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Review Article

Dual-Energy X-Ray Absorptiometry Monitoring With Trabecular Bone Score: The 2019 ISCD Official Positions

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Abstract

Trabecular bone score (TBS) is a textural index that evaluates pixel gray–level variations in the lumbar spine image by dual-energy X-ray absorptiometry. It provides an indirect assessment of trabecular microarchitecture that is an independent predictor of fracture risk. TBS does not appear to be clinically useful to monitor the skeletal effects of bisphosphonates and denosumab, but is potentially useful as a component of monitoring the skeletal effects of teriparatide and abaloparatide. The least significant change (LSC) for TBS can be conservatively estimated to be about 5.8% (the largest LSC in published data) or calculated by a dual-energy X-ray absorptiometry facility using the same methodology that is used for bone mineral density (BMD) precision assessment to calculate BMD LSC. A review of the best available evidence at the 2019 ISCD Position Development Conference concluded that the role of TBS in monitoring antiresorptive therapy is unclear and that TBS is potentially useful for monitoring anabolic therapy. For patients treated with teriparatide or abaloparatide, a statistically significant increase in TBS may represent a clinically meaningful improvement in trabecular structure. A significant decrease of TBS may represent a worsening of trabecular structure, suggesting the need for further clinical assessment and possible change in treatment strategies. Since BMD measures bone quantity and TBS measures bone quality, these tests can be considered complementary in assessing fracture risk and response to therapy in appropriate patients.

Key Words: Osteoporosis; TBS; monitor; DXA; fracture; treatment.

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Introduction

Bone strength is determined by bone mineral density (BMD) and non-BMD skeletal properties, such as bone geometry, mineralization, microdamage, remodeling, and microarchitecture. Trabecular bone score (TBS iNsight software, Medimaps Group, Geneva, Switzerland) is a textural index that evaluates pixel gray−level variations in the lumbar spine (LS) image by dual-energy X-ray absorptiometry (DXA). It provides an indirect assessment of trabecular microarchitecture *(1,2)* that is an independent predictor of fracture risk *(3)*. TBS is included as a risk factor with the fracture risk tool, FRAX, and may influence treatment decisions by altering the estimated 10-yr fracture probability. TBS has been cleared by the US Food and Drug Administration for use as a complement to DXA analysis and clinical examination for assessment of fracture risk and monitoring the effects of therapy *(4)*.

Clinical applications of TBS were addressed at a previous Position Development Conference (PDC) of the ISCD and reported in this journal *(5)*. It was determined that:

- TBS is associated with vertebral, hip and major osteoporotic fracture risk in postmenopausal women.
- TBS is associated with hip fracture risk in men over the age of 50 yr.
- TBS is associated with major osteoporotic fracture risk in men over the age of 50 yr.
- TBS should not be used alone to determine treatment recommendations in clinical practice.
- TBS can be used in association with FRAX and BMD to adjust FRAX-probability of fracture in postmenopausal women and older men.
- TBS is not useful for monitoring bisphosphonate treatment in postmenopausal women with osteoporosis.
- TBS is associated with major osteoporotic fracture risk in postmenopausal women with type II diabetes.

For the 2019 ISCD PDC, held in Kuala Lumpur, Malaysia, a task force was formed to review new medical evidence about the use of TBS for monitoring treatment with approved osteoporosis treatments. This is a report of relevant ISCD Official Positions developed from the PDC.

Methodology

A PubMed search limited to the English language was conducted for terms that included "trabecular bone score" or "TBS." Within these matches a search was made for "precision," "least significant change," "least significant change (LSC)," "reproducibility," "variation," "variability," "osteoporosis," "treatment," "pharmacologic treatment" and each of the US-approved osteoporosis medications at the time of the search in 2018 (prior to approval of romosozumab, a therapeutic agent with a "dual effect" of increasing bone formation while decreasing bone resorption, on April 9, 2019). In addition, the authors sought input from scientific and clinical experts in BMD/TBS determination to ensure they were aware of all the appropriate studies in the literature. The original search resulted in approximately 65 articles. Our search revealed 7 studies that were informative to assess the change in TBS while on pharmacologic therapy; 2 articles specifically assessed precision estimates for TBS. Appropriate articles are referenced and included in the bibliography.

Key Questions

1. Is TBS useful to monitor patients treated with antiresorptive agents?
2. Is TBS useful to monitor patients treated with teriparatide and abaloparatide?

