Evaluation of the Potential Use of Trabecular Bone Score to Complement Bone Mineral Density in the Diagnosis of Osteoporosis: A Preliminary Spine BMD—Matched, Case-Control Study

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Abstract

The trabecular bone score (TBS) is a new parameter that is determined from gray-level analysis of dual-energy X-ray absorptiometry (DXA) images. It relies on the mean thickness and volume fraction of trabecular bone microarchitecture. This was a preliminary case-control study to evaluate the potential diagnostic value of TBS as a complement to bone mineral density (BMD), by comparing postmenopausal women with and without fractures. The sample consisted of 45 women with osteoporotic fractures (5 hip fractures, 20 vertebral fractures, and 20 other types of fracture) and 155 women without a fracture. Stratification was performed, taking into account each type of fracture (except hip), and women with and without fractures were matched for age and spine BMD. BMD and TBS were measured at the total spine. TBS measured at the total spine revealed a significant difference between the fracture and nonfracture group, when considering all types of fractures and vertebral fractures. In these cases, the diagnostic value of the combination of BMD and TBS likely will be higher compared with that of BMD alone. TBS, as evaluated from standard DXA scans directly, potentially complements BMD in the detection of osteoporotic fractures. Prospective studies are necessary to fully evaluate the potential role of TBS as a complementary risk factor for fracture.

Key Words: DXA; image analysis; osteoporosis; trabecular bone microarchitecture; trabecular bone score.

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength, which predisposes an affected individual to bone fracture (1). Bone density, a factor affecting bone strength, is evaluated in routine clinical practice by dual-energy X-ray absorptiometry (DXA). A patient’s bone mineral density (BMD), measured by DXA, is expressed in g/cm²; however, by convention, the score then is converted to a T-score, which represents the number of standard deviations (SDs), plus or minus, from a reference value. That reference value, by convention, is the mean BMD of a young, healthy adult. The World Health Organization (WHO) (2) has established criteria for the diagnosis of osteoporosis, criteria that rely on a patient’s T-score, gleaned from DXA—based BMD measurement at the hip or spine. The classification criteria are as follows: a designation of “normal” is assigned to patients whose T-score is above −1.0; a designation of “low
bone mass (osteopenia)" is assigned for T-scores between −1.0 and −2.5; and a diagnosis of "osteoporosis" is reserved for T-scores at or below −2.5. This classification scheme commonly is referred to in the literature and in discussions on bone disease. However, in clinical practice, the scheme has certain limitations, and a large degree of overlap exists in BMD values between individuals who develop fractures and those who do not (3).

One of the possible explanations is that BMD does not capture all of the factors that contribute to bone strength (4), factors that encompass several characteristics of bone tissue at different scales of analysis, such as the macrogeometry of cortical bone, trabecular bone microarchitecture, bone microdamage, bone mineralization, and bone turnover (5,6). When referring to ex vivo studies (7,8) or to the definition of osteoporosis (2), trabecular bone microarchitecture constitutes an important component of bone strength and is complementary to bone density. Today, establishing an efficient clinical evaluation of trabecular bone microarchitecture remains a crucial challenge.

