ULTRA SONO GRAPHY

Hyperechoic pancreas on ultrasonography: an analysis of its severity and clinical implications

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ORIGINAL ARTICLE

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Purpose: This study investigated risk factors for hyperechoic pancreas (HP) on ultrasonography (US) according to HP severity.

Methods: Between December 2008 and February 2014, 1,459 subjects who underwent abdominal US as part of health examinations were retrospectively included. Two radiologists assessed and categorized the severity of HP as normal, mild, moderate, and severe. Subjects were allocated to two groups as follows: fatty pancreas 1 (FP1; mild to severe HP) and fatty pancreas 2 (FP2; moderate to severe HP). Clinico-metabolic parameters such as the body mass index and blood test profile of subjects with normoglycemia and prediabetes/diabetes were compared (normal vs. FP1; normal or mild HP vs. FP2). Logistic regression analysis was used to evaluate the associations between HP, nonalcoholic fatty liver disease (NAFLD), and diabetes/prediabetes with adjustment for clinico-metabolic parameters.

Results: Of the 1,459 subjects, 71.2% and 40.4% showed HP and NAFLD on US, respectively. Normoglycemia and prediabetes/diabetes were present in 74.3% and 25.7% of subjects, respectively. Univariable analysis revealed that all the clinico-metabolic parameters were significantly associated with HP (all $P<0.05$). In the adjusted multivariable analysis, prediabetes/diabetes, NAFLD, age, and body mass index were significantly associated with HP with the FP1 and FP2 criteria. The independent factor with the strongest association with HP was NAFLD using the FP1 criterion (odds ratio [OR], 7.93; $P<0.001$) and prediabetes/diabetes using the FP2 criterion (OR, 6.96; $P<0.001$).

Conclusion: NAFLD and prediabetes/diabetes were associated with US-diagnosed HP. Moderate to severe HP was a better predictor of prediabetes/diabetes, suggesting that evaluating HP severity may be useful in clinical practice.

Keywords: Ultrasonography; Hyperechoic pancreas; Fatty pancreas; Diabetes; Nonalcoholic fatty liver disease

Key points: Moderate to severe hyperechoic pancreas on ultrasonography is a good predictor for prediabetes/diabetes. Evaluation of the severity of hyperechoic pancreas may be useful in clinical practice.

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Introduction

Excessive visceral fat deposition is a known risk factor for diabetes mellitus (DM), metabolic syndrome, and cardiovascular disease [1,2]. The association between ectopic fat accumulation in the liver, termed nonalcoholic fatty liver disease (NAFLD), and metabolic syndrome is well established [3–5]. Fatty pancreas or nonalcoholic fatty pancreas disease (NAFPD) has also received attention recently, and NAFPD has been reported to be related to metabolic syndrome [6–8].

Several previous studies have used ultrasonography (US) as a diagnostic and screening tool for the evaluation of fatty pancreas, given its non-invasiveness and cost-effectiveness [6,9–13]. On US, fatty pancreas is defined as a hyperechoic pancreas (HP) with higher echogenicity than that of the liver or renal cortex [6,14,15]. However, the normal echogenicity of the pancreas is known to be equal to or slightly greater than that of the liver [16]. Therefore, the diagnostic criteria are vague, and it may be challenging to diagnose fatty pancreas if NAFLD exists at the same time. Additionally, the retroperitoneal location of the pancreas makes it more difficult to visualize, particularly in obese patients. Therefore, a quantitative analysis or stratification of pancreatic echogenicity is necessary.

To the authors' best knowledge, limited data exist on the severity or clinical implications of fatty pancreas [6,17], and the data were obtained from a few selected subjects. Therefore, the purpose of this study was to identify the risk factors for HP on US stratified by its severity.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the Institutional Review Board of Chung-Ang University Hospital (2007-037-19326), and the requirement for informed consent was waived due to the retrospective study design.

Study Population

The subjects of this cross-sectional study included examinees who underwent routine health screenings at the authors' affiliated hospital between December 2008 and February 2014. Individuals who underwent transabdominal US for health screening at a tertiary hospital were analyzed. The exclusion criteria were as follows: (1) age below 20 years, (2) history of viral hepatitis or seropositive for hepatitis B or C viral antigen, (3) >20 g/day estimated alcohol consumption, (4) history of liver or pancreatic surgery, (5) history of renal disease, and (6) incomplete laboratory tests. Patients with poor image quality impeding recognition of the pancreas were also excluded. The inclusion process of the study population is shown in Fig. 1.

Clinical and Biochemical Parameters

The data collected included the subjects' age (years), sex (male/female), waist circumference, systolic and diastolic blood pressure, comorbidities (e.g., prediabetes and diabetes), alcohol consumption, and medications used. Measurements of the subjects' height and body weight were used to calculate the body mass index (BMI; kg/m^2). Systolic and diastolic blood pressures were recorded in the sitting position. After an overnight 12-hour fast, all subjects underwent blood tests, including a complete blood count and routine biochemistry tests, with measurements of fasting plasma glucose, serum glycosylated hemoglobin (HbA1c), blood urea nitrogen (BUN), creatinine (Cr), triglycerides (TG), total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Diabetes and prediabetes were defined using the American Diabetes Association criteria. Prediabetes was diagnosed based on a fasting plasma glucose level of 100–125 mg/dL and an HbA1c of 5.7%–6.4%.

