

## Original Article



# Quantitative Analysis of Pancreatic Fat in Children with Obesity Using Magnetic Resonance Imaging and Ultrasonography

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## ABSTRACT

**Purpose:** The aim of this study was to evaluate the pancreatic fat fraction (PFF) using magnetic resonance imaging (MRI) in children with and without obesity and to correlate PFF with body mass index (BMI) z-score, hepatic fat fraction (HFF), and ultrasonography-derived pancreato-perihepatic fat index (PPHFI).

**Methods:** This prospective study included 45 children with obesity and 19 without obesity (control group). PFF and HFF were quantitatively assessed using the abdominal multi-echo Dixon method for MRI. The PPHFI was assessed using transabdominal ultrasonography. Anthropometric, MRI, and ultrasonographic characteristics were compared between the two groups. Correlations between PFF, HFF, PPHFI, and BMI z-scores in each group were also analyzed.

**Results:** The PFF, HFF, PPHFI, and BMI z-score were higher in the group with obesity than in the control group (PFF:  $6.65 \pm 3.42$  vs.  $1.78 \pm 0.55$ , HFF:  $19.5 \pm 13.0$  vs.  $2.31 \pm 1$ , PPHFI:  $3.65 \pm 1.63$  vs.  $0.94 \pm 0.31$ , BMI z-score:  $2.27 \pm 0.56$  vs.  $0.42 \pm 0.54$ ,  $p < 0.01$ , respectively). PFF was correlated with BMI z-scores, PPHFI, and HFF in the obesity group, and multivariate analysis showed that PFF was strongly correlated with BMI z-score and PPHFI ( $p < 0.05$ ). The BMI z-score was strongly correlated with PFF in the control group ( $p < 0.01$ ).

**Conclusion:** These results suggest that MRI-derived PFF measures are associated with childhood obesity. PFF and PPHFI were also highly correlated in the obesity group. Therefore, PFF may be an objective index of pancreatic fat content and has the potential for clinical utility as a non-invasive biomarker for the assessment of childhood obesity.

**Keywords:** Magnetic resonance imaging; Pancreas; Pediatric obesity; Ultrasonography

## INTRODUCTION

Over the past few decades, childhood obesity has increased worldwide [1,2], with the current prevalence of obesity in school-aged children estimated at 12.8% in South Korea [3]. Childhood obesity can lead to a variety of conditions, such as dyslipidemia, insulin resistance, cardiovascular disease, sleep apnea, liver disease, and precocious puberty, leading

**Conflict of Interest**

The authors have no financial conflicts of interest.

to substantial health problems and a high socioeconomic burden [4,5]. Increased lipolysis in individuals with obesity results in an increase in free fatty acids, which are deposited in certain organs, such as the liver and pancreas. Fat deposition in the pancreas leads to a reduced function of insulin-secreting beta cells [6,7]. Moreover, it is a risk factor for obesity-related cardiometabolic complications, including insulin resistance [8].

Although biopsy is the standard diagnostic method for assessing fat deposition in organs, biopsy of the pancreas, which is located in the retroperitoneal space, is highly challenging in children. Therefore, non-invasive imaging modalities are preferred for assessing the degree of fat deposition in the pancreas in children. A quantitative assessment of pancreatic fat can be performed using unenhanced computed tomography, but its use is not recommended in children due to the risk of radiation exposure [9]. Consequently, the majority of pancreatic fat assessments in children are performed via qualitative analysis using transabdominal ultrasonography [10-12]. Recent studies have applied a method for the quantitative analysis of the degree of pancreatic fat using the pancreato-perihepatic fat index (PPHFI), which is obtained by dividing pancreatic body echo brightness by perihepatic fat echo brightness on transabdominal ultrasonography [13,14]. However, to our knowledge, no study has investigated the direct relationship between PPHFI and actual pancreatic fat content.

Magnetic resonance imaging (MRI) is a valuable non-invasive imaging modality for quantifying the degree of fat deposition in the liver and pancreas. The modified Dixon method is a chemical shift imaging technique that is widely used to quantify the fat content of both the liver and pancreas in one scan. The technique is also operator-independent and has high reproducibility [15,16]. Previous studies have demonstrated an association between obesity and the pancreatic fat fraction (PFF) in adults using autopsy or MRI [17-20]. However, only a small number of studies have quantitatively analyzed the association between PFF and obesity in children and adolescents [4,21-23].

