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【 ORIGINAL ARTICLE 】

Correlation between Pancreatic Fat Deposition and Metabolic Syndrome: Relationships with Location in the Pancreas and Sex

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Abstract:

Objective To investigate the correlation between pancreatic fat deposition and metabolic syndrome (MetS) parameters, focusing on the locations of fat deposition in the pancreas and sex differences.

Methods Degrees of fat deposition in the head, body, and tail of the pancreas were evaluated using computed tomography (CT). We examined the relationships between pancreatic fat deposition and the age, body mass index (BMI), visceral and subcutaneous fat, serum lipid profiles, hepatic steatosis, diabetes mellitus (DM), and hypertension (HTN).

Results In this retrospective study, greater fat deposition was associated with a higher BMI, visceral and subcutaneous fat accumulation, and hepatic steatosis, with the pancreatic head showing the strongest correlation. Correlations of pancreatic fat deposition with the BMI and visceral and subcutaneous fat accumulation were stronger in females than in males, while correlations with hepatic steatosis were stronger in males than in females. In addition, a multivariate analysis did not suggest a direct causal relationship between pancreatic fat deposition and DM and HTN, but there was a significant correlation between pancreatic fat deposition in the pancreatic head and visceral fat area.

Conclusion Pancreatic fat deposition, as evaluated by CT, especially in the part of the pancreatic head adjacent to the ampulla of Vater, is a sensitive indicator of MetS. The correlations between pancreatic fat deposition and MetS parameters tended to be stronger in females than in males. These results may help further elucidate the pathophysiology of MetS and provide opportunities for its diagnosis.

Key words: non-alcoholic fatty pancreas disease, pancreatic steatosis, metabolic syndrome, obesity, diabetes mellitus

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Introduction

Pancreatic fat deposition is a common finding in abdominal imaging. Although the clinical significance of this observation has not yet been fully clarified, many recent studies have suggested an association between pancreatic fat deposition and metabolic syndrome (MetS) (1-5). Pancreatic fat deposition, as evaluated by computed tomography (CT), reportedly correlates with various parameters associated with MetS, such as the body mass index (BMI) (6), amount of visceral fat (7, 8), serum levels of high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) (3, 7, 9, 10), diabetes mellitus (DM) (9, 11, 12), and hypertension (HTN) (13, 14). In addition, many reports have pointed to correlations with age (6) and fatty liver (15-18).

Imaging modalities, such as ultrasonography (US), CT, and magnetic resonance imaging (MRI), are usually used to evaluate pancreatic fat deposition. Most previous studies on pancreatic fat deposition using CT have taken advantage of the fact that fat deposition reduces CT values, placing regions of interest (ROIs) of the same size at several locations

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from the head to the tail of the pancreas and then measuring and averaging CT values for all ROIs. However, although the degree of fat deposition in the pancreas is known to vary by location (19), not all studies have evaluated these values separately.

Fat accumulation is known to predominantly involve visceral fat in males and subcutaneous fat in females. Therefore, if a positive correlation exists between visceral and pancreatic fat deposition, sex differences in the degree of pancreatic fat deposition may also be present. However, the potential for such sex differences has not been considered in previous studies.

This study investigated the effects of location in the pancreas and sex differences on the relationship between pancreatic fat deposition and the age, BMI, visceral and subcutaneous fat, serum lipids [total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), non-HDL-C, and TG], hepatic steatosis, DM, and HTN.

Materials and Methods

Study participants

The ethics committee of our hospital approved the use of imaging data and a retrospective study design (#2022-053, Jan 31, 2023). This study was conducted in accordance with the Declaration of Helsinki.

A total of 703 patients who underwent plain CT of the upper abdomen at our hospital in August 2021 were enrolled. For patients who underwent multiple CT examinations during the study period, the CT scan closest to the time of serum lipid measurement (as described below) was used, while others were excluded. Patients <20 years old were excluded. First, serum lipid levels (TC, HDL-C, and TG) within 1 month before or after CT acquisition were extracted from electronic medical records. Cases in which even one of these values was not measured on the same day were excluded. As this was a retrospective study of the general patient population, the reasons for patients undergoing CT varied.

From these data, LDL-C levels were calculated using the Friedewald formula: LDL-C=TC-HDL-C-(TG/5). Non-HDL-C levels were calculated as follows: non-HDL-C=TC-HDL-C. Patients with TG >400 mg/dL were excluded because of the known large discrepancy between the true LDL-C values and the results calculated using the Friedewald formula.

We also calculated the BMI from the height and weight closest to the time of CT acquisition that were inputted into Digital Imaging and Communications in Medicine (DICOM) data or electronic medical records. Cases in which either height or weight data were unavailable were excluded.

In addition, the presence of a diagnosis of DM or HTN and the use of drugs for hyperlipidemia (statins, fibrates, ezetimibe, or ethyl icosapentate) at the time of CT acquisition were extracted from electronic medical records. The diagnosis of DM and HTN depends on the medical history documented in the electronic medical records. Since many patients are already under treatment for DM and/or HTN, we considered the measured blood glucose, HbA1c, and blood pressure to be less useful.

Imaging acquisition and the assessment of fat deposition in the pancreas and liver

Abdominal CT was performed using a 64- or 80-detector-row scanner (Aquilion; Toshiba Medical Systems, Tokyo, Japan). Images were acquired using the following settings: rotation time, 0.5-0.75 s; beam collimation, 1.0 mm (64-detector-row scanner) or 0.5 mm (80-detector-row scanner); pitch factor, 0.8; tube voltage, 120 kV; and scanning field of view, 32-36 cm. Imaging analyses were performed using 1-mm-thick reconstruction slices.