A 2-dimensional (2D) projection-based evaluation of trabecular bone microarchitecture that could be obtained from standard X-rays, and/or from DXA images, would be a good candidate for efficient clinical use, in that it would be inexpensive and convenient and associated with a low ionizing radiation dose. Transforming a 2D projection into a 3-dimensional (3D) one remains a difficult mathematical problem, however (9). The 3D microarchitecture of tissue or other objects is not directly measurable in 2D projection-based images. However, several kinds of texture analyses have been proposed as indirect measurements of 3D trabecular bone microarchitecture (9–16). Among them, fractal analysis has been widely used. For example, Benhamou et al (17) applied fractal analysis to calcaneus plain radiographs. In a square region of measurement, the gray-level profiles are fitted with a mathematical model dedicated to fractal process—the Fractional Brownian Motion model. This modeling, based on 1-dimensional (1D) gray-level profile, is repeated in different directions of the 2D image, leading to the evaluation of a mean Hurst parameter (Hmean). In the case of materials with surface fractal properties, a mathematical relationship can be established between the fractal dimension of the 3D microarchitecture and the fractal dimension evaluated on a 2D-projection image. Unfortunately, this 3D-2D relationship is not adequate for trabecular bone microarchitecture, because it does not satisfy surface fractal properties (18). Other limitations of fractal analysis concern the evaluation of the fractal dimension itself. An accurate estimate of fractal dimension on 2D-projection images necessitates taking into consideration a large surface of projection and, depending on the estimator used, the size of the projection image in the 2-power scale (17). Vokes et al (16) adopted a texture measurement based on combined Fourier and multifractal analyses, called the Minkowski fractal dimension. This approach was constrained by a square-shaped region of measurement of size in the 2-power scale, for example, a square region equal to $64 \times 64$ pixels (16). Statistical analyses were performed to compare (1) associating the Minkowski fractal dimension evaluated from heel images on a peripheral densitometer, especially equipped to provide high-resolution heel images and (2) BMD measured at the lumbar spine and proximal hip, using a standard central densitometer.

The trabecular bone score (TBS) is a novel gray-level texture measurement that is based on the exploitation of experimental variograms of 2D-projection images (19,20). TBS is not an estimate of fractal dimension. Rather, it measures the mean rate of local variation of gray levels in 2D-projection images. This evaluation is constrained neither by the size nor by the shape of the region measured. Hence, TBS is a good candidate as a texture measurement for small and/or irregular surfaces of analysis, such as the standard region of measurement defined in DXA images. TBS can be compared with BMD because both evaluate the same region. Based on numerical simulations and models of 3D microarchitecture, we have established an empirical 3D-2D relationship expressing TBS as a function of 2 3D bone characteristics: $\Theta$—mean solid thickness. TBS expresses a score for the 3D characteristics of bone microarchitecture and appears to be an indicator of variation in thickness, in cases of bone microarchitecture with the same bone volume (BV).

The aim of this preliminary case-control study has been to evaluate the potential diagnostic value of TBS, as a complement to BMD, in the prediction of osteoporotic fractures overall and vertebral fractures alone.

Materials and Methods

Clinical DXA Population and Subgrouping

Study subjects

A sample of 200 women was selected from the QDR4500A systems database at 2 different Hospitals—University Hospital of Lausanne (Switzerland) and University Hospital of Bordeaux (France). The subjects were randomly selected from lists of patients who had had their DXA on the same make and model machine, who were within a given age range, and who otherwise met inclusion/exclusion criteria. Subjects with (cases) and without (controls) fractures were selected at both sites and then merged into a common anonymized study data set after appropriate cross-calibration of DXA—based measurements. At each hospital, the principal investigators reviewed the lists of patients with fractures and selected all otherwise eligible postmenopausal women who had been measured on the same device (QDR4500A, Hologic, Bedford MA, US). Hip fractures were ascertained by X-ray, and cross-referenced with surgical records at the same hospital. A similar approach was used for spine fractures. Only patients who had had an X-ray-confirmed fracture, using the semiquantitative approach developed by Genant et al, were recruited for the study. All the other fractures were also confirmed radiographically. After recruitment of patients with fractures, a sample of age— and spine BMD—matched nonfracture controls was recruited from the pool of 155 eligible
controls, drawn from the same 2 hospitals. The main study group, therefore, consisted of 45 patients with osteoporotic fractures and 90 age- and spine BMD—matched controls.

Subjects with pathology and/or on treatment who could interfere with bone status were not included in the sample. At each hospital, in accordance with routine clinical protocol, body height was measured to the nearest 0.5 cm using a stadiometer and body weight was measured to the nearest 0.1 kg on a balance beam scale.

From the 45 women with fractures, a subgroup of 20 subjects with a vertebral fracture were matched with 60 age- and spine BMD—matched women without any fracture.

This study was conducted in accordance with the current version of the Declaration of Helsinki and under the laws and regulations enforced by the Department of Health.

