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RESEARCH ARTICLE | *Pancreatic Physiology/Pathophysiology*

Intrapancreatic fat deposition and visceral fat volume are associated with the presence of diabetes after acute pancreatitis

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Singh RG, Cervantes A, Kim JU, Nguyen NN, DeSouza SV, Dokpuang D, Lu J, Petrov MS. Intrapancreatic fat deposition and visceral fat volume are associated with the presence of diabetes after acute pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 316: G806–G815, 2019. First published March 28, 2019; doi:10.1152/ajpgi.00385.2018.—Ectopic fat and abdominal adiposity phenotypes have never been studied holistically in individuals after acute pancreatitis (AP). The aim of the study was to investigate phenotypical differences in ectopic fat and abdominal fat between individuals after AP (with and without diabetes) and to determine the role of pancreatitis-related factors. Eighty-four individuals were studied cross-sectionally after a median of 21.5 mo since last episode of AP and were categorized into "diabetes" and "no diabetes" groups. Twenty-eight healthy volunteers were also recruited. With the use of magnetic resonance imaging, intrapancreatic fat percentage, liver fat percentage, visceral fat volume (VFV), subcutaneous fat volume, and visceral-to-subcutaneous (V/S) fat volume ratio were quantified. Analysis of variance was used to investigate the differences in these phenotypes between the groups. All analyses were adjusted for age and sex. Linear regression analysis was used to investigate the association between pancreatitis-related factors and the studied phenotypes. Intrapancreatic fat percentage was significantly higher in the diabetes group (10.2 ± 1.2%) compared with the no diabetes (9.2 ± 1.7%) and healthy volunteers (7.9 ± 1.9%) groups ($P < 0.001$). VFV was significantly higher in the diabetes (2,715.3 ±1,077.6 cm^3) compared with no diabetes (1,983.2 ± 1,092.4 cm^3) and healthy volunteer (1,126.2 ± 740.4 cm^3) groups ($P < 0.001$). V/S fat volume ratio was significantly higher in the diabetes (0.97 ± 0.27) compared with no diabetes (0.68 ± 0.42) and healthy volunteer (0.52 ± 0.34) groups ($P = 0.001$). Biliary AP was associated with significantly higher intrapancreatic fat percentage (β = 0.67; 95% CI, 0.01, 1.33; $P = 0.047$). C-reactive protein levels during hospitalization for AP were associated with significantly higher VFV (β = 3.32; 95% CI, 1.68, 4.96; $P < 0.001$). In conclusion, individuals with diabetes after AP have higher intrapancreatic fat percentage, VFV, and V/S fat volume ratio. Levels of C-reactive protein during AP are significantly associated with VFV, whereas biliary AP is significantly associated with intrapancreatic fat percentage.

NEW & NOTEWORTHY Individuals with diabetes after acute pancreatitis have significantly higher intrapancreatic fat percentage and visceral fat volume compared with individuals without diabetes after acute pancreatitis and healthy controls. C-reactive protein levels during hospitalization for acute pancreatitis and biliary etiology of acute pancreatitis are associated with significantly larger visceral fat and pancreatic fat depots, respectively.

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INTRODUCTION

Excess accumulation of body fat increases the risk of several gastrointestinal diseases and has a deleterious effect on their clinical course (3). Acute pancreatitis (AP) is an exemplar disease in which excess body fat has been linked to local complications, systemic inflammation, and multi-organ failure (20). The notion that general adiposity, as measured by body mass index, worsens the course of AP was introduced nearly three decades ago (14). Later, body fat distribution and abdominal adiposity in the setting of AP was brought to the fore (24). Several clinical studies demonstrated that abdominal adiposity is an independent prognostic factor in AP, using both waist circumference as a proxy for abdominal adiposity and imaging modalities to measure abdominal adiposity (visceral and subcutaneous fat depots) directly. Furthermore, a large general population-based cohort study found that waist circumference, but not body mass index, is an independent risk factor for AP (28). Emerging evidence also indicates that excess body fat is associated with ectopic fat accumulation in the liver and pancreas (4, 34, 35).

The pathogenetic role of adiposity and ectopic fat accumulation in AP has been recently investigated in several clinical and experimental studies. It is believed that, in the presence of excess adiposity, increased amount of intrapancreatic fat and subsequent acute lipotoxicity lead to pancreatic acinar cell necrosis and systemic inflammation (19). Specifically, interstitial leakage of pancreatic lipase in the early course of AP initiates lipolysis of triglycerides in intrapancreatic adipocytes, generating unsaturated fatty acids (19). Local increase in levels of unsaturated fatty acids then exacerbates acinar cell necrosis by inhibition of mitochondrial complexes I and V (19). Moreover, unsaturated fatty acids exert secondary effect by upregulating expression of proinflammatory cytokines [such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6], which in turn increases inflammatory response and deteriorates clinical course of AP. Also, sustained exposure of the islets of Langerhans to elevated levels of fatty acids results in increased triglyceride content in islets, impaired insulin secretion, and abnormal gene expression (15, 25).

Although research on adiposity and ectopic fat accumulation in the setting of AP to date has focused predominantly on early

events and in-hospital outcomes, growing number of studies show that individuals after hospital discharge with AP develop new-onset metabolic derangements (6, 21, 22, 31). The increasing burden of pancreatitis and its metabolic sequelae has given rise to the concept of "holistic prevention of pancreatitis" (26). New-onset diabetes after AP is a sequela that is being actively investigated, with one of the key elements identified so far being increased lipolysis (7, 23). These findings, coupled with the fact that ectopic fat accumulation in the liver and the pancreas is frequently associated with diabetes mellitus (35), suggest that certain abdominal adiposity and ectopic fat phenotypes may be associated with diabetes after AP. A previous cross-sectional study, which was a part of the DORADO project by our group (32), investigated waist circumference (as a proxy for abdominal adiposity) and its interrelationship with insulin resistance. Abdominal adiposity was found to be associated with a significantly increased insulin resistance that was both general and adipose tissue specific (32). That study also derived, for the first time, two new indices deemed to reflect visceral adipose tissue-specific insulin resistance (based on omentin and vaspin, visceral adipose tissue-specific adipokines) (32). To date, no study has investigated magnetic resonance imaging (MRI)-derived abdominal adiposity or ectopic fat phenotypes after clinical resolution of AP.

