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Estimating of hepatic fat amount using MRI proton density fat fraction in a real practice setting

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Abstract

The recently developed magnetic resonance imaging (MRI) proton density fat fraction (PDFF) allows measurement of the fat in all segments of hepatic tissue. However, it is time consuming and inconvenient to measure each segment repeatedly. Moreover, volume of each segment also should be adjusted with arithmetic mean of the selected segments when total amount of liver fat is estimated. Therefore, we try to develop a clinically-relevant and applicable method of estimating hepatic fat in PDFF image.

A total of 164 adults were enrolled. We addressed the measurement frequency and segment selection to determine the optimal method of measuring intrahepatic fat. Total hepatic fat was estimated by the weighted mean of each segment reflecting their respective segmental volumes. We designed 2 models. In Model 1, we determined the segment order by which the mean was closest to the whole weighted mean. In Model 2, we determined the segment order by which the arithmetic mean of the selected segments was closest to the whole weighted mean.

Fat fraction (FF) was most important risk factor of hepatic heterogeneity in multivariable analysis ($\beta = 0.534$, $P < .001$). In severe fatty liver (FF > 22.1%), intrahepatic fat variability was 2.47% (1.16–6.26%). The arithmetic mean total intrahepatic FF was 12.66%. But the weighted mean that applied to each segmental volume was 12.90%. In Model 1, arithmetic mean of segments 4 and 5 was closest to the total estimated hepatic fat amount. However, when we added segment 8, the mean of segments 4, 5, and 8 was significantly different from the estimated total hepatic fat amount ($P = .0021$). In Model 2, arithmetic mean of segments 4 and 5 was closest to the total estimated hepatic fat amount. There was a significant reduction in variability between segment 4 and segments 4 and 5 ($P < .0001$).

Averaging the mean hepatic FF of segments 4 and 5 was the most reasonable method for estimating total intrahepatic fat in practice.

Abbreviations: BMI = body mass index, FF = fat fraction, ICC = intraclass correlation, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, NAFLD = non-alcoholic fatty liver disease, PDFF = proton density fat fraction, ROI = region of interest, SD = standard deviation.

Keywords: fat, magnetic resonance spectroscopy, measurement, non-alcoholic fatty liver disease, proton density fat fraction

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KEY POINTS

- Intrahepatic fat distribution is heterogeneous.
- Mean fat fraction was significantly higher in the right lobe than it was in the left. The left lobe had more variability than did the right lobe.
- Higher variability of intrahepatic fat deposition was associated with younger age, higher BMI, degree of steatosis, higher cholesterol and triglyceride levels.
- Averaging means of fat fraction in segments 4 and 5 were most reasonable to estimate total hepatic amount.

1. Introduction

Liver biopsy is the gold standard in the diagnosis of non-alcoholic fatty liver disease (NAFLD). However, it is an invasive procedure that carries the risk of pain, hemorrhage, infection, and even death. There may also be sampling bias and inter-observer variability in liver biopsies.[1,2] Therefore, noninvasive methods in the diagnosis of NAFLD would be preferable. Recently, there have been significant developments in the methods of hepatic fat measurement.[3,4] Magnetic resonance (MR) spectroscopy is widely regarded as the most accurate noninvasive method to measure hepatic fat.[5] However, MR spectroscopy is time consuming to perform and analyze, requires a specialist, and typically only samples a portion of the liver.[6] Recently, an MRI-based technique measuring the proton density fat fraction (FF) was developed. This technique is considered an alternative method to MRS, because MRI can accurately (and quickly) measure the fat amount in all hepatic areas, and post-processing is easier and faster than that with MRS.[5,7] Recently, many papers regarding measurement of intrahepatic fat using magnetic resonance imaging-proton density fat fraction (MRI-PDFF) have been published.[1,6,8–11] Tang et al[6] compared MRI-PDFF with liver biopsy, and found that the histologic steatosis grade was correlated to the FF using MRI-PDFF. MRI-PDFF can distinguish steatosis with moderate sensitivity (54–96%) and high specificity (81–100%).

One of most important advantage of the MRI-PDFF over ^{1}H-MRS (in addition to its wide availability) is its ability to measure all liver segments. Variability of hepatic fat distribution is also important issue when estimate total liver fat amount. Previous studies using MRI-PDFF demonstrated heterogeneity in the intrahepatic fat distribution. According to this result, the mean PDFF was higher in the right lobe than the left. In contrast, the mean PDFF variability was higher in the left lobe than the right. Segment II had the lowest mean segmental PDFF, while segment VIII had the highest. The difference value between the 2 segments was 1.9%.[9] However, there are no guidelines to estimate the total hepatic amount.

