

Trabecular bone score: perspectives of an imaging technology coming of age

Escore de osso trabecular: perspectivas de um método de imagem em aprimoramento

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ABSTRACT

The trabecular bone score (TBS) is a new method to describe skeletal microarchitecture from the dual energy X-ray absorptiometry (DXA) image of the lumbar spine. While TBS is not a direct physical measurement of trabecular microarchitecture, it correlates with micro-computed tomography (μ CT) measures of bone volume fraction, connectivity density, trabecular number, and trabecular separation, and with vertebral mechanical behavior in *ex vivo* studies. In human subjects, TBS has been shown to be associated with trabecular microarchitecture and bone strength by high resolution peripheral quantitative computed tomography (HRpQCT). Cross-sectional and prospective studies, involving a large number of subjects, have both shown that TBS is associated with vertebral, femoral neck, and other types of osteoporotic fractures in postmenopausal women. Data in men, while much less extensive, show similar findings. TBS is also associated with fragility fractures in subjects with secondary causes of osteoporosis, and preliminary data suggest that TBS might improve fracture prediction when incorporated in the fracture risk assessment system known as FRAX. In this article, we review recent advances that have helped to establish this new imaging technology. *Arq Bras Endocrinol Metab.* 2014;58(5):493-503

Keywords

Trabecular bone score; osteoporosis; fracture risk; bone mineral density; microarchitecture

RESUMO

TBS (do inglês, "trabecular bone score") é um novo método que estima a microarquitetura óssea a partir de uma imagem de densitometria óssea (DXA) da coluna lombar. Apesar de o TBS não ser uma medida física direta da microarquitetura trabecular, ele correlaciona-se com o volume ósseo, densidade da conectividade trabecular, número de trabéculas e separação trabecular medidos por microtomografia computadorizada (μ CT), e com medidas mecânicas da resistência óssea vertebral em estudos *ex vivo*. Estudos em humanos confirmaram que o TBS associa-se a microarquitetura trabecular e resistência óssea medidas por tomografia computadorizada quantitativa periférica de alta resolução (HRpQCT). Estudos transversais e prospectivos, envolvendo um grande número de indivíduos, mostraram que o TBS é associado com fratura vertebral, de colo de fêmur e com outros tipos de fraturas osteoporóticas em mulheres na pós-menopausa. Dados em homens, apesar de escassos, mostram resultados semelhantes. Além disso, o TBS foi associado a fraturas por fragilidade em indivíduos com diversas causas secundárias de osteoporose e, dados preliminares, sugerem que o uso do TBS pode melhorar a previsão de fratura quando incorporado ao sistema de avaliação de risco de fratura (FRAX). Este artigo faz uma revisão de avanços recentes que têm ajudado a estabelecer esse novo método de imagem. *Arq Bras Endocrinol Metab.* 2014;58(5):493-503

Descritores

TBS; osteoporose; risco de fratura; densidade mineral óssea; microarquitetura

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INTRODUCTION

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength, predisposing to an increased risk of fracture (1). The major determinants of bone strength are both bone mineral density (BMD) and skeletal microarchitecture. While BMD can be readily measured by dual-energy X-ray absorptiometry (DXA), the technologies used to determine skeletal microarchitecture, such as histomorphometric analysis and micro-computed tomography (μ CT) of the transiliac crest bone biopsy (2,3), high resolution peripheral quantitative computed tomography (HRpQCT) (4), and magnetic resonance imaging (MRI) (5) are not routinely available. To this end, and based upon previous studies using 2D X-ray images to estimate bone microstructure (6-8), the trabecular bone score (TBS), a new approach for assessing skeletal microarchitecture from 2D DXA images (9-11), has been developed.

TBS is an indirect index of trabecular microarchitecture based upon evaluating pixel gray-level variations in the DXA image. TBS is not a direct physical measurement of trabecular microarchitecture, but rather an overall descriptor of bone quality (9). A low TBS value is associated with fewer, less well-connected and more widely distributed trabeculae, while high TBS values are correlated with better trabecular structure (11). TBS can be readily applied to a DXA image through the use of a specific software, and has an attractive feature which is the possibility of being retrospectively calculated from an existing DXA image without the need for further imaging (12).

TRABECULAR BONE SCORE: TECHNICAL ASPECTS

TBS takes into account the pixel gray-level variations in the DXA image. The basic principles of TBS include the following points: a 2D projection image of a porous trabecular structure has a low number of pixel value variations of high amplitude, whereas the projection of a well-structured trabecular bone onto a plane produces an image with a large number of pixel value variations of small amplitude (9). TBS is derived from an experimental variogram of those projected images, calculated as the sum of the squared gray-level differences between pixels at a specific distance and angle. TBS is then calculated as the slope of the log-log transform of the 2D variogram. A low TBS value is associ-

ated with worse bone structure, while high TBS values are correlated with better bone structure (11). Table 1 shows the TBS cutoff points in postmenopausal women as suggested by expert opinion (13). Equivalent ranges for TBS in men have not yet been proposed.

Table 1. TBS cutoff points in postmenopausal women proposed by an international working group of TBS users (13)

TBS value (unitless)	Classification
≤ 1.200	Degraded microarchitecture
1.200 to 1.350	Partially degraded microarchitecture
≥ 1.350	Normal

TBS: trabecular bone score.

TBS, typically measured at the lumbar spine (LS), has a short-term *in vivo* precision of 1.12% - 2.1% (14-17). The TBS result is given for each vertebra and for the overall lumbar spine, as is done for the calculation of BMD. Fractured vertebrae are excluded from the TBS calculation. While a previous study has suggested that osteoarthritic changes of the LS have little effect on TBS (14), vertebrae with overt osteoarthritic changes are also excluded from the TBS analysis.

Several technical limitations of TBS analyses should be noted. As TBS is computed from DXA images, any image “noise” can influence the TBS evaluation. Additionally, TBS results may not be comparable across different densitometers, unless a TBS cross-calibration process utilizing a gray-level TBS phantom is utilized. Finally, excessive soft tissue in the abdomen, overlying the region of interest, may reduce the TBS estimate. In order to mitigate this problem *in vivo*, the TBS calculation is adjusted for body mass index (BMI). The use of BMI, however, is limited since it can not distinguish central abdominal weight accumulation, which would influence TBS derived from LS DXA, from adiposity at other sites. Of note, the adjustment in TBS for BMI is optimized when BMI is between 15 and 35 kg/m².