The primary aim was to investigate phenotypical differences in distribution of abdominal adipose tissue and ectopic fat between individuals after AP (with and without diabetes) and healthy volunteers using state-of-the-art MRI. The secondary aim was to determine pancreatitis-related factors associated with abdominal adiposity and ectopic fat phenotypes.

METHODS

Study Design

This was a cross-sectional MRI study as a part of the ARIES (Analytic moRphomics In pancrEatic diseaSes) project. It was nested into a prospective longitudinal study approved by the Health and Disability Ethics Committee. The study recruited 84 participants with a history of AP who had been admitted to Auckland City Hospital (Auckland, New Zealand) and diagnosed prospectively with AP at the time of hospitalization (as opposed to the use of hospital discharge codes). The cohort included 44 participants from the earlier DORADO project (that did not include MRI) by our group who agreed to participate in the ARIES project. Diagnosis of AP was established based on the international guidelines (17). Individuals with AP were eligible for the study if they were ≥18 yr of age and provided informed consent. Individuals were excluded if they had chronic pancreatitis, postendoscopic retrograde cholangiopancreatography pancreatitis, malignancy, interventions involving the pancreas (surgical, endoscopic, or radiological), ascites, chronic obstructive pulmonary disease severe enough to limit breath-holding, congenital anomalies of the pancreas, hereditary pancreatitis, cystic fibrosis, pancreatic lipomatosis or lipomatous pseudohypertrophy, or autoimmune pancreatitis, were pregnant at time of AP or afterwards, were on steroid therapy, or had metallic foreign body implantations, heart pacemakers, or other implanted electronic devices. Twenty-eight healthy controls were recruited into the study through fliers and advertisements around the community. They were eligible if they had no history or symptoms of pancreatic disease or diabetes, no upper abdominal pain or nausea, no family history of pancreatic diseases, diabetes, celiac disease, or cystic fibrosis, no history of acute infectious or inflammatory conditions requiring medical treatment or evaluation in the preceding 6 mo, and no history of cancer.

Laboratory Analyses

Fasting venous blood samples from all study participants were analyzed in tertiary referral medical laboratory. In line with the American Diabetes Association guidelines, glycated hemoglobin (HbA_{1c}) was measured using the boronate affinity chromatography assay (Trinity Biotech, Wicklow, Ireland), which is certified by the National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial reference assay. Fasting plasma glucose (FPG) was measured using an enzymatic colorimetric assay (F. Hoffmann-La Roche, Basel, Switzerland).

Study Groups

Individuals after an episode of AP were categorized into two groups, "diabetes" and "no diabetes," based on their FPG and/or HbA_{1c} levels at the time of the study, in line with the American Diabetes Association guidelines. The diabetes group included individuals with FPG ≥126 mg/dl (7 mmol/l) and/or HbA_{1c} ≥6.5% (48 mmol/mol) at the time of the study, whereas the no diabetes group included individuals with FPG <126 mg/dl (7 mmol/l) and HbA_{1c} <6.5% (48 mmol/mol) at the time of the study.

MRI Acquisition

Abdominal MRI scans for all participants were performed at the Centre of Advanced MRI (University of Auckland), using a 3.0 Tesla MAGNETOM Skyra MRI scanner (Siemens, Erlangen, Germany). Participants were instructed to lie in the supine position and hold their breath during end expiration. Axial T1-weighted volumetric interpolated breath-hold examination Dixon sequence was applied with the following parameters: true form abdomen shim mode; field of view, 420 mm; base resolution, 320; echo time (TE), 1.27 ms, 2.5 ms; repetition time (TR), 3.85 ms; flip angle, 9°; pixel bandwidth, 920 Hz. Four types of images were generated: in-phase, out-of-phase, fat, and water images. These images were retrieved from the scanner and exported for further analyses.

Quantification of Abdominal Adiposity and Ectopic Fat Phenotypes

Abdominal adipose tissue depots. For each participant, subcutaneous fat volume (SFV) and visceral fat volume (VFV) were quantified using ImageJ software (National Institutes of Health). A series of abdominal fat phase images identified from the second lumbar vertebral level (L2) to the fifth lumbar vertebral level (L5) were used for segmentation of subcutaneous and visceral fat depots (9). The threshold function of ImageJ was used to convert grayscale pixels into binary images using the global histogram-derived method. Subcutaneous and visceral fat regions were delineated from the abdominal musculature and measured separately. The nonadipose tissue/abdominal organs/blood vessels were excluded from the measurement of visceral fat. The final step for all of the above measurements involved summation of the pixel contents of all the slices in series and multiplying by the pixel area and slice thickness to obtain the total volume. Subsequently, the ratio of visceral to subcutaneous fat volume (V/S fat volume ratio) was calculated.

Liver fat and intrapancreatic fat. Single-voxel spectroscopy was used to determine liver fat percentage (LF%). The voxel ($20 \times 20 \times 20$ mm) was positioned in the right lobe of the liver away from the blood vessels and bile ducts and ≥10 mm away from the edge. Fifty acquisitions were recorded in a measuring time of 5 min, and automated abdominal shimming was performed with TR = 3,000 ms and TE = 33 ms. Both water-suppressed and non-water-suppressed spectra were taken in the same voxel, where the non-water-suppressed spectra served as reference for fat quantification. Spectra were processed and analyzed using the SIVIC software (open-source software package developed at University of California, San Francisco, CA) (5). The magnetic resonance spectroscopy fat fraction was

defined as fat fraction = area under fat peak/(area under fat and water peaks) × 100%.

