# Degraded Bone Microarchitecture in Women with PHPT–Significant Predictor of Fracture Probability

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## ABSTRACT

**INTRODUCTION:** Patients with primary hyperparathyroidism (PHPT) experience bone mineral density (BMD) loss and trabecular bone score (TBS) alteration, which current guidelines recommend assessing. Considering TBS alongside BMD for a 10-year fracture risk assessment (FRAX) may improve PHPT management.

**DESIGN:** Retrospective, cross-sectional study composed of 49 Caucasian females (62 ± 10.6 years, 27.7 ± 0.87 kg/m$^2$) with PHPT and 132 matched control subjects (61.3 ± 10.5 years, 27.5 ± 0.49 kg/m$^2$) evaluated in 3 years. We assessed lumbar spine (LS) and femoral neck (FN) BMD, T and Z scores (GE Healthcare Lunar Osteodensitometer) and TBS (iNsight 1.8), major osteoporotic fracture (MOF), and hip FRAX.

**RESULTS:** Patients with PHPT had statistically lower mean values for lumbar spine bone mineral density (LS BMD) (0.95 ± 0.25 vs 1.01 ± 0.14 g/cm$^2$, $P = .01$), LS T-scores (−2 ± 0.2 vs −1.4 ± 0.1 SD, $P = .009$), LS Z scores (−0.9 ± 0.19 vs −0.1 ± 0.11 SD, $P = .009$), femoral neck bone mineral density (FN BMD) (0.79 ± 0.02 vs 0.83 ± 0.01 g/cm$^2$, $P = .02$), FN T-scores (−1.8 ± 0.13 vs −1.5 ± 0.07 SD, $P = .017$), FN Z scores (−0.51 ± 0.87 vs −0.1 ± 0.82 SD, $P = .006$), and TBS (0.95 ± 0.25 vs 1.01 ± 0.14 g/cm$^2$, $P = .01$) compared with control subjects. 22.4% of patients with PHPT had degraded microarchitecture (TBS < 1.2) vs. 7.6% in control group ($\chi^2 = 0.008$). PHPT proved to be a covariate with unique contribution ($P = .031$) alongside LS BMD ($P = .040$) in a linear regression model [$R^2 = 0.532$, $F(4,16) = 4.543$] for TBS < 1.2. TBS adjustment elevated MOF FRAX both for PHPT (4.35 ± 0.6% vs 5.25% ± 0.73%, $P < .001$) and control groups (4.5 ± 0.24% vs 4.7% ± 0.26%, $P < .001$) compared with BMD-bases FRAX, but also increased differently between the 2 study groups (1.1-folds for PHPT patients and 1.04 for control subjects, $P = .034$).

**CONCLUSION:** Compared with control, TBS-adjusted FRAX provides significantly higher MOF risk than BMD-based FRAX in PHPT women.

**KEYWORDS:** Primary hyperparathyroidism, osteoporosis, trabecular bone score, degraded microarchitecture, 10-year probability of fracture

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## Introduction

### *Primary hyperparathyroidism and bone*

Primary hyperparathyroidism (PHPT) is characterized by hypercalcemia and elevated or inappropriately normal parathyroid hormone (PTH) levels, with an incidence of 0.4 to 82 cases per 100 000.[1,2]

Due to the widespread use of automated biochemical screening in the last decades, the incidence[2] and clinical presentation of PHPT have changed to a modern form of mild hypercalcemia, detected incidentally in asymptomatic patients with varying degrees of bone loss, accompanied by fragility fractures in symptomatic patients.[3,4]

The catabolic effect of PTH on the endocortical surfaces of bone is confirmed by bone biopsies showing cortical thinning and PTH levels that positively correlate with cortical porosity.[5,6] Meanwhile, it appears that in trabecular and cortical bone, the consequence of excess PTH may differ,[7] as the cancellous bone is presumably less affected through the preservation of well-connected trabecular plates, despite increased bone turnover levels.[3,4,8-10] This is indicated by the 3-dimensional analysis using micro computed tomography (μCT). Conventional dual-energy X-ray absorptiometry (DXA) measurement of the integrated bone provides no discrimination between the cortical and trabecular bone.[11]

