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The prevalence and clinical implications of pancreatic fat accumulation identified during a medical check-up

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Abstract

Fatty pancreas (FP) is characterized by pancreatic fat accumulation and the subsequent development of pancreatic and metabolic complications. However, FP has not been categorized in the manual for abdominal ultrasound in cancer screening and health check-ups in Japan, and the pathology of FP has not been fully elucidated.

Nine hundred and nineteen people who underwent a medical check-up had the severity of their pancreatic fat accumulation categorized after transabdominal ultrasonographic examination. The relationships between FP, lifestyle-related diseases, and fatty liver disease at this time were assessed using stratification analysis.

The prevalence of FP was 46.8% (430/919). People with FP were more likely to be male and had higher prevalences of lifestyle-related diseases, including fatty liver disease. Men and women were similarly represented in each tertile of pancreas brightness. Older age; high waist circumference, triglyceride and glucose index, serum low-density lipoprotein-cholesterol, hepatic steatosis index; and low serum amylase were associated with the presence of severe FP. Moreover, the group with severe liver steatosis had a higher prevalence of FP and a higher pancreatic brightness score. Logistic regression analysis showed that individuals with liver steatosis were more likely to have severe FP.

The severity of FP is associated with features of lifestyle-related diseases and the severity of liver steatosis. These findings suggest that high visceral fat content is associated with more severe fatty pancreas as a phenotype of ectopic fat accumulation, as well as fatty liver disease.

Abbreviations: γ-GT = gamma-glutamyltransferase, ALP = alkalinephosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, DL = dyslipidemia, DM = diabetes mellitus, FP = fatty pancreas, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein-cholesterol, HSI = hepatic steatosis index, HT = hypertension, LDL-C = low-density lipoprotein-cholesterol, NAFLD = non-alcoholic fatty liver disease, OR = odds ratio, RR = relative ratio, TG = triglyceride, TyG = triglyceride and glucose, USG = ultrasonography.

Keywords: fatty liver disease, fatty pancreas, lifestyle-related disease, ultrasonography

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Obesity causes numerous metabolic derangements and complications, including cardiovascular disease, metabolic syndrome, diabetes mellitus (DM) type 2, and non-alcoholic fatty liver disease (NAFLD).[1] In Japan, the prevalence of obesity in the adult population has increased to approximately 31.3% in men and 20.6% in women,[2] and the prevalences of lifestyle-related diseases, including hypertension (HT), dyslipidemia (DL), and impaired glucose tolerance are steadily increasing.[3] In particular, the prevalence of abnormal hepatic function is high, probably because of increases in the prevalences of alcoholic and NAFLD.[3]

NAFLD is a chronic disease that is characterized by the accumulation of fat deposits in the liver and is considered to be the hepatic phenotype of metabolic syndrome.[4] Although there have been numerous studies of NAFLD and the effects of obesity and fat deposition in the liver,[5] the effects of pancreatic fat accumulation have not been well characterized. The term fatty pancreas (FP) has been coined to describe fat deposition in pancreatic cells[6–8] that occurs in association with obesity, alcohol abuse, metabolic syndrome, and lifestyle-related diseases, such as HT, DL, DM, and NAFLD.[6–12]

A previous prospective study showed that body mass index (BMI), fatty liver, and alcohol use are closely associated with FP, and that hepatic steatosis is the strongest predictor for FP, with an odds ratio (OR) of 14.[13] Obesity is known to cause low-grade chronic inflammation, which involves the secretion of the pro-inflammatory cytokines interleukin-6 and tumor necrosis factor alpha by adipocytes.[5,13] In obesity, excess fat is stored in adipocytes, but there is also an accumulation of triglyceride (TG) in non-adipose tissues, such as liver and skeletal muscle.[14] However, it is uncertain whether the molecular mechanisms that link lifestyle-related diseases and fatty liver disease are shared with FP.

A previous population-based study showed the prevalence of FP to be approximately 16.1%.[15] Moreover, FP was reported in 35.0% of individuals who underwent a medical check-up in Japan that involved transabdominal ultrasonography (USG).[16] However, no interventions were prescribed in these individuals because the pathology of FP has not been fully elucidated and it is not categorized in the manual for abdominal ultrasound in cancer screening during medical check-ups in Japan.[17]

The aim of the present study was to elucidate the relationships between lifestyle-related diseases and fatty liver disease with FP. To this end, we assessed the severity of FP and quantified its associations with features of lifestyle-related diseases and the severity of liver steatosis.

2. Methods

2.1. Participants

We conducted a cross-sectional study using health check data collected between April 1, 2019 and March 31, 2020. A total of 929 individuals underwent a health check at Tsukuba Preventive Medicine Research Center, University of Tsukuba Hospital during this period, of whom 10 were excluded because they had previously undergone pancreatic resection (n = 1) or had an ambiguous pancreatic margin on USG (n = 9). The study flow diagram is shown in Fig. 1. The eligible participants were divided into 2 groups, according to whether their pancreas appeared normal or fatty (Fig. 1A), and 3 subgroups, according to whether their pancreatic brightness score was low, medium, or high (Fig. 1B) when they were evaluated using transabdominal USG.

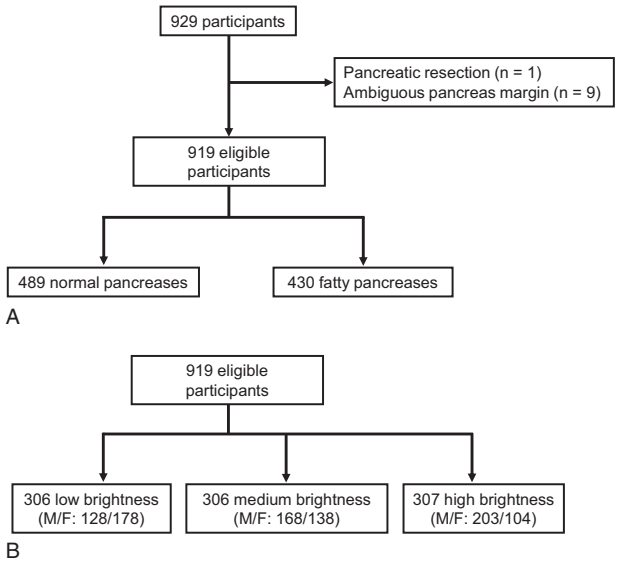

Figure 1. Study flow diagram. Participants who had undergone pancreatic resection or who had ambiguous pancreatic margins on transabdominal ultrasonography (USG) were excluded. For tertile stratification analysis, the 919 participants were divided and allocated into 3 subgroups according to the pancreatic brightness scores. The eligible participants were allocated to normal or fatty pancreas groups (A) and low, medium, or high pancreatic brightness groups (B), as determined using USG. F = female, M = male.