Intrapancreatic fat percentage (%) was determined using the "MR-opsy" technique that minimizes the probability of inclusion of non-parenchymal tissues, as described in detail elsewhere (1). In brief, of the abdominal scans with 5 mm thickness (to permit an adequate signal-to-noise ratio), two candidate slices were selected and three regions of interest were placed in the head, body, and tail of the pancreas. To prevent inclusion of nonparenchymal tissues (blood vessels, the main pancreatic duct, visceral fat) within the selected region of interest, a thresholding range of 1–20% was applied as per published recommendations (1). Intrapancreatic fat percentage was calculated as the average fat signal of both slices.

Inter-rater reliability. Intraclass correlation coefficients (ICCs) were used to evaluate inter-rater reliability, done independently by two raters blinded to the study groups. The mean absolute inter-rater differences were 28.5 cm^3 for SFV, 43.8 cm^3 for VFV, and 0.11 for intrapancreatic fat percentage. The reliability of measurements was high (13), with ICC of 0.99 for SFV, 0.99 for VFV, and 0.98 for intrapancreatic fat percentage. The average values of two independent MRI measurements were used for statistical analyses.

Pancreatitis-Related Factors

Etiology of AP was categorized as biliary or nonbiliary. Recurrence of AP was defined as hospitalization with one or more recurrent episodes of confirmed AP between first admission for AP and study date. Readmission within 30 days was not counted as a recurrence. Pancreatic necrosis was defined as nonenhancing parenchymal tissue on computed tomography during hospitalization. Blood levels of lipase, liver enzymes, white blood cell (WBC) count, and C-reactive protein (CRP) during hospitalization were also recorded.

Statistical Analyses

The differences in baseline characteristics between individuals with diabetes after AP and those without diabetes after AP were assessed using Student's *t*-test and chi-square test or Fisher's exact test for continuous and categorical variables, respectively. Data were presented as median and interquartile range (IQR), mean and standard deviation, or count frequencies. The statistical analyses were conducted in three stages.

First, analysis of variance, using a linear mixed model, was performed to compare the mean values of abdominal adiposity and ectopic fat phenotypes (SFV, VFV, V/S fat volume ratio, intrapancreatic fat%, and LF%) among the three groups, diabetes, no diabetes, and healthy, in both unadjusted and adjusted analyses. The adjusted analyses were controlled for age and sex. Extreme values (as assessed by cases with standardized residuals greater than ±3 standard deviations) were regarded as outliers and were excluded from the analyses. Statistically significant differences between the groups were assessed by *F* value, and *P* value <0.05. Furthermore, post hoc analyses were performed using Fisher's least significant difference test.

Second, having met all assumptions, the inter-relationships between the studied phenotypes in individuals after AP were assessed using linear regression analysis. To investigate the associations between ectopic fat phenotypes (LF% and intrapancreatic fat%) and abdominal adiposity phenotypes (SFV, VFV, and V/S fat volume ratio), each adiposity phenotype was analyzed as the dependent variable in unadjusted and adjusted (accounting for age and sex) models. Next, in a subgroup analysis, the cohort was stratified by diabetes status to determine whether the presence of diabetes affects the interrelationships between the studied MRI-derived phenotypes. Data from all analyses were reported as R^2 metric and *P* value.

Third, linear regression analyses were performed to investigate the associations between pancreatitis-related factors (etiology, recurrence, lipase, CRP, WBC, and pancreatic necrosis) and abdominal adiposity as well as ectopic fat phenotypes. Each phenotype was analyzed as the dependent variable in unadjusted and adjusted (accounting for age and sex) models. All data were reported as R^2 metric and β-coefficients with corresponding 95% confidence interval (CI).

Statistical analyses were performed using SPSS for Windows version 25 (SPSS, Chicago, IL) and MedCalc version 18 (MedCalc Software, Ostend, Belgium). $P < 0.05$ was accepted as statistically significant in all analyses.

RESULTS

Study Population

Of the recruited 84 individuals after AP, 56 were men and 28 were women, with a median (IQR) age of 56 (43–66) yr. The median (IQR) time since the last episode of AP until MRI acquisition was 21.5 (12.0–36.5) mo. The characteristics of the cohort are presented in Table 1. Participants in the diabetes group had median (IQR) HbA_{1c} of 6.6 (5.7–7.3)% or 49 (39.0–56.5) mmol/mol, and those in the no diabetes group 5.4 (5.3–5.7)% or 36.0 (34.0–39.0) mmol/mol ($P = 0.001$). Participants in the diabetes group had median (IQR) FPG concentration of 131.4 (124.2–156.6) mg/dl or 7.3 (6.9–8.7) mmol/l and those in the no diabetes group 93.6 (88.2–100.8) mg/dl or 5.2 (4.9–5.6) mmol/l ($P = 0.001$). The healthy cohort [body mass index: 24.3 (21.6–27.8) kg/m^2] was composed of 18 men and 10 women with a median (IQR) age of 45 (29–53) yr, Hb A_{1c} of 5.1 (4.9–5.3)% or 32 (30–34) mmol/mol, and FPG concentration of 84.6 (68.4–97.2) mg/dl or 4.7 (3.8–5.4) mmol/l.

Ectopic Fat and Abdominal Adiposity Phenotypes in the Study Groups

Intrapancreatic fat percentage in individuals with diabetes after AP was 10.2 ± 1.2% compared with 9.2 ± 1.7% in indi-

Table 1. *Characteristics of individuals after acute pancreatitis*

Characteristic	Diabetes ($n = 17$)	No Diabetes ($n = 67$)	*P* Value
Age, yr	60 (51–68)	55 (43–65)	0.047
Sex			0.124
Men	14	42	
Women	3	25	
BMI, kg/m^2	28.9 (24.8–33.6)	27.1 (24.7–33.5)	0.718
Waist circumference, cm	105.0 (91.5–119.0)	97.0 (88.0–106.0)	0.087
Etiology			0.963
Bilary	7	28	
Nonbilary	10	39	
Recurrent AP			0.542
No	14	49	
Yes	3	18	
Lipase, U/l ($n = 63$)	600.0 (255.5–833.5)	661.0 (413.75–3,000)	0.061
ALP, U/l	62.0 (83.0–97.0)	86.0 (62.0–113.0)	0.315
ALT, U/l	25.5 (37.0–51.5)	48.0 (20.0–178.0)	0.194
AST,U/l	30.5 (23.5–76.5)	38.0 (23.0–178.5)	0.307
GGT U/l	52.0 (30.5–153.0)	60.0 (23.0–315.3)	0.477
CRP, mg/l	139.0 (39.8–269.0)	105.5 (20.3–251.8)	0.825
WBC, $\times 10^9$/l	12.6 (9.4–14.8)	10.8 (7.8−14.9)	0.620
Pancreatic necrosis ($n = 58$)			0.898
No	12	42	
Yes	1	3	

