Published in final edited form as:

Eur Radiol. 2013 December ; 23(12): 3432–3439. doi:10.1007/s00330-013-2950-7.

Proton-density fat fraction and simultaneous R2* estimation as an MRI tool for assessment of osteoporosis

Jens-Peter Kühn

Department of Diagnostic Radiology and Neuroradiology, Medical University Greifswald,
Sauerbruch Strasse 1, 17489 Greifswald, Germany

Diego Hernando

Department of Radiology, University of Wisconsin, 1111 Highland Ave, Madison, WI 53705, USA

Peter J. Meffert

Institute for Community Medicine, Medical University Greifswald, Walther Rathenau Strasse 48,
17475 Greifswald, Germany

Scott Reeder

Departments of Radiology, Medical Physics, Biomedical Engineering and Medicine, University of
Wisconsin, 1111 Highland Ave, Madison, WI 53705, USA

Norbert Hosten

Department of Diagnostic Radiology and Neuroradiology, Medical University Greifswald,
Sauerbruch Strasse 1, 17489 Greifswald, Germany

Rene Laqua

Department of Diagnostic Radiology and Neuroradiology, Medical University Greifswald,
Sauerbruch Strasse 1, 17489 Greifswald, Germany

Antje Steveling

Department of Medicine, Medical University Greifswald, Sauerbruch Strasse 1, 17489 Greifswald,
Germany

Stephan Ender

Department of Orthopedics, Medical University Greifswald, Sauerbruch Strasse 1, 17489
Greifswald, Germany

Henry Schröder

Department of Neurosurgery, Medical University Greifswald, Sauerbruch Strasse 1, 17489
Greifswald, Germany

Dirk-Thomas Pillich

Department of Neurosurgery, Medical University Greifswald, Sauerbruch Strasse 1, 17489
Greifswald, Germany

Abstract

Objective—To investigate multi-echo chemical shift-encoded MRI-based mapping of proton density fat fraction (PDFF) and fat-corrected R2* in bone marrow as biomarkers for osteoporosis assessment.

Methods—Fifty-one patients (28 female; mean age 69.7 ± 9.0 years) underwent dual energy X-ray absorptiometry (DXA). On the basis of the *t* score, 173 valid vertebrae bodies were divided into three groups (healthy, osteopenic and osteoporotic). Three echo chemical shift-encoded MRI sequences were acquired at 3 T. PDFF and R2* with correction for multiple-peak fat (R2*MP) were measured for each vertebral body. Kruskal–Wallis test and post hoc analysis were performed to evaluate differences between groups. Further, the area under the curve (AUC) for each technique was calculated using logistic regression analysis.

Results—On the basis of DXA, 92 samples were normal (53 %), 47 osteopenic (27 %) and 34 osteoporotic (20 %). PDFF was increased in osteoporosis compared with healthy ($P=0.007$). R2*MP showed significant differences between normal and osteopenia ($P=0.004$), and between normal and osteoporosis ($P<0.001$). AUC to differentiate between normal and osteoporosis was 0.698 for R2*MP, 0.656 for PDFF and 0.74 for both combined.

Conclusion—PDFF and R2*MP are moderate biomarkers for osteoporosis. PDFF and R2*MP combination might improve the prediction in differentiating healthy subjects from those with osteoporosis.

Keywords

Magnetic resonance imaging; Osteoporosis; Osteopenia; Chemical shift; Transverse relaxation rate

Introduction

Osteoporosis is a systemic disease characterised by a low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility [1]. The disease typically occurs in postmenopausal women and elderly populations (primary osteoporosis), and patients with prolonged substitution of glucocorticoids (secondary osteoporosis) [2, 3]. Patients with osteoporosis are at increased risk of fractures with subsequent complications such as pain and immobilisation [4]. Reliable assessment of osteoporosis in the early stages is necessary for successful prevention of fractures and complications.

Currently, dual energy X-ray absorptiometry (DXA) is the non-invasive standard of reference to quantify bone mineral density (BMD). The BMD is normalised by age and compared to the ideal peak of a healthy 30-year-old adult and is called the *t* score. According to the World Health Organization (WHO) the *t* score is the best predictor to determine osteoporosis [5]. However, the ability to diagnosis osteoporosis using DXA is influenced by the presence of vertebral fractures, degenerative changes in the spine, scoliosis, arteriosclerosis in the abdominal aorta, other abdominal calcifications, and fat. For accurate assessment of osteoporosis it may be beneficial to investigate the role of alternative techniques, particularly those with no exposure to ionising radiation.