The purpose of the present study was to quantify PFF in children and adolescents using MRI and to investigate its association with obesity. In addition, we investigated the associations between PFF, body mass index (BMI), PPHFI, and hepatic fat fraction (HFF).

## MATERIALS AND METHODS

### Study design and participants

The study protocol was approved by the Institutional Review Board of the Jeju National University Hospital (No. 2017-06-039). Informed consent was obtained from all subjects, and from their parents or guardians after they were fully informed about the purpose and methods of the study.

This prospective study included 64 children and adolescents who were recruited from the pediatric outpatient clinic of Jeju National University Hospital from June 2017 to May 2019.

Based on the 2017 Korean National Growth Charts, subjects with a BMI at or above the 95th percentile for their age and sex were defined as obese. Once a subject's BMI reached 25 kg/m<sup>2</sup> or greater, they were classified as obese regardless of percentile score. In the control group, BMI ranged between the 5th and 85th percentiles for age and sex. Exclusion criteria for all

subjects were as follows: hepatitis A or B, Wilson's disease, autoimmune hepatitis, or the use of steatogenic drugs (e.g., methotrexate, glucocorticoids, amiodarone).

### MRI protocol

Abdominal MRI was performed using a 3T MRI system (Skyra; Siemens Medical Systems, Erlangen, Germany) with a 32-channel body coil. Imaging was performed in the supine position after an 8-hour fast. A three-dimensional multi-echo volumetric interpolated breath-hold examination (VIBE) Dixon sequence was obtained in all subjects with the following parameters: 6 echo times of 1.23, 2.46, 3.69, 4.92, 6.15, and 7.38 ms; repetition time, 9 ms; slice thickness, 2.5 mm; flip angle, 4° to reduce the T1 effect; matrix size, 220×140; field-of-view, 380×320 mm; and bandwidth, 1,060 kHz. A parallel acceleration technique was employed, the Controlled Aliasing in Parallel Imaging Results in Higher Acceleration (CAIPIRINHA)-VIBE sequence, with a 2×2 acceleration factor. The acquisition was performed during a single breath-hold of 16 seconds. Proton density fat fraction (PDFF), water fraction, R2\* maps, and T2\* maps were acquired automatically. An additional routine axial T2-weighted half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence was obtained to evaluate focal lesions in the liver or pancreas.

### MRI fat quantification of the pancreas and liver

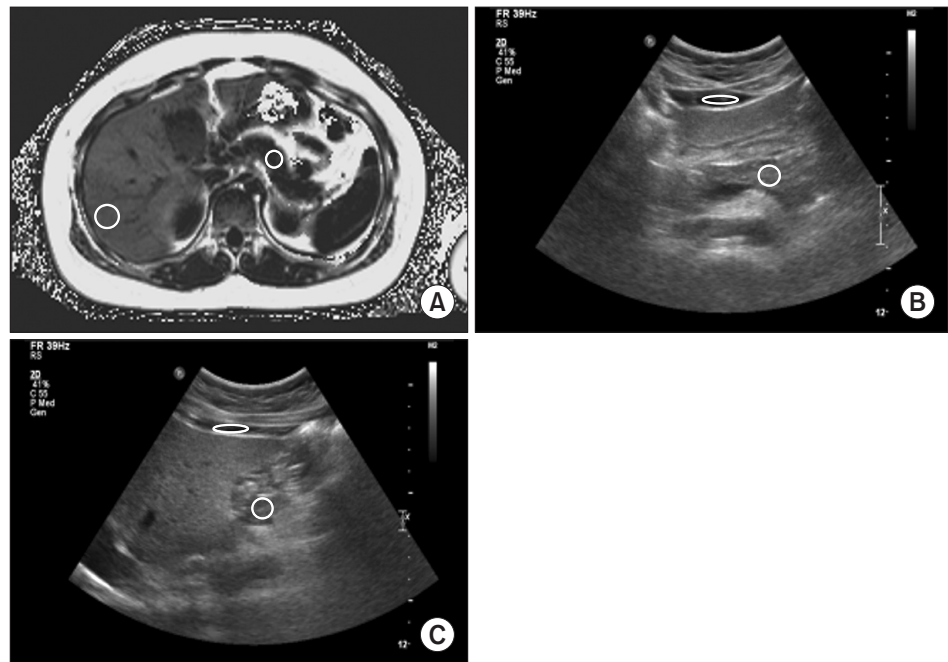
Quantitative analysis of PFF was performed using a picture archiving communication system workstation monitor (Infinit Healthcare, Seoul, Korea). For the quantification of pancreatic fat content, three 100-mm<sup>2</sup> elliptical regions of interest (ROIs) were drawn in the pancreatic head, body, and tail on the PDFF maps, and the mean value was taken as the PFF. For the quantification of hepatic fat content, 150-mm<sup>2</sup> elliptical ROIs were drawn in 8 segments of the liver, avoiding blood vessels and focal lesions, and the mean value was used as the HFF (**Fig. 1A**).

