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MUSCULOSKELETAL IMAGING

ORIGINAL ARTICLE

Fat fraction quantification of lumbar spine: comparison of T1-weighted two-point Dixon and single-voxel magnetic resonance spectroscopy in diagnosis of multiple myeloma

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PURPOSE

We aimed to investigate the value of T1-weighted two-point Dixon technique and single-voxel magnetic resonance spectroscopy (MRS) in diagnosis of multiple myeloma (MM) through quantifying fat content of vertebral marrow.

METHODS

A total of 30 MM patients and 30 healthy volunteers underwent T1-weighted two-point Dixon and single-voxel MRS imaging. The fat fraction map (FFM) was reconstructed from the Dixon images using the equation FFM = Lip/In, where Lip represents fat maps and In represents in-phase images. The fat fraction (FF) of MRS was calculated by using the integral area of Lip peak divided by the sum of integral area of Lip peak and water peak.

RESULTS

FF values measured by the Dixon technique and MRS were significantly decreased in MM patients (45.99%±3.39% and 47.63%±4.38%) compared with healthy controls (64.43%±0.96% and 76.22%±1.91%) ($P < 0.001$ with both methods). FF values measured by Dixon technique were significantly positively correlated to those measured by MRS in MM ($r = 0.837$, $P < 0.001$) and healthy control group ($r = 0.735$, $P < 0.001$), respectively. There was no significant difference between area under the curve (AUC) obtained by the Dixon technique (0.878±0.047; range, 0.785 to 0.971; optimal cutoff, 56.35 for healthy controls vs. MM) and MRS (0.883±0.047; range, 0.791 to 0.974; optimal cutoff, 61.00 for healthy controls vs. MM). The ability of Dixon technique to differentiate MM group from healthy controls was equivalent to single-voxel MRS.

CONCLUSION

Regarding detection of fat contents in vertebral bone, T1-weighted two-point Dixon technique exhibited equivalent performance to single-voxel MRS in the diagnosis of multiple myeloma. Moreover, two-point Dixon is a more convenient and stable technique for assessing bone marrow changes in MM patients than single-voxel MRS.

Multiple myeloma (MM) is a malignant hematologic disease, characterized by the accumulation of plasma cells in the bone marrow producing large quantities monoclonal immunoglobulins (1, 2). Bone lesions are one of the characteristic CRAB features (hypercalcemia, renal failure, anemia, and bone lesions) and the trabecula of osteolytic bone lesions is replaced by plasma cell tumors (2–4). Bone involvement causes morbidity and mortality; it remains a major problem in clinical treatment and affects quality of life of the patients (5, 6).

The bone marrow in healthy adults has two main different types: red bone marrow (consists of 30%–40% water, 40%–60% fat, and 10%–20% protein) and yellow bone marrow (consists of 15% water, 80% fat, and 5% protein) (4, 7). With increasing age, red bone marrow is transformed into the yellow marrow. However, infiltration of the plasma cells in the bone marrow causes reconversion from yellow to red marrow, resulting in fat content reduction in the bone marrow of MM patients (8). Therefore, the detection of fat fraction in vertebral marrow of MM patients plays a key role in early diagnosis and prognosis of MM patients after treatment.

So far, to define the amount of clonal bone marrow plasma cells by the bone marrow biopsy has been one of the necessary diagnostic criteria listed by the International Myeloma Working

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Group (2, 9). But the aspiration biopsy is an invasive examination, which causes a certain degree of physical pain and inconvenience in life. On the other hand, magnetic resonance imaging (MRI) is not only a nonradiative and noninvasive technology, but also considered to be the most sensitive diagnostic method for evaluating spinal bone marrow involvement and fat quantitative analysis of the bone marrow (10).

