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Quantitative MRI Assessment of Pancreatic Steatosis Using Proton Density Fat Fraction in Pediatric Obesity

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Objective: To assess the feasibility of quantitatively assessing pancreatic steatosis using magnetic resonance imaging (MRI) and its correlation with obesity and metabolic risk factors in pediatric patients.

Materials and Methods: Pediatric patients (≤ 18 years) who underwent liver fat quantification MRI between January 2016 and June 2019 were retrospectively included and divided into the obesity and control groups. Pancreatic proton density fat fraction (P-PDFF) was measured as the average value for three circular regions of interest (ROIs) drawn in the pancreatic head, body, and tail. Age, weight, laboratory results, and mean liver MRI values including liver PDFF (L-PDFF), stiffness on MR elastography, and T2* values were assessed for their correlation with P-PDFF using linear regression analysis. The associations between P-PDFF and metabolic risk factors, including obesity, hypertension, diabetes mellitus (DM), and dyslipidemia, were assessed using logistic regression analysis.

Results: A total of 172 patients (male:female = 125:47; mean ± standard deviation [SD], 13.2 ± 3.1 years) were included. The mean P-PDFF was significantly higher in the obesity group than in the control group (mean ± SD, 4.2 ± 2.5% vs. 3.4 ± 2.4%; $p = 0.037$). L-PDFF and liver stiffness values showed no significant correlation with P-PDFF ($p = 0.235$ and $p = 0.567$, respectively). P-PDFF was significantly associated with obesity (odds ratio 1.146, 95% confidence interval 1.006–1.307, $p = 0.041$), but there was no significant association with hypertension, DM, and dyslipidemia.

Conclusion: MRI can be used to quantitatively measure pancreatic steatosis in children. P-PDFF is significantly associated with obesity in pediatric patients.

Keywords: *Child; Pancreas; Fatty liver; Magnetic resonance imaging; Obesity*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a metabolic disease characterized by the accumulation of ectopic fat in the liver that can lead to liver cirrhosis and hepatocellular carcinoma without appropriate intervention [1]. Similar to NAFLD, non-alcoholic fatty pancreas disease (NAFPD) is characterized by fat infiltration and has recently emerged as a new metabolic disease [2-4]. Recently, several studies have been conducted on NAFPD, and pancreatic fat infiltration has been found to affect pancreatic insulin secretion and potentially act as a risk factor for pancreatic cancer, chronic pancreatitis, and diabetes mellitus (DM) in adults [5-7]. Although there have not been several studies on adults with liver disease or even NAFLD, recent studies have shown that pediatric NAFPD is not uncommon in children, and it can affect glucose metabolism, islet cell dysfunction, and liver fibrosis associated with pediatric NAFLD [2,8].

Pancreatic fat can be evaluated using ultrasonography (US), computed tomography (CT), magnetic resonance

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imaging (MRI), and magnetic resonance spectroscopy (MRS) [9-11]. However, the US has some disadvantages because it is difficult to identify the full length of the pancreas with a poor sonographic window, such as those used in obese patients, and because it is also relatively subjective because fat infiltration is measured qualitatively [12,13]. In contrast, CT and MRI can evaluate the entire pancreas, regardless of patient factors, and measure the amount of fat. Several previous studies have shown that their performance is comparable when measuring hepatic fat, even though studies have yet to directly compare their pancreatic fat measurements [13,14].

Among the various MRI-based methods for fat quantification, proton density fat fraction (PDFF) is considered the most practical and objective because the fat fraction can be obtained quantitatively by separating water and fat using a chemical shift technique [15]. In addition, MRI may seem more advantageous for pediatric patients because it allows patients to avoid radiation issues that can occur with CT. However, there are still not enough studies on factors related to pancreatic fat accumulation in pediatric patients. According to a previous study, pancreatic fat measured with MRS was significantly higher in obese children and not significantly related to prediabetes [16]. Two other studies evaluated fatty pancreas with US and found that insulin resistance was higher in pediatric patients with, than in those without, fatty pancreas [2]. However, there have been very few analyses of pancreatic fat using PDFF in pediatric patients.

