Simultaneous Estimation of the Fat Fraction and $R_2^*$ Via $T_2^*$-Corrected 6-Echo Dixon Volumetric Interpolated Breath-hold Examination Imaging for Osteopenia and Osteoporosis Detection: Correlations with Sex, Age, and Menopause

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**Objective:** To investigate the relationships of $T_2^*$-corrected 6-echo Dixon volumetric interpolated breath-hold examination (VIBE) imaging-based fat fraction (FF) and $R_2^*$ values with bone mineral density (BMD); determine their associations with sex, age, and menopause; and evaluate the diagnostic performance of the FF and $R_2^*$ for predicting osteopenia and osteoporosis.

**Materials and Methods:** This study included 153 subjects who had undergone magnetic resonance (MR) imaging, including MR spectroscopy (MRS) and $T_2^*$-corrected 6-echo Dixon VIBE imaging. The FF and $R_2^*$ were measured at the L4 vertebra. The male and female groups were divided into two subgroups according to age or menopause. Lin’s concordance and Pearson’s correlation coefficients, Bland-Altman 95% limits of agreement, and the area under the curve (AUC) were calculated.

**Results:** The correlation between the spectroscopic and 6-echo Dixon VIBE imaging-based FF values was statistically significant for both readers ($r = 0.940$ [reader 1], 0.908 [reader 2]; both $p < 0.001$). A small measurement bias was observed for the MRS-based FF for both readers (mean difference = -0.3% [reader 1], 0.1% [reader 2]). We found a moderate negative correlation between BMD and the FF ($r = -0.411$ [reader 1], -0.436 [reader 2]; both $p < 0.001$) with younger men and premenopausal women showing higher correlations. $R_2^*$ and BMD were more significantly correlated in women than in men, and the highest correlation was observed in postmenopausal women ($r = 0.626$ [reader 1], 0.644 [reader 2]; both $p < 0.001$). For predicting osteopenia and osteoporosis, the FF had a higher AUC in men and $R_2^*$ had a higher AUC in women. The AUC for predicting osteoporosis was highest with a combination of the FF and $R_2^*$ in postmenopausal women (AUC = 0.872 [reader 1], 0.867 [reader 2]; both $p < 0.001$).

**Conclusion:** The FF and $R_2^*$ measured using $T_2^*$-corrected 6-echo Dixon VIBE imaging can serve as predictors of osteopenia and osteoporosis. $R_2^*$ might be useful for predicting osteoporosis, especially in postmenopausal women.

**Keywords:** Osteoporosis; Magnetic resonance imaging; Fat fraction; $R_2^*$; Bone marrow

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**INTRODUCTION**

The Consensus Development Conference on Osteoporosis defined osteoporosis as “a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase
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in bone fragility and susceptibility to fracture” (1). Early detection and proper management are necessary for the prevention of osteoporotic fractures and complications (2). Bone mineral density (BMD), which can be measured using dual-energy X-ray absorptiometry (DXA), is the most widely used parameter for diagnosing osteoporosis and assessing fracture risk (2, 3). Recent studies have indicated strong connections between marrow adipogenesis and osteoporosis pathophysiology. Osteoblasts and adipocytes are derived from the same progenitor cells. When the conversion of progenitor cells to adipocytes is dominant, bone formation and BMD decrease (4). Consequently, vertebral marrow fat has become a target for the diagnosis of osteoporosis. Magnetic resonance spectroscopy (MRS) is widely used as the gold standard for fat quantification (5-10), and many previous MRS studies have demonstrated a negative correlation between vertebral marrow fat content and BMD (8-12).