Patients within one month after abdominal surgery with a diagnosis of pancreatic disease (e.g., acute pancreatitis, chronic pancreatitis, intraductal papillary mucinous neoplasm, pancreatic cancer), acute abdomen, severe ascites, or mesenteric edema or in whom the evaluation of pancreatic CT values was difficult for any reason were excluded.

Circular ROIs were assigned to the head, body, and tail of the pancreas on CT images, and CT values were measured according to a previous study (20). To reflect fat deposition at the pancreatic margin, as large an ROI as possible was assigned from the anterior to the posterior edge of the pancreas, excluding the common bile duct, portal vein, and artifacts, and including the main pancreatic duct and intrapancreatic fat tissue (Fig. 1). In cases where simultaneous contrast-enhanced CT was performed, the results were used to confirm the positional relationships of the pancreas with blood vessels and other surrounding organs. CT values were measured at three different slices for the head (portion between the ampulla of Vater and uncinate process), body (portion between the left border of the aorta and the right border of the portal vein), and tail (middle portion between the intersection of the pancreas and the left border of the aorta and the lateral end of the pancreas). Each median value was considered the degree of fat deposition at that location in the pancreas.

To evaluate hepatic steatosis, 3 ROIs of equal size (190-210 mm^2) were placed in the hepatic left lobe and the anterior and posterior regions of the right lobe, avoiding vessels, bile ducts, cysts, and calcifications. The CT values in the ROIs were measured, and the average was considered the degree of hepatic steatosis. Cases of post-lobectomy, acute hepatitis, untreated liver tumor, or those in which the patient was taking tamoxifen were excluded.

To evaluate areas of total, visceral, and subcutaneous fat, CT values of -190 to -30 Hounsfield units (HU) were considered as fat, and areas of visceral and subcutaneous fat were then measured using a Synapse Vincent volume analyzer (version 4.4; Fujifilm Medical, Tokyo, Japan) on the slice at the L2/3 level of the lumbar spine for each case (21). Although the umbilical level and L3/4 or L4/5 levels are usually used to assess visceral fat, the position of

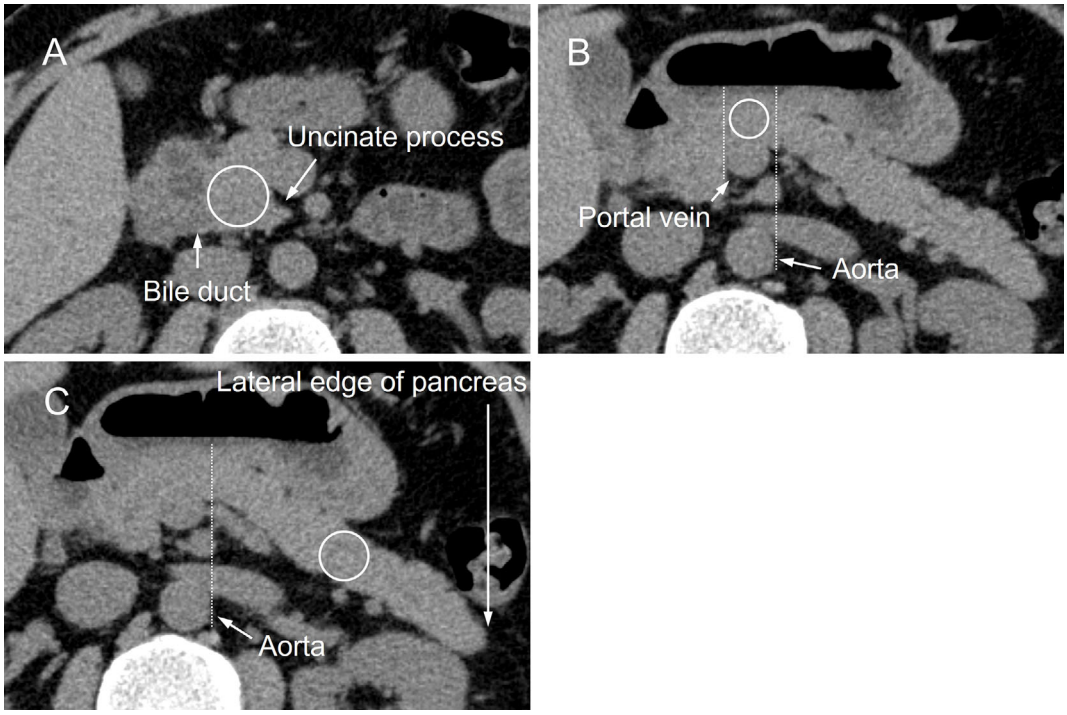

Figure 1. Method of region of interest assignment. A: Pancreatic head, B: pancreatic body, C: pancreatic tail.

the umbilical region is highly variable, particularly in obese individuals, and L3/4 or lower is often out of range when only the upper abdomen is imaged. Furthermore, previous reports have shown a greater correlation with pancreatic fat deposition at L2/3 than at L4/5 or at other levels (22-24).

Patients who died within one month after CT acquisition were excluded because they were more likely to have cachexia or other conditions that may have affected the BMI, amount of abdominal fat, and serum lipid profile the others.

We considered decreased CT values in the pancreas and liver to be indicative of fat deposition and evaluated the associations between CT values at each location in the pancreas and the age, BMI, visceral fat, subcutaneous fat, serum lipids, and hepatic steatosis. We also divided the patients into two groups according to the history of DM or HTN and examined whether or not significant differences in CT values at each location in the pancreas were present for each group.

