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HEPATOBILIARY-PANCREAS

Pancreas shrinkage following recurrent acute pancreatitis: an MRI study

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Abstract

Objective Transition from the first attack of acute pancreatitis (AP) to chronic pancreatitis (CP) via recurrent AP is common. Total pancreas volume (TPV) and pancreas diameters are often reduced in advanced CP but have never been studied after AP. The objective of this study was to investigate pancreas size after clinical resolution of AP and its association with the number of AP attacks.

Methods Individuals with a history of AP were grouped based on the number of attacks (1, 2, ≥ 3 attacks). Healthy individuals were also recruited. All participants underwent magnetic resonance imaging, from which TPV and pancreas diameters (across the head, body, and tail) were measured independently by two raters in a blinded fashion. Generalised additive models (including age, sex, body mass index, and glycated haemoglobin levels) were used.

Results A total of 123 participants were studied. Total pancreas volume and tail diameter were significantly reduced in both unadjusted (TPV ($p = 0.036$), tail diameter ($p = 0.009$)) and adjusted (TPV ($p = 0.026$), tail diameter ($p = 0.034$)) models in individuals with ≥ 3 attacks, but not with 1 or 2 attacks, compared with healthy individuals. Head and body diameters did not differ significantly.

Conclusions Reduced TPV and tail diameter characterise individuals after ≥ 3 attacks of AP and may represent one of the earliest irreversible morphological changes in individuals after AP. A high-risk population for transition to CP might include individuals with at least 3 attacks of AP whereas those with less than 3 attacks might be at a low risk.

Key Points

- *A significant reduction in total pancreas volume was demonstrated in individuals after 3 or more attacks of acute pancreatitis (without conventional signs of chronic pancreatitis).*
- *Pancreas tail diameter, but not head or body diameter, was reduced in individuals after 3 or more attacks of acute pancreatitis (without conventional signs of chronic pancreatitis).*
- *The above findings were independent of age, sex, body mass index, and glycated haemoglobin levels.*

Keywords Magnetic resonance imaging · Pancreas · Pancreatitis · Recurrence

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Abbreviations

AP	Acute pancreatitis
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
CP	Chronic pancreatitis
CRP	C-reactive protein
GAM	Generalised additive model
HbA1c	Glycated haemoglobin
ICC	Intra-class correlation coefficient

IQR Interquartile range
MR Magnetic resonance
TPV Total pancreas volume

Introduction

Pancreatitis is one of the most frequent gastrointestinal diseases, with the yearly global incidence of acute pancreatitis (AP) being 34 cases and chronic pancreatitis (CP)—10 cases per 100,000 people in the general population [1]. Diseases of the exocrine pancreas often lie on a continuum, with 36% of individuals with recurrent AP subsequently developing CP [2]. Chronic pancreatitis, an irreversible disease in its advanced stage, often leads to sequelae such as exocrine pancreatic insufficiency, post-pancreatitis diabetes mellitus, and osteoporosis [3]. Although there are limited treatment options in the advanced stage of CP, patients with early CP are suited well for therapeutic interventions that would prevent the development of advanced CP and, perhaps, pancreatic cancer [4]. Therefore, the identification of early signs of CP using a non-invasive and quantitative biomarker to monitor disease progression in patients with pancreatitis holds great potential in reducing the burden of advanced CP.

Emerging evidence indicates that individuals with advanced CP have reduced pancreas size, as measured by total pancreas volume (TPV) and regional pancreas diameters [5, 6]. Reduced pancreas size reflects parenchymal atrophy, the genesis of which is likely multifactorial: components of necrosis-fibrosis from bouts of autodigestion, obstruction of the main pancreatic duct, and a disrupted relationship between the endocrine and exocrine pancreas. The lattermost component, more specifically dysfunction of the insulo-acinar axis, likely plays a key role in this process as pancreatic β-cell dysfunction, death, and dedifferentiation have been reported in individuals with CP as compared with controls [5, 7, 8]. The insulo-acinar axis refers to the secretion, delivery, and action of insulin (a potent trophic hormone secreted by β-cells) on the pancreatic parenchyma, in particular acinar cells. Insulin normally stimulates the growth and repair of pancreatic exocrine tissue. Therefore, a loss of insulin's trophic effect leads to parenchymal atrophy. In contrast to reduced pancreas size in advanced CP, increased pancreas size has been reported during the clinical course of AP [9–12]. However, to date, no study has investigated pancreas size after clinical resolution of AP and it is not known whether the number of attacks of AP is associated with pancreas size.

We hypothesised that reduced pancreas size is an early morphological alteration in a sub-group of individuals with clinical resolution of recurrent AP. The aim of this study was to investigate magnetic resonance (MR) imaging–derived TPV and pancreas diameters in individuals with clinical resolution of AP and their associations with the number of AP attacks.

Methods

Study design and study population

This cross-sectional study nested into a prospective longitudinal study was part of the project ARIES (Analytic moRphomics In pancrEatic diseaSes). Individuals with a diagnosis of AP, who were admitted to Auckland City Hospital (Auckland, New Zealand), were recruited at the time of hospitalisation. Diagnosis of AP was determined prospectively according to the international guidelines [13]. Individuals were eligible for the study if they were at least 18 years of age and if they provided informed consent. Individuals were excluded if they had definite CP (histological diagnosis of CP, parenchymal calcifications, ductal calcifications, Cambridge grade ≥ 3) [14], congenital anomalies of the pancreas, hereditary pancreatitis, cystic fibrosis, pancreatic lipomatosis or lipomatous pseudohypertrophy, post-endoscopic retrograde cholangiopancreatography pancreatitis, pancreatic trauma, interventions involving the pancreas (surgical, endoscopic, or radiologic), autoimmune pancreatitis, use of steroid therapy, malignancy, were pregnant at the time of AP or afterwards, had metallic foreign body implantations, heart pacemakers, or other implanted electronic devices. Participants with an attack of AP within 3 months prior to the study date were also excluded [15].

