Title

Diabetes Mellitus in Children with Acute Recurrent and Chronic Pancreatitis: Data From the INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE Cohort.

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Diabetes Mellitus in Children with Acute Recurrent and Chronic Pancreatitis: Data from the INSPPIRE Cohort

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Abstract

Objectives: Adults with chronic pancreatitis (CP) have a high risk for developing pancreatogenic diabetes mellitus (DM), but little is known regarding potential risk factors for DM in children with acute recurrent pancreatitis (ARP) or CP. We compared demographic and clinical features of children with ARP or CP, with and without DM, in the INternational Study Group of Pediatric Pancreatitis: In Search of a CuRE (INSPPIRE) registry.

Methods: We reviewed the INSPPIRE database for the presence or absence of physician-diagnosed DM in 397 children, excluding those with total pancreatectomy with islet autotransplantation, enrolled from August 2012 to August 2017. Patient demographics, body mass index percentile, age at disease onset, disease risk factors, disease burden, and treatments were compared between children with DM (n=24) and without DM (n=373).

Results: 24 children (6.0% of the cohort) had a diagnosis of DM. Five of 13 tested were positive for beta cell autoantibodies. The DM group was 4.2 years (95% CI 3.0, 5.4) older at first episode of acute pancreatitis, and tended to more often have hypertriglyceridemia (odds ratio (OR) 5.21 (1.33, 17.05)), coexisting autoimmune disease (OR 3.94 (0.88, 13.65)) or pancreatic atrophy (OR 3.64 (1.13, 11.59)).

Conclusions: Pancreatic atrophy may be more common among children with DM, suggesting more advanced exocrine disease. However, data in this exploratory cohort also suggest increased autoimmunity and hypertriglyceridemia in children with DM, suggesting that risk factors for Type 1 and Type 2 DM respectively may play a role in mediating DM development in children with pancreatitis.

Keywords

Introduction

Acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP) result in recurrent injury to the pancreatic parenchyma. As a result, for patients afflicted with ARP and CP, the risk of developing diabetes mellitus (DM) is highly elevated compared to the average population (1–3). For adults with CP, the lifetime risk for glucose intolerance or DM is estimated at 25–80%, depending on the population, disease etiology, and treatments (1). Nearly all epidemiologic research on DM risk in pancreatitis has been based in adult populations, with little research around the risk for DM in children with CP and ARP (4).

Genetic risk factors for pancreatitis are frequent in children with ARP and CP, identified in nearly half of children with ARP and three quarters of those with CP enrolled in the INternational Study group of Pediatric Pancreatitis: In Search of a CuRE (INSPPIRE) (5). In two European series of individuals with hereditary pancreatitis, primarily due to a pathogenic mutation in the Protease Serine 1 (*PRSS1*) gene encoding cationic trypsinogen,

the lifelong risk for developing DM exceeded 60% by 60 years of age, but notably, onset of DM in childhood was rare, with only 4% with DM by age 20 years (6, 7). Thus, even though lifelong risk for DM is high with genetically-mediated pancreatitis, risk for *childhood-onset* DM is low (7). Other risk factors for DM identified in adults with CP include exocrine pancreatic insufficiency, pancreatic surgery, pancreatic calcifications or atrophy, and overweight/obese BMI (8–10). Whether these factors also convey risk for DM in childhood is unknown.

Using data collected in the INSPPIRE registry, we aimed to describe the burden of DM in children with ARP or CP, and to explore patient and disease characteristics that may differ in those children who developed DM versus those who had not. The latter is important in identifying parameters that should be considered in future studies for progression to DM in children with pancreatitis.

Methods

Subjects and Participating Centers

INSPPIRE is a multi-center, international consortium for the study of ARP or CP in children. Children ≤19 years of age were considered eligible for inclusion in the study if they met criteria for ARP and/or CP. ARP was defined as 2 or more episodes of acute pancreatitis (AP) confirmed by clinical symptoms and lipase or amylase >3x the upper limit of normal OR imaging features of AP, with episodes separated by 1 month. CP was diagnosed if at least one of the following criteria were met: (1) abdominal pain and imaging features of CP; (2) exocrine pancreatic insufficiency and imaging features of CP; or (3) endocrine insufficiency and imaging features of CP. Imaging studies were performed at the discretion of the clinical provider. For the purpose of these analyses, we excluded those patients who had total pancreatectomy (TP) with or without islet autotransplantation (IAT). Patients who have cystic fibrosis included only if they met study entry criteria for ARP or painful CP. All centers obtained local Institutional Review Board (IRB) approval or the equivalent for their country prior to enrolling subjects. All centers met the criteria of the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Consent was obtained from the parents of participants less than 18 years and directly from participants 18 years or older. Children gave assent at the age specified by the local IRB.