Although PTH may have only a mild effect on the bone mineral density (BMD) of trabecular bone, many prior studies identified an increased risk of vertebral fractures in patients with PHPT,[12-15] which suggests an underlying effect of PTH on bone that may be underestimated by assessing only BMD by DXA. Nevertheless, newer studies based on microfinite element models obtained from high-resolution peripheral quantitative computed tomography (HRpQCT) images showed that in PHPT, there is a significant stiffness decrease in cortical and trabecular scores,[16,17] along with a decreased trabecular number, volumetric BMD, and connectivity.[18-20]

*Trabecular bone score*

While HRpQCT is not widely and easily accessible, many studies have shown that additional information about bone microarchitecture in PHPT could be obtained with trabecular bone score (TBS), which is a quantitative value that is reproductible and simple to use, with higher scores indicating stronger and more fracture-resistant microarchitecture.[21-23] In contrast, low TBS indirectly reflects weak and fracture-prone microarchitecture,[12,24] as TBS from μCT correlates with the trabecular number, thickness, and separation.[21]

The *"Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop"* states that TBS could influence fracture proclivity.[25] Recent research has found a consistent link between low TBS values and increased prevalence of incident fractures partly independent of BMD in the general population.[24,26] This association has also been found in postmenopausal women,[23] secondary osteoporosis associated with hyperparathyroidism,[27] and other conditions associated with osteoporosis (OP).[28] In a case-control study from 2013, a cut-off value of 1.2 for TBS predicted vertebral fracture more precisely than BMD, which is both more sensitive and functional.[4]

There is evidence that TBS is lower in PHPT than in eucalcemic patients[4]; thus, guidelines recommend TBS measurement in this endocrinopathy,[25,29] but without conferring TBS a meaningful role in PHPT management.

*PHPT management*

Surgery, ideally preferred for most symptomatic patients, is the first-line and curative PHPT treatment and was shown to be more cost-effective than medical treatment, improving fracture risk and quality of life.[30,31] According to the current guidelines of clinical practice, BMD values in the osteoporotic range and prior vertebral or fragility fractures are criteria for parathyroidectomy (PTX).[25]

Mild PHPT may not require surgery; however, Rubin et al found that BMD at cortical sites begins to decline before 10 years of evolution. In addition, 37% of the patients studied had sufficient bone loss to require surgical intervention by 15 years.[30,32]

*FRAX*

The University of Sheffield came to the medical practitioners' aid with a questionnaire (FRAX–Fracture Risk Assessment Tool) based on clinical fracture risks, which predicts the 10-year probability of fracture,[33] and can be further refined using the femoral neck BMD and TBS values.[26,34] The result of the FRAX questionnaire does not modify for secondary OP—a well-known drawback of the FRAX tool,[35] and the only change PHPT could promote on the 10-year fracture probability is indirect, via BMD and TBS values.[36] Prior studies may seem contradictory in this regard,[26,37] and further evidence is necessary for a more accurate description of the FRAX–BMD–TBS triad in patients with PHPT to improve the clinical outcome.

The study objectives to assess the differences in BMD and TBS in PHPT versus control and how they influence the 10-year probability of fracture in women.

## Materials and Methods

Our cross-sectional study included 49 women diagnosed with solitary isolated PHPT between September 2018 and September 2021 at Elias University Emergency Hospital, Bucharest, scanned at PHPT-positive diagnosis (before surgical treatment).

Inclusion criteria were: age >40 years old to compute FRAX calculation; at least 2 bone Region of Interests (ROIs); PHPT diagnosed by hypercalcemia (measured by automated chemistry analyzer) and synchronous elevated iPTH (measured by electrochemiluminescence).

Exclusion criteria were: body mass index (BMI) >45 kg/m$^2$; multiple endocrine neoplasia (MEN) syndromes, parathyroid hyperplasia, and familial history of PHPT; other chronic bone metabolic disorders; endogenous Cushing syndrome; and insufficient data.

