doi: 10.4183/aeb.2018.208

TRABECULAR BONE SCORE (TBS) HAS A POOR DISCRIMINATIVE POWER FOR VERTEBRAL FRACTURES IN 153 ROMANIAN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

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Abstract

Context. Trabecular Bone Score (TBS) has been recently proposed as a good tool to investigate secondary osteoporosis.

Objective. The aim of this study was to assess TBS from spine DXA images in patients with primary hyperparathyroidism (PHPT) and look at its correlates.

Subjects and Methods. 153 patients, mean age 59.1 ± 12.1 yrs, females and males (10%), mean BMI 26.2 ± 4.8 kg/m^2, mean serum calcium and PTH of 11.3 ± 1.2 mg/dL and 232 ± 329 pg/mL, respectively; 89% had osteoporosis/ osteopenia by LS DXA and 46% had renal involvement. There were 7.6% patients with vertebral fractures, 13.2% patients with nonvertebral fractures. TBS indices were derived from LS-DXA images and cutoff points used were those previously reported.

Results. Mean TBS was in the partially degraded range (1.258 ± 0.115); 32% of patients had degraded microarchitecture (TBS ≤ 1.20), 51% had partially degraded microarchitecture (TBS > 1.20 and < 1.35) and 17% had normal TBS. TBS was significantly correlated with areal BMD both at the LS (r=0.544; p<0.001) and FN (r = 0.315; p < 0.001), and negatively with age (r= - 0.354; p < 0.001) and years since menopause - YSM (r = - 0.257, p = 0.005). Patients with vertebral fractures had mean values of TBS in the degraded range, significantly lower than those without vertebral fractures (1.173 ± 0.076 *vs.* 1.263 ± 0.115; p = 0.006). The presence of vertebral fracture was independently associated only with YSM (OR = 1.131, 95% CI = 0.032 – 0.214, p = 0.008) but not with TBS.

Conclusions. In a cohort of symptomatic PHPT patients, including postmenopausal, premenopausal and male patients, we have shown that TBS was in the partially degraded range, but it was not independently associated with fractures.

Key words: Primary hyperparathyroidism, Trabecular Bone Score, Bone Mineral Density, fractures, BMI.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a frequent endocrine disease consisting of hypercalcemia and elevated or inappropriately normal levels of PTH. After the introduction on a large scale of autoanalyzers in our country, in the last three decades, the phenotype of PHPT changed from symptomatic with frequent osteitis fibrosa cystica to a mixture of symptomatic and asymptomatic forms PHPT, as everywhere (1). We have previously shown that, currently, larger than 2.5 g parathyroid tumors represent less than 30% of PHPT cases in our series of 187 patients (2). Bone involvement is currently assessed by measuring bone mineral density (BMD) at the three anatomical sites (lumbar spine, femoral neck and specifically distal radius). For many decades involvement of the trabecular bone has been considered less important and less specific than that of cortical bone. Now we know, from studies using HRpQCT, that in PHPT both compartments are involved, including reduced whole bone and trabecular stiffness by finite element analysis (FEA) (3). Many studies found evidence of increased fracture risk at both vertebral and nonvertebral sites in PHPT (4-8). As the increased risk was not reflected by spine BMD changes (5, 8) it has been proposed that a decrease in bone quality (altered microarchitecture) might explain the increased risk of vertebral fractures (9).

In the absence of a fracture the diagnosis of osteoporosis relies on BMD measurements by DXA, but this has a low sensitivity for detecting fractures. Indeed, the majority of fragility fractures occur in patients who have an areal BMD (aBMD) T-score >-2.5 (10). As aBMD by DXA is not effective in capturing all the determinants of bone fragility, "Trabecular Bone Score" (TBS) has been recently proposed as an indirect measure of trabecular microarchitecture (11).

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TBS is an analytical tool that performs novel grey-level texture measurements on lumbar spine DXA images, and thereby captures information relating to trabecular microarchitecture (12). In prospective cohorts low TBS was associated with increased risk of fractures, partly independent of BMD and clinical risk factors included in the FRAX tool (12,13). It has been suggested that TBS could be useful in the evaluation of bone involvement in secondary osteoporosis. A few studies have specifically addressed the usefulness of TBS in primary hyperparathyroidism (9,14-16). This study aimed to investigate the role of TBS in defining bone involvement in mostly symptomatic patients with PHPT.

