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대한영상의학회지

Effect of Gadoxetic Acid on Quantification of Hepatic Steatosis Using Magnetic Resonance Spectroscopy: A Prospective Study

Gadoxetic Acid가 자기공명분광술을 이용한 지방간의 정량화에 미치는 영향: 전향적 분석

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Purpose: We prospectively evaluated whether gadoxetic acid (Gd-EOB-DTPA) administration for liver magnetic resonance (MR) imaging affects the quantification of hepatic steatosis using MR spectroscopy (MRS).

Materials and Methods: A total of 155 patients were included, who underwent gadoxetic acid-enhanced liver MR imaging and MRS during a 5-month period. Fast breath-hold high-speed T2-corrected multi-echo MRS was used before, and 20 min after, gadoxetic acid injection. The same location was maintained in the pre-contrast and post-contrast MRS. Changes in the fat fraction (FF) were compared between the pre- and post-contrast MRS using a paired *t*-test. The change in FF between cirrhotic and non-cirrhotic patients was compared using an independent *t*-test. In cirrhotic patients, the correlation between FF change and biochemical marker using Pearson's correlation test, was evaluated.

Results: The mean FF in the post-contrast MRS (5.05 ± 5.26%) was significantly higher than in the pre-contrast MRS (4.77 ± 0.57%) ($p < 0.000$). The FF change between pre-contrast and post-contrast MRS was significantly higher in non-cirrhotic patients (0.41 ± 0.77%) than in cirrhotic patients (0.14 ± 0.59) ($p = 0.010$). Albumin and alkaline phosphatase shows weak correlation with FF change (both $p < 0.02$).

Conclusion: Gadoxetic acid affects the quantification of hepatic steatosis by MRS. Hence, MRS should be performed before gadoxetic acid injection, particularly in non-cirrhotic patients.

Index terms
Magnetic Resonance Spectroscopy
Fatty Liver
Gadoxetic Acid
Liver Cirrhosis

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INTRODUCTION

Hepatic steatosis disease affects 10–30% of the general population across all ethnicities and age groups (1-5). This condition is associated with insulin resistance, type 2 diabetes mellitus, and hyperlipidemia (1, 6). Until the last few decades, hepatic steatosis was considered to be a relatively benign and common condition (7). However, hepatic steatosis has the potential to progress to fibrosis, cirrhosis, and hepatocellular carcinoma. The diagnosis may be missed in some individuals because many patients with hepatic steatosis are asymptomatic (8). The initial detection and precise quantification of hepatic steatosis disease is crucial for the successful management of these patients (1, 9).

The current gold standard methods for the detection and quantification of hepatic steatosis are liver biopsy and magnetic resonance spectroscopy (MRS) (10, 11). Liver biopsy has several disadvantages, such as the invasiveness of the procedure, risk of infection, and potential for hemorrhage (7); therefore liver biopsy alone is not recommended for identifying hepatic steatosis disease. MRS measures the chemical composition of a tissue di-

rectly and non-invasively (12, 13). Recently, MRS showed a strong and significant correlation with lipid content, and is regarded as the most accurate practical method for measuring liver fat in clinical practice (14).

Gadoxetic acid (Gd-EOB-DTPA), which offers an innovative option for imaging the liver, is used for improved medical diagnosis with MR imaging. Gadoxetic acid is believed to be actively taken up in hepatocytes by a canalicular multispecific organic anion transporter 8 (15). Approximately 50% of the injected dose of gadoxetic acid is taken up by hepatocytes and subsequently excreted into the biliary canaliculi (16). Peak enhancement of gadoxetic acid is obtained 20 minutes after injection (17), and hepatobiliary phase imaging is performed at this time (15).

A previous study reported that gadoxetic acid does not show a significant effect on measuring fat fractions (FF) between pre-contrast MRS and post-contrast MRS (18). The study had a relatively small sample size and was limited by the retrospective design. Since gadoxetic acid does not affect proton MRS, it could be performed during the interval of the dynamic phase to save time. Therefore, the purpose of this study was to prospectively evaluate whether gadoxetic acid administration for liver MR imaging affects the hepatic steatosis quantification using MRS.