The INSPPIRE study methodology has been described in detail previously (11). Physician and patients completed questionnaires at baseline and at 1 year longitudinal follow up intervals. Collected data included information on the diagnosis of ARP and CP, disease features, disease burden, and treatments. Diagnosis of DM was assessed by the physician completing the questionnaire based on standard American Diabetes Association (ADA) criteria, specifically any of: (1) fasting glucose 126 mg/dL, (2) HbA1c 6.5% (for #1 or 2, confirmed on repeat), or (3) random glucose >200 mg/dL with symptoms (12). Details of DM from the physician form included diagnostic tests used to make the diagnosis, date of diagnosis and history of whether any autoantibody testing for type 1 diabetes was performed. Autoantibody testing may include any of the clinically available assays: islet cell antibodies, insulin autoantibodies, glutamic acid decarboxylase antibodies, tyrosine

phosphatase (IA-2) antibodies, and Zinc Transporter 8 antibodies. Hypertriglyceridemia was defined by fasting triglyceride level above the upper limit of normal.

Statistical Analyses

Summary statistics for demographic, clinical, and treatment variables were computed for DM and non-DM groups, with mean (standard deviation) for continuous variables, median (interquartile range) for ordinal/count/rate variables, and frequency count (percent) for categorical variables. We then considered what variables might be associated with DM; because of the multiple variables examined, the analyses are designed to be exploratory. Comparison of DM and non-DM groups were examined for relevant variables by computing mean difference for age, median difference for ordinal/count/rate variables (i.e. number of ER visits, number of hospitalizations/year, number of days missed school), and odds ratio for categorical variables, with corresponding 95% confidence interval. The coverage of the 95% CIs (i.e. do not include zero for mean or median difference; do not include one for odds ratio) were examined to identify variables that suggest possible differences between groups. For the purpose of these exploratory analyses, p-values were not reported; rather, results should be considered hypotheses generating and need confirmation by future study. All statistical analyses were performed using SAS (version 9.4).

Results

Patient Characteristics

There were 397 children with CP or ARP included in the analyses, including 24 with a diagnosis of DM, 6% of the cohort. Patient demographics are displayed in Table 1. The patients with DM were older at the first episode of AP (12.9±2.6 vs 8.7±4.7, mean difference 4.2 years (3.0, 5.4)). Prevalence of overweight or obese BMI at study entry was similar in the DM and non-DM groups. Of the 24 children with DM, 23 had a history of AP, and 9 (38%) had CP while the other 15 (62%) had ARP alone.

Of the 24 children with diabetes, the diagnosis of DM was present at study entry in 19 cases based on elevated fasting glucose, elevated hemoglobin A1c (HbA1c) level, and abnormal glucose tolerance test in 4 patients; elevated fasting glucose and elevated HbA1c in 9 patients; elevated HbA1c alone in 5 patients, and abnormal glucose tolerance test alone in 1 patient. In the remaining 5 children, DM was diagnosed in the follow-up interval, after initial enrollment. Only 13 of the 24 children had been tested for beta cell autoantibodies, with positive autoantibodies in 5/13 cases. Diabetes was treated with insulin and non-insulin medications in 5 patients, insulin alone in 15 patients, and no pharmacologic therapies in 2 patients. Treatment regimen was unknown for 2 children.

With regard to the interval between first diagnosis of pancreatitis and diagnosis of DM, 11 (46%) patients were diagnosed with DM prior to pancreatitis diagnosis, 5 (21%) patients had simultaneous diagnosis of DM and pancreatitis (onset of DM within 60 days of pancreatitis diagnosis), and 8 (33%) patients had onset of DM after diagnosis of pancreatitis with a mean duration of 3.6 ± 1.7 years between pancreatitis diagnosis and DM onset. Of note, of the 11

participants with DM preceding their pancreatitis diagnosis, 10 had ARP alone while only 1 had been diagnosed with CP.