PATIENTS AND METHODS

Patients

One hundred and fifty three patients with PHPT, mean age 59.1 ± 12.1 yrs (range 16 to 78), both females (90% postmenopausal, years since menopause YSM 14.1 ± 8.6) and males (10%), mean BMI 26.1 ± 4.8 kg/m^2, were selected from our database (2010 to 2016) if they had a valid LS DXA scan, before surgery, 27% being on treatment with bisphosphonates. PHPT was diagnosed in the presence of hypercalcaemia and elevated or inappropriately normal PTH levels. Familial hypocalciuric hypercalcemia was excluded, as well as other disorders of bone and mineral metabolism, chronic kidney and liver diseases. In our 153 patients, mean serum calcium and mean serum PTH were 11.3± 1.2 mg/dL and 232± 329 pg/mL, respectively. Many patients were symptomatic, as 89% had osteoporosis/osteopenia by LS DXA and 46% had renal involvement (nephrolithiasis). The prevalence of patients with osteoporosis, osteopenia or normal LS BMD by DXA was 49%, 40% and 11%, respectively. By FN BMD (116 patients) the prevalence of patients with osteoporosis, osteopenia or normal was 25%, 62% and 13%, respectively. By both sites BMD the prevalence was 58.5%, 37.3% and 4.2%, respectively. There were 7.6% patients with vertebral fractures, 13.2% patients with nonvertebral fractures and 1.4% with both types. Baseline characteristics of the 153 patients with PHPT are described in Table 1. The cohort was grouped according to World Health Organization's definition of obesity into two subgroups: BMI ≥ 30 kg/m^2 (obese) and BMI< 30 kg/m^2 (non-obese).

Table 1. Patients demographic, anthropometric and densitometric characteristics

Characteristics	N	Mean	SD
Age (yrs)	153	59.1	12.1
YSM (yrs)	117	14.1	8.6
BMI (kg/m^2)	153	26.2	4.8
LS BMS g/cm^2	153	0.916	0.155
LS T-score (SD)	153	-2.3	1.3
LS Z-score	153	-1.4	1.0
FN BMD (g/cm^2)	117	0.783	0.124
FN T-score	116	-1.8	0.9
FN Z-score	116	-0.7	0.8
TBS	153	1.258	0.115
TBS T-score	153	-2.3	1.3
TBS Z-score	153	-0.5	1.2

YSM = years since menopause; BMI = body mass index; LS-BMD = Bone Mineral Density at Lumbar Spine; FN-BMD = Bone Mineral Density at Femoral Neck; TBS = Trabecular Bone Score.

METHODS

Biochemistries

Fasting samples for serum calcium, phosphate, albumin, and creatinine were measured by an automated chemistry analyzer. Serum intact PTH was measured by electrochemiluminescence automated assay (Cobas, Roche).

Dual-energy X-ray absorptiometry

Areal bone density was measured at the lumbar spine, L1–L4 (LS) and femoral neck (FN) (GE-Lunar iDXA, USA). *In vivo* precision, determined according to the standard method at this facility, is 1.2 % at the lumbar spine and 1.5% at the femoral neck.

Trabecular bone score

Site-matched spine TBS parameters were extracted from the DXA images using TBS iNsight software (v 3.0.2.0, Medimaps Group, Geneva, Switzerland). For normative data of TBS values we used the cutoff points recommended in the literature (12): TBS >1.350 is normal; TBS between 1.200 and 1.350 is indicative of partially degraded microarchitecture; and TBS<1.200 equals degraded microarchitecture.

TBS was calculated as the mean value of the individual measurements for vertebrae L1–L4. Vertebrae excluded for BMD assessment were also excluded for TBS evaluation at lumbar spine.

Conventional spinal radiographs (T4–L4) in lateral projection were obtained with standardized technique. Vertebral fractures were diagnosed on visual inspection by one of us and independently by the radiologist, using the semiquantitative visual assessment (Genant HK *et al.*, 1993).

Statistical analysis

Statistical analysis was performed by JASP Version 0.8.5.1 (https://jasp-stats.org/). The results are expressed as mean ± SD. The comparison of continuous variables was performed using Student's t-test or Mann–Whitney U test as appropriate, after checking for assumption for distribution normality (Shapiro-Wilk test) and equality of variances (Levene's test). The logistic regression analysis was used to analyze the association between the presence of a prevalent fracture and TBS after adjusting for the following variables: age, years since menopause, BMI, and LS and FN-BMD. The odds ratio (OR) of YSM for detecting vertebral fractures was calculated. Multiple regression analysis assessed the association between TBS and independent variables. ANCOVA was used to analyze TBS differences between obese and non-obese patients after controlling for covariates. P values of <0.05 were considered significant.