Exportation of DXA Scans

At both hospitals, DXA scans were restored from a QDR4500A Hologic system. Hip and spine scans were exported from Hologic QDR software (v12.3) to disk space. Then, Hologic files were Zip-compressed and exported onto a dedicated workstation. DXA—based measurements (BMD) and demographic data (age, weight, and height) were saved after DXA scan re-reading using a workstation installation of Hologic QDR software (v12.3).

BMD Measurements

Total spine L2–L4 (BMDspine) readings were examined. BMDspine was evaluated as the mean value of individual measurements, excluding, for this analysis, fractured and/or arthrosed vertebrae. This identification was done by a clinician who was an expert in DXA scan interpretation.

TBS Evaluation

TBS was evaluated in the same regions of measurement as those used for BMD. TBSspine was evaluated as the mean value of individual measurements of the L2, L3, and L4 vertebrae, excluding any fractured and/or arthrosed vertebrae (see earlier discussion). In each region of measurement, TBS was evaluated based on gray-level analysis of DXA images (see Appendix), as the slope at the origin of the log-log representation of the experimental variogram.

Statistical Analysis

All statistical analysis was performed using MedCalc v8.1 software (MedCalc Software, Mariakerke, Belgium).

Descriptive statistics (mean, SD, minimum value [min], and maximum value [max]) were evaluated within each subgroup.

Each investigated parameter was tested for normal distribution using the D’Agostino-Pearson method. Between-subgroup differences in means were evaluated by t-test or Mann-Whitney U-test, depending on the normality of the distribution. T-test was performed assuming equal or unequal variance, depending on the result of the test of variance (F-test).

The diagnostic value of each parameter was evaluated both by odds ratios (ORs)—expressed for each decrease of 1 SD—and by the area under the receiving operator curve (ROC: Receiving Operator Curve; AUC: Area under the ROC curve); 95% confidence intervals (CIs) for these estimates (OR and AUC) were calculated.

Results

None of the anthropometric parameters was significantly different between fracture and nonfracture subjects across the overall sample (Table 1). Similarly, appropriate statistics showed nonsignificant differences in the mean values of BMD between fracture and nonfracture subjects in the overall sample, confirming that the matching was performed correctly.

Table 1
Descriptive Statistics, Differences of Means, and Diagnostic Value in Fracture Subjects vs Age— and Spine BMD—matched Controls (Total Sample)

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>BMI (kg/m²)</th>
<th>BMD L2–L4 (g/cm²)</th>
<th>TBS L2–L4 (mm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All fracture patients</td>
<td>67.0 ± 8.1</td>
<td>64.8 ± 14.8</td>
<td>159.9 ± 6.8</td>
<td>25.3 ± 5.0</td>
<td>0.846 ± 0.189</td>
<td>0.784 ± 0.176</td>
</tr>
<tr>
<td>Controls (n = 90)</td>
<td>66.4 ± 7.9</td>
<td>61.2 ± 9.3</td>
<td>158.9 ± 6.5</td>
<td>24.3 ± 3.8</td>
<td>0.848 ± 0.136</td>
<td>0.899 ± 0.177</td>
</tr>
<tr>
<td>Test of difference (p)</td>
<td>0.663²</td>
<td>0.227³</td>
<td>0.424⁷</td>
<td>0.351⁵</td>
<td>0.942⁷</td>
<td>0.0005⁷</td>
</tr>
<tr>
<td>OR (CI: 95%)</td>
<td>1.95</td>
<td>[1.31–2.89]</td>
<td>0.685</td>
<td>[0.599–0.762]</td>
<td></td>
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<tr>
<td>ROC (AUC) (CI: 95%)</td>
<td></td>
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Abbr: BMD, bone mineral density; TBS, trabecular bone score; OR, odds-ratio; CI, confidence interval; AUC, area under the receiving operator curve.