Various chemical shift-based water-fat separation techniques have been recently developed, and their results are consistent with those of MRS (13-15). Many confounding factors affecting fat quantification when using water-fat separation techniques have been identified (14-16). It is crucial to correct for the T$_2$* shortening effect caused by the presence of trabecular bone, especially for vertebral marrow fat quantification (6, 7). Multi-echo three-dimensional (3D) gradient echo imaging, which corrects for T$_1$ bias and the T$_2$* effect, allows for accurate fat fraction (FF) estimation and has the advantages of high spatial resolution and rapid acquisition (17-20). An additional advantage of this technique is that the R$_2$* map is provided simultaneously with fat quantification since R$_2$* is equivalent to 1/T$_2$* (21, 22). To our knowledge, only a few studies have reported on the efficacy of R$_2$* as a marker for osteoporosis (22). In the English literature, correlations between the FF, R$_2$*, and BMD, including differences in the degree of correlation with age, have not been reported.

The purpose of our study was to investigate the relationships of T$_2$*-corrected 6-echo Dixon volumetric interpolated breath-hold examination (VIBE) imaging-based FF and R$_2$* values with BMD; determine their associations with sex, age, and menopause; and evaluate the diagnostic performance of the FF and R$_2$* for predicting osteopenia and osteoporosis.

MATERIALS AND METHODS

Study Population

Institutional Review Board approval was obtained and informed consent was waived. This retrospective study enrolled 228 patients who had undergone DXA and lumbar spine magnetic resonance imaging (MRI) for the evaluation of lower back pain between July and December 2016. These patients underwent MRS and T$_2$*-corrected 6-echo Dixon VIBE imaging. Patients who had previously undergone lumbar spinal surgery (n = 28) or had compression fractures at L4 (n = 21) or large osteophytes (n = 26) were excluded. Thus, the final study population consisted of 153 patients (69 men and 84 women; mean age, 63.2 ± 8.2 years; age range, 31–81 years). BMD was normal in 99 subjects. Osteopenia and osteoporosis were observed in 37 and 17 subjects, respectively. The men and women were divided into two subgroups according their age (≥ 50 years) and menopause status, respectively. Height and body weight data were collected from each subject’s medical records.

There were significant differences in age, vertebral BMD, and T-scores between men and women; however, there was no difference in body mass index. The demographic and clinical characteristics of the study population are listed in Table 1.

DXA Examination

All DXA examinations of the lumbar spine (L1–4) were performed using a Lunar Prodigy scanner (GE Medical Systems, Madison, WI, USA). The areal BMD (g/cm$^2$) and

| Table 1. Baseline Characteristics of Study Subjects |
|-----------------------------------------------|
|                                              |
|                               | Males (n = 69) | Females (n = 84) | P*      |
| Age, years | Age < 50 Years (n = 63) | Age ≥ 50 Years (n = 63) | Premenopausal (n = 77) | Postmenopausal (n = 77) |
|          |                |                |       |
| Age, years | 41.2 (7.4) | 63.5 (6.0) | 49.0 (3.1) | 65.9 (6.0) | 0.034* |
| Body mass index, kg/m$^2$ | 26.4 (3.4) | 24.8 (2.6) | 27.5 (3.5) | 24.8 (3.3) | 0.844* |
| L1–4 vertebral BMD (g/cm$^2$) | 1.19 (0.17) | 1.16 (0.15) | 1.24 (0.25) | 0.98 (0.15) | < 0.001* |
| T-score | -1.2 (1.6) | 0.4 (1.3) | -1.6 (1.7) | -0.7 (1.6) | < 0.001* |

Data are presented as mean and standard deviations (in parenthesis). *p values were obtained in comparison between male and female groups using following methods, P*Independent t test, *Mann-Whitney U test. BMD = bone mineral density.
T-scores were assessed for all enrolled patients. Normal BMD, osteopenia, and osteoporosis were defined as T-score ≥ -1.0 standard deviation (SD), -2.5 < T-score < -1.0 SD, and T-score ≤ -2.5 SD, respectively (2).

**MRI Protocol**

All MRI examinations were performed on a 3T MRI scanner (MAGNETOM Skyra; Siemens Healthineers, Erlangen, Germany). The mean interval between the DXA and MRI examinations was 3 days (range, 0–30 days). All images were acquired with subjects in the supine position using a standard spine array coil and an eight-channel phased array coil for the spine. Conventional MRI sequences for anatomical and morphological evaluation of the lumbar vertebrae were adopted, and the imaging parameters are summarized in Table 2.