All patients were given written informed consent.

RESULTS

Mean TBS was in the partially degraded range (1.258±0.115). 32% of patients with PHPT had degraded microarchitecture (TBS ≤1.20), an additional 51% had partially degraded microarchitecture (TBS>1.20 and <1.35) and only 17% had normal TBS. Only 9.7% of patients showing degraded or partially degraded microarchitecture by TBS had normal LS T-score, none with vertebral fractures.

In the whole group, TBS was significantly correlated with aBMD both at the LS (r = 0.544; p < 0.001) and FN (r = 0.315, p < 0.001), and negatively with age (r = - 0.354; p < 0.001) and years since menopause (YSM) (r = - 0.257, p = 0.005), but not with BMI.

The subjects with vertebral and nonvertebral fractures had TBS values significantly lower than in the subjects without fracture (1.212 ± 0.102 *vs.*1.268 ± 0.114, p = 0.01). The same was true also for TBS T-score (-2.8 ± 1.2 *vs.* -2.2 ± 1.3, p = 0.01) and LS BMD (0.837 ± 0.179mg/cm^2 *vs.* 0.933 ± 0.149 mg/cm^2, p < 0.001). Comparing patients with fracture *vs.* nonfracture by forward stepwise logistic regression analysis, including age, YSM, LS-BMD, FN-BMD and TBS as covariates, only age was significantly different (OR = 0.9, 95% CI = 0.842- 0.961, p = 0.002).

Patients with vertebral fractures had mean values of TBS in the degraded range, significantly lower than those without vertebral fractures (1.173 ± 0.076 *vs.* 1.263 ± 0.115; p = 0.006). They were also older, had a significantly longer YSM period and had lower LS and FN BMDs (Table 2). TBS and BMD Z-scores did not differ between groups. No patient with vertebral fracture had normal LS BMD or normal TBS.

There were three patients with vertebral fractures and osteopenia, only one in the TBS degraded range. Conversely, there were 5 patients with vertebral fractures in the range of partially degraded microarchitecture, 3 of them with osteoporosis and 2 with osteopenia by LS-BMD.

A forward stepwise logistic regression analysis, including age, YSM, LS-BMD, FN-BMD and TBS as covariates, was used to identify potential predictors of vertebral fractures. The presence of vertebral fractures in PHPT patients was independently associated only with YSM (OR = 1.131, 95% CI = 0.032 – 0.214, p = 0.008) but not with TBS.

In our cohort there were 32 obese (mean TBS =

Table 2. Mean values ± SD of demographic, anthropometric and densitometric data in PHPT patients categorized by the presence (VF+) or absence (VF−) of vertebral fractures

Characteristics	VF -	VF +	p	Effect size
Age (yrs)	58.2±12.1	68.9±7.9	<.001*	-0.570
YSM (yrs)	13.2±8.2	20.9±9.5	0.006*	-0.489
BMI (kg/m^2)	26.3±4.8	25.3±4.4	0.445	0.223
LS BMD g/cm^2	0.922±0.150	0.816±0.115	0.009*	0.441
LS T-score (SD)	-2.2±1.2	-3.1±0.9	0.007*	0.457
LS Z-score	-1.4±-1.0	-1.8±0.8	0.251	0.362
FN BMD (g/cm^2)	0.793±0.121	0.687±0.115	0.017*	0.459
FN T-score	-1.8±0.9	-2.5±0.8	0.012*	0.484
FN Z-score	-0.6±0.8	-0.9±0.9	0.325*	0.190
TBS	1.263±0.115	1.173±0.076	0.006	0.804
TBS T-score	-2.3±1.3	-3.3±0.9	0.005	0.821
TBS Z-score	-0.4±1.2	-0.9±0.8	0.08*	0.296

YSM = years since menopause; BMI = body mass index; LS-BMD = Bone Mineral Density at Lumbar Spine; FN-BMD = Bone Mineral Density at Femoral Neck; TBS = Trabecular Bone Score. *Mann Whitney U test. For the Student T-test effect size is given by the Cohen's d, for the Mann Whitney test by the rank biserial correlation.

