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Trabecular bone score as a supplementary tool for the discrimination of osteoporotic fractures in postmenopausal women with rheumatoid arthritis

Yong Jun Choi, MD, MS[a,*], Yoon-Sok Chung, MD, PhD[a], Chang-Hee Suh, MD, PhD[b], Ju-Yang Jung, MD, MS[b], Hyoun-Ah Kim, MD, PhD[b,*]

Abstract

Rheumatoid arthritis (RA) is a risk factor for bone fragility, and its effect on fracture risk is independent of bone mineral density (BMD). The trabecular bone score (TBS) is a new indirect parameter of bone quality. In this study, BMD and the TBS were compared between female postmenopausal RA patients with and those without vertebral fractures (VFs).

This study had a cross-sectional design. Two hundred seventy-nine postmenopausal women with RA aged 50 years or older were included in this study. TBS measurements were performed on the same vertebrae as those for the BMD measurements.

Among the 279 subjects, 34 had VFs (12.5%). There was a significant difference in the TBS ($P = .005$) but not L-spine BMD ($P = .142$) between the subjects with and those without VFs. The odds ratio (OR) for the TBS per standard deviation decrease was significant, even after adjusting for confounding factors such as age, height, rheumatoid factor positivity, the disease activity score for 28 joints (DAS28), the cumulative dose of glucocorticoids (GCs), the time since menopause and osteoporosis drug use (OR = 2.86; 95% CI, 1.34–6.09), and L-spine BMD (OR = 2.57; 95% CI, 1.19–5.54). The TBS was negatively correlated with the cumulative dose of GCs, but not with the DAS28 or erythrocyte sedimentation rate. However, the correlation was an L-shaped nonlinear relationship.

The TBS could be a supplementary tool for discriminating osteoporotic fractures in postmenopausal women with RA, and it may have a nonlinear relationship with the cumulative dose of GCs, but not with RA disease activity.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D, Adj. hip FRAX = TBS-adjusted 10-year probabilities of hip osteoporotic fracture, Adj. major FRAX = TBS-adjusted 10-year probabilities of major osteoporotic fracture, BMD = bone mineral density, CI = confidence interval, CRP = C-reactive protein, CV = coefficients of variation, DAS28 = the disease activity score for 28 joints, DXA = dual-energy X-ray absorptiometry, ESR = erythrocyte sedimentation rate, FRAX = the Fracture Risk Assessment Tool, GC = glucocorticoid, Hip FRAX = 10-year probabilities of hip fracture, L-spine = lumbar spine, Major FRAX = 10-year probabilities of major osteoporotic fracture, OR = odds ratio, QCT = quantitative computed tomography, RA = rheumatoid arthritis, SD = standard deviation, TBS = trabecular bone score, VF = vertebral fracture.

Keywords: bone densitometry, glucocorticoid, rheumatoid arthritis, trabecular bone score, vertebral fracture

1. Introduction

Rheumatoid arthritis (RA), which can cause cartilage loss, bone destruction, and disability, is one of the most prevalent chronic inflammatory diseases.[1] RA is a risk factor for bone fragility, and its effect on fracture risk is independent of bone mineral density (BMD).[2,3] In the Fracture Risk Assessment Tool (FRAX) algorithm, RA is the only secondary cause of osteoporosis considered to be independent of BMD, regardless of other traditional risk factors such as immobility, a greater risk of falling, or glucocorticoid (GC) use.[2,4] Vertebral fractures (VFs) are the most common type of fragility fracture and are associated with chronic back pain, shorter height, kyphosis, reduced pulmonary function, abdominal discomfort, disability, and death.[5,6] The risk of VFs is higher in patients with RA than in those with primary osteoporosis.[7,8] BMD accounts for ~70% of bone strength and is frequently used as a representative measure.[9] However, there is a discrepancy between low BMD and fracture risk, as many fractures are observed in RA patients who are not in the osteoporotic range.[10] In addition to BMD, bone quality can contribute to the increased fracture risk in patients with RA. However, it is difficult to measure bone quality. Novel imaging techniques such as quantitative computed tomography (QCT) and high-resolution (peripheral) QCT have been used in attempts to evaluate bone quality. Unfortunately, they are not widely used in clinical practice because of their general weaknesses regarding variability and validation in the clinical setting.[11]

