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TBS in Early Postmenopausal Women with Severe Vertebral Osteoporosis

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Abstract

Introduction/background: Severe vertebral osteoporosis is a rare condition in early postmenopausal women. We seek to determine whether Trabecular Bone Score (TBS), which is a new bone texture measurement, could be of additional value in evaluating trabecular bone properties in this population.

Methodology: Lumbar spine (LS) and femoral neck (FN) bone mineral densities (BMDs) and TBS were measured in 105 early postmenopausal women (group 1: “cases”, mean age: 53.1 ± 2.6 yrs.) with severe vertebral osteoporosis defined as a vertebral BMD T-score ≤ -3 , as well as in 105 healthy postmenopausal women matched for age (group 2) and 105 older osteoporotic women matched for vertebral BMD (group 3, mean age: 63.9 ± 4 yrs.). None of the women had a secondary cause for osteoporosis. Correlations between TBS values and BMD were calculated after controlling for clinical characteristics.

Results: The women in group 1 (cases) were significantly smaller and thinner and had a history of more fractures than the age-matched controls ($p < 0.05$). Mean LS and FN BMD values were significantly lower in the cases than in the age-matched controls (0.770 ± 0.05 vs 1.106 ± 0.11 g/cm² and 0.700 ± 0.07 vs 0.872 ± 0.12 g/cm², for LS and FN, respectively; $p < 0.001$). The mean TBS value was also significantly lower in the cases than in the age-matched controls (1.24 ± 0.08 vs 1.37 ± 0.07 , $p < 0.001$) but significantly higher than in the older osteoporotic controls (1.20 ± 0.07 , $p < 0.05$). After adjustment for vertebral BMD, the difference in TBS values between the cases and the age-matched controls was no longer significant although it remained significantly higher than in the older osteoporotic controls. This would suggest that in group 1, osteoporosis is rather the consequence of a low peak bone mass than of further bone degradation while the greater decrease in TBS value in elderly osteoporotic controls is more likely to reflect additional damage in bone microarchitecture associated with aging. In a multivariate analysis including age, vertebral and femoral neck BMD, height and weight ($R^2 = 0.60$, $p < 0.0001$), TBS was found to be negatively and independently associated with age ($r = -0.31$ $p < 0.0001$) and height ($r = -0.20$ $p < 0.001$). The FRAX score was significantly higher in group 1 and group 3 women than in the healthy control women (group 2). There were no changes in the results after adjustment for TBS.

Conclusions: Women presenting with severe vertebral osteoporosis at the beginning of menopause have TBS values that are, first and foremost, proportional to their BMD. Whether this indicates that osteoporosis in this population is the consequence of a low peak bone mass remains to be determined and further studies are required. Nevertheless, the value of measuring TBS in addition to BMD appears to be relatively negligible in early postmenopausal women with severe vertebral osteoporosis.

Keywords: idiopathic osteoporosis, DXA, TBS,

Abbreviations : BMD, bone mineral density; DXA, dual X-ray absorptiometry; FN, femoral neck; HR-pQCT, high-resolution peripheral quantitative computed tomography; LS, lumbar spine; μ CT, micro-computed tomography; QCT, quantitative computed tomography; TBS, trabecular bone score.

Introduction

Postmenopausal osteoporosis is the most common form of osteoporosis that affects approximately 40% of aging women [1]. A decline in ovarian function is the primary contributor to osteoporosis in postmenopausal women. Estrogen deficiency causes an increase in bone remodeling which leads to accelerated bone loss and alterations in the microarchitecture of bone. Therefore, the subsequent increase in the incidence of fragility fractures with aging is the consequence of low bone mass and microarchitecture defects as well extra-osseous factors (such as falls) [1]. In the absence of a fragility fracture, osteoporosis is defined as a T-score value below 2.5 standard deviations from the young adult mean [2]. The discovery of a very low BMD (T-score ≤ -3) at the beginning of menopause is a rare event that calls for the elimination of all causes of secondary osteoporosis in the first instance [3]. In the absence of any identifiable cause, it raises the question of its pathophysiology and consequence on the subsequent risk of fracture. In any event, and regardless of the underlying cause of low bone mass, it is logical to consider the risk of fracture to be particularly high in women who already have severe osteoporosis at the beginning of menopause [4]. Even though no prospective study has been conducted in this specific subset of women with very low BMD, several studies have demonstrated the value of BMD measured by DXA at the time of menopause to predict the risk of fragility fractures over 20 years [1]. Moreover, the gradient of risk for hip fracture is higher in women at a young age than at an older age and for the lowest BMD values [5].