The control group consisted of 132 women referred by general practitioners for DXA scans, having either risk factors for osteoporosis, prevalent fractures or previous abnormal DXA scans. The control number was higher for increased statistical significance as they were selected from the authors' DXA database by nearest neighbor matching for age the range of ±2 years and, simultaneously, matched for BMI in the range of ±1 kg/m$^2$.

For control group, inclusion criteria were: age >40 years old, at least 2 ROIs, blood calcium not consistent with PHTP, while exclusion criteria were: BMI > 45 kg/m$^2$ and a medical history of other metabolic bone disorders besides OP.

All participants signed a written informed consent, agreeing that their medical records may be used for scientific research. All the planning, collecting and reporting of the human data were in accordance with the Helsinki Declaration of 2013 and the study was approved by the Elias University Hospital Ethics Board, decision no. 9299/0f2.10.2017.

We clinically assessed personal history of fragility fractures, vertebral and non-vertebral altogether, parental hip fractures, secondary OP, glucocorticoid therapy, hyperthyroidism, rheumatoid arthritis, smoking, and alcohol intake for FRAX calculation, both for major osteoporotic fracture (FRAX MOF) and hip fracture (FRAX HIP), computed with BMD (DXA Prodigy GE Lunar Software) and TBS adjustment (TBS iNsight Software 1.8, Med-Imaps). The difference between the 10-year fracture risk value before and after TBS adjustment was defined as FRAX MOF or HIP Difference, whereas the relative percentage of changes before and after

TBS adjustment was defined as FRAX MOF or HIP % diff = (FRAX BMD – FRAX TBS) * 100/FRAX BMD.

All scans were performed using the same densitometer (DXA Prodigy GE Lunar) by the same experienced operator utilizing the standard procedures for quality control, and the results of the interpretations followed the international standards of OP diagnosis[38]: normal BMD (T-score −1 SD or above), osteopenia (T-score between −1 and −2.5 SD), OP (T-score −2.5 SD or lower or osteopenia with fragility fracture or high FRAX), and severe OP (T-score −2.5 SD or below in the presence of a fragility fracture). We assessed the lumbar spine (LS BMD, LS T, and Z score) and the femoral neck (FN BMD, FN T, and Z score).

TBS parameters were extracted from the same LS scan area of interest as LS BMD. The software established the bone microarchitecture thresholds; therefore, TBS $\leqslant$ 1.2 represents degraded microarchitecture, TBS between 1.2 and 1.3 corresponds to partially degraded microarchitecture, and TBS $\geqslant$ 1.3 outline normal microarchitecture.[39]

Statistical analysis was performed using SPSS version 26 and statistical significance was set at a value of $<$0.05. Continuous variables were described as mean ± standard deviation (SD), or median ± standard error of mean, and the normality of their distribution was checked using the Shapiro-Wilk test. Comparisons of continuous variables between groups were described using unpaired student's t test, analysis of variance (ANOVA) for more than 2 groups, or the Mann-Whitney U test for non-parametric variables. Their association was calculated using Spearman's correlation coefficients. Wilcoxon signed-rank test was used to conduct a paired difference test between repeated measures of non-parametric continuous variables. Categorical variables were expressed as numbers (percentages) and were compared among groups using the Chi-square test. Contingency tables were used to depict the frequency of categorical variables in a distribution table. To evaluate the predictive effect of age, BMI, different ROI's BMD, and PHPT on degraded microarchitecture as a categorical variable, we used binary multiple logistic regression. We used linear regression to predict the variability of the TBS value as a continuous variable.

## Demographics and Results

### *General characteristics*

The mean age of the PHPT group was 62.05 ± 10.58 and 61.27 ± 10.53 for the control group.

The median value of BMI in the PHPT group was 27.75 ± 0.875 and 27.55 ± 0.488 kg/m$^2$ in the control group. Weight distribution in the control group was as follows: 3 patients (2.3%) were underweight, 34 (25.8%) had normal weight, 47 (35.6%) were overweight, 28 (21.5%) had BMIs corresponding to grade I obesity, 17 (12.9%) grade II obesity, and 3 (2.3%) had BMIs above 39.9 kg/m$^2$. In the PHPT group, the corresponding weight distribution frequencies, in the same order, were: 2 (4.1%), 10 (20.4%), 19 (38.8%), 9 (18.4%), 6 (12.2%), and 3 (6.1%). The frequencies of fractures' clinical risk factors are described in Table 1.

