Trabecular Bone Score Change Is Not Predicted by Bone Turnover: Short-term Sequential Follow-up

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ABSTRACT **Background:** Trabecular bone score (TBS) reflects vertebrae microarchitecture and assists in fracture risk assessment. The International Society of Clinical Densitometry postulates that the role of TBS in monitoring antiresorptive therapy is unclear. Whether changes in TBS correlate with bone resorption measured by bone turnover markers is not known.

Objectives: To determine whether longitudinal changes in TBS correlate with C-terminal telopeptide (CTX) of type I collagen.

Methods: Examinees with two bone mineral density (BMD) measurements were detected via the institutional database. Over 5.8% change in TBS was considered least significant and patients were grouped accordingly (increment, decrement, or unchanged). CTX, BMD, co-morbidities, incident fractures, and medication exposure were compared between the groups by Kruskal-Wallis. The correlation between TBS and BMD change and CTX in a continuous model was analyzed by Pearson's correlation coefficient.

Results: In total, 110 patients had detailed medical records. In 74.5%, TBS change was below least significant change. Two other TBS categories, fracture incidence or medication exposure, did not differ by CTX. In the continuous model, BMD and TBS change was positively correlated (r = 0.225, *P* = 0.018). A negative correlation was observed between BMD change and CTX. The decrease in BMD level was associated with higher CTX (r = -0.335, *P* = 0.004). No correlation was observed between CTX and TBS.

Conclusions: No correlation between TBS dynamics and bone resorption marker was found. Clinical interpretation and implication of longitudinal TBS changes should be further explored.

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KEY WORDS: bone mineral density (BMD), bone resorption markers, C-terminal telopeptide (CTX), hip fractures, trabecular bone score (TBS)

Osteoporosis, most common in post-menopausal women and older men, is characterized both by deterioration of bone microarchitecture and an increased bone turnover leading to bone fragility and increased fracture risk [1]. Hip and vertebral fractures are associated with increased morbidity and mortality as well as deterioration of quality of life, In addition, these fractures can be a considerable economic burden [2].

Since its introduction in the late 1980s, dual-energy X-ray absorptiometry (DXA) measurements of hip and spinal bone mineral density (BMD) has been the mainstay of osteoporosis diagnosis [3]. The importance of sequential BMD measurements in the evaluation of osteoporotic patients is highlighted by data from several meta-analyses, which have shown that improvement in BMD is associated with reduction in the risk of vertebral fractures [4-6]. The role of DXA in predicting future fractures has been established [7,8]. Nevertheless, the discriminative power of BMD regarding fracture-risk stratification in individual patients is limited [9] and newer tools are continually being explored.

Bone turnover markers (BTMs) evaluating osteoblastic and osteoclastic activities are becoming widely available. Previous studies have shown that increased BTM levels are directly associated with fracture risks [10]. However, evidence regarding the ability of these markers to predict bone loss on an individual level is weak.

Trabecular bone score (TBS) is a newer tool for patient fracture-risk stratification, which is aimed at characterization of the bone microarchitecture via analysis of standard lumbar spine DXA images [11]. Studies have shown that treatment with teriparatide and denosumab increase both BMD and TBS beyond the least significant change (LSC), defined as > 95% confidence interval for the studied group [12,13].

While TBS is becoming a mainstream way of osteoporosis management, the significance of longitudinal changes in TBS for an individual patient is unsettled. A recently published study assessing antiresorptive therapy failed to demonstrate that changes in TBS over time can predict subsequent fractures [14]. The International Society of Clinical Densitometry (ISCD) does not currently recommend the use of TBS for monitoring response to bisphosphonates treatment; however, the organization states that the score might be potentially useful for monitoring anabolic therapy [15].

We examined whether longitudinal changes in TBS correlated with C-terminal telopeptide of type I collagen (CTX), a bone resorption marker, with BMD, and with other clinical parameters.

PATIENTS AND METHODS

This single-center cohort study included adult patients who underwent two DXA scan measurements between 31 March 2013 and 8 August 2017, and CTX measurement during the time between the two DXA scans. We excluded patients with body mass index (BMI) < 15 kg/m^2 or > 37 kg/m^2 due to inherent limitation of the TBS score calculation [16]. Information on co-morbidities, medication exposure, fractures, and CTX was extracted from patient electronic medical records.