The trabecular bone score (TBS) is a new texture parameter obtained from the analysis of dual-energy X-ray absorptiometry (DXA) images. The TBS is used to evaluate pixel gray level variations in the spine on DXA images and is related to bone microarchitecture and fracture risk, thereby providing informa-

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YJC and H-AK contributed equally to this work.

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[a] Department of Endocrinology and Metabolism, [b] Department of Rheumatology, Ajou University School of Medicine, Suwon, South Korea.

[*] Correspondence: Hyoun-Ah Kim, Department of Rheumatology, Ajou University School of Medicine, 164 Worldcup-ro, Yeongtong-gu, Suwon 16499, South Korea (e-mail: nakhada@naver.com); Yong Jun Choi, Department of Endocrinology and Metabolism, Ajou University School of Medicine, 164 Worldcup-ro, Yeongtong-gu, Suwon 16499, South Korea (e-mail: colsmile@hanmail.net).

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tion independent of BMD.[12–14] However, only a few studies have evaluated the effectiveness of the TBS for assessing fracture risk in RA patients.[15,16]

In the present study, we compared bone parameters including BMD and TBS between female postmenopausal RA patients with and those without VFs. We also evaluated the association between the TBS and parameters related to RA disease activity.

2. Methods

2.1. Subjects

Postmenopausal women aged 50 years or older at the time of DXA evaluation who were diagnosed with RA or who had started follow-up for RA at Ajou University Hospital between January 2010 and April 2015 were eligible for the study. All the RA patients satisfied the American College of Rheumatology 1987 revised criteria for the classification of RA.[17] Among the 288 eligible patients, 9 with other metabolic disorders, and/or secondary causes of osteoporosis were excluded. Finally, 279 women were included in this study. The medical records of the 279 subjects were reviewed retrospectively, including demographics (age, height, and weight), previous medical history including smoking, alcohol intake, secondary osteoporosis (untreated long-standing hyperthyroidism, hypogonadism, or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease) and diabetes. RA-related clinical information (disease duration, disease activity, and the use of disease-modifying antirheumatic drugs and GCs), and osteoporosis- or fracture-related information (menopausal age, antiosteoporosis drug use, prior fractures, and hip fracture in a parent). A clinical VF (clinical symptoms and a semiquantitative approach for diagnosis using lateral thoracolumbar radiography[18]) was defined as prevalent VF. For the subjects without VFs who had not undergone lateral thoracolumbar radiography, VF assessments were performed using DXA images and the absence of VFs was confirmed. RA disease activity was measured using the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, tender joint count, swollen joint count, and the disease activity score for 28 joints (DAS28).[19] This study was approved by the Institutional Review Board of the Ajou University Hospital (AJIRB-MED-MDB-16-053).

2.2. Biochemical and BMD measurements

Serum 25-hydroxyvitamin D (25(OH)D) concentrations were measured using a radioimmunoassay kit (DiaSorin Inc, Stillwater, MN). The densitometric examinations were performed using the Lunar Prodigy apparatus (GE Lunar, Madison, WI). For lumbar spine (L-spine) BMD measurements, BMD was calculated excluding the affected vertebrae when specific vertebrae were not suitable for analysis because of compression fractures, degenerative changes, or any other reasons. The coefficients of variation (CV) for BMD were 0.339% (L-spine), 0.679% (femur neck), and 0.794% (total hip).

2.3. Measurement of TBS

TBS measurements were obtained using TBS insight software version 2.1 (Med-Imaps, Pessac, France) with anonymized spine DXA files from the database. TBS measurements were performed on the same vertebrae as those used for the BMD measurements. The investigator was blinded to all clinical parameters and outcomes. The average short-term reproducibility (CV) for TBS was 1.408%.