ASSOCIATION OF TBS WITH 3D MEASUREMENTS OF TRABECULAR MICROSTRUCTURE AND BONE STRENGTH

TBS results derived from both simulated 2D-projection μ CT images and LS DXA images were compared, in *ex vivo* studies, with 3D indices of bone microarchitecture assessed by μ CT (9-11,18). In general, TBS directly correlates with μ CT measures of bone volume fraction (BV/TV) (10,11,18), connectivity density (Conn. D)

(10,11), and trabecular number (Tb.N) (10,11), and inversely associated with μ CT indices of trabecular separation (Tb.Sp) (10,11) and structural model index (SMI) (18). Surprisingly, TBS was either not associated (18) or negatively correlated (11) with trabecular thickness (Tb.Th). These reported associations between TBS and μ CT parameters were not adjusted for age, and it remains unclear whether or not age-adjusted correlations would remain significant. Of note, TBS was also correlated with vertebral mechanical behavior in an *ex vivo* study of 16 human L3 lumbar vertebrae (18).

Studies by our group examined, for the first time *in vivo*, the correlations between TBS and 3D microarchitecture parameters (19,20). We assessed TBS from spine DXA images and correlated it with HRpQCT measurements at the radius and tibia in 22 postmenopausal women with primary hyperparathyroidism (PHPT) and in 115 pre- and postmenopausal Chinese-American and Caucasian women. The study of subjects with PHPT revealed significant correlations between LS TBS and HRpQCT measurements of Tb.N ($r = 0.505$), Tb.Sp ($r = -0.492$), cortical thickness ($r = 0.453$), volumetric densities ($r = 0.476$ to 0.507), and whole bone stiffness ($r = 0.442$) at the radius (all $p < 0.05$) (19). TBS was also positively associated with measures of cortical thickness ($r = 0.515$), volumetric densities ($r = 0.471$ to 0.619), and whole bone stiffness at the tibia ($r = 0.516$; all $p < 0.05$), but its association with Tb.N and Tb.Sp was significant only after controlling for body weight ($r = 0.573$ and $r = -0.524$, respectively). TBS was not associated with Tb.Th or trabecular stiffness at either the radius or the tibia.

In the study of Chinese-American and Caucasian women (71 pre- and 44 postmenopausal), all HRpQCT indices at the radius and tibia, except cortical thickness at the radius and Tb.Th at the tibia, were correlated with LS TBS. These correlations, however, were weak to moderate ($r = 0.20$ to 0.52 ; all $p < 0.05$) (20). In this cohort, we have also examined the associations between LS TBS and indices of central quantitative computed tomography (QCT) at the LS and femur. TBS was directly associated with QCT parameters of LS trabecular volumetric BMD ($r = 0.664$), with trabecular and cortical volumetric densities and with an estimate of cortical thickness at the femoral neck ($r = 0.641$, 0.346 , and 0.540 respectively) and total hip ($r = 0.547$, 0.491 , and 0.541 , respectively) (all $p < 0.001$). Adjustment for weight or BMI did not change the direction or significance of the correlations. The combination of

TBS with LS aBMD better predicted the variance in QCT measures than aBMD alone.

More recently, the association of TBS with HRpQCT indices was investigated in 72 healthy premenopausal women (mean age 33.8 years) (21). TBS was associated with trabecular volumetric BMD ($r = 0.49$ to 0.57), Tb.N ($r = 0.43$ to 0.58), Conn.D ($r = 0.43$ to 0.46), and Tb.Sp ($r = -0.43$ to -0.57), at the radius and tibia (all $p < 0.01$). There was a weak correlation between TBS and Tb.Th at the radius ($r = 0.37$; $p < 0.01$), but not at the tibia. TBS was either weakly or not associated with HRpQCT measures of cortical density, thickness and porosity.

RELATIONSHIP OF TBS WITH AGE AND MAJOR CLINICAL RISK FACTORS

TBS tends to decline with age as shown in cross-sectional studies (14,22,23). Dufour and cols. observed, in 5,942 Caucasian French women (BMI < 40 kg/m²), a linear decline of 14.5% in L1-L4 TBS between 45 and 85 years of age (14). Age related declines in LS BMD and TBS were also observed in a large cross-sectional study of 29,407 women ≥ 50 years from the province of Manitoba, Canada (22). Similarly, a negative correlation between L2-L4 TBS and age ($r = -0.39$, $p < 0.001$) was observed in 4,907 Lebanese women from 20 to 90 years of age (23).

In addition, TBS was associated with many of the risk factors that are predictive of osteoporotic fractures (22). Reduced TBS (lowest versus highest tertile) was associated, after adjusting for age and bone preserving treatment, with prior major fracture, rheumatoid arthritis, chronic obstructive pulmonary disease, recent glucocorticoid use, alcohol or other substance abuse, and higher BMI.

ASSOCIATION OF TBS WITH FRACTURE RISK

A number of cross-sectional (24-29) and prospective (15,16,30,31) studies have shown an association between LS TBS and vertebral, hip, and other types of osteoporotic fractures in postmenopausal women. A recent published cross-sectional study has also demonstrated that TBS is associated with fractures in men (32).

Cross-sectional studies

Table 2 summarizes the data from cross-sectional studies. The studies in postmenopausal women were, in

general, retrospective case-control studies, in which cases were women with vertebral fractures [confirmed either by radiographs or vertebral fracture assessment (VFA)] or with a history of hip (27) or other types of osteoporotic fractures (24-26,28,29). Control groups comprised women without evidence of any type of fragility fracture either not matched for age or BMD with cases (27,29), or matched with cases for age (25,26,28) or for age and BMI (24). Overall, TBS was significantly lower in cases than in controls, and both TBS and any BMD measurement were associated with fractures (Table 2). In a few studies, the combination of TBS with LS BMD was a better predictor of vertebral fractures than LS BMD alone (25,26).