The DXA scans were obtained with Lunar Prodigy Advance 1RPA+130752 (GE Healthcare, Belgium). The TBS scores were calculated with the TBS iNsight® software (GE Healthcare, Belgium), calibrated for the specific DXA device. Measurement of the serum bone resorption marker, type 1 C-terminal telopeptide (CTX) was performed using the Cobas 6000 analyzer (Roche Diagnostics, Switzerland).

STATISTICAL ANALYSIS

We considered a 5.8% change in TBS to be significant (in accordance with the conservative estimation by the ISCD) and patients were grouped accordingly (increment, decrement, or unchanged).

We compared BMD, CTX, fractures, co-morbidities, and medical treatment for osteoporosis across the different TBS categories using the Kruskall-Wallis test. Continuous variables (CTX, TBS, BMD) were analyzed by Spearman correlation. As CTX may be influenced by kidney function, we recorded creatinine levels and calculated creatinine clearance using the Cockroft-Gault equation. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA) and used to calculate the Pearson correlation and analysis of variance (ANOVA). A probability level < 0.05 was considered significant for all analyses. A post-hoc power computation was performed using G*Power 3.1.9.4 software (© 2023 Heinrich-Heine-Universität Düsseldorf, Germany). The power achieved for CTX and TBS correlation analysis was 0.989.

RESULTS

PATIENT CHARACTERISTICS

During the study period, 700 patients underwent two consecutive DXA scans. Of those, 110 patients were followed in our insti-

Table 1. Patient characteristics according to the percentage of change in their TBS score

	TBS incrEMENT	TBS UNCHANGED	TBS DECREMENT
Number of patients, n (%)	15 (13.6)	82 (74.5)	13 (11.8)
Male, n (%)	1 (6.7)	12 (14.6)	3 (23.1)
Age at baseline in years, median (range)*	57 (49–78)	69 (30–86)	60 (29–71)
BMI kg/cm^2, median (range)	23.83 (17.43–27.56)	24.69 (17.98–36.52)	24.12 (18.73–29.74)
CTX pg/ml, median (range)	184.00 (140.00–550.00)	262.00 (101.00–759.00)	290.50 (69.00–685.00)
Time difference between DXA scans in days, median (range)	805 (659–1085)	818 (294–1364)	796 (371–1169)
BMD change gr/cm^2, median (range)	0.01 (-0.08–0.08)	0.01 (-0.14–0.13)	0.01 (-0.08–0.13)
eGFR mL/min/1.73m^2, median (range)	69.68 (37.86–109.64)	69.68 (31.68–149.78)	78.38 (63.58–127.44)
Creatinine mg/dl, median (range)	0.76 (0.54–1.10)	0.78 (0.31–1.34)	0.72 (0.52–1.11)
T-score vertebra, median (range)	-2.5 (-4.80–1.20)	-2.4 (-4.10–0.70)	-2.8 (-3.60–0.50)
T-score hip, median (range)	-1.9 (-3.00–1.40)	-2.3 (-3.60–0.40)	-1.9 (-3.50–0.70)
Drug exposure during study period, n (%)			
Antiresorptive drugs (including denosumab)	7 (46.7)	39 (47.6)	4 (30.8)
SERM/HRT	3 (20.0)	14 (17.1)	0 (00.0)
Teriparatide	1 (7.7)	2 (2.4)	0 (00.0)
Glucocorticoids	2 (13.3)	9 (11.0)	2 (15.4)
Patients with prevalent fractures, n (%)	5 (33.3)	28 (34.1)	2 (15.4)
Patients with incident fractures, n (%)	0 (00.0)	3 (3.7)	2 (15.4)

*P < 0.05

BMD = bone mineral density, BMI = body mass index, CXT = C-terminal telopeptide, DXA = dual-energy X-ray absorptiometry, HMT = hormone replacement therapy, SERM = selective estrogen-receptor modulators, TBS = trabecular bone score

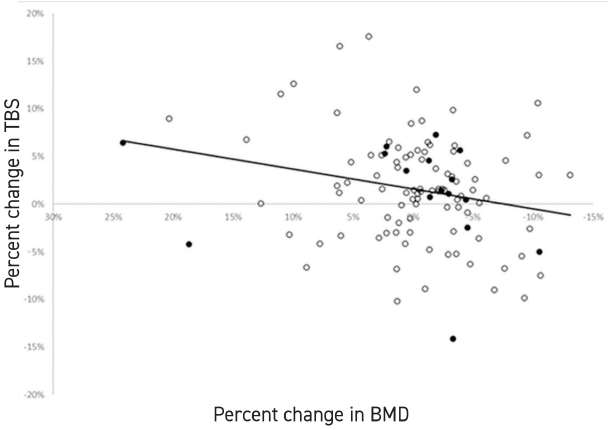
tution's tertiary-care bone diseases service with detailed medical records and CTX results measured during the study period and comprised our study cohort.