In order to assess the intrahepatic fat amount using MRI-PDFF, it is ideal to measure the FF repeatedly in all 8 segments. The average of each segmental value is then considered with regard to its respective segmental volume. Previous studies assessed hepatic fat using a region of interest in each of the 8 segments.[12] However, it is time consuming and inconvenient to measure each segment repeatedly. Moreover, volume of each segment also should be adjusted with arithmetic mean of the selected segments when total amount of liver fat is estimated. Segment VIII is largest and segment I is smallest. Segment VIII volume was 6 times higher than segment I (4.0% vs 26.1%).[13] So simple arithmetic mean from 8 segments can't represent real total liver fat amount. Therefore, now there is a need for standardization with regard to measurement frequency and which particular segments to measure.

No prior studies have addressed the ideal method of fat measurement, or which segment is most appropriate to measure. Therefore, we sought to comprehend hepatic fat distribution and the factors influencing it. Furthermore, we suggest a practical method to measure hepatic fat using MRI-PDFF in a clinical setting.

2. Method

2.1. Subjects

This is a cross-sectional study. We analyzed baseline data from 164 participants who underwent MRI-PDFF for intrahepatic fat measurement in 2 randomized clinical trials. The 2 intervention studies that we included were chronic liver disease (KCT 0001480) and obesity (KCT 0001588) trials. Both were single-center studies. Written informed consent was obtained from all participants. The study protocol was approved by the institutional review board of Hanyang University Hospital. This clinical trial was registered in the Korean Clinical Research Information Service (https://cris.nih.go.kr/cris/index.jsp; KCT 0001480, and KCT 0001588).

2.2. Inclusion criteria

All participants were adults between the ages of 19 and 75 years. Obesity was defined as a body mass index of 25 or greater. Participants with recent diagnoses of non-alcoholic fatty liver disease were included. Exclusion criteria included a prior diagnosis of fatty liver with previous education regarding diet, exercise, etc. Significant alcohol consumption was defined as 140 g/wk for men, and 70 g/wk for women.

2.3. Exclusion criteria

The exclusion criteria were as follows: >10% weight loss in 6 months; subjects who received diet or exercise therapy that may influence the hepatic fat distribution within 3 months; positive hepatitis B virus or hepatitis C virus; anorexia nervosa or bulimia nervosa; and use of medications (including diuretics, amphetamine, cyproheptadine, phenothiazine, probiotics, appetizer, anorectic agents) that may influence absorption, metabolism, or elimination within 2 weeks.

2.4. MRI-PDFF settings

A 3 T MR scanner (Ingenia; Philips Healthcare, Best, The Netherlands) was used. A three-plane localization imaging gradient echo sequence was obtained first. Next, an mDIXON-Quant sequence was obtained in a single breath hold. The mDIXON-Quant sequence can automatically reconstruct the PDFF map. The parameters of this sequence were as follows: 6 TEs (first TE 0.98 ms, delta TE 0.8 ms) and TR 6.3 ms, flip angle 3°, parallel imaging SENSE factor 2, number of signal average 1. Matrix size 300×300, field-of-view (FOV) 350×350 mm, number of slices 60, slice thickness 3 mm. We developed maps of water, fat, FF, R2* and T2* by post-processing the acquired images using a manufacture offering software.

2.5. Measurement of intrahepatic FF

One radiologist (with 5 years of experience) manually placed 3 non-overlapping regions of interest. These regions were approximately 100 mm^2 in size at each liver segment of the FF map. They were oriented to avoid the major vessels, bile ducts, and imaging artifacts. The right lobe included segments V, VI, VII, and VIII, and the left lobe included I, II, III, and IV. Twenty-four regions of interest (ROIs) were created. We measured the mean fat amount and standard deviation at each segment, lobe, and whole liver. We calculated the weighted mean for each segment with regard to their segmental volumes, and with reference to a previous study that measured intrahepatic segmental volumes using three-dimensional (3D) perfusion-based volumetry.[13] We characterized each case by fatty grade using MRI with reference to a previous study: Grade 1 (6.5–17.5%), Grade 2 (17.5–22.1%), and Grade 3 (>22.1%).[6,10]

2.6. Visceral fat measurement using MRI

One radiologist manually placed the ROIs at the level of the umbilicus in axial T2-weighted images using Rapidia 2.8 (INFINITT, Seoul, Korea). This radiologist also measured visceral fat and total abdominal fat. All of the clinical data and MRI scans were blinded. Visceral fat was defined as abdominal fat that is bounded by parietal peritoneum (or transversalis fascia). Subcutaneous fat was calculated as the difference between total abdominal fat and visceral fat.