Data are median (interquartile range) or no. of participants. ALP, alkaline phosphatase; ALT, alanine transaminase; AP, acute pancreatitis; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; GGT, γ-glutamyl transferase; WBC, white blood cells.

viduals with no diabetes after AP and 7.9 ± 1.9% in healthy volunteers. The overall difference between the groups was statistically significant in both unadjusted ($P < 0.001$) and adjusted analyses ($P = 0.002$). A statistically significant difference was observed between the diabetes and no diabetes groups ($P = 0.035$), the diabetes and healthy volunteer groups ($P < 0.001$), and the no diabetes and healthy volunteer groups ($P = 0.001$) (Fig. 1*A*).

Liver fat percentage in individuals with diabetes after AP was 11.2 ± 9.9% compared with 8.9 ± 7.6% in individuals with no diabetes after AP and 7.8 ± 6.3% in healthy volunteers. The overall difference between the groups was not statistically significant in either unadjusted ($P = 0.355$) or adjusted analyses ($P = 0.589$). Pairwise comparisons are presented in Fig. 1*B*.

Subcutaneous fat volume in individuals with diabetes after AP was 2,942.6 ± 1,198.3 cm^3 compared with 3,307.2 ± 1,528.6 cm^3 in individuals with no diabetes after AP and 2,376.2 ± 1,105.2 cm^3 in healthy volunteers. The overall difference between the groups was statistically significant in both unadjusted ($P = 0.014$) and adjusted analyses ($P = 0.007$). A statistically significant difference was observed between the no diabetes and healthy groups ($P = 0.004$). Other pairwise comparisons are presented in Fig. 1*C*.

Visceral fat volume in individuals with diabetes after AP was 2,715.3 ± 1,077.6 cm^3 as compared with 1,983.2 ± 1,092.4 cm^3 in individuals with no diabetes after AP and 1,126.2 ± 740.4 cm^3 in healthy volunteers. The overall difference between the groups was statistically significant in both unadjusted ($P < 0.001$) and adjusted analyses ($P < 0.001$). A statistically significant difference was observed between the diabetes and no diabetes groups ($P = 0.009$), the diabetes and healthy volunteer groups ($P < 0.001$), and the no diabetes and healthy volunteer groups ($P < 0.001$) (Fig. 1*D*).

The V/S fat volume ratio in individuals with diabetes after AP was 0.97 ± 0.27 compared with 0.68 ± 0.42 in individuals with no diabetes after AP and 0.52 ± 0.34 in healthy volunteers. The overall difference between the groups was statistically significant in the unadjusted analysis ($P = 0.001$). A statistically significant difference was observed between the diabetes and no diabetes groups ($P = 0.007$) and the diabetes and healthy volunteers groups ($P < 0.001$)