**Table 1.** Study groups–risk factors according to FRAX expressed as numbers (percentages).

| | PHPT (49) (%) | CONTROL (132) (%) |
|---|---|---|
| Clinical fragility fractures | 7 (14.3) | 29 (22) |
| Hip parental fractures | 1 (2) | 10 (7.6) |
| GCS | 3 (6.1) | 3 (2.3) |
| Hyperthyroidism | 2 (4.1) | 6 (4.6) |
| Rheumatoid arthritis | 2 (4.1) | 1 (0.8) |
| Tabbaco users | 9 (18.4) | 17 (13) |

### *Osteodensitometry*

Median values of bone mineral density, of both LS and FN, alongside their corresponding T and Z scores, were significantly lower in the PHPT group compared to control. The osteodensitometric characteristics of the study population can be seen in Table 2.

In the control group, 30 patients (22.7%) had normal BMD versus 4 (8.2%) in the PHPT group, 58 (43.9%) had osteopenia, 35 (26.5%) OP, and 9 (6.8%) severe OP. In the PHPT group, 18 (36.7%) had osteopenia, 23 (9.11%) OP, and 4 (8.2%) severe OP.

OP and severe OP were significantly ($\chi^2$ = 0.010) more prevalent in the PHPT group (27/49 patients, 55.1%) compared with the control group (44/132 patients, 33.3%).

### *TBS results*

TBS was statistically different between the 2 groups ($P$ = .008), with a lower mean value in the PHPT group versus control. Mean TBS Z scores were also statistically different ($P$ = .010) between the 2 groups. TBS negatively correlated with previous fragility fractures ($r$ = −.259, $P$ < .001) and the mean TBS values were statistically different ($P$ < .001) between the fractured (1.267 ± 0.086 g/cm$^2$) and the non-fractured (1.332 ± 0.1 g/cm$^2$) groups.

Regarding the TBS distribution, in the control group, 85 (64.4%) patients had normal microarchitecture (TBS $<$ 1.3), 37 (28%) had partially degraded microarchitecture (TBS between 1.2 and 1.3), and 10 (7.6%) had degraded microarchitecture (TBS $<$ 1.2). In the PHPT group, the TBS was in the range of normal architecture for 22 (44.9%) patients, partially degraded microarchitecture for 16 (32.7%) patients, and degraded microarchitecture for 11 (22.4%) patients; see Table 3.

The prevalence of abnormal microarchitecture defined by a TBS $<$ 1.3 was significantly higher ($\chi^2$ = 0.026) in the PHPT group (27/49 patients, 55.1%) than the control group (47/132 cases, 35.6%), a difference that remained significant even while

**Table 2.** Study groups–general characteristics as mean/medians values.

| | PHPT (49) | CONTROL (132) | |
|---|---|---|---|
| | MEAN/MEDIAN | MEAN/MEDIAN | |
| Age (years) | 62.05 ± 10.58 | 61.27 ± 10.53 | NS |
| BMI (kg/m²) | 27.75 ± 0.875 | 27.55 ± 0.488 | NS |
| LS T-score (SD) | −2 ± 0.204 | −1.4 ± 0.113 | *P* = .009 |
| LS Z score (SD) | −0.9 ± 0.197 | −0.1 ± 0.112 | *P* = .009 |
| LS BMD (g/cm²) | 0.945 ± 0.25 | 1.012 ± 0.139 | *P* = .010 |
| FN T-score (SD) | −1.8 ± 0.135 | −1.5 ± 0.07 | *P* = .017 |
| FN Z score (SD) | −0.515 ± 0.87 | −0.106 ± 0.822 | *P* = .004 |
| FN BMD (g/cm²) | 0.787 ± 0.018 | 0.827 ± 0.009 | *P* = .020 |
| TBS (g/cm²) | 1.287 ± 0.117 | 1.331 ± 0.091 | *P* = .008 |
| TBS T-score (SD) | −1.876 ± 1.401 | −1.56 ± 0.991 | NS |
| TBS Z score (SD) | −0.206 ± 1.174 | 0.225 ± 0.911 | *P* = .010 |