Magnetic resonance imaging techniques (MRI) such as $R2^*$ mapping have demonstrated promising results for the quantification of osteoporosis [6]. Subjects with osteoporosis have prolonged $T2^*$ decay in the bone marrow (i.e. reduced decay rate $R2^*=1/T2^*$), likely due to decreased microscopic susceptibility from remodelled trabecular bone [7, 8]. However at this time, $R2^*$ mapping is not clinically accepted because of the lack of robustness and reproducibility. $R2^*$ mappings have demonstrated platform and imaging parameter dependency and recently published apparent $R2^*$ values are different across studies [9].

In previous work to optimise $R2^*$ mapping for liver iron assessment, we demonstrated that the apparent $R2^*$ measured using in-phase echoes will be estimated incorrectly in the presence of fat because of the presence of multiple spectral peaks of the fat signal [10]. This systematic error depends on the amount of liver fat content [11]. Accurate spectral modelling of fat ("multi-peak fat") can remove this error and produce robust fat-corrected $R2^*$ measurements [12]. Recent studies described a very high fat content of the bone marrow in more than 60 % of elderly subjects, as well as in cases of known osteoporosis [13-16]. Therefore, it might be expected that accurate $R2^*$ mapping for the assessment of osteoporosis should use multi-spectral modelling of fat.

Further, several authors have recently postulated that accurate measurement of the fat content of the bone marrow itself is a reliable biomarker for quantification of osteoporosis [17]. Magnetic resonance techniques such as MR spectroscopy are sensitive to the presence of fat. MR spectroscopy has the potential to quantify bone marrow fat content [14-18]. An alternative MR technique is the multi-echo chemical shift-encoded MRI with water/fat separation that has been validated for the quantification of liver fat [10, 19]. It has already been confirmed that confounders of the chemical shift technique, such as $T2^*$, $T1$, multi-spectral nature of fat and noise bias, must be addressed for reliable quantification of fat content in organs [19-22]. After the correction of all these confounding factors the fat fraction is called the proton density fat fraction (PDFF) [19]. Further, $T2^*$ correction information of the chemical shift technique as an expression of the $T2^*$ decay itself can be used to calculate $R2^*$ in tissue [10]. Therefore multi-echo chemical shift imaging may enable simultaneous quantification of fat content and $R2^*$ in bone marrow as an expression of osteoporosis.

The purpose of this study was to investigate the use of multi-echo chemical shift-encoded MRI-based mapping of PDFF and fat-corrected $R2^*$ in bone marrow as reliable biomarkers for the assessment of osteoporosis. A secondary aim of this study was to assess the effect of multi-spectral modelling of fat on $R2^*$ measurements.

Material and methods

The institutional review board of the University Hospital of Greifswald approved this prospective study. Written informed consent was obtained for the study inclusion of each subject.

Study population

Between May 2012 and November 2012, 51 patients were enrolled in this study. The study population consisted of 23 men and 28 women with a mean age of 69.7 ± 9.0 years and body mass index of 28.1 ± 4.7 kg/m².

Clinically indicated DXA of the lumbar spine (L1–L4) was performed using a commercially available DXA system (Lunar Prodigy Advance; GE Healthcare, USA). Each vertebra was defined as one independent sample. According to the *t* score provided by DXA, vertebrae were divided into groups: normal group (*t* score larger than -1), osteopenia (*t* score between -1 and -2.5) and the osteoporosis group (*t* score smaller than -2.5). Inclusion criteria for this study were patients who had a clinical indication for DXA and who consented to the study. Further, each subject underwent MRI of the spine including a multi-echo chemical shift-encoded MRI with water/fat separation. The mean interval between DXA and MRI was 2 days (range 0–31 days). Patients with systemic diseases of the bone marrow defined by MRI (multiple myeloma, $n=1$ subject; 4 vertebrae) were excluded. Vertebrae with acute fractures ($n=10$ vertebrae in 6 subjects), old fractures with vertebral bone deformity ($n=5$ vertebrae in 3 subjects), metal implants ($n=9$ vertebrae in 7 subjects), percutaneous vertebroplasty ($n=1$ vertebra) and severe imaging artefacts ($n=2$ vertebrae in L1 in 2 subjects) were also excluded. Overall, 173 vertebrae were defined as valid and forwarded for data evaluation.

Magnetic resonance imaging and image reconstruction

Magnetic resonance imaging of the lumbar spine was performed in a commercially available 3-Tesla MR system (Verio, Siemens Healthcare, Erlangen, Germany) using a 24-channel spine matrix coil. Patients were placed in the supine position.