Disease features in children with ARP and CP with or without DM

Risk factors for ARP or CP and comorbidities are displayed in Table 2. Patients with DM commonly had hypertriglyceridemia (23% vs 5% of non-DM, OR 5.21 (1.33, 17.05)), and tended towards increased risk for other autoimmune diseases (17% vs 5%, OR 3.94 (0.88, 13.65)). Patients with DM had an increased prevalence of pancreatic atrophy (50% vs 22% without DM, OR 3.64 (1.13, 11.59)), but pancreas morphology on imaging was otherwise similar in DM and non-DM groups Table 3. Pancreatic calcifications were notably uncommon in children (7% of those with vs 8% of those without DM). Other pancreatitis risk factors were similar between groups, including genetic mutations.

Disease treatment and disease burden in children with ARP and CP with or without DM

Notably, endoscopic procedures and surgical therapies were similar in those with and without DM (Table 4). Pain medication usage in patients was similar between DM and non-DM groups for both provider reported use and patient self-report. Those children with DM were more likely to report any level of constant pain (45% vs 22% of those without DM, OR 5.05 (1.30, 16.27)). Exocrine pancreatic insufficiency trended towards more common among those with DM (36% vs 17%, OR 2.81 (0.97, 7.54)) (Table 5).

Discussion

DM is a well-described consequence of pancreatitis in adults, but features of and risk factors for DM in children with pancreatitis have been lacking in the medical literature to date. The INSPPIRE registry represents a unique opportunity to describe the burden of DM in children with pancreatitis. In this large, multi-center, international cohort of children with CP and ARP, 6% of children studied had been diagnosed with DM. Children with either CP or ARP were at risk for DM, with about 40% of children in the registry with a diagnosis of DM having a diagnosis of CP and the remainder, about 60%, having ARP. Other than an increased prevalence of pancreatic atrophy in the DM group, pancreatitis risk factors, imaging features, and treatment history were similar between the DM and non-DM groups. Five children with DM also had beta cell antibodies, and DM was more common in those children who also had hypertriglyceridemia and tended to be more common in those with other autoimmune disorders, suggesting classic risk factors for metabolic syndrome or type 1 DM, respectively, in addition to the underlying pancreatic disease, may play an important role in mediating risk for DM in children with ARP or CP.

In the United States, the crude prevalence of DM in children is estimated at 1.82 cases per 1,000 youth (13). In contrast, we observed 24 children (6%, or equivalent to 60 out of 1,000 youth) diagnosed with DM. These findings clearly support the hypothesis that, as in adults, children with CP or ARP have an increased risk for DM, and is similar to that reported in smaller series of children with CP elsewhere (14, 15). It is important for gastroenterologists, endocrinologists, primary care physicians, and other providers who encounter children with CP or ARP to be aware of this increased risk and screen these children appropriately for

DM. Annual screening for DM may include fasting glucose and hemoglobin A1c levels, with or without oral glucose tolerance testing (16). Notably, 46% of children had DM preceding the diagnosis of CP and ARP. It is possible that these children had subclinical pancreatitis that was undiagnosed at an earlier stage. Alternatively, one could postulate that there is a shared pathology underlying both DM and pancreatitis, or that the DM is actually increasing the risk for pancreatitis later.

This study provides novel exploratory data on potential risk factors for DM in children with pancreatitis, and sets the stage for future studies on mechanisms underlying DM in pediatric pancreatitis. While we have previously reported on pancreatitis features in this cohort of patients, and other previous series have reported the occurrence of DM in CP and beta cell dysfunction (without DM) in ARP, this is the first report to consider potential risk factors for DM in children with pancreatitis (14, 15, 17–19). Other studies to date on risks for DM in the setting of CP have focused nearly entirely in adult populations—adults may have different causes of pancreatitis (environmental vs genetic) and different co-morbidities and older age that impact DM risk.

Similar to findings in adults with CP and DM, children with DM in our series had features suggestive of more severe fibrosis, including increased odds of pancreatic atrophy and suggestion of increased risk of pancreatic exocrine insufficiency. One of the primary mechanisms leading to development of pancreatogenic DM is bystander destruction of the islets (and beta cells) as pancreatic parenchyma is replaced by fibrosis in CP. However, we did not find an association of other pancreatitis disease features classically associated with pancreatogenic DM in adults including pancreatic calcifications or prior surgical intervention with DM in our cohort, although these features are also less common in children than adults (8, 10, 20). It is possible that children with these features have a higher risk of progression to DM as they enter adulthood.

