepherd, and William D. Leslie	Review of TBS literature - several cohorts	2015 ISCD Official Positions

Table 2: Summary of key clinical studies evaluating TBS clinical added value

Possible Interpretation of TBS values in overall patient management

The TBS report is generated simultaneously with the standard DXA spine printout. The report (Figure 4) calculates an overall Trabecular Bone Score, displays a texture image of the spine, and provides age-matched reference values.

TBS can be easily combined with BMD T-score using, for example, the interpretation table shown in Figure 5. This interpretation table is derived from the Manitoba study¹³ 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. As an 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 fracture 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.

Use of TBS to Monitor Treatment: Review of Selected Studies

TBS has been employed 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 the drugs either against placebo or against another reference drug over a 24-month interval.

Pooled results are noted in Figure 6.

These initial results show that different drugs may have a similar effect on BMD but differ significantly in their effect on TBS.

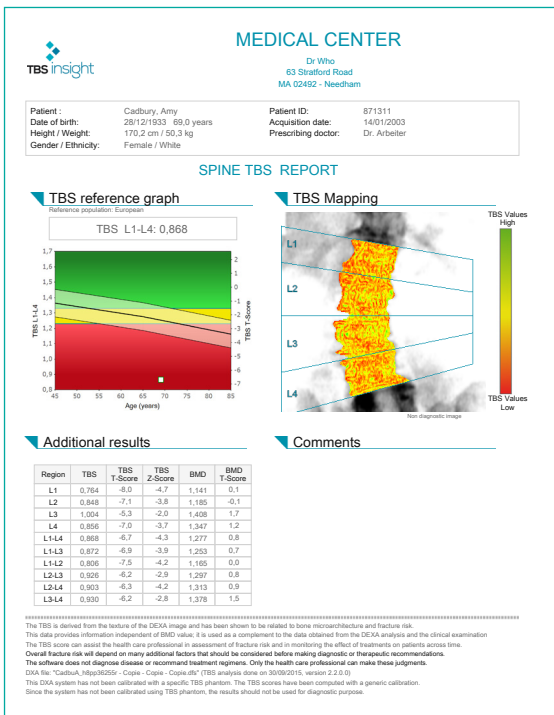


Figure 4: TBS iN Insight printout

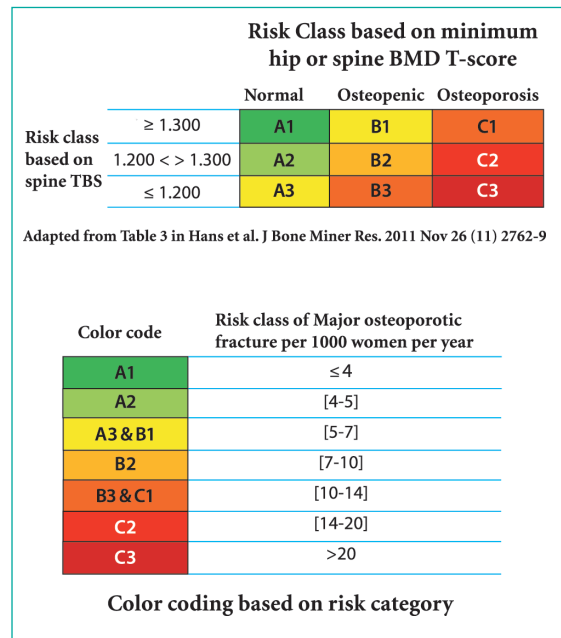


Figure 5: TBS iN Insight interpretation table

*fracture at hip, spine, forearm and humerus

Treatment	Effect on Spine BMD (at 24 months)	Effect on Spine TBS (at 24 months)	References
Alendronate vs Untreated	+3.8 % -0.8 %	+0.4 % -0.6 %	Krieg et al.: Effects of anti-resorptive agents on trabecular bone score (TBS) in older women. <i>Osteoporosis International</i> March 2013; 24(3):1073-8.
Zoledronate vs Placebo	+7.9 % +1.7 %	+1.1 % -0.5 %	Popp et al.: Beneficial effect of zoledronate compared to placebo on spine BMD and microarchitecture (TBS) parameters in postmenopausal women with osteoporosis. A 3-Year Study. <i>Journal of bone and mineral research</i> March 2013; 28(3):449-54.
Teriparatide vs Ibandronate	+7.6 % +2.9 %	+4.3 % +0.3 %	Günther et al.: Comparative effects of teriparatide and ibandronate on spine bone mineral density (BMD) and microarchitecture (TBS) in postmenopausal women with osteoporosis: A 2-year, open-label study. <i>Osteoporosis International</i> . July 2014; 25(7):1945-51.
Denosumab vs Placebo	+7.8 % +0.1 %	+1.9 % +0.2 %	McClung M. et al.: Denosumab significantly improved TBS, an index of trabecular microarchitecture in postmenopausal women with osteoporosis. Oral presentation at the ASBMR 2012.

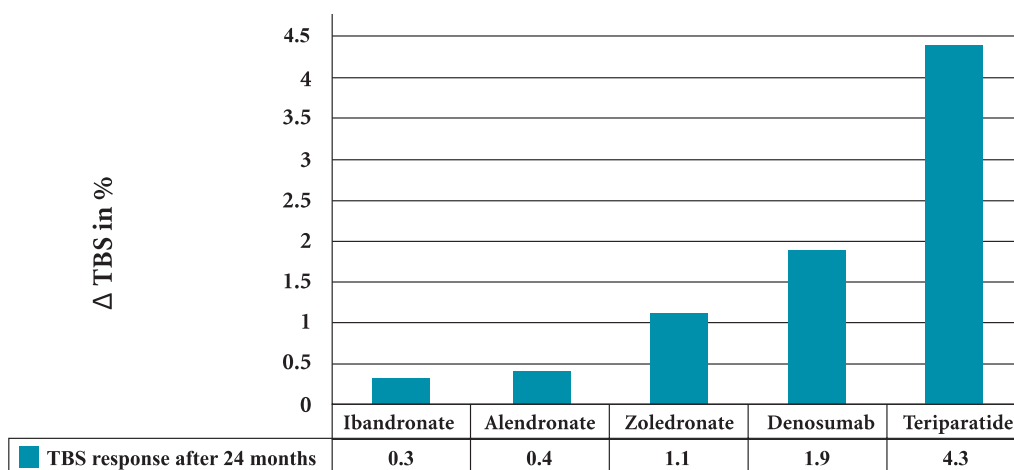


Figure 6: Graphical representation of the change in TBS over a standardized 24-month period. (Data pooled from the above referenced studies)

Summary

This document has provided a short overview of how a new software tool, TBS iN Sight, can be integrated with current bone density evaluations. 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.

The technique has been demonstrated to be reproducible and easy to perform. Published data has consistently confirmed that when used as a complement to bone density and clinical risk factors, TBS improves reliability of fracture risk prediction. TBS has also been shown to be an effective tool for monitoring response to therapy. Most of the data published to date describes the use of TBS on women and similar positive performances have also been recently reported for men.¹⁵ As a breakthrough, recent data have shown a possible incremental improvement in fracture prediction when spine TBS is used in combination with FRAX variables.

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 iN Sight is therefore a useful tool to enhance fracture risk prediction in clinical settings.

To learn more about TBS iN Sight :

- *TBS contribution in patient fracture risk evaluation :*

- Please review the white paper entitled : " TBS iN Sight™ : A Useful Tool to Potentially Reconsider Patient Fracture Risk ".

- *FRAX Adjusted for TBS :*

- Please review the white paper entitled: «FRAX Adjusted for TBS»

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