TBS Background

TBS Change With Treatment

Pharmacologic treatment studies that included repeat TBS measurements were reviewed. We used a conservative estimate of 5.8% for TBS LSC as the threshold to consider use of TBS to monitor changes for individual patients on osteoporosis medications, unless the individual study performed their own LSC with the investigators. We recognize the limitations of using this threshold, and that some clinical facilities are likely to have TBS LSC that is better than 5.8%. In general, with pharmacologic treatment studies for 1.5−2 yr duration, the LS BMD changes were consistently greater than TBS changes, with 4.1%−8.8% increase of LS BMD vs 1.4%−3.6% increase of TBS *(6)*. This suggests a longer time interval may be necessary to achieve a statistically significant change with TBS than with LS BMD.

Potent antiresorptive agents (eg, zoledronic acid, denosumab) may have an effect upon edge detection of mineralized bone that could potentially impact both BMD and TBS greater than with oral bisphosphonates. Since anabolic therapy deposits new bone in locations where there previously was no bone and improves trabecular microarchitecture *(7,8)*, it seems logical that both BMD and TBS would increase as the new bone matrix becomes more mineralized. In the 2015 ISCD Official Position report *(5)*, it was determined that TBS does not change beyond the LSC in patients treated with oral bisphosphonates. The recommendation at that time was that TBS was not appropriate for monitoring women with postmenopausal osteoporosis who were treated with bisphosphonates. Since that publication there have been reports evaluating TBS change with zoledronic acid *(9)*, denosumab *(10)*, and 2 anabolic agents, teriparatide *(11,12)* and abaloparatide *(13)*.

Precision of TBS

Knowing the reproducibility of a test result is critical to understanding its utility in disease progression or therapeutic monitoring. This is accomplished by precision

assessment and calculation of the LSC, which determine when a difference in the measurement is statistically significant or within the range of error of the test. Bone densitometrists are quite familiar with this concept for BMD LSC, which is well described in ISCD Official Positions.

Several studies have reported the precision of TBS with methods similar to the precision assessment for DXA BMD measurements on the same instrument. Precision in these studies is usually expressed as root mean square percentage coefficient of variation (RMS%CV), comparing TBS precision with LS BMD precision. TBS LSC with a 95% level of confidence can be derived from this value (TBS LSC = RMS%CV x 2.77). Here, TBS LSC is presented as a percentage rather than an absolute value of TBS units because precision error is given as a percentage in most published studies.

TBS precision was reported for 92 postmenopausal women in the Manitoba Bone Density program *(14)*. For all 3 DXA systems used in the study, TBS precision was 2.1%, compared with LS BMD precision of 1.7%. Repeat DXA studies were done within 28 days (51 same day, 41 different day).

In the Osteoporosis and Ultrasound Study of ambulatory European women over age 55 years, short-term TBS precision for 60 women was 1.44%, compared with 1.18 % for LS BMD *(15)*.

In a cohort of 30 French women age 45–85 yr, short-term TBS precision was assessed in 30 subjects at 2 centers *(16)*. TBS precision was reported as 1.9% and 1.5% for each center, compared with LS BMD precision of 1.1%–1.35%.

In the Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk study, TBS was measured in postmenopausal community-dwelling Swiss women, age 70–80 yr *(17)*. TBS precision was reported as 1.12%, compared with 0.90% for LS BMD.

In a study from Italy in 95 Caucasian women, mean age 66 yr, the effect of body mass index and waist circumference differences on TBS precision was assessed and compared with LS BMD precision *(18)*. TBS precision ranged from 1.21%–1.53%, depending on the study group, compared with LS BMD precision 0.91%–1.48%. It was concluded that TBS precision was not affected by body mass index or waist circumference.

All of the above precision studies were in female populations. Krueger et al compared TBS precision and LS BMD precision of 2 DXA models of the same manufacturer in 30 postmenopausal women with osteoporosis and also compared TBS precision in 90 men and 90 women measured with the same instrument *(19)*. It was found that precision for TBS and LS BMD was similar in men and women, with TBS precision slightly better with the DXA system having the higher image resolution. The reported TBS precision was 1.4% and 1.6%, depending on the DXA model used, compared with LS BMD precision of 1.9% and 1.5%.

Overall, TBS precision (1.12%–2.1%) was similar but slightly worse than LS BMD precision (0.91%–1.9%), with no major difference with different manufacturers of DXA systems. The published TBS precision data generate TBS LSC values (with a 95% level of confidence) in the range of 3.1%–5.8%. In general, it seems that TBS precision is better when LS BMD precision is better, suggesting that TBS LSC may be at the low end of this range at a facility with very low LS BMD LSC and at the high end of the range when LS BMD LSC is greater. For a DXA facility that has calculated TBS LSC, repeat TBS measurement may be considered to determine whether there has been a statistically significant change with a 95% level of confidence. Here we evaluate the medical evidence regarding the clinical utility of monitoring TBS for patients receiving pharmacological therapy for osteoporosis.