Data in men, while limited, are similar. A retrospective non-randomized case-control study enrolled 180 men ≥ 40 years old (BMI ranging from 17 to 36 kg/cm²), 45 of whom had a history of a low-energy fracture after the age of 40 (32). Study subjects had sustained 59 fractures, including spine (34%), hip (14%), forearm (19%), ankle (13%), humerus and rib (5% each) fractures. The control group consisted of 135 age- and LS BMD-matched men without evidence of low-energy fractures by self-report. TBS was lower in men with than in those without fractures (1.102 ± 0.129 vs. 1.159 ± 0.134, respectively; p = 0.013). Unadjusted odds ratios (ORs) for osteoporotic fractures and vertebral fracture (n = 17) were, respectively, 1.55 (95% CI 1.09–2.20), and

Table 2. Summary of cross-sectional studies

Citation	Participants	Outcome measure	OR (95% CI) for LS TBS	OR (95% CI) for LS BMD
Pothuaud and cols. 2009 (24)	135 postmenopausal women (45 Fx subjects and 90 age- and LS BMD-matched controls) For vertebral Fx analyses: (20 Fx subjects and 60 matched controls)	Vertebral, hip and other types of osteoporotic Fx (confirmed by radiographs)	Unadjusted: All Fx: 1.95 (1.31–2.89); Vertebral Fx: 2.66 (1.46–4.85)	Not applicable (cases and controls were matched for BMD)
Winzenrieth and cols. 2010 (25)	243 postmenopausal women with osteopenia at LS (81 subjects with vertebral Fx and 162 age-matched controls)	Vertebral Fx (on radiographs)	Body weight-adjusted: Vertebral Fx: 1.97 (1.31–2.96)	Body weight-adjusted: Vertebral Fx: 1.63 (1.20–2.22)
Rabier and cols. 2010 (26)	168 postmenopausal women with T-score < -1.0 at any site (42 subjects with vertebral Fx and 126 age-matched controls)	Vertebral Fx (on radiographs)	Body weight-adjusted: Vertebral Fx: 3.81 (2.17–6.72)	Body weight-adjusted: Vertebral Fx: 2.48 (1.61–3.83)
Del Rio and cols. 2013 (27)	191 postmenopausal women (83 Fx subjects and 108 not matched controls)	Osteoporotic femoral neck Fx (by self-report)	Age-adjusted: Femoral neck Fx: 1.71 (1.15–2.79)	Age-adjusted: Femoral neck Fx: 1.94 (1.35–2.79)
Krueger and cols. 2014 (28)	429 postmenopausal women (158 Fx subjects, including 91 vertebral Fx, and 271 age-matched controls)	Low-energy Fx (by self-report) and vertebral Fx (on VFA)	Age and BMI-adjusted: All Fx: 2.46 (1.9–3.1) Vertebral Fx: 2.49 (1.9–3.3)	Age and BMI-adjusted: All Fx: 1.36 (1.2–1.6) Vertebral Fx: 1.36 (1.1–1.7)
Lamy and cols. 2012 (29)	631 postmenopausal women (8.4% with vertebral Fx, 17% with major osteoporotic Fx, and 26% with at least 1 osteoporotic Fx)	Low-energy Fx (by self-report) and vertebral Fx (on VFA)	Age and BMI-adjusted: All Fx: 1.4 (1.1–1.7) Vertebral Fx: 2.0 (1.4–3.0) Major osteoporotic Fx: 1.9 (1.4–2.5)	Age and BMI-adjusted: All Fx: 1.3 (1.1–1.6) Vertebral Fx: 1.8 (1.2–2.5) Major osteoporotic Fx: 1.6 (1.2–2.1)
Leib and cols. 2013 (32)	180 men > 40 years old (45 Fx subjects, and 135 age- and LS BMD-matched controls)	Low-energy Fx (by self-report)	Unadjusted: All Fx: 1.55 (1.09–2.20)	Not reported
Nassar and cols. 2014 (33)	362 men and women > 50 years old (77% women) with a low-trauma non-vertebral Fx, including 133 with at least one concurrent vertebral Fx	Vertebral Fx (on VFA) Subjects with both non-vertebral and vertebral Fx were compared to subjects with non-vertebral Fx only	ORs not reported (see text for detailed results)	

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TBS: trabecular bone score; OR: odds ratio; Fx: fracture. LS: lumbar spine.

2.07 (95% CI 1.14–3.74), for each SD decline in TBS. It is noteworthy that the control men had a TBS score that would be considered to be low for women, underscoring the point that there are not normal TBS standards yet for men.

LS TBS in a group of men and women was also examined in a cross-sectional study that included 362 subjects over 50 years old (77% women, mean age 74 ± 12 years) who had been hospitalized, within 4 to 90 days prior to the enrollment, for the treatment of a low-trauma non-vertebral fracture (33). Vertebral fractures were then assessed by VFA, and subjects were allocated to one of 2 groups based on the absence ($n = 229$) or presence of at least one vertebral fracture ($n = 133$; 57 grade 1, 47 grade 2, and 29 grade 3). TBS was significantly lower in patients with vertebral and non-vertebral fractures than in those with non-vertebral fractures only (1.157 ± 0.108 vs. 1.227 ± 0.107 ; $p < 0.0001$), as was BMD T-score at the LS, femoral neck, and total hip. TBS, LS BMD and total hip BMD predicted vertebral fractures equally well, with areas under the receiving operator curve (AUCs) of 0.677, 0.669, and 0.692, respectively. The combination of TBS with LS BMD improved vertebral fracture discrimination as compared to LS BMD alone ($p = 0.043$), but not with total hip alone ($p = 0.327$). In the 173 subjects with BMD T-scores in the non-osteoporotic range, among whom 38 had a prevalent a vertebral fracture, TBS was a better discriminator of vertebral fractures than LS BMD alone (AUCs of 0.671 vs. 0.541; $p = 0.035$), but similar to total hip BMD alone (AUCs of 0.670 vs. 0.585; $p = 0.264$). The small number of cases, however, limits this analysis.

Prospective studies

Data from prospective studies are summarized in table 3 (15,16,30,31). The Manitoba study was the largest one to examine the ability of LS TBS to predict fracture risk (16). The study enrolled 29,407 women ≥ 50 years from the Canadian province of Manitoba, and showed that LS TBS at baseline predicted new clinical vertebral, hip and major osteoporotic fractures over a mean follow-up of 4.7 years. The combination of TBS with any BMD measurement (LS, femoral neck or total hip) was a better predictor of osteoporotic fracture than BMD alone ($p < 0.0001$). However, the AUC for TBS + BMD was only slightly greater than the AUC for BMD alone (+ 0.02, + 0.01, and + 0.01, compared to

LS, femoral neck and total hip, respectively). Of note, LS TBS remained a predictor of fracture even after adjusting for BMD and additional clinical risk factors.