A single-voxel high-speed T$_2$-corrected multi-echo (HISTO) MRS sequence was performed using a stimulated echo acquisition mode with the following parameters: repetition time = 3000 ms; echo time (TE) = 12, 24, 36, 48, and 72 ms; bandwidth = 1200 Hz; flip angle = 90°; and voxel size = 15 x 15 x 15 mm$^3$. The scan time was 45 seconds. A spectroscopic voxel was placed on the anterior aspect of the L4 vertebral body. An example of the water and fat spectral peaks at a specific TE and the automatically calculated FF from the HISTO scan are displayed in Figure 1A.

For water-fat separation and FF estimation, T$_2^*$-corrected 6-echo Dixon VIBE imaging was performed. The imaging parameters are summarized in Table 2. We used a small flip angle to minimize the T$_1$ bias. Images were obtained at the L4 vertebral body in the sagittal plane. For the calculation of the FF map, multi-peak fat spectral modeling was used for more precise T$_2^*$ correction. The FF and R$_2^*$ maps were automatically generated from the T$_2^*$-corrected 6-echo Dixon VIBE imaging series.

**Data Analysis**

Two experienced musculoskeletal radiologists who were blinded to the DXA results and MRS-based FF information performed all measurements independently and estimated the FF and R$_2^*$. These parameters were calculated from automatically reconstructed FF and R$_2^*$ maps loaded onto an imaging workstation (Syngo software version B17; Siemens Healthineers, Forchheim, Germany). Regions of interest (ROIs) were manually drawn on the L4 vertebral body in mid-sagittal view using a fat-only image. These ROIs were directly copied onto the FF and R$_2^*$ maps. The ROIs were located at least 2 mm from the endplate, and the basivertebral plexus and focal fat deposition were excluded (Fig. 1B). ROI size varied according to the area of the spine. The mean ROI sizes were 424 ± 82 mm$^2$ for reader 1 and 420 ± 50 mm$^2$ for reader 2.

**Statistical Analysis**

All continuous variables were assessed for normality using the Shapiro-Wilk test and are presented as mean ± SD. We used the independent t test or Mann-Whitney U test to assess differences between men and women.

The interobserver agreement between the FF and R$_2^*$ measurements was analyzed using the intraclass correlation coefficient (ICC) with a two-way random effects model of absolute agreement. The interobserver agreement was interpreted as follows: < 0.50, poor; 0.50–0.75, moderate; 0.75–0.90, good; and > 0.90, excellent (23).

To assess the consistency between the FF values obtained via T$_2^*$-corrected 6-echo Dixon VIBE imaging and MRS, Lin's
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Concordance correlation coefficient (p_c) and Bland-Altman plot with a 95% confidence interval (CI) were used. The p_c was classified as follows: > 0.99, almost perfect; 0.95–0.99, substantial; 0.90–0.95, moderate; and < 0.90, poor (24). Pearson’s correlation analysis was performed to analyze the correlation between the FF and BMD in all patients and each subgroup as well as the correlation between R₂* and BMD. Pearson’s correlation coefficient (r) was interpreted as follows: r = ± 1.0, perfect; ± 0.60–0.80, strong; ± 0.40–0.60, moderate; ± 0.20–0.40, weak; and 0, no correlation (25). The scatterplots are shown in Figures 2 and 3. To determine the diagnostic performance of the parameters for predicting osteopenia and osteoporosis, receiver operating characteristic (ROC) curves were constructed, and the areas under the curve (AUCs) were calculated by each reader. Using ROC curves, we compared a logistic regression model combining the FF and R₂* with those including the FF or R₂* alone. The AUCs were compared using the DeLong test and interpreted as follows: 0.90–1.0, excellent; 0.80–0.90, good; 0.70–0.80, fair; 0.60–0.70, poor; and 0.50–0.60, failed (26). A p value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 17.9.7 (MedCalc Software, Ostend, Belgium).