2.2. Assessment of pancreatic fat accumulation by transabdominal USG

We assessed pancreatic fat accumulation and diagnosed as FP by determining the hyperechogenicity of the pancreas compared with that of the kidneys and spleen on transabdominal ultrasonographic examination using an Aplio-i600 scanner (Canon Co. Ltd., Tokyo, Japan).[6,12] Because the brightness of the pancreas could be affected by the USG imaging conditions and the physical conditions of examines such as the thickness of subcutaneous adipose tissue, the conditions of brightness of the pancreas were adjusted by the echogenicity of kidneys and spleen as the basis. In the cases which were difficult to visualize the pancreas and kidney or spleen, the gain of USG was set to default value, and the echogenicity of pancreas were compared with kidney or spleen by moving the probe. Photographs of pancreas were obtained during the examination as the default gain and then the echogenicity was calculated by counting the pixels in 3 or 4 consistent areas of the pancreas to correct the size of pancreas using Photoshop (Adobe, San Jose, CA; Fig. 2). The mean number of pixels in areas designated by a single clinical radiologist, who was blinded to the clinical details of the participants, was recorded as the brightness score for the pancreas of each individual.

For tertile stratification analysis, the 919 participants were divided and allocated into 3 subgroups according to the pancreatic brightness scores: a low brightness group (n = 306, brightness score; 44.2–94.8), a medium brightness group (n = 306 brightness score; 94.9–122.3), and a high brightness group (n = 307, brightness score; 122.6–173.3) (Fig. 1B).

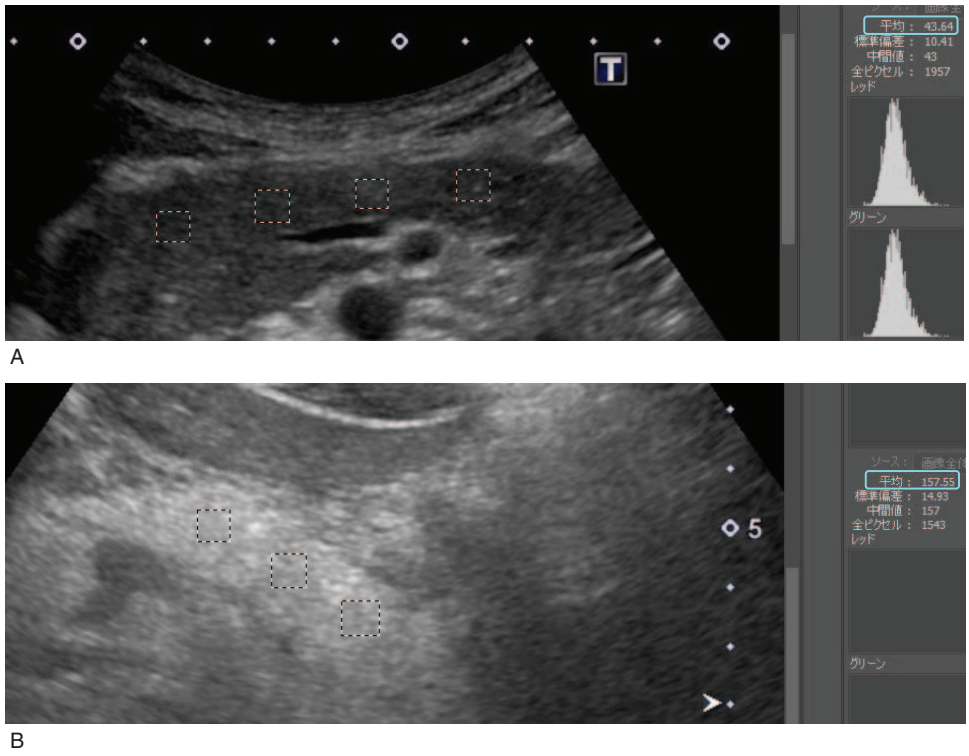

Figure 2. Calculation of the brightness score for the pancreas. The echogenicity of the pancreas was calculated as the number of pixels in 3 or 4 consistent areas in each pancreas. Representative photographs of participants in the low (A) and high (B) pancreatic brightness groups are shown. The values in the blue columns are the pancreatic brightness scores; mean values were calculated (A: 43.64, B: 157.55).

2.3. Lifestyle-related disease definitions and clinical laboratory measurements

HT was defined as a systolic blood pressure ≥160 mm Hg and/or a diastolic blood pressure ≥100 mm Hg measured during the medical check-up and/or during a subsequent medical intervention. Participants with a systolic blood pressure of 140 to 159 mm Hg and/or diastolic blood pressure of 90 to 99 mm Hg at their medical check-up, which might have represented white-coat hypertension, subsequently measured their blood pressure at home. DM type 2 was defined as a fasting plasma glucose (FPG) ≥126 mg/dL at the medical check-up and/or during a subsequent medical intervention. DL was defined as a serum low-density lipoprotein-cholesterol (LDL-C) concentration ≥140 mg/dL and/or a serum TG concentration ≥150 mg/dL at the medical check-up and/or during a subsequent medical intervention. The medical interventions that were prescribed included education for lifestyle improvement, diet therapy, exercise therapy, and medication administered via a medical institution.

In 2005, the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome defined metabolic syndrome as the presence of an excessive waist circumference (≥85 cm in men and ≥90 cm in women) and ≥2 of HT, glucose intolerance, and DL. For these purposes, HT was defined as a systolic blood pressure ≥130 mm Hg and/or a diastolic blood pressure ≥85 mm Hg, or the use of anti-hypertensive medication. Glucose intolerance was defined as an FPG ≥110 mg/dL or the use of anti-diabetic medication. DL was defined as a TG ≥150 mg/dL, a high-density lipoprotein-cholesterol (HDL-C) of <40 mg/dL, or the use of anti-hyperlipidemic medication.