1.307 ± 0.124) and 121 non-obese patients (mean TBS = 1.246 ± 0.110). After checking for assumption for distribution normality (Shapiro-Wilk test) and equality of variances (Levene's test) we compared TBS-score means for the 2 groups by independent samples t-Test: there was a significant difference (d = -0.545, p = 0.007). After controlling for LS BMD (ANCOVA), age, YSM, TBS remained significantly higher in the obese group, but the effect size is small (p = 0.03, η^2p = 0.042)

DISCUSSION

This is one of the few studies investigating the clinical value of TBS to assess skeletal fragility in patients with PHPT, but the largest published to date. In our group with rather symptomatic patients, the main observations are: 1. For the whole group, TBS-score's mean was in the partly degraded range. 2. Patients with vertebral fractures had mean values of TBS in the degraded range; 3. Prevalent vertebral fractures were associated independently only with YSM. The latter result is quite interesting as it suggests the fractures are the consequences of postmenopausal osteoporosis rather than of superimposed primary hyperparathyroidism. On the other hand, the study was performed in an osteoporosis referral center, which might have caused some selection bias.

The interest in looking at how well perform TBS in PHPT patients is double: the increased risk of fracture in this condition of secondary osteoporosis and evaluating the discriminative power of TBS in predicting fracture, as BMD does not capture all determinants of bone fragility. TBS is supposed to indirectly reflect bone microarchitecture and to correlate with fracture risk independent of BMD.

Even though osteitis fibrosa cystica is less seen today in our country, many of our patients are symptomatic, despite the increased prevalence of asymptomatic form in the last two decades. So, we expect to see differences from western PHPT besides the clinical activity. As a consequence, mean calcium and PTH were higher in our patients than in the previously described cohorts.

Our study partly confirms previously published data: Silva *et al.* showed that TBS was significantly correlated with some parameters measured by HRpQCT indices (14). Romagnoli *et al.* noted lower TBS in 73 postmenopausal women with primary hyperparathyroidism than in 74 age-matched controls and identified a TBS cutoff which discriminates prevalent vertebral fracture (15).

In a study that included both cross-sectional and longitudinal components, Eller-Vainicher *et al.* compared 92 patients with primary hyperparathyroidism (74 of them post-menopausal females and the remainder males over age 50 years) and 98 controls with other conditions. Again, TBS was lower in patients with primary hyperparathyroidism than in controls, and was statistically significantly associated with vertebral fracture, even after adjustment for age, gender, BMI and LS aBMD. On the contrary, our own data do not support a significant association of TBS with vertebral fractures, when analyzed by forward logistic regression; the only independent correlation was with YSM. What this study adds to previous knowledge: it included premenopausal and male patients; many of our patients were symptomatic, which is rare in western countries (14). Our data reinforce the observations made in milder groups of patients, especially regarding the TBS role in secondary osteoporosis. TBS was in the partially degraded range even in patients with normal LS BMD (only 9.7% in our study). The main observation of our study is that TBS was not associated independently with vertebral fractures; at the same time no patient with vertebral fractures had a normal TBS or normal BMD.

In this study TBS was significantly correlated with aBMD, which has been reported before (16,17). Boutroy *et al.* found significant correlations between TBS and L1–L4 aBMD (r = 0.58; p < 0.001) in 560 women from the OFELY cohort. In contrast to others, we observed a concordance between TBS and BMD, as less than 10% of patients showing degraded or partially degraded microarchitecture by TBS had normal LS T-score, and none with vertebral fractures.

A recent report observed a fully degraded microarchitecture, in obese patients with PHPT, with significantly lower TBS values than non-obese patients (18). Our own data do not confirm this observation, on more obese and more patients: both obese and non-obese patients were in the partially degraded range; mean TBS in obese patients was significantly higher than in non-obese patients even after adjusting for LS BMD, but with a small effect size. There might be also rare cases of normal or even high BMD concurrent with PHPT, involving WNT pathway (19).

In this study we enrolled only PHPT patients with a valid LS DXA scan, which did not alter the number of patients with vertebral fractures. This study had several limitations, mostly the low number of vertebral fractures; there were also nine patients with

missing data. Although we did not have a healthy control group, this could be justified by the validation of TBS cutoffs in many studies (14).

An important contribution of our study, based on the largest number of symptomatic patients reported to date, is the concordance between TBS and BMD in primary hyperparathyroidism; moreover TBS was not independently associated with vertebral fractures. Prospective studies with a larger number of fractures are needed for definitive conclusions. Looking at all the data provided by our study, they suggest that TBS measurement adds little information beyond aBMD in the assessment of PHPT bone involvement.

In conclusion, in a large retrospective cohort of symptomatic PHPT patients, including postmenopausal, premenopausal and male patients, we have shown that TBS was in the partially degraded range, but was not independently associated with fractures, adding little information beyond BMD.

Conflict of interest

No potential conflicts of interest were disclosed.