2.7. Biochemical tests

After 8 hours of fasting, the following laboratory values were measured: total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), glucose, insulin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT)

2.8. Estimating the total hepatic FF

We addressed the measurement frequency and segment selection to determine the optimal method of measuring intrahepatic fat. First, total hepatic fat was estimated by the weighted mean of each segment reflecting their respective segmental volumes.[13] We designed 2 models. In Model 1, we selected the segment with the nearest fat value to the whole weighted mean. We then decided on the segment's order by the fat value closest to the whole weighted mean. In Model 2, we selected the segment with the nearest fat value to the whole weighted mean. We then decided the segment order that the arithmetic mean of the selected segments was close to the whole weighted mean. In these 2 models, we made segment's order and added 1 of segment $\times$ 1 of segment according to each order. We then calculated the arithmetic mean of the selected segments and compared these combinations with the whole weighted mean to determine which combination was closest to the whole weighted mean. The detailed method is described below.

First, total intrahepatic fat (T) was estimated based on the weighted mean of each segment, reflecting the segmental volumes. The mean and volume of the segments i were represented by T_i, V_i, respectively. The weighted value reflecting segmental volume is represented by W_i. The intrahepatic fat was estimated according to the following equation:

$$T = W_1T_1 + W_2T_2 + \cdots + W_8T_8, \text{ where } W_i = \frac{V_i}{V_1 + \cdots V_8}$$

Next, we chose a segment in which T_i is closest to T. The selection of the adding segment was processed as in the 2 following models:

Model 1. Adding segments in the order of which T_i is closest to T.

Model 2. Adding segments in the order of which the arithmetic mean (A_i) of T_i is closest to T.

After selection of the adding segment, we increased the frequency, and calculated the arithmetic mean (A_i) of the selected segments. For example, if T_i is given in the order $k \rightarrow l \rightarrow m \rightarrow \ldots$, then the arithmetic means (A_i) are defined as follows:

$$A_1 = T_k$$
$$A_2 = \frac{1}{2}(T_k + T_l)$$
$$A_3 = \frac{1}{3}(T_k + T_l + T_m)$$
$$\vdots$$

After assessing the similarity between A_i and the whole weighted mean (T), we assessed the variability of A_i to determine whether there is significant reduction of variability with increasing measuring frequency. Finally, we attempted to determine the measurement frequency and segment selection based on the assessment results.

2.9. Statistical analysis

The following characteristics were summarized: intrahepatic fat distribution, baseline laboratory data, and body mass index. We examined the potential risk factors of fat distribution variability, such as non-alcoholic fatty liver disease, age, and sex using univariable and multivariable linear regression analyses. In order to assess differences in fat amount between segments, 3 ROIs were measured and averaged in each of the 8 segments. We also compared the segment means and SDs in the repeated measurement analysis using the linear mixed effects model.[14] The 8 segments were compared by 2 segments using contrast tests in multiple comparison.[15,16] Next, in order to determine the optimal method of measuring intrahepatic fat, the arithmetic means and SDs of selected sections were also assessed by contrast tests in the repeated measurement analysis using the linear mixed effects model. P values <0.05 were considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics and intrahepatic fat distribution

There were a total of 164 subjects with a mean age of 44 years. There was a relatively even sex distribution. With regard to the etiology of fatty liver, 92 patients had non-alcoholic fatty liver disease, 21 alcoholic steatohepatitis, 14 liver cirrhosis, and 37 had simple obesity or other liver disease (Table 1). The mean segmental fat amount was significantly different across each segment (Table 2). Therefore, we compared each 2 segments using a priori comparison. Again, most segments had significant differences (Supplemental Figure 1, http://links.lww.com/MD/B830). Mean total intrahepatic fat was 12.66%. Segment II had the lowest mean segmental FF, while segment VII had the highest. Comparing the right and the left

Table 1

Baseline characteristics.

n	164
Age, yr	44.84 ± 13.98
Male: female, %	83 (50.6)
Etiology	
NAFLD	92
Alcoholic fatty liver	21
Cirrhosis	14
Other	37
Body mass index, kg/m^2	28.40 ± 5.05
Triglyceride, mg/dL	165.7 ± 114.8
HDL, mg/dL	45.53 ± 13.08
Cholesterol, mg/dL	194.7 ± 41.81
Glucose, mg/dL	110.3 ± 47.96
AST, U/L	66.04 ± 104.16
ALT, U/L	72.67 ± 83.66
BUN, mg/dL	13.25 ± 4.15
HOMA-IR	70.8 ± 102.8
Creatinine, mg/dL	0.99 ± 1.87
Total body fat (%)	37.6 ± 7.0
Skeletal muscle mass, kg	28.4 ± 7.1
Visceral fat area, cm^2	153.2 ± 58.5
Abdominal fat area, cm^2	346.0 ± 91.3

Mean ± SD, n(%).