Therefore, this study aimed to quantitatively measure pancreatic fat deposition using PDFF values of MRI and evaluate its correlation with obesity and metabolic risk factors in children.

MATERIALS AND METHODS

Subjects

This retrospective study was approved by the Institutional Review Board of our institution, and the requirement for informed consent was waived (IRB No. 4-2020-0470). Pediatric patients (≤ 18 years) who underwent abbreviated liver MRI containing the PDFF sequence according to clinical demands between January 2016 and June 2019 were consecutively included. We included patients who underwent abbreviated liver MRI because they were suspected to have NAFLD due to elevated liver enzymes, obesity, or abnormal hyperechogenicity of the liver parenchyma on US. In patients who underwent repeated liver MRI, we only included results from the initial examination before the patients were treated for the disease. We excluded patients with laboratory results obtained more than 1 month before and after the MRI examinations. We excluded patients who underwent MRI because of a suspicion of liver fibrosis due to other causes, such as biliary atresia.

After reviewing the medical records of the entire population, the age, weight, height, and presence of metabolic risk factors, such as hypertension, DM, and dyslipidemia, were reviewed. Hypertension, DM, and dyslipidemia were diagnosed by pediatric endocrinologists according to previous studies and guidelines [17-19]. The laboratory results were reviewed for the serum levels of aspartate aminotransferase (AST, IU/L), alanine transaminase (ALT, IU/L), γ-glutamyl transferase (GGT, IU/L), fasting glucose (mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), high-density lipoprotein cholesterol (HDL, mg/dL), low-density lipoprotein cholesterol (LDL, mg/dL), amylase (U/L), and lipase (U/L). The patients were divided into two groups: the control and obesity groups. The obesity group was defined as having a body mass index (BMI) falling within the 95th percentile or above.

MRI Acquisition

All abbreviated liver MRIs were performed using a 3T system (Discovery MR750w; GE Healthcare) with a pediatric body coil. Patients who could cooperate with image acquisition and breath-holding could undergo MRI because sedation was not supported in this MRI system at our institution. For MRI, axial single-shot fast-spin-echo T2 weighted images were included for anatomic imaging of the liver. The three-dimensional volumetric multi-echo gradient echo sequence (IDEAL-IQ) sequence was used to obtain PDFF and T2* (= 1/R2*) values, using the following parameters: repetition time (TR), 5.9 ms; echo time (TE), 2.6 ms; field of view, 42 cm; matrix, 128 x 128; flip angle, 3°; slice thickness, 8.0 mm; and acquisition time, 16 seconds. The fat and R2* maps were generated automatically after acquisition. In addition, the MR elastography (MRE) sequence was included using a passive driver placed over the right anterior abdominal wall to deliver 60-Hz pneumatic vibrations. The two-dimensional spin-echo echo-planar imaging (SE-EPI) sequence was used to obtain four axial stiffness maps of the liver using the following parameters: TR, 1000 ms; TE, 62 ms; field of view, 38 cm; matrix, 64 x 64; flip angle, 90°; slice thickness, 8.0 mm;

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and acquisition time, 24 seconds. The MRE acquisition technique was the same as that used in previous pediatric studies [20,21].

MRI Analysis

To obtain pancreatic PDFF (P-PDFF, %), a radiologist with six months of experience in pediatric radiology drew circular regions of interest (ROIs) on the pancreas using a picture archiving and communication system (PACS, Centricity, General Electric Corporation). A total of three round ROIs with an approximate area of 100 mm^2 were drawn over the pancreas head, body, and tail portions on the fat map according to previous studies (Figs. 1, 2) [9,22]. The average P-PDFF value calculated from the three fat fractions in the pancreas was used as the representative value. An average pancreas T2* value was also obtained using the three-round ROIs drawn on the R2* map in the pancreas head, body, and tail. The liver PDFF (L-PDFF, %) and T2* values were acquired from the three circular ROIs in the liver from the fat and R2* maps while avoiding hepatic vessels.