In another prospective study, Boutrouy and cols. (30) evaluated 560 postmenopausal Caucasian women from the OFELY cohort, and showed that TBS and LS BMD predicted any type of fragility fracture equally well. The association between TBS and fracture remained even after controlling for age, body weight and prevalent fracture at baseline. Thirty-seven percent of fractures occurred in women with LS TBS < 1.209 (lowest quartile), and having a TBS below that threshold was a predictor of fracture risk in non-osteoporotic women [OR 2.75 (95% CI 1.47-5.17)], but not in osteoporotic subjects.

In the prospective study by Iki and cols. (31), TBS was a predictor of incident vertebral fractures on VFA (Table 3). LS BMD, TBS, and LS BMD + TBS predicted vertebral fractures equally well, with AUCs of 0.673, 0.682, and 0.700, respectively. There was a higher incidence rate of vertebral fracture in the lower TBS tertile group in each BMD stratum.

Finally, the Osteoporosis and Ultrasound Study (OPUS) (15) examined the added value of TBS to BMD for prediction of fractures in 1,007 postmenopausal women (Table 3). Women with incident fractures were older than non-fractured subjects. The AUCs for TBS, BMD (at LS, femoral neck, and total hip), and the combination of TBS with any BMD measurement were similar. The performance of TBS, BMD and TBS + BMD for fracture prediction was examined using reassignment analysis assessed by net reclassification improvement (NRI). While for prediction of incident clinical osteoporotic fractures the combination of TBS with LS BMD was similar to LS BMD alone (NRI = 10.5%, $p = 0.105$), for prediction of vertebral fractures, TBS and LS BMD together increased the performance over LS BMD alone (NRI = 8.6%, $p = 0.046$).

ROLE OF TBS IN SECONDARY OSTEOPOROSIS

Diabetes mellitus

A retrospective cohort study examined, in the Manitoba cohort described above, 29,407 women ≥ 50 years, including 2,356 (8.1%) who had *diabetes mellitus* (34). While BMD at all sites was higher among those with diabetes, TBS was consistently lower, in unadjusted and adjusted models (all $p < 0.001$). Over a mean follow-

Table 3. Summary of prospective studies

Citation	Participants	Mean follow-up period	Outcome measure	Risk ratio (95% CI) for LS TBS	Risk Ratio (95% CI) for LS BMD	Risk Ratio (95% CI) TH BMD
Manitoba Hans and cols. 2011 (16)	29,407 postmenopausal women \geq 50 years (5.7% (1,668) of subjects presented incident osteoporotic Fx, including 1.5% clinical vertebral and 1.0% hip Fx)	4.7 years	Incident clinical vertebral, hip and major osteoporotic Fx (assessed in health service records by fracture codes)	Age-adjusted: Clinical vertebral Fx: HR = 1.45 (1.32–1.58); Major osteoporotic Fx: HR = 1.35 (1.29–1.42); Hip Fx: 1.46 (1.30–1.63)	Age-adjusted: Clinical Vertebral Fx: HR = 1.72 (1.55–1.91); Major osteoporotic Fx: HR = 1.47 (1.39–1.55); Hip Fx: 1.31 (1.16–1.48)	Age-adjusted: Clinical Vertebral Fx: HR = 1.75 (1.58–1.96); Major osteoporotic Fx: HR = 1.67 (1.58–1.76); Hip Fx: 2.55 (2.22–2.93)
OFELY Boutroy and cols. 2013 (30)	560 postmenopausal women (94 subjects had an incident fragility Fx at any site)	8.0 years	Incident clinical and radiographic vertebral Fx and fragility Fx at any site, except head, toes and fingers (all Fx were confirmed by radiographs)	Adjusted for age, weight and prevalent Fx at baseline: Any type of osteoporotic Fx: OR = 1.34 (1.04–1.73)	Adjusted for age, weight and prevalent Fx at baseline: OR = 1.30 (1.06–1.58)	Adjusted for age, weight and prevalent Fx at baseline: OR = 1.99 (1.52–2.62)
JPOS Iki and cols. 2014 (31)	665 postmenopausal women (92 subjects had an incident vertebral Fx)	8.3 years	Incident vertebral Fx (by VFA)	Age- and LS BMD-adjusted: Vertebral Fx: OR = 1.54 (1.17–2.02)	Age- and TBS-adjusted: Vertebral Fx: OR = 1.27 (1.02, 1.59)	Not measured
OPUS Briot and cols. 2013 (15)	1,007 postmenopausal women $>$ 50 years (8.1% (82) e 4.6% (46) of subjects presented with incident osteoporotic Fx, and vertebral Fx, respectively)	6.0 years	Incident vertebral Fx (by radiographs) and low-trauma Fx (by self-report)	Unadjusted: Vertebral Fx: OR = 1.54 (1.17–2.03); Clinical osteoporotic Fx: OR = 1.62 (1.30–2.01)	Unadjusted: Vertebral Fx: OR = 1.75 (1.25–2.48); Clinical osteoporotic Fx: OR = 1.47 (1.16–1.89)	Unadjusted: Vertebral Fx: OR = 1.73 (1.26–2.38); Clinical osteoporotic Fx: OR = 1.65 (1.30–2.11)

TBS: trabecular bone score; BMD: bone mineral density; OR: odds ratio; HR: hazard ratio; Fx: fracture; LS: lumbar spine; TH: total hip.

up period of 4.7 years, and after covariate adjustment, the risk for major osteoporotic fracture was 49% greater (HR 95% CI 1.27–1.74) in women with diabetes than in those without diabetes. While BMD did not predict fracture among the diabetes cohort, TBS was a BMD-independent predictor of fracture, and predicted fractures in those with diabetes (adjusted HR 1.27, 95%CI 1.10–1.46) as well as in nondiabetic women (HR 1.31, 95%CI 1.24–1.38).

Primary hyperparathyroidism

The association of vertebral fracture and TBS was examined in a cross-sectional study of 73 postmenopausal women with primary hyperparathyroidism (PHPT) compared to 74 age-matched healthy women (35). While LS BMD and femoral neck BMD were similar between the groups, TBS was significantly lower in subjects with PHPT (1.19 ± 0.10) than in controls (1.24 ± 0.09 , $p < 0.01$). Total hip and 1/3 radius

BMDs were also lower in PHPT subjects ($p < 0.01$). In the PHPT group, TBS was significantly lower in subjects with ($n = 29$) than in those without ($n = 44$) radiographic vertebral fractures (1.14 ± 0.10 vs. 1.22 ± 0.10 , respectively; $p < 0.01$), with an AUC of 0.716 (95%CI: 0.590–0.841; $p = 0.002$). PHPT patients with ($n = 18$) and without ($n = 55$) non-vertebral fractures had similar TBS values.