Definition of Metabolic Syndrome

Metabolic syndrome was defined using the modified NCEP-Adult Treatment Panel III and the criteria for visceral obesity followed by the Korean Society for the Study of Obesity. Metabolic syndrome was characterized by three or more of the following criteria: waist circumference of ≥90 cm for men and ≥80 cm for women, elevated TG level of ≥50 mg/dL or drug treatment for elevated TG, reduced HDL-cholesterol of <40 mg/dL for men and <50 mg/dL for women or drug treatment for reduced HDL-cholesterol, systolic blood

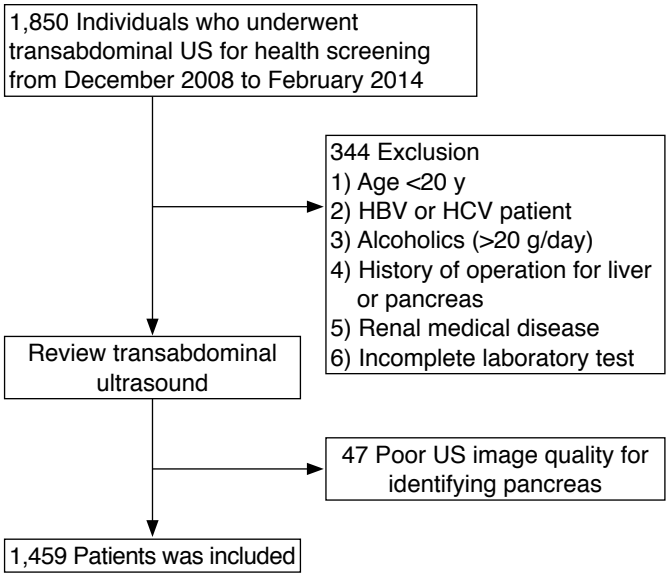

Fig. 1. **Flow diagram showing the patient selection criteria and study flow.** US, ultrasonography; HBV, hepatitis B virus; HCV, hepatitis C virus.

pressure of ≥130 mmHg or diastolic blood pressure of ≥85 mmHg or antihypertensive drug treatment, and elevated fasting glucose level of ≥100 mg/dL or drug treatment for elevated glucose.

Assessment of Abdominal US

All subjects underwent abdominal US including the liver, pancreas, and spleen using a convex 3.5-MHz transducer (LOGIQ7 and LOGIQ9, GE Healthcare, Milwaukee, WI, USA) after an overnight 12-hour fast. Three experienced senior radiologists who were blinded to the clinical and laboratory parameters performed the US examinations. Routine abdominal US for the pancreas was standardized according to the Ultrasound Practice Guidelines published by The Korean Society of Radiology and Korean Society of Ultrasound in Medicine, which performed axial scans under the xiphoid process; they found the splenic vein in the anterior aspect of the pancreas with deep inspiration or when pushing the abdomen out to make it bulge [18] (Fig. 2).

Two radiologists (H.O. and H.J.P., with 2 years and 13 years of experience in abdominal US, respectively), who were blinded to the clinical and laboratory data, independently reviewed the abdominal US images to grade HP and identify NAFLD on the same commercial workstation with a 2,000×2,000 PACS monitor (Centricity, GE