RESULTS

Interobserver Agreement

The interobserver agreement between the two radiologists for the FF and R₂* measurements was excellent. The ICC values for the FF and R₂* were 0.955 (95% CI, 0.938–0.967) and 0.953 (95% CI, 0.936–0.966), respectively.

Consistency between the FF Values Obtained Via T₂*-Corrected 6-Echo Dixon VIBE Imaging and MRS

Lin’s p_c showed a moderate correlation between the
FF values obtained via T2*-corrected 6-echo Dixon VIBE imaging and MRS for readers 1 and 2 (pc = 0.940 [reader 1], 0.908 [reader 2]; both p < 0.001) (Fig. 2). Figure 4 shows the mean measurement bias with limits of agreement for the FF derived from T2*-corrected 6-echo Dixon VIBE imaging relative to the FF measured with MRS. The mean measurement biases were -0.3% (95% limits of agreement, -6.4–5.8%) for reader 1% and 0.1% (95% limits of agreement, -4.8–5.0%) for reader 2.

**Correlations between BMD and the FF or R2***

A moderate negative correlation was observed between...
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**Fig. 2.** Comparison between FF values measured with $T_2^*$-corrected 6-echo Dixon VIBE imaging and MRS at L4 vertebra.

$p$, for assessment of agreement between FF values measured via MRS and $T_2^*$-corrected 6-echo Dixon VIBE imaging (reader 1, A; reader 2, B). Correlation between spectroscopic and $T_2^*$-corrected 6-echo Dixon VIBE-based FF values was statistically significant for readers 1 and 2 (both $p < 0.001$). $p$ values for readers 1 and 2 were 0.940 and 0.908, respectively. CCC = concordance correlation coefficient, GRE = gradient echo, 3D = three-dimensional

**Fig. 3.** Correlations between BMD and FF or $R_2^*$.  
A. Scatterplot displaying correlation between FF obtained via T$2^*$-corrected 6-echo Dixon VIBE imaging and areal BMD (g/cm$^2$; reader 1, A-left; reader 2, A-right). Moderate negative correlation between FF and areal BMD was found ($r = -0.411$ [reader 1], $-0.436$ [reader 2]; both $p < 0.001$).  
B. Scatterplot displaying correlation between $R_2^*$ and areal BMD (g/cm$^2$; reader 1, B-left; reader 2, B-right). Weak positive correlation between $R_2^*$ and areal BMD was found ($r = 0.358$ [reader 1], 0.353 [reader 2]; both $p < 0.001$). BMD = bone mineral density
the FF and areal BMD (g/cm²) for both readers ($r = -0.411$ [reader 1], -0.436 [reader 2]; both $p < 0.001$) (Fig. 3A). There was no significant difference in the degree of correlation between men and women, and the most negative correlation was observed in younger men for both readers ($r = -0.831$ [reader 1], -0.801 [reader 2]; $p = 0.041$, 0.056) (Table 3).

A weak positive correlation was found between the $R_2^*$ and areal BMD values (g/cm²) (Fig. 3B). The $R_2^*$ and areal BMD values showed a significantly higher correlation in women than in men ($r = 0.166$ vs. 0.459 [reader 1]; $r = 0.123$ vs. 0.463 [reader 2]; $p = 0.048$ [reader 1], 0.023 [reader 2]). For both readers, the highest correlation was found in postmenopausal women (Table 3).

**Diagnostic Performance of the FF and $R_2^*$ for Predicting Osteopenia and Osteoporosis**

The AUCs for the FF and $R_2^*$ for the prediction of osteopenic subjects were 0.651 and 0.664, respectively, for reader 1 and 0.647 and 0.654, respectively, for reader 2. Furthermore, the AUCs for normal and osteoporotic subject differentiation were 0.694 and 0.743, respectively, for reader 1 and 0.741 and 0.736, respectively, for reader 2. We found no significant differences in the diagnostic performance of the FF and $R_2^*$ for predicting osteopenia and osteoporosis. The ROC analysis showed that the combination of the FF and $R_2^*$ resulted in a higher AUC than that for the FF or $R_2^*$ alone for predicting osteopenia and osteoporosis. The AUC_{osteopenia} and AUC_{osteoporosis} were 0.716 and 0.758, respectively, for reader 1, and 0.720, and 0.763, respectively, for reader 2 (Table 3).