A prospective observational study has also evaluated TBS in patients with PHPT ($n = 92$; 74 females; mean age 62.7 ± 10.1 years) and 98 control subjects (36). Vertebral fractures were assessed by radiographs. PHPT subjects had, at baseline, a lower TBS Z-score (-2.39 ± 1.79), and higher prevalence of vertebral fracture (43.5%) than controls (Z-score of -0.98 ± 1.07 and 8.2%, respectively, both $p < 0.0001$). Compared to controls, subjects with PHPT also had significantly lower BMD measurements at all sites. Among subjects with PHPT, each SD decline in TBS conferred 40%

greater risk of vertebral fracture (OR 1.4, 95%CI 1.1-1.9, $p = 0.02$), regardless of LS BMD, age, BMI and gender. In the PHPT group, 20 subjects who underwent parathyroidectomy were compared with 10 non-surgically treated cases after 24 months. At month 24, TBS improved in surgically treated patients, whereas it remained stable in conservatively treated subjects. A recent study confirmed that TBS improves at 1 year following parathyroidectomy in subjects with PHPT (37).

Rheumatoid arthritis

A cross-sectional study evaluated 185 women (mean age 56 ± 14 years) known to have rheumatoid arthritis (RA) for 15.5 ± 9.9 years (38). Approximately 60% of the study population ($n = 112$) was in use of glucocorticoids (mean daily dose of 6.4 mg equivalent to prednisone). Both BMD T-scores and TBS were significantly lower among patients with vertebral fracture ($n = 33$; 17.8%) than in non-fractured individuals. The AUCs for vertebral fracture were similar for TBS (0.704), LS BMD (0.621), femoral neck BMD (0.727), and total hip BMD (0.719).

Adrenal incidentaloma and subclinical hypercortisolism

The association between TBS and fractures was explored in 102 patients with adrenal incidentaloma [AI; 63 females; 34 with subclinical hypercortisolism (SH)], and 70 matched controls (39). In patients, vertebral fractures were assessed by X-rays. Z-scores were used to report TBS and BMD. TBS (-3.18 ± 1.21) was lower in subjects with SH than in patients without SH (-1.70 ± 1.54 , $p < 0.0001$) or controls (-1.19 ± 0.99 , $p < 0.0001$), as was LS BMD and total femur BMD. A low TBS, as defined by a TBS Z-score < -1.5 , was associated with the presence of vertebral fracture, regardless of age, BMI, and gender [OR = 4.8 (95% CI 1.85-12.42), $p < 0.001$]. A subgroup of 40 patients was followed for 24 months, and among them, TBS predicted the occurrence of a new fracture even after adjusting for LS BMD, BMI, and age (OR = 11.2; 95%CI, 1.71-71.41, $p < 0.012$).

Other conditions

A recent prospective study evaluated the effect of growth hormone (GH) replacement on TBS in 147 subjects with growth hormone deficiency (GHD; mean age 35.1 years; 84 males) (40). Compared to baseline,

there was a significant increase in BMD at LS (+14%) and total femur (+7%) at 2 years of GH replacement (both $p \leq 0.001$). TBS, obtained in a subgroup of 32 subjects with GHD, was also improved after 2 years of GH replacement. However, the reported result (4% gain at 2 years) was recorded at the level of L4 only, which limits this analysis.

Data reported in abstracts also showed that TBS is related to fractures in individuals with chronic kidney disease (41) and on long-term glucocorticoid (GC) therapy (42). The study of 47 women with CKD (grade not reported), and 94 healthy women (73% postmenopausal) showed that, compared to controls, subjects with CKD have reduced TBS ($p < 0.0001$) (41). In the CKD group, while no difference was seen for BMD ($p = 0.46$), TBS was significantly lower in subjects with a prior fracture (number of fractures not reported) than in non-fractured subjects ($p = 0.034$), with an unadjusted OR of 2.5 (95% CI 1.02-6.15), and AUC of 0.756 (0.609-0.870). Age- or BMI-adjusted ORs were not reported.

Finally, the impact of long-term GC therapy on TBS was explored in 136 women, aged 45 to 80 years, treated with GCs (≥ 5 mg/day) for ≥ 1 year (42). Compared with the age-matched normal values, GC-treated patients had a 4% decrease in TBS ($p < 0.0001$), but no change in BMD ($p = 0.49$). In GC treated-patients, the age-adjusted OR for TBS was 1.62 (95% CI 1.02-2.59) for vertebral fracture and 1.60 (95% CI 1.04-2.47) for osteoporotic peripheral fracture. The association between fracture risk and BMD was not significant.

EFFECT OF OSTEOPOROSIS THERAPY ON TBS

The impact of different osteoporosis therapy on TBS has been evaluated (17,43-47) and the results are summarized in table 4. In general, the change in TBS in response to osteoporosis therapy was of smaller magnitude than the change in LS BMD. Additionally, the change in TBS appears to be a function of the therapeutic class, with greater improvements observed upon treatment with teriparatide and strontium ranelate. Overall, the treatment with bisphosphonates led to a slight increase or maintenance of TBS over ~ 3 years (Table 4). Further research is needed to determine the role of TBS for monitoring treated or untreated osteoporosis and, if this is class-specific, which agents are more likely to show increases in TBS.