MRI techniques for quantitative evaluation of bone marrow fat content include T1-weighted MRI, Dixon method, and magnetic resonance spectroscopy (MRS) (11–13). Dixon method is a water-fat imaging method based on chemical shift water-fat separation, proposed by Dixon in 1984 for the first time (11, 14, 15). Two-point Dixon technique generates water and fat images, relying on the phase shifts made by fat-water resonance frequency differences (15). Although it has the advantages of short total scanning time, high signal-to-noise ratio, relative sensitivity to magnetic field heterogeneity, and sufficient spatial resolution (7, 15), it is lacking correction of magnetic resonance relaxation (15, 16). MRS reflects the frequency and chemical shift of different metabolites in biological tissues in the form of spectral lines, and its basic principle is based on chemical shift. MRS is considered as the gold standard method for assessing quantitative measurement of fat fraction, since it is capable of separating lipid signals from water signals in the total magnetic resonance signal (11, 17), but the examination area of this technique is limited to a single voxel and the accuracy of the data is operator dependent, which limits the application of this technique in clinical practice. Other drawbacks of MRS include the long acquisition and chemical shift displacement (11, 18). Previous study has proved that Dixon technique and MRS have wide applications in muscle, liver and bone marrow of osteoporosis for quantitative assessment of fat fraction (11, 17, 19–22). However, to our best knowledge, only a few studies have evaluated the diagnostic performance of Dixon and MRS techniques for spinal lesions in MM patients (8, 15).

This study aimed to investigate and compare the value of two-point Dixon technique and single-voxel MRS in diagnosing MM through quantifying fat fraction of the vertebral marrow.

Main points

- Multiple myeloma (MM) is a malignant hematologic disease, which is characterized by the accumulation of plasma cells in the bone marrow producing large quantities monoclonal immunoglobulins, resulting in reduced fat content.
- There was significant positive correlation between fat fraction measured by the Dixon and MRS techniques in MM patients.
- Dixon and MRS techniques exhibited equivalent performance to differentiate MM from the healthy control group. The sensitivity and specificity of the Dixon technique were 96.7% and 80%, while the sensitivity and specificity of MRS were 96.7% and 73.3%.

Methods

Patients

Thirty pathologically confirmed MM patients (16 male and 14 female subjects; mean age, 63.4±8.94 years; range, 45–79 years) underwent MRI of the lumbar spine with two-point Dixon and MRS. MM patients identified by the International Myeloma Working Group criteria were included in the study (23). Because of the variety of MM imaging types, patients with imaging manifestations of "salt and pepper" or "salt and pepper with nodules" were selected to control the uniqueness of the experimental subjects. Other imaging phenotypes were excluded for the purpose of this study.

Thirty healthy volunteers (16 male and 14 female subjects; mean age, 63.0±5.44 years; range, 52–76 years) including 16 male and 14 females were also examined by using the same MRI protocol to calculate mean fat fraction of healthy bone marrow. The healthy volunteers were recruited based on no history of malignancy, hematological diseases, vertebral fracture, metabolic syndrome, insulin resistance, type 2 diabetes mellitus (DM) or obesity.

Patients and volunteers were scanned with the approval from the regional Ethics Committee of our hospital. All volunteers signed informed written consents.

MRI acquisition

All MRI was accomplished using a 3 T MRI scanner (MAGNETOM Skyra, Siemens) with spine matrix coil.

The standard MRI protocol for lumbar spine was composed of sagittal T2-weighted spin-echo and axial T2-weighted turbo spin-echo sequence. In order to obtain anatomical images, the following parameters were used. Sagittal T2-weighted sequence: TR/TE, 3000/88 ms; FOV, 100×200 mm; matrix, 320×80; slice thickness, 4 mm; slice gap, 0.2 mm; averages, 2; number of slices, 12; flip angle, 150°; acquisition time, 2 min 19 s; respiratory gating, off.

Axial T2-weighted sequence: TR/TE, 3021/101 ms; FOV, 220×100 mm; matrix, 285×85; slice thickness, 3 mm; slice gap, 0.3 mm; averages, 2; number of slices, 24; flip angle, 140°; acquisition time, 1 min 43 s; respiratory gating, off.