2.4. Calculation of FRAX probabilities

FRAX probability[20] was computed for each woman using the algorithm available online at http://www.shef.ac.uk/FRAX (South Korea version) with 9 clinical variables (age, body mass index (BMI), previous fracture, hip fracture in a parent, alcohol use, smoking status, systemic glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and total hip BMD). TBS adjusted 10-year probabilities were also calculated using the algorithm available online at http://www.shef.ac.uk/TBS/CalculationTool.aspx.

2.5. Statistical analyses

All data are expressed as the mean ± standard deviation (SD) of each index evaluated. The TBS and L-spine BMD values were log-transformed for the statistical analyses because of their non-normal distribution. Student t tests were used to compare the continuous variables of RA patients with versus without VFs. Categorical variables were analyzed using χ^2 tests. To further assess the performance of the TBS for detection of VFs in patients with RA, odds ratios (ORs) per SD decrease in the TBS were estimated from logistic regression models after adjusting for confounding factors. Three models were constructed: model 1 was not adjusted for confounding factors; model 2 was adjusted for age, height, RF positivity, DAS28, cumulative dose of GCs, time since menopause, and osteoporosis drug use; and model 3 incorporated the variables of model 2 plus L-spine BMD per SD. The OR per SD decrease in the TBS was presented with the 95% dual-energy X-ray absorptiometry Pearson correlation coefficient was used to estimate the relationships between bone parameters and RA disease activity. The subjects were categorized according to quartiles of the cumulative GC dose or as nonsteroid users. To further assess the performance of conventional FRAX and TBS adjusted FRAX scores in the prediction of VFs in patients with RA, per SD increases in FRAX scores were estimated from logistic regression models with adjustment for age, height, positivity of rheumatoid factor, disease activity score for 28 joints, cumulative dose of glucocorticoids, time postmenopause, osteoporosis drug use, and lumbar spine bone mineral density per SD. One-way ANOVA was used to compare the TBS according to the cumulative GC dose quartile. Fisher least significant difference analysis was used as a post-hoc test. Analysis of covariance was used to compare the TBS according to the cumulative GC dose quartile after adjusting for age, DAS28, serum 25(OH)D concentration, RA disease duration, and osteoporosis drug use. A locally weighted regression method was used to evaluate the potential non-linear relationship between the log TBS and cumulative GC dose. All analyses were conducted using SPSS ver. 23.0 (SPSS, Chicago, IL), except for the locally weighted regression conducted using R version 3.2.2. A P value $< .05$ was considered statistically significant.

3. Results

3.1. Characteristics of RA patients with and those without VFs

Table 1 summarizes the characteristics of the study subjects. Among the 279 subjects, 34 had VFs (12.5%). The mean age of the subjects with VFs (64.4 ± 8.4 years) was significantly higher than that of those without VFs (59.0 ± 6.5 years, $P < .001$). The time since menopause was longer in subjects with VFs ($P < .001$). The mean height of patients with VFs (151.3 ± 5.7 cm) was

Table 1

Characteristics of rheumatoid arthritis (RA) patients with and those without vertebral fractures (VF).

