

Clinical Utility of Trabecular Bone Score (TBS) in Fracture Risk Assessment of Patients with Rheumatic Diseases Treated with Glucocorticoids

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ABSTRACT

Chronic glucocorticoid therapy is associated with osteoporosis and can cause fractures in up to 50% of patients. Increased risk of fractures in patients with glucocorticoid-induced osteoporosis does not result only from the decreased bone mineral density (BMD) but also bone microarchitecture deterioration. Trabecular bone score (TBS) is a method complementary to DXA, providing additional information about trabecular bone structure. The aim of this study was to assess the clinical utility of TBS in fracture risk assessment of patients treated with glucocorticoids. Patients with rheumatic diseases treated with glucocorticoids for at least 3 months were enrolled. All recruited patients underwent DXA with additional TBS assessment. We analyzed the frequency of osteoporosis and osteoporotic fractures and assessed factors that might be associated with the risk of osteoporotic fractures. A total of 64 patients were enrolled. TBS and TBS T-score values were significantly lower in patients with osteoporosis compared to patients without osteoporosis. Low energy fractures occurred in 19 patients. The disturbed bone microarchitecture was found in 30% of patients with fractures without osteoporosis diagnosis based on BMD. In the multivariate analysis, only TBS and age were significantly associated with the occurrence of osteoporotic fractures. TBS reflects the influence of glucocorticoid therapy on bone quality better than DXA measured BMD and provides an added value to DXA in identifying the group of patients particularly prone to fractures.

Introduction

Treatment with glucocorticoids (GCs) is associated with a variety of adverse effects including osteoporosis, which can occur in up to 50% of patients with chronic GCs therapy [1, 2]. The fractures associated with osteoporosis result in disability, impaired quality of life, increased mortality, and are a tremendous burden, both personal and economic [3]. The fracture risk in people with glucocorticoid-induced osteoporosis (GIO) increases with the duration of therapy and doses of GCs. The risk is increased even in patients using GCs in as small doses as 2.5 mg of prednisolone per day and with GCs therapy longer than 3 months [4]. Dual X-ray absorpti-

ometry (DXA) of the proximal femur (hip) and lumbar spine, measuring bone mineral density (BMD), is the gold standard technique for osteoporosis diagnosis. However, the increased risk of low-energy fractures in patients with GIO does not result only from decreased BMD but also from bone microarchitecture deterioration and myopathy [1, 2, 4]. DXA BMD measurement does not assess the quality of trabecular bone structure, and therefore may not detect all patients at risk of low-energy fractures. To better assess the risk of fractures, tools that would allow an easy assessment of bone microarchitecture were sought.

Currently, the most widely used tool for the evaluation of bone microarchitecture is the Trabecular Bone Score (TBS). TBS insight is a software tool available for DXA scanners, that enables the assessment of bone texture (an index correlated to bone microarchitecture) based on gray-level variations in DXA scans of the lumbar spine. The result is expressed as TBS, with higher scores in patients with better quality bone microarchitecture. TBS is a method complementary to DXA, providing additional information about the bone structure, and is an independent predictor of fracture risk [5]. European guidance for the diagnosis and management of osteoporosis in postmenopausal women emphasizes that TBS can supplement the FRAX calculator in the estimation 10-year risk of fractures [6].

TBS may be particularly useful in some types of secondary osteoporosis, where bone quality is especially affected [7]. Several studies have shown the usefulness of TBS in assessing bone microarchitecture in GIO [8], osteoporosis associated with diabetes mellitus [9], primary hyperparathyroidism [10], and chronic kidney disease [11]. More importantly, TBS seems to be more sensitive than BMD for the detection of fracture risk related to GCs therapy [12]. The aim of this study was to assess the clinical utility of TBS in fracture risk assessment in patients with inflammatory rheumatic diseases treated with GCs. So far, this issue has only been addressed in a few studies [13–16]. To our knowledge, this is also the first study performed in the Polish population.