Table 4. Summary of studies that evaluated the impact of different osteoporosis therapies on LS TBS

Citation	Participants	Mean follow-up period	Treatment	Number of subjects per treatment group	Percent change in LS TBS relative to baseline	Percent change in LS BMD relative to baseline
Krieg and cols. 2013 (43)	1,684 women ≥ 50 years old	3.7 years	Antiresorptive agents*	534	+0.2 ± 1.9 % / year*	+1.86 ± 1.8 % / year*
			Untreated subjects	1,150	-0.31 ± 0.06 % / year*	-0.36 ± 0.05 % / year*
Popp and cols. (17) 2013	Subset of 107 postmenopausal women from the HORIZON trial	3 years	Zoledronic acid	54	At 3 years: +1.41 ± 0.79%*	At 3 years: +9.58 ± 0.6%*
			Placebo	53	At 3 years: -0.49 ± 0.62%	At 3 years: +1.38 ± 0.9%*
Kalder and cols. 2014 (44)	Subset of 36 postmenopausal women with hormone-sensitive primary breast cancer from the TEAM trial	2 years	Tamoxifene	17	At 2 years: +3.3 ± 1.6%*	At 2 years: +1.9 ± 0.8%*
			Exemestane	19	At 2 years: -2.3 ± 1.1%*	At 2 years: -5.3 ± 0.9%*
McClung and cols. 2012 (45)®	285 postmenopausal women from the FREEDOM trial, with LS or total hip BMD T-score < -2.5, and with both > -4.0	3 years	Denosumab	157	At 3 years: +2.4%*	At 3 years: +9.8%*
			Placebo	128	At 3 years: -0.7%	At 3 years: +0%
Günther and cols. 2012 (46)®	82 postmenopausal women with osteoporosis (open label study)	2 years	Teriparatide	82	At 2 years: +4.3%*	At 2 years: +7.6%*
Hans and cols. 2012 (47)®	Subgroup of a 79 postmenopausal women with osteoporosis included in a double blind, double dummy study randomized to strontium ranelate or alendronate	2 years	Strontium ranelate	Not reported	At 2 years: +3.1%*	At 2 years: +9.0%*
			Alendronate		At 2 years: +1.0%	At 2 years: +7.6%*

TBS: trabecular bone score; LS: lumbar spine; BMD: bone mineral density; HORIZON trial: Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly; FREEDOM trial: Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; TEAM Study: Tamoxifene Exemestane Adjuvant Multinational Study.

* P < 0.05 compared to baseline. * 86% bisphosphonates, 10% raloxifene, and 4% calcitonin. ®Data reported in abstracts.

CONCLUSIONS – TRABECULAR BONE SCORE: FACTS AND FUTURE

TBS is an indirect index of bone microarchitecture that has a major clinical advantage of being readily available from DXA images. It is associated with 3D direct measures of trabecular microarchitecture, and with direct and indirect measures of bone strength. TBS declines with age, and is correlated with major clinical risk factors that are predictive of osteoporotic fractures. Several cross-sectional and prospective studies, involving a large number of postmenopausal women, have confirmed the association of TBS with vertebral and non-vertebral fractures. Data in men, while much less extensive, show similar findings. There is also evidence that, while TBS and LS BMD predict fracture equally well, TBS slightly improves fracture prediction when combined with any BMD measurement.

Indeed, these results provide support for utilizing TBS in conjunction with BMD to estimate fracture

risk. This approach may be especially useful in individuals with BMD values in the osteopenic range. This is of interest, since most individuals with fragility fractures will have BMD values not in the osteoporotic range but rather in the osteopenic or even normal range (48,49). This observation could be explained by other aspects of bone quality, such as bone microarchitecture, or even by readily assessable clinical risk factors that increase fracture risk independent of the BMD measurement. Thus, for those with BMD in the osteopenic range, TBS, when used in combination with the fracture risk assessment system (FRAX®), which incorporates clinical risk factors along with BMD (50), may have a role in fracture risk assessment. In fact, preliminary data have shown that TBS may improve fracture prediction when used in combination with FRAX® (51,52).

In addition to these data in primary osteoporosis, TBS was also shown to be associated with fractures in subjects with diverse secondary causes of osteoporosis.

sis. This is particularly attractive in those conditions in which the increase in fracture risk is largely independent of BMD by DXA, such as diabetes mellitus or long-term GC exposure. Similarly, in asymptomatic PHPT, the trabecular bone as assessed by LS BMD appears relatively well preserved, whereas epidemiological studies show increased fracture risk in vertebral and non-vertebral sites. While these unexpected findings between fracture risk and BMD by DXA may be explained by an inferior bone microarchitecture, current methods to assess microstructure are not routinely available, so that TBS could be used, combined with BMD, for fracture-risk assessment in such cases of secondary osteoporosis.

Finally, current data do not support the use of TBS to estimate antifracture effectiveness of diverse osteoporosis treatments, and further research is needed to evaluate the value of TBS for monitoring treatment effect.

There are a number of areas for future research and delineation. A well-established TBS cut-point that classifies normal and abnormal TBS values has not yet been defined. The TBS reference range that has been proposed so far (Table 1), which applies to postmenopausal women only, was recommended by a working group of TBS users. This definition remains to be definitively established across age and gender. Also, as noted before, the use of TBS in subjects with BMI below 15 kg/m² and over 35 kg/m² has not been validated.

Additionally, while there are extensive data establishing an association between TBS and fracture risk in postmenopausal women, data in men are limited. Of note, when TBS is derived from DXA images obtained in GE-Lunar densitometers, TBS appears to be lower in men than in women, which is surprising given the previous observations of better trabecular microarchitecture in aging men than in women by histomorphometry and HRpQCT (53,54).

Finally, despite the strong correlations between TBS and 3D measures of trabecular microarchitecture in *ex vivo* studies, studies *in vivo* have shown only moderate correlations. Additionally, the majority of the studies did not find an association between TBS and trabecular thickness, indicating that TBS may not fully capture some aspects of bone microstructure assessed by higher resolution imaging modalities.

In conclusion, current data on lumbar spine TBS are promising. If further studies establish TBS cut-points across age and gender, and confirm that TBS improves fracture prediction from FRAX, TBS could become a valuable adjunctive clinical tool in fracture risk assess-

ment, assisting in therapeutic decision-making particularly in those at intermediate risk for fracture.