ALT = alanine transaminase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, HDL = high density lipoprotein, HOMA-IR = homeostasis model assessment-insulin resistance, NAFLD = non-alcoholic fatty liver disease.

lobe, the mean FF was significantly higher in the right lobe than it was in the left ($P < .0001$). Segment VI had the lowest mean segmental variability, while segment II had the highest (Supplemental Figure 2, http://links.lww.com/MD/B830). The left lobe had more variability than did the right lobe ($P < .0001$).

3.2. Risk factors affecting intrahepatic fat variability

We analyzed the factors influencing fat distribution variability. In univariable analysis, higher variability was associated with younger age, higher BMI, higher FF, higher cholesterol, and higher triglyceride level. Visceral fat and total fat were not correlated with the variability of intrahepatic fat distribution. Fat fraction was the only significant risk factor influencing the variability of intrahepatic fat distribution in multivariable analysis ($\beta = 0.436$, $P < .001$) (Table 3).

There was no significant difference in fat distribution variability between non-alcoholic fatty liver disease and alcoholic steatohepatitis (NAFLD: 1.71 ± 0.96 vs ASH 1.87 ± 0.98, $P = .36$). Men had higher fat variability than did women (man: 1.88 ± 1.08 vs woman: 1.47 ± 0.78, $P = .007$). However, this difference was not significant after we adjusted variability for intrahepatic FF ($P = .063$).

Table 2

Heterogeneity of FF (%) in MRI: mean and variability (SD).

	Fat fraction	Significantly different segments*	Variability (SD)	Significantly different segments*
Segment I	11.88 ± 9.98	II,IV,V,VI,VII,VIII	0.91 ± 0.72	V,VI,VII,VIII
Segment II	11.30 ± 9.70	I,III,IV,V,VI,VII,VIII	1.01 ± 0.66	IV,V,VI,VII,VIII
Segment III	12.01 ± 10.36	II,IV,V,VI,VII,VIII	0.99 ± 0.72	IV,V,VI,VII,VIII
Segment IV	12.79 ± 10.32	I,II,III,V,VI,VII,VIII	0.82 ± 0.67	II,III,V,VI,VII
Segment V	13.05 ± 10.59	I,II,III,IV,VI,VII,VIII	0.69 ± 0.45	I,II,III,IV,VI
Segment VI	13.48 ± 10.33	I,II,III,IV,V	0.57 ± 0.39	I,II,III,IV,V,VIII
Segment VII	13.51 ± 9.89	I,II,III,IV,V	0.64 ± 0.44	I,II,III,IV
Segment VIII	13.29 ± 10.15	I,II,III,IV,V	0.74 ± 0.64	I,II,III,VI
Right lobe	13.33 ± 10.1	<0.0001†	1.13 ± 0.63	<0.0001†
Left lobe	12.00 ± 10.24		1.52 ± 0.97	
Whole liver	12.66 ± 10.19	–	1.69 ± 0.97	–

Mean ± SD.

* $P < .05$ by the contrast test in the linear mixed model.

† P value by the contrast test in the linear mixed model.

Table 3

Univariable and multivariable analyses affecting to the variability of intrahepatic fat distribution.

	Univariable			Multivariable		
	β	*P	95% CI	β	*P	95% CI
Age, yr	**−0.203**	**.009**	**(−0.025, −0.004)**	−0.055	.480	(−0.104, 0.007)
Sex	**−0.021**	**.007**	**(−0.070, −0.116)**	−0.095	.222	(−0.475, 0.111)
Etiology	0.074	.359	(−0.188, 0.514)			
BMI, kg/m^2	**0.254**	**.002**	**(0.019, 0.078)**	0.050	.526	(−0.020, 0.039)
Fat fraction, %	**0.534**	**<.001**	**(0.039, 0.065)**	**0.436**	**<.001**	**(0.026, 0.058)**
Cholesterol, mg/dL	**0.209**	**.009**	**(0.001, 0.008)**	0.023	.787	(0.0003, 0.004)
Triglyceride, mg/dL	**0.176**	**.029**	**(0.001, 0.003)**	0.035	.665	(−0.001, 0.002)
Glucose, mg/dL	−0.043	.589	(−0.004, 0.002)			
AST, U/L	−0.068	.393	(−0.002, 0.001)			
ALT, U/L	−0.089	.268	(−0.003, 0.001)			
Insulin, μU/mL	−0.005	.948	(−0.012, 0.011)			
HOMA, mg/dL	−0.014	.865	(−0.002, 0.001)			
Viceral fat	0.091	.456	(0.000, 0.000)			
Total fat	0.081	.648	(0.000, 0.000)			
Total fat (%)	−0.147	.231	(−0.050, 0.012)			

ALT = alanine transaminase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence intervals, HOMA = homeostasis model assessment.