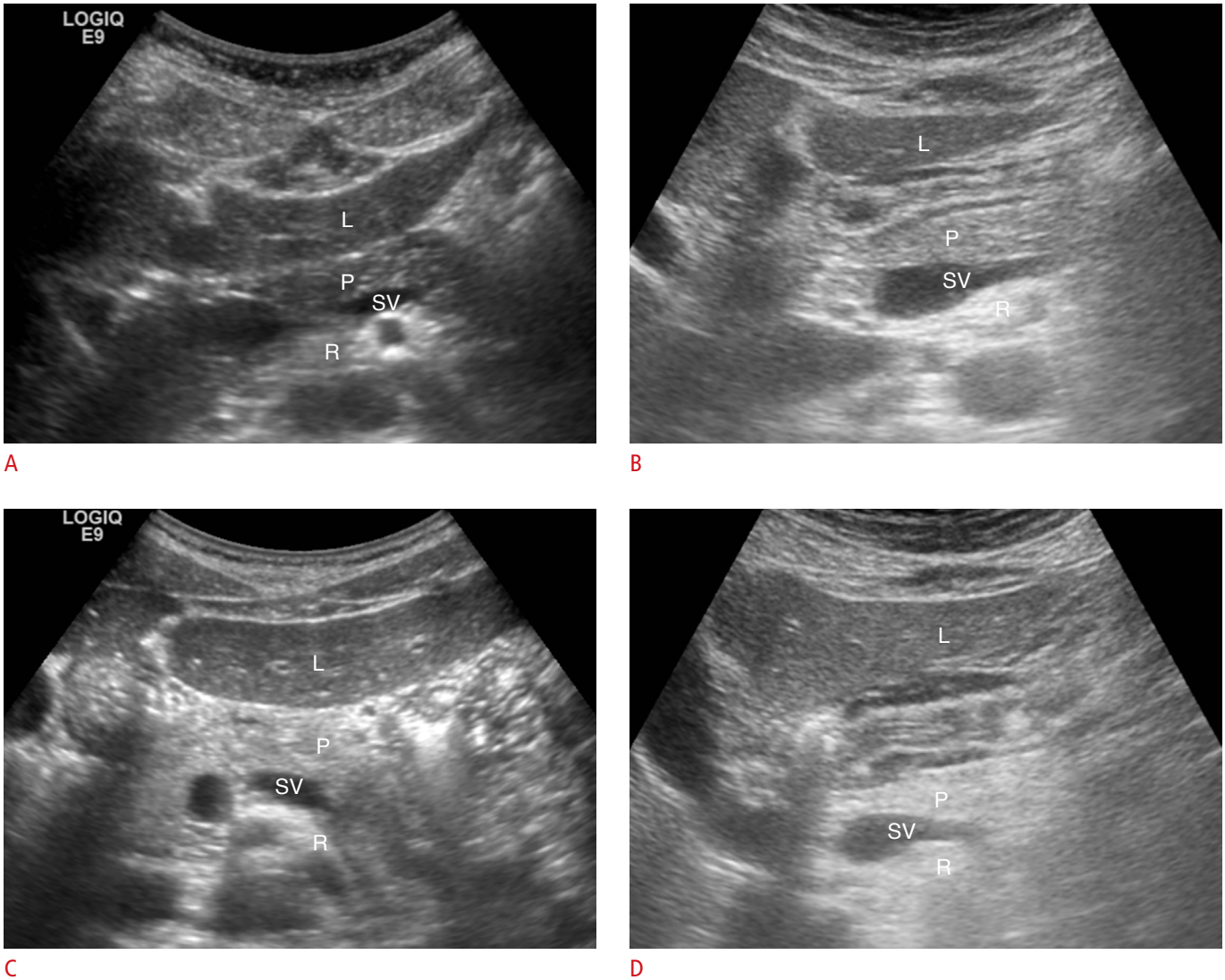

Fig. 2. Classification of pancreatic echogenicity on abdominal ultrasound.
The pancreas is detected in the anterior aspect of the splenic vein. A. Abdominal ultrasonography shows non-fatty pancreas; similar to the echogenicity of the liver. B. Mild degree of hyperechoic pancreas shows slightly increased echogenicity compared to the echogenicity of the liver. C. Moderate degree of hyperechoic pancreas shows definite increased echogenicity, but lower than that of retroperitoneal fat. D. Severe degree of hyperechoic pancreas shows similar to or higher than the echogenicity of retroperitoneal fat. P, pancreas; L, left hemiliver; R, retroperitoneal fat; SV, splenic vein.

Healthcare). A third observer (E.S.L. with 13 years of experience in abdominal US) reviewed the grading of NAFLD and HP if there was interobserver disagreement.

The observers graded liver echogenicity as normal, mild, moderate, and severe according to the criteria described by Needleman et al. [19]. Mild echogenicity was characterized by the increased hepatic brightness with normal visualization of the border of the hepatic vasculature and the diaphragm. Moderate echogenicity was characterized by a diffuse increase in hepatic echogenicity with an obscured intrahepatic vessel border; the echogenicity of the diaphragm was still appreciable. Severe echogenicity was represented by a marked increase in hepatic echogenicity with impaired periportal and diaphragmatic echogenicity.

According to previous studies [6,7,15,17], the US diagnostic criteria for HP were defined as follows: (1) non-fatty pancreas: echogenicity similar to that of the liver or hypoechoic or isoechoic compared with the spleen; (2) mild fatty pancreas: slightly increased echogenicity compared with the liver or spleen; (3) moderate fatty pancreas: definitely increased echogenicity compared with the liver and spleen, but lower than the echogenicity of retroperitoneal fat; (4) severe fatty pancreas: echogenicity similar to or higher than that of retroperitoneal fat (Fig. 2). If the liver appeared hyperechoic or the left lobe was not displayed in the same window as the pancreas, the echogenicity of the pancreas was judged relative to the renal cortex or spleen [14,20].

Statistical Analysis

The statistical analysis was conducted using R version 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria). All continuous variables were expressed as mean±standard deviation.

Two HP definitions were applied based on US severity as follows: fatty pancreas 1 (FP1), corresponding to mild HP or more, and fatty pancreas 2 (FP2), as moderate HP or more. All the analyses described below were performed using the FP1 and FP2 criteria.

The Student t-test was used to compare continuous variables between the two groups based on the presence of HP. The chi-square test was used for nominal variables. Univariable and multivariable logistic regression analyses were performed for the FP1 and FP2 criteria, respectively, to determine independent risk factors with major effects on HP. Multicollinearity was assessed using the variance inflation factor (VIF). A VIF >10 was considered to indicate multicollinearity. Correlations between two nominal variables (FP and prediabetes/diabetes) were assessed with Cramer's V; a level of >0.250 was considered indicative of a strong relationship. The Spearman correlation coefficient was used to evaluate the association between each variable and the severity of HP and the Tukey method for multiple comparisons.