Healthy controls were recruited only if they had no personal or family history of pancreatic diseases, diabetes, malignancy, coeliac disease, cystic fibrosis, and no symptoms of upper abdominal pain and nausea. Further, there must not have been a history of acute infectious or inflammatory conditions requiring medical treatment or evaluation in the preceding 6 months.

Study groups

Individuals with a history of AP were categorised into three groups based on the number of attacks—1, 2, and ≥ 3 attacks—between the first hospital admission for AP and the time of study. Re-admission within 30 days was not counted as a new attack [2].

Magnetic resonance image acquisition

Abdominal MR scans for all participants were performed at the Centre of Advanced Magnetic Resonance Imaging (University of Auckland), using 3.0-Tesla MAGNETOM Skyra® MR scanner (Siemens Healthineers). Participants in supine position were instructed to hold breath during the end expiration. Axial T1-weighted volumetric interpolated breath-hold examination Dixon sequence was applied with the following parameters: true form abdomen shim mode; FOV, 420 mm; base resolution, 320; TE, 1.27 ms, 2.5 ms; TR, 3.85 ms; flip angle, 9°; pixel bandwidth, 920 Hz; and slice thickness, 3 mm and 5 mm. Four types of images were generated—in-phase, out-of-phase, fat, and

water images. These images were retrieved from the MR scanner and exported as DICOM files for further analyses using ImageJ (National Institutes of Health).

Quantification of pancreas size

Total pancreas volume

Total pancreas volume was calculated using out-of-phase images with 5-mm slice thickness according to the previously published protocol [16]. In brief, the outline of the pancreas was traced on each slice in which it was visible and the associated pixel content was calculated (Fig. 1). Water images served as a reference for each slice and care was taken to exclude any surrounding vasculature. The TPV, measured in cubic centimetres (cm^3), was obtained by multiplying the pixel content from all the slices in series with the pixel area and slice thickness.

Pancreas diameters

Pancreas diameters were calculated using out-of-phase images with 3-mm slice thickness. The anteroposterior diameter of the pancreas head was measured in line with the right-most point of the confluence of the superior mesenteric and splenic veins (Fig. 2) [17]. The greatest anteroposterior diameter of the pancreas body was measured in line with the left lateral border of the lumbar vertebrae (Fig. 3) [17]. The diameter of the pancreas tail was measured as a line perpendicular to the organ midline, at a point 20 mm from the distal-most point of the pancreas in the slice. The slice used for tail diameter measurement was the one that offered the best tail visualisation within close proximity to the splenic hilum (Fig. 4). Care was taken to exclude surrounding vasculature. Pancreas diameters were measured in millimetres (mm).

Inter-rater reliability

For all study participants, TPV and the three diameters of the pancreas were measured independently by two raters, blinded to study group allocation and clinical characteristics. Intra-class correlation coefficients (ICCs) and associated 95% confidence intervals (CIs) were used to evaluate inter-rater reliability of measurements. Intra-class correlation coefficients of < 0.5, 0.5–0.75, 0.75–0.9, and > 0.9 were indicative of poor, moderate, good, and excellent inter-rater reliability, respectively. The average values of the two independent sets of measurements were used for all statistical analyses.

Other variables

At the time of hospitalisation for AP, fasting venous blood samples were analysed for C-reactive protein (CRP) using an immunoturbidimetric assay on the Roche/Hitachi Cobas C 701/702 system (Roche Diagnostics). The other AP-related variables recorded were aetiology (categorised as biliary, alcohol-related, or other) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Given the two prior complementary systematic reviews from our group showed that pancreas size is affected by body mass index (BMI) and levels of glycated haemoglobin (HbA1c) [17, 18], BMI and HbA1c were measured at the time of MR image acquisition.

Statistical analyses

The differences in baseline characteristics between individuals with 1 attack, 2 attacks, ≥ 3 attacks, and healthy controls were assessed using the Kruskal-Wallis *H* test or the one-way ANOVA for non-parametric and parametric continuous variables, respectively, and the Fisher's exact test for categorical variables. Data were presented as median and interquartile ranges (IQR) or count frequencies and percentages. The extreme values in the data (as assessed by cases with values/standardised residuals greater than ± 3 standard deviations) were regarded as outliers and were excluded from the analyses. Missing value analysis was conducted where data for continuous variables were missing. The statistical analyses were conducted in two stages.