**Table 3.** Study groups—distribution of microarchitectural damage groups among osteoporosis diagnosis.

| | | NORMAL BMD | OSTEOPENIA | OP | SEVERE OP | TOTAL |
|---|---|---|---|---|---|---|
| PHPT group | TBS > 1.3 | 4 | 10 | 7 | 1 | 22 |
| | TBS 1.2-1.3 | 0 | 4 | 11 | 1 | 16 |
| | TBS < 1.2 | 0 | 4 | 5 | 2 | 11 |
| | Total | 4 | 18 | 23 | 4 | 49 |
| Control group | TBS > 1.3 | 28 | 41 | 14 | 2 | 85 |
| | TBS 1.2-1.3 | 2 | 13 | 15 | 7 | 37 |
| | TBS < 1.2 | 0 | 4 | 6 | 0 | 10 |
| | Total | 30 | 58 | 35 | 9 | 132 |

accounting for the prevalence of degraded microarchitecture, defined by TBS < 1.2; 11 cases (22.4%) in the PHPT group versus 10 cases (7.6%) in the control group ($\chi^2 = 0.008$).

The TBS median values for different categories of microarchitectural damage did not statistically differ between the PHPT and control groups in the normal and partially damaged microarchitecture subgroups, except in patients with TBS < 1.2 ($P = .043$); see Table 4.

In the study group, TBS had a statistically significant positive correlation with BMI ($P < .001$, $r = .279$), LS BMD ($P < .001$, $r = .659$), FN BMD ($P < .001$, $r = .439$), and negative correlations with PHPT ($P = .023$, $r = -.169$), and age ($P < .001$, $r = -.332$).

Logistic regression model on the entire study group with age, BMI, LS BMD, and PHPT as covariates and TBS < 1.2 as the dependent variable, identified age ($P = .020$) and LS BMD ($P = .002$) as significant predictor factors for degraded microarchitecture, and BMI and PTH as poor predictors, with a total correct case prediction of 87.8%.

A linear regression model on the entire study group (PHPT and control) predicted 49.6% of the TBS variability as a continuous variable and identified age at scan, BMI, and LS BMD as predictors with unique contributions. However, running the same linear regression model in the TBS < 1.2 subgroup, with TBS variability as the dependent variable, we identified PTH ($P = .031$) and LS BMD ($P = .040$) as unique contributing factors; see Table 5.

### *FRAX results*

Although there were no statistical differences between FRAX MOF BMD and FRAX HIP BMD among PHPT

**Table 4.** Study groups–median values of TBS for each microarchitectural deterioration subgroup.

| | TBS > 1.3 | TBS 1.2–1.3 | TBS < 1.2 ($P = .043$) |
|---|---|---|---|
| PHPT | 1.39 ± 0.013 | 1.251 ± 0.007 | 1.144 ± 0.016 |
| Control | 1.368 ± 0.007 | 1.257 ± 0.004 | 1.174 ± 0.008 |

**Table 5.** Linear regression model for TBS value variation for the whole study lot and for those with degraded microarchitecture (TBS < 1.2).

| | ENTIRE STUDY GROUP | TBS < 1.2 |
|---|---|---|
| Overall statistical significance | $F(4,176) = 43.288$<br>$R^2 = 0.496$<br>$P < .001$ | $F(4,16) = 4.543$<br>$R^2 = 0.532$<br>$P = .012$ |
| Age at scan | $P < .001$ | $P = .749$ |
| BMI | $P = .002$ | $P = .330$ |
| LS BMD | $P < .001$ | $P = .040$ |
| PHPT | $P = .079$ | $P = .031$ |

and control, or for TBS-adjusted FRAX MOF and HIP, we identified a significant difference for FRAX MOF before and after TBS adjustment for control ($P < .001$) and PHPT ($P < .001$) groups, but not for FRAX HIP. Additionally, there was a significant difference in how the 10-year risk of MOF changes after TBS adjustment in PHPT vs. control ($P = .044$), expressed as FRAX MOF difference. The same difference remained when calculating the variance of fracture risks as % of the initial FRAX (FRAX MOF % diff): the risk for MOF increases 1.1-fold in the PHPT group and 1.04-fold in the control group after TBS adjustment, $P = .034$; see Table 6.