To obtain liver stiffness values, the circular ROIs were drawn on each of the four axial liver stiffness maps with 95% confidence intervals (CIs), while avoiding artifacts and vessels. The mean liver stiffness value for the four ROIs (one from each axial stiffness map) was used as the representative value. The ROIs used were different from those of the fat map because the stiffness map was obtained for four axial slices of different slice thicknesses from the fat map, and copying ROIs to the same areas was not possible with our PACS. All measurements were obtained by radiologists blinded to the clinical information.

Statistical Analysis

The statistical analyses were performed using SPSS version 25 (IBM Corp.). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were summarized as frequencies and percentages. To determine the reliability of the P-PDFF measurements, another pediatric radiologist with seven years of experience in pediatric radiology drew round ROIs on the pancreas head, body, and tail on the fat map while blinded to previous measurements and patient history. The mean P-PDFF values were calculated from the three ROIs. To assess the intraobserver variability for the P-PDFF measurements, the same pediatric radiologist drew three ROIs on the pancreas head, body, and tail on the fat map two weeks later, while blinded to the previous measurements and patient history. The intraclass correlation coefficient (ICC) values were calculated to evaluate interobserver and intraobserver variability for the P-PDFF

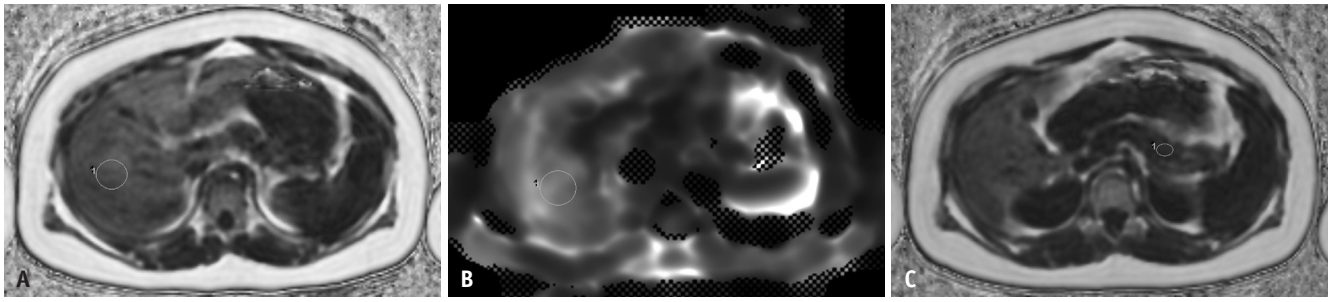

Fig. 1. A 10-year-old obese boy showed (A) increased liver-PDFF (33%) and (B) increased liver stiffness (3.2 kPa). (C) His mean pancreatic-PDFF value was 7.2%. PDFF = proton density fat fraction

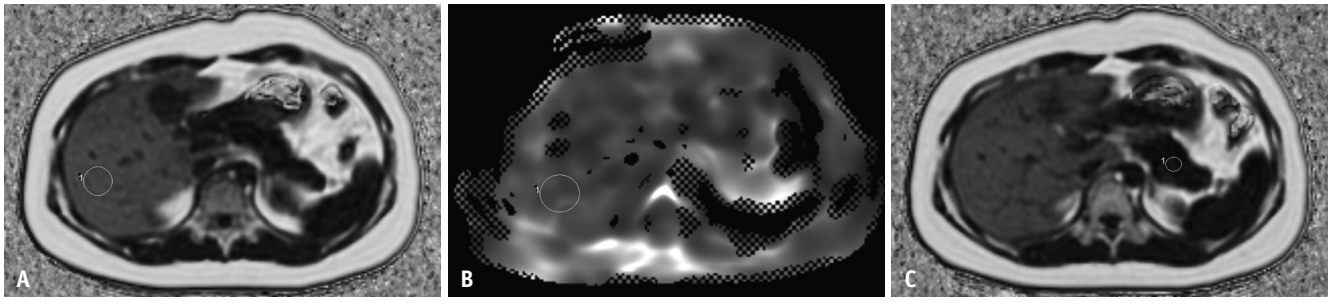

Fig. 2. A 16-year-old non-obese boy showed (A) increased liver-PDFF (34%) and (B) normal range of liver stiffness (1.7 kPa). (C) His mean pancreatic-PDFF value was 1.9%. The pancreatic-PDFF was not increased in this patient with a normal range of liver stiffness. PDFF = proton density fat fraction

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measurements. The ICC values were interpreted as follows: < 0.5, poor reliability; 0.5 and 0.75, moderate reliability; 0.75 and 0.9, good reliability; and values greater than 0.9, excellent reliability.