The Fibrosis (Fib)-4 index, a non-invasive index of hepatic fibrosis, was calculated using the formula: age (years) × aspartate aminotransferase (AST) (U/L)/(platelet count [10^9/L] × (alanine aminotransferase [ALT] [U/L])$^{1/2}$). The triglyceride and glucose (TyG) index, which is an indirect index of insulin resistance, was calculated using the formula: log ([fasting TG concentration] [mg/dL] × fasting glucose [mg/dL]/2).[18] The hepatic steatosis index (HSI), which is a simple means of predicting NAFLD that correlates with liver steatosis grade, was calculated using the formula: 8 × ALT/AST + BMI (+2, if DM type 2 is present; +2 if for women).[19,20]

The frequency of alcohol intake and the amount consumed were assessed using questionnaires. The frequency of alcohol intake was categorized as G0, no or almost no intake; G1, intake several times a week; or G2, intake every day. The amount of alcohol consumed was categorized as G0, <20 g a day; G1, 20 to 40 g a day; or G2, >40 g a day.

2.4. Evaluation of liver steatosis by USG

AnAplio-i600 scanner (Canon Co. Ltd.) was used to evaluate the severity of liver steatosis. The grade of steatosis (G0, normal echogenicity; G1, slight, diffuse increase in fine echoes in the liver parenchyma, with normal visualization of the diaphragm and intrahepatic vessel borders; G2, moderate, diffuse increase in fine echoes, with slightly impaired visualization of intrahepatic vessels and diaphragm; or G3, marked increase in fine echoes, with poor or no visualization of the intrahepatic vessel borders, diaphragm, or posterior right lobe of the liver) was determined by clinical

radiologists using previously reported criteria.[21] Individuals with active hepatitis B or C were not included in the study.

2.5. Statistical analysis

SPSS Statistics 24.0 (IBM, Inc., Armonk, NY) was used for all the statistical analyses. Data are expressed as mean ± standard deviation. The relationships between the tertile of pancreatic brightness score and the prevalence of each disease or disease feature were evaluated using Pearson chi-square test. The relationship of each pathophysiological factor with brightness score were evaluated using ANCOVA. In addition, factors that contributed to the brightness score were identified using univariate and multivariate analyses. ORs were obtained using logistic regression analysis, and are presented with 95% confidence intervals (CIs). $P < .05$ was defined as indicating statistical significance.

2.6. Ethical considerations

We conducted this study in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects, published by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour, and Welfare of Japan. The study was approved by the ethics committee of the University of Tsukuba Hospital (approval No. R01-147). Informed consent was not required because of the study's retrospective nature.

3. Results

3.1. Characteristics of the participants

Table 1 shows the characteristics of the study participants. They were 59.5 ± 13.2 years old and 54.3% (499/919) were men. The prevalence of FP was 46.8% (430/919) and the participants with

Table 1

Characteristics of 919 participants including anthropometric characteristics, pancreatic abnormalities, lifestyle-related diseases, glucose and lipid profiles, and hepatic abnormalities.

	Normal pancreas (n = 489)	Fatty pancreas (n = 430)	*P* value
Age, yrs	57.4 ± 14.0	61.8 ± 11.7	<.001
Sex, males/females (n)	227/262	272/158	<.001
Weight, kg	57.4 ± 11.1	67.9 ± 12.8	<.001
BMI	21.8 ± 3.0	25.4 ± 3.5	<.001
Waist circumference, cm	80.1 ± 8.4	90.5 ± 8.5	<.001
Pancreatic abnormalities			
Amylase, U/L	86.9 ± 28.2	76.6 ± 25.7	<.001
Lipase, U/L	33.5 ± 15.5	32.5 ± 23.8	.318
Brightness score of pancreas	88.6 ± 16.0	130.8 ± 14.3	<.001
Pancreatic cyst (%)	5.6	4.9	.762
Life style-related diseases			
Hypertention (%)	7.8	12.1	.034
Diabetes mellitus (%)	5.1	15.8	<.001
Dyslipidemia (%)	27.8	48.6	<.001
Metabolic syndrome (%)	12.7	50.2	<.001
Frequency of alcohol intake 0/1/2	249/149/91	209/107/114	.010
Amount of alcohol intake 0/1/2	364/85/31	285/81/58	.001
Gallbladder stones (%)	4.5	11.2	<.001
Glucose metabolism and lipid profiles			
FPG, mg/dL	99.2 ± 13.3	106.4 ± 19.1	<.001
HbA1c, %	5.6 ± 0.4	5.9 ± 0.6	<.001
HDL-C, mg/dL	67.4 ± 17.1	57.8 ± 14.2	<.001
LDL-C, mg/dL	117.2 ± 29.5	123.7 ± 28.0	.001
TG, mg/dL	91.5 ± 58.4	129.1 ± 123.2	<.001
Triglyceride and glucose (TyG) index	8.3 ± 0.5	8.7 ± 0.6	<.001
Hepatic abnormalities			
Steatosis grade by US 0/1/2/3	421/20/22/26	184/51/54/141	<.001
Platelet, $\times 10^{10}$/L	22.7 ± 5.0	22.9 ± 6.0	.132
Albumin, g/dL	4.4 ± 0.3	4.4 ± 0.3	.126
AST, U/L	22.7 ± 7.7	25.6 ± 10.6	<.001
ALT, U/L	19.7 ± 11.6	27.2 ± 18.3	<.001
ALP, U/L	202.7 ± 65.1	218.1 ± 64.7	.005
γ-GT, U/L	30.3 ± 43.6	41.1 ± 38.4	<.001
Fib-4 index	1.43 ± 0.76	1.47 ± 0.68	<.001
Hepatic steatosis index (HSI)	29.8 ± 4.2	34.6 ± 5.5	<.001
Others			
CRP, mg/dL	0.1 ± 0.4	0.1 ± 0.2	.702

Values are presented as the group means ± standard deviation. To compare between 2 groups, all dependent variables were analyzed by ANOVA. Categorical variables were analyzed by using Pearson chi-square test.

γ-GT = gamma-glutamyltransferase, ALP = alkalinephosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CRP = C-reactive protein, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, TG = triglyceride.

Table 2

The anthropometric characteristics, pancreatic abnormalities, lifestyle-related diseases, glucose and lipid profiles, and hepatic abnormalities for 919 participants with tertile stratification according to the brightness score of pancreas.