Most patients (86%) were females with a mean age of 68.2 ± 10.7 years; 77 patients had osteoporosis in either the hip or the vertebra. The rest had BMD in the osteopenic range. Among the 16 male patients included in this analysis, 6 (37%) were osteoporotic and 10 (63%) were within the osteopenic range. The mean interval between DXA tests was 2.3 ± 0.6 years. In most patients (74.5%) TBS change was lower than LSC (5.8%).

Patient characteristics were classified according to TBS changes categories (increment, unchanged or decrement in TBS) and presented in Table 1. TBS remained stable in 74.5% of the patients, decreased in 11.8% and increased in 13.6% of the patients [Table 1].

There were no significant differences in BMI, serum CTX, eGFR, past glucocorticoid exposure, history of previous osteoporotic fracture, or incident fractures during the study period, across the three TBS dynamics categories. There was no difference in osteoporosis drug exposure in the different TBS change categories. Of note, in the subgroup of male patients (n=16), 11 (69%) had previous glucocorticoid exposure and 4 (25%) had diabetes. There were two cases of fractures in this subgroup of patients (12%).

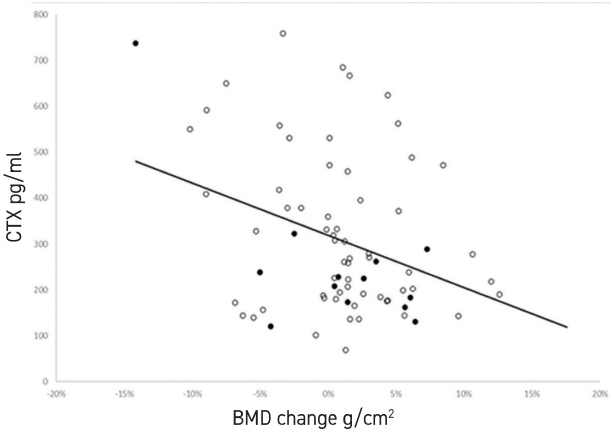
Figure 1. Correlation between percent of change in BMD and TBS during the study period. The hallow circle represent female and the black circle represent male patients



r=0.225, *P* = 0.018

BMD = bone mineral density, TBS = trabecular bone score

Figure 2. Correlation between absolute change in BMD (g/cm^2)and CTX (pg/ml). The hallow circle represent female and the black circle represent male patients



r = -0.335, *P* = 0.004

BMD = bone mineral density, CXT = C-terminal telopeptide

CORRELATION OF LUMBAR SPINE BMD, TBS, AND CTX

We found a significant correlation between the changes in lumbar spine BMD and TBS during the study period (r = 0.225, *P* = 0.018) [Figure 1].

A negative correlation was observed between BMD change and CTX; thus, decrease in BMD was associated with higher CTX (r = -0.335, *P* = 0.004) but not between CTX and TBS [Figure 2].

There was no significant association between TBS change and CTX or between changes in TBS and a prevalent or incident fracture.

DISCUSSION

As TBS is becoming widely available, the clinical significance and interpretation of TBS changes on the subsequent BMD tests is becoming a relevant question. Bone resorption markers are extensively used, mainly for monitoring of osteoporosis therapy. TBS provides an indirect evaluation of the trabecular bone architecture and a numerical score for bone quality while CTX correlates with the rate of bone resorption [11,14,17]. Our results demonstrated that changes in bone architecture, reflected by changes in TBS, do not correlate with the rate of bone resorption reflected by serum CTX measured in the time window between two DXA tests. Other studies reported conflicting results when assessing the correlation between CTX and TBS. In one study involving acromegalic patients, no correlation between CTX and TBS was found [18] while a report on HIV patients revealed an inverse correlation between CTX and both BMD and TBS [19]. To the best of our knowledge, our analysis is the first retrospective cohort study to examine the relationship between changes in TBS over time and CTX in a general population of osteoporotic patients.