We compared the continuous variables for the control and obesity groups using an independent *t* test. The chi-squared and Fisher's exact tests were used to compare the categorical variables. Univariable linear regression analysis was performed to assess the correlations between P-PDFF and the clinical, laboratory, and liver MRI features. Univariable logistic regression analysis was used to find associations between P-PDFF and metabolic risk factors, such as obesity, hypertension, DM, and dyslipidemia. Statistical significance was set at $p < 0.05$.

RESULTS

Patient Demographics

All 264 patients underwent abbreviated liver MRI containing the PDFF sequence during the study period. Among them, 54 patients were excluded because they did not have laboratory results within 1 month of the MRI examination. In addition, 38 patients were excluded because they underwent MRI to evaluate liver fibrosis, such as biliary atresia. Therefore, a total of 172 pediatric patients (male:female = 125:47; mean ± SD, 13.2 ± 3.1 years; range 7–18 years) were included. Among them, 138 patients were consequently diagnosed with NAFLD after liver MRI using a cutoff value of 6% for the L-PDFF [23]. The remaining 34 patients did not have NAFLD despite undergoing MRI because of suspicions of increased liver parenchymal echogenicity on abdominal US. Eighty-eight patients were classified into the obesity group with a BMI falling within the 95% percentile or higher (51.2%; mean ± SD, 13.6 ± 3.1 years; range 7–18 years). Ten patients had hypertension (5.8%), 21 had DM (12.2%), and 8 had dyslipidemia (4.7%). All the DM cases were type 2.

P-PDFF Value and Its Reliability on Measurement

The mean P-PDFF ± SD of all patients was 3.8 ± 2.5%. The ICC value of the interobserver variability for the P-PDFF measurement was 0.798, indicating a good agreement. The ICC value for intraobserver variability was 0.924, indicating excellent reliability.

Comparison of the Control and Obesity Group

AST (mean ± SD, 91.2 ± 151.6 IU/L vs. 44 ± 43.4 IU/L, $p = 0.006$) and ALT (mean ± SD, 160.7 ± 215.0 IU/L vs. 73.2 ± 102.0 IU/L, $p = 0.001$) were significantly higher in the obesity group. HDL levels were significantly lower in the obesity group than in the control group (mean ± SD, 44.3 ± 10.9 mg/dL vs. 49.1 ± 13.7 mg/dL, $p = 0.025$).

When comparing MRI results, P-PDFF was significantly higher in the obesity group (mean ± SD, 4.2 ± 2.5% vs. 3.4 ± 2.4%, $p = 0.037$). The T2* values of the pancreas could not be measured in six patients due to artifacts. In these patients, the unmeasurable area, including the pancreas, appeared as a black signal intensity from motion artifacts or air in the stomach. Based on the pancreas T2* values available in 166 patients, there was no significant difference between the two groups ($p = 0.503$).

L-PDFF was significantly higher in the obesity group (mean ± SD, 24.7 ± 13.4% vs. 16.5 ± 14.1%, $p < 0.001$). Liver T2* values and stiffness values were not significantly different between the two groups ($p = 0.957$ and $p = 0.125$, respectively).

DM was more frequently observed in the obesity group than in the control group (15 vs. 6 patients, $p = 0.047$), while the incidence of hypertension and dyslipidemia were not significantly different. The clinical, laboratory, and MRI results are shown in Table 1.