ISCD Official Position

Question: Is TBS useful to monitor patients treated with antiresorptive agents?

ISCD Official Position: The role of TBS in monitoring antiresorptive therapy is unclear.

Grade: Good-A-W

Rationale for oral bisphosphonates: Approved bisphosphonates, whether administered orally or parenterally, reduce bone remodeling, increase BMD, and reduce fracture risk, but are not known to alter bone structure. Many of the reports evaluating TBS while on oral bisphosphonates include subjects receiving other osteoporosis treatments. Other studies are comparative studies with anabolic agents, specifically, teriparatide. There is very good consistency across the studies that patients treated with oral bisphosphonates (alendronate, risedronate, and ibandronate) have minimal changes in TBS with about 2 or more years of treatment *(5)*. The changes are well below the LSC for TBS and therefore it is logical that TBS should not be used to follow patients on oral bisphosphonates.

Rationale for zoledronic acid: Intravenous zoledronic acid is a more potent bisphosphonate than oral bisphosphonates; when given properly, there is 100% compliance for a year and no concerns about absorption that are important for oral bisphosphonates. Popp et al published 3-yr data from the HORIZON study with baseline and follow up BMD and TBS *(9)*. Patients received either placebo or zoledronic acid 5 mg annually for 3 yr. At the end of 3 yr, the mean change in BMD at the LS was 9.58% ± 0.6% compared to placebo arm which showed a 1.38% ± 0.9% gain in postmenopausal women with osteoporosis. The mean changes in TBS at 36 months were −0.49% ± 0.62% in the placebo arm and +1.41% ± 0.79% increase in patients receiving active treatment. The mean increase was statistically significant ($p = 0.031$) but below the LSC for TBS. Due to the stringent training of the DXA technologists and the nature of a large clinical trial, the authors were able to calculate a TBS LSC of 3.1%, which is better than most of the previously published LSC determinations for TBS. The mean value

increase in TBS fell below the LSC for this study, but authors stated that 35% of the patients achieved an increase in TBS beyond the LSC of 3.1%. Therefore, 65% of treated patients did not have an increase in TBS beyond the LSC in spite of DXA BMD increases and fracture risk reduction. TBS alone would not have been a good predictor of fracture risk reduction. Based upon this well-conducted study, it is not appropriate to use TBS to monitor patients on IV zoledronic acid.

Rationale for denosumab: Denosumab is a fully human monoclonal antibody to RANK ligand, an important regulator of osteoclastic bone resorption. Despite being associated with large increases in BMD and increases in PTH levels *(8)*, it has not been shown to have anabolic properties in clinical trials *(20)*. In a subset (128 placebo and 157 denosumab) of subjects in the FREEDOM trial comparing denosumab to placebo, LS BMD and TBS measurements were done at 12, 24, and 36 mo *(10)*. At 36 mo, the mean increase in LS BMD was 9.8% in the denosumab arm and 0.0% in the placebo arm. The mean change of TBS was a 2.4% increase in the denosumab arm and decrease of 0.7% in the placebo arm. The change in TBS in the denosumab arm was statistically significant compared to baseline and placebo at 36 mo. The authors stated that 20% of denosumab-treated women had a gain in TBS at 36 mo that exceeded 5.82%, which has been a published LSC for TBS. Therefore, 80% of denosumab patients did not have a gain in TBS that exceeded the LSC. While the increase in TBS with denosumab appears to be greater than with oral or IV bisphosphonates, it is difficult to support the use of TBS for routine monitoring with denosumab patients. In general, it appears that TBS would not be valuable in the monitoring of patient taking antiresorptive drugs for the treatment of osteoporosis for treatment periods of up to 3 yr.

Question: Is TBS useful to monitor patients treated with teriparatide and abaloparatide?

ISCD Official Position: TBS is potentially useful for monitoring anabolic therapy.

Grade: Fair-B-W.