²Student’s t-test (normal distribution).
³Wilcoxon test (non-normal distribution).
⁴Value with their respective 95% CI.
Comparing fracture (all types) vs age—and spine BMD—matched nonfracture subjects (Table 1), the mean values for TBS$_{\text{spine}}$ were significantly different ($p = 0.0005$). In addition, TBS$_{\text{spine}}$ was a statistically significant predictor of disease, with an OR of fracture vs no fracture equal to 1.95 (95% CI: 1.31–2.89) and a corresponding AUC of 0.685 (0.599–0.762) (Fig. 1).

In the comparison between vertebral fracture and age—and spine BMD—matched nonfracture subjects (Table 2), TBS$_{\text{spine}}$ also was the only parameter that was significantly different ($p = 0.0004$), with an OR of 2.66 (1.46–4.85) and a corresponding AUC of 0.776 (0.669–0.862) (Fig. 1).

**Discussion**

In this study, we evaluated the potential diagnostic value of TBS, independent of BMD, in the differentiation of postmenopausal women with vs without fractures. Total spine TBS was significantly different between those with and without fractures, when one considered (1) all types of fractures combined ($p = 0.0005$) and (2) vertebral fractures alone ($p = 0.0004$). And, although not directly comparable, the higher values of OR and AUC for vertebral vs all fractures seem to indicate that that TBS$_{\text{spine}}$ can better discriminate vertebral fractures compared with all fracture types combined (Fig. 1), in both instances, independent of the BMD of the spine.

In the context of preliminary studies applied to clinical data, our choice was to conduct a retrospective case-control study as a first step. As a consequence, our results must be interpreted with caution, recognizing the need for future prospective studies to better evaluate the potential value of TBS as an additional and independent risk factor for osteoporosis-related fractures. Nevertheless, our data correlate prevalent fracture with TBS independent of BMD. The TBS greatest potential will result from demonstrating similar predictive power for incident fracture in prospective clinical trials. Such a study is currently underway.

Our study was single-blinded. At both recruitment centers (University hospitals), each DXA scan was evaluated without any knowledge of the fracture status of the corresponding patient. The level of intervention of the operator in the TBS calculation procedure consisted of adapting the format of the DXA gray level and regions of interest (ROI) images only, without any involvement in calculating the TBS value itself. Statistical analyses were performed with knowledge of the association of BMD and TBS values and the fracture status of the corresponding patient. Nevertheless, these statistical analyses were performed respecting the following rules: (1) BMD, age, height, and weight were extracted from the DXA scans directly; (2) TBS values were the output of an automatic computing algorithm, taking as input the DXA images (ROI and gray-level images); and (3) all of the patients initially recruited and eligible were included in all of the statistical analyses.

In another recent study (20), we used numerical simulations and models of 3D microarchitecture to establish an empirical mathematical 3D-2D relationship, expressing the correlation between TBS (as evaluated on 2D-projection images) and certain 3D characteristics of microarchitecture—Th and fs. Based on the theoretical relationship Th' = F(fs, TBS), TBS was directly correlated with Th in 3D microarchitecture samples with the same fs. The accuracy of this empirical relationship has been successfully evaluated in trabecular bone microarchitecture reconstructed by microcomputed tomography from a set of 57 human cadaver bone pieces from different anatomical sites. The error rate was 1.1% in a set of spine samples (N = 20), 2.0% in a set of hip samples (N = 17), and 1.3% in a set of radius samples (N = 20). In this set of bone samples, Th was highly correlated with standard trabecular thickness—TbTh (0.87 ≤ r ≤ 0.94) and fs was highly correlated with standard BV over total volume (TV)—BV/TV (0.98 ≤ r ≤ 0.99). Furthermore, TBS was significantly correlated with both the trabecular number (TbN) (−0.86 ≤ r ≤ −0.52) and the density of connectivity—connD (−0.87 ≤ r ≤ −0.57). There exists a significant but very low correlation between TBS and BMD as evaluated from several in vivo studies (in-house data), for example, r = 0.21 ($p = 0.0073$) in a population of 168 postmenopausal women with low BMD; r = 0.23 ($p = 0.0002$) in a population of 243 osteopenic postmenopausal women. In addition, from another ex vivo study (in-house data) based on experimentation of human cadaver bone pieces, the correlation between TBS and BMD as evaluated from the same DXA image was r = 0.29 ($p = 0.07$). The correlations between DXA—based measurements and 3D parameters of bone microarchitecture related that the highest correlations were r = 0.53 ($p = 0.0005$) between BMD and BV/TV and r = 0.86 ($p < 0.0001$) between TBS and connectivity density (connD), respectively. Such results clearly show that TBS does not apprehend the same physical meaning. BMD measures bone mineral density (BMD), and is highly correlated with bone fracture volume.

