Association of Pancreatic Steatosis With Chronic Pancreatitis, Obesity, and Type 2 Diabetes Mellitus

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Abstract

Objective: The aim of this study was to determine the association of the pancreatic steatosis with obesity, chronic pancreatitis (CP), and type 2 diabetes mellitus.

Methods: Patients (n = 118) were retrospectively identified and categorized into no CP (n = 60), mild (n = 21), moderate (n = 27), and severe CP (n = 10) groups based on clinical history and magnetic resonance cholangiopancreatography using the Cambridge classification as the diagnostic standard. Visceral and subcutaneous compartments were manually segmented, and fat tissue was quantitatively measured on axial magnetic resonance imaging.

Results: Pancreatic fat fraction showed a direct correlation with fat within the visceral compartment ($r = 0.54$). Patients with CP showed higher visceral fat ($P = 0.01$) and pancreatic fat fraction ($P < 0.001$): mild, 24%; moderate, 23%; severe CP, 21%; no CP group, 15%. Patients with type 2 diabetes mellitus showed higher pancreatic steatosis ($P = 0.03$) and higher visceral ($P = 0.007$) and subcutaneous fat ($P = 0.004$). Interobserver variability of measuring fat by magnetic resonance imaging was excellent (r 0.90–0.99).

Conclusions: Increased visceral adipose tissue has a moderate direct correlation with pancreatic fat fraction. Chronic pancreatitis is associated with higher pancreatic fat fraction and visceral fat. Type 2 diabetes mellitus is associated with higher pancreatic fat fraction and visceral and subcutaneous adiposity.

Keywords

diabetes mellitus; obesity; pancreas; steatosis

Pancreatic steatosis, which comprehends fatty replacement and fatty infiltration of the pancreas, is a commonly observed but often neglected finding by radiologists. The estimated prevalence of pancreatic steatosis from population-based studies in Asia is approximately 16%.[1,2] A higher prevalence has been noted in hospital-based populations and those with type 2 diabetes mellitus (T2DM) and obesity.[3,4] There is notable evidence from both the pathological and imaging point of view that pancreatic steatosis is an increasing problem due to increasing incidence of obesity.[3,5] Obesity is a heterogeneous condition that may manifest itself with considerable individual differences regarding distribution of body fat. Much of previous research has focused on the association between obesity with metabolic syndrome, cardiovascular risk, diabetes, and hepatic steatosis.[6] The association of abdominal fat distribution with the development of pancreatic steatosis and chronic pancreatitis (CP) is underinvestigated and not clear. A recent study reported an association between pancreatic steatosis, visceral fat, and metabolic syndrome using computed tomography and ultrasound.[7] Using different fat quantification techniques of the magnetic resonance imaging (MRI), the pancreatic fat fraction can be reliably quantified[8] with higher accuracy than computed tomography and ultrasound.[9] To our knowledge, there have been no studies that investigated the correlation of pancreatic steatosis with the distribution of abdominal fat using precise fat quantification methods of MRI. The purpose of this study was to determine the association of the pancreatic steatosis with obesity, CP, and T2DM.

MATERIALS AND METHODS

Patient Selection

This study was approved by the institutional review board and complied with the Health Insurance Portability and Accountability Act. We retrospectively identified 143 consecutive patients who presented to a tertiary referral center for pancreatic diseases and had an magnetic resonance cholangiopancreatography (MRCP) examination within a month of their visit between May 2016 and February 2017 (Fig. 1). Patients who presented to the gastroenterology clinic (n = 113) had unexplained upper abdominal pain suspected to be of pancreatic in origin as described in the American Pancreatic Association guidelines.[10] The remaining 30 patients were enrolled in the pancreatic cancer screening program. These patients were annually screened with MRI/MRCP for pancreatic cancer due to either family history of pancreatic cancer or having a genetic predisposition (eg, presence of germline *BRCA* mutation) for pancreatic cancer. These patients were otherwise healthy and screened with amylase, lipase, aspartate aminotransferase, alkaline phosphatase, carcinoembryonic antigen, carbohydrate antigen 19–9, and C-peptide before enrolling in the program. Of the 143 patients, 118 were included in the analysis after 25 patients were excluded secondary to the diagnosis of pancreatic cancer (n = 1), acute pancreatitis (n = 17), artifacts affecting the pancreas (n = 4), and previous pancreatic surgery (n = 3). Data on T2DM status, body mass index (BMI), weight, hyperlipidemia, smoking, and alcohol use were obtained from the electronic medical records.

This study categorized the patients based on MRCP ductal findings using the Cambridge classification as the diagnostic standard.[11] Cambridge 0 patients comprised the no-disease group (n = 60), whereas the patients in the Cambridge 2 (mild CP), 3 (moderate CP), and 4

(severe CP) were combined as the disease group (n = 58). There were no patients with Cambridge grade 1 (ie, equivocal or 1–2 side-branch ectasias).