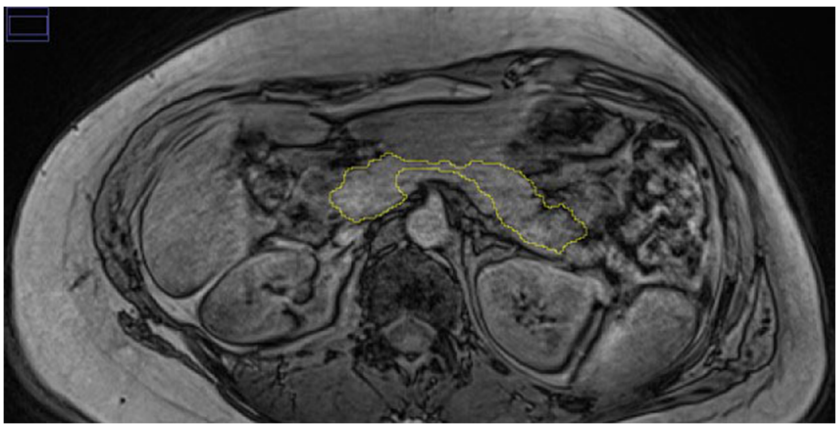

Fig. 1 Pancreas cross-sectional area

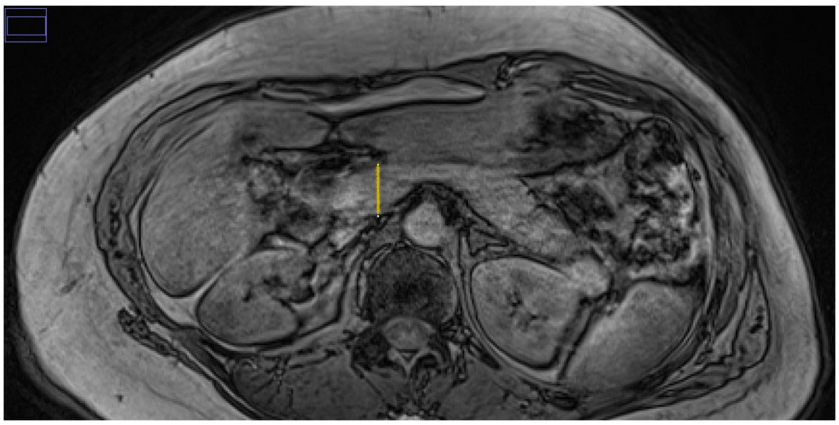

Fig. 2 Pancreas head diameter measurement. The anteroposterior diameter of the pancreas head was measured in line with the right most point of the confluence of the superior mesenteric and splenic veins

First, to examine the associations between the number of AP attacks and TPV/pancreas diameters (head, body, and tail), generalised additive models (GAM) were used. In the present study, BMI and HbA1c were treated as non-parametric covariates because the analysis of deviance yielded significance for the two variables. The number of AP attacks (1, 2, or ≥ 3 attacks) was included as a categorical variable and healthy controls were considered as the reference group. Model 1 (unadjusted), model 2 (adjusted for age and sex), and model 3 (adjusted for age, sex, BMI, and HbA1c) were constructed, with TPV/each pancreas diameter being a dependent variable. Additionally, a receiver operating characteristic curve analysis was conducted on the measures of pancreas size that were found to be significantly different between the study groups in model 3. Area under the curve (AUC) values with associated 95% CIs were reported.

Second, constrained to individuals with a history of AP, the associations between TPV and pancreas diameters were investigated using univariate and multivariate linear regression models. Model 1 (unadjusted), model 2 (adjusted for age and sex), and model 3 (adjusted for age, sex, BMI, and HbA1c) were constructed. Weighted least squares regression analysis was conducted when the assumption of homogeneity of residuals was violated. All data were reported as B coefficients, R^2 metrics of the overall model, and p values.

SPSS for Windows Version 25 (SPSS Inc) and SAS for Windows Version 9.4 (SAS Institute Inc) were used for analyses. A p value of less than 0.05 was accepted as statistically significant in all analyses.

Results

Characteristics of participants

Ninety-five individuals with a history of AP were included, comprising 62 men and 33 women. The median (IQR) age was 57 (44–67) years, the median (IQR) BMI was 27.2 (24.5–33.3) kg/m^2, and the median (IQR) HbA1c was 37 (34–39) mmol/mol. The median (IQR) duration from the last attack of AP to the study date was 21 (11.5–29.5) months. Of the 95 individuals, 73 individuals had 1 attack, 13 had 2 attacks, and 9 had ≥ 3 attacks. There were no differences in peak CRP levels and APACHE II scores between the study groups (Table 1). Twenty-eight healthy controls, comprising 18 men

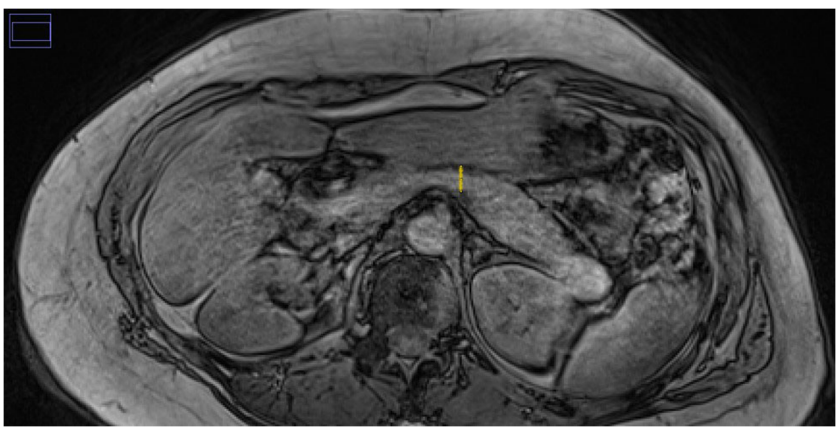

Fig. 3 Pancreas body diameter measurement. The greatest anteroposterior diameter of the pancreas body was measured in line with the left lateral border of the lumbar vertebrae