	VF group (n = 35)	Non-VF group (n = 244)	*P* value
Age, y	64.4 ± 8.4	59.0 ± 6.5	<.001
Height, cm	151.3 ± 5.7	154.9 ± 5.3	<.001
Weight, kg	52.8 ± 8.3	55.3 ± 7.8	.074
BMI, kg/m^2	23.0 ± 3.1	23.1 ± 3.2	.863
Smoking, %			.348
Never	97.5	100	
Ever	2.5	0	
Alcohol (3 or more units/d; %)	2.9	4.9	0.589
Disease duration of RA, y	7.8 ± 7.6	6.6 ± 5.9	.296
RF positivity, %	88.6	66.4	.008
DAS28	3.9 ± 1.2	3.3 ± 1.2	.014
ESR, mm/h	26.7 ± 22.5	19.4 ± 17.8	.030
25(OH)D, ng/mL	19.4 ± 8.4	19.4 ± 10.0	.997
DMARD use, %	91.4	94.7	.440
Biologic use, %	2.9	4.5	.653
GC use, %	91.4	73.4	.020
Cumulative GC dose (mg, prednisolone equivalent)	5910.6 ± 6065.0	3710.7 ± 4989.4	.018
Time postmenopause, y	14.6 ± 8.6	10.0 ± 6.7	< .001
Type 2 diabetes, %	8.6	10.7	.706
Osteoporosis drug use, %	37.1	19.3	.016
Vitamin D use, %	65.7	56.1	.285
Prior fracture, %	97.1	3.3	< .001
Parental fracture, %	0	0	–
Secondary osteoporosis, %	2.9	0	.310
Femur neck BMD, g/cm^2	0.719 ± 0.104	0.768 ± 0.104	.010
Major FRAX, %	25.0 ± 8.4	12.6 ± 5.7	< .001
Adj.major FRAX, %	23.4 ± 8.5	11.7 ± 5.6	< .001
Hip FRAX, %	11.1 ± 7.2	4.5 ± 3.8	< .001
Adj.hip FRAX, %	9.7 ± 7.0	3.6 ± 3.5	< .001

Student *t* tests were used to compare continuous characteristics between RA patients with and those without VF. χ^2 tests were used to compare categorical variables between RA patients with and those without VF.

25(OH)D = 25-hydroxyvitamin D, Adj. hip FRAX = TBS-adjusted 10-year probabilities of hip osteoporotic fracture, Adj. major FRAX = TBS-adjusted 10-year probabilities of major osteoporotic fracture, BMD = bone mineral density, BMI = body mass index, DAS28 = disease activity score for 28 joints, DMARD = disease-modifying antirheumatic drug, ESR = erythrocyte sedimentation rate, FRAX = the Fracture Risk Assessment Tool, GC = glucocorticoid, Hip FRAX = 10-year probabilities of hip fracture, Major FRAX = 10-year probabilities of major osteoporotic fracture, RF = rheumatoid factor.

Table 2

Adjusted odd ratios for vertebral fractures according to trabecular bone score per standard deviation decrease obtained from logistic regression models adjusted for multiple covariates.

	Odds ratios	95% CI	*P* value
Model 1	2.41	1.32–4.39	.008
Model 2	2.86	1.34–6.09	.007
Model 3	2.57	1.19–5.54	.016

Model 1 = no adjustment, Model 2 = adjustments for age, height, positivity of rheumatoid factor, disease activity score for 28 joints, cumulative dose of glucocorticoids, time postmenopause, and osteoporosis drug use, Model 3 = adjustments for the parameters described in Model 2 plus lumbar spine bone mineral density per standard deviation.

significantly lower than that of those without VFs (154.9 ± 5.3 cm, $P < .001$). RA disease activity, as assessed by the DAS28 and ESR, was significantly greater in the subjects with VFs ($P = .014$ and $P = .030$, respectively). The cumulative GC dose was also higher in the subjects with VFs ($P = .018$). Femur neck BMD was significantly lower in subjects with VFs ($P = .010$). FRAX scores and TBS-adjusted FRAX scores were significantly higher in subjects with VFs ($P < .001$). There were no significant differences between patients with and those without VFs in terms of the other continuous parameters such as weight, BMI, disease duration of RA, and 25(OH)D concentration. For categorical variables, the percentages of GC ever-users and osteoporosis drug users and prior fracture were higher among the subjects with VFs.

3.2. Comparison of the TBS and L-spine BMD between RA patients with and those without VFs

Figure 1 shows the mean TBS and L-spine BMD values in postmenopausal RA patients with and those without VFs. There was a significant difference in the TBS ($P = .005$, Fig. 1A), but not L-spine BMD ($P = .142$, Fig. 1B), between the groups.