![Fig. 1. Visual comparison between ROC curves of TBS in the discrimination of all fractures combined and vertebral fractures alone.](image-url)
(BV/TV). On the contrary, TBS measures bone microarchitecture, and is highly correlated with conuD (the manner of how bone trabeculae are overconnected in 3D volume).

The calculation for TBS is based on variogram characterization, which itself is calculated based on the squared differences of gray levels (see Appendix). Hence, variation in the gray scale of DXA images does not make any difference in the calculation of TBS, because this calculation uses variations in gray levels and not the gray levels themselves. The technical feasibility of using existing DXA examinations and evaluating TBS and BMD in the same regions of measurement already has been evaluated. The present study, designed as a transversal retrospective study, constitutes an additional validation study but provides a glimpse of the potential of TBS measurements in the evaluation of fracture risk; longitudinal studies are needed now.

At this stage in its development, an operator intervention is still required for the TBS evaluation procedure. This intervention consists of preparing the DXA gray level and ROI images, without any intervention affecting the definition of the ROI or the calculation of TBS. The time required for TBS analysis, including this manual preprocessing step, has been on the order of half an hour per patient, taking into account both hip and spine analyses. Some developments are in progress to remove this preprocessing operator intervention and to develop an automatic analysis process that will accept DXA scan files as input directly. Such a process will permit us to automatically re-analyze a large set of data (retrospective study) and to analyze individual patients in about 3 min, taking into account both hip and spine DXA scans. Hence, this duration will become compatible with real-time evaluation of TBSs in clinical practice.

Although it is well recognized that the trabecular bone microarchitecture is an important contributor to bone strength, independent of BMD, it is not considered in the evaluation of fracture risk in clinical practice. Several imaging techniques are “periodically” reviewed as potential candidates for the clinical evaluation of trabecular bone microarchitecture (5,21). However, to date, no technique has emerged as sufficiently efficient for routine clinical use. In parallel, DXA technology has been developed extensively, both in terms of its hardware and software components (22). Recent generations of DXA systems provide not only accurate and reproducible measurements of BMD, but also the opportunity to use high-quality DXA scans in place of standard X-rays to confirm and characterize existing fractures. Hence, Genant’s indices of vertebral deformations (23,24) and certain indices related to hip geometry (25,26) can be evaluated from high-quality DXA images directly. These macroscopic geometrical measurements constitute risk factors that are independent of BMD and being able to obtain them from the same DXA examination is an additional advantage. Langton and Thorpe (27) have developed a new technique called finite element analysis of X-ray images (FEXI) based on a finite element analysis model applied to DXA gray-level images. This technique allows one to evaluate a new DXA-based measure, FEXI stiffness. An in vitro validation study (27) has shown that FEXI stiffness is highly correlated with BMD, which means that the new FEXI stiffness measure will not add independent information to the standard BMD measure.