	Low brightness (n = 306)	Medium brightness (n = 306)	High brightness (n = 307)	*P*-value	
				Low versus medium	Low versus high
Age, yrs	56.0 ± 14.3	59.8 ± 13.0	62.6 ± 11.1	.001	<.001
Sex, males/females (n)	128/178	168/138	203/104	<.001	
Weight, kg	54.8 ± 10.0	63.0 ± 12.2	69.1 ± 12.6	<.001	<.001
BMI	21.0 ± 2.7	23.8 ± 3.4	25.7 ± 3.3	<.001	<.001
Waist circumference, cm	77.5 ± 7.8	85.7 ± 8.5	91.6 ± 8.0	<.001	<.001
Pancreatic abnormalities					
Amylase, U/L	91.3 ± 31.0	80.4 ± 26.4	74.9 ± 23.2	.001	<.001
Lipase, U/L	35.4 ± 13.6	34.8 ± 13.1	33.2 ± 19.3	.931	.431
Brightness score of pancreas	78.9 ± 11.5	108.7 ± 7.7	137.3 ± 11.0	<.001	<.001
Pancreatic cyst (%)	6.3	4.1	5.5	.528	
Life style-related diseases					
Hypertention (%)	6.2	11.4	11.7	.035	
Diabetes mellitus (%)	4.2	8.8	17.3	<.001	
Dyslipidemia (%)	21.2	39.5	51.8	<.001	
Metabolic syndrome (%)	6.5	29.1	54.7	<.001	
Frequency of alcohol intake 0/1/2	160/98/48	148/82/76	150/76/81	.012	
Amount of alcohol intake 0/1/2	233/50/17	211/63/28	205/53/44	.003	
Gallbladder stones (%)	4.6	8.2	10.1	.033	
Glucose metabolism and lipid profiles					
FPG, mg/dL	97.4 ± 10.9	103.6 ± 18.8	106.8 ± 17.8	<.001	<.001
HbA1c, %	5.6 ± 0.4	5.8 ± 0.5	5.9 ± 0.6	.025	<.001
HDL-C, mg/dL	70.1 ± 17.1	61.6 ± 16.3	56.9 ± 13.1	<.001	<.001
LDL-C, mg/dL	114.6 ± 28.7	121.8 ± 28.9	124.3 ± 28.5	.006	<.001
TG, mg/dL	80.6 ± 42.6	114.1 ± 72.5	132.4 ± 139.1	<.001	<.001
Triglyceride and glucose (TyG) index	8.2 ± 0.5	8.5 ± 0.5	8.7 ± 0.6	<.001	<.001
Hepatic abnormalities					
steatosis grade by US 0/1/2/3	278/10/11/7	211/26/24/45	116/35/41/115	<.001	
Platelet, $\times 10^{10}$/L	23.4 ± 5.3	23.8 ± 6.1	23.2 ± 5.4	0.660	.896
Albumin, g/dL	4.4 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	1.000	.208
AST, U/L	22.5 ± 7.6	24.0 ± 9.3	25.7 ± 10.4	.138	<.001
ALT, U/L	18.5 ± 10.4	23.4 ± 15.7	27.6 ± 18.3	<.001	<.001
ALP, U/L	198.7 ± 61.9	209.7 ± 66.2	221.3 ± 66.1	0.342	0.002
γ-GT, U/L	25.9 ± 30.7	37.9 ± 52.8	42.2 ± 36.3	<.001	<.001
Fib-4 index	1.41 ± 0.72	1.44 ± 0.76	1.50 ± 0.68	.017	<.001
Hepatic steatosis index (HSI)	28.7 ± 3.7	32.3 ± 5.0	35.0 ± 5.4	<.001	<.001
Others					
CRP, mg/dL	0.08 ± 0.42	0.12 ± 0.31	0.10 ± 0.16	1.000	1.000

Values are presented as the group means ± standard deviation. To compare between groups, all dependent variables were analyzed by using ANCOVA.
Categorical variables were analyzed by using Pearson chi-square test.
γ-GT = gamma-glutamyltransferase, ALP = alkalinephosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CRP = C-reactive protein, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein-cholesterol, LDL-C = low-density lipoprotein-cholesterol, TG = triglyceride.

FP were older than those with normal pancreas: 61.8 ± 11.7 years versus 57.4 ± 14.0 years, respectively. The participants with FP were more likely to be men than those without: 63.3% (272/430) versus 46.4% (227/489). The participants with FP had a higher pancreatic brightness score than those with a normal pancreas: 130.8 ± 14.3 versus 88.6 ± 16.0, respectively. Participants with FP had higher body mass, BMI, waist circumference, and prevalences of lifestyle-related diseases (HT, DM, DL, metabolic syndrome, and gallbladder stones) than those with a normal pancreas. Moreover, participants with FP had a higher liver steatosis grade; serum AST, ALT, alkaline phosphatase (ALP), and gamma-glutamyl transferase (γ-GT); Fib-4 index; and HSI than those with a normal pancreas. Participants with FP also had higher FPG; serum hemoglobin A1c (HbA1c), LDL-C, and TG; and TyG index; and lower serum HDL-C than those with a normal pancreas. The serum amylase of participants with FP was lower than that of participants with a normal pancreas, but the serum lipase did not differ between the 2 groups. In addition, the prevalence of pancreatic cyst did not differ between the groups.