### Ultrasonographic fat quantification of the pancreas

All subjects underwent transabdominal ultrasonography after a midnight fast to assess ultrasonographic fat quantification. The examinations were performed using a 1-5 MHz convex transducer (Philips iU22; Philips Medical Systems, Bothell, WA, USA) by two radiologists with 8 and 15 years of experience. Simultaneously, transverse and longitudinal scans were performed to include sufficient pancreatic parenchyma and perihepatic fat. For quantitative analysis, an elliptical ROI was drawn to measure the brightness of the pancreas and perihepatic fat in each of the transverse and longitudinal images. An ROI (50 mm<sup>2</sup>) was applied to the head or body portion containing the most pancreatic parenchyma, avoiding the main pancreatic duct and retroperitoneal fat. Perihepatic fat was defined as the fat between the muscular layer of the anterior abdominal wall and the hepatic capsule. An ROI (25 mm<sup>2</sup>) was drawn on the perihepatic fat, showing homogeneous echogenicity. When perihepatic fat tissue content was low, and an ROI of the predetermined size could not be drawn entirely within the tissue of interest, the ROI was drawn to include as much perihepatic fat tissue as possible. The average mean brightness value for each part in the transverse and longitudinal scans was calculated, and these were defined as the mean pancreatic brightness and the mean brightness of perihepatic fat. Subsequently, the ratio of these two values was used to obtain PPHFI (**Fig. 1B, C**).

### Statistical analyses

Continuous variables are expressed as mean±standard deviation, and categorical variables are expressed as numbers and percentages. Independent *t*-tests and chi-square tests were used to compare anthropometric characteristics, PFF, HFF, and PPHFI between the two groups.



**Fig. 1.** Example of fat quantification by ultrasonography and magnetic resonance imaging in an 11-year-old boy with obesity. (A) Fat fraction was obtained by drawing circular regions of interest (ROIs) within the pancreas and liver on fat fraction images acquired using a three-dimensional multi-echo volumetric interpolated breath-hold examination (VIBE) Dixon sequence. (B) Transverse and (C) longitudinal ultrasonography images. Circular ROIs were drawn within the center of the pancreatic body, and elliptical ROIs were drawn within the perihepatic fat. The pancreato-perihepatic fat index was defined as  $(\text{Pancreas}_{\text{transverse}} + \text{Pancreas}_{\text{longitudinal}}) / (\text{Perihepatic fat}_{\text{transverse}} + \text{Perihepatic fat}_{\text{longitudinal}})$ .

Associations between the PFF, HFF, PPHFI, and BMI z-scores were analyzed using Pearson correlations. Multivariate regression analysis was performed to determine independent associations between the variables. Statistical significance was set at  $p < 0.05$ . Statistical analyses were performed using SPSS (ver. 24.0; IBM Co., Armonk, NY, USA).