Imaging Technique

All patients were imaged on the 3-T MRI scanner (Magnetom Verio; Siemens Healthcare GmbH, Erlangen, Germany) using the same imaging protocol. Imaging parameters of the axial breath-hold 2-point DIXON T1-weighted images were as follows repetition time, 5.45 milliseconds; echo time 1, 2.45 milliseconds; echo time 2, 3.675 milliseconds; flip angle, 9°; and slice thickness, 4 mm. Secretin (ChiRhoStim; ChiRhoClin Inc, Burtonsville, Md) was given in all patients to enhance the visualization of the pancreatic ducts using the manufacturer-recommended dose of 16 μg. Pancreatic ducts were imaged via coronal 2-dimensional single-shot turbo spin echo sequence, which was repeated every 60 seconds up to 10 minutes. Patients were fasting at least 4 hours before the MRCP. No adverse events were identified.

Image Data Analysis

Two image analysts collected data, and 1 abdominal radiologist with 16 years of experience graded the MRCP findings using Cambridge classification. All DICOM Dixon images were deidentified and imported into Analyze 12.0 (AnalyzeDirect, Stilwell, Kan) for image processing. See the supplemental materials http://links.lww.com/MPA/A706, for step-by-step details of the image postprocessing. Image analysts who performed region-of-interest measurements were blinded to the patient information. The pancreatic fat fraction was calculated by measuring signal intensity on the fat-only and water-only fractions of the T1-weighted axial breath-hold 2-point Dixon series.[12] Visceral adipose tissue (VAT) is defined as intra-abdominal fat (including intraperitoneal and retroperitoneal fat) bound by parietal peritoneum or transversalis fascia, excluding the vertebral column and the paraspinal muscles. The subcutaneous adipose tissue (SAT) is defined as fat superficial to the abdominal and back muscles. The pancreatic and abdominal segmentation was verified by the abdominal radiologist.

Statistical Analysis

Fisher-Freeman-Halton, Kruskal-Wallis, and Mann-Whitney-Wilcoxon tests were used to determine differences between the 4 groups. Spearman rank correlation coefficient was used to assess relationships between the independent variables and interob-server concordance. Correlation coefficients were interpreted as follows: weak, 0.2; moderate, 0.5; strong, 0.8; and perfect, 1.0.[13] Receiver operating characteristic curves and multivariate logistic model were used to compare different models. Conventional risk factors for diabetes and CP (age, alcohol, smoking, hyperlipidemia, and BMI) were included in the base model of multivariate logistic regression. Likelihood ratio tests were used in assessing each new measure to be added to the logistic models. Youden index was used for determining threshold values of pancreatic fat. Probit regression was used to estimate the probability of CP and T2DM. The predicted probability was plotted for each model to demonstrate the effectiveness of each measure alone. Statistical analyses were performed using MedCalc version 18.2.1 (MedCalc Software, Mariakerke, Belgium) and R software version 3.3.0 (R Foundation, Vienna, Austria).

RESULTS

The patients' age, sex, amylase, lipase, BMI, weight, and other independent variables are listed in Table 1, and comparisons of results in the disease versus no-disease groups are presented in Table 2. Distribution of patient's sex was similar in patients with and without CP ($P = 0.30$) and T2DM ($P = 1.0$). Patients in the CP group were older (age, 60 years; range, 22–75 years; $P < 0.001$) than those in the no CP group (age, 50 years; range, 19–78 years). Patients with and without T2DM had similar age (57 vs 55 years, respectively, $P = 0.58$). Interobserver variability for measuring pancreatic fat determined by the Spearman rank correlation was excellent ($r = 0.90$).

Pancreatic Fat and Visceral Adiposity

Pancreatic fat fraction showed a moderate positive correlation ($r = 0.54$) with VAT (Fig. 2). There was a weak correlation of pancreatic fat with the SAT ($r = 0.23$) and visceral-to-subcutaneous adiposity ratio (V/S) ($r = 0.26$) (Fig. 3).

Pancreatic Fat and CP

Patients in the no CP group showed significantly lower pancreatic fat fraction (15%; 95% confidence interval [CI], 14%–17%) compared with the groups with mild CP (24%; 95% CI, 21%–27%; $P < 0.0001$), moderate CP (23%; 95% CI, 20%–25%; $P < 0.0001$), and severe CP (21%; 95% CI, 16%–26%; $P = 0.02$). Pancreatic fat fraction between the mild, moderate, and severe CP groups was statistically similar ($P = 0.48$) (Fig. 4). Multivariate logistic analysis (Fig. 5A) showed that pancreatic fat has the highest diagnostic potential for CP (area under the curve [AUC], 0.83), followed by VAT (AUC, 0.72) and SAT (AUC, 0.70). Pancreatic fat fraction of 56% was 74% sensitive and 85% specific for CP.

Pancreatic Fat and T2DM

Patients with T2DM showed higher pancreatic fat (23%; 95% CI, 21%–25%) as compared with the no-diabetes group (15%; 95% CI, 14%–17%; $P = 0.03$). Multivariate logistic model analysis including pancreatic fat, SAT, VAT, and V/S showed that pancreatic fat has the highest diagnostic potential for T2DM (AUC, 0.85), closely followed by VAT (AUC, 0.84), SAT (AUC, 0.82), and V/S (AUC, 79) (Fig. 5B). Fat fraction of 24% was 69% sensitive and 87% specific for T2DM.