The sequence protocol included a T2-weighted series with fat saturation. The T2-weighted acquisition was performed to assess bone marrow oedema, and for acute vertebrae fractures. Imaging parameters of the T2-weighted sequence included TR/TE=3,500/99 ms; flip angle=150°; averages=1; bandwidth=±233 Hz/pixel; matrix=162×320; field of view=300 mm; 12 slices, slice thickness=3 mm.

In addition, 3D gradient-echo chemical shift-encoded imaging with three echoes was acquired in a sagittal orientation through the lumbar spine. Imaging parameters of the chemical shift encoded sequence were TR/TE₁/TE₂/TE₃ = 6.51/1.22/2.45/4.90 ms; flip angle=9°; averages=1; bandwidth=±910 Hz/pixel; matrix=125×288; field of view=300 mm; parallel imaging (GRAPPA) effective acceleration factor near 2; 60 slices, slice thickness=3.0 mm. The sequence was acquired in 16 s.

Estimation of PDFF and R2* was performed from the chemical shift-encoded acquisition (Fig. 1). Image phase was used to remove ambiguities in water–fat separation. A fitting algorithm was used to separate water and fat signals at each voxel (including correction for R2* and multi-peak fat signals), and to estimate R2* with and without correction for multi-peak fat [23–25]. The separated water and fat signal amplitudes were subsequently corrected for T1 effects using assumed T1 values for water and fat (T1_{water} = 809 ms, T1_{fat} = 382 ms) [26] and PDFF was calculated including correction for noise bias [10]. Three

reconstructions: PDFF, R2* fat corrected, and R2* not corrected for fat were calculated offline using a defined script for MathWorks software package (version 7.12.0; R2011a, MathWorks, Natick, MA, USA) (Fig. 1). The post-processing script and data reconstruction were described previously [10].

Image analysis

One observer with more than 8 years' experience in MR imaging analysed the reconstructed data sets (JK). All image analysis was performed using Osirix (version 5; Pixmeo Sarl, Bernex, Switzerland). A circular region of interest (ROI) was placed in each vertebral body using the first in-phase series in mid-sagittal view of vertebral bodies. Care was taken to exclude motion artefacts, vertebral discs, the cortical bone of the vertebral bodies, focal lesions, the venous plexus and the spinal canal. Additionally focal fatty degenerations of the subchondral vertebrae were avoided during ROI placement. The ROI size was variable and was chosen according to the area of the vertebral body. The ROIs were copied onto the reconstructed PDFF map, the R2* map uncorrected for multi-peak fat and the R2* map corrected for multi-peak fat using the copy and paste function to ensure perfect co-localisation.

Statistics

Measurements were documented and saved in Excel (Microsoft, Redmond, WA, USA). Additionally, statistical analyses were performed using STATA 12.1 (Stata Corp., College Station, TX, USA). All measurements in this study were described as mean value, the corresponding standard deviation and the range of data. Differences between overall groups (normal, osteopenia, osteoporosis) in PDFF, R2* uncorrected for multi-peak fat, and R2* corrected for multi-peak fat were calculated using a Kruskal–Wallis test. Further, a post hoc analysis using a Mann–Whitney U test was performed to evaluate statistical differences between single groups for each technique. Additionally, logistic regression analysis was performed to calculate the area under the curve (AUC) for each technique (PDFF, R2* uncorrected for multi-peak fat, and R2* corrected for multi-peak fat) and combination of techniques (PDFF and R2* corrected for multi-peak fat). Because we measured several vertebrae in the same patients, we calculated clustered sandwich estimators as standard errors.

Results

Dual energy X-ray absorptiometry revealed a mean BMD of $1.14 \pm 0.26 \text{ g/cm}^2$. According to the *t* score, 92 vertebrae were normal (53 %) with a mean BMD of $1.33 \pm 0.18 \text{ g/cm}^2$, 47 osteopenic (27 %) with a mean BMI of $0.98 \pm 0.06 \text{ g/cm}^2$ and 34 osteoporotic (20 %) with a mean BMI of $0.82 \pm 0.13 \text{ g/cm}^2$.

All MR images, particularly the first in-phase echo (TE=2.45 ms), had diagnostic image quality that allowed an anatomical depiction of the lumbar spine. The second in-phase images showed a severe signal decay compared with the first in-phase image and the out-phase series showed a signal loss as a result of water–fat signal cancellation (Fig. 1).