MATERIALS AND METHODS

Patients

This prospective study was approved by the institutional review board of Chonnam National University Hwasun Hospital. Written informed consent was obtained from all patients. In January 2015, a pilot study including 41 patients was conducted to determine feasibility. The mean FF change was 0.27 ± 0.57%. We assumed that a $p < 0.01$ was acceptable with a study power of 95%. The estimated sample size was 83 patients, using a one-sample design. Between February 2015 and June 2015, individuals who were clinically suspected of having focal hepatic lesions were evaluated (Fig. 1). Criteria for inclusion were: 1) age–between 20 to 85 years; 2) exclusion of contraindications to enhanced MR imaging (claustrophobia, metal implants, or pacemakers); and 3) absence of any history of transarterial chemoembolization, radiofrequency ablation, and hepatectomy. After analyzing the abdominal MR images, the following patients were excluded: patients who had diffuse or disseminated hepatic lesions [infiltrative or multinodular hepatocellular carcinoma (HCC), *n* = 20; disseminated metastasis, *n* = 10; numerous cysts *n* = 3, uneven fatty infiltration, *n* = 2] or large lesions replacing liver parenchyma (HCC, *n* = 5; hemangioma, *n* = 2), and patients (*n* = 35) who were not able to hold their breath sufficiently or for whom it was difficult to select a voxel for the analysis. Finally, 155 patients (93 men and 62 women) were included (mean age, 61 yrs; range, 26–85 yrs). The patients had the following underlying liver diseases: hepatitis B (*n* = 40), hepatitis C (*n* = 10), alcohol-induced liver cirrhosis (*n* = 22) and cryptogenic liver cirrhosis (*n* = 5). The patients were divided into two groups: non-cirrhotic (*n* = 78) and cirrhotic (*n* = 77). Liver cirrhosis was diagnosed by a combination of physical findings, biochemical tests, and radiological imaging features. In the cirrhosis group, the severity of cirrhosis was classified according to the Child-Pugh classification. Of the 77 cirrhosis patients, 70 were class A, 6 were class B, and 1 was class C. The other 78 patients were grouped as non-cirrhotic. This group showed no evidence of liver cirrhosis in physical findings, biochemical tests, and radiological imaging features. Hepatic metastasis was detected in 4 patients of the non-cirrhotic group. They were not excluded due to small size and peripheral location of metastasis.

MR imaging and MRS

MR imaging and MRS were performed concomitantly using a 3.0-T unit (MAGNETOM Skyra; Siemens, Erlangen, Germany). Three plain localizers were used to plan the MRS, and the

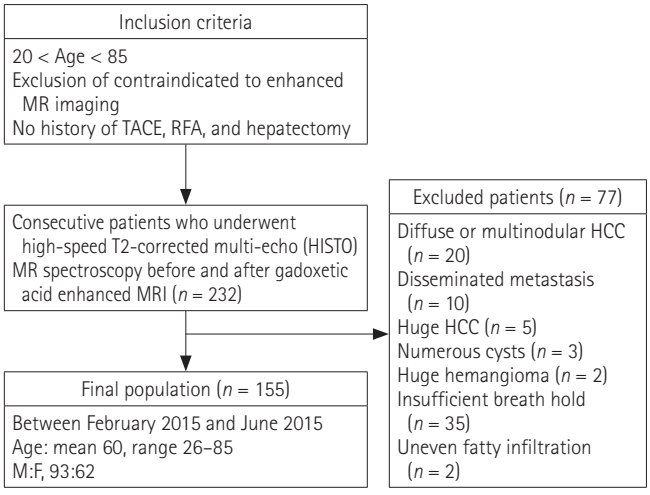


Fig. 1. Flow chart of patient enrollment. HCC = hepatocellular carcinoma, MR = magnetic resonance, RFA = radiofrequency ablation, TACE = transarterial chemoembolization

spectra were obtained using an 18-channel body matrix coil and table-mounted 32-channel spine matrix coil.