TBS constitutes a novel DXA-based measure, independent of BMD, which provides indirect evaluation of trabecular bone microarchitecture by analyzing the gray levels of DXA images. This preliminary case-control study is a first glimpse at the potential use of TBS as a complement to BMD in the detection of osteoporotic fractures. Prospective studies are necessary, however, to truly evaluate the role of TBS as a complementary risk factor in the prediction of fracture, particularly in the osteopenia population, where

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>BMI (kg/m^2)</th>
<th>BMD L2–L4 (g/cm^2)</th>
<th>TBS L2–L4 (mm^3/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral fracture</td>
<td>68.9 ± 7.7</td>
<td>65.2 ± 16.3</td>
<td>160.7 ± 7.3</td>
<td>25.1 ± 5.3</td>
<td>0.824 ± 0.179</td>
<td>0.747 ± 0.140</td>
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<td>patients (n = 20)</td>
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<tr>
<td>Controls (n = 60)</td>
<td>65.8 ± 7.3</td>
<td>60.2 ± 9.2</td>
<td>158.5 ± 5.8</td>
<td>24.0 ± 3.6</td>
<td>0.829 ± 0.152</td>
<td>0.908 ± 0.178</td>
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<tr>
<td>Test of difference (p)</td>
<td>0.1187^a</td>
<td>0.2479^b</td>
<td>0.1172^b</td>
<td>0.4367^b</td>
<td>0.9075^a</td>
<td>0.0004^a</td>
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<tr>
<td>OR^c</td>
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<td>[CI: 95%]</td>
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<td>[1.46–4.85]</td>
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<td>ROC (AUC)^γ</td>
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<td>0.776</td>
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<tr>
<td>[CI: 95%]</td>
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<td>[0.669–0.862]</td>
</tr>
</tbody>
</table>

**Abbr:** BMD, bone mineral density; OR, odds-ratio; CI, confidence interval; AUC, area under the receiving operator curve, ROC, receiving operator curve.

^aStudent’s t-test (normal distribution).

^bWilcoxon test (non-normal distribution).

^cValue with their respective 95% CI.
a well-recognized large overlap exists between those who develop and those who do not develop fractures. The recognition of TBS as a valuable complementary risk factor would increase the efficiency of DXA examinations in the prediction of fracture risk in individuals and in the validation and follow-up of preventative and therapeutic modalities. Further work will be done to meet this objective. New references for TBS measures could be established rapidly, with the opportunity to re-analyze existing clinical databases.

Appendix Procedure for TBS Evaluation

Exportation of DXA—based images

Each DXA scan was reloaded using a workstation installation of Hologic QDR software (v12.3). A first screen copy/paste was performed from the individual ROI selection screen to the image viewer/analizer software (ImageJ v1.33). This pasted RGB—colored image was then used to detect ROI lines and to create ROI binary masks (Fig. 2). A second screen copy/paste was performed from the global ROI selection screen (Hologic QDR software) to ImageJ software. This pasted RGB—colored image then was converted into an 8-bit encoded gray-level image. This global gray-level image was cut following ROI binary masks, so as to create individual ROI gray-level images (Fig. 2).

Calculation of TBS

Each ROI gray-level image, $I$, was used for TBS evaluation. Point $P$ of $I$ was located by using the corresponding vector $\vec{P}(x, y)$, where $(x, y)$ were the spatial coordinates for $I$.

The experimental variogram $V(k)$ was calculated by averaging the difference squared of $I$ values over several pairs of points located at a specified distance, $k$:

$$V(k) = \frac{1}{C_{10}} \left( \frac{I(P_0 + k \cdot \vec{u}) - I(P_0)}{C_{138}^2} \right)$$

where

$P_0$ = the initial point in the 2D image $I$

$\theta$ = the angle defining a direction from the horizontal line passing through $P_0$
\[ \overrightarrow{u}_\theta = \text{the unit vector in the } \theta \text{ direction} \]
\[ k = \text{the distance} \]

For each value of \( k \), averaging was performed over a large number of calculations (\( N = 5 \times 10^5 \)) using different (\( P_0, \theta \)) initializations. To perform a mean evaluation of the gray level difference between 2 points of \( I \), independent of the orientation of this pair of points, each initialization (\( P_0, \theta \)) was determined randomly using the isoprobability for each angle over the \( 2\pi \) rotation.

TBS was evaluated as the slope at the origin of the log-log representation of \( V(k) \), measuring the mean rate of local variation of gray levels per unit of distance. TBS was expressed in gray levels per centimeter (cm\(^{-1}\)), taking into consideration the resolution of DXA images.

References