The interobserver agreement for the severity of HP and presence of NAFLD on US between the two radiologists was analyzed using κ statistics and interpreted as follows: poor, <0.20; fair, 0.20–0.39; moderate, 0.40–0.59; substantial, 0.60–0.79; almost perfect, ≥0.80. A P-value of less than 0.05 was considered to indicate statistical significance.

Results

Characteristics of the Study Subjects

In total, 1,459 subjects were included in the cross-sectional analysis. Of them, 854 were men (58.5%) and 605 were women (41.5%). Their mean age and BMI were 47.3±10.6 years and 23.5±3.2 kg/m^2, respectively. There were 210 subjects (14.4%) with metabolic syndrome. The normoglycemic group and prediabetes/diabetes group accounted for 74.3% (n=1,084) and 25.7% (n=375, prediabetes/diabetes=356/19) of the subjects, respectively.

Of 1,459 subjects, 589 participants (40.4%) had NAFLD on US. HP was observed on US in 71.2% (1,039/1,459) of subjects, and the distribution of mild, moderate, and severe HP was as follows: 415 (28.4%), 398 (27.3%), and 226 (15.5%), respectively.

The baseline characteristics of the study participants in the HP and non-HP groups according to the FP1 and FP2 criteria are summarized in Table 1. Age, weight, BMI, waist circumference, and fasting blood glucose, TG, Cr, and LDL levels were significantly higher in the HP group than in the non-HP group for both FP1 and FP2 (all P<0.05). The HP group also showed a higher proportion of NAFLD, prediabetes/diabetes, and male sex (P<0.001). The interobserver agreement for the US severity of HP and the presence of NAFLD was substantial (κ=0.77, κ=0.75, respectively).

Associations between HP and Clinical Variables

To analyze the factors related to fatty pancreas, a multivariable analysis was conducted with the variables that had significant relationships with fatty pancreas in the univariable analysis using a logistic regression model. In the univariable analysis of the FP1 and FP2 criteria, all the evaluated factors showed significant differences between the HP and non-HP groups (all P<0.05) (Table 2). Prediabetes/diabetes was also a significant risk factor for HP (odds ratio [OR], 11.0; P<0.001 in FP1 and OR, 11.7; P<0.001 in FP2).

Multivariable logistic analysis was conducted with HP as a dependent variable; the selected factors were added as independent variables in six steps involving six models (Tables 3, 4). In the first step, model 1, prediabetes/diabetes and NAFLD were used as independent variables. Subsequently, other independent variables were added as follows: model 2, age and sex were added to those of model 1; model 3, plasma glucose and HbA1c were added to

Table 1. Baseline characteristics of study participants according to the severity of HP

Characteristic	Normal (n=420)	FP1 (n=1,039)	P-value	Normal and mild HP (n=835)	FP2 (n=624)	P-value
Sex (male/female)	174/246	680/359	<0.001	424/411	430/194	<0.001
Age (year)	42.98±9.56	49.05±10.51	0.022	45.15±9.93	50.17±0.43	0.022
Weight (kg)	58.52±9.65	68.40±11.94	<0.001	61.61±10.72	70.84±12.01	0.002
BMI	21.46±2.51	24.59±3.07	<0.001	22.41±2.74	25.39±3.07	0.002
WC (cm)	75.96±7.63	85.35±8.99	<0.001	78.84±8.26	87.75±8.89	0.048
SBP (mmHg)	114.68±12.23	122.88±12.74	0.328	117.59±13.02	124.44±12.22	0.094
DBP (mmHg)	68.85±9.32	74.24±9.97	0.106	70.74±9.72	75.29±9.98	0.481
FBG (mg/dL)	88.96±10.61	98.19±19.26	<0.001	91.31±14.49	101.18±19.94	<0.001
HbA1c (%)	5.38±0.42	5.70±0.66	<0.001	5.45±0.51	5.82±0.68	<0.001
TG (mg/dL)	81.72±45.31	132.71±85.61	<0.001	97.66±68.98	145.30±84.69	<0.001
Cr	0.94±0.17	1.01±0.23	<0.001	0.98±0.21	1.00±0.23	0.003
BUN	12.95±3.41	13.88±3.61	0.175	13.22±3.54	14.13±3.57	0.798
LDL	117.25±28.45	127.31±34.11	<0.001	120.61±30.56	129.50±35.14	<0.001
NAFLD	22 (5.2)	567 (54.7)	<0.001	154 (18.4)	435 (69.7)	<0.001
Prediabetes/diabetes	19 (4.5)	356 (34.4)	<0.001	65 (7.8)	310 (49.7)	<0.001

Values are presented as mean±SD or number (%).

The FP1 criterion referred to at least mild HP, and the FP2 criterion referred to at least moderate HP.