The only pancreatic morphologic finding associated with DM in our cohort was pancreatic atrophy. Pancreatic atrophy has been well-described in insulin-dependent DM, particularly type 1 DM (21–25). Thus, while the atrophy in our DM cases could be reflecting more severe fibrosis and islet loss related to more advanced pancreatitis, conversely atrophy could also be a consequence of the underlying DM. Similarly, exocrine pancreatic insufficiency, which was two-fold higher in the DM group (36% vs 17%), may be a consequence of CP, or associated with insulin-dependent DM (26, 27).

A particularly novel observation in this study, which has not been previously reported, is the presence of beta cell antibodies in children with CP and DM and suggestion for underlying autoimmunity. Type 1 DM is an autoimmune disorder against the insulin-producing beta cells of the pancreas (28, 29). In addition to a trend towards increased odds for other autoimmune disorders, 5 of 13 tested were positive for beta cell autoimmunity (38%). The latter is particularly notable as these findings suggest that some of the children with DM in this cohort may have beta cell autoimmunity, more similar to a Type 1 DM phenotype, rather than classic Type 3c DM. In the setting of genetic predisposition for type 1 DM, repeated episodes of inflammation may trigger onset of beta cell autoimmunity. Mechanistically, inflammatory cytokines and reactive oxygen species in pancreatic tissue may trigger post-

translational protein modifications of beta cell antigens that alter the immunogenicity of these antigens, thereby increasing the risk for loss of self-tolerance (30). To this point, investigators in Europe have recently identified an increased prevalence of beta cell autoimmunity in patients with cystic fibrosis (CF) who develop CF related diabetes (CFRD), a different form of pancreatogenic diabetes. Onset of CFRD occurred at a younger age in patients with beta cell autoantibodies (31). Glutamic acid decarboxylase antibodies have also been reported in a subset of patients with CP but without DM during evaluation for TPIAT (32). Nearly one-fourth of children with DM had hypertriglyceridemia, which is one component of metabolic syndrome and associated with insulin resistance (33, 34). In the setting of metabolic syndrome, loss of functional beta cell mass could increase the risk for progression to DM in individuals with insulin resistance as they are no longer able to compensate for insulin resistance by increasing insulin secretion. In our cohort, overweight and obesity by BMI percentile was not different in children with or without DM, in contrast to recent data in adults in the North American Pancreatitis Study cohort, in which odds for DM in those with CP was significantly increased in the setting of obesity (8). While the greater prevalence of hypertriglyceridemia could be a manifestation of metabolic syndrome in the DM group, an alternative explanation is that DM, particularly if poorly controlled, increases the risk for hyperlipidemia (35). We lack data in our cohort that show whether hypertriglyceridemia preceded the onset of DM or vice versa.

We did not find an association of DM with *PRSS1* gene mutations, despite a high lifetime risk of DM in hereditary pancreatitis, but prior case series suggest a much older median age of onset (37–51 years). (6, 7). Thus, presumably our children with *PRSS1* mutations in this series remain at high lifetime risk for development of DM, but onset is more often in adulthood.

While this represents the largest and only multi-center international cohort to describe DM in children with ARP and CP, our findings are based on a relatively small number of children with DM and intended to generate hypothesis for future studies. In this retrospective registry, we considered the potential associations of many patient and disease variables with development of DM. As noted in the methodology, because of the multiple variables explored, we intentionally did not present p-values in our statistical approach for DM risk factors. The findings in this preliminary report should be considered exploratory and require confirmation in future studies. However, we suggest these putative risk factors, including beta cell autoimmunity and hypertriglyceridemia, should be considered in future biorepository or clinical studies.

Longitudinal studies will be needed to define who is at risk for progression to DM among children with ARP and CP. In addition, our analyses rely upon physician report and patient report from standard clinical care. Hypertriglyceridemia was defined by triglyceride levels above the upper limit of normal for the reference lab, so while this is a metabolic abnormality, mild elevations can increase pancreatitis risk (36). In the ARP cohort, it is possible that some patients have progressed to CP not yet evident on imaging, and we lack data on severity of AP; necrotic episodes of AP, although rare in children, may convey a higher risk of DM due to loss of pancreatic parenchyma (37). Likewise, we do not have data on whether HbA1c and fasting glucose were measured in the non-DM group and cannot

entirely exclude mild undiagnosed DM in the non-DM controls, introducing risk for selection bias. Not all children with DM were tested for beta cell autoimmunity. Because of the clinical nature of the testing, in those who were tested we lack details on which antibodies and how many antibodies were positive.