Visceral Adiposity, CP, and T2DM

Chronic pancreatitis patients had higher VAT (172 cm^2; 95% CI, 150–194 cm^2) compared with the no CP group (138 cm^2; 95% CI, 118–158 cm^2; $P = 0.01$) (Table 2). A higher VAT was also seen in patients with T2DM (202 cm^2; 95% CI, 158–247 cm^2) compared with those without T2DM (146 cm^2; 95% CI, 131–161 cm^2). A higher SAT was seen in T2DM ($P = 0.004$) but not in the CP group ($P = 0.13$) (Table 2). The V/S ratio was not a significant factor for either CP ($P = 0.35$) or T2DM ($P = 0.80$).

Other Factors

There was a weak positive correlation between the pancreatic fat fraction and age in the no-disease group ($r = 0.33$, $P = 0.01$). The weak correlations between the age and VAT ($r = 0.21$, $P = 0.10$), SAT ($r = 0.05$, $P = 0.69$), and V/S ($r = 0.16$, $P = 0.22$) were not statistically significant. There was a weak correlation of the pancreatic fat with BMI ($r = 0.12$), but this was not statistically significant ($P = 0.20$). Patients with history of smoking showed higher pancreatic fat ($P \leq 0.01$), and smoking had a strong association with CP ($P = 0.005$). Alcohol consumption was higher in patients with CP ($P = 0.03$) and T2DM ($P = 0.03$), whereas hyperlipidemia was associated with T2DM only ($P = 0.006$).

Probability Analysis

Figure 6 shows predicted probability curves for pancreatic steatosis, CP, and T2DM as a dose-response analysis. The probability of CP increases together with the amount of VAT (Fig. 6A) and with pancreatic fat fraction (Fig. 6B). Increasing pancreatic fat fraction also increases the probability of T2DM (Fig. 6C).

DISCUSSION

Extensive research has been done on hepatic steatosis showing its association with abdominal obesity. Interest in pancreatic steatosis and its clinical significance has gained attention only in recent years. Some studies emphasized the importance of pancreatic steatosis by reporting that exposure of pancreatic islets to increased fatty acids causes β-cell dedifferentiation, and this is likely the underlying mechanism for T2DM.[14–16] Magnetic resonance imaging has superior in vivo sensitivity for quantification of fat compared with computed tomography and ultrasound.[17–19] In this study, we quantitatively measured pancreatic steatosis and abdominal fat by MRI and analyzed the relationship among the pancreatic steatosis, abdominal fat, CP, and T2DM.

Pancreatic Fat Content and CP

Our results showed that patients with CP were more likely to have higher pancreatic fat, but this relationship was not linear with the severity of CP. In vitro and animal model studies suggest that pancreatic lipomatosis may contribute to β-cell lipotoxicity and lipoapoptosis, with consequent loss of function.[20] However, data on humans are inconsistent. Unlike the liver, where the triglycerides accumulation is mainly intracellular, pancreatic steatosis is histologically characterized by an increased number of adipocytes.[21] However, the intracellular fat accumulation can be visualized by electronic microscopy or immunohistochemistry in both acinar and islet cells and may precede adipocytes infiltration.[20,22] It is unknown if intracellular or extracellular triglycerides have a different clinical significance, but it is possible that adipocytes influence the function of acinar and islet cells by a paracrine effect, whereas intracellular lipids may lead to lipotoxicity and therefore islet or acinar cells injury.[23,24] Based on the review of the literature and findings of our cross-sectional study, the possibility of steatopancreatitis as an etiological factor for CP and T2DM can be considered. However, proof of this association will require histopathologic confirmation, which is usually performed in human studies.

Pancreatic Fat Content and T2DM

There has been a dearth of studies on the relationship between pancreatic fat and exocrine pancreatic disease, although experts alluded this to a hypothetical relationship.[25] In a study of patients with T2DM, pancreatic fat content was not linearly correlated with exocrine pancreatic function, as measured by pancreatic enzymes, or bicarbonate secretion.[26] The null finding may have been due to the assumption of a linear relationship, when in fact the relationship may be nonlinear, as evident in our study.

Whereas some of the prior studies have investigated the clinical impact of pancreatic fat and how it is related to endocrine pancreatic function,[2,27,28] our study looked into this relationship in the context of visceral adiposity and pancreatic steatosis, which independently could influence the risk of T2DM. We found that T2DM had the highest association with pancreatic steatosis, closely followed by VAT, SAT, and V/S. These findings are consistent with studies that have examined pancreatic fat and T2DM,[4,29] most of which point to a positive association between the 2 conditions with a summary odds ratio of 2. Our results contradict with a large cohort study that did not find a relationship between the T2DM and pancreatic steatosis.[18] However, that study was population based, and recruited volunteers and the number of T2DM patients were very small.

Studies on the relationship between pancreatic fat and endocrine dysfunction have been inconsistent. In the largest study to date, Ou et al[29] investigated 7464 subjects using ultrasound and found that subjects with T2DM were more likely to have pancreatic fat, which agrees with our results. Postmortem studies[18,30] found no association between pancreatic fat and T2DM. Pancreatic fat measured in postmortem settings may not accurately portray the level of fat because pancreatic tissue degrades rapidly after death. Heni et al[27] demonstrated that pancreatic fat is negatively associated with insulin secretion, whereas Wong et al[2] showed that persons with fatty pancreas were more likely to have insulin resistance. van der Zijl et al[28] found no direct relationship between pancreatic fat and β-cell function. North American Pancreatitis 2 study showed that CP, exocrine insufficiency, calcifications, and pancreas surgery conveyed higher odds of having diabetes.[31] However, the traditional risk factors of obesity and family history were similarly important in the latter study.