HP, hyperechoic pancreas; FP1, fatty pancreas 1; FP2, fatty pancreas 2; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting plasma glucose; HbA1c, serum glycosylated hemoglobin; TG, triglycerides; Cr, creatinine; BUN, blood urea nitrogen; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; SD, standard deviation.

Table 2. Univariable logistic regression analysis for variables associated with HP

	FP1 group		FP2 group	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Male sex	0.37 (0.30–0.47)	<0.001	0.47 (0.37–0.58)	<0.001
Age (year)	1.06 (1.05–1.08)	<0.001	1.05 (1.04–1.06)	<0.001
Weight (kg)	1.09 (1.08 –1.10)	<0.001	1.07 (1.06 –1.09)	<0.001
BMI	1.54 (1.46–1.62)	<0.001	1.45 (1.38–1.52)	<0.001
WC (cm)	1.14 (1.12–1.16)	<0.001	1.14 (1.12–1.15)	<0.001
SBP (mmHg)	1.05 (1.04–1.06)	<0.001	1.04 (1.03–1.05)	<0.001
DBP (mmHg)	1.06 (1.05–1.07)	<0.001	1.05 (1.04–1.06)	<0.001
FBG (mg/dL)	1.06 (1.04–1.07)	<0.001	1.05 (1.04–1.05)	<0.001
HbA1c (%)	4.34 (3.20–5.90)	<0.001	4.18 (3.20–5.46)	<0.001
TG (mg/dL)	1.02 (1.01–1.02)	<0.001	1.01 (1.01–1.01)	<0.001
Cr	6.95 (3.52–13.71)	<0.001	1.77 (1.06–2.95)	0.028
BUN	1.08 (1.04–1.12)	<0.001	1.07 (1.04–1.11)	<0.001
LDL	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001
NAFLD	21.73 (13.91–33.96)	<0.001	10.18 (7.97–13.00)	<0.001
Prediabetes/diabetes	11.00 (6.82–17.74)	<0.001	11.70 (8.68–15.75)	<0.001

The FP1 criterion referred to at least mild HP, and the FP2 criterion referred to at least moderate HP.

HP, hyperechoic pancreas; FP1, fatty pancreas 1; FP2, fatty pancreas 2; OR, odds ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting plasma glucose; HbA1c, serum glycosylated hemoglobin; TG, triglycerides; Cr, creatinine; BUN, blood urea nitrogen; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.

Table 3. Multivariable logistic regression analysis for variables associated with HP using the FP1 criterion

Model		OR (95% CI)	P-value
1	Prediabetes/diabetes	6.34 (3.84–10.45)	<0.001
	NAFLD	16.51 (10.51–25.93)	<0.001
2	Prediabetes/diabetes	4.81 (2.88–8.02)	<0.001
	NAFLD	15.03 (9.45–23.90)	<0.001
3	Prediabetes/diabetes	4.50 (2.51–8.04)	<0.001
	NAFLD	14.82 (9.30–23.63)	<0.001
4	Prediabetes/diabetes	4.02 (2.21–7.33)	<0.001
	NAFLD	8.75 (5.40–14.16)	<0.001
5	Prediabetes/diabetes	3.83 (2.09–7.01)	<0.001
	NAFLD	7.86 (4.82–12.81)	<0.001
6	Prediabetes/diabetes	3.90 (2.12–7.18)	<0.001
	NAFLD	7.93 (4.86–12.94)	<0.001

FP1 criterion, at least mild HP.

Model 1, prediabetes/DM and NAFLD as independent variables; Model 2, adjusted for the variables of model 1, age, and sex; Model 3, adjusted for the variables of model 2, plasma glucose, and HbA1c; Model 4, adjusted for the variables of model 3, weight, BMI, and waist circumference; Model 5, adjusted for the variables of model 4, TG, and LDL; Model 6, fully adjusted model.

HP, hyperechoic pancreas; FP1, fatty pancreas 1; OR, odds ratio; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; DM, diabetes mellitus; HbA1c, serum glycosylated hemoglobin; BMI, body mass index; TG, triglycerides; LDL, low-density lipoprotein.

Table 4. Multivariable logistic regression analysis for variables associated with HP using the FP2 criterion

Model		OR (95% CI)	P-value
1	Prediabetes/diabetes	8.53 (6.61–11.81)	<0.001
	NAFLD	6.94 (6.09–10.34)	<0.001
2	Prediabetes/diabetes	7.31 (5.26–10.17)	<0.001
	NAFLD	7.71 (5.85–10.17)	<0.001
3	Prediabetes/diabetes	8.43 (5.69–12.50)	<0.001
	NAFLD	7.88 (5.96–10.42)	<0.001
4	Prediabetes/diabetes	7.14 (4.78–10.68)	<0.001
	NAFLD	4.96 (3.68–6.70)	<0.001
5	Prediabetes/diabetes	7.00 (4.68–10.49)	<0.001
	NAFLD	4.70 (3.46–6.38)	<0.001
6	Prediabetes/diabetes	6.96 (4.64–10.43)	<0.001
	NAFLD	4.68 (3.44–6.36)	<0.001

FP2 criterion, at least moderate HP.