An experienced radiologist selected a single voxel of 27 cm^3 (30 × 30 × 30 mm) within the normal liver tissue in segment VIII, VII, or VI, avoiding major vessels, bile ducts, focal hepatic lesions, and the edge of the liver (Fig. 2). MRS was performed twice, using a high-speed T2-corrected multi-echo (HISTO) MR spectroscopic technique: one before and one after contrast intravenous injection. Pre-contrast MRS was performed just before the dynamic phase, and post-contrast MRS was performed 20 minutes after contrast injection. All spectra were obtained with a stimulated echo acquisition mode sequence, setting the following parameters: repetition time = 3000 ms, mixing time = 10 ms, 5 echo times = 12, 24, 36, 48, 72). A total of 2048 points were acquired at a bandwidth of 3000 Hz. Data acquisition was performed within a single breath hold.

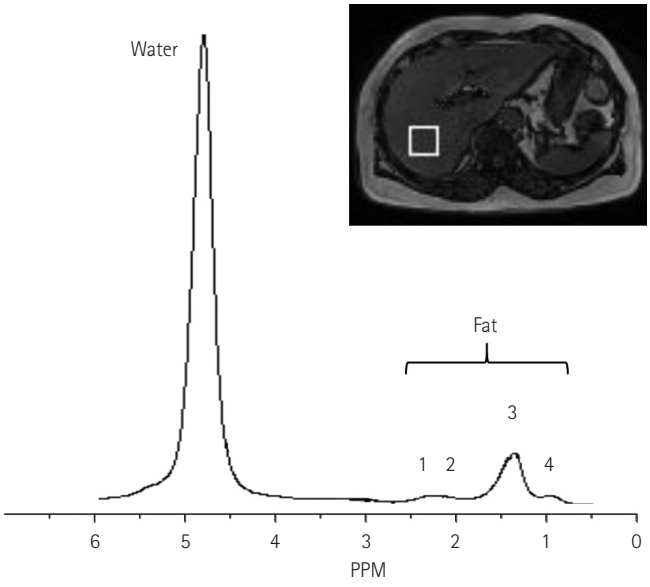


Fig. 2. Hepatic steatosis spectrum of a 77-years-old female with suspicious focal hepatic lesion. Proton of fat appears as several peaks, including a diacyl peak at 2.75 ppm (1), an α-olefinic and α-carboxyl peak at 2.1 ppm (2), a methylene peak at 1.3 ppm (3), and a methyl peak at 0.9 ppm (4). Whereas, proton in water appears as a single peak at 4.7 ppm. Fat fraction can be calculated as (Sum of fat peaks) / (Sum of fat peaks + water peak).

The MR data were analyzed by off-line software from the MR vendor. At the echo time, the water (4.7 ppm) and fat (0.9, 1.3, 2.1, and 2.75 ppm) peaks were measured. Each measurable peak area was individually corrected for the T2 decay using non-linear least-square fits, to determine their relative proton densities. The relative proton densities of the fat peaks located underneath the water peaks were determined according to Hamilton et al. (19). The total proton density was defined as the sum of all T2-corrected individual fat peaks. The proton density FF was calculated as the ratio of the fat proton density to the sum of the fat and water proton densities (Fig. 2).

Biochemical Studies

Common biochemical parameters were considered for serum markers, such as creatinine, urea, albumin, prothrombin time, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase, alkaline phosphatase (APH), gammaglutamyl transpeptidase, Child–Pugh class, and Model for End Stage Liver Disease (MELD) score. The MELD score was calculated using the following formula: 11.2 × loge (INR) + 9.57 × loge (creatinine, mg/dL) + 3.78 × loge (bilirubin, mg/dL) + 6.43, where INR is the international normalized ratio, the lower bound for all three variables is 1, and the upper bound for creatinine is 4 mg/dL (20). In all patients, the serum markers were measured in the same laboratory and on the same day that the MR imaging was performed.