Subjects and Methods

Patients

The study was conducted at the Department of Radiology in the National Institute of Geriatrics, Rheumatology, and Rehabilitation in Warsaw, Poland. Patients treated with GCs (prednisone dose ≥ 5 mg per day or other glucocorticoids with equivalent dose) for at least 3 months were enrolled. The exclusion criteria were: age < 20 years, BMI < 17 kg/m² or > 37 kg/m² (criteria provided by the manufacturer [17]), patients with diabetes mellitus or primary hyperparathyroidism, and patients with significant motor impairment preventing proper DXA examination. All recruited patients underwent DXA with additional TBS assessment. The study protocol has been approved by the hospital bioethics committee (KBT-2/3/2019). All participants have signed informed consent for inclusion in the study. The study was conducted according to the Declaration of Helsinki.

Measurements

DXA scans were performed using Hologic Discovery A densitometer. DXA reports included the BMD value, expressed as grams per square centimeter (g/cm²), the T-score, and the Z-score values. In all analyzes of femur DXA reports the lower BMD value of the femoral neck or the total hip was used. As recommended by WHO, the T-score and Z-score were evaluated in analyzes depending on patient age. T-score was taken into account for postmenopausal women and men over 50, while Z-score for premenopausal women and men under 50. According to the WHO definitions, in men over 50 and postmenopausal women osteoporosis was diagnosed when

T-score was ≤ -2.5 , and osteopenia when T-score was < -1 and > -2.5 [18]. In men under 50 years of age and women before menopause, osteoporosis was diagnosed based on Z-score ≤ -2.0 . Osteoporosis was also diagnosed in patients with osteopenia with low-energy fractures according to current guidelines [6].

TBS was assessed by automated analysis of lumbar spine DXA results using TBS insight version 3.0.3.0 software. The TBS reports included the absolute TBS value and the TBS-T score for the sum of L1-L4 vertebrae. The absolute values of TBS were divided into those suggesting disturbed bone microarchitecture (< 1.23), intermediate (≥ 1.23 and < 1.31), or normal (≥ 1.31) [19].

Statistical analysis

We analyzed the frequency of osteoporosis and osteoporotic fractures (depending on demographic and clinical characteristics or DXA/TBS results), the correlation between TBS and classical DXA parameters, the correlation of DXA/TBS parameters with patients' characteristics, and assessed factors that might be associated with the risk of osteoporotic fractures. The compliance of the data with the normal distribution was assessed using the Shapiro-Wilk test. The significance of the observed differences between the two groups was assessed using the Student's *t*-test for variables with a normal distribution, the Mann-Whitney U-test for variables without a normal distribution, and for categorical variables the Chi-square test or the Fisher's exact test (for tables with values < 5). For more than two groups with normal distribution, we used analysis of variance with posthoc analysis with Bonferroni test. For more than two groups without normal distribution, we used Kruskal-Wallis test and Dunn's test respectively. The correlation was assessed using the Pearson correlation coefficient for parametric variables and Spearman's rank correlation coefficient with non-parametric variables. The significance of the correlation after adjusting for the confounding factors was checked by linear regression. To identify the predictors of osteoporotic fractures, logistic regression was used, with the backward stepwise analysis. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using Statistica 13.1 software.

Results

A total of 64 patients (49 females and 15 males) were enrolled. The patient characteristics are presented in ► **Table 1**. All patients were treated with GCs due to inflammatory rheumatic diseases – the majority suffered from rheumatoid arthritis (53.1% of all patients). Osteoporosis was diagnosed in 27 patients (42.2%) – in 17 patients based on DXA, and in 10 patients based on the occurrence of low-energy fractures. Osteoporotic fractures (mostly vertebral fractures 63%) occurred in 19 patients. According to TBS, 26 patients (40.6%) revealed disturbed bone microarchitecture (TBS < 1.23).

The TBS and TBS T-score values were significantly positively correlated with other bone density parameters – lumbar BMD, lumbar T-score, femoral BMD, femoral T-score (► **Table 15**). The correlation of patients characteristics with the parameters of bone density and microarchitecture was assessed (► **Table 2**) – showing a negative correlation of BMI with TBS values (TBS and T-score TBS), as well as a negative correlation of age with some BMD results (lumbar BMD, femoral BMD, and femoral T-score). Female gender was

► **Table 1** Patients characteristics.