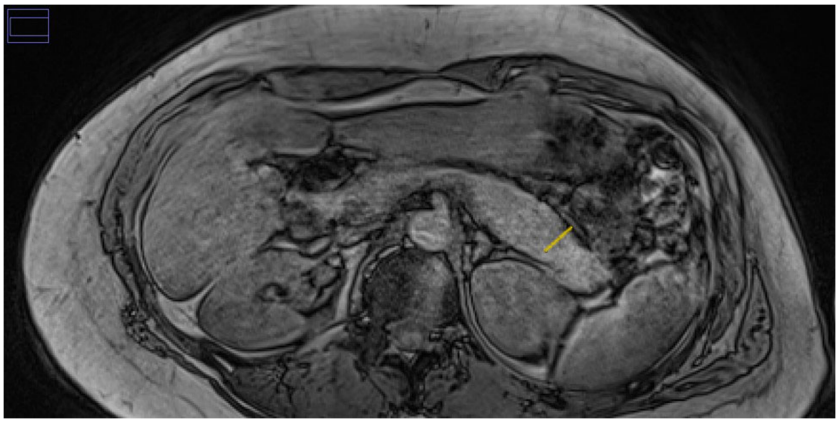

Fig. 4 Pancreas tail diameter measurement. The diameter of the pancreas tail was measured as a line perpendicular to the organ midline, at a point 20 mm from the most distal point of the pancreas in the slice. The slice used for tail diameter measurement was the one that offered the best tail visualisation within close proximity to the splenic hilum

and 10 women, were also included. Their median (IQR) age was 44.5 (29–53.3) years, the median (IQR) BMI was 24.6 (21.8–28.8) kg/m^2, and the median (IQR) HbA1c was 32.5 (30–34.8) mmol/mol (Table 1).

Inter-rater reliability

The absolute inter-rater difference in means was 0.6 cm^3 for TPV, 0.8 mm for head diameter, 0.6 mm for body diameter, and 0.6 mm for tail diameter. The ICC (95%CI) was 0.96 (0.94–0.97) for TPV and 0.95 (0.93–0.97) for head, body, and tail diameters (Fig. 5).

Pancreas size in the study groups

Total pancreas volume

Total pancreas volume was 70.2 ± 17.5 cm^3 in the ≥ 3 attack group, 80.7 ± 15.7 cm^3 in the 2 attack group, 85.8 ± 24.5 cm^3 in the 1 attack group, and 87.7 ± 15.5 cm^3 in the healthy control group (Fig. 6a). It was significantly reduced by 17.5 cm^3 in the ≥ 3 attack group compared with the healthy control group in the unadjusted analysis ($p = 0.036$). This difference remained statistically significant in the two adjusted analyses (Table 2). The AUC (95%CI) was 0.79 (0.62–0.97) ($p = 0.009$).

Table 1 Characteristics of the study groups

Characteristic	1 attack ($n = 73$)	2 attacks ($n = 13$)	≥ 3 attacks ($n = 9$)	Healthy controls ($n = 28$)	p value
Age (years)	57 (44–68)	56 (41–65)	58 (41–68.5)	44.5 (29–53.3)	0.009
Sex					0.902
Men	47 (64.4%)	8 (61.5%)	7 (77.8%)	18 (64.3%)	
Women	26 (35.6%)	5 (38.5%)	2 (22.2%)	10 (35.7%)	
BMI (kg/m^2)	27.5 (24.7–33.7)	27.7 (24.4–32.6)	26.3 (23.2–28.4)	24.6 (21.8–28.8)	0.058
HbA1c (mmol/mol)	37 (34–39)	37.5 (33.3–40)	35 (31–41.8)	32.5 (30–34.8)	< 0.001
Ethnicity					0.486
NZ European	31 (42.5%)	5 (38.5%)	5 (55.6%)	13 (46.4%)	
Māori	16 (21.9%)	2 (15.4%)	2 (22.2%)	5 (17.9%)	
Pacific Islander	2 (2.7%)	1 (7.7%)	0 (0%)	1 (3.6%)	
Asian	10 (13.7%)	3 (23.1%)	1 (11.1%)	9 (32.1%)	
Other	14 (19.2%)	2 (15.4%)	1 (11.1%)	0 (0%)	
Aetiology					0.008
Biliary	38 (52.1%)	5 (38.5%)	2 (22.2%)	N/A	
Alcohol-related	7 (9.6%)	3 (23.1%)	5 (55.6%)	N/A	
Other	28 (38.4%)	5 (38.5%)	2 (22.2%)	N/A	
Peak CRP during hospitalisation (mg/L)	92 (16–241.5)	151 (8.5–320)	84 (39.5–141)	N/A	0.582
Peak APACHE II score during hospitalisation	5 (3–8)	7 (3–8)	4.5 (0.8–5.9)	N/A	0.253

Data are presented as median and interquartile ranges (IQR) or counts frequencies and percentages

APACHE II, acute physiology and chronic health evaluation II; *BMI*, body mass index; *CRP*, C-reactive peptide; *HbA1c*, glycated haemoglobin; *N/A*, not applicable