Statistical Analysis

The changes in the calculated FF between the pre-contrast MRS and the post-contrast MRS were compared using the paired *t*-test. The FF change between the cirrhotic group and the non-

Table 1. The Mean FFs and the Changes in the FF between Pre-Contrast MRS and Post-Contrast MRS

Group	Mean FF (Mean ± SD, %)		Change of FF (Mean ± SD, %)	*p*-Value
	Pre-Contrast MRS	Post-Contrast MRS		
Non-cirrhosis (*n* = 78)	5.47 ± 5.66	5.88 ± 5.94	0.41 ± 0.68	< 0.000
Cirrhosis (*n* = 77)	4.05 ± 4.31	4.20 ± 4.33	0.15 ± 0.59	0.032
Child A (*n* = 70)	4.08 ± 4.37	4.25 ± 4.36	0.17 ± 0.59	0.020
Child B (*n* = 6)	3.70 ± 4.23	3.57 ± 4.72	-0.13 ± 0.62	0.620
Child C (*n* = 1)	4.0	4.30	0.30	
Total (*n* = 155)	4.77 ± 5.07	5.05 ± 5.26	0.28 ± 0.65	< 0.000

FF = fat fraction, MRS = magnetic resonance spectroscopy, SD = standard deviation

cirrhotic group were compared using an independent *t*-test. In the cirrhotic group, the FF changes between the Child-Pugh classifications were compared using the Mann Whitney U test. The correlation between the change in the FF and the blood markers were assessed using Pearson's correlation test. A p value < 0.05 was considered significant. The SPSS version 21 software package (SPSS, Chicago, IL, USA) and MedCalc version 15.8 (MedCalc Software Inc., Mariakerke, Belgium) were used for analysis.

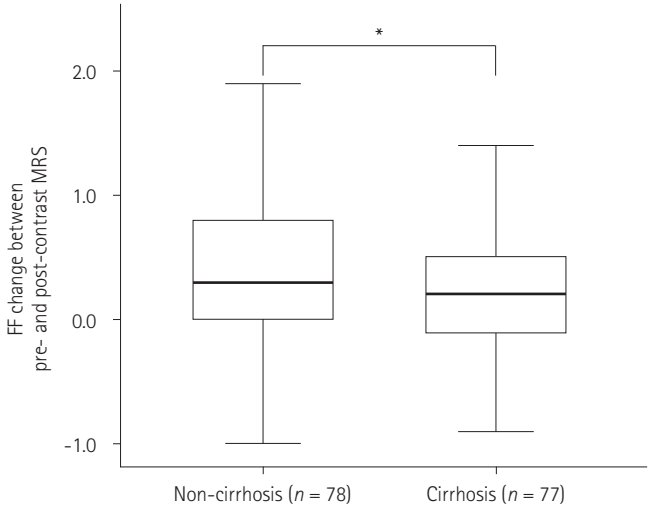


Fig. 3. Relationship between the FF change and liver cirrhosis in the entire patient cohort. The mean value is significantly higher for patients in the non-cirrhotic group (*p < 0.000). The lower edge of each box indicates the 25th percentile, and the upper edge indicates the 75th percentile. The horizontal line in the middle of the box indicates the median. Lines extending from either end of the box indicate the extent of the data beyond the 25th and 75th percentile but within 1.5-times the interquartile range. Outliers were not noted. FF = fat fraction, MRS = magnetic resonance spectroscopy