The OR per SD decrease in the TBS was estimated from logistic regression models (Table 2). The OR was significant for the TBS per SD decrease, even after adjusting for confounding factors such as age, height, RF positivity, DAS28, cumulative GC dose, the time since menopause, osteoporosis drug use (OR = 2.86; 95% CI, 1.34–6.09), and even L-spine BMD (OR = 2.57; 95% CI, 1.19–5.54).

Table 3 shows the correlations between bone parameters, including the L-spine BMD and TBS, and other RA disease activity. The TBS was negatively correlated with the RA disease duration and the cumulative GC dose. However, the TBS was not significantly correlated with the DAS28 or ESR. L-spine BMD

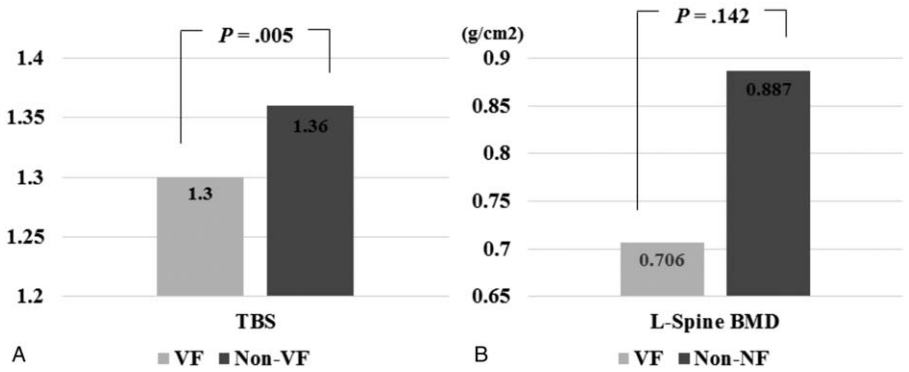

Figure 1. Comparison of the trabecular bone score (TBS) and L-spine bone mineral density (BMD) between rheumatoid arthritis patients with and those without vertebral fractures (VFs).

Table 3

Correlations of trabecular bone score (TBS) and bone mineral density (BMD) with the parameters related to rheumatoid arthritis (RA) disease activity.

	RA disease duration		Cumulative dose of GCs		DAS28		ESR	
	r	*P* value	r	*P* value	R	*P* value	r	*P* value
TBS	−0.137	.023	−0.250	<.001	−0.094	.116	−0.093	.120
L-spine BMD	−0.110	.067	−0.222	<.001	−0.014	.820	0.000	.995
Femur Neck BMD	−0.141	.019	−0.243	<.001	−0.140	.019	−0.224	<.001
Total Hip BMD	−0.188	.002	−0.290	<.001	−0.164	.006	−0.222	<.001

L-spine = lumbar spine, GCs = glucocorticoids, DAS28 = disease activity score for 28 joints, ESR = erythrocyte sedimentation rate.

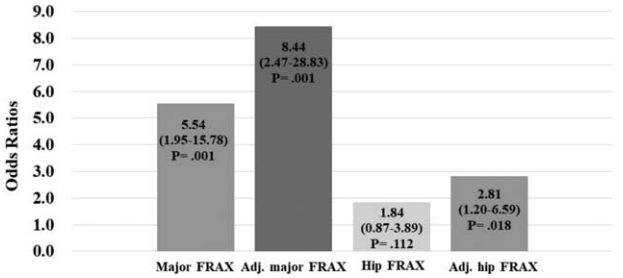

Figure 2. Odds ratios for original FRAX and TBS adjusted FRAX per SD increase with 95% confidential intervals (CIs) from logistic regression models adjusting for age, height, positivity of rheumatoid factor, disease activity score for 28 joints, cumulative dose of glucocorticoids, time postmenopause, osteoporosis drug use and lumbar spine bone mineral density per SD. FRAX = the Fracture Risk Assessment Tool, TBS = trabecular bone score, SD = standard deviation.

was correlated only with the cumulative GC dose. In contrast, femur neck and total hip BMD were negatively correlated with the RA disease duration, cumulative GC dose, DAS28, and ESR.