In AUC comparisons, using the FF resulted in a higher AUC than using $R_2^*$ for predicting osteopenia and osteoporosis in older men; however, there were no significant differences (AUC_{osteopenia}, $p = 0.015$ [reader 1], 0.198 [reader 2]; AUC_{osteoporosis}, $p = 0.620$ [reader 1], 0.806 [reader 2]). In

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**Table 3. Correlations between BMD versus or $R_2^*$ in Each Group**

| Group                | Reader 1 | Reader 2 |
|----------------------|----------|----------|
|                      | FF       | $R_2^*$  | FF       | $R_2^*$  |
|                      | $r$      | $p$      | $r$      | $p$      | $r$      | $p$      | $r$      | $p$      |
| Male                 |          |          |          |          |
| Age < 50 years (n = 6) | -0.419   | < 0.001  | 0.166    | 0.172    | -0.427   | < 0.001  | 0.123    | 0.315    |
| Age ≥ 50 years (n = 63) | -0.370   | 0.003    | 0.207    | 0.103    | -0.402   | 0.001    | 0.140    | 0.275    |
| Female               |          |          |          |          |
| Premenopausal (n = 7) | -0.410   | < 0.001  | 0.459    | < 0.001  | -0.442   | < 0.001  | 0.463    | < 0.001  |
| Postmenopausal (n = 77) | -0.403   | < 0.001  | 0.626    | < 0.001  | -0.396   | < 0.001  | 0.644    | < 0.001  |
| All                  | -0.411   | < 0.001  | 0.358    | < 0.001  | -0.436   | < 0.001  | 0.353    | < 0.001  |

$p$ values were calculated by Pearson's correlation analysis. FF = fat fraction.

Fig. 4. Bland-Altman plots showing mean measurement bias with limits of agreement for FF derived from T2*-corrected 6-echo Dixon VIBE imaging relative to that measured with MRS.

Mean measurement bias for reader 1 (A) was -0.3% (range, -6.4–5.8%), and mean measurement bias for reader 2 (B) was 0.1% (range, -4.8–5.0%). Mean bias is shown as solid line, and limits of agreement are shown as dashed lines.
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In postmenopausal women, the AUCs obtained using R2* were higher than those obtained using the FF; however, significant differences were not observed (AUCosteopenia, p = 0.260 [reader 1], 0.147 [reader 2]; AUCosteoporosis, p = 0.257 [reader 1], 0.180 [reader 2]). The groups comprising younger men and premenopausal women had only one osteopenic and osteoporotic subject, which resulted in insufficient data for ROC curve analysis. In postmenopausal women, high sensitivity (90% for both readers) and excellent R2* discriminatory capacity (AUC > 0.80 for both readers, p < 0.001) between normal individuals and patients with osteoporosis were observed. The FF combined with R2* achieved a > 0.70 AUC value for predicting osteopenia and osteoporosis in older men and postmenopausal women. The AUCs for predicting osteopenia and osteoporosis in each group are summarized in Tables 5, 6 and Figures 6, 7.