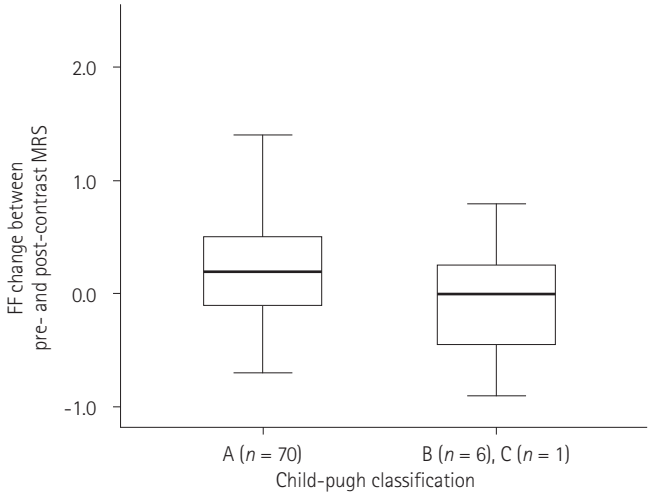


Fig. 4. Relationship between the changes in FF and the Child-Pugh class in the cirrhotic group (n = 77). No significant difference of FF change is observed between Child-Pugh classification A vs. B and C (Child-Pugh A, 0.17 ± 0.58; B and C, -0.71 ± 0.59) (p = 0.856). FF = fat fraction, MRS = magnetic resonance spectroscopy

RESULTS

The mean FFs of the entire study population in pre-contrast and post-contrast MRS are shown in Table 1. In the 155 patients, the mean FF was 4.77 ± 5.07% (range, 0.4–25.5%) and 5.05 ± 5.26% (range, 0.5–26.8%) on pre-contrast and post-contrast MRS, respectively. The FF values in the post-contrast MRS were significantly higher than that in the pre-contrast MRS (p < 0.000). The FF values in the post-contrast MRS were significantly higher than those in the pre-contrast MRS in the non-cirrhotic group (p < 0.000) as well as in the cirrhotic group (p = 0.032).

The FF change in the non-cirrhotic group between the pre- and post-contrast MRS was significantly higher than that in the cirrhotic group (p = 0.010). The relationship between the FF change and cirrhosis is shown in Fig. 3 (non-cirrhosis, 0.41 ± 0.77; cirrhosis, 0.14 ± 0.59). The relationship between the FF change and the Child-Pugh classification in cirrhotic group is shown in Fig. 4 (Child-Pugh A, 0.17 ± 0.58; B and C, -0.71 ± 0.59). No significant change in FF was observed between Child-Pugh classification A vs. B and C (p = 0.856). Correlation between the FF change and the biochemical markers are shown in Table 2. In the liver cirrhosis group, APH and albumin show weak correlation with the FF change (Fig. 5).

DISCUSSION

The mean FF was 4.77 ± 5.07% and 5.05 ± 5.26% on pre-contrast and post-contrast MRS, respectively. There was a significant change in the FF between the pre- and post-contrast MRS (p < 0.000). This suggests that gadoxetic acid influences the hepatic steatosis quantification using MRS. In post-contrast MRS, mean FF was more exaggerated than pre-contrast MRS by 0.28 ± 0.65%. Since MRS performed after gadoxetic acid enhanced the MR sequence, overestimation of FF and resultant false-positive diagnosis can be obtained. In the clinical field this can be negligible, thus making it insignificant whether hepatic quantification using MRS is performed before or after gadoxetic acid administration. However, for precise examination, hepatic steatosis quantification using MRS should be performed before