T1-weighted two-point Dixon method

To determine the percentage of fat content in the bone marrow, all subjects underwent a sagittal T1-weighted two-point Dixon imaging sequence with the following parameters: TR, 600 ms, TEs, 8.8/10 ms (out-of-phase [OP] and in-phase [IP], respectively), FOV, 280×100 mm; slice thickness, 4 mm; slice gap, 0.2 mm; average, 2; number of slices, 24; flip angle, 150°; acquisition time, 2 min 25 s; respiratory gating, off.

Magnetic resonance spectroscopy (MRS)

The data was acquired by using a standard point resolved spectroscopy (PRESS) sequence with a single spectroscopy voxel positioned centrally in the L4 vertebral body. The acquisition parameters were as follows: TR/TE, 2000/33 ms; averages, 80; voxel, 15×15×15 mm; number of slices, 12; flip angle, 90°; acquisition time, 2 min 19 s; respiratory gating, off.

Imaging analysis

The fat fraction map (FFM) was reconstructed using Dixon images via the equation FFM= Lip/In, where Lip represents fat images and In represents in-phase images on a workstation called MRWP (11, 24). The quantitative parameters were measured by placing the region of interest (ROI) in the regions corresponding to the MRS voxel, avoiding the basivertebral veins. The mean FF values obtained by both investigators were averaged and regarded as the final value. As a reference, the ROI was manually depicted on the T2-weighted midline sagittal image to reduce the location error. The MRS data were post-processed using Syngo spectroscopy software (Siemens Healthcare). Manually selected resonance frequency and line width of water (4.7 ppm) and fat (1.3 ppm) peaks were used as starting values in the nonlinear least squares fitting algorithm (24). By using the nonlinear least square method, an equation of mean square difference (MSE) was established. The equation of first derivative of this equation was calculated, and then quantitative values to guarantee the minimum MSE were calculated. The fat fraction of MRS (MRS-FF) was calculated by using the integral area of Lip peak divided by the sum of integral area of Lip peak and water peak.

Statistical analysis

Statistical analysis is conducted with SPSS V.17.0 statistical software (SPSS Inc.) and Prism software (Prism version 7.0, GraphPad Software, Inc.). The independent samples *t* test was used to compare the difference among quantitative parameters. Homogeneity test was performed before t test. If the data showed heterogeneity of variance, t' test was used to analyze the data. The relationship of FF between two-point Dixon and MRS was assessed by using the Pearson correlation test. Receiver operating characteristic (ROC) analysis of two-point Dixon and MRS was performed to obtain the diagnostic threshold, area under curve (AUC), sensitivity and specificity for both methods in order to evaluate the detection efficiency of fat fraction. All data are presented as mean ± standard error. $P \leq 0.05$ is considered statistically significant.

Table. Fat fraction of T1-Dixon and MRS in the MM group and healthy control group

Group	Dixon (mean±SE) (%)	MRS (mean±SE) (%)
MM group (n=30)	45.99±3.39	47.63±4.38
Healthy control group (n=30)	64.43±0.96	76.22±1.91
t	-5.236	-5.982
P	≤0.001	≤0.001

MRS, magnetic resonance spectroscopy; MM, multiple myeloma; SE, standard error.

Results

The MRI characteristics of lumbar spine in healthy volunteers and MM patients were shown in Fig. 1. T1-weighted and T2-weighted images showed uniform bone marrow with intermediate signal in healthy adult lumbar spine, which was slightly higher than that in the intervertebral disc (Fig. 1a, 1b). The lumbar spine in elderly people showed slightly higher signal on T1-weighted image (Fig. 1a). Both T1-weighted and T2-weighted images of the MM group showed low signals than those of the healthy control group. T1-weighted images showed multiple low-signal small nodules within the high signal background caused by plasma cell infiltration (Fig. 1e, 1f). Sagittal FFM images of the healthy control group and MM group were shown in Fig. 1c, 1g, respectively. The fat fraction data was obtained by using circular ROI on L4 vertebral body in the FFM images. The FFM images in MM group showed signal reduction of vertebral body compared with that in the healthy control group and revealed multiple low signal small nodules caused by plasma cell infiltration (Fig. 1g). Spectrum acquired from healthy control and MM groups showed the water and lipid peaks. The lipid peak was higher than water peak in the healthy adult lumbar spine (Fig. 1d), but lower than water peak in the MM group (Fig. 1h). Compared with healthy controls, water and marrow fat content was decreased in the MM group; in particular fat content was decreased, indicating bone marrow replacement (yellow marrow mainly) by plasma cell tumors.