Model 1, prediabetes/DM and NAFLD as independent variables; Model 2, adjusted for variables of model 1, age, and sex; Model 3, adjusted for variables of model 2, plasma glucose, and HbA1c; Model 4, adjusted for variables of model 3, weight, BMI, and waist circumference; Model 5, adjusted for variables of model 4, TG, and LDL; Model 6, fully adjusted model.

HP, hyperechoic pancreas; FP2, fatty pancreas 2; OR, odds ratio; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; DM, diabetes mellitus; HbA1c, serum glycosylated hemoglobin; BMI, body mass index; TG, triglycerides; LDL, low-density lipoprotein.

those of model 2; model 4, weight, BMI, and waist circumference were added to those of model 3; and model 5, TG and LDL were added to those of model 4. Model 6 was fully adjusted.

In FP1, NAFLD showed the most significant association with HP followed by prediabetes/diabetes, even after correction for other variables throughout the analysis (all P<0.001) (Table 3, Supplementary Tables 1, 2). BMI, age, and TG also had significant associations with HP (all P<0.05) (Supplementary Table 1), albeit with lower ORs. In the fully adjusted model, the ORs for the risk associations of HP were 7.93 (95% confidence interval [CI], 4.86 to 12.94; P<0.001) for NAFLD and 3.90 (95% CI, 2.12 to 7.18; P<0.001) for prediabetes/diabetes.

In FP2, prediabetes/diabetes revealed the most significant association with HP, followed by NAFLD, even after correction for other variables throughout the analysis (Table 4, Supplementary Tables 2, 3). BMI and age also had significant associations with HP (all P<0.05) (Supplementary Table 2), albeit with lower ORs. In the fully adjusted model, the ORs for the risk associations of HP were 6.96 (95% CI, 4.64 to 10.43; P<0.001) for prediabetes/diabetes and 4.68 (95% CI, 3.44 to 6.36; P<0.001) for NAFLD.

The Cramer V statistic also revealed a significantly stronger association between HP and prediabetes/diabetes using the FP2 criterion (0.474, P<0.001) than using the FP1 criterion (0.308, P<0.001).

Association with Clinical Variables according to HP Severity

Table 5 shows associations between the clinical variables and HP severity. NAFLD, age, weight, BMI, waist circumference, systolic and diastolic blood pressures, fasting plasma glucose, HbA1c, BUN, Cr, TG, and LDLs tended to increase with the severity of HP (all P<0.001).

Discussion

HP is not an uncommon US finding, but its clinical significance and diagnostic criteria have yet to be established. Our study demonstrated that NAFLD and prediabetes/diabetes were the strongest predictors of HP on US (OR, 7.93 for NAFLD and OR, 3.90 for prediabetes/diabetes in FP1; OR, 4.68 for NAFLD and OR, 6.96 for prediabetes/diabetes in FP2). When the severity of HP was at least mild (FP1), NAFLD showed the highest association with HP. However, for moderate severity (FP2), prediabetes/diabetes revealed the strongest association with HP, even after correction for other variables throughout the entire analysis.

Table 5. Associations of variables with severity of hyperechoic pancreas using Spearman correlation coefficients (r)

Variable	r	P-value
Male sex	−0.216	<0.001
Age	0.278	<0.001
Weight	0.432	<0.001
Body mass index	0.533	<0.001
Waist circumference	0.542	<0.001
Systolic blood pressure	0.308	<0.001
Diastolic blood pressure	0.260	<0.001
Fasting plasma glucose	0.373	<0.001
Serum glycosylated hemoglobin	0.416	<0.001
Triglycerides	0.412	<0.001
Creatinine	0.109	<0.001
Blood urea nitrogen	0.142	<0.001
Low-density lipoprotein	0.152	<0.001
Nonalcoholic fatty liver disease	0.588	<0.001

Fatty pancreas or nonalcoholic fatty pancreatic disease is a new clinical entity characterized by evidence of excessive pancreatic fat accumulation in patients without significant alcohol consumption [21]. Previous studies using autopsy or transabdominal US reported that age and BMI were related factors [7,15,22,23]. Recent studies have demonstrated additional potential related factors, including NAFLD, visceral fat, insulin resistance, and diabetes [6,20,24]. Previous studies also demonstrated that HP, as a result of pancreatic fat deposition on US, is closely associated with these factors [12,14,17,20].

While the pathophysiological mechanism underlying HP is not fully understood, excessive visceral fat and the related elevation of circulating free fatty acid levels lead to fat infiltration of the pancreas, which may contribute to the damage of β-cells. Similarly, obesity leads to fat infiltration of the liver, which may also play a significant role in NAFLD [25]. Strong associations between fatty pancreas and DM and NAFLD have been reported in several studies [6,9–12,14,17,20,26]. The concurrence rates of DM and NAFLD with fatty pancreas on US have been reported as 7%–48.5% and 25.7%–67.9%, respectively [6,11,13,26]. Similarly, in the present study, a considerable number of participants with fatty pancreas had prediabetes/diabetes (34.4% in FP1, 49.7% in FP2) and NAFLD (52.7% in FP1, 68.4% in FP2).