We can infer that the degraded microarchitecture is responsible for the different FRAX MOF prediction trajectories between the 2 study groups. Therefore, when applying a linear model regression on this difference between MOF FRAX with BMD and after TBS adjustment as a dependent variable, with age, BMI, LS BMD, and PHPT as covariates, we identified PHPT ($P = .043$), age ($P = .048$), BMI ($P = .024$), and LS BMD ($P < .001$) as unique contributors; see Table 7.

## Discussion

Our data reveal a significant lower TBS mean in PHPT patients compared to control. PHTH was proved to be a unique contributor to TBS variability in a linear regression model conducted in the subgroup of patients with degraded microarchitecture, accountable, as well, for the difference of major osteoporotic fracture probability based on FRAX tool after TBS adjustment in another linear regression model.

To accurately represent the health spectrum for the general population for both groups, we chose not to exclude previous glucocorticoid treatments, as they are commonly prescribed chronic medications for various comorbidities, including rheumatoid arthritis. We acknowledge that a significant fraction of our entire study group (11.6%) had a BMI higher than the 37 kg/m$^2$ threshold recommended by the manufacturer for valid BMI-adjusted values of TBS,[40] as it is known that increased soft tissue thickness can interfere with TBS analysis. However, excluding them would only limit the descriptive power for this distinct category of overweight patients who lack reference ranges in the literature. Also, high BMI positively correlates with TBS values, although with no statistical significance in BMI >37 kg/m$^2$.[41] In another study of 352 patients with BMI 30 to 37 kg/m$^2$, BMI correlated negatively with TBS.[42] An interesting discussion emerges when considering the Camacho et al[38] study, which also described a positive correlation between TBS and BMI for the Romanian population with PHPT. Overweight patients are prone to diabetes,[43] a proven risk factor for OP and its vascular components.[44] A large prospective study from Manitoba, Canada[45] found that 2365 patients with type 2 diabetes had lower TBS and higher BMD, and that TBS was more functional than BMD in assessing the influence of diabetes on fracture risk. In patients with diabetes, TBS also correlates better than BMD with fracture risk.[40] Although we knew the number of patients with diabetes in the PHPT cohort, we chose not to introduce diabetes as a predicting factor in any of our analyses, as the control group was not screened for this disease and only declared it if they knew of its existence.

An explanation for the higher number of fractures in the control group might reside in an increased referral from general practitioners for DXA scan after the occurrence of a fragility fracture. TBS is negatively correlated with prevalent fragility fractures, having lower values in the subgroup with prevalent frailty fracture compared with the non-fractured patients. This finding is supported in other studies. For example, 243 French white postmenopausal women aged 50 to 80 with osteopenia[46] had TBS values of 0.97 for patients with vertebral fracture versus 1.061 for the control cohort ($P < .0001$). The obvious difference in TBS values from our study probably resides in the osteopenic population described in the French study and the overall lower BMIs (23.3 kg/m$^2$ for the unfractured group and 25.4 kg/m$^2$ for the fractured postmenopausal French women vs 27.6 kg/m$^2$ in our entire study group). Research shows that TBS values are lower in postmenopausal women and similar in vertebral, hip, or other osteoporotic fracture.[40]

The LS BMD and FN BMD values were significantly lower in the PHPT group than the control and their