* $P < .05$ by linear regression analysis.

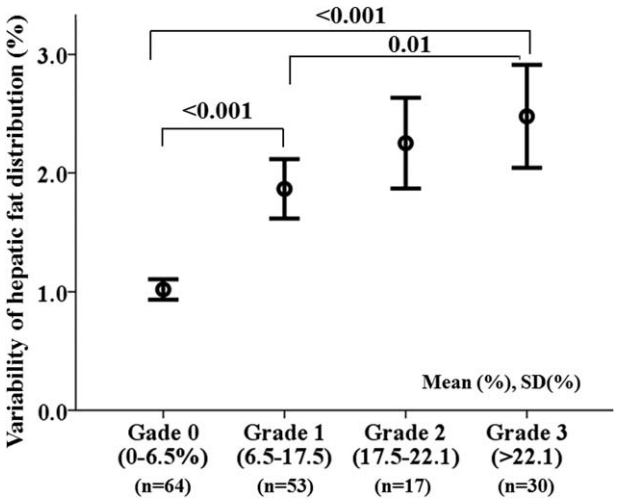

Figure 1. Intrahepatic fat variability according to degree of steatosis. Boxplot graphs show the intrahepatic fat variability according to fat grades. There were significant differences between grades 0 and 1 ($P < .001$), grades 1 and 3 (P value .01), and grades 0 and 3 ($P < .001$).

3.3. Intrahepatic fat variability according to the degree of steatosis

The standard deviation of intrahepatic fat distribution increases with increasing fatty liver grade (Fig. 1). In Grade 0 fatty liver (FF: 0–6.5%), the mean standard deviation of 24 ROIs was 1.0% (range, 0.47–2.01%). In Grade 1 fatty liver (mild fatty liver, FF: 6.5–17.5%), the mean standard deviation of 24 ROIs was 1.86% (range, 0.83–5.95%). In Grade 2 fatty liver (moderate fatty liver, FF: 17.5–22.1%), the mean standard deviation of 24 ROIs was 2.25% (range, 0.92–4.20%). In Grade 3 fatty liver (severe fatty liver, FF: >22.1%), the mean standard deviation of 24 ROIs was 2.47% (range, 1.16–6.26%). In moderate fatty liver or severe fatty liver, the FFs measured at each site had differences of at least 2%.

3.4. Estimating total hepatic fat amount using hepatic proton density FF

We estimated the total intrahepatic FF by averaging the segmental FF with consideration of each respective segmental volume. The arithmetic mean total intrahepatic FF was 12.66%. But the weighted mean that applied to each segmental volume was 12.90%. In order to predict the total intrahepatic FF in the most optimal way, we suggested 2 models of combining the segments and measuring frequency. In Model 1, we determined the segment order by which the mean was closest to the whole weighted mean. In Model 2, we determined the segment order by which the arithmetic mean of the selected segments was closest to the whole weighted mean.

In Model 1, the segment's order was as follows: segment 4 > segment 5 > segment 8 > segment 6 > segment 7 > segment 3 > segment 1 > segment 2. In Model 1, mean of each selected segment is described in Table 4. The arithmetic mean of segments 4 and 5 was closest to the total hepatic fat amount (Fig. 2A). There was no significant difference between the arithmetic means of segments 4, 5, and the whole weighted hepatic fat amount using the paired t test ($P = .7063$). However, when we added segment 8, the mean of segments 4, 5, and 8 was significantly different from the estimated total hepatic fat amount ($P = .0021$). We estimated the dispersion of the arithmetic mean of selected segments with increasing frequency (Fig. 2B). We used the linear mixed effects model in the repeated measurement analysis to determine whether there was a significant reduction with increasing frequency. There was a significant reduction in dispersion between segment 4 and segments 4 and 5 ($P < .0001$). Also, there were significant reduction in dispersion between segment 4 and 5 and segment 4, 5, and 8 ($P = .0002$) and between segment 4, 5, and 8 and segment 4, 5, 8, and 6 ($P = .0007$). However, there was no significant reduction of dispersion between segments 4, 5, 8, and 6 and segment 4, 5, 8, 6, and 7 ($P = .3075$). In Model 2, the segment's order was as follows: segment 4 > segment 5 > segment 8 > segment 3 > segment 6 > segment 7 > segment 1 > segment 2. The results from Model 2 were similar to those of Model 1. The arithmetic mean of segments 4 and 5 was closest to the total hepatic fat amount

Table 4

Mean and variability (SD) whenever adding segment.