The mean bone marrow fat content for all subjects was 57.7 ± 14.4 %. The fat content demonstrated a significant difference in a comparison of all groups ($P=0.0274$) using a Kruskal–Wallis test. The post hoc analysis revealed that osteoporotic vertebrae showed a significantly higher mean fat content of 62.4 ± 11.0 % compared with the mean fat content of healthy vertebrae 56.3 ± 14.8 % ($P=0.007$). In contrast, there was no difference between PDFF in normal vertebrae and osteopenic vertebrae, which showed a mean fat content of 56.3 ± 14.8 % ($P=0.803$; Fig. 2).

Mean $R2^*$ (uncorrected for multi-peak fat) in the subgroup of normal subjects was 206.6 ± 36.5 s⁻¹ (range 78.0–270.8 s⁻¹). Osteopenic subjects showed a reduced mean $R2^*$ of 192.9 ± 35.4 s⁻¹ (range 108.5–262.125 s⁻¹) and osteoporotic subjects had a mean $R2^*$ of 197.7 ± 28.9 s⁻¹ (122.6–244.2 s⁻¹). Kruskal–Wallis test revealed a significant difference in $R2^*$ among the three groups ($P=0.027$). However, in a post hoc analysis a significant difference was only observed between normal and osteopenic subjects ($P=0.014$) and not between normal and osteoporotic subjects ($P=0.076$; Fig. 3).

When correction for multi-peak fat was included, mean $R2^*$ values were reduced compared with the non-fatcorrected $R2^*$, with values of 107.4 ± 28.3 s⁻¹ (range 51.3–181.4 s⁻¹) for healthy subjects, 92.9 ± 28.9 s⁻¹ (range 47.6–180.4 s⁻¹) for osteopenic subjects and 88.5 ± 20.6 s⁻¹ (range 54.7–124.3 s⁻¹) for osteoporotic subjects. The Kruskal–Wallis test also demonstrated a significant difference among $R2^*$ in all three groups ($P<0.001$). Unlike the $R2^*$ technique without correction for multi-peak fat, the post hoc analysis also revealed a significant difference between normal and osteopenic subjects ($P=0.004$), as well as between normal and osteoporotic subjects ($P<0.001$; Fig. 4).

The AUC calculated by the logistic regression analysis for each technique is depicted in Table 1. The AUC for $R2^*$ without a multi-peak fat correction in the detection of osteoporotic subjects was 0.603 and was significantly increased using a multi-peak fat-corrected $R2^*$ estimation with an AUC of 0.698 ($P=0.002$). Further, the AUCs for differentiation of healthy and osteoporotic samples were improved using a combination of fat-corrected $R2^*$ and PDFF of the bone marrow (AUC 0.740).

Discussion

Our results demonstrate the feasibility of quantifying bone marrow fat content and $R2^*$ simultaneously using multi-echo chemical shift-encoded MRI with water/fat separation. Bone marrow fat content and multi-peak fat-corrected $R2^*$ have moderate diagnostic accuracies for the assessment of osteoporosis. Further, combined information of multi-peak fat-corrected $R2^*$ mapping and bone marrow PDFF improved the diagnostic accuracy for the detection of osteoporosis.

The bone marrow fat content is a promising biomarker for assessing osteoporosis, as suggested in several studies [14–18]. Recent studies using MR spectroscopy revealed comparable results for subjects without osteoporosis (48.8–56.3 %) and also showed increased bone marrow fat content in osteoporotic subjects (58.2–65.5 %) [16–18]. At this time, MR spectroscopy is a widely accepted technique for quantifying bone marrow fat

content [15, 18]. Our results show that multi-echo chemical shift-encoded MRI is an alternative technique that can also provide reliable bone marrow fat quantification. Multi-echo chemical shift imaging has several important advantages in the assessment of osteoporosis, relative to spectroscopy: it allows quantification of the PDFF and simultaneous $R2^*$ estimation in one acquisition. Further, chemical shift imaging also provides anatomical evaluation of the spine within a very short imaging time.