3.3. Odd ratios for trabecular bone score (TBS) per SD decrease and original FRAX and TBS adjusted FRAX per SD increase from logistic regression models

To further assess the performance of TBS, conventional FRAX and TBS adjusted FRAX scores in the prediction of VFs in patients with RA were estimated from logistic regression models with adjustment for age, height, positivity of rheumatoid factor, disease activity score for 28 joints, cumulative dose of glucocorticoids, time postmenopause, osteoporosis drug use and lumbar spine bone mineral density per SD. As shown in Fig. 2, the TBS- adjusted FRAX probability for major osteoporotic fracture resulted in an increase in the OR (OR = 8.44; 95% CI, 2.47–28.83; $P = .001$ vs OR = 5.54; 95% CI, 1.95–15.78; $P = .001$). An increase in OR for hip fracture was also observed in the TBS-adjusted FRAX probability for hip fracture (OR = 2.81; 95% CI, 1.20–6.59; $P = .018$ vs OR = 1.84; 95% CI, 0.87–3.89; $P = .112$).

3.4. The TBS according to cumulative GC dose quartiles

Because the TBS was found to be significantly correlated with the cumulative GC dose but not with the DAS28 or ESR, the TBS was compared among the cumulative GC dose quartiles (Fig. 3).

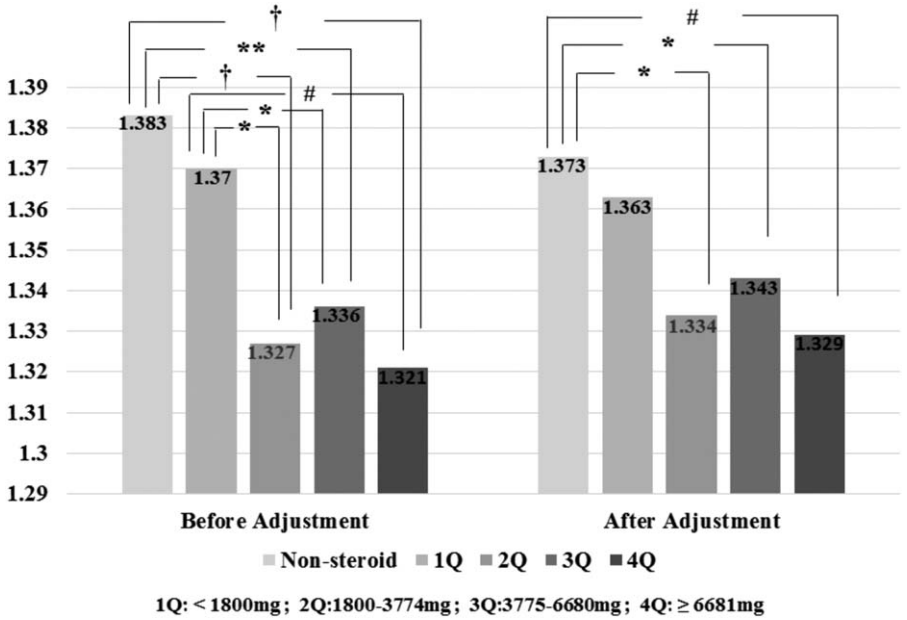

Figure 3. Comparison of the trabecular bone score (TBS) according to cumulative glucocorticoid (GC) dose quartiles before and after adjusting for confounding factors (age, DAS28, serum 25(OH)D concentration, RA disease duration, and osteoporosis drug use). $^{*}P < .05$, $^{\#}P < .01$, $^{**}P < .005$, $^{\dagger}P < .0001$. 25(OH)D = 25-hydroxyvitamin D, DAS28 = disease activity score for 28 joints, RA = rheumatoid arthritis.