The mean values of fat fraction obtained by the Dixon and MRS in the MM patients (45.99%±3.39% for Dixon, 47.63%±4.38% for MRS, respectively) were significantly decreased when compared with that of healthy volunteers (64.43%±0.96% for Dixon, 76.22%±1.9% for MRS, respectively, $P<0.001$) (Table).

The data were analyzed by using Pearson correlation coefficient to confirm the linear relationship of the fat fraction between Dixon and MRS in MM and healthy control groups. There was a significant positive linear relationship between Dixon and MRS in MM patients ($r= 0.837$, $P \leq 0.001$) (Fig. 2) and in healthy controls ($r= 0.735$, $P \leq 0.001$) (Fig. 3).

Receiver operating characteristic (ROC) analysis showed that there was no significant difference between AUC of Dixon technique (0.878±0.047; range, 0.785 to 0.971; optimal cutoff, 56.35 for healthy control vs. MM) and MRS (0.883±0.047; range, 0.791 to 0.974; optimal cutoff, 61.00 for healthy control vs. MM). The sensitivity and specificity were calculated as 96.7% and 80% for the Dixon technique and 96.7% and 73.3% for MRS, respectively (Fig. 4). There was no significant difference between the Youden Index of two-point Dixon and MRS ($P = 0.849$), indicating that the ability of Dixon technique to differentiate MM group from healthy control group exhibited equivalent performance to single-voxel MRS.

Discussion

The present study aimed to investigate the value of two-point Dixon technique and single-voxel MRS in diagnosis of MM through quantifying fat contents of the vertebral marrow. Our results showed that there was significant positive correlation between fat fraction measured by the two techniques and both techniques exhibited equivalent performance to differentiate MM from the healthy control group.

In our study, we demonstrated that the mean values of fat fraction obtained by the Dixon and MRS techniques in the MM patients were significantly decreased when compared with that of healthy volunteers. Previous studies have shown that fat fraction of the lumbar spine obtained by Dixon technique can distinguish benign and malignant bone marrow lesions (12, 25). Bone marrow in patients with malignant vertebral fractures is usually replaced by tumors, resulting in reduced fat and water content, quite similar to our results (12).

The bone marrow in healthy adults has two main types: red bone marrow (consists of 30%–40% water, 40%–60% fat, and 10%–20% protein) and yellow bone marrow (consists of 15% water, 80% fat, and 5% protein) (4, 7). With increasing age, red bone marrow is transformed into yellow bone marrow. The fat fraction of vertebral bone marrow in elderly is higher than young people. Moreover, because of the short T1 relaxation time in fat, the yellow marrow appears as high signal in T1-weighted images. Therefore, T1-weighted images of lumbar spinal appear to have high signal intensity in elderly people (Fig. 1a). Owing to re-inversion of red marrow in MM group, the yellow bone marrow decreases and gradually reverts to more cellular marrow. Because it is mainly made up of red bone marrow in MM patients, fat fraction of bone marrow is lower than that of healthy peo-