Chemical shift-encoded MRI allows accurate fat quantification, as long as all relevant confounding factors are addressed. Potential confounders include relaxation effects ($T2^*$, $T1$ effects), multispectral complexity of fat, noise bias and eddy currents [19]. Chemical shift-encoded fat quantification has been well validated in the liver, where it has been shown to be equivalent to MR spectroscopy [20, 21, 27]. It should be noted that fat quantification can be performed from magnitude images (i.e. discarding the signal phase) or from complex images (i.e. preserving the signal phase) [28]. Magnitude techniques are typically limited to a dynamic range of PDFF approximately between 0 and 50 % (because of ambiguity regarding $\text{PDFF} > 50\%$), whereas complex-based techniques have a full range of 0-100 %. For liver imaging, PDFF rarely surpasses 50 %; therefore, magnitude-based or complex-based techniques are both appropriate [28]. On the other hand, for the assessment of osteoporosis it is necessary to have a full dynamic range of PDFF between 0 and 100 %, as the fat content in bone marrow is often significantly above 50 %. Therefore, accounting for the complex signal is necessary in fat quantification for the assessment of osteoporosis in the spine. This factor might be the reason why previous studies concluded that magnitude-based chemical shift-encoded techniques are not accurate for the assessment of osteoporosis [29]. On the contrary, complex chemical shift imaging used in this study considers the phase information (fat/water ambiguity) and allows quantification of the fat fraction between 0 and 100 % [19].

Further, our results demonstrate that $R2^*$ measured from the same chemical shift-encoded acquisition can also be employed to assess osteoporosis. Recent studies demonstrated the feasibility of differentiating osteoporosis from healthy subjects using $R2^*$ mapping [6, 7, 30-32]. Patients with osteoporosis have a slower $T2^*$ decay in bones compared with healthy subjects [6, 7]. Further, there is a correlation between the $R2^*$ as an expression of the $T2^*$ decay and the trabecular bone density [31]. In our study, the mean $R2^*$ not accounting for multi-peak fat was significantly reduced in osteopenic subjects compared with healthy subjects. However, there was no significant difference in $R2^*$ between healthy and osteoporotic cases. In summary, our results revealed that, if not corrected for multi-peak fat, $R2^*$ mapping using the three-echo technique does not allow reliable assessment of osteoporosis.

However, $R2^*$ measurements are affected by the presence of bone marrow fat containing multiple spectral peaks. Previous techniques did not correct for the multi-peak fat signal and modelled fat incorrectly as a single resonance at the methylene peak (CH_2). This peak accounts for only approximately 70 % of the fat signal. The remaining 30 % of the fat signal arises from smaller fat peaks with different resonance frequencies, and thus introduces additional oscillations in the measured signal decay. In the presence of fat, $R2^*$ uncorrected for multi-peak fat will be estimated incorrectly [9, 10, 24]. A mathematical model described

by Reeder et al. can remove this error [12, 24, 33]. $R2^*$ with multi-peak fat correction has been shown to provide improved accuracy and robustness for liver iron quantification [10, 11]. The role of the multi-peak modelling of fat has not been previously described for the assessment of osteoporosis. Our results showed significant differences between fat-corrected $R2^*$ in healthy and osteopenic subjects and also in healthy and osteoporotic subjects. Our results indicate that the assessment of osteoporosis is significantly improved compared with $R2^*$ mapping without multipeak fat correction.

Nonetheless, the difference in the mean fat content between normal subjects (56 %) and osteoporotic subjects (62 %) observed in our study and described in recently published studies was small and showed a large variability. We found the same effect using both $R2^*$ techniques with only a small range between $R2^*$ of healthy and osteoporotic subjects. Therefore, it is doubtful whether bone marrow fat or $R2^*$ alone can be used as a reliable biomarker to assess osteoporosis in a blinded study population. However, our study results show there might be an advantage in using both techniques in combination to assess osteoporosis. Using a complex multi-echo chemical shift technique it is possible to quantify the bone marrow fat content and simultaneous $R2^*$ in one step. Combining the two techniques results in improved assessment of osteoporosis.

The study has several limitations. We used only a three-echo method to evaluate the $T2^*$ decay and to calculate $R2^*$. At this time it is not clear how many echoes are optimal for the estimation of the $T2^*$ decay in tissue. In our experience with liver imaging and estimation of liver iron content, the three-echo technique showed excellent results [2, 3, 10]. Likely, the specific choice of the echo times is also critical in addition to the number of echoes used for $R2^*$ estimation. Another limitation is the use of a non-invasive reference standard DXA. DXA is only able to measure the BMD as a predictor of the bone strength, but other factors, such as bone microarchitecture, also play an important role in determining bone strength. $R2^*$ mapping might capture the microarchitecture of the bone, but further work is needed to evaluate this. At this time, DXA (t score and BMD) is the reference standard for the detection of osteoporosis. We chose the t score to select our groups following the recommendation of the World Health Organization. In agreement with recent studies, DXA (BMD, and also t score) might lack robustness for the quantification of BMD [4, 34]. In some subjects of this study, the t score was fundamentally different between vertebral bodies in the same patient. This result is not concordant with the hypothesis that osteoporosis is a systemic disease or confirmed that DXA has limitations in the assessment of osteoporosis. All in all, this might contribute to the moderate correlations between $R2^*$ and t score, and between PDFF and t score. This matter deserves further exploration. A further limitation is that we did not exclude patients undergoing anti-osteoporotic treatment; this could have an effect on our results. Additionally, the number of included patients is low and L1–L4 vertebrae of each patient were defined as independent measurements. This is a limitation in the study design, because t score reference values are derived from the lumbar spine as a whole.