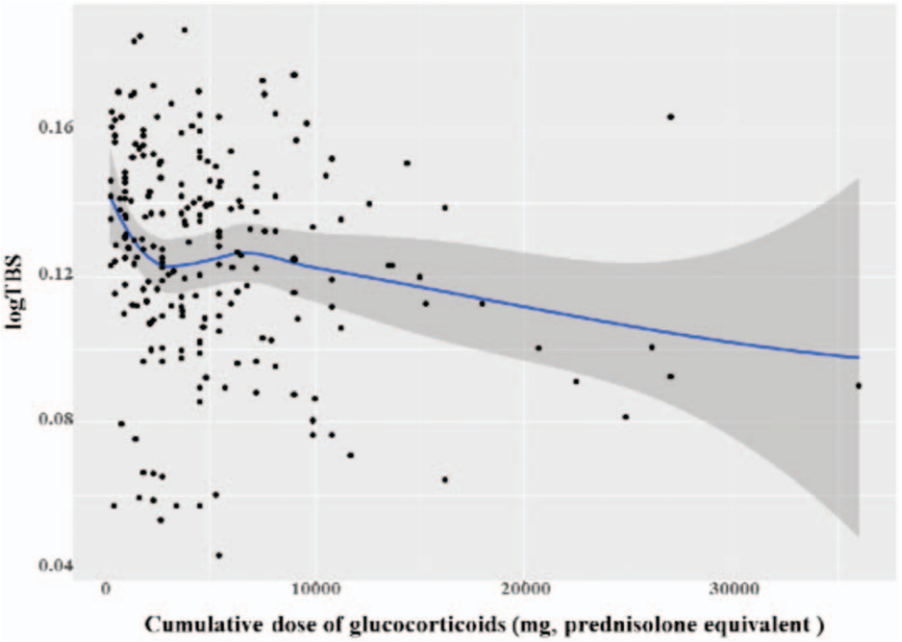

Figure 4. Nonlinear relationship between the log trabecular bone score (TBS) and cumulative glucocorticoid (GC) dose.

There was a significant difference in the TBS between subjects in the first and those in the second cumulative GC dose quartiles. However, there were no significant differences among the second, third, and fourth cumulative GC dose quartiles, even after adjusting for confounding factors. A potential nonlinear relationship between the log TBS and cumulative GC dose was then evaluated (Fig. 4). The curves were L-shaped, and the negative trends were more apparent in the lower cumulative GC dose range.

4. Discussion

In this study, female postmenopausal RA patients with VFs exhibited a lower vertebral TBS than that of subjects without VFs, whereas there was no significant difference in BMD between subjects with and those without VFs. Furthermore, the TBS was significantly associated with the presence of VFs, even after adjusting for confounding factors such as age, DAS28, and L-spine BMD. The TBS was significantly correlated with the cumulative GC dose but not with the DAS28 or ESR. However, the correlation was L-shaped and nonlinear.

Previous studies demonstrated an association between TBS and the presence of fragility fractures in diseases with an altered bone structure such as primary hyperparathyroidism[21,22] and type 2 diabetes.[23,24] However, only 2 studies evaluated the effectiveness of TBS for assessing the fracture risk in RA patients; these 2 studies reported the efficacy of TBS for detecting patients with VFs using only a small number of subjects.[15,16] This study confirmed the results of those previous studies using a larger cohort of RA patients. The current study also showed that the TBS was associated with a higher risk of VFs in RA patients, even after adjusting for confounding factors. Although BMD measured via DXA can be used to assess fracture risk in patients with RA, it may underestimate the true fracture probability. FRAX may have similar deficiencies.[2] Because a better fracture prediction method is required, more detailed imaging techniques such as QCT and high-resolution (peripheral) QCT have been used to evaluate bone quality. However, they are difficult to use in clinical practice.[11] Compared with these, the TBS can be measured easily and used in the clinical setting.[12] Moreover, the TBS-adjusted FRAX algorithm showed the better performance than original FRAX algorithm in the prediction of fracture risk in RA patients in our study. These results showed the potential benefit of TBS to FRAX algorithm in the prediction of fracture risk in RA patients. Therefore, the TBS could be a good supplementary tool for discriminating or predict VFs for RA patients in clinical practice.