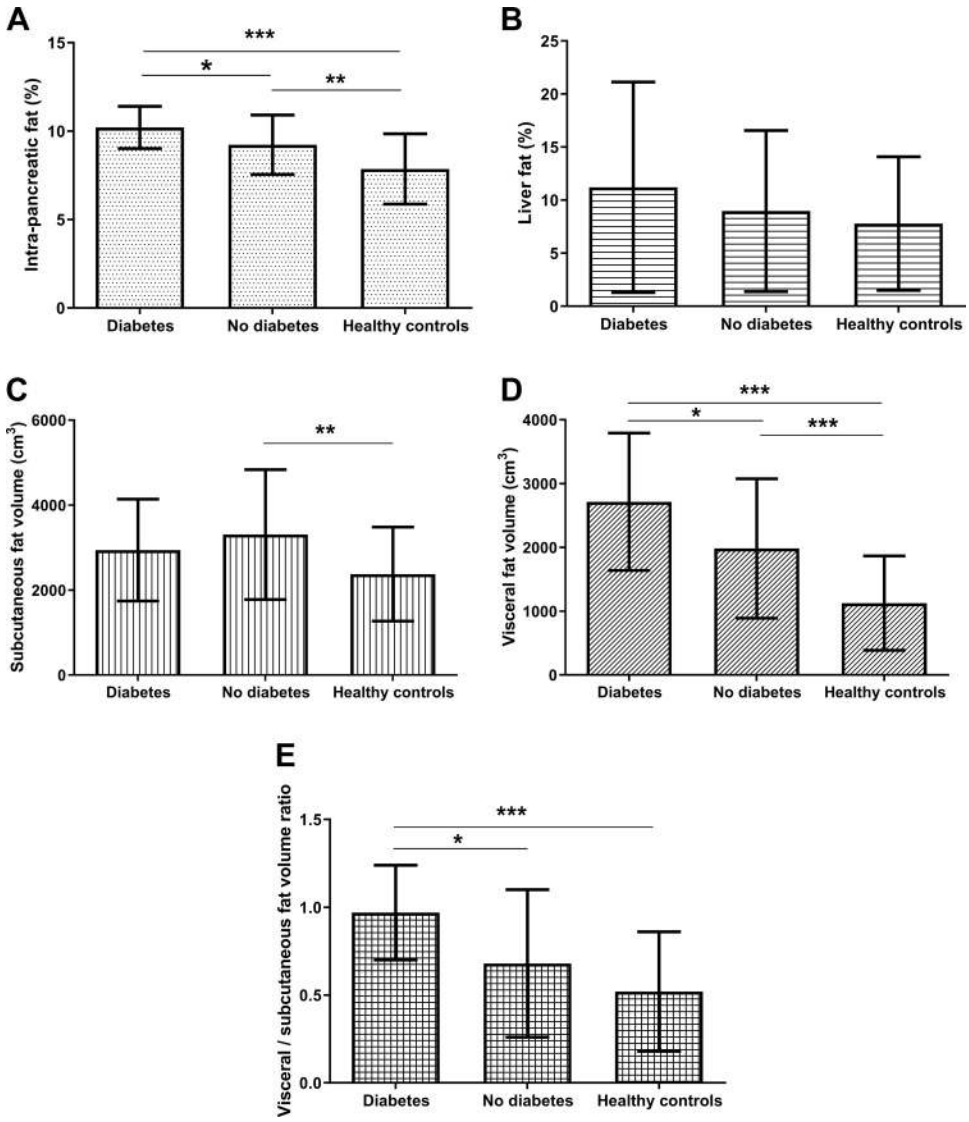

Fig. 1. Differences in ectopic fat and abdominal adiposity phenotypes between the study groups. The phenotypes shown are intra-pancreatic fat% (*A*) liver fat% (*B*), subcutaneous fat volume (cm^3; *C*), visceral fat volume (cm^3; *D*), and visceral-to-subcutaneous fat volume ratio (*E*). Graphs represent means SD (error bars). *$P < 0.05$, **$P < 0.005$, and ***$P < 0.001$, statistically significant differences between the groups.

Table 2. *Inter-relationships between the studied phenotypes stratified by diabetes status*

	Diabetes (n = 17)			No Diabetes (n = 67)		
Phenotype	VFV	Liver Fat%	Intrapancreatic Fat%	VFV	Liver Fat%	Intrapancreatic Fat%
SFV	0.43	0.08	0.07	0.36	0.21	0.29
VFV		0.31	0.14		0.37	0.44
V/S fat volume ratio	NA	0.29	0.14	NA	0.49	0.51
Liver fat%			0.11			0.10

NA, not applicable; SFV; subcutaneous fat volume; VFV, visceral fat volume; V/S fat volume ratio, visceral-to-subcutaneous fat volume ratio. Each cell reports on an R^2 derived from linear regression analyses adjusted for age and sex.

but not between the no diabetes and healthy volunteers groups (Fig. 1*E*).

Inter-Relationships Between the Studied Phenotypes in Individuals After Acute Pancreatitis

In the overall cohort of individuals after AP, LF% had a stronger association with VFV (as compared with SFV, V/S fat volume ratio), in both unadjusted ($R^2 = 0.22$, $P < 0.001$) and adjusted ($R^2 = 0.38$; $P < 0.001$) models. Similarly, intrapancreatic fat percentage had a stronger association with VFV (as compared with SFV and V/S fat volume ratio) in both unadjusted ($R^2 = 0.22$; $P < 0.001$) and adjusted ($R^2 = 0.36$, $P < 0.001$) models. These associations were more pronounced in the no diabetes group compared with the diabetes group (Table 2).

Associations Between Pancreatitis-Related Factors and the Studied Phenotypes

Nonbiliary etiology of AP was associated with a significantly decreased SFV in both unadjusted (β = −831.15; 95% CI, −1,438.87, −223.43; $P = 0.007$) and adjusted (β = −692.96; 95% CI, −1,281.74, −104.18; $P = 0.021$) models. Furthermore, it was associated with a significantly higher V/S fat volume ratio in both unadjusted (β = 0.21; 95% CI, 0.04, 0.38; $P = 0.018$) and adjusted (β = 0.13; 95% CI, 0.26, 0.001; $P = 0.048$) models (Table 3). Biliary etiology of AP was also associated with a significantly higher intrapancreatic fat percentage (β = 0.67; 95% CI, 0.01, 1.33; $P = 0.047$) in the adjusted model only (Table 4). C-reactive protein during hospitalization for AP was associated with a significantly higher VFV during follow-up in both unadjusted (β = 3.32; 95% CI, 1.68, 4.96; $P < 0.001$) and adjusted (β = 2.71; 95% CI, 1.24, 4.19; $P < 0.001$) models. It was also associated with a significantly higher V/S fat volume ratio in both unadjusted (β = 0.001; 95% CI, 0.001, 0.002; $P < 0.001$) and adjusted (β = 0.001; 95% CI, <0.001, 0.001; $P < 0.001$) models (Table 3). White blood cell count during hospitalization for AP was associated with a significantly higher V/S fat volume ratio during follow-up in the unadjusted (β = 0.02; 95% CI, 0.003, 0.043; $P = 0.024$) model only (Table 3). Other pancreatitis-related factors were not significantly associated with any of the studied phenotypes (Tables 3 and 4).

DISCUSSION

Excessive body fat is recognized as a condition in which individuals with excess adiposity vary in metabolic profiles and the degree of associated cardiovascular and metabolic risk. In

Table 3. *Associations between pancreatitis-related factors and the abdominal adiposity phenotypes*