Factors associated with Pancreatic Fat Fraction and Its Relationship with Metabolic Risk Factors

In the univariable linear regression analysis, only amylase was significantly associated with P-PDFF ($\beta = -0.034$, $p = 0.022$) (Table 2). Other MRI values, including pancreas T2* values, L-PDFF, and liver stiffness, showed no significant association with P-PDFF in the linear regression analysis. Among the metabolic risk factors, P-PDFF was associated with obesity (odds ratio [OR] 1.146, 95% CI 1.006–1.307, $p = 0.041$) in the univariable logistic regression analysis. There were no significant associations between P-PDFF and hypertension (OR 1.019, 95% CI 0.791–1.312, $p = 0.885$), DM (OR 1.035, 95% CI 0.866–1.236, $p = 0.705$) and dyslipidemia (OR 0.946; 95% CI 0.689–1.298, $p = 0.730$) (Table 3).

DISCUSSION

In this study, P-PDFF was significantly associated with obesity in pediatric patients (OR 1.193; 95% CI 1.057–1.348). In obese patients, P-PDFF was 4.2%, compared to 3.4% in the control group. Although P-PDFF was not

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Table 1. Patient Demographics for the Clinical, Laboratory and MRI Results of Control and Obesity Groups

Characteristics	Control Group (n = 84)	Obesity Group (n = 88)	*P*
Age, years	12.8 ± 3.0	13.6 ± 3.1	0.056
Sex, male:female*	60:24	65:23	0.720
Height, cm	153.1 ± 14.8	162.9 ± 13.3	< 0.001
Weight, kg	53.2 ± 14.8	82.0 ± 20.3	< 0.001
BMI percentage, %	72.5 ± 26.3	98.5 ± 1.3	< 0.001
AST, IU/L	44.0 ± 43.4	91.2 ± 151.6	0.006
ALT, IU/L	73.2 ± 102.0	160.7 ± 215.0	0.001
γGT, IU/L	56.9 ± 29.0	66.3 ± 51.9	0.555
Fasting glucose, mg/dL	98.6 ± 34.8	101.8 ± 31.0	0.531
Total cholesterol, mg/dL	185.8 ± 45.9	187.8 ± 72.5	0.830
Triglyceride, mg/dL	137.3 ± 87.3	152.6 ± 80.4	0.282
HDL, mg/dL	49.1 ± 13.7	44.3 ± 10.9	0.025
LDL, mg/dL	130.8 ± 63.0	137.9 ± 123.5	0.835
Amylase, U/L	66.8 ± 31.5	52.4 ± 16.9	0.098
Lipase, U/L	26.5 ± 10.7	26.7 ± 8.5	0.951
P-PDFF, %	3.4 ± 2.4	4.2 ± 2.5	0.037
Pancreas T2*, msec	33.6 ± 8.0	32.8 ± 7.6	0.503
L-PDFF, %	16.5 ± 14.1	24.7 ± 13.4	< 0.001
Liver T2*, msec	20.5 ± 5.3	20.4 ± 6.6	0.957
Liver stiffness, kPa	2.4 ± 0.7	2.6 ± 0.6	0.125
Hypertension*	4 (4.8)	6 (6.8)	0.747
Diabetes mellitus*	6 (7.1)	15 (17)	0.047
Dyslipidemia*	4 (4.8)	4 (4.5)	> 0.999

Values are presented as mean ± SD or numbers or patient number with percentage in parentheses. *Chi-square test or Fisher's exact test was used. ALT = alanine transaminase, AST = aspartate aminotransferase, BMI = body mass index, HDL = high-density lipoprotein cholesterol, L = liver, LDL = low-density lipoprotein cholesterol, P = pancreatic, PDFF = proton density fat fraction, SD = standard deviation, γGT = γ-glutamyl transferase