DISCUSSION

Clinical interest in methods for accurately measuring vertebral marrow fat is increasing because vertebral marrow fat content is negatively correlated with BMD (8, 10-12, 27). Chemical shift-based water-fat separation techniques, such as iterative decomposition of water and fat with echo asymmetry and least-squares estimation and the modified Dixon technique, have a similar accuracy to MRS for fat quantification and are widely accepted as alternative techniques to MRS (15, 28). These techniques allow for more consistent water-fat separation by correcting for various confounding factors, such as main magnetic field inhomogeneity, multiple fat spectral peaks, and T2*, T1 relaxation, and eddy current effects (13, 15, 28). The 3D T2*-corrected 6-echo Dixon VIBE technique can obtain up to 32 echoes. This technique also supports multi-peak fat modeling and can quickly produce water- or fat-only images and R2* maps using parallel acquisition and VIBE techniques (15, 17, 22). Compared with two-dimensional-acquisition water-fat imaging, the 3D T2*-corrected 6-echo Dixon VIBE technique has certain advantages, including higher spatial resolution and wider coverage with a short scan time (15, 17, 22). Our study used the 3D T2*-corrected 6-echo Dixon VIBE technique and simultaneously performed T1 bias and T2* corrections to more accurately quantify marrow fat.

Our results showed that T2*-corrected 6-echo Dixon VIBE imaging allows for accurate quantification of vertebral marrow fat and is comparable to MRS. We found sex-, age-, and menopause-related differences in associations between the FF, R2*, and BMD. These results indicate that various conclusions can be reached depending on which group is included. We also investigated whether

Table 4. Diagnostic Performance of FF, R2*, and Combination of FF and R2* for Predicting Osteopenia and Osteoporosis

| Parameters | Normal vs. Osteopenia | Normal vs. Osteoporosis |
|------------|----------------------|------------------------|
|            | FF                   | R2*                   | FF + R2*                 | FF | R2* | FF + R2* |
| AUC        |                      |                       |                         |     |     |          |
| (Reader 1) | 0.651 (0.561–0.727)  | 0.664 (0.568–0.734)   | 0.716 (0.636–0.793)     | 0.694 (0.609–0.776) | 0.743 (0.653–0.819) | 0.758 (0.669–0.832) |
| Sensitivity (%) | 97.3 (85.8–99.9) | 40.5 (24.8–57.9) | 59.5 (42.1–75.2) | 47.1 (23.0–77.0) | 64.7 (38.3–85.8) | 64.7 (38.3–85.8) |
| Specificity (%) | 36.4 (26.9–46.6) | 84.8 (76.2–91.3) | 79.8 (70.5–87.2) | 93.9 (87.3–97.1) | 83.8 (75.1–90.5) | 85.9 (77.9–92.0) |
| Cutoff value | > 49.6 ≤ 14.9 | > 62.5 ≤ 15.0 | > 62.5 ≤ 15.0 | > 62.5 ≤ 15.0 | > 62.5 ≤ 15.0 | > 62.5 ≤ 15.0 |
| p value | 0.002 | 0.002 | < 0.001 | 0.028 | 0.001 | 0.003 |

| (Reader 2) | 0.647 (0.561–0.727)  | 0.654 (0.568–0.734)   | 0.720 (0.636–0.793)     | 0.741 (0.652–0.818) | 0.736 (0.646–0.813) | 0.763 (0.675–0.837) |
| Sensitivity (%) | 89.2 (74.6–97.0) | 45.9 (29.5–63.1) | 56.8 (39.5–72.2) | 58.8 (32.9–81.6) | 70.6 (44.0–89.7) | 70.6 (44.0–89.7) |
| Specificity (%) | 41.4 (31.6–51.8) | 79.8 (70.5–87.2) | 77.8 (63.8–85.5) | 90.9 (83.4–95.8) | 67.7 (57.5–76.7) | 81.8 (72.8–88.9) |
| Cutoff value | > 50.8 ≤ 14.9 | > 61.1 ≤ 15.5 | > 61.1 ≤ 15.5 | > 61.1 ≤ 15.5 | > 61.1 ≤ 15.5 | > 61.1 ≤ 15.5 |
| p value | 0.003 | 0.003 | < 0.001 | 0.002 | 0.001 | < 0.001 |

Numbers in parentheses are lower and upper bounds of 95% CIs. p value of AUC. AUC = area under curve, CI = confidence interval
These parameters can be used as biomarkers for predicting osteopenia and osteoporosis. The combination of the FF and R₂* showed fair to excellent diagnostic performance for the detection of osteopenia and osteoporosis. However, compared with the FF or R₂* alone, the combination of the FF and R₂* showed only a minor or no improvement in performance. This finding might be due to differences in individual bone marrow composition and various microenvironmental conditions related to medical history or physical activity. Although the difference did not reach significance, it showed optimal specificity and sensitivity in postmenopausal women.