	Number of sampling segment	Including segments	Arithmetic mean (%)	Whole weighted mean (%)*	P†	Variability (SD)	P‡
Model 1	1	4	12.7902	**12.9035**	.0141	0.8241	–
	2	**4,5**	**12.9208**		**.7063**	**0.5646**	**<.0001**
	3	4,5,8	13.0454		.0021	0.4605	**.0002**
	4	4,5,8,6	13.1529		<.0001	0.3646	**.0007**
	5	4,5,8,6,7	13.2235		<.0001	0.3357	.3075
	6	4,5,8,6,7,3	13.0218		.0103	0.3238	.6728
	7	4,5,8,6,7,3,1	12.859		**.3345**	0.3113	.6589
	8	4,5,8,6,7,3,1,2	12.6647		<.0001	0.3037	.7894
Model 2	1	4	12.7902	**12.9035**	.0117	0.8241	–
	2	**4,5**	**12.9208**		**.6988**	**0.5646**	**<.0001**
	3	4,5,8	13.0454		.0016	0.4605	**.0003**
	4	4,5,8,3	12.7875		.0098	0.4289	.2724
	5	4,5,8,3,6	12.925		**.6314**	0.3548	**.0099**
	6	4,5,8,3,6,7	13.0218		.0084	0.3238	.281
	7	4,5,8,3,6,7,1	12.859		**.3218**	0.3113	.6638
	8	4,5,8,3,6,7,1,2	12.6647		<.0001	0.3037	.7925

* Whole liver FF is estimated by weighted mean of 8 segments.

† Comparison with respect to the estimated whole liver FF by the contrast test in the linear mixed effects model.

‡ Comparison with respect to the former segment group's FF by the contrast test in the linear mixed effects model.

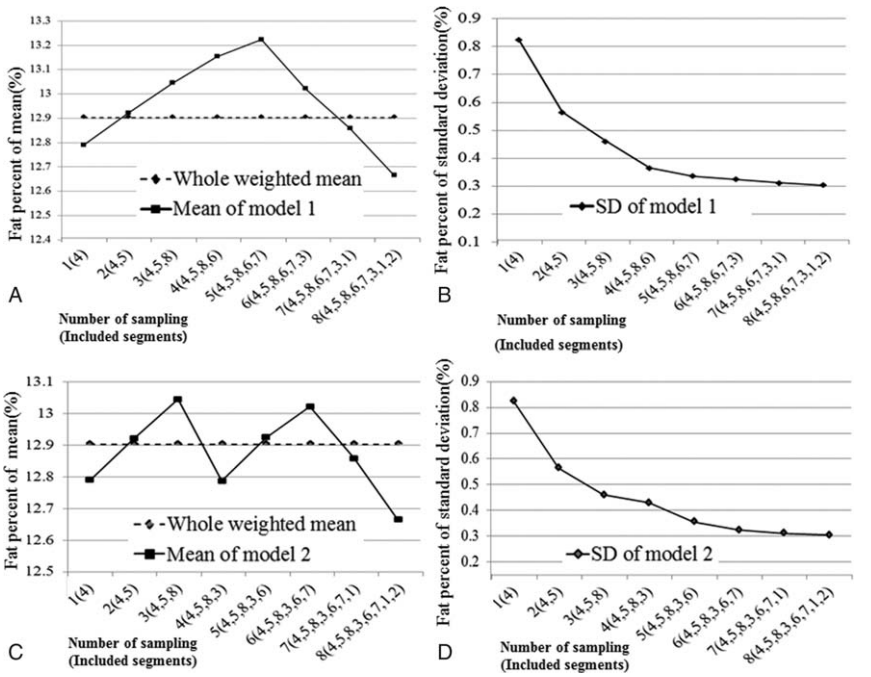

Figure 2. Evaluations of mean and standard deviation (SD) according to model 1 and model 2 for representative value. (A) Comparison of the arithmetic mean of model 1 (full line) to the whole weighted mean (dotted line) according to the number of sampling segment. The full line is closest to the dotted line when the number of sampling segments is 2. (B) The SD of model 1 is decreasing as the number of sampling increases. But significant differences were detected between sampling numbers 1 and 2, 2 and 3, and sampling numbers 3 and 4. (C) Comparison of the arithmetic mean of model 2 (full line) to the whole weighted mean (dotted line) according to the number of sampling segment. The full line is closest to the dotted line when the number of sampling segments is 2. (D) The SD of model 2 is decreasing as the number of sampling increases. But significant differences were detected between sampling numbers 1 and 2, 2 and 3, and sampling numbers 4 and 5.

(Fig. 2C). There was a significant reduction in dispersion between segment 4 and segments 4 and 5 ($P < .0001$).