Previous studies conducted in premenopausal women with fragility fractures and/or low BMD have also reported deteriorations in both cortical and trabecular microarchitecture [6]. Such deterioration has been noted both at the distal radius and the tibia by high-resolution peripheral computed tomography (HRpQCT) and at the central skeleton by quantitative computed tomography (QCT) [7,8]. A severe deficit in areal and volumetric BMD has also been observed [9]. It is important to note that women with low BMD who had never experienced a fracture were as severely affected as those with low BMD and fragility fractures. While BMD is routinely measured by DXA, the assessment of bone microarchitecture requires the use of invasive techniques (bone biopsies) or research tools such as HR-pQCT which is not available in routine clinical practice. Trabecular bone score (TBS) is a bone texture measurement that quantifies variations in pixel grey level from lumbar spine DXA images [10]. Significant correlations have been reported between TBS and 3D trabecular bone structure parameters assessed by micro-computed tomography (μ CT) in bone biopsies of the iliac crest [11]. Strong positive associations between TBS, trabecular number and bone volume fraction [11] have been found. Therefore, TBS was suggested as a surrogate technique to assess cancellous bone microarchitecture as well as an additional tool to determine trabecular bone properties. Even though there is a correlation between TBS and BMD values such as approximately 10 to 25% of TBS variance is explained by BMD [10], several cross-sectional and prospective studies have also shown that TBS is an independent predictor of the risk of fracture in patients with osteoporosis or other bone fragility-related conditions [10,12].

Therefore, the goal of this cross-sectional study was to evaluate the properties of trabecular bone using TBS in postmenopausal women with severe vertebral osteoporosis at the beginning of menopause. By comparing the association between TBS and BMD values, our aim was to formulate hypotheses on the pathophysiology of osteoporosis in this population. Accordingly, if TBS is decreased to a greater extent than lumbar spine BMD, this would

indicate that rapid bone loss is the major contributor to vertebral osteoporosis in this population. It is indeed likely that the impact of bone loss would degrade bone quality more rapidly than bone mineral density. On the other hand, if a strong correlation is found between TBS and lumbar spine BMD, this would suggest that osteoporosis is rather related to a low peak bone mass than to further degradation. Therefore, we compared TBS values between early postmenopausal women with severe idiopathic vertebral osteoporosis and healthy control women who were matched either for age or vertebral BMD.

Subjects and methods

Study population:

Among the postmenopausal women who attended our outpatient menopause clinic over the last 10 years, we identified all early postmenopausal women whose DXA measurement had shown severe vertebral osteoporosis defined as a vertebral T-score ≤ -3 . According to the inclusion criteria described below, 105 women ("cases", group 1) for whom the duration of menopause was less than 5 years were selected:

Two control groups were also selected from the women who attended our menopause clinic during the same period of time:

- Group 2: 105 healthy women with normal vertebral BMD matched for age and years since menopause;
- Group 3: 105 otherwise healthy older osteoporotic women (duration of menopause of more than 10 years) who were matched for vertebral BMD.

All cases and controls had been referred to our menopause clinic by their general practitioner or gynecologist for evaluation of the consequences of postmenopausal estrogen deficiency on metabolism and bone. They were evaluated through the same standard procedure as already described elsewhere [13,14] including a personal interview, a medical examination, a fasting blood sample with particular focus on secondary causes of osteoporosis (when needed) and bone densitometry measurements.