Sex, number (%)	
female	49 (76.6%)
Age, median (min, max)	63 (20, 87)
BMI, mean (\pm SD)	27.4 (\pm 4.9)
GCs treatment duration, median in months (min, max)	54 (3, 480)
Disease, number (%)	
Rheumatoid arthritis	34 (53.1%)
Systemic lupus erythematosus	9 (14%)
Giant cell arteritis	4 (6.3%)
Polymyalgia rheumatica	4 (6.3%)
Vasculitis	4 (6.3%)
Systemic sclerosis	3 (4.7%)
other	6 (9.4%)
Osteoporosis diagnosis based on, number (%)	
DXA (lumbar spine or femur)	17 (26.6%)
- DXA of lumbar spine	10 (15.6%)
- DXA of femur	11 (17.1%)
osteoporotic fracture	10 (15.6%)
Osteoporotic fractures, number (%)	
vertebrae	12 (18.9%)
proximal femur	2 (3.1%)
other low-energy fractures	5 (7.8%)
Osteoporosis treatment, number (%)	
bisphosphonates	14 (21.9%)
denosumab	2 (3.1%)

GCs: Glucocorticoids.

► **Table 2** Correlations of parameters of bone density and architecture disturbances with age, BMI, and duration of GCs therapy.

	Age	BMI	Duration of GCs therapy
Lumbar BMD	r = -0.26 p = 0.0356	ns	ns
Lumbar T-score	ns	ns	ns
Lumbar Z-score	ns	ns	ns
Femoral BMD	r = -0.49 p < 0.0001	ns	ns
Femoral T-score	r = -0.39 p = 0.0039	ns	ns
Femoral Z-score	ns	ns	ns
TBS	ns	r = -0.35 p = 0.0048	ns
T-score TBS	ns	r = -0.35 p = 0.0060	ns

GCs: Glucocorticoids; ns: Correlation not significant.

associated with significantly ($p = 0.04$) lower TBS T-scores compared to the male gender, but after adjusting for confounding factors lost its statistical significance.

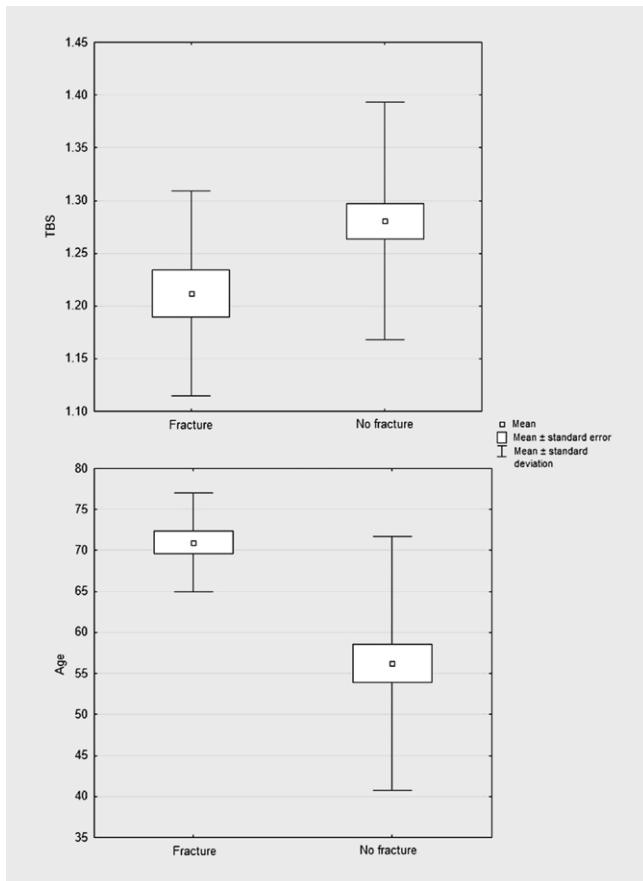
The bone microarchitecture status and BMD status in patients with osteoporotic fractures are presented in ► **Table 3**. There was no significant difference in the incidence of fractures in both groups – 9 patients with fractures in the group with osteoporosis diagnosed with BMD measurements and 10 in the group with disturbed bone microarchitecture according to TBS. No significant difference was also observed comparing patients with partially disturbed bone microarchitecture and osteopenia. The disturbed bone architecture was present in 30% of patients with fractures who did not meet the diagnostic criteria of osteoporosis based on DXA. In a group of patients with low-energy fractures, the univariate analysis showed significantly lower TBS ($p = 0.02$), TBS T-score ($p = 0.012$), femoral BMD ($p = 0.023$), and older age ($p < 0.0001$). Additionally, the female gender was associated with a higher incidence of osteoporotic fractures ($p = 0.013$). However, after the multivariate analysis, only TBS ($p = 0.033$) and age ($p = 0.002$) remained significantly associated with the occurrence of osteoporotic fractures (► **Fig. 1**).