In this study, NAFLD showed the highest association with HP in cases of fatty pancreas characterized by mild HP (FP1), which is consistent with findings from previous studies [12,17,20]. However, when moderate to severe HP was present (FP2 criterion), prediabetes/diabetes demonstrated the strongest association with HP. Several studies reported that fat deposition in the pancreas was significantly higher in patients with diabetes than in controls following qualitative and quantitative analyses using imaging modalities [9,27,28]. Additionally, Chai et al. [27] and Heber et al. [28] reported significantly higher median values for the quantitative measurement of pancreatic fat in subjects with prediabetes/diabetes than in normal controls using magnetic resonance imaging. Therefore, the authors speculate that the close association between HP and prediabetes/diabetes in the FP2 criterion is related to the association between moderate to severe HP and higher pancreatic fat, which may lead to damage and dysfunction of the pancreas. Thus, pancreatic fat was higher in patients with diabetes than in those without diabetes.

Previous studies of fatty pancreas have used various diagnostic modalities, including magnetic resonance imaging, computed tomography, magnetic resonance spectroscopy, and endoscopic US [14,17,20,24,27,29]. However, US has been widely used to screen for fatty pancreas due to its accessibility, cost-effectiveness, and non-invasiveness [6,9–13]. The reported prevalence of fatty pancreas in previous studies varies widely from 8.5% to 61.4% [12,14,17,30–32], probably owing to insufficient evidence based on the use of a widely accepted imaging modality or uncertainty regarding the subjective definition of HP. Although some investigators have attempted the quantitative analysis of pancreatic echogenicity, the method is complicated and not generally accepted [33]. In the present study, the severity of HP was stratified into mild and moderate using a cutoff value. This study demonstrated that HP of a moderate degree or beyond was the most significant predictor of prediabetes/diabetes.

There are several limitations to this study. First, the participants were recruited from self-referred examinations in a single center, and they may not be representative of the general population. Second, the prevalence of fatty pancreas was higher in the present study than in previous studies; however, considering the wide range of fatty pancreas prevalence, the authors believe that this may be acceptable. A large sample could have been beneficial for generalization to the larger population of interest. Further research is warranted to clarify the effects of fatty pancreas. Third, since the present study included a small number of patients with DM, both prediabetes and diabetes were evaluated as markers of insulin resistance. This study only included participants who presented for health screening examinations, whereas patients with diabetes would receive follow-up at the Department of Endocrinology. Therefore, further studies with a larger number of participants are needed to validate these results. Fourth, there could be some interpretation errors associated with different gain levels during US examinations and it would be possible that the actual echogenicity

of each organ is greater or lesser than shown on the image. Finally, histological evaluations of the pancreas were not performed; however, pancreatic biopsy is very invasive and is not suitable in healthy subjects. This study used US as one of the best non-invasive methods for evaluating liver and pancreas fat, which has been proven in previous studies as a reliable, reproducible, and non-invasive screening tool for fatty pancreas.

In conclusion, NAFLD and prediabetes/diabetes were significantly associated with HP diagnosed using US. Additionally, moderate to severe HP was found to be a better predictor of prediabetes/diabetes than more than mild HP. Therefore, evaluating the severity of HP may be useful in clinical practice.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Supplementary Material

Supplementary Table 1. Multivariable logistic regression analysis by variables associated with HP using FP1 criterion (https://doi.org/10.14366/usg.21099).

Supplementary Table 2. Fully adjusted model using multivariable logistic regression analysis by variables associated with HP (https://doi.org/10.14366/usg.21099).

Supplementary Table 3. Multivariable logistic regression analysis by variables associated with HP using FP2 criterion (https://doi.org/10.14366/usg.21099).

References

1. Despres JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol 2008;28:1039-1049.
2. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683-689.
3. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10:330-344.
4. Hamaguchi M, Kojima T, Takeda N, Nagata C, Takeda J, Sarui H, et al. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. World J Gastroenterol 2007;13:1579-1584.
5. Kotronen A, Yki-Jarvinen H. Fatty liver: a novel component of the metabolic syndrome. Arterioscler Thromb Vasc Biol 2008;28:27-38.
6. Lee JS, Kim SH, Jun DW, Han JH, Jang EC, Park JY, et al. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. World J Gastroenterol 2009;15:1869-1875.
7. Worthen NJ, Beabeau D. Normal pancreatic echogenicity: relation to age and body fat. AJR Am J Roentgenol 1982;139:1095-1098.
8. Pezzilli R, Calculli L. Pancreatic steatosis: is it related to either obesity or diabetes mellitus? World J Diabetes 2014;5:415-419.
9. Ou HY, Wang CY, Yang YC, Chen MF, Chang CJ. The association between nonalcoholic fatty pancreas disease and diabetes. PLoS One 2013;8:e62561.
10. Wu WC, Wang CY. Association between non-alcoholic fatty pancreatic disease (NAFPD) and the metabolic syndrome: case-control retrospective study. Cardiovasc Diabetol 2013;12:77.
11. Uygun A, Kadayifci A, Demirci H, Saglam M, Sakin YS, Ozturk K, et al. The effect of fatty pancreas on serum glucose parameters in patients with nonalcoholic steatohepatitis. Eur J Intern Med 2015;26:37-41.
12. Wang CY, Ou HY, Chen MF, Chang TC, Chang CJ. Enigmatic ectopic fat: prevalence of nonalcoholic fatty pancreas disease and its associated factors in a Chinese population. J Am Heart Assoc 2014;3:e000297.
13. Lesmana CR, Pakasi LS, Inggriani S, Aidawati ML, Lesmana LA. Prevalence of non-alcoholic fatty pancreas disease (NAFPD) and its risk factors among adult medical check-up patients in a private hospital: a large cross sectional study. BMC Gastroenterol 2015;15:174.
14. Choi CW, Kim GH, Kang DH, Kim HW, Kim DU, Heo J, et al. Associated factors for a hyperechogenic pancreas on endoscopic ultrasound. World J Gastroenterol 2010;16:4329-4334.
15. Marks WM, Filly RA, Callen PW. Ultrasonic evaluation of normal pancreatic echogenicity and its relationship to fat deposition. Radiology 1980;137:475-479.
16. Ghorashi B, Rector WR. Gray scale sonographic anatomy of the pancreas. J Clin Ultrasound 1977;5:25-29.
17. Sepe PS, Ohri A, Sanaka S, Berzin TM, Sekhon S, Bennett G, et al. A