To be included, all the women had to have experienced natural menopause (not the consequence of oophorectomy or chemotherapy/radiotherapy) after the age of 45 years. Participants were excluded if they had a history of or presented with conditions that affect bone metabolism including endocrinopathies (hypogonadism or a prior history of hypo-estrogenic amenorrhea for more than 3 months, hyperthyroidism, glucocorticoid excess, type 1 or type 2 diabetes mellitus, primary hyperparathyroidism or prolactinoma), anorexia nervosa, bulimia, celiac disease or other gastrointestinal malabsorption syndromes, inflammatory or autoimmune diseases (rheumatoid arthritis, connective tissue diseases), renal dysfunction, hypercalciuria or any history of malignancy (except for dermatological cancers). Women who had taken glucocorticoids, anticonvulsants, chemotherapy and/or any anti-osteoporotic drugs (estrogens, bisphosphonates, raloxifene, denosumab, teriparatide) for more than 3 months were also excluded. Treatment with calcium and/or vitamin D was allowed. In addition, women with DXA measurements that were not evaluable due to degenerative spinal changes or artifacts were not selected.

The study was approved by the local ethics committee.

Interview:

All the women completed a standardized computer-assisted questionnaire, described extensively elsewhere [13], and this was recorded by the same trained research nurse. The following clinical and historical data were extracted for each woman: age, weight, height, body mass index (kg/m^2), reproductive history, risk factors for osteoporosis, self-reported personal and family history of low-trauma fracture after 40 years and medications. A family history of fracture was considered positive if a parent or sibling had a typical fragility fracture including hip, vertebral, humeral or wrist fracture. Information on smoking habits and alcohol consumption were also obtained. Current smoking was defined as consumption of more than 10 cigarettes per day for more than 1 year at the time of the survey.

Medical examination:

Each woman underwent a medical examination whereby all recorded data were validated and completed when necessary. Height (cm) and weight (kg) were measured with an automatic scale and body mass index (kg/m^2) was calculated.

Bone mineral density measurement:

For all the women, lumbar spine and femoral neck bone mineral densities (BMDs, g/cm^2) were measured by an IOF-ISCN certified technician using a single DXA scanner (GE Lunar iDXA, GE Healthcare, Madison, WI - software version 14.10). T-scores (SD from young normal) for each measurement site were calculated using the Lunar normative database for France for age 25-35 as previously published ($n = 110$, mean spine BMD= $1.18 \pm 0.12 \text{ g}/\text{cm}^2$; mean FN= 0.990 ± 0.12) [13].

Vertebral Fracture assessment:

All women in groups 1 and 3 had vertebral fracture assessment (VFA) of the thoracolumbar spine (T4-L5) by DXA scans. Confirmatory X-ray radiographs were performed whenever a vertebral abnormality that could indicate a fracture was found.

Trabecular Bone Score (TBS) measurement

Lumbar spine TBS was obtained using DXA scans at the same region of interest (L2-L4) using TBS Insight software (Version Medimaps, Bordeaux France) by a technician blinded to the patients' clinical outcome. For scans performed before January 2012, the DXA files were digitally exported to a specific TBS calculation workstation that uses the latest version of TBS software (courtesy Didier Hans, Center of Bone Diseases, Lausanne University Hospital Switzerland).

FRAX score:

We used the algorithm available at www.shef.ac.uk/FRAX to calculate individual FRAX values based on each woman's hip BMD measurement and clinical characteristics at baseline.

Statistical analysis:

Statistical analyses were performed using MedCalc (software version 18.11.3, Belgium). A p-value of 0.05 was set as the threshold for statistical significance.

One-way analysis of variance (ANOVA) was used to compare clinical characteristics, TBS, BMD values and biochemical parameters among the three groups (patients, age-matched and BMD-matched controls). Categorical variables were analyzed using the χ^2 test. Analysis of covariance was used to calculate adjusted mean BMD and TBS after controlling for

confounders. Spearman's rank correlation coefficient was used to analyze the correlations between TBS and clinical characteristics and BMDs. Multivariate logistic regression analyses were then performed to analyze the relation of the different clinical variables found to significantly affect TBS values

Results

Clinical characteristics of the women:

The mean age of cases was 53.1 ± 2.6 years with a mean duration of menopause of 2.4 years. Cases were significantly ($p < 0.05$) smaller and thinner and had a history of more fractures than age-matched controls (23% vs 3.8% ($p < 0.05$)). There was no significant difference in fractures between the cases and the older BMD-matched controls (23 % vs 27 %) (Table 1). In the group 1 women, fractures involved ribs ($n=8$), vertebrae ($n=8$), wrist ($n=5$), proximal humerus ($n=2$) and other minor bone sites ($n=7$). Six patients had more than 1 fracture. In group 3, the distribution of fractures was as follows: ribs $n= 6$, vertebrae $n= 8$, wrist $n=8$, proximal humerus $n=1$ and other $n=5$. Four patients had more than 1 fracture. Moreover, a family history of non-hip fractures was more frequently reported in the group 1 women than in the women in both control groups ($p < 0.05$). The percentage of smokers was also higher among the women in group 1 than among those in the 2 control groups ($p < 0.05$) (table 1).

Bone mineral density and TBS values:

Mean lumbar spine (LS) and femoral neck (FN) BMD values (and T-scores) were significantly lower in the cases than in the age-matched non osteoporotic women (group 2) (0.770 ± 0.05 g/cm² vs 1.106 ± 0.11 g/cm²; $p < 0.001$ and 0.700 ± 0.07 g/cm² vs 0.872 ± 0.12 g/cm²; $p < 0.001$, respectively). Differences in BMD between the cases and the age-matched women remained significant ($p < 0.0001$) after controlling for weight and height (and BMI).

There was no significant difference in mean LS and FN BMDs (and T-scores) between the cases and the older osteoporotic women (BMD-matched control group, group 3) (table 2).

Mean TBS values were significantly different within the 3 groups ($p < 0.001$). The mean TBS value was significantly lower in the cases than in the age-matched women (1.24 ± 0.08 vs 1.37 ± 0.07 , $p < 0.001$) but significantly higher than in the older osteoporotic controls (1.20 ± 0.07 , $p < 0.05$). Adjustment for height did not modify the results in covariance analyses. On the other hand, after adjustment for vertebral BMD ($p < 0.0001$), there was no longer a difference in mean TBS values between the cases and the age-matched controls while it remained significantly higher in the cases than in the older osteoporotic controls (table 2). However the difference in mean TBS values was no longer significant between the cases and the older osteoporotic controls after adjustment for age (1.23 vs 1.23).

A femoral neck T-score below -2.5 was found in 46 out of 105 women in group 1. However, there was no significant difference in mean TBS values (1.23 ± 0.06 vs 1.24 ± 0.07 , $p=0.67$) or lumbar spine BMD (0.763 ± 0.06 g/cm² vs 0.774 ± 0.04 g/cm², $p= 0.29$) between those with and those without femoral neck osteoporosis in this group. There was also no difference in mean BMD and TBS values between women who reported a history of fragility fractures and those who did not, neither in group 1 nor in group 3 (data not shown).

Predictors of TBS values:

In univariate analysis, a significant correlation ($p < 0.05$) was found between TBS and lumbar spine, and femoral neck BMD, age, years since menopause, and height (no association with weight, parental history of fracture or parity). TBS was negatively and independently associated with age ($r = -0.31$; $p < 0.0001$) and height ($r = -0.20$; $p < 0.001$) in a multivariate analysis including age, vertebral and femoral neck BMD, height and weight ($R^2 = 0.60$; $p < 0.0001$) (table 3).

The regression slopes between TBS and vertebral BMD values were not significantly different within the 3 groups although there was a trend toward a greater correlation between TBS and lumbar spine BMD values in the healthy control group than in the other 2 osteoporotic groups (group 1: $r = 0.34$ vs group 2: $r = 0.53$ ($p = 0.21$) and in group 1 vs group 3: $r = 0.34$ ($p = 0.99$)) (figure 1).

FRAX probability of fracture:

The probabilities of fracture as calculated by the FRAX algorithm were significantly higher in the 2 osteoporotic groups (group 1 and 3) than in the healthy control group ($p < 0.05$ to 0.01) (table 2). After adjusting for TBS values, the FRAX score was slightly higher in both osteoporotic groups but not in the healthy control group (table 2).