Pancreatic Fat Content and Abdominal Fat Distribution

The association of the abdominal fat distribution with pancreatic fat is underinvestigated. Our study showed that abdominal obesity and pancreatic fat are related, with the highest correlation being with visceral obesity. This finding supports the hypothesis that pancreatic fat is exacerbated by visceral fat and has an impact on pancreatic disease, independent of general obesity. This is also consistent with the literature reporting that ectopic fat content of the pancreas is independent of BMI.[32] In our study, BMI or total body weight was not a significant factor for CP or T2DM as there was a weak correlation of the pancreatic fat with BMI ($r = 0.12$). Previous studies acknowledge that the correlation between BMI and visceral obesity can vary considerably.[33] It has been suggested that individual differences in visceral fat remain considerable, even when subjects with relatively similar BMI and percent body fat are investigated.[34]

This study was limited by its retrospective design and limited patient population size. For measurement of pancreatic fat content, we used T1-weighted 2-point Dixon series. Although Dixon technique is very accurate, prospective studies can be performed using proton density fat fraction, which could be more precise. Most studies used the level of the L4/L5 lumbar vertebra for intra-abdominal fat measurements to capture the highest percentage of the body fat. This study measured the abdominal fat at the level of the pancreas. There were 2 reasons for this; MRI/MRCP usually does not extend to the level of the L4/L5 vertebra, and we were interested in finding the correlation between the abdominal and pancreatic fat, rather than measuring the highest amount of fat in the abdomen. Finally, our study was cross-sectional. Thus, we were not able to establish the temporal relationship between pancreatic steatosis, CP, and T2DM. Future longitudinal studies—including those emerging from the Chronic Pancreatitis, Diabetes, and Pancreatic Cancer research consortium—will be necessary to establish a causal relationship between pancreatic fat and CP.

In summary, this study demonstrated that increased VAT has a moderate direct correlation with pancreatic fat fraction. Chronic pancreatitis is associated with higher pancreatic fat fraction and visceral fat. Type 2 diabetes is associated with higher pancreatic fat fraction and visceral and subcutaneous adiposity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations:

BMI	body mass index
CP	chronic pancreatitis
MRCP	magnetic resonance cholangiopancreatography
SAT	subcutaneous adipose tissue
T2DM	type 2 diabetes mellitus
VAT	visceral adipose tissue
V/S	visceral-to-subcutaneous adipose tissue ratio