Rationale: Teriparatide and abaloparatide are PTH-related osteoanabolic compounds that increase bone remodeling and are known to improve bone structure. Senn et al assessed changes in LS BMD and TBS in postmenopausal women treated with either teriparatide (n = 65) or IV ibandronate 3 mg (n = 122) every 3 mo *(11)*. The calculated LSC was 2.49% for LS BMD and 3.10% for TBS. While both drugs statistically increased LS BMD, only teriparatide increased TBS (mean of 4.3%). TBS was essentially unchanged at 2 yr with IV ibandronate, while 61.5% of subjects treated with teriparatide showed a statistically significant increase of TBS at 2 yr.

In a patient population on chronic glucocorticoid treatment (prednisone >5 mg/day for at least 90 d), Saag et al compared the changes in LS BMD and TBS in a subpopulation (n = 53 for subjects on alendronate, n = 56 for those on teriparatide) treated for 3 yr in a blinded clinical trial *(12)*. Some of the patients in the original trial had DXA data from systems that were not adequate for post-hoc TBS determination. The teriparatide-treated patients had a mean increase in TBS of 3.7% at 3 yr compared with baseline ($p < 0.05$). Subjects receiving alendronate did not have a significant change in TBS at 3 yr. LS BMD increased by 5.5% in the alendronate group and 10.3% in the teriparatide group. Calculation of TBS LSC was not reported for the study population.

Bilezikian et al published 24-wk TBS data on postmenopausal women treated with abaloparatide 20 mcg, 40 mcg, and 80 mcg SC/d, teriparatide 20 mcg SC/d and placebo *(13)*. TBS LSC was estimated to be 4.2%, a value derived from an average of the calculated LSC from 4 other clinical trials. Examining only the results for the Food and Drug Administration-approved 80 mcg abaloparatide dose, the mean increases in TBS were 4.21% in the abaloparatide and 2.21% in the teriparatide-treated groups. The placebo group lost a mean of 1.08% at 24 mo. At 24-wk, 52.2% of subjects receiving the abaloparatide 80 mcg dose and 30.0% of the teriparatide 20 mcg dose exceeded the estimated TBS LSC; 17% of the placebo patients lost at least 4.2%. None of the abaloparatide-treated subjects lost more than 4.2%, but 6.7% in the teriparatide 20 mcg group lost more than 4.2%. A significant decrease of TBS on treatment may represent a poor response to treatment and increasing fracture risk.

Research Agenda

The clinical utility of monitoring with TBS is highly dependent on knowledge of LSC, which is variable as reported with clinical trials. We suggest a minimum acceptable precision be established for TBS, as has been done for BMD with the ISCD Official Positions (eg, minimal acceptable precision for lumbar spine is 1.9% [LSC = 5.3%]) *(21)*. Further study is suggested to determine whether TBS precision in the clinical practice setting approximates what has been reported in clinical trials or is different. Further study of TBS change with or without treatment is needed in populations in addition to postmenopausal women (eg, men, children, and premenopausal women), for newly approved medications (eg, romosozumab), and for special clinical situations (eg, glucocorticoid-induced osteoporosis, diabetes mellitus, hyperparathyroidism, and chronic kidney disease).

In conlcusion, the available evidence does not support routine monitoring of TBS for patients treated with antiresorptive agents. TBS changes with oral bisphosphonates are small and unlikely to reach the LSC. More potent antiresorptives such as denosumab or zoledronic acid seem to be associated with greater changes in TBS over 2–3 yr, but not enough to be confident that it would be clinically useful to monitor TBS for patients treated with these agents.

Anabolic drugs clearly increase mean TBS over 2–3 yr. However, there is no uniform response, with the rate of

change beyond the estimated LSC estimated to be about 52% over 24 wk for abaloparatide and probably less for teriparatide. Monitoring TBS for patients on anabolic therapy can provide additional information beyond measuring BMD and bone turnover markers, but a change in TBS alone is not recommended as the sole test to determine whether a patient has had a good response to an anabolic agent.

The published data on changes of TBS generally were from sponsored clinical trials with strict quality control on DXA measurements. As noted, some of the trials were able to calculate TBS LSC for that specific dataset. If TBS is used to monitor treated patients in clinical practice, we suggest that the DXA facility calculate a facility TBS LSC with the same methodology used for DXA BMD precision assessment. This can easily be accomplished, retrospectively, by analyzing data already available from previous LS BMD precision assessment, if it has been done. If LSC is not calculated, then a conservative estimation for TBS LSC of 5.8% can be used, based on the largest published value. BMD measures bone quantity and TBS measures bone quality. These tests can be considered complementary in assessing fracture risk and response to therapy in appropriately selected patients. A statistically significant decrease of TBS in a treated or untreated patient may represent a clinically relevant worsening of trabecular structure and increasing fracture risk.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jocd.2019.07.006.