Statistical analyses

Statistical analyses were performed using the EZR software program (version 1.50; Saitama Medical Center, Jichi Medical University, Saitama, Japan) (25). Statistical comparisons were performed using the Mann-Whitney U test for the ratio or interval scale variables and Fisher's exact test for ordinal or nominal scales. The Friedman test followed by Bonferroni's post hoc test was used to compare the degrees of fat deposition between different locations in the pancreas. Correlations were evaluated using Spearman's correlation coefficient. We performed a multivariate analysis using logistic regression to evaluate the association between metabolic parameters and the presence of DM or HTN. Statistical significance was set at $p<0.05$.

Results

Patients

A total of 140 patients (82 males 58 females) were included in the study (Fig. 2). The patient profiles are shown in Table 1. No significant differences in the BMI or total abdominal fat were evident between male and female patients, but the amount of visceral fat was significantly larger in males than in females ($p<0.001$), and that of subcutaneous fat was significantly larger in females than in males ($p=0.026$). In terms of serum lipids, significant differences between males and females were observed in TC ($p=0.037$), TG ($p=0.009$), and HDL-C ($p=0.001$). In the overall patient cohort, fat deposition was significantly more prominent in the pancreatic head than in the body ($p<0.001$) or tail ($p<0.001$); however, no significant difference was evident between the pancreatic body and tail ($p=0.3$). The same tendency was observed in males (head vs. body, $p<0.001$; head vs. tail, $p<0.001$; body vs. tail, $p=1$). In contrast, the difference between the pancreatic head and body was not significant in females (head vs. body, $p=0.061$; head vs. tail, $p=0.024$; body vs. tail, $p=0.241$). No significant sex differences in pancreatic fat deposition were observed at any location. Hepatic steatosis was significantly more pronounced in males than in females ($p=0.027$). No sex differences were observed in the use of drugs for dyslipidemia or in the pres-

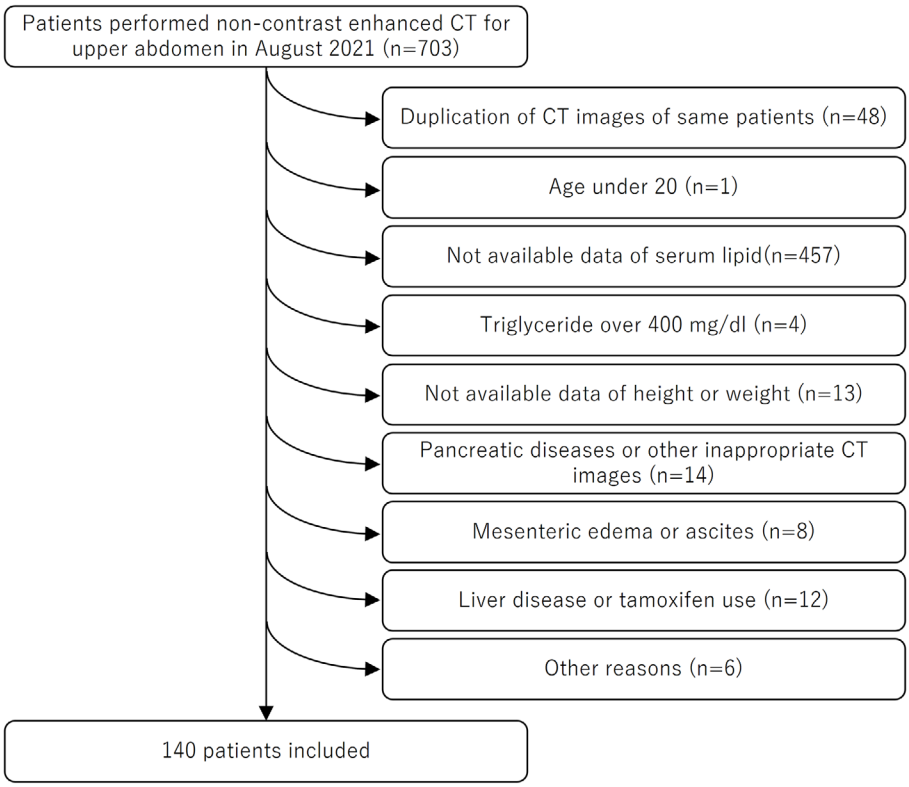

Figure 2. **Study flow for selection of participants. CT: computed tomography**

ence of DM or HTN.

Differences in the correlation between pancreatic fat deposition and metabolic parameters due to location in the pancreas

The correlations between the average CT value for all locations in the pancreas (whole pancreas) or CT values for each location in the pancreas and the age, BMI, visceral and subcutaneous fat, serum lipids, and hepatic steatosis are shown in Table 2.

• Age

A significant but very weak negative correlation was identified between CT values in the pancreatic head, body, and tail and the patient age. Correlations were weakest in the head (rho=-0.183, p=0.031), followed by the body (rho=-0.227, p=0.007) and tail (rho=-0.241, p=0.004).

• BMI

Significant negative correlations were observed between CT values in the pancreatic head, body, and tail and the BMI. Correlations were strongest in the head (rho=-0.453, p<0.001), followed by the body (rho=-0.358, p<0.001) and tail (rho=-0.311, p<0.001).