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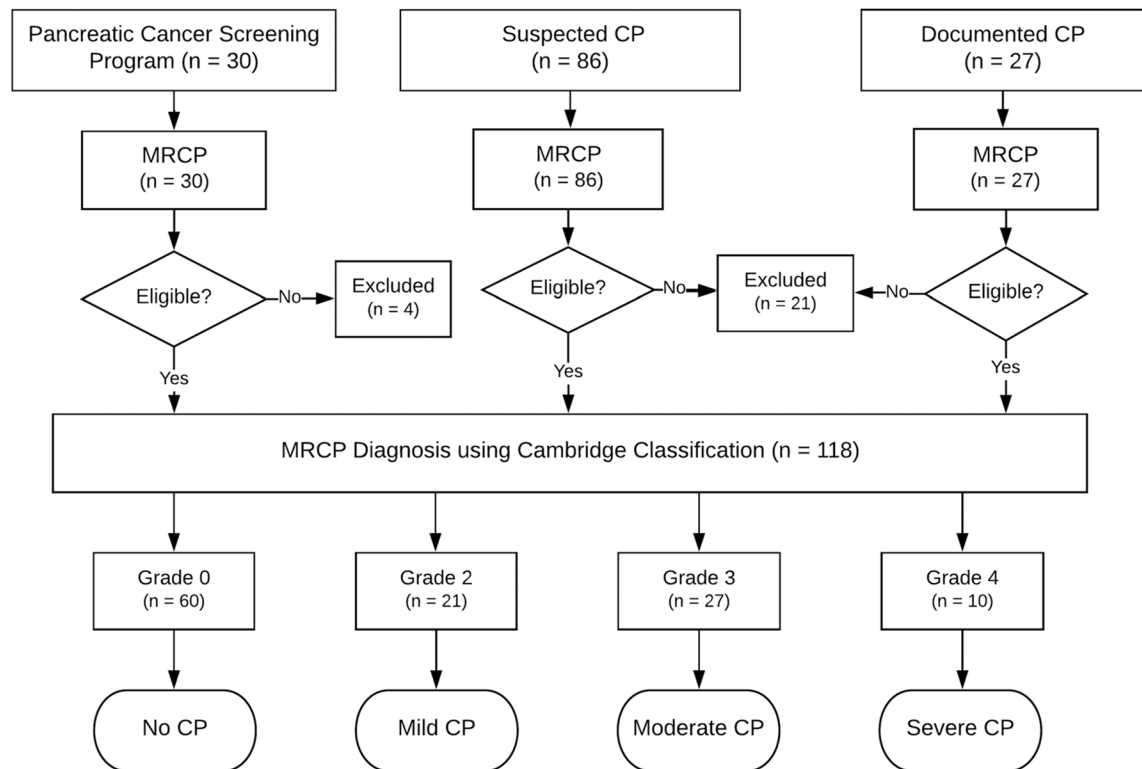
FIGURE 1.
Patient selection algorithm. Categorization of the patient groups was done by secretin-enhanced MRCP using the Cambridge classification as the diagnostic standard. Cambridge 0 patients comprised the no CP group.