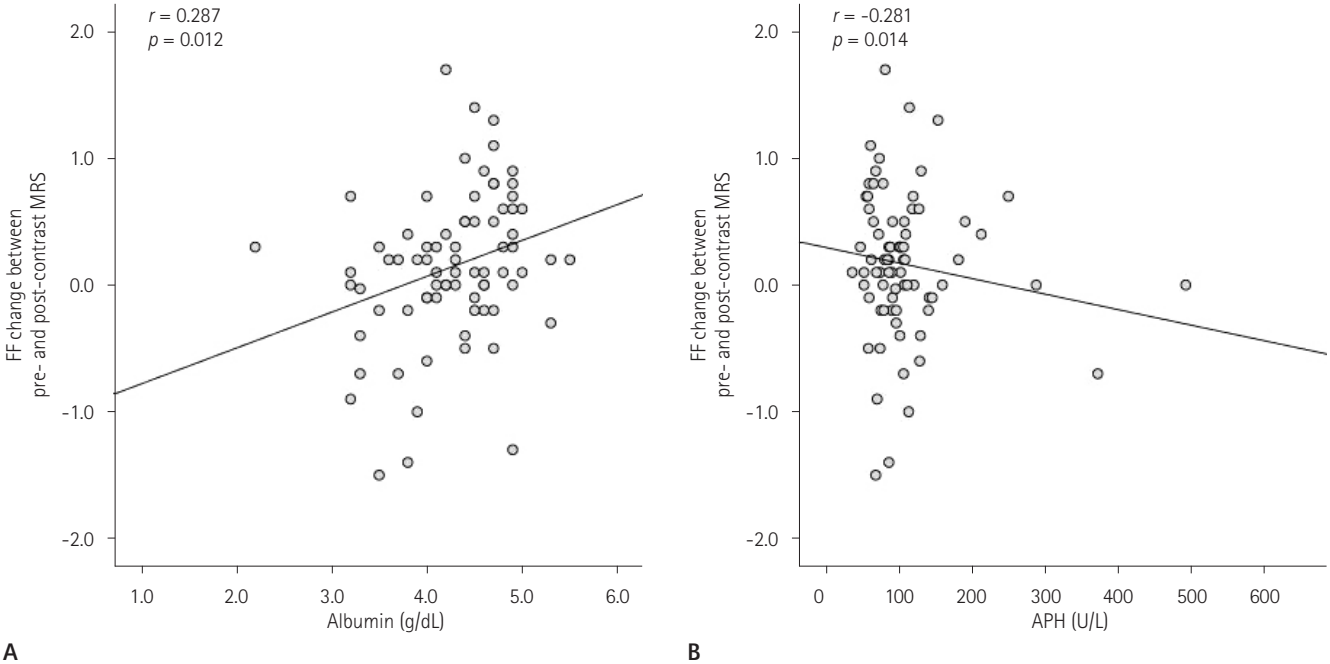
gadoxetic acid injection, or after a sufficient interval to allow for the excretion of gadoxetic acid.

A previous study, which used the same MR scanner with a similar protocol, showed that the mean FF was 6.50 ± 0.51% on pre-contrast MRS, and 6.70 ± 6.61% on post-contrast MRS. However, a significant difference was not observed in the mean FF between the pre- and post-contrast MRS (18). The mean FF changes between the pre- and post-contrast MRS showed a slight difference of 0.20% in a previous study and of 0.28% in our study. Compared to the previous study, our study differed in two points. First, the size of the cohort in our study was double than of the previous study. Second, our prospective study had stricter

Table 2. Relationships between Clinical Factors and the Changes in the Fat Fraction between Pre-Contrast MRS and Post-Contrast MRS

Parameter	Total Cohort				Liver Cirrhosis Group			
	Mean	SD	Correlation Coefficient	*p*-Value	Mean	SD	Correlation Coefficient	*p*-Value
Age (years)	60.4	11.0	*r* = -0.137	0.089	62.5	9.7	*r* = -1.149	0.197
Platelet count (10^3/μL)	212.8	85.3	*r* = 0.146	0.072	181.1	88.5	*r* = 0.192	0.097
Prothorombin time (INR)	1.1	0.4	*r* = -0.052	0.554	1.1	0.19	*r* = -0.029	0.806
Total bilirubin (mg/dL)	0.8	0.9	*r* = -0.035	0.678	0.9	0.6	*r* = -0.183	0.117
Albumin (g/dL)	4.3	0.8	*r* = 0.151	0.074	4.2	0.8	*r* = 0.287	0.012*
AST (U/L)	45.0	54	*r* = -0.084	0.305	54.0	55.7	*r* = -0.145	0.211
ALT (U/L)	34.2	44.2	*r* = 0.029	0.720	37.8	38.1	*r* = -0.015	0.897
APH (U/L)	112.7	132.2	*r* = -0.163	0.061	121.4	135.6	*r* = -0.281	0.014*
Sodium (mEq/L)	141.6	2.9	*r* = 0.185	0.122	141.8	2.8	*r* = 0.168	0.166
Creatinine (mg/dL)	0.9	0.2	*r* = -0.048	0.554	0.9	0.2	*r* = -0.157	0.177
Child-pugh (score)	5.3	0.8	*r* = -0.045	0.579	5.3	0.8	*r* = -0.132	0.254
MELD (score)	8.3	2.8	*r* = -0.082	0.355	8.5	2.3	*r* = -0.153	0.188