In conclusion, we report a higher prevalence of DM than expected in the general population in youth with ARP or CP, with 6% of children with ARP or CP also diagnosed with DM. Children with DM more often have pancreatic atrophy, but also show evidence of beta cell autoimmunity and hypertriglyceridemia, suggesting that risk factors for Type 1 and Type 2 DM, respectively, may play a role in mediating DM development in this cohort of children with pancreatitis and warrant further investigation.

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Conflicts of Interest: Dr. Mark Lowe is on the Board of Directors of the National Pancreas Foundation; receives royalties from Millipore Inc and UpToDate. Drs. Tanja Gonska and Michael Wilschanski received a research grant from Vertex Pharmaceuticals. Dr. Sohail Husain owns equity in PrevCon. Dr. John Pohl is on the speaker's bureau for Medical Education Resources, Inc.; Dr. Melena Bellin has served as a consultant for AbbVie Inc, NovoNordisk, and ARIEL Precision Medicine, and receives research funding from ViaCyte. Dr. Aliye 4 Uc is a member of American Board of Pediatrics, Subboard of Pediatric Gastroenterology. The other authors declare no conflicts of interest.

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WHAT IS KNOWN

- Adults with chronic pancreatitis (CP) and acute recurrent pancreatitis (ARP) are at high risk for developing diabetes mellitus (DM).

- Little is known regarding risk of and risk factors for DM in children with CP and ARP.

WHAT IS NEW

- The INSPPIRE registry is the first multi-center, international study to explore diabetes risk in a geographically diverse cohort of children with ARP and CP. We observed a 6% prevalence of DM, about 30-fold higher than expected in the general pediatric population.

- DM may be common in children with other features of autoimmunity or with hyperlipidemia, suggesting risk features of type 1 or type 2 diabetes warrant future investigation in this population.

Table 1:

Demographics of the study population

Variables	Diabetes=Yes (n=24)	Diabetes=No (n=373)	OR or Mean Difference (95% CI)
Female, No. (%)	16 (67%)	211 (57%)	1.53 (0.64, 3.68)[a]
	(n=23)	(n=351)	
Ethnicity (Hispanic)	8 (35%)	87 (25%)	1.62 (0.66, 3.95)[a]
Race	(n=20)	(n=330)	
White	16 (80%)	268 (81%)	0.93 (0.28, 3.94)[b]
African American	2 (10%)	9 (3%)	
Asian	0 (0%)	19 (6%)	
Multi-racial	1 (5%)	25 (8%)	
Other	1 (5%)	9 (3%)	
Age at enrollment, years	(n=23)	(n=366)	
Mean±SD	14.7±3.0	11.4±4.6	**3.3 (1.9, 4.6)**[c]
Age at first diagnosis AP [*]	(n=23)	(n=342)	
Mean±SD	12.9±2.6	8.7±4.7	**4.2 (3.0, 5.4)**[c]
With CP	9 (38%)	150 (40%)	
Age at diagnosis of CP	(n=7)	(n=132)	
Mean±SD	14.2±2.4	9.9±4.4	4.3 (1.0, 7.5)[c]
Time from AP to CP, years [**]	(n=20)	(n=333)	Hazard Ratio
Median (25th-75th percentile)	4.80 (4.41-5.50)	4.48 (0.95-14.25)	0.78 (0.34, 1.77)
BMI (percentile)	(n=23)	(n=355)	
Underweight (<5)	0 (0%)	19 (5%)	
Normal (5-<85)	12 (52%)	195 (55%)	
Overweight (85-<95)	5 (22%)	65 (18%)	
Obese (≥95)	6 (26%)	76 (21%)	1.39 (0.60, 3.24)[d]

Abbreviations: AP, acute pancreatitis; BMI, body mass index; CP, chronic pancreatitis; OR, odds ratio

[*]
Of those who had an acute pancreatitis attack, 23 in Diabetes and 354 in no Diabetes (12 with missing age data)

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[**] median time from Kaplan-Meier curve, with no CP considered as censored with duration of disease as follow-up time

[a] Value is expressed as OR (95% CI) of Diabetes

[b] Value is expressed as OR (95% CI) of Diabetes for White

[c] Value is expressed as mean difference (95% CI) for Diabetes minus No Diabetes

[d] Value is expressed as OR (95% CI) of Diabetes for Overweight/Obese

Table 2:

Risk factors for ARP and CP

Variables	Diabetes=Yes (n=24)	Diabetes=No (n=373)	OR (95% CI) of Diabetes
Family history			
Acute pancreatitis, No./sample size[a] (%)	6/22 (27%)	84/315 (27%)	1.03 (0.39, 2.72)
Chronic pancreatitis	1/20 (5%)	67/319 (21%)	0.20 (0.00, 1.29)
Genetic Risk Factors:			
PRSS1	1/17 (6%)	62/252 (25%)	0.19 (0.00, 1.29)
SPINK1	1/15 (6%)	47/233 (20%)	0.28 (0.01, 1.96)
CFTR	5/18 (28%)	78/253 (31%)	0.86 (0.30, 2.50)
CTRC	1/13 (8%)	12/158 (8%)	1.01 (0.02, 8.06)
Obstructive factors	8 (33%)	114/368 (31%)	1.11 (0.46, 2.68)
Pancreas divisum	3/22 (14%)	38/361 (11%)	1.34 (0.24, 4.88)
Sphincter of Oddi disorders	1/22 (5%)	8/353 (2%)	2.05 (0.04, 16.55)
Gallstones	0/23 (0%)	20/361 (6%)	0.00 (0.00, 2.56)
Pancreatic duct mal-union	0/22 (0%)	15/362 (4%)	0.00 (0.00, 3.72)
Post-traumatic pancreatic stricture	0/23 (0%)	2/362 (1%)	0.00 (0.00, 55.50)
Preampullary duodenal diverticulum	0/22 (0%)	1/364 (0.3%)	0.00 (0.00, 314.36)
Duct obstruction	0/23 (0%)	9/364 (2%)	0.00 (0.00, 6.45)
Annular pancreas	1/22 (5%)	2/365 (1%)	8.64 (0.14, 170.00)
Choledochal cyst	0/23 (0%)	10/366 (3%)	0.00 (0.00, 5.73)
Toxic/Metabolic	8/23 (35%)	89/346 (26%)	1.54 (0.63, 3.76)
Alcoholic	0/23 (0%)	7/372 (2%)	0.00 (0.00, 8.93)
Active/Passive smoking exposure	3/21 (14%)	32/354 (9%)	1.68 (0.30, 6.21)
Hyperlipidemia (above normal limits)	5/22 (23%)	17/318 (5%)	**5.21 (1.33, 17.05)**
Medications	2/22 (9%)	37/335 (11%)	0.80 (0.09, 3.54)
Autoimmune pancreatitis	1/20 (5%)	10/289 (3%)	1.47 (0.03, 11.34)
Other autoimmune diseases *	4 (17%)	17/352 (5%)	3.94 (0.88, 13.65)

*
Includes Chron's disease, ulcerative colitis, indeterminate colitis IBD-U, hepatitis, and other autoimmune diseases

[a]
The differences in sample sizes between rows reflect available data for these parameters

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Table 3:

Imaging features of pancreatitis

Variables	Diabetes=Yes (n=24)	Diabetes=No (n=373)	OR (95% CI) of Diabetes
Imaging studies performed			
ERCP	7 (29%)	153 (41%)	0.59 (0.24, 1.46)
CT scan	10 (42%)	164 (44%)	0.91 (0.39, 2.10)
MRI	11 (46%)	249 (67%)	**0.42 (0.18, 0.97)**
MRCP	15 (63%)	278 (75%)	0.57 (0.24, 1.34)
EUS	0 (0%)	38 (10%)	0.00 (0.00, 1.22)
Findings (CT/MRI)			
Focal Acute Pancreatitis	3/15 (20%)	43/220 (16%)	1.28 (0.22, 5.02)
Inflammatory changes in Pancreas	6/15 (40%)	98/298 (37%)	1.14 (0.39, 3.31)
Pancreatic Gland Enlargement	5/15 (33%)	69/267 (26%)	1.43 (0.37, 4.80)
Pancreatic Atrophy Present	8/16 (50%)	58/269 (22%)	**3.64 (1.13, 11.59)**
Calcifications in Pancreas present	1/15 (7%)	22/268 (8%)	0.80 (0.02, 5.75)
Duct Irregularities	2/16 (12%)	92/267 (34%)	0.27 (0.06, 1.22)
Pancreatic duct dilatation present	3/16 (19%)	97/268 (36%)	0.41 (0.11, 1.46)
Lesions present in the pancreas	0/16 (0%)	9/272 (3%)	0.00 (0.00, 7.04)
Gallstones/Sludge	1/16 (6%)	23/266 (9%)	0.70 (0.02, 5.01)
Intrahepatic biliary dilatation	1/16 (6%)	27/269 (10%)	0.60 (0.01, 4.20)
Changes suggestive of cirrhosis and/or portal hypertension	2/16 (12%)	17/266 (6%)	2.09 (0.21, 10.33)
Findings (CT/MRI/ MRCP/ ERCP)			
Pancreatic duct obstruction (stricture)	1/22 (5%)	63/321 (20%)	0.20 (0.00, 1.26)
CBD stricture (Intrapancreatic portion)	0/22 (0%)	17/334 (5%)	0.00 (0.00, 2.97)
Dilated CBD	5/22 (23%)	49/336 (15%)	1.72 (0.47, 5.15)
CBD Stone	0/22 (0%)	20/337 (6%)	0.00 (0.00, 2.49)
Findings (CT/MRI/EUS)			
Peripancreatic inflammation/fat stranding	7/15 (47%)	90/274 (33%)	1.79 (0.63, 5.09)
Findings (CT/MRI/MRCP/ ERCP /EUS)			
Cysts/Pseudocysts	4/22 (18%)	50/338 (15%)	1.28 (0.30, 4.11)
Findings (MRCP/ERCP)			
Main Pancreatic Duct - Abnormal	7/18 (39%)	149/291 (51%)	0.61 (0.23, 1.61)

Variables	Diabetes=Yes (n=24)	Diabetes=No (n=373)	OR (95% CI) of Diabetes
Abnormal Side Branches	4/16 (25%)	76/284 (27%)	0.91 (0.21, 3.13)
Intraductal filling defects of Calculi	2/16 (12%)	54/290 (19%)	0.62 (0.07, 2.85)

ERCP= Endoscopic retrograde cholangiopancreatography; CT = Computed tomography; MRI= Magnetic resonance imaging; MRCP= Magnetic resonance cholangiopancreatography; EUS= Endoscopic ultrasound;

Table 4:

Treatments administered for pancreatitis

Variables	Diabetes=Yes (n=24)	Diabetes=No (n=373)	OR (95% CI) of Diabetes
Medications (from provider response)			
Pain medications	4/17 (24%)	94/279 (34%)	0.61 (0.19, 1.91)
Medical therapies	11/23 (48%)	150/371 (40%)	1.35 (0.58, 3.14)
Pancreatic enzymes	9/23 (39%)	121/371 (33%)	1.33 (0.56, 3.15)
PERT for pain or recurrent pancreatitis	9/23 (39%)	103/365 (28%)	1.64 (0.69, 3.89)
Vitamins/anti-oxidants	1/22 (5%)	28/363 (8%)	0.57 (0.01, 3.83)
Steroids	1/22 (5%)	7/359 (2%)	2.39 (0.05, 20.05)
Octreotide	0/22 (0%)	6/365 (2%)	0.00 (0.00, 11.12)
Medical PPI	6/19 (32%)	52/307 (17%)	2.26 (0.67, 6.73)
Medications (from patient response)			
Pain medications	8/23 (35%)	140/342 (41%)	0.77 (0.32, 1.86)
Pancreatic enzymes	8/23 (35%)	95/341 (28%)	1.38 (0.57, 3.36)
Vitamins/anti-oxidants	10/22 (45%)	131/344 (38%)	1.36 (0.57, 3.22)
Steroids	0/23 (0%)	9/346 (3%)	0.00 (0.00, 6.12)
Medication helpful in treating pancreatitis			
(from patient response of those using medication)			
Pain medications helpful	5/7 (71%)	91/107 (85%)	0.44 (0.07, 5.04)
Pancreatic enzymes helpful	2/2 (100%)	46/51 (90%)	--
Vitamins/anti-oxidants helpful	0/4 (0%)	13/55 (24%)	0.00 (0.00, 4.00)
Steroids helpful	--	2/2 (100%)	--
Procedures			
Any ERCP	7/21 (33%)	141/369 (38%)	0.81 (0.32, 2.05)
Biliary sphincterotomy	2/21 (10%)	51/364 (14%)	0.65 (0.07, 2.81)
Pancreatic sphincterotomy	5/21 (24%)	83/365 (23%)	1.06 (0.30, 3.15)
Pancreatic duct stent	3/21 (14%)	66/365 (18%)	0.76 (0.14, 2.70)
Biliary stent	0/21 (0%)	10/366 (3%)	0.00 (0.00, 6.30)
Pancreatic duct stone removal	1/21 (5%)	40/366 (11%)	0.41 (0.01, 2.69)
Surgeries			