Our data indicate a moderate inverse correlation between the FF and BMD in all of the patients, consistent with the results of previous studies (27-29). However, we found that the correlation was weaker in older men and postmenopausal women. Physiological changes related to aging or menopause might be considered potential causes of the relatively weak correlation between the FF and BMD in these subgroups. For example, red marrow reconversion can increase with age due to the increased risk of cancer, infection, trauma, or other stress that occurs with aging.
Moreover, the prevalence of Modic changes increases with age (30, 31). Modic type 1 and 2 changes are uncommon in patients before 50 years of age, but they increase after the age of 50 years with type 2 changes being more common. Modic type 1 and 2 changes are most frequently encountered at L4–5 and L5–S1, and L4–5 is the most common site of such changes (30, 31). The mean ages of the older men and postmenopausal women were significantly higher than those of the other groups combined. Additionally, relative estrogen deficiency accelerates vertebral endplate and disc degeneration. In fact, severe lumbar disc degeneration tends to be more common in postmenopausal women than in elderly men (32). Recent studies have demonstrated that Modic type 2 change is primarily associated with severe disc degeneration (33, 34). Compared with Modic type 2 changes, which are associated with fatty degeneration,
Modic type 1 changes are associated with increased vascularity and marrow edema (30, 31). However, Modic type 1 changes have been associated with higher FF values than those in normal marrow. We drew ROIs at least 2 mm from the endplate to exclude the cortical bone. Moreover, focal fat deposits were excluded. However, Modic changes were observed in both sides of the endplates as well as in large confluent areas of the vertebral body (30). The various degrees of Modic changes included in the ROIs are assumed to affect the vertebral marrow composition.

MRS is currently used as the non-invasive gold standard for the clinical assessment of vertebral marrow fat content (5-10). MRS presents no risk of exposure to ionizing radiation and adequately reflected marrow fat as demonstrated by a histopathological study (35). However, MRS has certain limitations, such as the inability to cover an entire vertebral marrow segment with a single voxel and certain technical challenges (14, 16, 28). Moreover, performing fat measurements is impracticable because MRS requires the creation of a more homogeneous $B_0$ field with shimming. In contrast to previous studies (16, 36), for the FF measurements, we attempted to draw ROIs including as much bone marrow as possible, while excluding the vertebral endplate and cortical bone. We confirmed excellent

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**Fig. 6.** ROC analysis of FF, $R_1^*$, and combination of FF and $R_1^*$ for predicting osteopenia (reader 1, A-left; reader 2, A-right) and osteoporosis (reader 1, B-left; reader 2, B-right) in older men. ROC analysis demonstrated that AUCs for FF were higher than those for $R_1^*$ for both readers. However, ROC curve showed only minor improvements in diagnostic performance for predicting osteopenia and osteoporosis.
consistency between $T_2^*$-corrected 6-echo Dixon VIBE imaging and MRS measurements. Therefore, $T_2^*$-corrected 6-echo Dixon VIBE imaging is expected to enable accurate quantification of vertebral marrow fat in a short scan time as well as provide both quantitative and spatially-resolved information on vertebral marrow fat. Although our study only measured a single vertebra, the $T_2^*$-corrected 6-echo Dixon VIBE technique can collect data for multiple vertebral levels in one acquisition.