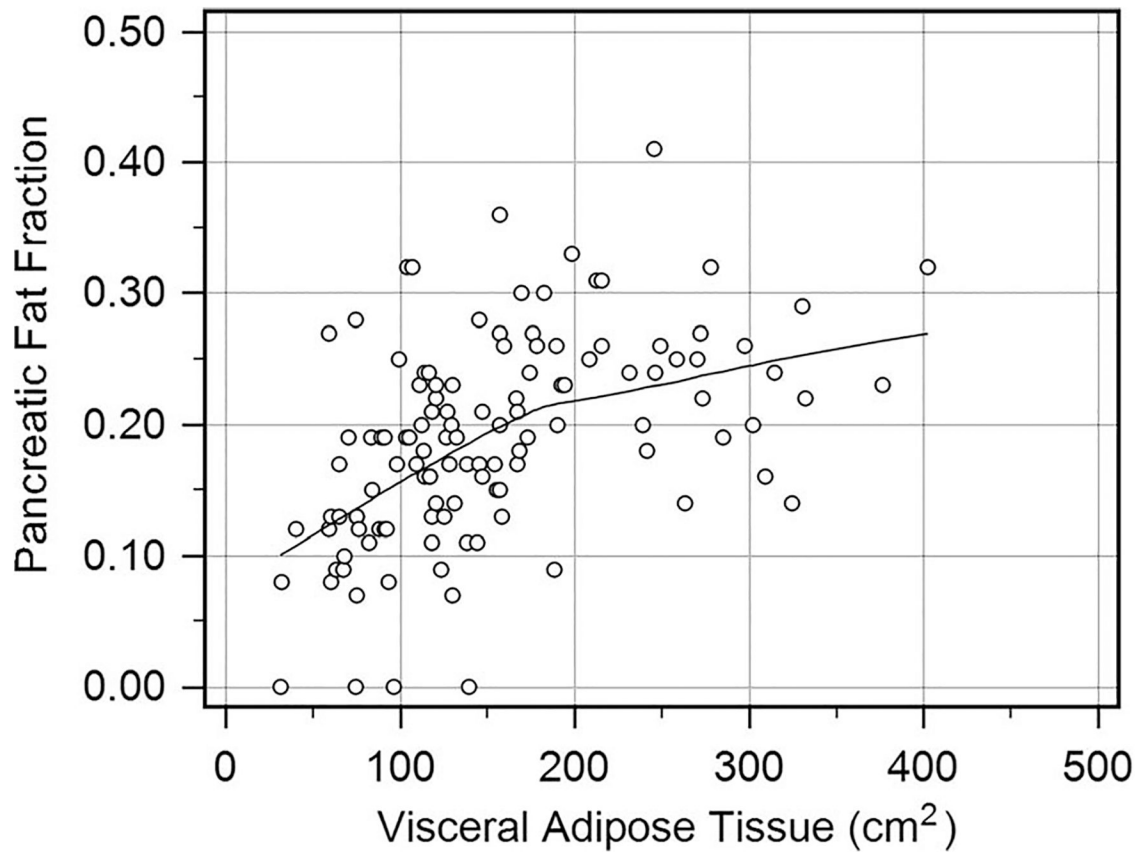
FIGURE 2.
Correlation of pancreatic fat fraction and visceral fat amount. This plot shows the moderate correlation between the pancreatic and visceral fat (r = 0.54, P < 0.0001), which is stronger than the SAT and V/S.
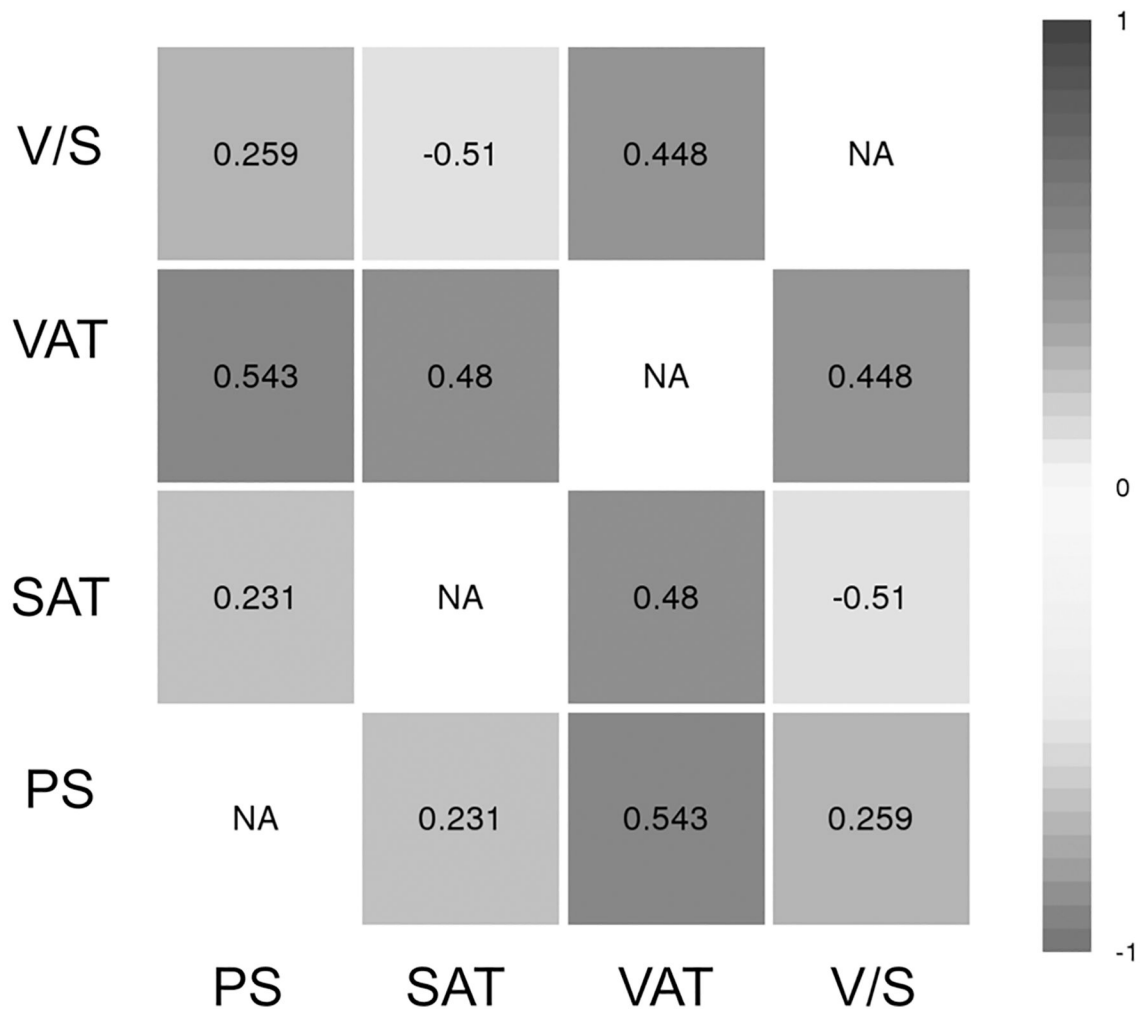
Spearman Correlation