	VFV					SFV					V/S Fat Volume Ratio				
		CI					CI					CI			
Factor	β	Lower	Upper	P value	R^2	β	Lower	Upper	P Value	R^2	β	Lower	Upper	P value	R^2
Etiology†															
Model 1	107.40	−376.09	590.90	0.663	<0.01	−831.15	−1,438.87	−223.43	**0.007**	0.08	0.21	0.04	0.38	**0.018**	0.06
Model 2	−47.14	−474.77	380.49	0.829	0.24	−692.96	−1,281.74	−104.18	**0.021**	0.16	0.13	0.001	0.26	**0.048**	0.50
Recurrent AP															
Model 1	−281.46	−829.27	266.35	0.314	0.01	−285.41	−1,003.73	432.91	0.436	<0.01	0.02	−0.18	0.22	0.857	<0.01
Model 2	−342.85	−817.90	132.20	0.157	0.26	−224.30	−904.88	456.28	0.518	0.11	−0.01	−0.16	0.13	0.855	0.47
Lipase*															
Model 1	−110.79	−328.82	107.23	0.319	0.02	−17.37	−320.44	285.69	0.911	0.01	−0.05	−0.13	0.03	0.250	0.01
Model 2	−75.07	−272.12	121.99	0.455	0.23	−19.72	−298.91	259.47	0.890	0.20	−0.03	−0.09	0.02	0.253	0.52
CRP, mg/l															
Model 1	3.32	1.68	4.96	**<0.001**	0.16	−0.37	−2.73	1.98	0.756	<0.01	0.001	0.001	0.002	**<0.001**	0.15
Model 2	2.71	1.24	4.19	**<0.001**	0.34	0.19	−2.09	2.46	0.872	0.10	0.001	<0.001	0.001	**<0.001**	0.53
WBC, $\times 10^9$/l															
Model 1	40.09	−15.95	96.12	0.161	0.02	−58.00	−130.95	14.95	0.119	0.03	0.02	0.003	0.043	**0.024**	0.06
Model 2	26.91	−25.07	78.88	0.310	0.25	−38.36	−112.21	35.48	0.309	0.12	0.02	<0.001	0.03	0.051	0.50
Pancreatic necrosis															
Model 1	382.61	−781.28	1546.50	0.519	<0.01	−354.70	−1,762.0	1,052.6	0.621	<0.01	0.20	−0.24	0.63	0.374	0.01
Model 2	319.83	−713.04	1352.71	0.544	0.22	−275.66	−1,563.05	1,011.72	0.675	0.17	0.16	−0.17	0.49	0.337	0.44

AP, acute pancreatitis; CI, confidence interval, CRP, C-reactive protein; SFV; subcutaneous fat volume; VFV, visceral fat volume; V/S fat volume ratio, visceral-to-subcutaneous fat volume ratio; WBC, white blood cells. All data are presented as β-coefficient (95% confidence intervals). Significant ($P < 0.05$) associations are shown in boldface. *Data were log transformed; *Model 1* was unadjusted, *model 2* was adjusted for age and sex; †biliary etiology was taken as reference.

Table 4. *Associations between pancreatitis-related factors and the ectopic fat phenotypes*

	Intrapancreatic Fat%					Liver Fat%				
		CI					CI			
Factor	β	Lower	Upper	*P* value	R^2	β	Lower	Upper	*P* value	R^2
Etiology†										
Model 1	−0.56	−1.25	0.14	0.116	0.03	3.05	−0.48	6.59	0.090	0.04
Model 2	−0.67	−1.33	−0.01	**0.047**	0.15	2.69	−0.84	6.21	0.135	0.06
Recurrent AP										
Model 1	−0.04	−0.85	0.76	0.916	<0.01	−0.41	−4.49	3.68	0.850	<0.01
Model 2	−0.08	−0.84	0.68	0.837	0.11	−0.60	−4.62	3.42	0.769	0.04
Lipase *										
Model 1	−0.17	−0.52	0.18	0.352	0.01	−0.10	−1.82	1.63	0.911	0.01
Model 2	−0.10	−0.44	0.24	0.570	0.11	0.01	−1.74	1.74	0.999	0.05
CRP, mg/l										
Model 1	0.002	−0.001	0.004	0.257	0.02	0.01	−0.01	0.02	0.148	0.03
Model 2	0.001	−0.002	0.004	0.460	0.10	0.01	−0.01	0.02	0.219	0.05
WBC, $\times 10^9$/l										
Model 1	0.02	−0.06	0.10	0.634	<0.01	0.40	−0.04	0.83	0.074	0.04
Model 2	0.03	−0.06	0.11	0.516	0.11	0.37	−0.08	0.82	0.110	0.07
Pancreatic necrosis										
Model 1	0.38	−1.21	1.98	0.638	<0.01	4.57	−4.34	13.47	0.315	0.02
Model 2	0.39	−1.12	1.89	0.616	0.12	4.36	−4.46	13.18	0.332	0.04

AP, acute pancreatitis; CI, confidence interval, CRP, C-reactive protein; WBC, white blood cells. All data are presented as β-coefficient (95% CI). Significant ($P < 0.05$) associations are shown in boldface. *Data were log transformed; *Model 1* was unadjusted, *model 2* was adjusted for age and sex; †biliary etiology was taken as reference.

recent years, it was proposed that, in addition to the impact of excess fat mass, adipose tissue dysfunction also plays an important role in promoting metabolic derangements. Specifically, metabolic dysfunction of the adipose tissue transforms it into "sick fat" characterized by cellular hypertrophy, excessive deposition of extracellular matrix, fibrosis, and abnormal fat accumulation in distinct adipose tissue depots (25, 36). Abdominal fat distribution has gained considerable clinical attention in chronic metabolic disorders, particularly type 2 diabetes mellitus. Our earlier study from the DORADO project (32) provided new insights into the inter-relationships between general insulin resistance, tissue-specific insulin resistance, and abdominal obesity (using waist circumference as a proxy) (32). However, studies on direct measurement of abdominal obesity using a comprehensive assessment of MRI-derived ectopic fat and abdominal adiposity phenotypes and their associations with diabetes after disease of the exocrine pancreas are lacking. In the present study, state-of-the-art MRI was used to determine abdominal adiposity and ectopic fat phenotypes in individuals with or without diabetes after AP. The main finding of this study is that VFV and intrapancreatic fat percentage (but not SFV or LF%) were significantly different between the three groups (diabetes, no diabetes, and healthy volunteers), with a stepwise increase from the healthy volunteers group to the diabetes group. Further, several pancreatitis-related factors were significantly associated with VFV and intrapancreatic fat percentage.