Trabecular bone is the most metabolically active compartment in bone [20]. Considering the existing coupling between bone formation and resorption, bone turnover markers reflect changes in the metabolic rate of this compartment [21]. TBS reflects bone microarchitecture rather than the mineral content and quantity; therefore, the lack of correlation between TBS and the rate of bone resorption should not be surprising, at least during the interval investigated in the present study.

We found that CTX inversely correlated with longitudinal change in BMD. As CTX is a well-accepted marker of bone resorption, correlation between CTX and BMD is expected and supported by other studies [22,23].

A weak, but significant correlation was observed between changes in BMD and TBS during the study interval, which is also supported by results of other studies in healthy [24] and osteoporotic women treated with bisphosphonates [25].

While bone mineral density is a well-accepted means for follow-up of osteoporotic patients and treatment course [3,5], the role of TBS in follow-up is still unsettled. Previous large studies provided conflicting results [13,14]. In a large prospective Manitoba cohort study, change in TBS could not predict osteoporotic fractures in women who initiated osteoporosis treatment [14]. In a more recent study of patients receiving denosumab, TBS was significantly improved, independent of BMD [13]. The official ISCD position in 2019 stated that the role of TBS in monitoring antiresorptive therapy was unclear [15]. We did not observe correlations between treatment with any anti-resorptive drug, including denosumab, and changes in TBS. Our observations correspond with the official ISCD position. However, it should be noted that the number of patients treated with denosumab was very small (probably because CTX measurement is not routinely performed during denosumab treatment).

Our study has several limitations. First, it was retrospective and included a relatively small number of patients with TBS change above the LSC. Moreover, the different treatment allocation subgroups were small and as such, underpowered for a subgroup analysis for the effect of treatment. Second, CTX was measured at different time points with respect to the initiation of treatment and the relative interval between the subsequent DXA examinations, which may not reflect the bone resorption process during the entire study period. Last, the overall number of patients with fractures was too small to draw any conclusions regarding the impact of longitudinal change in TBS with fracture risk.

CONCLUSIONS

No association was found between changes in TBS and bone resorption rate (reflected by CTX). Our data, as well as that from other studies, add to the accumulating knowledge regarding the clinical significance of sequential TBS assessments as a surveillance means in patients with osteoporosis. We suggest that the significance of the longitudinal dynamics of TBS warrants further evaluation.

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They know enough who know how to learn.
Henry Adams (1838–1918), American historian and teacher

Capsule

A STANd against tumors

Effective antitumor T cell responses are often hampered by the constraints of aberrant tumor-associated vasculature. **Wang-Bishop** et al. presented an approach harnessing activation of the stimulator of interferon genes (STING) pathway to promote vascular normalization and enhance antitumor responses. The authors evaluated STING-activating nanoparticles (STANs) intravenously in multiple tumor models. STANs were able to normalize tumor vasculature and integrity, decrease tumor hypoxia, and promote the expression of T cell adhesion molecules, which enhanced antitumor T cell infiltration and improved the efficacy of immune checkpoint inhibitors and adoptive cell therapy. These findings suggest that STANs are a potential therapeutic approach that can target tumor vasculature and enhance the effects of immunotherapy.

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Capsule

Walking naturally after spinal cord injury using a brain–spine interface

A spinal cord injury interrupts the communication between the brain and the region of the spinal cord that produces walking, leading to paralysis. **Lorach** and colleagues restored this communication with a digital bridge between the brain and spinal cord that enabled an individual with chronic tetraplegia to stand and walk naturally in community settings. The brain–spine interface (BSI) consisted of fully implanted recording and stimulation systems that established a direct link between cortical signals and the analogue modulation of epidural electrical stimulation targeting the spinal cord regions involved in the production of walking. A highly reliable BSI was calibrated within a few minutes. The reliability remained stable over one year, including during independent use at home. The participant reported that the BSI enabled natural control over the movements of his legs to stand, walk, climb stairs, and even traverse complex terrains. Moreover, neurorehabilitation supported by the BSI improved neurological recovery. The participant regained the ability to walk with crutches overground even when the BSI was switched off. This digital bridge establishes a framework to restore natural control of movement after paralysis.

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