FIGURE 3.

Correlation of abdominal fat content within the visceral (VAT) and subcutaneous (SAT) compartments, V/S, and pancreatic fat fraction (PS). Low to moderate correlations were observed between each pair. The highest correlation was between the VAT and pancreatic fat. NA indicates not applicable.
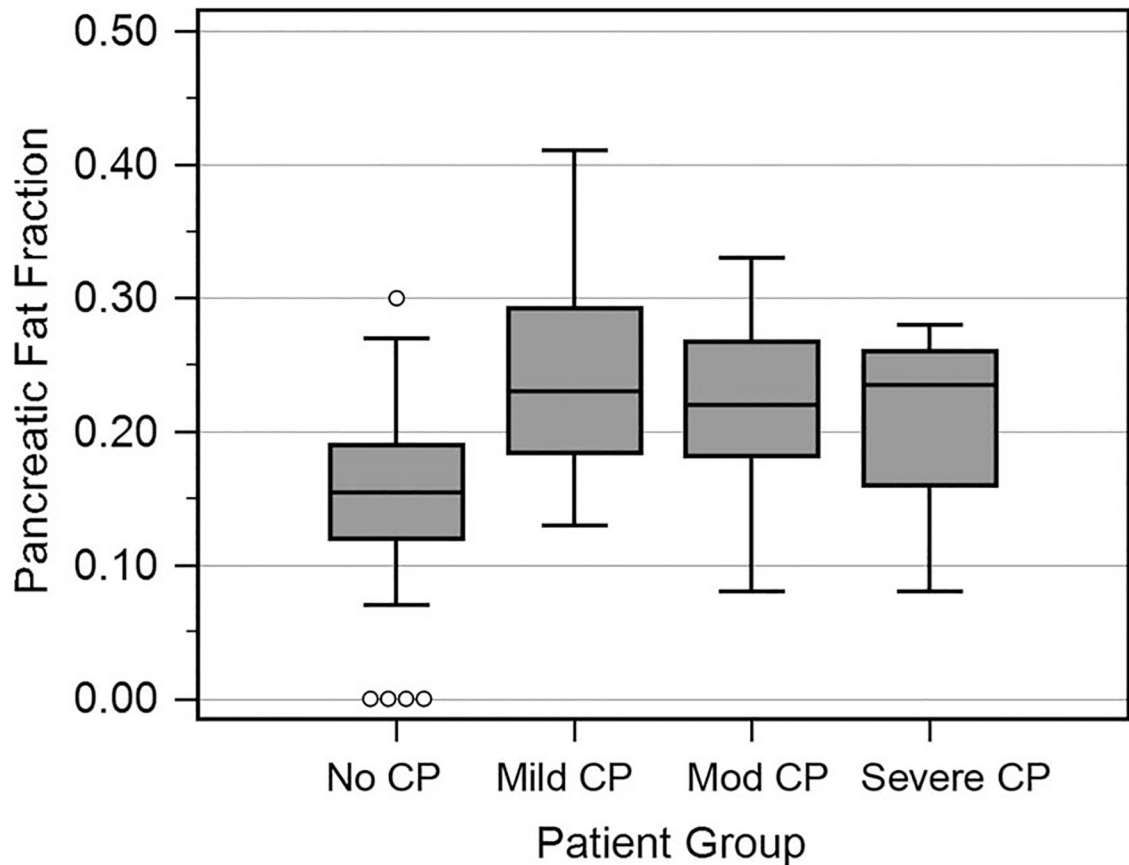
FIGURE 4.
Box-and-whisker plot showing the distribution of pancreatic fat fraction in the no CP, mild, moderate, and severe CP groups. Patients with CP showed significantly higher percentage of pancreatic fat compared with the no CP group. Pancreatic fat fractions in the mild (average, 24%), moderate (23%), and severe CP (21%) groups were significantly higher than normal group (15%), with the highest difference between the no CP and mild CP group. There was no statistically significant difference in the fat fraction between the CP groups ($P = 0.48$).
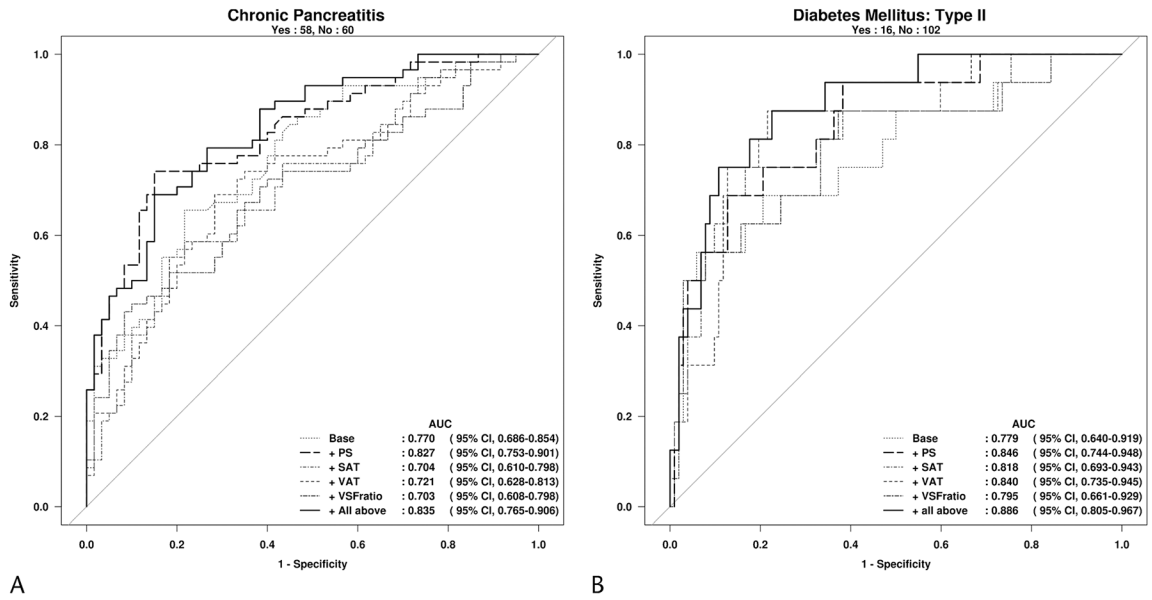
FIGURE 5.