Discussion

GCs induce osteoporosis in several ways [1, 2], including hormonal dysregulation (decreased production of gonadotrophins, estrogen, and testosterone; reduced growth hormone secretion; reduced gastrointestinal calcium absorption and renal calcium reabsorption) and disturbance of bone metabolism (leading to inhibition of the differentiation and replication of osteoblasts, induction of os-

► **Table 3** The incidence (number, %) of disturbed (<1.23), intermediate (≥ 1.23 and <1.31), or normal (≥ 1.31) bone microarchitecture and BMD status.

	Disturbed bone microarchitecture	Intermediate bone microarchitecture	Normal bone microarchitecture
Osteoporosis			
- lumbar DXA	4 (21.1%)	–	–
- femoral DXA	4 (21.1%)	1 (5.3%)	1 (5.3%)
- both	7 (36.8%)	1 (5.3%)	1 (5.3%)
Osteopenia			
- lumbar DXA	5 (26.3%)	4 (21.1%)	2 (10.5%)
- femoral DXA	5 (26.3%)	4 (21.1%)	2 (10.5%)
- both	2 (10.5%)	5 (26.3%)	2 (10.5%)
Healthy			
- lumbar DXA	1 (5.3%)	2 (10.5%)	1 (5.3%)
- femoral DXA	1 (5.3%)	1 (5.3%)	–
- both	1 (5.3%)	–	–



► **Fig. 1** Age and TBS in relation to the incidence of osteoporotic fractures, after adjusting for confounding factors.

teoblast and osteocytes apoptosis, and promoted osteoclast survival – resulting in increased bone resorption and reduction in bone formation). Alterations in bone metabolism may lead to an increased risk of fractures due to the effect on bone microarchitecture that occurs before the significant loss of BMD. The risk of fractures is further increased because of steroid-induced myopathy, which increases the risk of falls [1].

Incidence of osteoporosis and fractures

In our study, we diagnosed osteoporosis in 42.7% of patients, which is consistent with other reports, showing that osteoporosis can occur in up to 50% of patients with chronic GCs therapy [1, 2, 16]. Osteoporotic fractures occurred in 29.7% of our patients, which is also comparable to previous studies, reporting fractures in about 30–50% of patients with chronic GCs therapy [1, 2, 16]. The variability in the incidence of both osteoporosis and fractures can be explained by the differences in the characteristics of the patients studied (different age groups, menopausal status, doses, duration, and cause of GCs therapy) and the lack of a uniform diagnostic definition of GIO. Most of the osteoporotic fractures in our study were vertebral fractures (63% of all fractures). This is in line with our knowledge that GCs mostly disrupt the structure of the trabecular bone that dominates in the vertebral bodies, and patients with GIO are at higher risk of vertebral fractures compared to hip fractures [1, 2, 4].

Effect of glucocorticoids on bone microarchitecture

The effects of chronic GCs therapy on bone microarchitecture (TBS) have been assessed in several previous studies. In the most recent study by Florenz et al. with 127 patients during chronic GC therapy disturbed bone microarchitecture was found in 52% of patients [16] – more frequently than in our study (40.6% of all patients). They also found that disturbed microarchitecture occurred significantly more often than the BMD-based diagnosis of osteoporosis in patients with fractures (69 vs. 36%). We did not find such a difference – in our study, the frequency of disturbed microarchitecture and osteoporosis diagnosed based on DXA BMD measurement in the group of patients with fractures was similar (52.6 vs. 47.4%, respectively). As both studies used the same TBS thresholds, this difference may be caused by different rheumatological conditions treated with GCs in both studies – in our mainly rheumatoid arthritis and study by Florenz et al. vasculitis. Nonetheless, this discrepancy should be investigated further in future studies. Another issue that should be taken into account when assessing bone microarchitecture in patients treated with GCs is the negative correlation of TBS with BMI. A similar correlation was reported in the small study by Torgutalp et al. [20], suggesting that abnormalities of the bone tissue microarchitecture may be present more frequently in patients with higher BMI. Still, BMI was not associated with increased fracture occurrence in our study.