4. Discussion

In this study, higher variability of intrahepatic fat deposition was associated with younger age, higher BMI, degree of steatosis, higher cholesterol, and triglyceride levels. However, the only significant factor influencing variability was the intrahepatic FF. The mean of segments 4 and 5 was closest to the total intrahepatic FF, which could reduce the standard deviation significantly.

Our findings confirmed those of a previous study, which showed that intrahepatic fat distribution is heterogeneous.[9] Our other results were also similar to those previously shown. The right lobe had a higher mean PDFF than the left lobe. The right lobe also had a lower mean PDFF variability than the left lobe. When we analyzed each segmental level, we found that segment II had the lowest mean segmental value, while segment VII had the highest. Segment VI had the lowest mean segmental variability, while segment II had the highest. A difference of >1.8% in intrahepatic FF using MRI-PDFF is representative of real intrahepatic fatty change.[17,18] The difference between the segments of the highest and the lowest FF was 2.21% in our study, which is similar to that found previously (1.9%). There were large differences in the intrahepatic FFs by segments from the same individuals. Therefore, it is important to carefully select a segment for measurement of intrahepatic fat.

We analyzed the risk factors influencing variability of intrahepatic fat distribution. We sought to identify high-risk groups in the clinical setting, as characterized by severe heterogeneity of intrahepatic fat distribution. In this study, higher variability was associated with younger age, higher BMI, higher FF, higher cholesterol and triglyceride level. However, the FF was the only significant risk factor that influenced the variability in intrahepatic fat distribution. This result demonstrates that the FF ought to be measured very carefully in patients with moderate or severe degrees of fatty liver disease, as well as young patients, and those with higher BMIs. Similarly, it is important to define the measuring site when we estimate improvements in fatty liver before and after treatment of fatty liver disease. In moderate fatty liver (Grade 2, FF: 17.5–22.1%), variability in intrahepatic fat distribution was 2.25% (0.92–4.20%). In severe fatty liver (Grade 3, FF: >22.1%), variability in the intrahepatic FF was 2.47% (1.16–6.26%). This variability could have clinical significance, as a difference of >1.8% in the intrahepatic FF using MRI-PDFF is considered real intrahepatic fatty change.[17,18]

Our another aim was to develop a realistic method of measuring intrahepatic FF in the clinical setting using MRI-PDFF. Multiple repeated hepatic FF measurements were required to estimate the total liver fat amount. This was because of the significant variability in intrahepatic fat distribution. In a previous study (that proceeded MRI and liver biopsy) in 81 living liver donors for liver transplantation, there were differences (range, 3.2–5.3%) in the FFs between each peripheral and deep region of S4, S6, S7, and S8. The fat amounts in S1, S2, S3 and the deep regions of S4 to S8 were significantly different from one another.[19] Therefore, the group suggested that multifocal fat measurements are needed in donor candidates to measure the fat content of the whole liver. The ideal method of measuring the total hepatic fat amount is taking multiple measurements from all 8 hepatic segments repeatedly, and adjusting it by each respective segmental volume. However, this method is time intensive and unrealistic in a clinical setting. Therefore, we suggested a

measurement method for representative intrahepatic fat value that compares the arithmetic mean of each selected segment and the whole weighted mean. In our study, the arithmetic mean of segments 4 and 5 was not significantly different from that of the whole weighted mean, and it reduced dispersion significantly. In Model 1, there was a significant reduction of dispersion until adding 4th segment (segment 6). In Model 2, there was a significant reduction of dispersion until adding 3th segment (segment 8). However, considering the significance and efficiency, measuring segments 4 and 5 and calculating their arithmetic mean is an adequate estimate of overall intrahepatic fat.

This is the first study to suggest an optimal method of measuring intrahepatic fat distribution using MRI-PDFF. We believe that offers a clinically meaningful and practical method of estimating intrahepatic FF using MRI-PDFF. We assessed inter-observer and intra-observer variability of the MRI-PDFF protocol in this study. We also measured the inter-observer and intra-observer variability. The inter-observer variability was 0.19% (range, 0–0.8%, SD: 0.2), and the intra-observer variability was 0.23% (range, 0–0.7%, SD: 0.16). The interclass correlation coefficiency was 0.999, demonstrating very high consistency.