**Table 6.** Study groups–median values of FRAX.

| | PHPT (49) | CONTROL (132) | |
|---|---|---|---|
| | MEAN/MEDIAN | MEAN/MEDIAN | |
| FRAX MOF BMD (%) | 4.35 ± 0.6 | 4.5 ± 0.24 | NS |
| FRAX HIP BMD (%) | 0.9 ± 0.38 | 0.9 ± 0.1 | NS |
| FRAX MOF TBS (%) | 5.25 ± 0.73 | 4.7 ± 0.26 | NS |
| FRAX HIP TBS (%) | 0.95 ± 0.45 | 0.75 ± 0.11 | NS |
| FRAX MOF Difference (%) | 0.4 ± 0.2 | 0.2 ± 0.06 | $P = .044$ |
| FRAX HIP Difference (%) | 0.0 ± 0.11 | 0.0 ± 0.026 | NS |
| FRAX MOF % diff (%) | 10.25 ± 3.25 | 4.7 ± 1.22 | $P = .034$ |
| FRAX HIP % diff (%) | 0.0 ± 5.39 | 0.0 ± 3.02 | $P = .087$ |

**Table 7.** Linear regression model for the variation of FRAX before and after TBS adjustment in the entire study group.

| FRAX MOF BMD–FRAX MOF TBS VALUE VARIATION | |
|---|---|
| Overall statistical significance | $F(4,174) = 23.651$<br>$R^2 = 0.352$<br>$P < .001$ |
| Age at scan | $P = .048$ |
| BMI | $P = .024$ |
| LS BMD | $P < .001$ |
| PHPT | $P = .043$ |

corresponding T and Z scores were different between the 2 study groups. These differences led to a statistically higher prevalence of OP and severe OP in the PHPT group. Moreover, the prevalence of degraded microarchitecture was higher in the PHPT group.

Overall, we noticed that TBS was significantly lower in the PHPT group, similar to other studies in literature. Silva et al[27] found a TBS value of 1.240 in a study of 22 postmenopausal women with PHPT.[27] Romagnoli et al[4] described a TBS value of 1.19 ± 0.10 for 73 patients with PHPT versus 1.24 ± 0.09 for 74 patients from the control group ($P < .01$). An interesting contrast between these studies and ours is the higher TBS results for our control group, which may be explained by the mean BMI or LS BMD values.

A study from 2013 published by Stein et al,[16] which assessed cortical and trabecular microstructure by HR-pQCT in postmenopausal women with PHTP versus control, revealed decreased whole bone and trabecular stiffness, with thinner and fewer trabeculae in PHTP women, providing insights that PHPT's out-turns are not limited to the cortical compartment of the bone; decreased TBS in PHPT reported by our results and some other previous papers suggests a similar effect.[4,27]

Our data show that the difference between PHPT and control TBS values resides mainly in patients with degraded microarchitecture (TBS < 1.2), suggesting that PTH comes into play in the degraded microarchitecture subgroup, as our linear regression model confirmed this hypothesis.

TBS is a reliable predictor of fracture risk independently of FRAX; however, the impact of adjusting TBS for this risk is still being studied as part of clinical assessment guidelines.[26] We compared the 10-year fracture risk after TBS adjustment. Our study showed a significant difference in the MOF risk prediction trajectory between the 2 study groups after TBS adjustment, which underlines a limit of both clinical and BMD-adjusted FRAX. We assumed that the degraded microarchitecture was responsible for this contrast, as we found significantly lower values of TBS in the degraded microarchitecture groups between PHTP and control. When a linear regression model was applied to the entire group for this FRAX difference resulting from TBS adjustment, PHPT was identified as the predictor with a unique contribution.

The dynamics of how the FRAX changes before and after TBS adjustment are more important than the non-significant differences between the absolute values of FRAX with BMD or TBS among the 2 study groups. The small but statistically significant change that PHPT produces on FRAX after TBS adjustment compared with the FRAX BMD values could be subjected to a snowball effect because in the absence of treatment, PHPT is a slow-paced progressive disorder.