• Visceral and subcutaneous fat content

Both visceral and subcutaneous fat areas showed significant negative correlations with the CT values of the pancreatic head, body, and tail. Correlations were strongest in the head, followed by the body and tail (visceral fat: rho=-0.525, -0.433, and -0.321, respectively; all p<0.001; subcutaneous fat: rho=-0.329, -0.301, and -0.223, respectively; all p<0.01). In all locations of the pancreas, the correlations were stronger for areas of visceral fat than for areas of subcutaneous fat.

• Serum lipids

Correlations between CT values of the pancreatic head and body and serum TG (head, rho=-0.198, p=0.019; body, rho=-0.198, p=0.019) or HDL-C (head, rho=0.211, p=0.012; body, rho=0.241, p=0.004) were very weak but significant. Conversely, no significant correlations were found between the CT values of the pancreatic tail and the lipid profile. No correlation was identified between pancreatic CT values and LDL-C or non-HDL-C levels.

• Hepatic steatosis

A significant correlation (rho=0.246, p=0.003) was found between the CT values of the pancreas and liver only for the pancreatic head, but the correlation was weak.

Sex differences in correlations between pancreatic fat deposition and metabolic parameters

Sex differences in the correlations between CT values of the whole pancreas or of each location in the pancreas and the age, BMI, visceral and subcutaneous fat, serum lipids, and hepatic steatosis are shown in Table 3.

• Age

A significant negative correlation between CT values of the pancreas and age was observed only for the pancreatic tail in females (rho=-0.334, p=0.010).

• BMI

Pancreatic CT values and BMI showed significant negative correlations in both sexes for all pancreatic locations. Correlations were stronger in females (head: rho=-0.515, p<

Table 1. Characteristics of Participants and Sex Differences for Each Metabolic Parameter.

	Total (n=140)	Male (n=82)	Female (n=58)	p
Age (years)	68.4±13.2	67.4±12.0	69.7±14.8	0.240
BMI (kg/m^2, mean±SD)	23.8±4.1	23.9±3.7	23.7±4.7	0.581
Total abdominal fat (cm^2)	272.2±126.9	286.8±115.3	251.5±140.1	0.052
Visceral fat (cm^2)	159.5±84.1	185.8±79.7	122.3±76.3	<0.001
Subcutaneous fat (cm^2)	112.6±63.7	101.0±51.1	129.1±75.6	0.026
Serum lipids (mg/dL, mean±SD)				
TG	137.6±66.1	148.6±65.8	121.9±63.9	0.009
TC	187.4±42.1	180.9±40.9	196.6±42.4	0.037
HDL-C	57.4±19.7	53.3±19.1	63.1±19.2	0.001
LDL-C	102.5±36.1	97.8±35.9	109.1±35.6	0.107
Non-HDL-C	130.0±39.4	127.6±39.5	133.5±39.2	0.528
CT attenuation value (HU, mean±SD)				
Whole pancreas	36.8±13.8	37.5±11.3	35.7±16.8	0.780
Pancreatic head	32.3±20.6	32.8±17.3	31.6±24.6	0.548
Pancreatic body	38.4±12.8*	39.7±10.2*	36.6±15.6	0.648
Pancreatic tail	39.5±10.8*	40.0±9.2*	38.9±12.8*	0.814
Liver	62.5±9.5	61.0±9.6	64.6±9.1	0.027
Drugs for dyslipidemia (yes/no) †	52/88	33/49	19/39	0.381
DM (yes/no) †	51/89	33/49	18/40	0.289
HTN (yes/no) †	90/50	52/30	38/20	0.859

BMI: body mass index, TG: triglyceride, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, HU: Hounsfield units, DM: diabetes mellitus, HTN: hypertension
†Fisher's exact test; other values were analyzed using the Mann-Whitney U test. Underlines represent values of p<0.05.
*Significant difference by Friedman's test compared to each CT attenuation value of the head of the pancreas.

Table 2. Correlations between Fat Deposition in Each Pancreatic Location and Metabolic Parameters.

	Whole pancreas		Pancreatic head		Pancreatic body		Pancreatic tail	
	rho	p	rho	p	rho	p	rho	p
Age	-0.227	0.007	-0.183	0.031	-0.227	0.007	-0.241	0.004
BMI	-0.416	<0.001	-0.453	<0.001	-0.358	<0.001	-0.311	<0.001
Total abdominal fat	-0.498	<0.001	-0.544	<0.001	-0.448	<0.001	-0.342	<0.001
Visceral fat	-0.480	<0.001	-0.525	<0.001	-0.433	<0.001	-0.321	<0.001
Subcutaneous fat	-0.312	<0.001	-0.329	<0.001	-0.301	<0.001	-0.223	0.008
Serum lipids								
TG	-0.195	0.021	-0.198	0.019	-0.198	0.019	-0.127	0.135
TC	0.043	0.615	0.061	0.477	0.037	0.663	0.000	0.999
HDL-C	0.205	0.015	0.211	0.012	0.241	0.004	0.121	0.155
LDL-C	0.034	0.692	0.050	0.556	0.004	0.964	0.015	0.864
Non-HDL-C	-0.025	0.767	-0.011	0.895	0.037	0.663	-0.016	0.856
CT value of liver	0.195	0.021	0.246	0.003	0.155	0.067	0.058	0.498

BMI: body mass index, TG: triglyceride, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, HU: Hounsfield units. All results show Spearman's correlation coefficients (rho and p). Underlines represent values of p<0.05.

0.001; body: rho=-0.421, p=0.001; tail: rho=-0.345, p=0.008) than in males (head: rho=-0.376, p=0.001; body: rho=-0.291, p=0.008; tail: rho=-0.247, p=0.026) for all locations in the pancreas.