Discussion

In this study, we found that postmenopausal women with severe vertebral osteoporosis (as defined by a lumbar spine T-score ≤ -3) at the beginning of menopause had significantly lower TBS values than age-matched healthy postmenopausal women. However, it was significantly higher in the cases than in the older osteoporotic women who were matched for vertebral BMD. Nevertheless, this difference was no longer significant when age (or years since menopause) was taken into account. This could indicate that women with severe vertebral osteoporosis at the beginning of menopause have trabecular bone microarchitecture that is proportional to their vertebral BMD. Therefore, low bone mass could be more the consequence of a low peak bone mass than of subsequent degradation. This contrasts with the findings in older osteoporotic women where it is more likely that the greater decrease in mean TBS value reflects further deterioration of bone microarchitecture, probably related to postmenopausal bone loss (and/or aging). However, it could be noted that even though there was no significant difference in the regression slopes between TBS and vertebral BMD values within the 3 groups, there was a trend towards a greater difference between the 2 osteoporotic groups and the healthy control group than between the 2 osteoporotic groups. This could indicate that the dependency of TBS on vertebral BMD is weaker in women with severe vertebral osteoporosis at the beginning of menopause than in healthy age-matched controls. Therefore, this suggests that in group 1, additional alterations in bone microarchitecture cannot be completely excluded.

To our knowledge there is no study in early postmenopausal women with severe vertebral osteoporosis. A few studies are available on premenopausal women with idiopathic osteoporosis (with or without fractures). In these studies, data similar to ours, such as smaller size, lower BMI and a family history of osteoporosis were found in these women [3,15-17]. Microstructural deficits in both the central and peripheral skeleton assessed by different computed tomography techniques as well as by finite element analysis were often reported [6,8,15]. This contrasts with our study in which there was no significant difference in TBS values between early postmenopausal women with and without severe vertebral osteoporosis after adjustment for vertebral BMD. TBS is a bone texture parameter which is related to bone microarchitecture and proposed as a surrogate marker for the assessment of

trabecular bone properties [11]. Our study is consistent with previous studies [8-20] in that we found a negative correlation between TBS, age and height and a positive correlation with lumbar spine and femoral neck BMD. Since TBS is derived from DXA images of the lumbar spine, it is not surprising that vertebral BMD contributed more to TBS variance than femoral neck BMD [10]. In addition, in our study there was no difference in mean TBS values in group 1 women with and without femoral neck T-scores below -2.5.

Several studies conducted in postmenopausal women with osteoporosis [10-12] as well as in patients with secondary osteoporosis [21,22] have shown that TBS is a predictor of the risk of fracture independently, at least in part, of BMD. As expected, because of the low BMD and the history of a higher fracture rate, the 10 year-risk of major osteoporotic fracture calculated by the FRAX tool was significantly higher in the cases than in the age-matched controls. It remained significantly lower than in the group of older women as one of the major determinants of FRAX score is age as well as decreased femoral BMD and a history of fracture. After adjustment for TBS, mean FRAX values were only slightly higher in the two osteoporotic groups but not in the healthy postmenopausal control group. These factors could indicate that the additional value of TBS in predicting the risk of fracture is relatively negligible in postmenopausal women with severe osteoporosis. It is of note that at present, there is no guideline to recommend the assessment of TBS to predict the risk of fracture in postmenopausal women with a very low vertebral T-score.

This study has several strengths and limitations. It concerns a relatively large number of women with very low vertebral BMD at the beginning of menopause, which is unusual. Although data were collected over a 10-year period, all the women were selected at the same facility through the same selection process. We were particularly careful in matching cases with women in the 2 control groups for either age or vertebral BMD. Since several diseases have various impacts on cortical or trabecular bone which can affect the TBS value in different ways, we eliminated all women with a secondary cause of osteoporosis to obtain the most homogeneous population possible. The main limitation of our study is related to its cross-sectional nature which does not allow us to assess the risk of fracture. Only through a longitudinal follow-up would it be possible to evaluate the real risk of fracture over time, although effective anti-fracture therapy is more likely to be warranted in this population. In addition, TBS does not allow direct measurement of bone micro-architecture and our results would need to be confirmed by a benchmark technique such as HRpQCT. Our working hypothesis that TBS could help to clarify the underlying mechanisms of osteoporosis in this population also remains quite theoretical and further studies are required. Finally, our results were obtained in a specific population of early postmenopausal women with severe vertebral osteoporosis and may not apply to women with other causes of osteoporosis.