Table 2. Univariable Linear Regression Analysis Results for P-PDFF Values

Parameters	β	Standard Error	*P*
Age, years	0.055	0.062	0.373
Height, cm	0.009	0.013	0.477
Weight, kg	0.013	0.008	0.113
BMI percentage, %	0.012	0.008	0.158
AST, IU/L	0.001	0.002	0.809
ALT, IU/L	0.001	0.001	0.937
γGT, IU/L	-0.005	0.008	0.536
Fasting glucose, mg/dL	-0.003	0.006	0.633
Total cholesterol, mg/dL	-0.002	0.003	0.540
Triglyceride, mg/dL	0.002	0.002	0.480
HDL, mg/dL	-0.025	0.017	0.125
LDL, mg/dL	-0.003	0.006	0.558
Amylase, U/L	-0.034	0.014	0.022
Lipase, U/L	-0.072	0.039	0.070
Pancreas T2, msec	-0.019	0.024	0.415
L-PDFF, %	0.016	0.013	0.235
Liver T2, msec	-0.052	0.031	0.098
Liver stiffness, kPa	0.159	0.276	0.567

ALT = alanine transaminase, AST = aspartate aminotransferase, BMI = body mass index, HDL = high-density lipoprotein cholesterol, L = liver, LDL = low-density lipoprotein cholesterol, P = pancreatic, PDFF = proton density fat fraction, γGT = γ-glutamyl transferase

Table 3. Univariable Logistic Regression Analysis Results for Pancreatic Proton Density Fat Fraction Values according to Metabolic Risk Factors

	Odds Ratio (95% Confidence Interval)	*P*
Obesity	1.146 (1.006–1.307)	0.041
Hypertension	1.019 (0.791–1.312)	0.885
Diabetes mellitus	1.035 (0.866–1.236)	0.705
Dyslipidemia	0.946 (0.689–1.298)	0.730

significantly associated with L-PDFF or liver stiffness values in our study cohort, this study demonstrated the usefulness of MRI for the quantification of pancreatic fat in pediatric populations with good to excellent reliability. The importance of pancreatic steatosis has been less investigated than that of NAFLD. However, pancreatic steatosis, also called NAFPD, has recently emerged as an important early marker of metabolic syndrome in adults. A previous study mentioned that NAFPD may play a role in the future development of DM, metabolic syndrome, atherosclerosis, and even pancreatic cancer in adults [3]. However, quantifying pancreatic fat with pathology is almost impossible, and this may be the reason for the late research on NAFPD. Therefore, noninvasive and quantitative measurement of P-PDFF may demonstrate the clinical importance of NAFPD in the metabolic disease of adults and, especially, children.

In adults, increased fatty infiltration is observed in the pancreas of obese patients on MRI [3,24]. However, a few studies have dealt with fatty pancreas in children and have tried to quantify pancreatic fat using MRI. Most of these studies assessed the degree of fatty pancreas using US [8,25]. Elhady et al. [8] demonstrated that obesity is associated with higher pancreatic fat on US in children, which is consistent with the results of our study. They diagnosed fatty pancreas when the pancreas showed similar or higher echogenicity compared to the renal sinus fat on US. However, this is not a quantitative measurement. As an alternative method for quantifying the degree of

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fat deposition, the pancreato-perihepatic fat index was obtained from US [25,26]. Kim et al. [25] revealed that this index was a significant independent factor for diagnosing metabolic syndrome in pediatric patients. However, this method cannot represent a large volume of the pancreas, and artifacts decrease the accuracy of measurements. The operators and techniques they use can affect US measurements. One study utilized MRI to measure the volume and fat content of the pancreas in children [27]. They demonstrated that the volume of the pancreas was smaller in patients with type 1 DM than in controls, while P-PDFF was not significantly different. They suggested that pancreatic fat content may differ according to the etiology of DM, because other researchers have found increased fat infiltration in patients with cystic fibrosis [28].

In the present study, P-PDFF was not significantly associated with DM. We postulate that the etiology of pediatric DM is different from that of adults, but the diabetic patients included in this study all had type 2 DM. Another explanation is that the low incidence of DM (12.2% of 172 patients) lowered the statistical significance of the results. However, pancreatic fat in patients with DM is also debated in adults [29]. Some studies demonstrated increased pancreatic fat in type 2 DM patients, while others found no differences in autopsy in a retrospective cohort study even after adjusting for confounders such as BMI [29,30]. Further studies with a large number of patients for each etiology of DM are needed to validate these results in children.