## RESULTS

### Basic characteristics

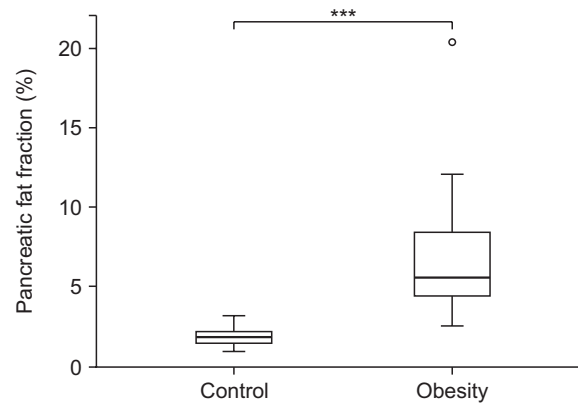
The overall anthropometric, MRI, and ultrasonographic characteristics of the subjects are presented in **Table 1**.

**Table 1.** Comparison of anthropometric, magnetic resonance imaging, and ultrasonographic characteristics between children and adolescents with and without obesity

Variable	Control group (n=19)	Group with obesity (n=45)	p-value
Age (yr)	12.050±2.415	13.180±2.443	0.096
Sex (M/F)	10/9	29/16	0.376
BMI z-score	0.418±0.541	2.273±0.560	<0.001
PPHFI	0.942±0.315	3.645±1.632	<0.001
PFF (%)	1.779±0.553	6.652±3.421	<0.001
HFF (%)	2.270±0.800	18.600±13.100	<0.001

Values are expressed as mean±standard deviation or number only.

BMI: body mass index, PPHFI: pancreato-perihepatic fat index, PFF: pancreatic fat fraction, HFF: hepatic fat fraction.



**Fig. 2.** Tukey's plot showing the mean±standard deviation for pancreatic fat fraction of the obesity and control groups. \*\*\* $p<0.001$ .

In total, 64 children and adolescents were included (39 boys and 25 girls, mean age  $12.84\pm 2.47$ ; age range 9-17 years). Of these, 45 were classified into the group with obesity (29 boys and 16 girls, mean age  $13.180\pm 2.443$ ; age range 9-17 years), and 19 into the control group (10 boys and 9 girls, mean age  $12.050\pm 2.415$ ; age range 9-16 years). Obesity-related comorbidities among subjects in the group with obesity included: nonalcoholic fatty liver disease ( $n=32$ ), dyslipidemia ( $n=28$ ), hypertension ( $n=4$ ), and diabetes mellitus ( $n=1$ ). There was no incidence of polycystic ovary syndrome among female subjects in the obesity group.

There were no significant differences in age or sex ratios between the two groups. The obesity group had significantly higher mean BMI z-scores, PFF, HFF, and PPHFI than the control group ( $p<0.05$ ) (Table 1). As shown in Fig. 2, the mean PFF of the obese group was more than three times that of the control group ( $6.652\pm 3.421$  and  $1.779\pm 0.553$ , respectively). The mean PPHFI and HFF of the group with obesity were more than 3 and 8 times, respectively, those of the control group (PPHFI,  $3.645\pm 1.632$  and  $0.942\pm 0.315$ , respectively; HFF,  $18.600\pm 13.100$  and  $2.270\pm 0.800$ , respectively).