3.2. Comparison of the participants in each tertile of pancreas brightness

As shown in Table 2 and Fig. 3A, comparisons of participants with low, medium, and high pancreatic brightness score showed that the mean age of the high brightness group was significantly higher than those of the low and medium brightness groups. The high brightness group contained more participants who were ≥60 years old (low: 46.4%, medium: 56.5%, high: 64.2%, Fig. 2A) and more men than the low brightness group. The body mass, BMI, and waist circumference of the participants in the high brightness group were significantly higher than those of the

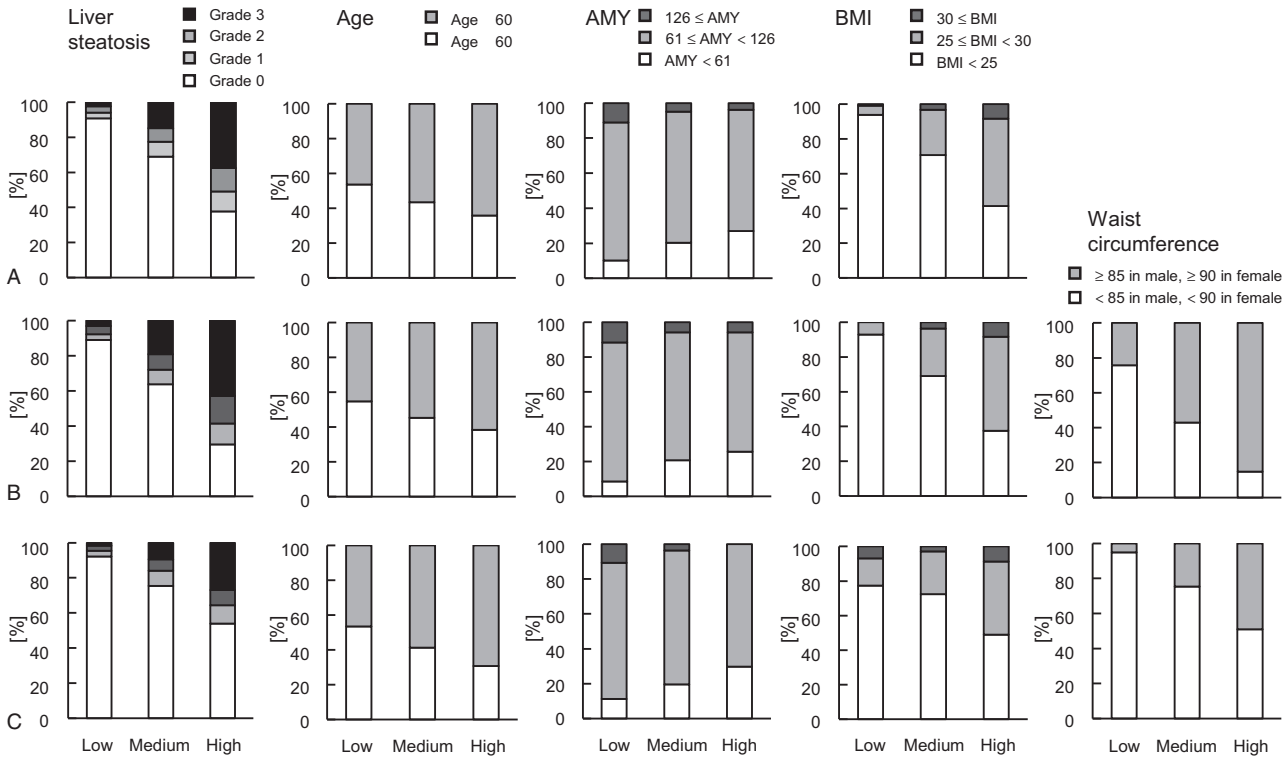

Figure 3. Relationships of the pathophysiological factors associated with fatty pancreas with the tertiles of pancreatic brightness score. Liver steatosis grade, age, serum amylase, BMI, and waist circumference were assessed. (A) Entire sample; (B) male participants; and (C) female participants. AMY = amylase, BMI = body mass index.

participants in the low and medium groups. The high brightness group also contained more participants with moderate or severe obesity (BMI ≥ 30 kg/m^2) (Fig. 3A): the proportions of participants with moderate or severe obesity were 1.0% in the low brightness group, 3.3% in the medium brightness group, and 8.5% in the high brightness group. The prevalences of a waist circumference that fulfilled the diagnostic criterion for metabolic syndrome in Japan (≥85 cm for men and ≥90 cm for women) were significantly higher in the medium and high brightness groups than in the low brightness group (low: 24.2%, medium: 57.1%, and high: 85.2% in men; low: 5.1%, medium: 24.6%, and high: 49.0% in women; Fig. 3B and C), and in men than in women.

The serum amylase of the medium and high brightness groups were lower than that of the low brightness group, and the medium and high brightness groups contained more participants with a serum amylase <60 U/L (low: 10.1%, mid: 20.2%, and high: 27.0%; Fig. 3A). However, the serum lipase did not differ among the 3 groups. In addition, the prevalence of pancreatic cyst did not differ among the groups.

3.3. Comparisons of the prevalences of lifestyle-related diseases between the tertile groups of pancreas brightness score

As shown in Table 2, comparisons of the 3 pancreatic brightness groups showed that the high brightness group had higher prevalences of lifestyle-related diseases (HT, DM, DL, metabolic syndrome, and gallbladder stones). Both the frequency of alcohol intake and the amount consumed were higher in the high brightness group than in the low brightness group. The medium and high brightness groups had higher FPG; serum HbA1c, LDL-C, and TG; and TyG index; and lower serum HDL-C than the low brightness group.

3.4. Comparisons of the prevalences of liver steatosis and abnormal hepatic indices between the tertiles of pancreas brightness score

As shown in Table 2 and Fig. 3A (left panel), the high pancreas brightness group had a higher prevalence of severe liver steatosis, assessed using USG. The medium and high brightness groups had higher serum AST, ALP, ALT, and γ-GT activities; Fib-4 index; and HSI than the low brightness group. However, the platelet count and serum albumin concentration did not differ among the groups.

3.5. Comparisons of the male and female participants in each pancreas brightness tertile group

Supplemental Digital Content (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A541 and Table S2, Supplemental Digital Content, http://links.lww.com/MD2/A542), and Fig. 3B and C show comparisons of the male and female participants in the low, medium, and high pancreatic brightness groups. Both male and female participants in the high brightness group were older, and had higher body mass, BMI, waist circumference, and prevalences of lifestyle-related diseases than

Table 3

Multivariate regression analysis for pathophysiological factors associated with brightness score of pancreas for 919 participants.

Parameter	Multivariate analysis			
	B	Std.error	Beta	*P* value
Brightness of pancreas				
Waist circumference, cm	1.194	0.114	0.455	<.001
Age, yrs	0.339	0.053	0.171	<.001
Triglyceride and glucose (TyG) index	5.941	1.321	0.129	<.001
LDL-C, mg/dl	0.057	0.023	0.064	.011
Amylase, U/L	-0.055	0.025	-0.059	.025
Hepatic steatosis index (HSI)	0.454	0.214	0.094	.034

LDL-C = low-density lipoprotein-cholesterol.

those in the other 2 groups. In addition, both sexes in the high brightness group had higher FPG; serum HbA1c, TG, ALT, and γ-GT; TyG index; Fib-4 index; and HSI; and lower HDL-C than in the other groups.