The visceral and subcutaneous fat depots in the abdomen vary in their structural, biochemical, and physiological functions. It is believed that subcutaneous fat is less metabolically active and is the primary storage site for excess fat, whereas visceral fat is a secondary depot receiving the spillover fat due to limited expandability of subcutaneous fat depot (12). Gene expression profiling studies have reported an inverse relationship between the metabolic and immune response-related gene expression in these depots (11). In the present study, individuals after AP had a significantly higher VFV (but not SFV) in comparison with the healthy volunteer group in both unadjusted and adjusted analyses. This finding suggests that accumulation of visceral fat may specifically contribute to increased abdominal adiposity in individuals after AP. Furthermore, of the studied abdominal adiposity phenotypes, VFV and V/S fat volume ratio (but not SFV) were significantly higher in the diabetes after AP group in comparison with the no diabetes group in unadjusted analyses. This differential association of phenotypes with metabolic profile of individuals after AP can be explained by depot-specific complex interplay between adipocytes and the surrounding environment. With an increase in adiposity, the visceral adipose tissue depot shows increased expression of pro-inflammatory and angiogenic genes, greater inflammatory cell infiltration and abundant cytokine secretion profile (29). The finding of higher VFV in the diabetes group is indicative of a hypometabolic state of adipocytes that favors inflammation. Given the distinct molecular mechanisms in these depots, their individual contributions toward the pathogenic potential of excess fat mass is of interest but not fully understood. It is likely that excess fat mass in the subcutaneous fat depot increases the secretion of proinflammatory cytokines (particularly leptin), which are elevated with an increase in adiposity (18). In the setting of AP, increased concentrations of leptin are significantly associated with in-hospital persistent hyperglycemia (10) and excess adiposity after hospital discharge (33). The present study is the first to have quantified abdominal fat depots in a postpancreatitis setting, and it appears that the relative distribution of abdominal fat (as evidenced by the V/S fat volume ratio) may be important in identifying individuals at high metabolic risk after an episode of AP. However, future studies need to confirm this finding.

Also, for the first time, ectopic fat phenotypes were investigated in a postpancreatitis setting (Fig. 2). A significantly higher intrapancreatic fat percentage (but not LF%) was found in all individuals after AP in comparison with healthy volun-

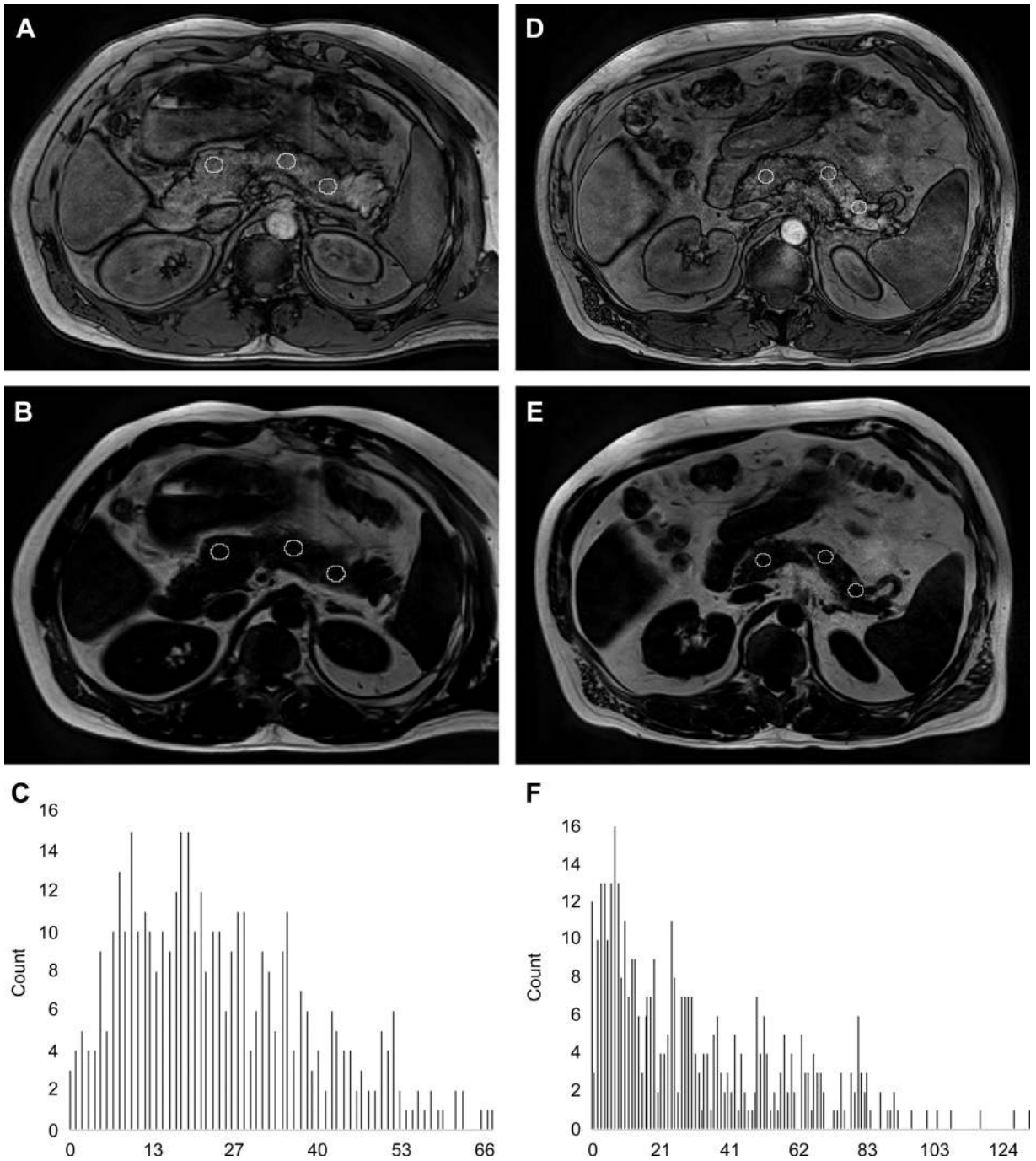

Fig. 2. Intrapancreatic fat measurements in individuals with and without diabetes after acute pancreatitis. *A–C*: data on a 43-yr-old man with diabetes after acute pancreatitis. *D–F*: present data on a 44-yr-old man without diabetes after acute pancreatitis. *Top*: out-of-phase images. *Middle*: fat-only images. *Bottom*: histograms of gray pixel count (total) within the selected regions of interest.