• Visceral and subcutaneous fat content

Pancreatic CT values and the area of visceral fat showed significant negative correlations in both sexes for all locations in the pancreas, with stronger correlations found in females (head: rho=-0.589; p<0.001; body: rho=-0.567, p<0.001; tail: rho=-0.392, p=0.002) than in males (head: rho=-0.496, p<0.001; body: rho=-0.384, p<0.001; tail: rho=-0.275, p=0.013). In the pancreatic head, CT values and the

Table 3. Sex Differences in Correlation Coefficients between Pancreatic Fat Deposition and Metabolic Parameters.

Location	Whole pancreas				Pancreatic head				Pancreatic body				Pancreatic tail			
Sex	Male		Female		Male		Female		Male		Female		Male		Female	
	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
Age	-0.187	0.093	-0.286	0.030	-0.143	0.200	-0.233	0.079	-0.196	0.078	-0.217	0.102	-0.186	0.095	-0.334	0.010
BMI	-0.340	0.002	-0.477	<0.001	-0.376	0.001	-0.515	<0.001	-0.291	0.008	-0.421	0.001	-0.247	0.026	-0.345	0.008
Total abdominal fat	-0.426	<0.001	-0.564	<0.001	-0.499	<0.001	-0.572	<0.001	-0.347	0.001	-0.558	<0.001	-0.274	0.013	-0.395	0.002
Visceral fat	-0.434	<0.001	-0.576	<0.001	-0.496	<0.001	-0.589	<0.001	-0.384	<0.001	-0.567	<0.001	-0.275	0.013	-0.392	0.002
Subcutaneous fat	-0.191	0.086	-0.467	<0.001	-0.230	0.038	-0.467	<0.001	-0.155	0.164	-0.461	<0.001	-0.127	0.254	-0.338	0.010
Serum lipids																
TG	-0.050	0.654	-0.327	0.012	-0.021	0.853	-0.343	0.008	-0.119	0.288	-0.327	0.012	-0.030	0.793	-0.208	0.117
TC	0.118	0.289	-0.089	0.506	0.129	0.247	-0.050	0.707	0.122	0.273	-0.087	0.514	0.078	0.484	-0.126	0.344
HDL-C	0.161	0.147	0.338	0.009	0.171	0.126	0.339	0.009	0.258	0.019	0.326	0.013	0.104	0.352	0.210	0.114
LDL-C	0.141	0.206	-0.142	0.289	0.131	0.241	-0.082	0.538	0.095	0.397	-0.130	0.330	0.142	0.204	-0.172	0.196
Non-HDL-C	0.123	0.272	-0.254	0.055	0.121	0.281	-0.211	0.112	0.046	0.683	-0.244	0.065	0.128	0.252	-0.222	0.094
CT value of pancreas																
Pancreatic head	-	-	-	-	-	-	-	-	0.756	<0.001	0.903	<0.001	0.743	<0.001	0.669	<0.001
Pancreatic body	-	-	-	-	-	-	-	-	-	-	-	-	0.752	<0.001	0.723	<0.001
CT value of liver	0.293	0.008	0.065	0.626	0.321	0.003	0.161	0.226	0.275	0.013	-0.001	0.993	0.159	0.154	-0.086	0.518

BMI: body mass index, TG: triglyceride, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, HU: Hounsfield units

All results show Spearman's correlation coefficients (rho and p). Underlines represent values of p<0.05.

area of subcutaneous fat were significantly negatively correlated in both sexes, with a stronger correlation found in females (rho=-0.467, p<0.001) than in males (rho=-0.038, p=0.038). In contrast, in the pancreatic body and tail, these correlations were only observed in females, with no significant correlations observed in males.

• Serum lipids

A significant negative correlation was observed between pancreatic CT values and serum TG levels in the pancreatic head (rho=-0.343, p=0.008) and body (rho=-0.327, p=0.012) in females. Pancreatic CT values and serum HDL-C also showed significant positive correlations in the pancreatic head (rho=0.339, p=0.009) and body (rho=0.326, p=0.013) in females and in the pancreatic body in males (rho=0.258, p=0.019).

• Hepatic steatosis

CT values of the pancreas and liver showed significant positive correlations only for the pancreatic head and body in males. Correlation coefficients between liver CT values and visceral fat area showed a significant negative correlation in males (rho=-0.544, p<0.001) but a weak, non-significant relationship in females (rho=-0.251, p=0.058).

Association of DM with pancreatic fat deposition

The CT values at each location in the pancreas in the non-DM and DM groups are shown in Table 4. Significant differences in pancreatic CT values between the DM and non-DM groups were observed for all pancreatic locations in females. However, no significant differences were observed for any location of the pancreas in males. However, a logistic regression analysis using the presence of DM as the objective variable and age, visceral fat area, and CT values of each location in the pancreas as explanatory variables showed that only the visceral fat area was significantly correlated with DM in both males and females, and CT values of the pancreatic head, body, and tail were not significantly correlated with the presence of DM (Table 4).

Associations of HTN with pancreatic fat deposition

The CT values for each location in the pancreas in the non-HTN and HTN groups are shown as medians and interquartile ranges in Table 5. Significant differences in CT values were observed between the HTN and non-HTN groups in the head and body of the pancreas in males and in all locations of the pancreas in females. Although no significant difference was observed in the pancreatic tail in males, a similar trend might be expected, given the p value of 0.057. However, a logistic regression analysis using the presence of HTN as the objective variable and age, visceral fat area, and CT values of each part of the pancreas as explanatory variables showed that only the visceral fat area in males and the age and visceral fat area in females showed a significant correlation with HTN, whereas CT values of the pancreatic head, body, and tail did not show a significant correlation with the presence of HTN (Table 5).