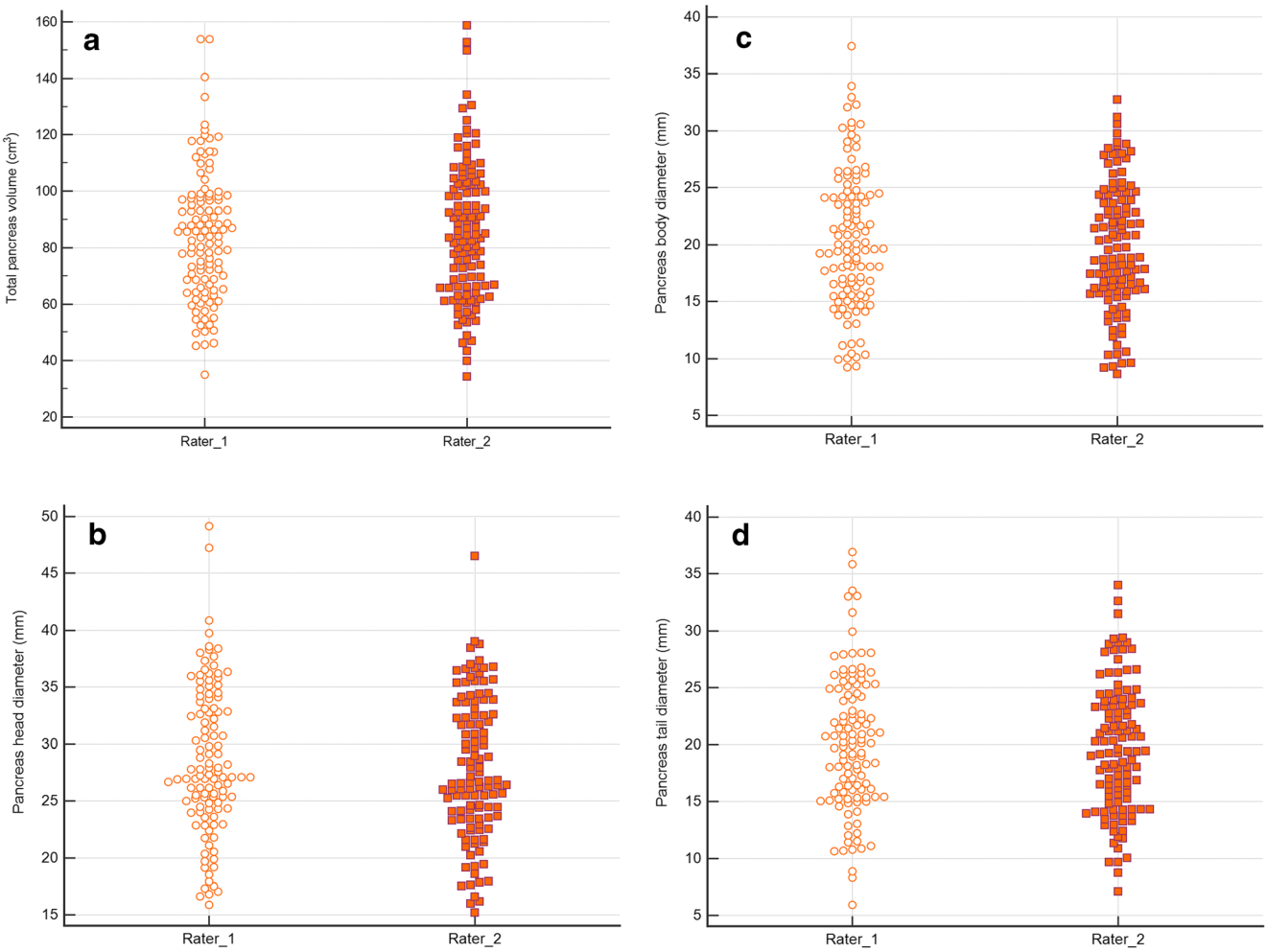

Fig. 5 Comparison of total pancreas volume (**a**), head (**b**), body (**c**), and tail (**d**) diameter measurements between the two raters