### Correlations between PFF and other variables

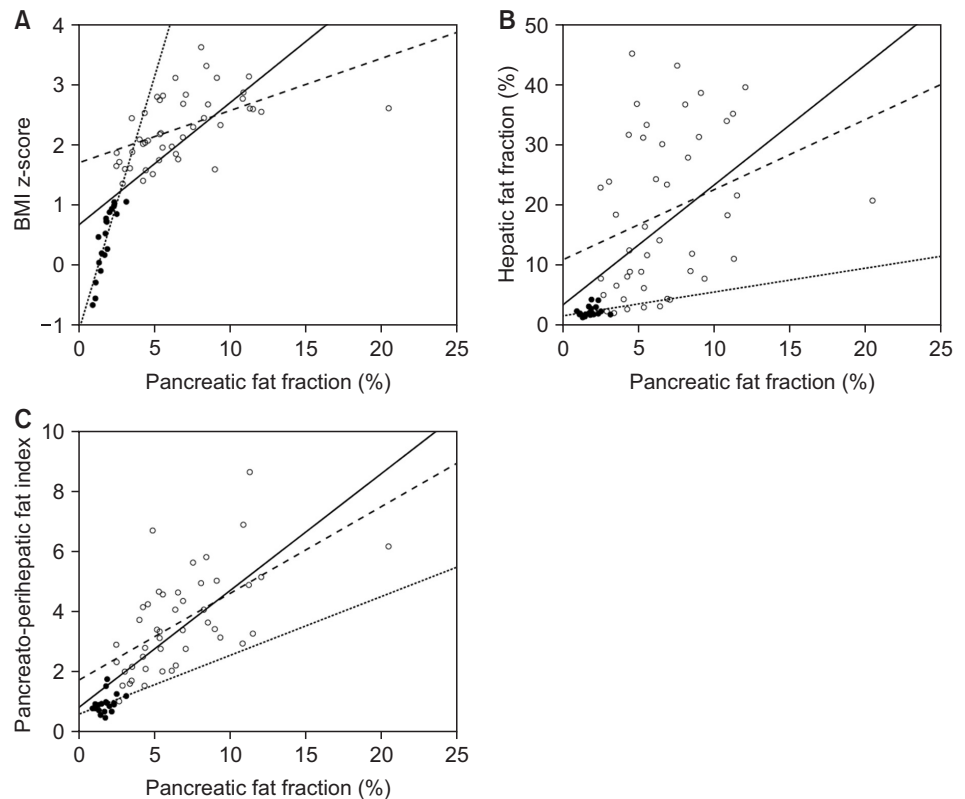
As presented in Table 2, correlations between PFF and other variables (BMI z-score, HFF, PPHFI, and age) were examined in all subjects and in the group with obesity and without obesity separately. As shown in Fig. 3A, PFF was strongly correlated with BMI z-score (in order of strength) in the control group, all subjects, and the group with obesity ( $r=0.863$ ,  $r=0.729$ , and  $r=0.529$ ,  $p<0.001$ , respectively). As shown in Fig. 3B, PFF and HFF were correlated in all subjects ( $r=0.545$ ,  $p<0.001$ ) and the group with obesity ( $r=0.304$ ,  $p=0.042$ ), but not in the control group. As shown in Fig. 3C, PFF and PPHFI were correlated among all subjects ( $r=0.764$ ,  $p<0.001$ ) and the group with obesity ( $r=0.605$ ,  $p<0.001$ ), but not in

**Table 2.** Pearson correlations between pancreatic fat fraction and anthropometric data

Variable	All (n=64)		Control group (n=19)		Group with obesity (n=45)	
	Pearson	p-value	Pearson	p-value	Pearson	p-value
Age	0.297	0.017*	0.012	0.960	0.260	0.085
BMI z-score	0.729	<0.001***	0.863	<0.001**	0.529	<0.001***
PPHFI	0.764	<0.001***	0.344	0.149	0.605	<0.001***
HFF	0.545	<0.001***	0.262	0.279	0.304	0.042*

BMI: body mass index, PPHFI: pancreato-perihepatic fat index, HFF: hepatic fat fraction.

\* $p<0.05$ , \*\*\* $p<0.001$ .



**Fig. 3.** (A-C) Scatter plots and regression lines for the pancreatic fat fraction values versus (A) the body mass index (BMI) z-scores, (B) hepatic fat fraction values, and (C) pancreato-perihepatic fat index based on the subgroup analysis. Control group: full circles and dotted line. Obesity group: open circles and dashed line. All subjects: solid line.

the control group. A positive correlation between PFF and age was observed in all subjects ( $r=0.297$ ,  $p=0.017$ ), but not in each group separately.

As presented in **Table 3**, multivariate regression analysis was performed to determine the variables that were independently correlated with PFF. PPHFI and BMI z-scores were independently correlated with PFF in all subjects ( $p=0.001$  and  $p=0.003$ , respectively) and the obesity group ( $p=0.003$  and  $p=0.016$ , respectively), but HFF and age were not.