Multivariate logistic regression analysis is showing the association between the pancreatic steatosis (PS) and distribution of the abdominal fat with CP (A) and T2DM (B). A, Multivariate logistic model analysis of CP with base model, PS, VAT, SAT, and V/S. Base model included these conventional risk factors: alcohol, smoking, and BMI. Pancreatic steatosis has the highest diagnostic potential for CP (AUC,0.83), followed by VAT (AUC, 0.72) and SAT (AUC, 0.70). Using pancreatic fat fraction of 56% as the threshold, PS was 74% sensitive and 85% specific for CP. B, Multivariate logistic regression analysis of T2DM with PS, VAT, SAT, and V/S. Base model included these conventional risk factors: alcohol, hyperlipidemia, and BMI. Pancreatic steatosis has the highest diagnostic potential for T2DM (AUC, 0.85), closely followed by VAT (0.84), SAT (AUC, 0.82), and V/S (AUC, 0.79). Using pancreatic fat fraction of 24% as the threshold, PS was 69% sensitive and 87% specific for T2DM.
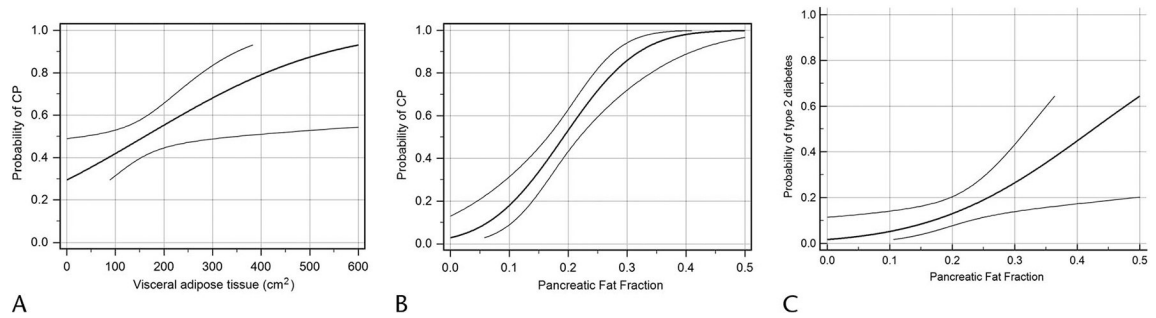
FIGURE 6.
These 3 diagrams are created using probit regression to analyze the dose-response analysis between the visceral adiposity, pancreatic fat fraction, and T2DM. The probit regression procedure fits a probit sigmoid dose-response curve and calculates values (with 95% CI) of the dose variable that corresponds to a series of probabilities. A, Predicted probability curve of visceral adiposity (VAT measured as cm^2) and CP. B, Predicted probability curve of pancreatic fat fraction and CP. C, Predicted probability curve of pancreatic fat fraction and T2DM.

TABLE 1.

Demographics and Summary of Results in the Study Groups

	No CP	Mild CP	Moderate CP	Severe CP	P
Patient demographics					
n	60	21	27	10	
Sex (female:male), n	47:13	16:5	18:9	4:6	0.45[*]
Age, mean (range), y	50 (19–78)	64 (40–83)	57 (22–85)	61 (41–83)	0.003[†]
Amylase, mean (range), U/L	59 (31–225)	50 (13–156)	52 (23–177)	66 (13–214)	0.24[†]
Lipase, mean (range), U/L	96 (11–359)	74 (11–471)	84 (32–391)	120 (7–124)	0.14[†]
BMI, mean (range), kg/m^2	29 (17–47)	29 (21–41)	30 (17–42)	25 (18–44)	0.09[†]
Weight, mean (range), kg	80 (47–130)	78 (53–110)	84 (41–123)	69 (51–123)	0.11[†]
Pancreatic fat					
Fat fraction, mean (95% CI), %	15 (14–17)	24 (21–27)	23 (20–25)	21 (16–26)	<0.001[†]
Abdominal fat distribution, mean (95% CI), cm^2					
Visceral fat	138 (118–158)	180 (149–212)	181 (143–219)	129 (83–175)	0.01[†]
Subcutaneous fat	211 (181–241)	260 (195–325)	240 (203–277)	191 (88–294)	0.01[†]
V/S ratio, %	74 (64–83)	86 (62–109)	88 (65–111)	87 (50–124)	0.79[†]
T2DM					
Prevalence, n (%)	4/60 (7)	5/21 (24)	6/27 (22)	1/10 (10)	0.08[*]

The reference range for amylase is 20 to 85 U/L. The reference range for lipase is 0 to 160 U/L.

[*] Fisher-Freeman-Halton test.

[†] Kruskal-Wallis test.

TABLE 2.

Comparison of Results Between the Disease and No-Disease Groups

	CP			T2DM		
	No (n = 60)	Yes (n = 58)	P	No (n = 102)	Yes (n = 16)	P
Sex (female:male), n	47:13	40:18	0.30*	75:27	12:4	1.00*
Age, mean (range), y	50 (19–78)	60 (22–85)	<0.001†	55 (19–85)	57 (28–76)	0.58†
BMI, mean (range), kg/m²	29 (17–47)	29 (17–44)	0.91†	28 (17–47)	31 (21–44)	0.08†
Weight, mean (range), kg	80 (47–130)	80 (41–123)	0.88†	79 (41–130)	87 (59–123)	0.08†
Pancreatic fat fraction, mean (95% CI), %	15 (14–17)	23 (21–25)	<0.001†	15 (14–17)	23 (21–25)	0.03†
Visceral fat mean, (95% CI), cm²	138 (118–158)	172 (150–194)	0.01†	146 (131–161)	202 (158–247)	0.007†
Subcutaneous fat, mean (95% CI), cm²	211 (181–241)	239 (207–271)	0.13†	212 (189–234)	308 (236–380)	0.004†
V/S, mean (95% CI), %	74 (64–83)	87 (73–101)	0.35†	74 (64–83)	87 (73–101)	0.80†
Smoking ratio, n (%)	18/60 (30)	33/58 (57)	0.005*	43/102 (42)	8/16 (50)	0.59*
Alcohol ratio, n (%)	23/60 (38)	35/58 (60)	0.03*	46/102 (45)	12/16 (75)	0.03*
Hyperlipidemia ratio, n (%)	14/60 (23)	21/58 (36)	0.16*	25/102 (25)	10/16 (62)	0.006*

*
Fisher-Freeman-Halton test.

†
Mann-Whitney-Wilcoxon test.