In summary, $R2^*$ mapping for staging of osteoporosis is affected by bone marrow fat. Multi-peak spectral modelling improved the relationship between osteoporosis and $R2^*$. Multi-peak fat-corrected $R2^*$ and PDFF are moderate biomarkers for osteoporosis. Combination of

PDF and fat-corrected $R2^*$ might improve the ability to differentiate between healthy and osteoporotic subjects.

Acknowledgments

This work is part of the research project Greifswald Approach to Individualized Medicine (GANI_MED). The GANI_MED consortium is funded by the German Federal Ministry of Education and Research (FKZ 03IS2061A) and the Ministry of Cultural Affairs of the Federal State of Mecklenburg West Pomerania (UG 09 033). We also acknowledge the support of the National Institutes of Health (NIH) (R01 DK083380 and R01 DK088925).

We acknowledge the help of the medical technical assistants of the Department of Radiology and Neuroradiology of the University Hospital Greifswald.

References

1. WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organ Tech Rep Ser. 1994; 843:1–129. Report of a WHO Study Group. [PubMed: 7941614]
2. Glaser DL, Kaplan FS. Osteoporosis. Definition and clinical presentation. Spine. 1997; 22:12S–16S. [PubMed: 9431639]
3. McDonnell JM, Lane JM, Zimmerman PA. Osteoporosis: definition, risk factors, etiology, and diagnosis. AAOHN J. 1987; 35:527–530. [PubMed: 3689499]
4. Sanflix Gimeno G, Sanflix Genovs J, Hurtado I, et al. Vertebral fracture risk factors in postmenopausal women over 50 in Valencia, Spain. A population based cross-sectional study. Bone. 2013; 52:393–399. [PubMed: 23103928]
5. Blake GM, Fogelman I. The role of DXA bone density scans in the diagnosis and treatment of osteoporosis. Postgrad Med J. 2007; 83:509–517. [PubMed: 17675543]
6. Wehrli FW, Ford JC, Haddad JG. Osteoporosis: clinical assessment with quantitative MR imaging in diagnosis. Radiology. 1995; 196:631–641. [PubMed: 7644622]
7. Damilakis J, Maris T, Papadokostakis G, et al. Discriminatory ability of magnetic resonance T2* measurements in a sample of postmenopausal women with low-energy fractures: a comparison with phalangeal speed of sound and dual x-ray absorptiometry. Invest Radiol. 2004; 39:706–712. [PubMed: 15486532]
8. Maris TG, Damilakis J, Sideri L, et al. Assessment of the skeletal status by MR relaxometry techniques of the lumbar spine: comparison with dual X ray absorptiometry. Eur J Radiol. 2004; 50:245–256. [PubMed: 15145484]
9. Sirlin CB, Reeder SB. Magnetic resonance imaging quantification of liver iron. Magn Reson Imaging Clin N Am. 2010; 18:359–381. ix. [PubMed: 21094445]
10. Kuehn J-P, Hernando D, Muoz Del Rio A, et al. Effect of multipeak spectral modeling of fat for liver iron and fat quantification: correlation of biopsy with MR Imaging results. Radiology. 2012; 265:133–142. [PubMed: 22923718]
11. Hernando D, Kuehn J-P, Mensel B, et al. $R2^*$ estimation using “in phase” echoes in the presence of fat: the effects of complex spectrum of fat. J Magn Reson Imaging. 2012 doi:10.1002/jmri.23851.
12. Reeder SB, Robson PM, Yu H, et al. Quantification of hepatic steatosis with MRI: the effects of accurate fat spectral modeling. J Magn Reson Imaging. 2009; 29:1332–1339. [PubMed: 19472390]
13. Baum T, Yap SP, Karampinos DC, et al. Does vertebral bone marrow fat content correlate with abdominal adipose tissue, lumbar spine bone mineral density, and blood biomarkers in women with type 2 diabetes mellitus? J Magn Reson Imaging. 2012; 35:117–124. [PubMed: 22190287]
14. Griffith JF, Yeung DKW, Antonio GE, et al. Vertebral marrow fat content and diffusion and perfusion indexes in women with varying bone density: MR evaluation. Radiology. 2006; 241:831–838. [PubMed: 17053202]