References

1. Muschitz C, Kocijan R, Haschka J, et al. 2015 TBS reflects trabecular microarchitecture in premenopausal women and men with idiopathic osteoporosis and low-traumatic fractures. Bone 79:259–266.
2. Ramalho J, Marques IDB, Hans D, et al. 2018 The trabecular bone score: relationships with trabecular and cortical microarchitecture measured by HR-pQCT and histomorphometry in patients with chronic kidney disease. Bone 116:215–220.
3. Shevroja E, Lamy O, Kohlmeier L, et al. 2017 Use of Trabecular Bone Score (TBS) as a complementary approach to Dual-energy X-ray Absorptiometry (DXA) for fracture risk assessment in clinical practice. J Clin Densitom 20:334–345.
4. US Food and Drug Administration. 2016Indications for Use, TBS iNsight. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf15/K152299.pdf. Accessed: February 2, 2019.
5. Silva BC, Broy SB, Boutroy S, et al. 2015 Fracture Risk Prediction by Non-BMD DXA Measures: the 2015 ISCD Official Positions Part 2: Trabecular Bone Score. J Clin Densitom 18:309–330.
6. Krieg MA, Aubry-Rozier B, Hans D, et al. 2013 Effects of anti-resorptive agents on trabecular bone score (TBS) in older women. Osteoporos Int 24:1073–1078.
7. Dempster DW, Zhou H, Ruff VA, et al. 2018 Longitudinal effects of teriparatide or zoledronic acid on bone modeling- and remodeling-based formation in the SHOTZ Study. J Bone Miner Res 33:627–633.
8. Dempster DW, Zhou H, Recker RR, et al. 2016 Differential effects of teriparatide and denosumab on intact PTH and bone formation indices: AVA Osteoporosis Study. J Clin Endocrinol Metab 101:1353–1363.
9. Popp AW, Guler S, Lamy O, et al. 2013 Effects of zoledronate versus placebo on spine bone mineral density and microarchitecture assessed by the trabecular bone score in postmenopausal women with osteoporosis: a three-year study. J Bone Miner Res 28:449–454.
10. McClung MR, Lippuner K, Brandi ML, et al. 2017 Effect of denosumab on trabecular bone score in postmenopausal women with osteoporosis. Osteoporos Int 28:2967–2973.
11. Senn C, Gunther B, Popp AW, et al. 2014 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. Osteoporos Int 25:1945–1951.
12. Saag KG, Agnusdei D, Hans D, et al. 2016 Trabecular Bone Score in patients with chronic glucocorticoid therapy-induced osteoporosis treated with alendronate or teriparatide. Arthritis Rheumatol 68:2122–2128.
13. Bilezikian JP, Hattersley G, Fitzpatrick LA, et al. 2018 Abaloparatide-SC improves trabecular microarchitecture as assessed by trabecular bone score (TBS): a 24-week randomized clinical trial. Osteoporos Int 29:323–328.
14. 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 26:2762–2769.
15. Briot K, Paternotte S, Kolta S, et al. 2013 Added value of trabecular bone score to bone mineral density for prediction of osteoporotic fractures in postmenopausal women: the OPUS study. Bone 57:232–236.
16. Dufour R, Winzenrieth R, Heraud A. 2013 Generation and validation of a normative, age-specific reference curve for lumbar spine trabecular bone score (TBS) in French women. Osteoporos Int 24:2837–2846.
17. Popp AW, Meer S, Krieg MA, et al. 2016 Bone mineral density (BMD) and vertebral trabecular bone score (TBS) for the identification of elderly women at high risk for fracture: the SEMOF cohort study. Eur Spine J 25:3432–3438.
18. Messina C, Buonomenna C, Menon G, et al. 2019 Fat mass does not increase the precision error of Trabecular Bone Score measurements. J Clin Densitom Epub 22:359–366.
19. Krueger D, Libber J, Binkley N. 2015 Spine Trabecular Bone Score precision, a comparison between GE lunar standard and high-resolution densitometers. J Clin Densitom 18:226–232.
20. Dempster DW, Zhou H, Recker RR, et al. 2018 Remodeling- and modeling-based bone formation with teriparatide versus denosumab: a longitudinal analysis from baseline to 3 months in the AVA study. J Bone Miner Res 33:298–306.
21. Shepherd JA, Schousboe JT, Broy SB, et al. 2015 Executive summary of the 2015 ISCD position development conference on advanced measures from DXA and QCT: fracture prediction beyond BMD. J Clin Densitom 18:274–286.