prospective evaluation of fatty pancreas by using EUS. Gastrointest Endosc 2011;73:987-993.
18. The Korean Society of Radiology, Korean Society of Ultrasound in Medicine. Ultrasound practice guidelines. Seoul: Tarae, 2014;17-26.
19. Needleman L, Kurtz AB, Rifkin MD, Cooper HS, Pasto ME, Goldberg BB. Sonography of diffuse benign liver disease: accuracy of pattern recognition and grading. AJR Am J Roentgenol 1986;146:1011-1015.
20. Al-Haddad M, Khashab M, Zyromski N, Pungpapong S, Wallace MB, Scolapio J, et al. Risk factors for hyperechogenic pancreas on endoscopic ultrasound: a case-control study. Pancreas 2009;38:672-675.
21. Alempijevic T, Dragasevic S, Zec S, Popovic D, Milosavljevic T. Non-alcoholic fatty pancreas disease. Postgrad Med J 2017;93:226-230.
22. Glaser J, Stienecker K. Pancreas and aging: a study using ultrasonography. Gerontology 2000;46:93-96.
23. Olsen TS. Lipomatosis of the pancreas in autopsy material and its relation to age and overweight. Acta Pathol Microbiol Scand A 1978;86:367-373.
24. Sijens PE, Edens MA, Bakker SJ, Stolk RP. MRI-determined fat content of human liver, pancreas and kidney. World J Gastroenterol 2010;16:1993-1998.
25. Fraulob JC, Ogg-Diamantino R, Fernandes-Santos C, Aguila MB, Mandarim-de-Lacerda CA. A mouse model of metabolic syndrome: insulin resistance, fatty liver and non-alcoholic fatty pancreas disease (NAFPD) in C57BL/6 mice fed a high fat diet. J Clin Biochem Nutr 2010;46:212-223.
26. Fu J, Lesmana CR, Subekti I, Hasan I, Sanityoso A, Harimurti K, et al. Non-alcoholic fatty pancreas disease and its associated factors in type 2 diabetes mellitus patients. J Pancreas 2017;18:387-392.
27. Chai J, Liu P, Jin E, Su T, Zhang J, Shi K, et al. MRI chemical shift imaging of the fat content of the pancreas and liver of patients with type 2 diabetes mellitus. Exp Ther Med 2016;11:476-480.
28. Heber SD, Hetterich H, Lorbeer R, Bayerl C, Machann J, Auweter S, et al. Pancreatic fat content by magnetic resonance imaging in subjects with prediabetes, diabetes, and controls from a general population without cardiovascular disease. PLoS One 2017;12:e0177154.
29. Kuhn JP, Berthold F, Mayerle J, Volzke H, Reeder SB, Rathmann W, et al. Pancreatic steatosis demonstrated at MR imaging in the general population: clinical relevance. Radiology 2015;276:129-136.
30. Hung CS, Tseng PH, Tu CH, Chen CC, Liao WC, Lee YC, et al. Increased pancreatic echogenicity with US: relationship to glycemic progression and incident diabetes. Radiology 2018;287:853-863.
31. Sotoudehmanesh R, Tahmasbi A, Sadeghi A, Hosseini H, Mohamadnejad M. The prevalence of nonalcoholic fatty pancreas by endoscopic ultrasonography. Pancreas 2019;48:1220-1224.
32. Weng S, Zhou J, Chen X, Sun Y, Mao Z, Chai K. Prevalence and factors associated with nonalcoholic fatty pancreas disease and its severity in China. Medicine (Baltimore) 2018;97:e11293.
33. Jeong HT, Lee MS, Kim MJ. Quantitative analysis of pancreatic echogenicity on transabdominal sonography: correlations with metabolic syndrome. J Clin Ultrasound 2015;43:98-108.