The current study evaluated the association between the TBS and parameters related to RA disease activity. Interestingly, the TBS was significantly correlated with the cumulative GC dose but not with the DAS28 or ESR. In contrast, femur neck and total hip BMD were significantly associated with disease activity, including the DAS28 and ESR. Multiple factors such as high disease activity (inflammation), immobility, and the use of GCs are common factors that substantially increase the risk of osteoporosis and fractures in RA patients.[25] In particular, inflammation could affect femurs, because they have more abundant cortical bones than do vertebrae, even though we did not evaluate the microarchitecture of femurs in the current study.[26] In fact, high disease activity was predictive of cortical hand bone loss in postmenopausal patients with established RA in a 5-year multicenter longitudinal study.[27] In another study, CRP levels were independently associated with cortical volumetric BMD but not trabecular thickness or inhomogeneity of the trabecular network.[28]

RA patients are one of the largest groups of chronic GC users worldwide.[29] GC-induced bone damage varies with the skeletal site and the nature of the bone compartment (cortical or trabecular).[30] The trabecular compartment should be more affected than the cortical compartment because of its higher surface area and rate of bone turnover.[31] Furthermore, disruption of the trabecular bone microarchitecture (such as

trabecular perforations) may occur depending on the GC dose, thus leading to an increase in the trabecular space and a decrease in both the trabecular number and structural connectivity.[32] However, in the current study, the TBS and cumulative GC dose exhibited an L-shaped nonlinear relationship. The negative trends were more apparent with lower cumulative GC doses. The most rapid loss of BMD occurs during the first 6 to 12 months of GC therapy, ranging from 2% to 20% at a dose of 10 mg/d. However, the rate of bone loss slows to 1% to 3% per year following ~2 years of GC therapy.[33] Therefore, the association might be more apparent at a lower cumulative GC dose range. Otherwise, higher cumulative GC doses might compromise the disease activity, which could indirectly affect the decrease in the TBS at the higher cumulative GC dose range. Definite conclusions will not be possible until a properly sized, prospective, randomized, controlled trial is performed.

There are some limitations to the current study. It was a retrospective cross-sectional study that was performed only in 1 institution. Therefore, it is not widely representative of Korea or other countries. Prospective randomized trials are needed to confirm these findings. Second, osteoporosis drug users were not excluded from this study, because the rate of osteoporosis drug users among the study subjects with VFs was too high (37.1%) to exclude them and still retain sufficient power to investigate the association between the L-spine TBS and vertebral fractures. However, antiresorptive agents have no harmful effects on the TBS in postmenopausal women.[34] and so this was unlikely to affect the results related to VFs and a low TBS. Furthermore, the TBS was significantly associated with the presence of VFs, even after adjusting for osteoporosis drug use. Third, clinical VF was defined as prevalent VF. It is therefore possible that subjects with nonsymptomatic radiographic VFs were not included in the VF group. Nevertheless, VF assessments were performed using DXA images to confirm the absence of VFs among the subjects without VFs who had not undergone lateral thoracolumbar radiography.

The current study provided evidence of the effectiveness of the TBS for assessing the fracture risk in RA patients, even after adjusting for confounding factors, in a larger study cohort than those of previous studies. The results also showed that the TBS was correlated with the cumulative GC dose but not with RA disease activity. In this regard, this study has several strengths.

In conclusion, a significantly lower TBS was observed in patients with VFs compared with those without VFs, despite the lack of a significant difference in BMD between subjects with and those without VFs after adjusting for confounding factors. This suggests that the TBS provides a supplementary tool for discriminating osteoporotic fractures in postmenopausal women with RA. TBS may have a nonlinear relationship with the cumulative GC dose but not with RA disease activity.

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