References

1. Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, Udesky J, Silverberg SJ. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab. 2008; 93(9):3462–3470.
2. Grigorie D, Caragheorgheopol A, Teodorescu A, Sucaliuc A. Vitamin D status, seasonal variations and parathyroid adenoma weight in primary hyperparathyroidism. Osteoporos Int 2015; 26 (Suppl):S71-S380 DOI 10.1007/s00198-015-3068-3.
3. Stein EM, Silva BC, Boutroy S, Zhou B, Wang J, Udesky J, Zhang C, McMahon DJ, Romano M, Dworakowski E, Costa AG, Cusano N, Irani D, Cremers S, Shane E, Guo XE, Bilezikian JP. Primary hyperparathyroidism is associated with abnormal cortical and trabecular microstructure and reduced bone stiffness in postmenopausal women. J Bone Miner Res. 2013; 28(5): 1029-1040.
4. Khosla S, Melton LJ 3rd, Wermers RA, Crowson CS, O'Fallon W, Riggs B. Primary hyperparathyroidism and the risk of fracture: a population-based study. J Bone Miner Res. 1999; 14(10):1700–1707.
5. Vignali E, Viccica G, Diacinti D, Cetani F, Cianferotti L, Ambrogini E, Banti C, Del Fiacco R, Bilezikian JP, Pinchera A, Marcocci C. Morphometric vertebral fractures in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab. 2009; 94(6):2306–2312.
6. Vestergaard P, Mosekilde L. Fractures in patients with primary hyperparathyroidism: nationwide follow-up study of 1201 patients. World J. Surg. 2003; 27(3):343–349.
7. Kenny AM,MacGillivray DC, Pilbeam CC, Crombie HD, Raisz LG. Fracture incidence in postmenopausal women with primary hyperparathyroidism. Surgery 1995; 118(1):10914.
8. De Geronimo S, Romagnoli E, Diacinti D, D'Erasmo E, Minisola S. The risk of fractures in postmenopausal women with primary hyperparathyroidism. Eur J Endocrinol 2006; 155(3):415–420.
9. Eller-Vainicher C, Filopanti M, Palmieri S, Ulivieri FM, Morelli V, Zhukouskaya VV, Cairoli E, Pino R, Naccarato A, Verga U, Scillitani A, Beck-Peccoz P, Chiodini I.. Bone quality, as measured by trabecular bone score, in patients with primary hyperparathyroidism. Eur J Endocrinol. 2013; 169(2):155–162.
10. Miller PD, Siris ES, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, Chen YT, Berger ML, Santora AC, Sherwood LM. 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):2222–2230.
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):302–312.
12. Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, McCloskey EV, Kanis JA, Bilezikian JP. Trabecular bone score: a noninvasive analytical method based upon the DXA image. J Bone Miner Res. 2014; 29(3):518–530.
13. Harvey NC, Glüer CC, Binkley N, McCloskey EV, Brandi ML, Cooper C, Kendler D, Lamy O, Laslop A, Camargos BM, Reginster JY, Rizzoli R, Kanis JA. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. Bone. 2015; 78(1):216-224.
14. Silva BC, Boutroy S, Zhang C, McMahon DJ, Zhou B, Wang J, Udesky J, Cremers S, Sarquis M, Guo XD, Hans D, Bilezikian JP.. Trabecular bone score (TBS)-a novel method to evaluate bone microarchitectural texture in patients with primary hyperparathyroidism.JClinEndocrinolMetab.2013;98(5):1963-1970.
15. Romagnoli E, Cipriani C, Nofroni I, Castro C, Angelozzi M, Scarpiello A, Pepe J, Diacinti D, Piemonte S, Carnevale V, Minisola S.. Trabecular bone score (TBS): an indirect measure of bone micro-architecture in postmenopausal patients with primary hyperparathyroidism. Bone. 2013; 53(1):154–159.
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): 2762–2769.
17. 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.
18. Donovan Tay YK, Cusano NE, Rubin MR, Williams J, Omeragic B, Bilezikian JP. Trabecular Bone Score in Obese and Non-obese Subjects with Primary Hyperparathyroidism Before and After Parathyroidectomy. J Clin Endocrinol Metab. 2018, doi: 10.1210/jc.2017-02169.
19. Grigorie D, Constantini A, Sucaliuc A. Suspected Non-Lrp5 Mutation Associated with High Bone Mass Unaltered by Concurrent Symptomatic Primary Hyperparathyroidism of Long Duration. Acta Endocrinologica-Bucharest 2016; 12(4):461-464.