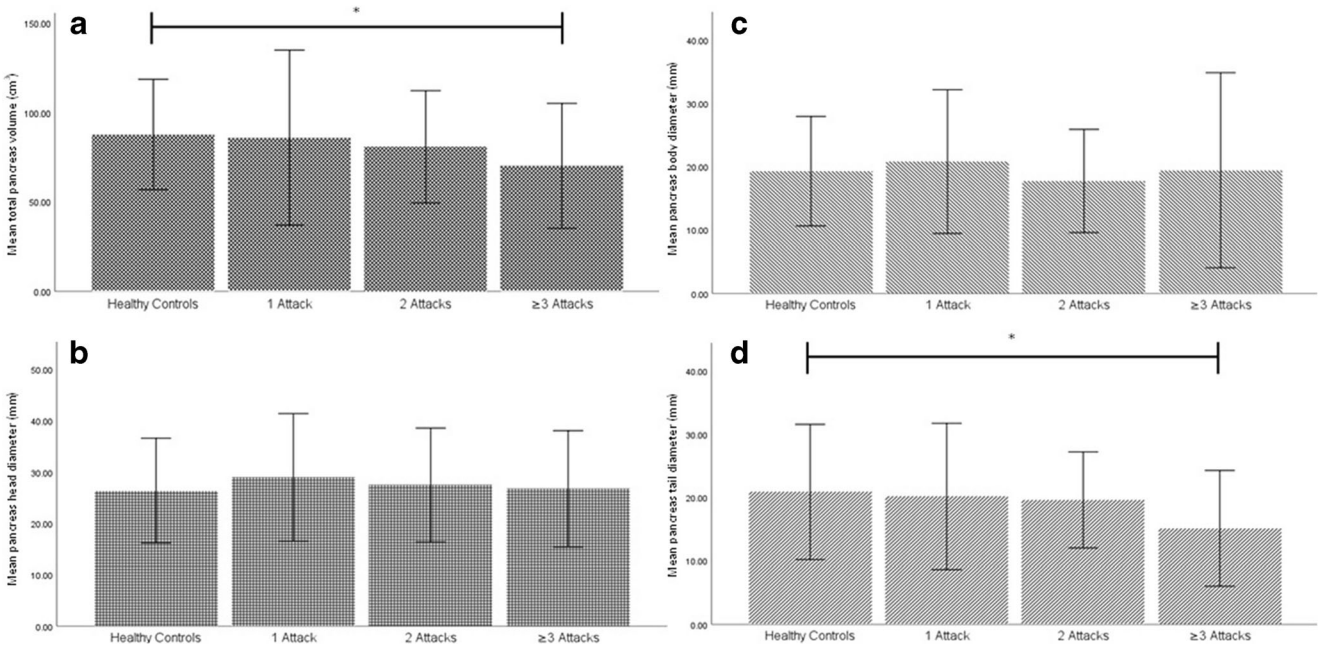

Fig. 6 Total pancreas volume (**a**), head (**b**), body (**c**), and tail (**d**) diameters in the study groups. Bars represent mean value whereas whiskers represent 2 standard deviations. * $p < 0.001$

Table 2 Differences in total pancreas volume and the three diameters between the acute pancreatitis study groups

	Model 1		Model 2		Model 3	
	Mean difference	*p*	Mean difference	*p*	Mean difference	*p*
Total pancreas volume						
1 attack	− 2.4 (4.8) cm^3	0.613	+ 1.8 (4.6) cm^3	0.696	− 1.0 (4.9) cm^3	0.841
2 attacks	− 3.9 (7.1) cm^3	0.585	+ 0.14 (6.6) cm^3	0.983	− 2.3 (6.7) cm^3	0.731
≥ 3 attacks	*− 17.5 (8.3) cm^3*	*0.036*	*− 15.3 (7.7) cm^3*	*0.049*	*− 17.8 (7.9) cm^3*	*0.026*
Pancreas head diameter						
1 attack	+ 2.5 (1.3) mm	0.059	*+ 2.8 (1.3) mm*	*0.031*	+ 1.8 (1.4) mm	0.197
2 attacks	+ 1.6 (1.9) mm	0.399	+ 2.0 (1.9) mm	0.298	+ 1.0 (1.9) mm	0.581
≥ 3 attacks	+ 0.4 (2.3) mm	0.868	+ 0.1 (2.2) mm	0.949	− 0.8 (2.2) mm	0.719
Pancreas body diameter						
1 attack	+ 1.8 (1.2) mm	0.141	*+ 2.5 (1.2) mm*	*0.039*	+ 1.7 (1.3) mm	0.192
2 attacks	− 0.2 (1.8) mm	0.923	+ 0.5 (1.7) mm	0.762	− 0.5 (1.7) mm	0.785
≥ 3 attacks	+ 0.6 (2.1) mm	0.780	+ 1.0 (2.0) mm	0.632	+ 0.4 (2.0) mm	0.832
Pancreas tail diameter						
1 attack	− 0.6 (1.2) mm	0.637	+ 0.7 (1.2) mm	0.298	+ 0.7 (1.3) mm	0.580
2 attacks	− 0.7 (1.8) mm	0.712	+ 0.5 (1.7) mm	0.756	+ 0.8 (1.8) mm	0.666
≥ 3 attacks	*− 5.5 (2.1) mm*	*0.009*	*− 4.5 (2.0) mm*	*0.026*	*− 4.5 (2.1) mm*	*0.034*

Data are presented as mean difference (standard error), relative to healthy controls. Statistically significant ($p < 0.05$) differences are shown in italics. *Model 1*, unadjusted; *Model 2*, adjusted for age and sex; *Model 3*, adjusted for age, sex, body mass index, and glycated haemoglobin

Pancreas head diameter

Pancreas head diameter was 26.7 ± 5.7 mm in the ≥ 3 attack group, 27.4 ± 5.6 mm in the 2 attack group, 28.9 ± 6.2 mm in the 1 attack group, and 26.3 ± 5.2 mm in the healthy control group (Fig. 6b). This diameter was significantly increased by 2.8 mm in the 1 attack group when compared with the healthy control group in the age- and sex-adjusted analysis, but not in the unadjusted and age, sex, BMI, and HbA1c-adjusted analyses (Table 2).

Pancreas body diameter

Pancreas body diameter was 19.4 ± 7.7 mm in the ≥ 3 attack group, 17.7 ± 4.1 mm in the 2 attack group, 20.8 ± 5.7 mm in the 1 attack group, and 18.9 ± 3.9 mm in the healthy control group (Fig. 6c). This diameter was significantly increased by 2.5 mm in the 1 attack group compared with the healthy control group in the age- and sex-adjusted analysis, but not in the unadjusted and age, sex, BMI, and HbA1c-adjusted analyses (Table 2).