15. Li X, Kuo D, Schafer AL, et al. Quantification of vertebral bone marrow fat content using 3 Tesla MR spectroscopy: reproducibility, vertebral variation, and applications in osteoporosis. *J Magn Reson Imaging*. 2011; 33:974–979. [PubMed: 21448966]
16. Yeung DKW, Griffith JF, Antonio GE, et al. Osteoporosis is associated with increased marrow fat content and decreased marrow fat unsaturation: a proton MR spectroscopy study. *J Magn Reson Imaging*. 2005; 22:279–285. [PubMed: 16028245]
17. Griffith JF, Yeung DKW, Antonio GE, et al. Vertebral bone mineral density, marrow perfusion, and fat content in healthy men and men with osteoporosis: dynamic contrast enhanced MR imaging and MR spectroscopy. *Radiology*. 2005; 236:945–951. [PubMed: 16055699]
18. Tang GY, Lv ZW, Tang RB, et al. Evaluation of MR spectroscopy and diffusion-weighted MRI in detecting bone marrow changes in postmenopausal women with osteoporosis. *Clin Radiol*. 2010; 65:377–381. [PubMed: 20380936]
19. Reeder SB, Hu HH, Sirlin CB. Proton density fat-fraction: a standardized MR based biomarker of tissue fat concentration. *J Magn Reson Imaging*. 2012; 36:1011–1014. [PubMed: 22777847]
20. Meisamy S, Hines CDG, Hamilton G, et al. Quantification of hepatic steatosis with T1-independent, T2-corrected MR imaging with spectral modeling of fat: blinded comparison with MR spectroscopy. *Radiology*. 2011; 258:767–775. [PubMed: 21248233]
21. Yokoo T, Shiehorteza M, Hamilton G, et al. Estimation of hepatic proton-density fat fraction by using MR imaging at 3.0 T. *Radiology*. 2011; 258:749–759. [PubMed: 21212366]
22. Kang GH, Cruite I, Shiehorteza M, et al. Reproducibility of MRI-determined proton density fat fraction across two different MR scanner platforms. *J Magn Reson Imaging*. 2011; 34:928–934. [PubMed: 21769986]
23. Hamilton G, Yokoo T, Bydder M, et al. In vivo characterization of the liver fat ¹H MR spectrum. *NMR Biomed*. 2011; 24:784–790. [PubMed: 21834002]
24. Yu H, Shimakawa A, McKenzie CA, et al. Multiecho water fat separation and simultaneous R2* estimation with multifrequency fat spectrum modeling. *Magn Reson Med*. 2008; 60:1122–1134. [PubMed: 18956464]
25. Hernando D, Liang Z-P, Kellman P. Chemical shift based water/fat separation: a comparison of signal models. *Magn Reson Med*. 2010; 64:811–822. [PubMed: 20593375]
26. de Bazelaire CMJ, Duhamel GD, Rofsky NM, Alsop DC. MR imaging relaxation times of abdominal and pelvic tissues measured in vivo at 3.0 T: preliminary results. *Radiology*. 2004; 230:652–659. [PubMed: 14990831]
27. Hines CDG, Frydrychowicz A, Hamilton G, et al. T(1) independent, T(2) (*) corrected chemical shift based fat water separation with multi-peak fat spectral modeling is an accurate and precise measure of hepatic steatosis. *J Magn Reson Imaging*. 2011; 33:873–881. [PubMed: 21448952]
28. Reeder SB, Sirlin CB. Quantification of liver fat with magnetic resonance imaging. *Magn Reson Imaging Clin N Am*. 2010; 18:337–357. ix. [PubMed: 21094444]
29. Gokalp G, Mutlu FS, Yazici Z, Yildirim N. Evaluation of vertebral bone marrow fat content by chemical shift MRI in osteoporosis. *Skeletal Radiol*. 2011; 40:577–585. [PubMed: 21069523]
30. Wehrli FW, Ma J, Hopkins JA, Song HK. Measurement of R' 2 in the presence of multiple spectral components using reference spectrum deconvolution. *J Magn Reson*. 1998; 131:61–68. [PubMed: 9533907]
31. Rosenthal H, Thulborn KR, Rosenthal DI, et al. Magnetic susceptibility effects of trabecular bone on magnetic resonance imaging of bone marrow. *Invest Radiol*. 1990; 25:173–178. [PubMed: 2312252]
32. Funke M, Bruhn H, Vosschenrich R, et al. The determination of the T2* relaxation time for characterizing trabecular bone. *Rofo*. 1994; 161:58–63. [PubMed: 8043766]
33. Reeder SB, Brittain JH, Grist TM, Yen Y-F. Least-squares chemical shift separation for (13)C metabolic imaging. *J Magn Reson Imaging*. 2007; 26:1145–1152. [PubMed: 17896366]
34. Bolotin HH, Sievänen H. Inaccuracies inherent in dual-energy X-ray absorptiometry in vivo bone mineral density can seriously mislead diagnostic/prognostic interpretations of patient-specific bone fragility. *J Bone Miner Res*. 2001; 16:799–805. [PubMed: 11341324]