In this study, the mean P-PDFF of the control group was 3.4% ± 2.4%. Although the normal standard for pancreatic fat fraction has not yet been clearly determined, the average pancreatic fat fraction in a healthy population was 4.5% ± 0.9% in a meta-analysis of nine MRI studies [31]. However, as fat deposition increases with age, adults and children may have different normal values [32]. Thus, this standard in adults cannot be applied equally to children, even though two studies with pediatric subjects were included in this meta-analysis. One study that evaluated P-PDFF using the Dixon method divided children into three groups: lean without metabolic syndrome, obese without metabolic syndrome, and obese with metabolic syndrome, where the pancreatic fat fraction was 3.6 ± 0.9%, 4.7 ± 1.1%, and 5.3 ± 1.5%, respectively [33]. The mean P-PDFF of the control group in our study was also lower than that in the adults. Because the control group in our study was determined by the BMI percentage only, the included subjects may differ from previous studies and may not fully represent healthy controls. For example, the mean L-PDFF in the control group was 16.5%. This value was above the cutoff known to represent fat deposition in the liver of children [23]. Therefore, even though we divided groups according to BMI percentage, the control group did not represent healthy normal children. However, because quantifying pancreatic fat using histologic confirmation is realistically impossible in children, we need to validate the normal fat signal percentage using MRI with a large number of subjects for future and deeper analyses of pediatric NAFPD.

In addition, P-PDFF was significantly higher in the obesity group than in the control group. Although L-PDFF and liver stiffness were not significantly associated with P-PDFF in our study, there is still not enough data on the relationship between liver fibrosis and fat infiltration in the pancreas. Previous studies have demonstrated that patients with fatty pancreas have more advanced NAFLD than patients without fatty pancreas [2,29]. However, one study reported a positive correlation between fatty liver and fatty pancreas, but a negative correlation between liver fibrosis and fatty pancreas [34]. This finding suggests that further research is required.

This retrospective study had several limitations. First, this study analyzed the fat fraction measured indirectly by MRI and not the histological fat fraction obtained through biopsy or surgery on the liver and pancreas. As we mentioned earlier, because of the retrospective nature of this study, the control group did not represent healthy and normal children. However, obtaining histological confirmation has many limitations. For the same reason, previous studies have shown that PDFF can accurately predict fat percentage, with a reasonable agreement between histological measurements and P-PDFF [35,36]. Second, the number of patients with metabolic risk factors was relatively low. This is because we included patients who underwent liver MRI due to the suspicion of liver disease and not metabolic disease. In addition, because metabolic syndrome, DM, and pancreatitis are chronic diseases, long-term follow-up is necessary for more accurate assessments. Future studies incorporating a long-term follow-up will provide a more accurate picture of the associations between P-PDFF and chronic diseases in pediatric patients.

In conclusion, pancreatic steatosis can be measured quantitatively using MRI in pediatric patients with good to excellent reliability. P-PDFF is significantly associated with

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obesity in pediatric patients. Further studies are needed to assess the clinical implications of pediatric NAFPD using MRI.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Hyun Joo Shin. Data curation: Salman S. Albakheet, Jisoo Kim, Hyun Joo Shin. Formal analysis: Hyun Joo Shin, Kyunghwa Han. Investigation: Jisoo Kim, Salman S. Albakheet, Hyun Joo Shin. Methodology: Hyun Joo Shin, Kyunghwa Han. Resources: Hong Koh, Seung Kim, Seok Joo Han, Kyong Ihn, Junghwan Suh. Software: Hyun Joo Shin, Haesung Yoon, Mi-Jung Lee. Supervision: Hyun Joo Shin. Validation: Jisoo Kim, Hyun Joo Shin. Visualization: Jisoo Kim, Salman S. Albakheet, Hyun Joo Shin. Writing—original draft: Jisoo Kim, Hyun Joo Shin. Writing—review & editing: Hyun Joo Shin, Jisoo Kim, Mi-Jung Lee, Haesung Yoon.

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