*p-value < 0.05. ALT = alanine aminotransferase, APH = alkaline phosphatase, AST = aspartate aminotransferase, MELD = Model for End-Stage Liver Disease, MRS = magnetic resonance spectroscopy, SD = standard deviation



A B

Fig. 5. Scatter plots of the correlation in the liver cirrhosis group.
A. The relationship between alkaline phosphatase and FF change.
B. The relationship between albumin and FF change.
APH = alkaline phosphatase, FF = fat fraction, MRS = magnetic resonance spectroscopy

inclusion and exclusion criteria. Hence, our data would be more reliable due to the difference in the size of the sample and the characteristics of the cohort in our study.

As shown in Fig. 2, the MRS spectra of the liver reveals a single peak of proton in water appearing at 4.7 ppm, and multiple peaks of proton in triglyceride appear at 1.3 ppm (methylene), 0.9 ppm (methyl), 2.1 ppm (α-olefinic and α-carboxyl), and 2.75 ppm (diacyl) (12, 19). In Fig. 6, predicted MRS spectra of gadoxetic acid shows several peaks at similar frequency at 1.3 and 2.75 ppm, by MestReNova LITE Ver. 5.2.5-5780 (Mestrelab Research S.L., Santiago de Compostela, Spain) as the MRS processing software. Thus, we can explain that calculated FF of liver could be overestimated by overlapped fat spectra of gadoxetic acid.

Impaired gadoxetic acid uptake and transport mechanisms in cirrhotic liver reduce the liver parenchymal enhancement (21). Impaired uptake by hepatocytes in cirrhotic liver tissue may reduce the change in FF detected between pre- and post-contrast MRS. In our study, the change in FF in the non-cirrhotic group between the pre- and post-contrast MRS was significantly higher than that of the cirrhotic group. Although the severity of cirrhosis can be assessed by measuring the relative enhancement of gadoxetic acid (22), our data showed that it cannot be assessed by the FF change between pre-contrast and post-contrast MRS.

We observed a non-significant difference of approximately 0.9% in the FF change between patients with mild liver cirrhosis (Child A) and those with moderate to severe liver cirrhosis (Child B and C). This result may be related to the very small proportion of patients with severe liver cirrhosis, in our inclusion cohort. Therefore, we expect that a future study which includes more patients with moderate to severe liver cirrhosis will demonstrate a correlation between the FF change and the severity of liver cirrhosis.

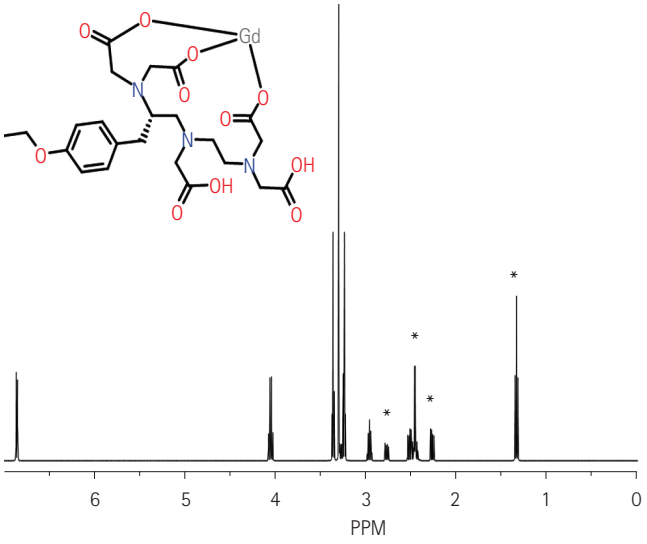


Fig. 6. Molecular structure and predicted MR spectra of gadoxetic acid. Several peaks (*) are located in similar frequencies with triglyceride in hepatocyte (Fig. 2). We hypothesize that these peaks may produce overestimation of fat fraction on post-contrast MRS. MRS = magnetic resonance spectroscopy