Both male and female participants in the high brightness group had lower serum amylase, but the female participants also had lower serum lipase than those in the other 2 groups. The prevalence of pancreatic cyst tended to higher in the female participants in the medium and high brightness groups ($P = .076$). As shown in Fig. 3B and C, both male and female participants in the high brightness group had higher prevalences of severe liver steatosis, evaluated using USG, were more likely to be ≥60 years of age, were less likely to have a serum amylase concentration <60 U/L, had higher prevalences of moderate or severe obesity, and higher prevalences of waist circumference ≥85 cm for men and ≥90 cm for women. Thus, men and women showed similar relationships.

3.6. Analysis of the pathophysiological factors associated with pancreatic fat accumulation

A multiple regression analysis was performed using the pancreatic brightness score, to reflect the severity of pancreatic fat accumulation, as the dependent variable to determine the effect of specific pathophysiological factors. High waist circumference, age, TyG index, serum LDL-C concentration, and HSI were shown to independently affect the pancreatic brightness score with positive slope, and low amylase activity independently affect with negative slope (Table 3). These results suggest that pancreatic fat accumulation is associated with visceral fat accumulation and lifestyle-related diseases, including fatty liver disease, which was indicated by high HSI. Moreover, insulin resistance was associated not only with fatty liver disease, but also FP, because the TyG index, an indirect index insulin resistance, was identified to have an independent influence on the severity of pancreatic fat accumulation.

3.7. Comparisons of pancreatic indices, the prevalences of lifestyle-related diseases, and hepatic indices among participants in each liver steatosis grade, determined using USG

To evaluate the relationship between FP and liver steatosis, the participants were allocated to liver steatosis grades 0 to 3, determined using USG (Table 4). Participants with severe liver steatosis (grade 3) were more likely to be men than those in the normal liver (grade 0) group. The body mass, BMI, and waist circumference of the liver steatosis groups (grades 1–3) were significantly higher than those of the normal liver group. The serum amylase of the liver steatosis groups were lower than that of the normal liver group, but the serum lipase did not differ among the 4 groups. The prevalences of FP and high pancreatic brightness score were significantly higher in the liver steatosis groups than in the normal liver group. The prevalence of pancreatic cyst did not differ among the 4 groups. The liver steatosis groups had higher prevalences of lifestyle-related diseases (HT, DM, DL, metabolic syndrome, and gallbladder stones). The frequency of alcohol intake did not differ among the 4 groups, but the amount of alcohol consumed was higher in the liver steatosis groups than in the normal liver group.

The severe liver steatosis groups had higher FPG; serum HbA1c and TG; and TyG index; and lower serum HDL-C concentration than the normal liver group. The most severe liver steatosis group (grade 3) had higher serum albumin, AST, ALT, ALP, and γ-GT; higher HSI; and lower Fib-4 index than the normal liver group. However, platelet count did not differ among the 4 groups.

3.8. Analysis of the relationship between liver steatosis and the tertile of pancreatic fat accumulation

Logistic regression analysis was performed to estimate the relative risks of liver steatosis, according to the category of pancreatic brightness score (Table 5). When the risk of liver steatosis in the low pancreatic brightness group was set to 1, the relative risks (RRs) were 4.47 and 16.35 for participants in the medium and high pancreatic brightness groups. The results of the analyses performed after adjustment for potential cofounders were similar. These results indicate that liver steatosis may represent a risk factor for severe fatty pancreas.

4. Discussion

The results of this cross-sectional study of 919 participants show that FP is associated with lifestyle-related diseases, including HT, DM, DL, metabolic syndrome, gallbladder stones, and fatty liver disease. Multiple regression analysis showed that older age and higher waist circumference, serum triglyceride concentration, and TyG index, serum LDL-C, and hepatic steatosis index (HSI); and low serum amylase independently affect the pancreatic brightness score, which reflects the severity of pancreatic fat accumulation. These findings suggest that high waist circumference, which reflects a high degree of visceral fat accumulation, is associated with more severe pancreatic fat accumulation, as well as with the development of recognized lifestyle-related diseases,

Table 4

The anthropometric characteristics, pancreatic abnormalities, lifestyle-related diseases, glucose and lipid profiles, and hepatic abnormalities for 919 participants in each liver steatosis grade from 0 to 3.