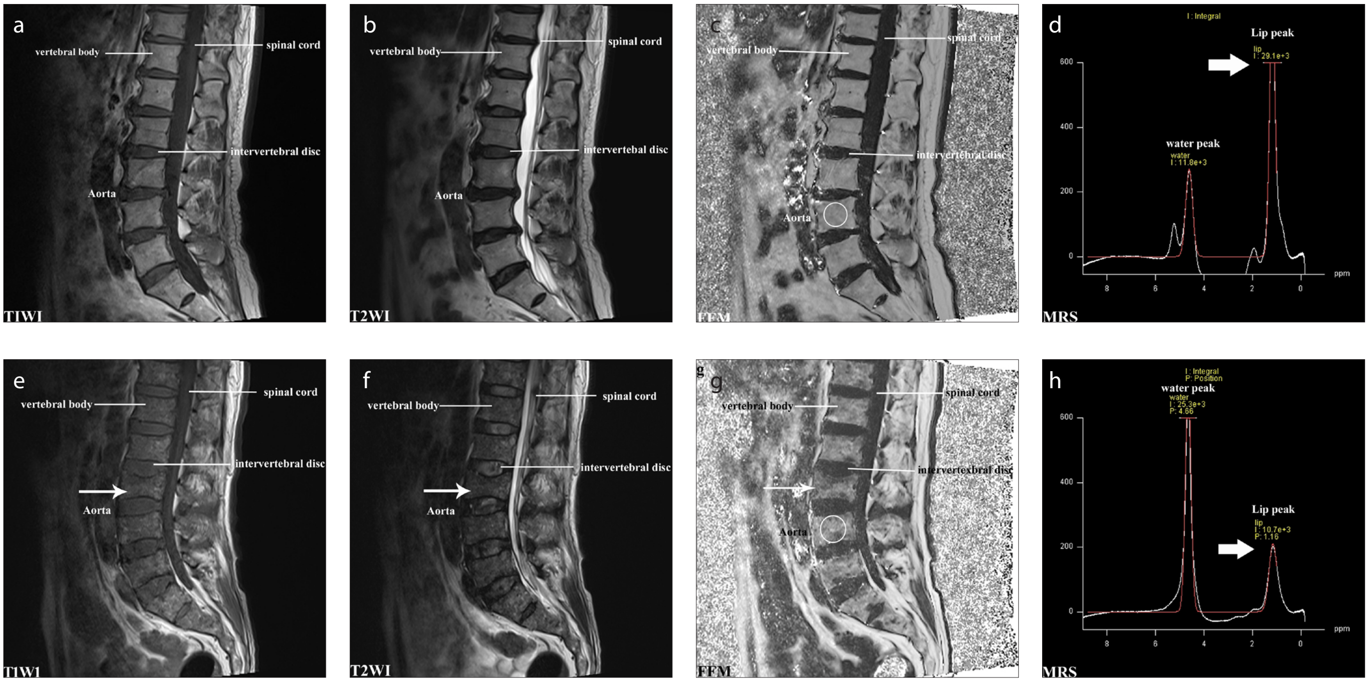

Figure 1. a–h. Exemplary sagittal T1-weighted **(a)** and T2-weighted **(b)** images from the healthy control group shows uniform bone marrow with intermediate signal in adult lumbar spine, which is slightly higher than that in the intervertebral disc. The lumbar spine in elderly people showed slightly higher signal on T1-weighted image. Fat fraction map (FFM) **(c)** from the control group shows signal uniformity. The FFM was reconstructed using Dixon images via the equation FFM = Lip / In, where Lip represented fat images and In represented in-phase images. A 3.5 mm^2 ROI *(circle)* was drawn in L4 vertebral body to measure the fat fraction. Size and location of ROIs were kept as similar as possible in FFM images. Graph **(d)** shows the spectrum acquired from the healthy control group. The lipid peak *(white arrow)* was higher than water peak in healthy adult lumbar spine. The fat fraction of MRS (MRS-FF) was calculated by using the integral area of lipid peak divided by the sum of integral area of lipid peak and water peak. Exemplary sagittal T1-weighted **(e)** and T2-weighted **(f)** images from the MM group show multiple low signal small nodules within the high signal background caused by plasma cell infiltration. FFM **(g)** from the MM group shows signal reduction in the vertebral body compared with the healthy control group, as well as multiple low signal small nodules *(white arrow)* caused by plasma cell infiltration. Graph **(h)** shows the spectrum acquired from the MM group. The lipid peak *(white arrow)* was lower than water peak in the MM group. Compared with normal group, water peak and lipid peak show decreased water and marrow fat content in the MM group, especially for bone marrow fat contents, indicating that bone marrow (yellow marrow mainly) was replaced by plasma cell tumors.