Results of a logistic regression analysis examining the effects of age, visceral fat, DM and HTN on pancreatic fat deposition

Finally, for our examination of the effects of visceral fat mass, DM, and HTN on pancreatic fat deposition, CT values <36 HU were considered to indicate fat deposition, according to previous studies (10), and a logistic regression analysis was performed with the pancreatic fat deposition pres-

Table 4. Comparison of the Cases in Non-DM and DM Patients and Logistic Regression Analysis with the Presence of DM as the Objective Variable.

Univariable analysis (Mann-Whitney U test)	Male			Female		
	Non-DM	DM	p	Non-DM	DM	p
Age median [interquartile range]	65.0 [55.0-74.0]	70.0 [67.0-74.0]	0.090	69.0 [58.0-80.0]	74.5 [68.0-81.75]	0.229
VFA median [interquartile range]	177.2 [115.3-218.6]	211.0 [145.4-272.3]	0.026	85.3 [50.1-135.3]	175.2 [124.6-251.4]	<0.001
CT value of pancreas median [interquartile range]						
Pancreatic head	36.5 [27.2-46.6]	34.8 [22.8-43.4]	0.168	44.9 [29.2-51.2]	25.9 [15.6-33.1]	0.006
Pancreatic body	42.4 [36.3-47.0]	39.4 [35.3-43.5]	0.139	44.4 [38.9-48.6]	30.5 [25.5-37.8]	<0.001
Pancreatic tail	42.4 [36.4-47.1]	38.4 [36.0-45.7]	0.424	44.8 [38.5-49.1]	35.2 [30.3-43.1]	0.006

Multivariable analysis (Logistic regression analysis)	Male			Female		
	Explanatory variable	Odds ratio [95% CI]	p	Explanatory variable	Odds ratio [95% CI]	p
Pancreatic head	Age	1.04 [0.997-1.08]	0.0731	Age	1.03 [0.983-1.08]	0.223
	VFA	1.01 [1.00-1.01]	0.0382	VFA	1.02 [1.01-1.03]	0.00173
	Pancreatic CT value	1.00 [0.974-1.03]	0.805	Pancreatic CT value	1.00 [0.975-1.03]	0.844
Pancreatic body	Age	1.04 [0.994-1.08]	0.0977	Age	1.03 [0.982-1.08]	0.231
	VFA	1.01 [1.00-1.01]	0.051	VFA	1.02 [1.01-1.03]	0.00289
	Pancreatic CT value	0.991 [0.943-1.04]	0.727	Pancreatic CT value	0.997 [0.955-1.04]	0.903
Pancreatic tail	Age	1.04 [0.997-1.08]	0.0696	Age	1.03 [0.98-1.07]	0.272
	VFA	1.01 [1.00-1.01]	0.0274	VFA	1.02 [1.01-1.03]	0.00234
	Pancreatic CT value	1.01 [0.958-1.07]	0.698	Pancreatic CT value	0.981 [0.931-1.03]	0.482

CT: computed tomography, DM: diabetes mellitus, VFA: visceral fat area, CI: confidence interval.
Underlines represent values of p<0.05.

Table 5. Comparison of the Cases in Non-HTN and HTN Patients and Logistic Regression Analysis with the Presence of HTN As the Objective Variable.

Univariable analysis (Mann-Whitney U test)	Male			Female		
	Non-HTN	HTN	p	Non- HTN	HTN	p
Age Median [interquartile range]	62.0 [55.3-72.0]	71.0 [64.5-77.5]	0.041	61.5 [57.0-68.25]	77.0 [66.5-83.75]	0.001
VFA Median [interquartile range]	140.9 [79.9-205.9]	207.1 [149.3-262.4]	0.001	52.5 [28.6-81.5]	135.0 [93.6-192.0]	<0.001
CT value of pancreas Median [interquartile range]						
Pancreatic head	37.1 [32.5-50.8]	34.4 [19.9-42.9]	0.019	50.0 [41.8-51.7]	32.0 [20.0-44.3]	0.002
Pancreatic body	44.7 [41.0-49.1]	39.4 [33.6-43.3]	<0.001	48.0 [42.3-49.1]	37.2 [25.8-42.9]	<0.001
Pancreatic tail	44.7 [38.1-47.8]	39.6 [33.1-45.6]	0.057	46.9 [43.6-51.4]	39.3 [30.3-44.8]	<0.001

Multivariable analysis (Logistic regression analysis)	Male			Female		
	Explanatory variable	Odds ratio [95% CI]	p	Explanatory variable	Odds ratio [95% CI]	p
Pancreatic head	Age	1.03 [0.99-1.08]	0.111	Age	1.07 [1.02-1.13]	0.007
	VFA	1.01 [1.00-1.02]	0.025	VFA	1.02 [1.01-1.04]	0.003
	Pancreatic CT value	0.982 [0.95-1.02]	0.326	Pancreatic CT value	1.01 [0.98-1.04]	0.667
Pancreatic body	Age	1.03 [0.99-1.08]	0.169	Age	1.08 [1.02-1.14]	0.007
	VFA	1.01 [1.00-1.02]	0.028	VFA	1.03 [1.01-1.04]	0.003
	Pancreatic CT value	0.948 [0.89-1.02]	0.127	Pancreatic CT value	1.02 [0.965-1.08]	0.469
Pancreatic tail	Age	1.03 [0.99-1.08]	0.116	Age	1.07 [1.01-1.13]	0.013
	VFA	1.01 [1.00-1.02]	0.008	VFA	1.02 [1.01-1.04]	0.003
	Pancreatic CT value	0.978 [0.92-1.04]	0.443	Pancreatic CT value	0.996 [0.931-1.06]	0.897

CT: computed tomography, HTN: hypertension, VFA: visceral fat area, CT: confidence interval
Underlines represent values of p<0.05.