Pancreas tail diameter

Pancreas tail diameter was 15.2 ± 4.6 mm in the ≥ 3 attack group, 19.7 ± 3.8 mm in the 2 attack group, 20.2 ± 5.8 mm in the 1 attack group, and 20.7 ± 5.3 mm in the healthy control group (Fig. 6d). This diameter was significantly reduced by 5.5 mm in the ≥ 3 attack group compared with the healthy control group in the unadjusted analysis ($p = 0.009$). The difference remained statistically significant in the two adjusted analyses (Table 2). The AUC (95%CI) was 0.79 (0.61–0.94) ($p = 0.015$).

Associations between total pancreas volume and pancreas diameters

In individuals with a history of AP, TPV and the three diameters had statistically significant positive associations with each other, in both the unadjusted and adjusted analyses. After adjustment for age, sex, BMI, and HbA1c, TPV had the strongest association with tail diameter ($B = 2.45$, $R^2 = 0.54$, $p < 0.001$). The inter-relationships between head and body diameter as well as between head and tail diameters were not significant in the adjusted analyses. Table 3 presents the R^2 metrics in each analysis. Supplementary Table 1 presents *B* coefficients and *p* values in each analysis.

Discussion

The present study of individuals with a history of 1 or more attacks of prospectively diagnosed AP and no typical imaging features of CP has three main findings. First, TPV was significantly lower in individuals after ≥ 3 attacks than healthy controls. Second, tail diameter was significantly smaller in

Table 3 Inter-relationships between total pancreas volume and the three diameters in individuals with a history of acute pancreatitis

TPV	Model	PHD	PBD	PTD
	1	0.19	0.33	0.46
	2	0.26	0.38[a]	0.49[a]
	3	0.38[a]	0.42[a]	0.54[a]

PHD	Model	PBD	PTD	TPV
	1	0.07	0.42	0.17
	2	0.14	0.12	0.21
	3	0.21	0.16[a]	0.28[a]

PBD	Model	PTD	TPV	PHD
	1	0.13	0.29	0.07
	2	0.17	0.34[a]	0.13
	3	0.26[a]	0.38[a]	0.18[a]

PTD	Model	TPV	PHD	PBD
	1	0.47	0.03	0.13
	2	0.51[a]	0.21	0.27
	3	0.58	0.23[a]	0.32[a]

R^2
≤0.15
0.16 - 0.30
0.31 - 0.44
≥0.45

Variables in rows are the dependent variables and variables in columns are the independent variables. Shade coding is based on R^2 values of the overall models that were statistically significant. Statistical insignificance is coded white

PBD, pancreas body diameter; *PHD*, pancreas head diameter; *PTD*, pancreas tail diameter; *TPV*, total pancreas volume; *Model 1*, unadjusted; *Model 2*, adjusted for age and sex; *Model 3*, adjusted for age, sex, body mass index, and glycated haemoglobin

[a] A weighted least squares regression analysis was conducted as the assumption for homogeneity of residuals was violated

individuals after ≥ 3 attacks than healthy controls. Third, tail diameter had the strongest positive association with TPV out of the three pancreas diameters. Notably, the above findings were independent of age, sex, BMI, and levels of HbA1c—the variables found to considerably affect pancreas size in the two 2018 systematic reviews on the topic [17, 18].

While TPV in individuals after either 1 or 2 attacks of AP did not differ significantly from that of healthy controls, it was reduced significantly by 22% in individuals after ≥ 3 attacks of AP. The latter finding is similar to a 21% reduction in TPV in individuals with histology-verified CP, as compared with controls, reported in the study by Schrader and colleagues [5]. Markedly reduced TPV in definite CP represents parenchymal atrophy underpinned by a persistent inflammation of the pancreas. The pancreas has a remarkable potential for regeneration [19]; hence, if each attack of AP had been independent of each other, it would have been expected that TPV should not have differed from that of healthy controls given sufficient time for recovery (in the present study, the average time since the last attack of AP to the time of MR scan was 21 months). The mechanism explaining parenchymal atrophy in individuals with definite CP may also explain the finding of reduced TPV in individuals after ≥ 3 attacks of AP. Acinar cell atrophy could manifest as a reduction in TPV taking into account that 95% of pancreatic cell mass is the exocrine tissue. Dysfunction of the insulo-acinar axis contributes to the observed alterations and mounting evidence in individuals after AP supports this tenet [20]. Acinar cell atrophy may occur due to impaired action of insulin by means of reduced secretion due to β-cell dysfunction, death, or dedifferentiation, impaired delivery, and/or altered local receptor action [21, 22]. The impaired insulin action may be masked by a compensatory hyperinsulinaemia that is sustained by a reduction in clearance of insulin, which counters the increased insulin resistance in individuals after AP [23, 24]. It is also worth noting that β-cell dysfunction, death, and dedifferentiation have been found to correlate positively with fibrosis, atrophy, and inflammatory cell infiltration in individuals with definite CP [5, 7, 8]. Beta-cell dysfunction has also been reported in individuals with a history of AP and no characteristic imaging features of CP [25–28].

The other main findings were that tail diameter was reduced by 33% in individuals after ≥ 3 attacks of AP and had the strongest positive associtaion with TPV (in both the unadjusted and adjusted analyses). These findings are similar to those reported in the setting of type 1 diabetes where the tail was the first to shrink and displayed the greatest extent of atrophy relative to other regions of the pancreas [17]. Given that two histopathological studies found the highest density of islets in the tail of the pancreas [29, 30], the effect of β-cell dysfunction, death, and dedifferentiation (parenchymal atrophy via the insulo-acinar axis) may be most pronounced in the tail. The possible practical implication of the above findings related to tail diameter is that it has the potential as a quick and relatively straightforward imaging biomarker to identify high-risk individuals after clinical resolution of episodes of AP. A downward trend in tail diameter during follow-up would herald CP whereas no change would indicate a low risk of developing CP. Using this imaging biomarker would be especially

useful in individuals with alcohol-related AP, who have a markedly high rate of recurrence [2]. However, this hypothesis needs to be investigated in a prospective longitudinal study before measurement of pancreas tail diameter can be recommended to be added to the standard pancreas imaging protocol with a view to providing an opportunity for early targeted diagnostics and follow-up [31].