Variables	Diabetes=Yes (n=24)	Diabetes=No (n=373)	OR (95% CI) of Diabetes
Surgical therapies	3/23 (13%)	57/373 (15%)	0.83 (0.15, 2.94)
Cholecystectomy	2/23 (9%)	35/372 (9%)	0.92 (0.10, 4.02)
Celiac nerve block	0/23 (0%)	1/372 (0.3%)	0.00 (0.00, 307.3)
Cyst/pseudo-cyst operation	1/23 (4%)	12/372 (3%)	1.36 (0.03, 10.03)
Lateral pancreaticojejunostomy	0/23 (0%)	14/372 (4%)	0.00 (0.00, 3.95)
Partial pancreatectomy	0/23 (0%)	1/372 (0.3%)	0.00 (0.00, 307.3)

Table 5:

Burden of disease in patients ARP and CP with and without DM

Variables	Diabetes=Yes (n=24)	Diabetes=No (n=373)	OR or Median Difference (95% CI)
Pattern of abdominal pain	(n=22)	(n=345)	
0) no abdominal pain	2 (9%)	42 (12%)	
1) usually pain free; episodes of mild-moderate pain	3 (14%)	54 (16%)	
2) constant mild-moderate pain	1 (5%)	17 (5%)	
3) usually pain free; episodes of severe pain	3 (14%)	127 (37%)	
4) constant mild-moderate pain+ episodes of severe pain	8 (36%)	86 (25%)	
5) constant severe pain	5 (23%)	19 (6%)	**5.05 (1.30, 16.27)**[a]
Constant Pain score	(n=22)	(n=327)	
Median (IQR)	0 (0–54)	0 (0–0)	
Range	0–100	0–100	
With any level of constant pain	10 (45%)	71 (22%)	**3.00 (1.25, 7.24)**[b]
Episodic Pain score	(n=21)	(n=314)	
Median (IQR)	56 (38–88)	61 (3–80)	−5 (−28, 18)[c]
Range	0–100	0–100	
With any level of episodic pain	17 (81%)	237 (75%)	
Number of ER visits, lifelong (average */yr)	(n=12)	(n=191)	
Median (IQR)	2.2 (0.9–4.6)	1.2 (0.3–2.4)	1.0 (−1.0, 3.0)[c]
Range	0–13.9	0–14.9	
Number of ER visits, past year	(n=19)	(n=326)	
Median (IQR)	2 (1–3)	2 (0–3)	0 (−0.7, 0.7)[c]
Range	0–4	0–30	
Number of hospitalizations, lifelong (average */yr)	(n=13)	(n=193)	
Median (IQR)	2.0 (0.9–4.1)	1.0 (0.4–2.0)	1.0 (−1.0, 2.9)[c]
Range	0–13.9	0–14.9	
Number of hospitalizations, past year	(n=19)	(n=330)	
Median (IQR)	2 (1–2)	1 (0–2)	1.0 (0.3, 1.7)[c]

Variables	Diabetes=Yes (n=24)	Diabetes=No (n=373)	OR or Median Difference (95% CI)
Range	0–4	0–23	
Days missed school past month	(n=20)	(n=275)	
Median (IQR)	2 (0–5.5)	1 (0–6)	1.0 (−1.8, 3.8)[c]
Range	0–22	0–45	
Abdominal pain related to pancreatitis	17/21 (81%)	290/361 (80%)	1.04 (0.33, 4.38)[d]
Exocrine insufficiency	8/22 (36%)	59/349 (17%)	2.81 (0.97, 7.54)[d]
Number of attacks (attacks/yr) –parent response	(n=20)	(n=257)	
Median (IQR)	1.9 (0.9–3.5)	1.5 (0.8–2.8)	0.4 (−0.8, 1.6)[c]
Range	0–13.9	0–27.3	

*
average lifelong events per year was computed for those that had condition for ≥1yr

[a]Value is expressed as OR (95% CI) for constant severe pain

[b]Value is expressed as OR (95% CI) for any pain

[c]Value is expressed as median difference (95% CI) for Diabetes minus No Diabetes

[d]Value is expressed as OR (95% CI)