Several studies have investigated the clinical or histologic factors that cause decreased hepatic enhancement on gadoxetic acid-enhanced MR imaging (22-26). Among various parameters, the indocyanine green retention rate, AST, platelet count, prothrombin activity, total bilirubin, albumin, sodium, MELD score, MELD-Na score, Child-Pugh score, and the presence of ascites are important factors correlated with liver enhancement (22-26). We expected that these parameters may be correlated with the change in the calculated FF. In total cohort, none of these biochemical markers showed a significant correlation with the FF change. However, APH shows a weak negative correlation, and albumin shows a weak positive correlation, with the FF change. These results support that impaired hepatocyte function may reduce the FF change as well as reduce the liver parenchymal enhancement.

Our study has several limitations. First, the proportion of patients with severe liver cirrhosis was relatively small. Only 9% of cirrhosis patients are Child-Pugh classification B or C. We suspect that the insufficient number of patients with severe cirrhosis prevented the detection of a significant change in FF among the Child Pugh classifications, and significant correlation of FF change with most of biochemical markers. Second, the location of the region of interest was slightly different between the pre- and post-contrast MRS. In spite of our effort to instruct the patients to hold their breath to the same degree, minor differences were inevitable. To overcome this limitation, several patients with an insufficient ability to hold their breath were excluded. Third, this study did not yield reproducible analysis . We performed MRS just two times in a patient, once before and once after administration of gadoxetic acid, because several recent studies demonstrated good reproducibility and feasibility of hepatic fat quantification using MRS (10, 18, 27).

In conclusion, gadoxetic acid influenced hepatic steatosis quantification using MRS. Our results suggest that there is a risk

of overestimation of hepatic steatosis and false-positive diagnosis when MRS is performed after gadoxetic acid injection. For precise quantification of hepatic steatosis, MRS should be performed before intravenous gadoxetic acid injection or after a sufficient interval, to allow for the excretion of gadoxetic acid, particularly in non-cirrhotic patients.

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Gadoxetic Acid가 자기공명분광술을 이용한 지방간의 정량화에 미치는 영향: 전향적 분석

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목적: Gadoxetic acid의 사용이 자기공명분광술(magnetic resonance spectroscopy; 이하 MRS)을 이용한 지방간의 정량화에 미치는 영향을 분석하고자 하였다.

대상과 방법: 전향적인 연구를 시행하였으며 155명의 환자가 등록되었다. Fast breath-hold high-speed T2-corrected multi-echo기법의 MRS를 이용하여, gadoxetic acid 주입 전과 주입 후 20분에 한번씩, 동일한 위치에서 지방분율을 측정하였다. Gadoxetic acid 주입 전과 후에 지방분율의 변화가 있는지 비교하였고, 간경화 유무와 Child-Pugh classification에 따라서 지방분율 변화에 차이가 있는지 비교하였다.

결과: Gadoxetic acid 주입 후 MRS에서 측정된 평균 지방분율(5.05 ± 5.26%)은 gadoxetic acid 주입 전 MRS에서 측정된 평균 지방분율(4.77 ± 5.07%)과 비교하여 유의하게 높았다($p < 0.000$). Gadoxetic acid 주입 전과 후의 지방분율의 차이는 정상환자군(0.41 ± 0.77%)이 간경화환자군(0.14 ± 0.59)에 비하여 유의하게 높았다($p = 0.010$). Albumin과 alkaline phosphatase가 지방분율의 변화와 유의한 상관관계를 보였다.

결론: Gadoxetic acid는 MRS를 이용한 지방간의 정량화에 영향을 미치며, 특히 간경화가 없는 환자에서 그 영향이 더 크다. 그러므로, MRS를 이용한 지방간의 정량화는 gadoxetic acid 주입 전에 시행되어야 한다.

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