The diagnoses of both AP and advanced CP are relatively straightforward to make; however, identifying individuals transitioning between the two states has imposed a formidable clinical challenge. Historically, attempts to classify an intermediate category of pancreatitis have alternated between terms such as 'possible', 'probable', 'early', and 'indeterminate' CP. Invariably, they all have considered recurrent AP as a sub-group of individuals at high risk of developing CP. A 2018 international guideline, based on expert opinions only, defined recurrent AP as the presence of ≥ 2 attacks of AP [15]. Further, attacks of AP were deemed to be pathophysiologically independent of each other such that periods of convalescence were characterised by return to normal morphology of the organ. However, the former statement, while being intuitive, merely suggests using the term 'recurrent AP' to describe any repeated attack, without an attempt to determine if there is a critical number of attacks that significantly increases the risk of developing CP (which one would expect from a clinically meaningful intermediate category of pancreatitis). This is not an evidence-based recommendation given that there have been more consensus guidelines than original studies investigating early morphological alterations in pancreatitis. The present study takes the field further by demonstrating that not all repeated attacks of AP are the same. Individuals after just incident AP or 1 repeated attack do not have morphological changes (as evidenced by pancreas size) and, hence, might be at a low risk of transitioning to CP. By contrast, individuals after 2 or more repeated attacks of AP have pancreas shrinkage and, hence, might be at a high risk of transitioning to CP. We have also shown that normal morphology of the pancreas is not observed in all individuals after repeated attacks of AP (as implied by the 2018 guideline [15]), but only in those after 1 repeated attack. These findings will inform the development of future evidence-based guidelines in the field and make the selection of individuals for future studies focused on 'holistic prevention of pancreatitis' more cost-effective [3].

This study has several strengths. First, it was informed by two complementary systematic literature reviews conducted by our group [17, 18] that showed (among other findings) that, to date, only three studies [5, 6, 32] have investigated MR- or computed tomography–derived TPV or pancreas diameters during the course of pancreatitis (with no study on both TPV and pancreas diameters in the context of pancreatitis). Hence, the present study adds to the literature by presenting first data on the relationship between TPV/pancreas diameters and the number of attacks of AP in individuals after clinical resolution of AP. Second, given that the two systematic literature reviews [17, 18] identified that pancreas size is significantly altered in individuals with impaired glucose metabolism and excess adiposity, all the associations investigated in the present study were adjusted for HbA1c and BMI (as well as age and sex). An overwhelming majority of previous studies did not conduct any adjusted analyses at all, let alone accounting for both impaired glucose metabolism and excess adiposity. Third, the derivation of pancreas size was robust. A previously published method was used [16, 33]. Further, it was applied to all the 123 participants independently by two raters blinded to study group allocation and characteristics. The inter-rater reliability was excellent with ICCs of 0.96 for TPV and 0.95 for all the three diameters. To the best of our knowledge, this is only the second study to have used two raters to assess all study participants in regard to TPV (Burute and colleagues reported on an ICC score of 0.87 for TPV measurements between two raters in the cohort of 82 individuals [33]) and the first study to do it for all the three pancreas diameters. Last, the study was nested into a prospective cohort study; hence, the diagnosis of AP was established prospectively in all patients and in line with the international recommendations (as opposed to the use of hospital discharge codes, which are prone to a misclassification bias [34]) and participants were followed up prospectively (including the development of repeated attacks of AP).

The study also has a number of limitations. First, it was a cross-sectional study and, hence, no inference about causality can be made yet. While it is tempting to imply that the reduced pancreas size is the result of multiple attacks of AP, it is theoretically possible that individuals with smaller TPVs and tail diameters are more likely to develop multiple attacks of AP. A prospective cohort study is now warranted to address this issue unequivocally. Second, the ≥ 3 attack group included only nine individuals. It is worth noting though that the pattern of pancreas size values was consistent between this group and the larger groups. Further, the significant associations of both TPV and tail diameter observed in this group, consistently in both the unadjusted and all the adjusted analyses, suggest a large effect size. Third, investigation of the relationship between pancreas size and endocrine or exocrine function of the pancreas was beyond the scope of the present study. However, it reports on early structural changes in the pancreas in a comprehensive manner, accounting for glucose metabolism (among other factors). Last, our findings cannot be extrapolated to paediatric setting as pancreas size is known to normally increase from infancy to adolescence [18].

In conclusion, TPV and pancreas tail diameters are significantly reduced in individuals after 3 or more attacks of AP, but not in individuals after 1 or 2 attacks. The latter might be at a low risk of developing CP. A reduction in pancreas size might be an early characteristic of individuals transitioning from AP to CP.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Associate Professor Max Petrov, MD, MPH, PhD.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Two of the authors have significant statistical expertise.

Informed consent Written informed consent was obtained from all participants in this study.

Ethical approval Health and Disability Ethics Committee approval was obtained.

Methodology
- prospective
- cross-sectional study
- performed at one institution

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