**Table 3.** Multivariate regression analysis for independent variables associated with pancreatic fat fraction

Variable	All (n=64)		Group with obesity (n=45)	
	$\beta$ (95% CI)	p-value	$\beta$ (95% CI)	p-value
Age	0.121 (0.053 to 0.409)	0.128	N/A	N/A
BMI z-score	0.344 (0.436 to 2.032)	0.003**	0.322 (0.381 to 3.552)	0.016*
PPHFI	0.422 (0.364 to 1.295)	0.001**	0.422 (0.314 to 1.455)	0.003**
HFF	0.107 (-0.023 to 0.082)	0.265	0.112 (-0.035 to 0.093)	0.363
	Adjusted $R^2=0.645$ $F=29.59$ $p<0.001$		Adjusted $R^2=0.420$ $F=11.63$ $p<0.001$	

Age was excluded from the model for the group with obesity.

BMI: body mass index, PPHFI: pancreato-perihepatic fat index, HFF: hepatic fat fraction,  $\beta$ : standardized coefficient, CI: confidence interval, N/A: not applicable.

\* $p<0.05$ , \*\* $p<0.01$ .

## DISCUSSION

Within organs, fat is stored as triglycerides, and steatosis is most accurately assessed by molecular quantification of these triglycerides. MRI is the only imaging modality that can detect the abnormal accumulation of triglycerides. The multi-echo Dixon method for PDFF measurement corrects for confounding factors, including  $T2^*$  decay, T1 bias, noise bias, and the multispectral complexity of fat, and has a high diagnostic performance. In particular, MRI-PDFF has been demonstrated as a non-invasive biomarker of hepatic steatosis in a number of validation studies [24,25]. Because of the retroperitoneal location of the pancreas, histological analysis by biopsy has a limited role in the assessment of pancreatic steatosis. Therefore, non-invasive imaging methods play a major role in the quantitative assessment of pancreatic fat [25].

Although a number of studies have been conducted to determine the associations between obesity, PFF, and HFF in children and adolescents, some controversies remain [4,21-23]. The main findings of our study showed that PFF, as measured by MRI-PDFF, was significantly higher in the obesity group than in the control group. In addition, PFF was strongly correlated with BMI z-scores, a quantitative measure of childhood obesity. These results support previous studies that have reported an association between pancreatic steatosis and obesity in both children and adults [4,11] and a positive association between BMI z-scores and PFF [8]. Furthermore, the present study found a significant correlation between PFF and HFF in all subjects and in the group with obesity separately. However, Maggio et al. [4] reported that PFF was associated with BMI z-scores in adolescents with obesity, but not with HFF. Furthermore, Staaf et al. [21] reported that PFF was not associated with BMI z-scores or HFF in children with obesity. Based on these conflicting reports, further studies are needed on factors other than obesity that can affect PFF and HFF in children and adolescents.

There have been several studies on pancreatic steatosis in children, but the majority have used ultrasonography [10-12], with only a few studies using a quantitative MRI approach. In particular, no previous study has compared MRI- to ultrasonography-derived quantitative measures of pancreatic fat content. Based on the results of the present study, PFF and PPHFI showed a strong correlation in all subjects and in the group with obesity separately, but not in the control group. Furthermore, multivariate analysis showed that PFF was independently correlated with BMI z-scores and PPHFI in all subjects and in the obesity group separately. These findings, taken together with previous reports that PPHFI is associated with insulin resistance and metabolic syndrome in children and adolescents, suggest that PFF may be used as a biomarker for metabolic syndrome in children and adolescents with obesity. However, further studies are required to validate this hypothesis.

The present study has several limitations. First, the number of subjects in the control group was small. Second, an assessment of metabolic syndrome, which is known to be associated with pancreatic steatosis, was not included. This was because blood sampling was excluded from the study methods for recruitment of the control group. Subsequent large prospective studies with complete laboratory blood testing are needed to address this potential confounding factor. Lastly, an ROI-based method was used in the MRI-based fat fraction analysis of each organ, and there is a risk of sampling error due to the uneven distribution of fat in the organs.

In conclusion, MRI is a readily accessible and non-invasive imaging modality that can directly assess triglyceride deposition and is highly valuable for objectively assessing

steatosis. The current study revealed that MRI-derived PFF measures were significantly correlated with childhood obesity. A highly significant correlation between MRI-derived PFF and transabdominal ultrasonography-derived PPHFI was also observed in children and adolescents with obesity. Therefore, MRI-derived PFF may be considered as an objective index of pancreatic fat content and has the potential for clinical utility as a non-invasive biomarker for the assessment of childhood obesity.

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