Liver steatosis grade by US	Grade 0 (n=605)	Grade 1 (n=71)	Grade 2 (n=76)	Grade 3 (n=167)	*P*-value 0 versus 1	0 versus 2	0 versus 3
Age, yrs	59.6±13.9	60.6±11.9	60.1±12.3	58.2±11.3	1.000	1.000	1.000
Sex, males/females (n)	281/324	42/29	53/23	123/44		<.001	
Weight, kg	57.7±10.6	64.1±10.5	67.7±10.0	75.9±12.8	<.001	<.001	<.001
BMI	22.1±2.9	24.3±2.8	24.9±2.5	27.5±3.9	<.001	<.001	<.001
Waist circumference, cm	81.4±8.6	87.1±6.8	89.0±6.0	95.2±9.0	<.001	<.001	<.001
Pancreatic abnormalities							
Amylase	87.1±28.6	77.4±27.7	73.6±21.2	69.7±20.2	.022	<.001	<.001
Lipase	33.5±22.8	31.2±12.0	31.2±10.4	33.0±12.7	1.000	1.000	1.000
Normal pancreas/fatty pancreas (n)	421/184	20/51	22/54	26/141		<.001	
Brightness of pancreas, low/medium/high	278/211/116	10/26/35	11/24/41	7/45/115		<.001	
Brightness score of pancreas	99.4±24.1	119.7±21.7	123.7±22.5	128.8±17.6	<.001	<.001	<.001
Pancreatic cyst (%)	5.6	4.4	7.0	5.5		.732	
Life style-related diseases							
Hypertention (%)	6.9	11.3	9.2	19.8		<.001	
Diabetes mellitus (%)	4.6	4.2	18.4	28.7		<.001	
Dyslipidemia (%)	27.1	52.1	51.3	62.9		<.001	
Metabolic syndrome (%)	15.2	32.4	47.4	75.4		<.001	
Frequency of alcohol intake 0/1/2	316/170/119	33/21/17	32/20/24	77/45/45		.176	
Amount of alcohol intake 0/1/2	451/105/40	48/16/5	44/15/15	106/30/29		<.001	
Gallbladder stones (%)	4.8	15.5	7.9	14.4		<.001	
Glucose metabolism and lipid profiles							
FPG, mg/dL	81.4±8.6	87.1±6.8	89.0±6.0	95.2±9.0	<.001	<.001	<.001
HbA1c, %	5.6±0.4	5.8±0.3	5.8±0.6	6.1±0.8	.388	.007	<.001
HDL-C, mg/dL	67.2±16.7	57.8±12.0	56.5±13.0	52.4±12.4	<.001	<.001	<.001
LDL-C, mg/dL	118.0±28.6	126.3±30.3	123.3±26.4	124.4±29.9	.131	.776	.069
TG, mg/dL	87.4±45.9	131.8±70.2	136.1±69.0	165.7±183.9	.001	<.001	<.001
Triglyceride and glucose (TyG) index	8.3±0.5	8.7±0.5	8.8±0.5	9.0±0.6	<.001	<.001	<.001
Hepatic abnormalities							
Platelet, $\times 10^{10}$/L	23.3±5.8	24.1±4.4	22.9±5.3	24.0±5.6	1.000	1.000	.757
Albumin, g/dL	4.4±0.3	4.4±0.2	4.4±0.3	4.5±0.2	.613	1.000	<.001
AST, U/L	22.5±7.2	22.2±6.1	25.2±7.7	30.1±13.9	1.000	.061	<.001
ALT, U/L	18.6±10.1	20.7±8.4	25.4±11.3	39.8±22.9	1.000	<.001	<.001
ALP, U/L	205.2±65.1	216.8±77.0	208.5±62.8	224.7±59.8	.934	1.000	.004
γ-GT, U/L	28.0±30.4	37.2±37.5	50.4±61.7	54.3±56.5	.409	<.001	<.001
Fib-4 index	1.5±0.7	1.3±0.6	1.5±0.8	1.3±0.6	.359	1.000	.002
Hepatic steatosis index (HSI)	29.8±3.8	32.6±4.0	33.9±3.4	39.0±5.4	<.001	<.001	<.001

Values are presented as the group means±standard deviation. To compare between groups, all dependent variables were analyzed by using ANCOVA.
Categorical variables were analyzed by using Pearson chi-square test.
γ-GT=gamma-glutamyltransferase, ALP=alkalinephosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BMI=body mass index, CRP=C-reactive protein, FPG=fasting plasma glucose, HbA1c=hemoglobin A1c, HDL-C=high-density lipoprotein-cholesterol, LDL-C=low-density lipoprotein-cholesterol, TG=triglyceride.

including fatty liver disease. Moreover, the severity of pancreatic fat accumulation is associated with the severity of liver steatosis, evaluated by USG, as well as HSI, which is used to predict, and correlates with, the severity of fatty liver disease. Furthermore, logistic regression analysis showed that individuals with liver steatosis were more likely to have severe FP.

A previous systematic review and meta-analysis of 6 cross-sectional studies (n=10,278) conducted by Singh revealed that

Table 5

Unadjusted and adjusted odds ratios with 95% confidence intervals of having liver steatosis by tertile of pancreatic brightness after adjusting for potential compounding factors.

Pancreatic brightness	Low brightness	Medium brightness	High brightness	*P* for trend
Liver steatosis evaluated by USG				
Unadjusted	1	4.47 (2.83–7.07)	16.35 (10.40–25.69)	<.001
Model 1	1	4.81 (3.03–7.65)	19.72 (12.32–31.60)	<.001
Model 2	1	3.17 (1.97–5.10)	9.05 (5.62–14.56)	<.001
Model 3	1	3.96 (2.49–6.31)	14.81 (9.36–23.45)	<.001

All 919 participants (499 men and 420 women) were divided appropriately into the brightness score of pancreas tertile.
Model 1 adjusted for age. Model 2 adjusted for presence of metabolic syndrome. Model 3 adjusted for serum amylase.

pancreatic fat accumulation is associated with HT (RR 1.67; 95% CI 1.32–2.10; $P < .001$), DM (RR 2.08; 95% CI 1.44–3.00; $P < .001$), metabolic syndrome (RR 2.37; 95% CI 2.07–2.71; $P < .001$), and NAFLD (RR 2.67; 95% CI 2.00–3.56; $P < .001$).[9] Another cross-sectional study also demonstrated a highly significant association between NAFLD and the presence of FP, and suggested that the metabolic syndrome of participants was more severe when it was associated with both NAFLD and FP.[16,22] Moreover, in a large cross-sectional study of 8097 patients, the prevalence of NAFLD was found to be higher in those with FP than in those without (67.2% vs 35.1%).[23]

In the present study, participants with severe FP and those with severe liver steatosis shared many pathophysiological risk factors. They were more likely to be men, and had higher body weight, BMI, waist circumference, and prevalences of lifestyle-related diseases (HT, DM, DL, metabolic syndrome, and gallbladder stones). They also had higher FPG; serum HbA1c, LDL-C, TG, AST, ALT, and γ-GT; TyG index; and HSI; and lower serum HDL-C concentration compared with participants with mild or no pathology (Tables 2 and 4). Interestingly, the TyG index, an indirect index of insulin resistance, was identified to independently affect pancreatic brightness score (Table 3) and was significantly higher in both the severe FP and severe liver steatosis groups than in the groups with no or mild pathology (Tables 2 and 4). Although the mechanism of the relationship between insulin resistance and FP has not been determined, pancreatic fat accumulation has previously been shown to be associated with insulin resistance and prediabetes.[15,24] The presence of insulin resistance in individuals with FP could affect the onset and development of fatty liver disease, because insulin resistance plays a central role in the relationship between obesity and fatty liver disease.[5]