teers. Furthermore, intrapancreatic fat percentage (but not LF%) was significantly higher in the diabetes after AP group in comparison with the no diabetes group. The above finding is in line with the results of a recent meta-analysis that demonstrated the presence of fatty pancreas is associated with a twofold increased risk of diabetes mellitus (35). This suggests a possible link between intrapancreatic fat percentage, abnormal glucose metabolism, and β-cell function (8). Furthermore, it was speculated that visceral fat is a strong determinant of intrapancreatic fat percentage in individuals with excess adiposity and abnormal glucose metabolism (38). However, whereas VFV contributed to 36% of variance in intrapancreatic fat% in the overall AP cohort (adjusted for age and sex), its contribution was markedly lower (14 vs. 44%) in individuals with diabetes versus no diabetes after AP (adjusted for age and sex). This differential association between visceral fat and intrapancreatic fat may be reflective of distinct signaling pathways and cross-talk between the pancreas and adipose tissue in individuals with diabetes after AP. Purposely designed studies are now warranted to investigate molecular

signatures of these adiposity phenotypes in individuals with diabetes after AP.

There are two key findings from the analyses of associations between the studied phenotypes and pancreatitis-related factors. First, a marker of severity of AP (CRP level during hospitalization for AP) was significantly associated with higher VFV during follow-up. It is known that production of CRP in the liver is augmented by proinflammatory cytokines IL-6 and TNF-α. Elevated circulating levels of CRP and IL-6 are associated with increased risk of diabetes mellitus. Our 2017 study showed that both IL- 6 and TNFα, which are primarily secreted by the adipose tissue, are significantly associated with excess abdominal adiposity in individuals after AP (33). In early stages of AP, elevated CRP levels and their relation to excess adiposity were reported previously. The new finding of the present study is that elevated CRP levels are also associated with VFV after nearly two years since AP episode. Second, biliary etiology of AP was significantly associated with higher intrapancreatic fat%. This could be attributed to the fact that, with an increase in adiposity, bile is increasingly saturated with cholesterol, resulting in higher risk of cholesterol gallstones. Moreover, it was demonstrated that intraluminal fatty acid concentrations (and the ratio of intraluminal bile acids to fatty acids) substantially influence gallbladder response to fatty acids (16). In light of this evidence, it appears that excess adiposity accompanied by increased dietary input of saturated fatty acids may be linked to formation of gallstones (37). Based on the above findings, effective reduction of inflammation during the course of AP and healthy dietary intake after hospital discharge may be potentially beneficial in reducing the incidence of diabetes after AP.

This study has several strengths. First, robust state-of-the-art protocols were used to investigate abdominal adiposity and ectopic fat phenotypes. Moreover, subcutaneous and visceral fat depots were reported as volumes, not areas (the latter is used most frequently in the literature because it is the least time-consuming approach). By calculating both SFV and VFV, we obtained a comprehensive estimation of abdominal adipose tissue distribution, which would not be possible using cross-sectional area measurements alone. Second, MRI measurements were acquired independently by two raters for the entire cohort and showed excellent inter-rater reliability (ICC $>$ 0.90), whereas most studies in the literature assessed reliability only in a small subset (27, 41) or reported on MRI measurements done by merely a single rater (2, 30). Third, strict eligibility criteria were set for both AP cases and healthy volunteers, which allowed robust investigation of abdominal adiposity phenotypes in individuals with different metabolic backgrounds. Fourth, we elected to investigate all adiposity phenotypes on a continuous scale because there is a lack of consensus on cutoff values for most of the studied adiposity phenotypes (perhaps, with the exception of LF%). This approach increases generalizability of the reported findings.

The study also has limitations that need to be acknowledged. First, the cross-sectional design of the study did not allow determination of causality. Ideally, we would have liked to have all participants to undergo MRI at the time of hospitalization or soon after that; however, this is logistically challenging, costly, and has never been reported in the pancreatitis literature. Furthermore, to the best of our knowledge, there is a paucity of prospective longitudinal studies on intrapancreatic fat deposition even in the generally much larger diabetes literature (39, 40). Unlike the latter studies and other cross-sectional studies that have focused on one or two MRI-derived adiposity phenotypes, the present study conducted a comprehensive assessment of all relevant MRI-derived phenotypes in postpancreatitis setting. Future well-designed prospective longitudinal studies, particularly recording body composition changes over time in postpancreatitis setting, are needed to determine the exact pathogenic potential of adiposity phenotypes as a risk factor for diabetes after AP. Second, the age of participants in the diabetes group was significantly higher compared with the no diabetes group. However, adjusted analyses conducted in the present study accounted for age. Last, the no diabetes group after AP included individuals with both prediabetes after AP and normoglycemia after AP. Hence, the phenotypical differences observed between the no diabetes group and controls could be attributed, at least in part, to history of AP and not glucose metabolism. However, the main aim of this study was not to characterize prediabetes versus normoglycemia after AP (the importance of which has not been conclusively demonstrated) but rather to investigate phenotypical alterations that characterize diabetes after AP (the importance of which is well recognized).

In conclusion, the present study advances the field by demonstrating the importance of certain MRI-derived ectopic fat and abdominal adiposity phenotypes in metabolic derangements following AP. Individuals after an episode of AP have larger visceral fat and pancreatic fat depots, which are significantly associated with the presence of diabetes after AP. Several characteristics of AP (i.e., levels of CRP during hospitalization for AP and etiology of AP) are associated with visceral fat and pancreatic fat depots. The findings of the present study set the stage for a purposely designed prospective longitudinal study to investigate changes in ectopic fat and abdominal adiposity phenotypes over time following an attack of AP.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.G.S., A.C., J.U.K., N.N.N., S.V.D., and D.D. performed experiments; R.G.S. and A.C. analyzed data; R.G.S., J.L., and M.S.P. interpreted results of experiments; R.G.S., J.U.K., and S.V.D. prepared figures; R.G.S. drafted manuscript; R.G.S., A.C., J.U.K., N.N.N., S.V.D., D.D., J.L., and M.S.P. approved final version of manuscript; A.C., J.U.K., N.N.N., S.V.D., D.D., J.L., and M.S.P. edited and revised manuscript; M.S.P. conceived and designed research.

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