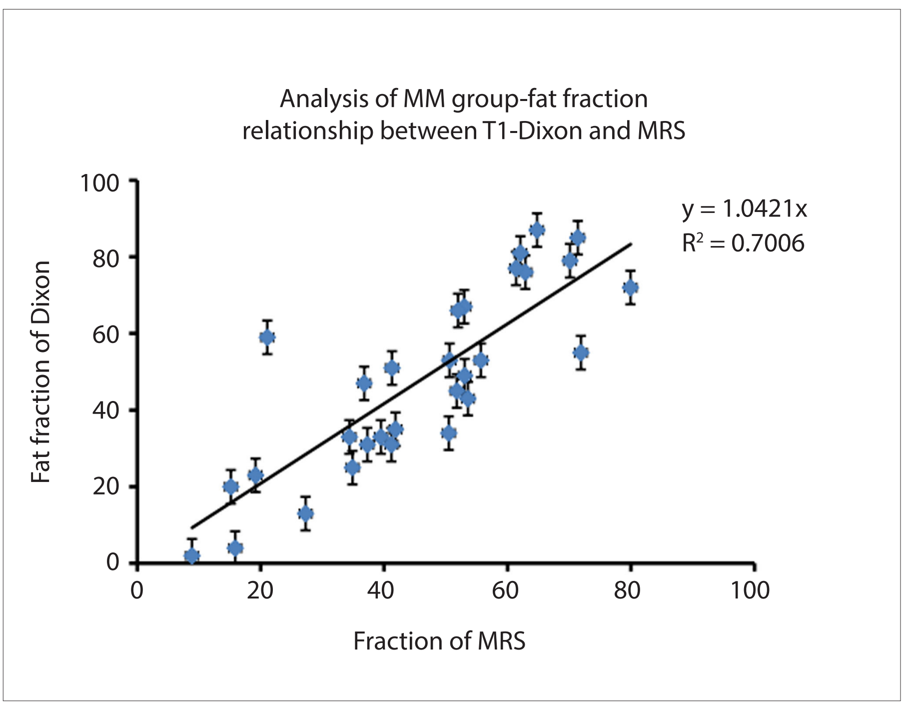

Figure 2. Analysis of fat fraction relationship between two-point Dixon and magnetic resonance spectroscopy (MRS) in multiple myeloma (MM) patients. There is a significant positive linear relationship between two-point Dixon and MRS in MM patients (r = 0.837, $P \leq 0.001$).

ple; thus, the T1-weighted and T2-weighted images in MM group both showed low signals compared with those in the healthy control group (Fig. 1e, 1f). This result may be attributed to the replacement of bone marrow by plasma tumor cells, resulting in reduced fat fraction in MM patients (4).

In the present study, we not only found that FF values measured by Dixon were significantly positively correlated to those measured by MRS in MM group (r= 0.837, $P < 0.001$) and healthy control group (r= 0.735, $P < 0.001$), respectively, but also demonstrated that the ability of Dixon (0.878±0.047; range, 0.785 to 0.971) to differentiate MM group from healthy control group was equivalent to single-voxel MRS (0.883±0.047; range, 0.791 to 0.974) through ROC analysis. The present results demonstrated that Dixon technique exhibited equivalent performance to that with single-voxel MRS in differentiating MM group from healthy control group as assessed by the ROC curve analysis for fat fraction. Shen et al. (11) reported that differ-