Although participants with severe FP and those with severe liver steatosis shared many pathophysiological risk factors in the present study, the ages of the participants in each quartile of the liver steatosis grade did not significantly differ (Table 4), unlike the ages of the participants in each tertile of the FP grade (Table 2). Pancreatic fat content has been shown to increase with age, to a peak in the third and fourth decades.[25] A recent study of medical check-up data showed that otherwise healthy people with FP were older than those with a normal pancreas (52.1 ± 9.3 years vs 46.2 ± 8.7 years; $P < .001$).[10] In the present study, the mean age of the participants was 59.5 ± 13.2 years, and those with FP were older than those with a normal pancreas (Table 1). Moreover, the mean age of the high brightness group was higher than those of the low or medium brightness groups (62.6 ± 11.1 years vs 56.0 ± 14.3 years or 59.8 ± 13.0 years, respectively; $P < .001$; Table 2). Taken together, these findings indicate that FP might be a part of the aging process, to a greater extent than liver steatosis. The high brightness group had a higher Fib-4 index than the low and medium brightness groups (Table 2), but the severe liver steatosis group (grade 3) had a lower Fib-4 index, despite having a higher AST activity and a similar platelet count to the normal liver group (Table 4). Thus, the high Fib-4 index in the high brightness group may reflect the older age of this group, rather than severe fibrosis of their livers. Indeed, the participants in the present study were not considered to include individuals with advanced hepatic fibrosis.

A previous prospective cohort study of healthy people who underwent a medical check-up (n = 9933) showed that fat accumulation in the pancreas may represent a risk factor for subclinical chronic pancreatitis.[10] In the present study, serum amylase and lipase were measured in all the participants, and the FP group (Table 1) and the high brightness group (Table 2) were found to have significantly lower serum amylase, but similar serum lipase to participants in the other groups. Moreover, low serum amylase was shown in multiple regression analysis to independently affect pancreatic brightness score (Table 3). A previous case-control study showed that the ratio of serum pancreatic isoamylase (pancreatic type amylase in amylase isozyme) to serum lipase is associated with the stage of chronic pancreatitis.[26] Although the severe liver steatosis group also had significantly lower serum amylase than the other groups with similar serum lipase (Table 4) and the pancreatic isoamylase was not measured in the present study, the significantly lower serum amylase in the FP group and the high brightness group might reflect the pathogenesis of chronic pancreatitis. In the present study, the influence of alcohol intake on these parameters could not be excluded: it might have affected the prevalences of both FP and fatty liver.[8] In addition, the severe FP and severe liver steatosis groups had higher prevalences of gallbladder stones (Tables 2 and 4), which are the most common cause of acute pancreatitis. However, they do not cause chronic pancreatitis.[27] Thus, the associations identified with gallbladder stones in the present study are considered to reflect the higher prevalences of lifestyle-related diseases in general, rather than reflecting an association with chronic pancreatitis.

There are no current consensus guidelines regarding the treatment of FP, because it is a recently recognized pathological change that requires further investigation. Moreover, it is not clear whether the pathologic changes associated with FP can be ameliorated by specific interventions. A previous study showed that pancreatic fat volume is reduced alongside the weight loss induced by bariatric surgery.[28] Because this study and previous studies have shown that FP is closely associated with obesity and lifestyle-related diseases, FP could be included on the list of lifestyle-related diseases to be monitored in medical check-ups, and lifestyle improvements, such as weight loss and/or alcohol reduction might be necessary to ameliorate it. Future studies should aim to identify effective treatments for FP.

The present study had several limitations. First, the study participants underwent health checks in a single center in an Asian country. Previous studies have estimated the prevalence of FP to be between 16% and 51%.[6,11,16] In the present study, the prevalence of FP was 46.8%, and this high prevalence may reflect the higher age of the participants (59.5 ± 13.2 years; Table 1). Moreover, participants who consumed alcohol were not excluded, which might also have contributed to the high prevalence in the present study.

Second, pancreatic fat content was assessed using trans-abdominal USG, rather than by histological examination of a biopsy, which is the gold standard method of assessment. However, the pancreas is not an easy organ to access non-invasively, because of its deep retroperitoneal location, and even fine needle aspiration/biopsy using endoscopic ultrasonography is relatively invasive. In addition, it is difficult to obtain samples from non-tumor tissue of the pancreas because it is not a solid organ.[6,7,12] Therefore, USG, computed tomography, magnetic resonance imaging (MRI), magnetic resonance-proton density fat fraction, and magnetic resonance spectroscopy are frequently used to assess pancreatic fat accumulation. However, there is no consensus regarding the most appropriate method for the diagnosis of FP.[6,7] Transabdominal USG is widely available,

cheap, and not associated with risks or radiation exposure, in contrast to the other modalities. However, its principal disadvantage is that the pancreas cannot always be visualized in obese individuals. Thus, participants with ambiguous pancreatic borders on USG were excluded from the present study (Fig. 1).

Third, because this was a cross-sectional study, it is not possible to evaluate the risk of pancreatic cancer associated with FP. Previous studies showed significant positive correlations of pancreatic carcinoma/intra-epithelial neoplasia with pancreatic fat accumulation (OR 6.1; $P < .001$[29] and OR 17.86; 95% CI 4.94–88.12[11]). In addition, the risk of development of pancreatic carcinoma was found to be higher in individuals with FP than in those without, and pancreatic steatosis might be associated with differences in the pancreatic microenvironment that promote tumor progression.[30] To more fully evaluate the relationship between FP and cancer, and the molecular mechanisms involved, large, longitudinal clinical trials should be performed.

In conclusion, age, lifestyle-related diseases, and liver steatosis may increase the risk of the development of FP. The present findings suggest that high visceral fat volume is associated with more severe FP, as one component of the phenotype of ectopic fat accumulation, as well as with lifestyle-related diseases, including fatty liver disease. The evaluation of FP by USG might be appropriate during medical check-ups and lead to the institution of appropriate lifestyle interventions.

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Author contributions

Kosuke Okada, Takashi Shida, Kazunori Ishige, and Hideo Suzuki designed the study. Kosuke Okada, Kaoru Horie, Takako Takayama, Takashi Shida, and Yuka Aida collected the data. Kosuke Okada, Takahisa Watahiki, Keii To, and Kazunori Ishige analyzed the data. Kosuke Okada, Takahisa Watahiki, Kaoru Horie, Takako Takayama, Yuka Aida, Keii To, Takashi Shida, Kazunori Ishige, Hideo Suzuki, Hiroyuki Nishiyama, and Junichi Shoda reviewed, revised, and approved the article before its submission.

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