Key Points

- Magnetic resonance imaging offers new insights into bone composition.
- PDFF and $R2^*$ are moderate biomarkers for the assessment of osteoporosis.
- $R2^*$ mapping for staging of osteoporosis is affected by bone marrow fat.
- Multi peak spectral modelling improved the relationship between osteoporosis and $R2^*$.
- PDFF/multi peak fat corrected $R2^*$ together might improve differentiation between healthy and osteoporotic subjects.

Fig. 1.

A 67 year old female patient with osteoporosis. Multi echo chemical shift imaging with complex water fat separation allows quantification of the bone marrow fat content. R2* correction was automatically performed for each subject and is necessary for correct fat quantification. The R2* maps themselves are also calculated and available for analysis. a Raw data for the multi echo chemical shift technique (out phase; in phase; late in phase). b R2* maps without and with correction for multi peak fat. c Proton density fat fraction map allows assessment of the bone marrow fat content

Fig. 2.

Box plot analysis of the bone marrow fat content in three groups: normal, osteopenia, and osteoporosis. Pathological subjects with manifest osteoporosis showed increased fat content compared with normal subjects ($P=0.007$). There was no significant difference between normal and osteopenic subjects

Fig. 3.

Box plot analysis of R2* (uncorrected for multi peak fat), estimated from the R2* correction information of the three echo complex chemical shift encoded MRI. Kruskal Wallis test revealed a significant difference among the groups: normal, osteopenia and osteoporosis ($P=0.027$). However, a post hoc analysis showed only a statistical difference between normal and osteopenic subjects ($P= 0.014$). This technique is not reliable for the assessment of osteoporosis

Fig. 4.

Box plot analysis of fat corrected R2* (corrected for multi peak fat signals) for the different groups: healthy, osteopenia and osteoporosis. Mean fat corrected R2* was lower compared with the non fat corrected R2*. Kruskal Wallis test revealed a significant difference in R2* between groups. Post hoc analysis confirmed the difference between normal and osteopenic subjects ($P=0.004$) and between normal and osteoporotic subjects ($P<0.001$).

Table 1

Logistic regression analysis with a calculation of the area under the curve (AUC) for each technique (PDFF, R2* uncorrected for multi-peak fat, and R2* corrected for multi-peak fat) and a combination of the techniques (PDFF and R2* corrected for multi-peak fat). Combination of R2* corrected for multi-peak fat and PDFF increased the AUC for differentiation between healthy and osteoporotic subjects

Comparison of healthy and osteoporotic vertebrae				
	R2* uncorrected for multi-peak fat	R2* corrected for multi-peak fat	PDFF	R2* corrected for multi-peak fat+PDFF
AUC (* cut-off 0.5)	0.603	0.698	0.656	0.740
Correctly classified	73.0 %	73.0 %	72.2 %	74.6 %
Comparison of healthy and osteopenic vertebrae				
	R2* uncorrected for multi-peak fat	R2* corrected for multi-peak fat	PDFF	R2* corrected for multi-peak fat+PDFF
AUC (* cut-off 0.5)	0.628	0.650	0.513	0.655
Correctly classified	66.2 %	69.0 %	66.2 %	69.8 %
Comparison of Osteopenic and Osteoporotic Vertebrae				
	R2* uncorrected for multi-peak fat	R2* corrected for multi-peak fat	PDFF	R2* corrected for multi-peak fat+PDFF
AUC (* cut-off 0.5)	0.522	0.529	0.632	0.631
Correctly classified	58.0 %	58.0 %	58.0 %	58.0 %