In conclusion, low TBS values were found in early postmenopausal women with severe vertebral osteoporosis even though they were almost entirely explained by a decrease in vertebral BMD. Although this requires confirmation by further studies, our results could indicate that low bone mass is rather the consequence of a low peak bone mass than of further bone degradation. In any event, it is unlikely that TBS provides additional information to BMD measurement in the evaluation of trabecular bone properties in this population.

Table 1: Clinical characteristics of cases and matched controls

	Cases (group 1) (n = 105)	Age-matched controls (group 2) (n = 105)	BMD-matched controls (group 3) (n= 105)
Age (yrs.)	53.1 ± 2.6§	53.4 ± 2.4	63.9 ± 4
Weight (kg)	53.1 ± 5.7*§	59.5 ± 8.6	55.3 ± 8.5
Height (cm)	160 ± 6*	162 ± 6	159 ± 6
BMI (kg/m ²)	20.8 ± 2.1*§	22.7 ± 3.1	22 ± 3.1
Current smokers, n (%)	18*§	12	11
Number packs/yr.	22 ± 8	26 ± 9	27 ± 11
Personal history of fracture, n (%)	25* (23)	4 (3.8)	28 (27)
Parental history of hip fracture, n (%)	15 (14.3)	15 (14.3)	13 (12.4)
Parental history of non-hip fracture, n (%)	26*§ (24.8)	12 (11.4)	15 (14.3)
Age at menarche (yrs.)	13.3 ± 1.7	13 ± 1.5	12.9 ± 1.3
Nulliparity (%)	16§	17	12
Age at menopause (yrs.)	50.8 ± 2.3	51.4 ± 2.3	50.5 ± 2.3
Years since menopause	2.4 ± 1.3§	2.1 ± 1.1	13.2 ± 1.1

* p<0.05 between groups 1 and 2

§ p<0.05 between groups 1 and 3

Table 2: Comparison of BMD and TBS values between cases and controls

	Cases (group1) (n = 105)	Age-matched controls (group 2) (n = 105)	BMD-matched controls (group 3) (n = 105)
Lumbar spine BMD (g/cm ²)	0.770 ± 0.05*	1.106 ± 0.11	0.775 ± 0.04
Lumbar spine T-score	-3.4 ± 0.4*	-0.6 ± 0.9	-3.4 ± 0.4
Femoral neck BMD (g/cm ²)	0.700 ± 0.07*	0.870 ± 0.12	0.710 ± 0.07
Femoral neck T-score	-2.3 ± 0.6*	-0.9 ± 1	-2.3 ± 0.6
Lumbar spine TBS (no unit)	1.24 ± 0.08*§	1.37 ± 0.07	1.20 ± 0.07
TBS ≤ 1.20 (%)	28.6*§	1.9	48.6
Lumbar spine BMD adjusted TBS	1.29 ± 0.08£	1.28 ± 0.07	1.25 ± 0.07
FRAX MOF	6.1 ± 3.2*§	3.3 ± 1.5	7.9 ± 3.8
FRAX TBS-adjusted MOF	7.4 ± 3.2*§	3.4 ± 1.7	9.7 ± 4.2
FRAX Hip	2.3 ± 2.4*§	0.4 ± 0.5	2.6 ± 1.7
FRAX TBS-adjusted Hip	2.6 ± 2.7*§	0.3 ± 0.5	3.1 ± 2.1