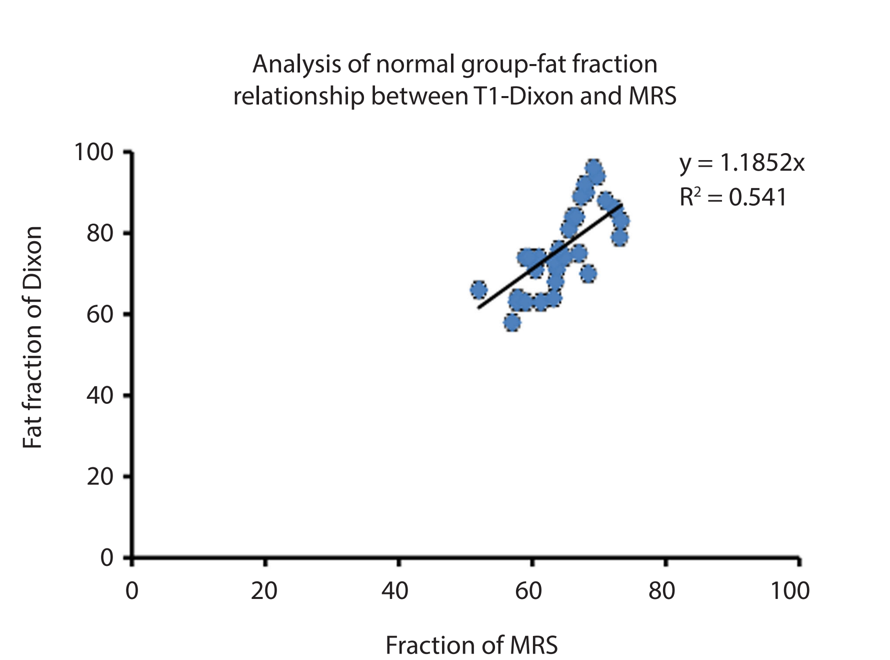

Figure 3. Analysis of fat fraction relationship between two-point Dixon and MRS in healthy volunteers. There is a significant positive correlation between two-point Dixon and MRS in normal group ($r = 0.735$, $P \leq 0.001$).

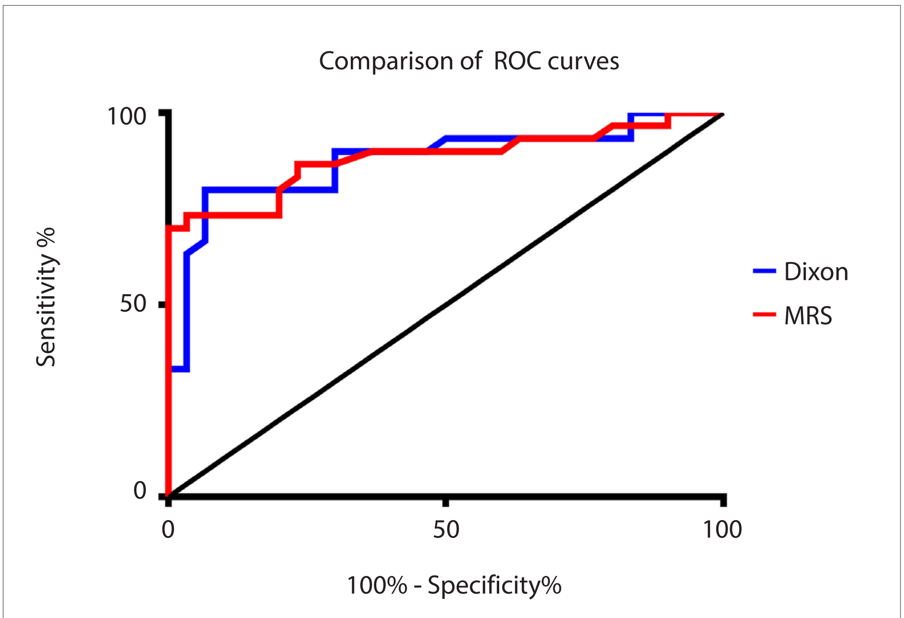

Figure 4. Analysis of ROC curve between two-point Dixon and MRS. There was no significant difference between area under the curve of two-point Dixon (0.878±0.047; 0.785 to 0.971; optimal cutoff, 56.35 for normal vs. MM) and MRS (0.883±0.047; 0.791 to 0.974; optimal cutoff, 61.00 for normal vs. MM). The sensitivity and specificity of two-point Dixon are 96.7% and 80%, respectively. The sensitivity and specificity of MRS are 96.7% and 73.3%, respectively.