Despite the absence of data outweighed by fracture prediction models containing BMD, results from a meta-analysis support a broader, more comprehensive fracture risk assessment that includes TBS as a standalone measure and as an independent contributor to universal risk assessment.[26] Our results show that TBS may compensate for the non-existing

effect of secondary OP in FRAX, as TBS was shown to be useful in clinical situations such as type 2 diabetes and PHPT, where FRAX without TBS may underestimate fracture risk.[38] Fracture risk may also be underestimated when patients with PHPT are screened using DXA analyzers that do not incorporate TBS software.

To date, PHPT treatment guidelines bypass fracture risk unless it refers to it by the established diagnosis of OP, which is a PTX criterion. However, as international standards of OP diagnosis change, considering the high values of FRAX in osteopenic patients,[38] it is only normal to address the lack of sufficient data that would investigate the clinical fracture risk or TBS as a treatment criterion for PHPT.

The study limits are represented by the lack of clear evidence of morphometrical vertebral fractures and the abdominal circumference for the patients with a BMI higher than 37 kg/m$^2$, as the effect of waist circumference on TBS is more pronounced than that of BMI.[41] However, there will be a corrected formula of TBS for BMI starting with a newer version of MedImaps.[42] Besides the scarcity of TBS cut-offs for obese patients, another obvious limitation is the absence of a widely accepted TBS threshold for normal or abnormal microarchitecture for premenopausal women. The values we have used were suggested by the manufacturer for postmenopausal women and patients with PHPT. The control group was referred for DXA screening in an OP center, suggesting that they probably already had different fracture risk. Another evident limit is the relatively small number of patients with PHPT and the lack of data regarding menopausal status or years since menopause, hormonal treatment and the usage of other agents that can influence bone metabolism, like vitamin D, for the control group, which may be a confounder in BMD and TBS comparison. Larger cohorts may provide more information about PTH-related microarchitectural changes. Moreover, there is a need for further prospective research to assess the 10-year risk of fracture, but this cannot be done in PHPT patients with PTX recommendations.

This is the first Romanian study that we know of that assessed the relationship between PHPT, TBS, and FRAX in this manner. Another distinctive characteristic of our study is the well-matched BMI and age control group, which made age and weight adjustments for BMD, T and Z scores, and TBS or FRAX unnecessary.

Some guidelines provide recommendations for OP management based on BMD and a 10-year fracture risk probability[38]; however, there are no sufficient data to conclude that a similar fracture prevention approach may be feasible for PHPT. Research on new techniques or larger cohort studies may prove helpful in assessing fracture risk and preventing the underdiagnosis of high-risk patients in the PHPT population.[12]

## Conclusions

Both BMD and TBS appeared to have statistically lower values in PHPT than the control group, indicating that the PTH damages the bone in terms of quality and quantity, revealing a holistic multilayered effect. The prevalence of damaged microarchitecture was higher in the PHPT group (22.4%) than in the control group (7.6%).

TBS adjustment significantly increases the 10-year probability of MOF compared to when its value is adjusted only with BMD, both in the PHPT and control subgroups. TBS adjustment also led to a statistical difference in the FRAX MOF difference between the 2 study groups. The linear regression model helped us identify PHPT as a predictor with a unique contribution to this change in the entire study cohort.

Although not overwhelmingly, the way PHPT changes FRAX's dynamics via TBS is significant, being, perhaps a small forward step toward a better refinement of the 10-year probability of fracture for these patients.

## Declarations

### *Ethics Approval and Consent to Participate*

The study design was approved by the Elias University Hospital Ethics Board, decision number 9299/02.10.2017 and all participants signed an informed consent.

### *Consent for Publication*

All authors gave their consent for publication.

### *Author Contributions*

**Theodor Eugen Oprea:** Conceptualization; Formal analysis; Methodology; Writing—original draft. **Carmen Gabriela Barbu:** Conceptualization; Supervision; Writing—review and editing. **Sorina Carmen Martin:** Investigation; Resources. **Anca Elena Sarbu:** Investigation; Resources. **Simona Gabriela Duta:** Data curation. **Irina Manuela Nistor:** Data curation; Formal analysis; Software. **Simona Fica:** Conceptualization; Supervision; Writing—review and editing.

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### *Availability of Data and Materials*

All data are available on request.

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