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REFERENCES

1. Osteoporosis prevention, diagnosis, and therapy. NIH Consens Statement. 2000;17(1):1-45.
2. Kulak CA, Dempster DW. Bone histomorphometry: a concise review for endocrinologists and clinicians. *Arq Bras Endocrinol Metabol.* 2010;54(2):87-98.
3. Hildebrand T, Laib A, Müller R, Dequeker J, Rüdiger P. Direct three-dimensional morphometric analysis of human cancellous bone: microstructural data from spine, femur, iliac crest, and calcaneus. *J Bone Miner Res.* 1999;14(7):1167-74.
4. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab.* 2005;90(12):6508-15.
5. Krug R, Carballido-Gamio J, Banerjee S, Burghardt AJ, Link TM, Majumdar S. In vivo ultra-high-field magnetic resonance imaging of trabecular bone microarchitecture at 7 T. *J Magn Reson Imaging.* 2008;27(4):854-9.
6. Prouteau S, Ducher G, Nanyan P, Lemineur G, Benhamou L, Courteix D. Fractal analysis of bone texture: a screening tool for stress fracture risk? *Eur J Clin Invest.* 2004;34(2):137-42.
7. Chappard D, Guggenbuhl P, Legrand E, Baslé MF, Audran M. Texture analysis of X-ray radiographs is correlated with bone histomorphometry. *J Bone Miner Metab.* 2005;23(1):24-9.
8. Vokes TJ, Giger ML, Chinander MR, Karrison TG, Favus MJ, Dixon LB. Radiographic texture analysis of densitometer-generated calcaneus images differentiates postmenopausal women with and without fractures. *Osteoporos Int.* 2006;17(10):1472-82.
9. Pothuaud L, Carceller P, Hans D. Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: applications in the study of human trabecular bone microarchitecture. *Bone.* 2008;42(4):775-87.
10. Winzenrieth R, Michelet F, Hans D. Three-dimensional (3D) microarchitecture correlations with 2D projection image gray-level variations assessed by trabecular bone score using high-resolution computed tomographic acquisitions: effects of resolution and noise. *J Clin Densitom.* 2013;16(3):287-96.
11. Hans D, Barthe N, Boutroy S, Pothuaud L, Winzenrieth R, Krieg MA. Correlations between trabecular bone score, measured using anteroposterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae. *J Clin Densitom.* 2011;14(3):302-12.
12. Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, et al. Trabecular bone score: a non-invasive analytical method based upon the DXA image. *J Bone Miner Res.* 2014;29(3):518-30.
13. Cormier C, Lamy O, Poriau S. TBS in routine clinical practice: proposals of use. For the Medimaps Group, 2012: Accessed on: <http://www.medimapsgroup.com/upload/MEDIMAPS-UK-WEB.pdf>.

14. Dufour R, Winzenrieth R, Heraud A, Hans D, Mehsen N. Generation and validation of a normative, age-specific reference curve for lumbar spine trabecular bone score (TBS) in French women. *Osteoporos Int.* 2013;24(11):2837-46.
15. Briot K, Paternotte S, Kolta S, Eastell R, Reid DM, Felsenberg D, et al. Added value of trabecular bone score to bone mineral density for prediction of osteoporotic fractures in postmenopausal women: The OPUS study. *Bone.* 2013;57(1):232-6.
16. Hans D, Goertzen AL, Krieg MA, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. *J Bone Miner Res.* 2011;26(11):2762-9.
17. Popp AW, Guler S, Lamy O, Senn C, Buffat H, Perrelet R, et al. 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.* 2013;28(3):449-54.
18. Roux JP, Wegrzyn J, Boutroy S, Bouxsein ML, Hans D, Chapurlat R. The predictive value of trabecular bone score (TBS) on whole lumbar vertebrae mechanics: an ex vivo study. *Osteoporos Int.* 2013;24(9):2455-60.
19. Silva BC, Boutroy S, Zhang C, McMahon DJ, Zhou B, Wang J, et al. Trabecular bone score (TBS)--a novel method to evaluate bone microarchitectural texture in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2013;98(5):1963-70.
20. Silva BC, Walker MD, Abraham A, Boutroy S, Zhang C, McMahon DJ, et al. Trabecular bone score is associated with volumetric bone density and microarchitecture as assessed by central QCT and HRpQCT in Chinese American and white women. *J Clin Densitom.* 2013;16(4):554-61.
21. Popp AW, Buffat H, Eberli U, Lippuner K, Ernst M, Richards RG, et al. Microstructural Parameters of Bone Evaluated Using HR-pQCT Correlate with the DXA-Derived Cortical Index and the Trabecular Bone Score in a Cohort of Randomly Selected Premenopausal Women. *PLoS One.* 2014;9(2):e88946.
22. Leslie WD, Krieg MA, Hans D; Manitoba Bone Density Program. Clinical Factors Associated With Trabecular Bone Score. *J Clin Densitom.* 2013;16(3):374-379.
23. El Hage R, Khairallah W, Bachour F, Issa M, Eid R, Fayad F, et al. Influence of Age, Morphological Characteristics, and Lumbar Spine Bone Mineral Density on Lumbar Spine Trabecular Bone Score in Lebanese Women. *J Clin Densitom.* 2013 Apr 9. pii: S1094-6950(13)00049-8.
24. Pothuau L, Barthe N, Krieg MA, Mehsen N, Carceller P, Hans D. Evaluation of the potential use of trabecular bone score to complement bone mineral density in the diagnosis of osteoporosis: a preliminary spine BMD-matched, case-control study. *J Clin Densitom.* 2009;12(2):170-6.
25. Winzenrieth R, Dufour R, Pothuau L, Hans D. A retrospective case-control study assessing the role of trabecular bone score in postmenopausal Caucasian women with osteopenia: analyzing the odds of vertebral fracture. *Calcif Tissue Int.* 2010;86(2):104-9.
26. Rabier B, Heraud A, Grand-Lenoir C, Winzenrieth R, Hans D. A multicentre, retrospective case-control study assessing the role of trabecular bone score (TBS) in menopausal Caucasian women with low areal bone mineral density (BMDa): Analysing the odds of vertebral fracture. *Bone.* 2010;46(1):176-81.
27. Del Rio LM, Winzenrieth R, Cormier C, Di Gregorio S. Is bone microarchitecture status of the lumbar spine assessed by TBS related to femoral neck fracture? A Spanish case-control study. *Osteoporos Int.* 2013;24(3):991-8.
28. Krueger D, Fidler E, Libber J, Aubry-Rozier B, Hans D, Binkley N. Spine trabecular bone score subsequent to bone mineral density improves fracture discrimination in women. *J Clin Densitom.* 2014;17(1):60-5.
29. Lamy O, Krieg MA, Stoll D, Aubry-Rozier B, Metzger M, Hans D. The OsteoLaus Cohort Study: Bone mineral density, microarchitecture score and vertebral fracture assessment extracted from a single DXA device in combination with clinical risk factors improve significantly the identification of women at high risk of fracture. *Osteologie.* 2012;21:77-82.
30. Boutroy S, Hans D, Sornay-Rendu E, Vilayphiou N, Winzenrieth R, Chapurlat R. Trabecular bone score improves fracture risk prediction in non-osteoporotic women: the OFELY study. *Osteoporos Int.* 2013;24(1):77-85.
31. Iki M, Tamaki J, Kadowaki E, Sato Y, Dongmei N, Winzenrieth R, et al. Trabecular bone score (TBS) predicts vertebral fractures in Japanese women over 10 years independently of bone density and prevalent vertebral deformity: the Japanese Population-Based Osteoporosis (JPOS) cohort study. *J Bone Miner Res.* 2014;29(2):399-407.
32. Leib E, Winzenrieth R, Aubry-Rozier B, Hans D. Vertebral microarchitecture and fragility fracture in men: A TBS study. *Bone.* 2014;62:51-5. doi: 10.1016/j.bone.2013.12.015. Epub 2013 Dec 19.
33. Nassar K, Paternotte S, Kolta S, Fechtenbaum J, Roux C, Briot K. Added value of trabecular bone score over bone mineral density for identification of vertebral fractures in patients with areal bone mineral density in the non-osteoporotic range. *Osteoporos Int.* 2014;25(1):243-9.
34. Leslie WD, Aubry-Rozier B, Lamy O, Hans D. TBS (Trabecular Bone Score) and Diabetes-Related Fracture Risk. *J Clin Endocrinol Metab.* 2013;98(2):602-9.
35. Romagnoli E, Cipriani C, Nofroni I, Castro C, Angelozzi M, Scarpicello A, et al. "Trabecular Bone Score" (TBS): an indirect measure of bone micro-architecture in postmenopausal patients with primary hyperparathyroidism. *Bone.* 2013;53(1):154-9.
36. Eller-Vainicher C, Filopanti M, Palmieri S, Olivieri FM, Morelli V, Zhukouskaya VV, et al. Bone quality, as measured by trabecular bone score, in patients with primary hyperparathyroidism. *Eur J Endocrinol.* 2013;169(2):155-62.
37. Rolighed L, Rejnmark L, Sikjaer T, Heickendorff L, Vestergaard P, Mosekilde L, et al. Vitamin D treatment in primary hyperparathyroidism: a randomized placebo controlled trial. *J Clin Endocrinol Metab.* 2014; jc20133978.
38. Breban S, Briot K, Kolta S, Paternotte S, Ghazi M, Fechtenbaum J, et al. Identification of rheumatoid arthritis patients with vertebral fractures using bone mineral density and trabecular bone score. *J Clin Densitom.* 2012;15(3):260-6.
39. Eller-Vainicher C, Morelli V, Olivieri FM, Palmieri S, Zhukouskaya VV, Cairoli E, et al. Bone quality, as measured by trabecular bone score in patients with adrenal incidentalomas with and without subclinical hypercortisolism. *J Bone Miner Res.* 2012;27(10):2223-30.
40. Kuzma M, Kuzmova Z, Zelinkova Z, Killinger Z, Vanuga P, Lazurova I, et al. Impact of the growth hormone replacement on bone status in growth hormone deficient adults. *Growth Horm IGF Res.* 2014;24(1):22-8.
41. Leib E, Stoll D, Winzenrieth R, Hans D. Lumbar spine microarchitecture impairment evaluation in chronic kidney disease: a TBS study. *J Clin Densitom.* 2013;16(Suppl):266(abstract).
42. Colson F, Picard A, Rabier B, Piperno M, Vignon E. Trabecular bone microarchitecture alteration in glucocorticoids treated women in clinical routine?: A TBS Evaluation. *J Bone Miner Res.* 2009;24(Suppl 1.):Abstract.
43. Krieg MA, Aubry-Rozier B, Hans D, Leslie WD. Effects of anti-resorptive agents on trabecular bone score (TBS) in older women. *Osteoporos Int.* 2013;24(3):1073-8.
44. Kalder M, Hans D, Kyvernitakis I, Lamy O, Bauer M, Hadji P. Effects of Exemestane and Tamoxifen treatment on bone texture analysis assessed by TBS in comparison with bone mineral density as-