ent MRI techniques including T1-weighted imaging, modified Dixon method, and MRS could be used to quantify bone marrow fat in osteoporosis, and observed that there were good correlations between MRS and Dixon in 27 Caucasian postmenopausal women (11).

As it is well known, MRI techniques in evaluating vertebral fat content include T1-weighted MRI, the Dixon technique and MRS (11–13), the most important of which are Dixon and MRS techniques. But the underlying theory of the Dixon and MRS techniques for measuring the fat fraction are quite distinct from each other, and the two methods have advantages and disadvantages, respectively.

Two-point Dixon technique relies on the phase shifts made by fat-water resonance frequency differences to separate water from fat. By strategically acquiring images at specific echo time (TE) values, two separate images can be obtained in which water and fat signals are located in-phase and out-of-phase, respectively. By adding and subtracting the two images, Dixon technique provides both water-only and fat-only images (15). The advantages of Dixon technique are summarized below. First, it has high scanning efficiency, flexible selection of echo time, and rapid separation of adipose tissue. With a single acquisition, two-point Dixon provides multiple images including water, fat, in-phase and out-phase images, hence the total scanning time is significantly shortened (15). Second, it is relatively sensitive to the heterogeneity of B0 field (15). Third, it provides maps with good compatibility, high signal-to-noise ratio and quantitative detection of adipose tissue. More importantly, Dixon water-lipid imaging sequence based on chemical shift demonstrates superiority than single-voxel MRS in assessment of bones with uneven distribution of red bone marrow, such as the spine, where sufficient spatial resolution is required (7). The disadvantages of the Dixon technique includes lack of correction of magnetic resonance relaxation (16). When the magnetic field B0 is inhomogeneous or has significant susceptibility, the phase error will be invalid, resulting in water-fat exchange (26).

Magnetic resonance spectroscopy (MRS) reflects the frequency and chemical shift of different metabolites in biological tissues in the form of spectral lines, and its basic principle is based on chemical shift. Concerning the quantification of fat content via MRI techniques in current literature, MRS technique is regarded as the gold standard for assessing quantitative measurements fat fraction, but requires the technician to locate the ROI accurately. Therefore, MRS has relatively high technical requirements for data acquisition (11), which hinders the application of this technique. Another drawback of MRS is the long acquisition time (11). Other drawbacks of this technique include chemical shift MRI resulting in a number of confounding factors (7), inhomogeneity of the main magnetic field, presence of fat multispectral peaks, T2* delay effect, T1 migration effect, and eddy current effect (7, 16, 18, 27). The accuracy of the results may be influenced by all these factors.

The limitations of our study are as follows. First, we included only MM cases with "salt and pepper sign" imaging findings; the vertebral MRI manifestations of MM patients are various and complex, and further research should include all types and acquire multimodal imaging data. Second, this study had fewer cases with initial diagnosis of MM. It is more meaningful to study the changes of fat content in patients with initial diagnosis and to predict the prognosis of MM disease as a biological imaging indicator. In further research, we should increase the sample size of newly diagnosed cases. Third, we collected a relatively small number of cases, but we aim to expand the sample size in further research.

In conclusion, Dixon technique and MRS have good correlation in quantitative evaluation of vertebral fat content, and both are suitable for MM patients. Dixon technique and MRS can quantitatively evaluate vertebral fat content and have comparable value in diagnosis of MM. But Dixon technique is more conventional and rapid than MRS, and may possess more value in clinical practice.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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