This study has several limitations. First, we estimated total hepatic fat after adjusting each segmental volume. However, there could be a difference in the ratio of segmental volumes to the whole liver between races. Unfortunately, there was only 1 available study regarding liver segment volume per total volume. With regard to this topic, studies are very insufficient. We referenced a Japanese study and applied their intrahepatic segmental volumes. However, further studies in Korea and other countries are needed. In addition, this study did not use a colocalized program to reduce inter/intra-observer variation. However, the intrahepatic FF was visually matched. We attempted to measure the same hepatic area using vessels (as landmarks) in order to reduce the measuring error of 24 ROIs. With regard to these measurements, we calculated the intra-inter-observer variation, and found an intraclass correlation of 0.999. In the literature, the mean differences between ROI- and map-based PDFF estimates range from 0.04% to 0.24%, with all intraclass correlations (ICCs) $\geq$0.999. Therefore, agreement between the ROIs and parametric map-based PDFF estimation was satisfactory over a wide range of imaging and analysis conditions.[20]

Intrahepatic fat distribution is very heterogeneous, and particularly so in fatty liver. Patients with moderate or severe fatty liver disease, of young age, and those with high triglyceride/cholesterol levels should undergo MRI-PDFF for intrahepatic fat measurement. The mean FF from segments 4 and 5 was closest to total liver fat in this study. This suggests that these segments give an adequate estimate of the entire hepatic fat amount.

References

[1] Doycheva I, Cui J, Nguyen P, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. Aliment Pharmacol Ther 2016;43:83–95.

[2] Blake L, Duarte RV, Cummins C. Decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multiparametric magnetic resonance imaging. BMJ Open 2016;6:e010507.

[3] Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Am J Gastroenterol 2012;107:811–26.

[4] Bedossa P, Patel K. Biopsy and noninvasive methods to assess progression of nonalcoholic fatty liver disease. Gastroenterology 2016;150:1811 e1814–22 e1814.

[5] Di Martino M, Pacifico L, Bezzi M, et al. Comparison of magnetic resonance spectroscopy, proton density fat fraction and histological analysis in the quantification of liver steatosis in children and adolescents. World J Gastroenterol 2016;22:8812–9.

[6] Tang A, Tan J, Sun M, et al. Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis. Radiology 2013;267:422–31.

[7] Heba ER, Desai A, Zand KA, et al. Accuracy and the effect of possible subject-based confounders of magnitude-based MRI for estimating hepatic proton density fat fraction in adults, using MR spectroscopy as reference. J Magn Reson Imaging 2016;43:398–406.

[8] Noureddin M, Lam J, Peterson MR, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology 2013;58:1930–40.

[9] Bonekamp S, Tang A, Mashhood A, et al. Spatial distribution of MRI-determined hepatic proton density fat fraction in adults with nonalcoholic fatty liver disease. J Magn Reson Imaging 2014;39:1525–32.

[10] Tang A, Desai A, Hamilton G, et al. Accuracy of MR imaging-estimated proton density fat fraction for classification of dichotomized histologic steatosis grades in nonalcoholic fatty liver disease. Radiology 2015;274:416–25.

[11] Permutt Z, Le TA, Peterson MR, et al. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non-alcoholic fatty liver disease—MRI accurately quantifies hepatic steatosis in NAFLD. Aliment Pharmacol Ther 2012;36:22–9.

[12] Patel J, Bettencourt R, Cui J, et al. Association of noninvasive quantitative decline in liver fat content on MRI with histologic response in nonalcoholic steatohepatitis. Therap Adv Gastroenterol 2016;9:692–701.

[13] Mise Y, Satou S, Shindoh J, et al. Three-dimensional volumetry in 107 normal livers reveals clinically relevant inter-segment variation in size. HPB (Oxford) 2014;16:439–47.

[14] Krueger C, Tian L. A comparison of the general linear mixed model and repeated measures ANOVA using a dataset with multiple missing data points. Biol Res Nurs 2004;6:151–7.

[15] Casella G. Statistical Design. 2008; Springer, New York: ISBN 978-0-387-75965-4.

[16] Howell DC. Statistical Methods for Psychology. 7th ed.2010;Thomson Wadsworth, Belmont, CA:ISBN 978-0-495-59784-1.

[17] Tyagi A, Yeganeh O, Levin Y, et al. Intra- and inter-examination repeatability of magnetic resonance spectroscopy, magnitude-based MRI, and complex-based MRI for estimation of hepatic proton density fat fraction in overweight and obese children and adults. Abdom Imaging 2015;40:3070–7.

[18] Sofue K, Mileto A, Dale BM, et al. Interexamination repeatability and spatial heterogeneity of liver iron and fat quantification using MRI-based multistep adaptive fitting algorithm. J Magn Reson Imaging 2015;42:1281–90.

[19] Choi Y, Lee JM, Yi NJ, et al. Heterogeneous living donor hepatic fat distribution on MRI chemical shift imaging. Ann Surg Treat Res 2015;89:37–42.

[20] Manning PM, Hamilton G, Wang K, et al. Agreement between region-of-interest- and parametric map-based hepatic proton density fat fraction estimation in adults with chronic liver disease. Abdom Radiol (NY) 2017;42:833–41.