- essed by DXA in women with breast cancer. *J Clin Densitom.* 2014;17(1):66-71.
45. McClung M, Lippuner K, Brandi M, Kaufman J-M, Zanchetta J, Krieg M, et al. Denosumab significantly improved trabecular bone score (TBS), an index of trabecular microarchitecture, in postmenopausal women with osteoporosis. *J Bone Miner Res.* 2012;27(Suppl 1):S58-S59 (abstract).
 46. Günther B, Popp A, Stoll D, Rosier B, Perrelet R, Hans D, et al. Beneficial effect of PTH on spine BMD and microarchitecture (TBS) parameters in postmenopausal women with osteoporosis. A 2-year study. *Osteoporosis Int.* 2012;23(Suppl 2):S332-S333(abstract).
 47. Hans D, Krieg M, Lamy O, Felsenberg D. Beneficial Effects of strontium ranelate compared to alendronate on trabecular bone score in post menopausal osteoporotic women. A 2-year study. *Osteoporosis Int.* 2012;23(Suppl 2):S265-S267(abstract).
 48. Siris ES, Miller PD, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA.* 2001;286(22):2815-22.
 49. Miller PD, Siris ES, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, et al. Prediction of fracture risk in postmenopausal white women with peripheral bone densitometry: evidence from the National Osteoporosis Risk Assessment. *J Bone Miner Res.* 2002;17(12):2222-30.
 50. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporosis Int.* 2007;18(8):1033-46.
 51. Leslie W, Kanis J, Lamy O, Johansson H, Oden A, McCloskey E, et al. Adjustment of FRAX probability according to lumbar spine Trabecular Bone Score (TBS): The Manitoba BMD Cohort. *J Clin Densitom.* 2013;16(Suppl):267-268(abstract).
 52. Lamy O, Krieg M, Stoll D, Aubry-Rozier B, Metzger M, Hans D. What is the performance in vertebral fracture discrimination by Bone mineral density (BMD), micro-architecture estimation (TBS), and FRAX in stand-alone, combined or adjusted approaches: The OsteoLaus Study. ECTS abstract. 2013.
 53. Aaron JE, Makins NB, Sagreiya K. The microanatomy of trabecular bone loss in normal aging men and women. *Clin Orthop Relat Res.* 1987(215):260-71.
 54. Khosla S, Riggs BL, Atkinson EJ, Oberg AL, McDaniel LJ, Holets M, et al. Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive in vivo assessment. *J Bone Miner Res.* 2006;21(1):124-31.