Table 6. Logistic Regression Analysis with Pancreatic CT Values As the Objective Variable.

Male			Female		
Explanatory variable	Odds ratio [95% CI]	p	Explanatory variable	Odds ratio [95% CI]	p
Pancreatic head			Pancreatic head		
Age	0.986 [0.947-1.03]	0.515	Age	0.975 [0.929-1.02]	0.289
VFA	0.987 [0.980-0.994]	<0.001	VFA	0.980 [0.967-0.994]	0.004
DM	0.832 [0.290-2.39]	0.733	DM	0.438 [0.089-2.15]	0.310
HTN	0.838 [0.279-2.52]	0.753	HTN	0.331 [0.060-1.82]	0.204
Pancreatic body			Pancreatic body		
Age	0.963 [0.919-1.01]	0.125	Age	0.998 [0.953-1.04]	0.918
VFA	0.994 [0.987-1.00]	0.137	VFA	0.989 [0.979-1.00]	0.041
DM	1.80 [0.565-5.70]	0.321	DM	0.355 [0.086-1.46]	0.152
HTN	0.263 [0.0637-1.08]	0.065	HTN	0.678 [0.129-3.57]	0.647
Pancreatic tail			Pancreatic tail		
Age	0.973 [0.929-1.02]	0.241	Age	0.992 [0.950-1.04]	0.710
VFA	0.997 [0.989-1.00]	0.372	VFA	0.997 [0.988-1.01]	0.594
DM	1.71 [0.544-5.36]	0.359	DM	0.412 [0.101-1.68]	0.215
HTN	0.392 [0.105-1.46]	0.162	HTN	0.235 [0.039-1.41]	0.114

CI: confidence interval, VFA: visceral fat area, DM: diabetes mellitus, HTN: hypertension
Underlines represent values of p<0.05.

ence as the objective variable and the age, visceral fat area, DM, and HTN as explanatory variables. The results showed a significant negative correlation with CT values of the pancreatic head in males and the pancreatic head and body in females, but only for visceral fat area (Table 6).

Discussion

This study revealed that the degree of fat deposition in the pancreas is not uniform but strongly related to location and sex differences. To our knowledge, this is the first study to investigate the relationship between pancreatic fat deposition and these factors.

Relationship between location in the pancreas and fat deposition

First, regarding the location in the pancreas, fat deposition was higher in the head than in the body or tail. In all locations of the pancreas, greater fat deposition was associated with a higher BMI and visceral and subcutaneous fat accumulation, with the pancreatic head showing the strongest correlation. Greater fat deposition was also associated with higher TG and lower HDL-C levels; this tendency was most prominent in the pancreatic head, although the correlation was very weak. The correlation between pancreatic fat deposition and sex, discussed later, is stronger than that between pancreatic fat deposition and the location of the pancreas. These results suggest that pancreatic fat deposition associated with MetS may predominantly occur in the pancreatic head.

The uncinate process and ventral side of the pancreatic head are embryologically derived from the ventral pancreatic bud, and parenchymal tissue is sparse and histologically adipocyte-rich (19, 26, 27). Consequently, this region is more prone to fat deposition than other locations in the pancreas derived from the dorsal pancreatic bud. The present study selected the region between the ampulla of Vater and uncinate process as the location of the ROI for the pancreatic head, which is thought to contain a greater amount of tissue derived from the ventral pancreatic bud than that derived from the dorsal pancreatic bud. The results of this study presumably reflect the histological differences in the degree of pancreatic fat deposition. In contrast, fat deposition was least prominent in the pancreatic tail, and deposition in the pancreatic body was intermediate between the pancreatic head and tail. In addition, the pancreatic body often has a very small anteroposterior diameter, making it unsuitable for a morphometric assessment. These results suggest that pancreatic fat deposition at locations thought to be derived from the ventral pancreatic bud should be evaluated for greater sensitivity to changes arising from MetS.

In contrast, the correlation between pancreatic fat deposition and age was stronger in the pancreatic tail than in the pancreatic head. However, the overall correlation coefficient was small, suggesting that the correlation between fat deposition and age in the pancreatic head was masked by obesity and other factors and that the correlation was relatively strong in the pancreatic tail.

Relationship between sex and pancreatic fat deposition

Regarding sex, although no significant difference was observed in pancreatic fat deposition itself, the correlations between pancreatic fat deposition and the age, BMI, visceral and subcutaneous fat, and serum lipids (high TG and low HDL-C) were stronger in females than in males.

The correlations between pancreatic fat deposition and age were significant only in the pancreatic tail of females,

whereas no significant correlations were found in any location in the pancreas of males. Because pancreatic fat deposition is affected more by obesity and other factors in males than in females, age-related fat deposition may have been masked in the pancreatic head.

The correlations between pancreatic fat deposition and the BMI, visceral fat, and subcutaneous fat were stronger in females than in males. Visceral fat showed the strongest correlation in both sexes, which is consistent with previous studies (2, 8, 12, 13). Visceral fat is reportedly a more sensitive indicator of MetS in females than in males (28), which is similar to the present results. This may be because visceral fat deposition, including involvement of the pancreas, is less likely to occur in females than in males, and fat deposition becomes obvious after obesity has progressed sufficiently.