TBS in fractures risk assessment

In our study, in patients with low-energy fractures, we assessed not only osteoporosis diagnosed based on DXA BMD measurement and disturbed bone microarchitecture (TBS < 1.23), but also intermediate states – osteopenia and partially disturbed bone microarchitecture (► **Table 3**). It is noteworthy that in patients with low-energy fractures only 15.8% had normal bone microarchitecture and 5.3% normal BMD. When all 3 bone parameters (TBS, femoral BMD, and lumbar BMD) were considered combined no patient with low-energy fracture had normal bone status. However, the most interesting part of our study is the analysis of risk factors for osteoporotic fractures, which suggests that TBS may be more sensitive than BMD for GCs-related fracture detection. In our study, both the univariate and multivariate analysis showed significantly lower TBS values in patients with the presence of low-energy fractures. Such a relationship for BMD-based parameters was not confirmed in the multivariate analysis. Similar results were found in a few previous studies. In the study by Leib et al., comparing 416 GCs treated patients with 1104 matched controls, there was a significant decrease of TBS values compared with the control group (while there was no change in BMD values). What's more a decrease in TBS values in GCs treated patients was associated with osteoporotic fractures, while there was no significant difference in BMD values between patients treated with GCs with and without osteoporotic fractures [12]. In the study by Choi et al., among 279 patients with rheumatoid arthritis and chronic GCs therapy, significantly lower values of TBS were found in patients with vertebral fractures compared to patients without vertebral fractures, with no difference in BMD values of lumbar spine between both groups [13]. These observations are further confirmed by studies reporting that TBS shows the better (higher) receiver operating characteristic areas under curves than lumbar spine BMD in patients with chronic GCs therapy with

vertebral fractures [14–16]. FRAX adjusted with TBS also seems to be a better tool than ordinary FRAX for patients treated with GCs. Chuang et al. assessed the effect of GCs therapy on the values of TBS, BMD, FRAX, and FRAX adjusted with TBS during a 12–24 months interval pre-post study of 30 patients [21]. They found that while the treatment with GCs significantly reduced the TBS values and increased the risk of fractures according to FRAX adjusted with TBS, the GCs treatment did not significantly affect the values of BMD and FRAX in the multivariate analysis.

Summary

These results suggest that TBS with a properly selected cut-off point should be able to predict the occurrence of osteoporotic fractures in patients with chronic GCs treatment in a better way than BMD measured with DXA. In our study disturbed bone microarchitecture was diagnosed in 30% of patients with fractures and without a densitometric diagnosis of osteoporosis, confirming beyond doubt that TBS adds value to the classic DXA. The biggest limitation of our study is a relatively small sample size and the cross-sectional character of the study. Longitudinal observational studies that can demonstrate the usefulness of TBS in predicting osteoporotic fractures in patients with chronic GCs treatment would have the greatest clinical value. Up to date, only one study by Martineau et al. examined it using Manitoba BMD Registry [22]. They showed that lowering TBS by 1 SD in the group of patients with chronic GCs therapy increases major osteoporotic fractures HR to 1.15. Moreover, FRAX adjusted with TBS shows a modest but statistically significant improvement in predicting major osteoporotic fractures by 3.9%. The other limitation of our study is the fact that we could not assess doses of GCs used, and in our analysis only the duration of GCs treatment was taken into account. The greatest strength of our study is the expansion of the available knowledge on the clinical utility of TBS in fracture risk assessment of patients with inflammatory rheumatic diseases treated with GCs, a topic that has been so far covered only by a few studies.

Our study proves that TBS reflects the influence of GCs therapy on bone quality better than BMD and provides an added value to classic DXA in identifying the group of patients particularly prone to fractures. However, prospective research is still needed to prove the usefulness of TBS in predicting fractures in patients treated with GCs.

Conflict of Interest

The authors declare that they have no conflict of interest.

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