* p <0.001 between groups 1 and 2

§ p <0.05 between groups 1 and 3

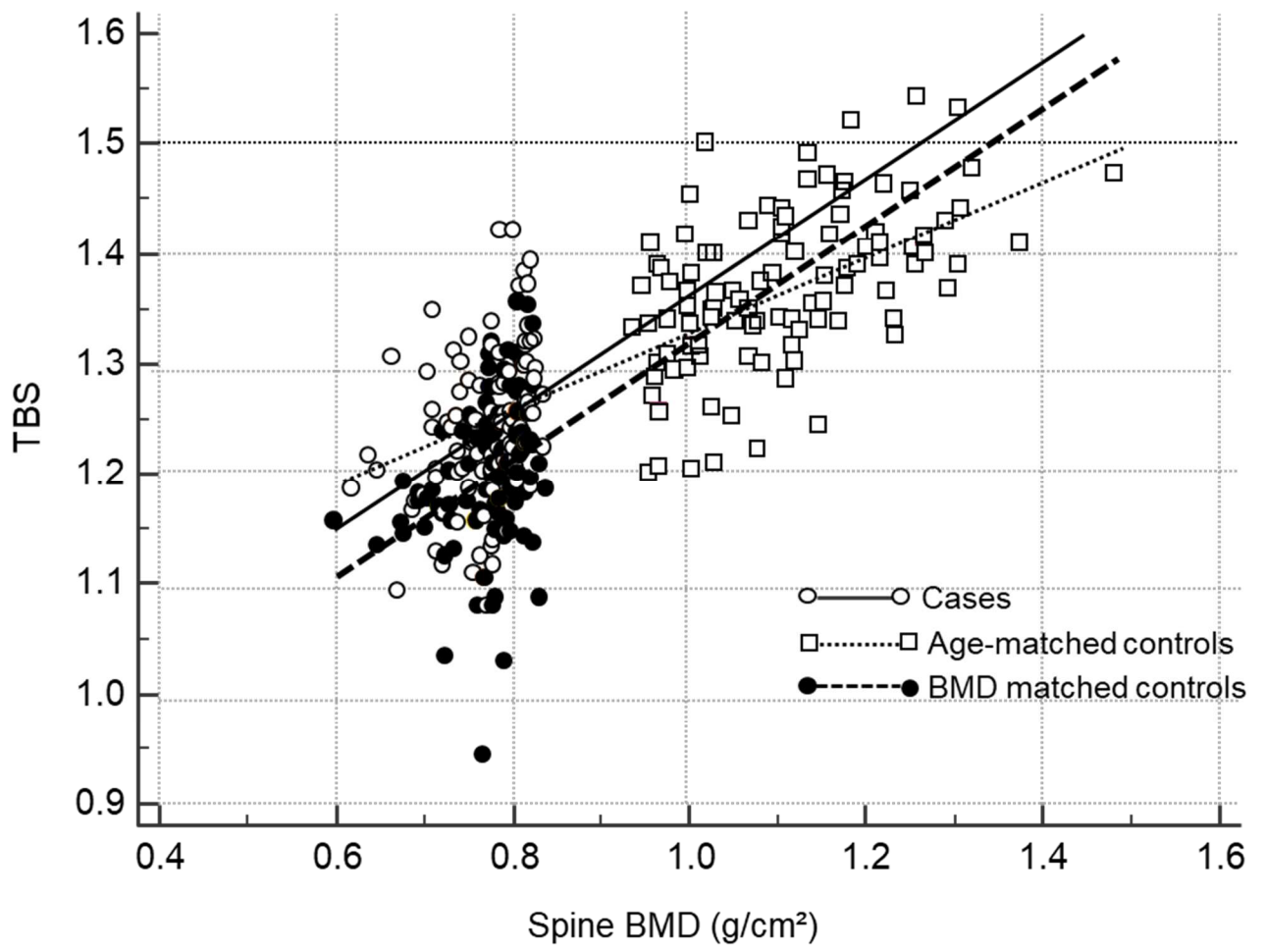
£ p <0.0001 between groups 1 and 3

Table 3: Parameters independently associated with TBS in a multiple regression analysis (n=315)

Independent variables	Coefficient	Standard Error	p	Partial R
Years since menopause	-0.00376	0.000668	< 0.0001	-0.30
Lumbar spine BMD	0.3834	0.0240	< 0.0001	0.67
Height	-0.00237	0.000664	0.0004	-0.20

* $p < 0.05$ between cases and age-matched controls

§ $p < 0.05$ between cases and BMD-matched controls



Legends:

Figure 1: Correlation between TBS and lumbar spine BMD in the 3 groups. The regression slopes are not statistically different between the 3 groups.

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