$T_2^*$-corrected 6-echo Dixon VIBE imaging has the additional advantage of simultaneously obtaining the $R_2^*$ value with fat quantification (21). Previous studies showed that multi-peak modeling of fat signals yielded better accuracy than single-peak fat modeling, which induced an underestimation of the fat signals (20, 21). We also performed multi-peak fat modeling. We found a positive correlation between the $R_2^*$ and areal BMD values, which is consistent with the results of a previous study, and both studies used $R_2^*$ with multi-peak fat correction (22). The $R_2^*$ map is a byproduct of $T_2^*$-corrected fat quantification and equivalent to $1/T_1^*$ (20, 21). In patients with osteoporosis, $T_2^*$ decay is assumed to be delayed because of trabecular bone loss, which will decrease $R_2^*$ (22). We found that there was a significant difference between men

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**Fig. 7. ROC analysis of FF, $R_2^*$, and combination of FF and $R_2^*$ for predicting osteopenia (reader 1, A-left; reader 2, A-right) and osteoporosis (reader 1, B-left; reader 2, B-right) in postmenopausal women.** ROC analysis demonstrated that AUCs for $R_2^*$ were excellent for both readers. However, there was no significant difference in AUCs between FF, $R_2^*$, and combination of FF and $R_2^*$. 

A

B
and women in the relationship of $R_2^*$ with areal BMD. It is well known that quantitatively measured serum ferritin is a reliable indicator of bone marrow iron stores (37). A recent study showed a significant correlation between serum ferritin and BMD in women ≥ 45 years of age (38). This finding may be explained by the rapid loss of estrogen in these women. In agreement with that study, the highest correlation coefficient between $R_2^*$ and BMD was observed in postmenopausal women in the present study.

In a previous study, the question of whether the FF or $R_2^*$ alone could be used as a marker to assess osteoporosis was raised (22). Moreover, the FF and $R_2^*$ are not reliable for osteopenia assessment. We found that the FF and $R_2^*$ showed poor to fair performance in all subjects. Additionally, ROC curve analysis showed that the AUC of the combination of the FF and $R_2^*$ was higher than that of the FF or $R_2^*$ alone. We focused on differences in diagnostic performance between the FF and $R_2^*$ according to sex and menopause status. The AUC of $R_2^*$ was higher than that of the FF in postmenopausal women and showed good discriminatory performance in predicting osteoporosis. The FF showed good performance in older men, but poor performance in postmenopausal women. The combination of the FF and $R_2^*$ showed good performance (AUC > 0.7) in older men and postmenopausal women; however, it only showed minor or no improvement in performance compared with the FF and $R_2^*$ alone. Vertebral marrow fat increases sharply in postmenopausal women (39), and this disproportionate increase in marrow fat consequently contributes to the loss of trabecular bone (40). A possible explanation for our finding may be that the loss of trabecular bone eventually led to a reduction in $R_2^*$, which led to better diagnostic performance.

Our study has certain limitations. First, the sample sizes of the younger men and premenopausal women were smaller than those of the other two subgroups. Second, the MRS data were used as the reference standards for fat content quantification. True marrow fat content can only be assessed via bone biopsy; however, this was practically impossible. Third, we only used DXA to assess bone mineralization, even though bone strength is determined by various factors, including bone mass and microarchitecture; however, DXA only reflects bone mass (41). Fourth, all subjects were patients who reported low back pain. Thus, the possibility of bias cannot be ruled out. Fifth, we did not compare the diagnostic efficacy between the uncorrected FF and $T_2^*$-corrected FF. Finally, patients with severe osteophytes or degenerative changes were excluded because of the possibility of distorted BMD results, which potentially limits the applicability of the study outcomes to normal vertebrae.

In summary, $T_2^*$-corrected 6-echo Dixon VIBE imaging is feasible and can be used as an alternative technique for estimating the vertebral marrow FF. In addition, the $R_2^*$ value can be obtained as a byproduct of $T_2^*$ correction. The FF and $R_2^*$ values obtained using $T_2^*$-corrected 6-echo Dixon VIBE imaging could potentially serve as predictors of osteopenia and osteoporosis. $R_2^*$ might be useful for predicting osteoporosis, especially in postmenopausal women.

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

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