High TG and low HDL-C levels correlated significantly with fat deposition in the head and body of the pancreas in females, while no significant correlation was seen in males beyond a weak correlation between low HDL-C and fat deposition in the pancreatic body. Visceral fat is known to correlate with high TG and low HDL-C levels (29-31), which may be consistent with the correlation between pancreatic fat deposition and high TG and low HDL-C levels in females observed in this study. However, no correlation was found between pancreatic fat and serum lipid levels in males. This may reflect sex-based differences in the relationship between pancreatic fat deposition and visceral fat accumulation.

Based on these observations, fat deposition predominantly in the pancreatic head, especially in females, may serve as a marker for the presence of obesity and dyslipidemia.

Association of hepatic steatosis with pancreatic fat deposition

Regarding the relationships among pancreatic fat deposition, hepatic steatosis, and amount of visceral fat, both pancreatic fat deposition and hepatic steatosis correlated with the amount of visceral fat in males, and a weak but significant correlation was also identified between pancreatic fat deposition and hepatic steatosis. In contrast, in females, although a strong correlation was observed between pancreatic fat deposition and visceral fat, no significant correlations were noted between hepatic steatosis and visceral fat or between pancreatic fat deposition and hepatic steatosis. Therefore, if the amount of visceral fat in males and females is similar, pancreatic fat deposition in the females can be expected to be similar to that in the males, whereas females are less likely to have hepatic steatosis than the males. Females are known to be less prone to hepatic steatosis than males during their reproductive years due to estrogen, and hepatic steatosis increases after menopause (32). Thus, pancreatic fat deposition and hepatic steatosis are unlikely to correlate in females because the liver is protected by estrogen.

Association of DM with pancreatic fat deposition

In females, pancreatic fat deposition was more pronounced in the DM group than in the non-DM group for all locations in the pancreas, with no such difference observed in males. However, a logistic regression analysis did not reveal a direct causal relationship between pancreatic fat deposition and DM in both males or females. In addition, when correlations with pancreatic CT values were examined in the selection of included cases in which HbA1c was measured, no significant correlations were found (data not shown). These findings suggest that pancreatic fat deposition has no direct effect on the presence or control of DM and that the correlation observed is an indirect effect of the visceral fat mass.

Associations of HTN with pancreatic fat deposition

Pancreatic fat deposition was more intense in the HTN group than in the non-HTN group at almost all locations in the pancreas, and no sex difference was observed, unlike in the case of DM. HTN has also been reported to reflect visceral fat deposition more sensitively than the BMI (14), which is consistent with the present results. However, since a direct causal relationship between HTN and pancreatic fat deposition is unlikely, both may well represent the results of MetS, especially visceral fat accumulation, which is supported by the results of a logistic regression analysis. The reason for the smaller sex difference than with DM may be attributed to the earlier onset of HTN than DM, suggesting that pancreatic fat deposition may be one of the most sensitive indicators of MetS.

Results of a logistic regression analysis examining the effects of age, visceral fat, DM and HTN on pancreatic fat deposition

The results of the logistic regression analysis with pancreatic CT values as the objective variable indicated a significant negative correlation only with visceral fat area, and no significant correlations were observed with age, DM, or HTN. Therefore, pancreatic fat deposition is considered to reflect the visceral fat mass more strongly than age, DM, or HTN. Furthermore, when considering the pancreatic region, a strong correlation was observed in the pancreatic head for both sexes, a correlation was found in the pancreatic body for females only, and no significant correlation was detected in the pancreatic tail for both sexes. These results support the notion that fat deposition in the pancreatic head strongly reflects the amount of visceral fat, whereas fat deposition in the pancreatic tail is less strongly affected by visceral fat accumulation.

Several limitations associated with the present study warrant mention. First, some selection biases may have been present, as this was a single-center, retrospective study, and almost all patients were Japanese. In addition, because most patients with close measurement of serum lipids have cardiovascular disease, a higher percentage of patients in this

study may have had a history of cardiovascular disease than the general patients. Second, pancreatic atrophy was not considered. Although the pancreas atrophies with age (33) and type 2 DM (6), we assessed CT values without considering the impact of atrophy. Whether the evaluation of the pancreas with or without atrophy is appropriate using the same method remains unclear. Third, because the population of this study was general patients, many had several background diseases or were using multiple drugs. These issues may have affected the results. Fourth, the effects of menopause on women were not considered. Menopause not only increases fatty liver but also increases visceral fat (34), which is likely to affect pancreatic fat deposition. However, as this was a retrospective study, and menopause was not always mentioned in the medical records, it was difficult to investigate this in detail. These points should be addressed in future studies.

In conclusion, our study suggests that pancreatic fat deposition, as evaluated by CT, may serve as a sensitive indicator of MetS. In particular, fat deposition in parts of the pancreatic head derived from the ventral pancreatic buds appears to be the most sensitive indicator. Regarding sex differences, pancreatic fat deposition may be a stronger indicator of MetS in females than in males. In addition, a multivariate analysis results did not suggest a direct causal relationship between pancreatic fat deposition and DM and HTN, but there was a significant correlation between pancreatic fat deposition in the pancreatic head and visceral fat area. The results of this study may help further elucidate the pathophysiology of MetS. Furthermore, if fat deposition is incidentally found in the pancreatic head, it is presumed that the patient is likely to be in the high-risk group for MetS, and this may provide opportunities for a prompt diagnosis.

The authors state that they have no Conflict of Interest (COI).

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