

Diabetes mellitus as a consequence of acute severe pancreatitis: Unraveling the mystery

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Specialty type: Endocrinology and metabolism

Provenance and peer review:
Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Aslam M, India;
Gornik I, Croatia; Xiao B, China;
Islam MS, South Africa

Received: March 28, 2023

Peer-review started: March 28, 2023

First decision: April 26, 2023

Revised: May 19, 2023

Accepted: July 6, 2023

Article in press: July 6, 2023

Published online: August 15, 2023



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Abstract

The occurrence of diabetes mellitus (DM) in pancreatitis is being increasingly recognized lately. Diabetes can develop not only with chronic pancreatitis but even after the first episode of acute pancreatitis (AP). The incidence of diabetes after AP varies from 18% to 23% in 3 years and reaches up to 40% over 5 years. The exact pathogenesis of diabetes after AP is poorly understood and various mechanisms proposed include loss of islet cell mass, AP-induced autoimmunity, and alterations in the insulin incretin axis. Risk factors associated with increased risk of diabetes includes male sex, recurrent attacks of pancreatitis, presence of pancreatic exocrine insufficiency and level of pancreatic necrosis. Diagnosis of post-pancreatitis DM (PPDM) is often excluded. Treatment includes a trial of oral antidiabetic drugs in mild diabetes. Often, insulin is required in uncontrolled diabetes. Given the lack of awareness of this metabolic disorder after AP, this review will evaluate current information on epidemiology, risk factors, diagnosis and management of PPDM and identify the knowledge gaps.

Key Words: Post-pancreatitis diabetes; Diabetes of exogenous pancreas; Endocrine insufficiency; Acute pancreatitis; Post-pancreatitis diabetes mellitus

Core Tip: Diabetes mellitus (DM) due to diseases of the exocrine pancreas, diabetes of exocrine pancreas (DEP), is a common but underrecognized clinical entity. Post-pancreatitis DM (PPDM), which develop after pancreatitis, is classified as a subtype of DEP. The PPDM can develop even after acute pancreatitis; it is termed as post-acute pancreatitis DM. It differs in pathogenesis and natural history from type 1 and type 2 DM. There is a loss of pancreatic endocrine tissue, fibrosis and a component of autoimmunity. Both insulin deficiency and resistance play a role in this process. There are a number of knowledge gaps in diagnostic criteria, natural history and treatment options of PPDM.

Citation: Manrai M, Singh AK, Birda CL, Shah J, Dutta A, Bhadada SK, Kochhar R. Diabetes mellitus as a consequence of acute severe pancreatitis: Unraveling the mystery. *World J Diabetes* 2023; 14(8): 1212-1225

URL: <https://www.wjgnet.com/1948-9358/full/v14/i8/1212.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v14.i8.1212>

INTRODUCTION

Metabolic abnormalities in, during and after an episode of acute pancreatitis (AP) are frequent. Diabetes mellitus (DM) due to pancreatic diseases is a commonly seen disorder. Earlier, terminologies like ‘pancreatic diabetes’ or ‘pancreatogenic diabetes’ were used to describe diabetes after pancreatic diseases[1,2]. Subsequently, American Diabetes Association (ADA) gave the term ‘type 3c diabetes’ in 2002 which later was abandoned[3,4]. Recently, ADA came up with a unified nomenclature of diabetes of exocrine pancreas which include 3 subtypes: (1) Post-pancreatitis DM (PPDM); (2) Pancreatic cancer-related diabetes; and (3) Cystic fibrosis-related diabetes[5].

Until recently, it was considered that PPDM is associated with chronic pancreatitis only. In 2014, Das *et al*[6] reported in a systematic review that PPDM can develop in pancreatitis patients even after a single episode of AP, identified as post-AP DM (PPDM-A). Subsequently a number of high-quality population-based studies confirmed these findings[7,8]. Despite a number of available studies, PPDM-A remains an under-recognized entity for most physicians, gastroenterologists, surgeons, and endocrinologists. This review consists of diagnostic criteria, epidemiology, pathophysiology, natural course of DM related to AP. We also discuss the predictors, screening recommendations and management of the same.

SPECTRUM OF DYSGLYCEMIA IN PANCREATITIS

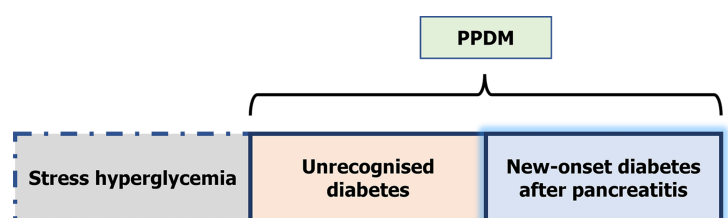
Often, an episode of AP is not limited to a single episode in a number of patients. A systematic review in 2015 looked at this aspect and found that recurrent AP developed in 21% of the patients within 1 year of the initial episode of AP[9]. Also, chronic pancreatitis developed in 36% of patients after recurrent AP. Dysglycemia can develop in any of these subtypes of pancreatitis. It has been suggested that pathophysiological mechanisms of diabetes are different in these extreme forms of pancreatitis. Since there are two main types of pancreatitis *i.e.*, AP and chronic pancreatitis, PPDM is also subdivided into two types: (1) PPDM-A; and (2) post-chronic pancreatitis DM[10].

Irrespective of the type of pancreatitis, dysglycemia could be a manifestation of stress hyperglycemia, unrecognized diabetes or new-onset diabetes after pancreatitis[5] (Figure 1). Stress hyperglycemia is defined as an elevated level of blood glucose, without elevated glycated hemoglobin A1c (HbA1c $\geq 6.5\%$), during the course of pancreatitis and/or within 3 mo after hospital admission in patients without a previous diagnosis of diabetes. This stress hyperglycemia is usually transient, and the elevated levels of blood glucose normalize during the follow up period.

Unrecognized diabetes can be unveiled during an episode of pancreatitis and is defined as elevated glycated HbA1c $\geq 6.5\%$ above the diabetes diagnostic threshold, first detected during the course of pancreatitis and/or within 3 mo after hospital admission[5]. New onset diabetes after pancreatitis (NODAP) acknowledges the metabolic effect of acute or chronic pancreatitis on previously normal glucose homeostasis[5]. The NODAP excludes the diabetic patients diagnosed during the episodes of pancreatitis or up to 3 mo after hospital discharge. PPDM includes patients with diabetes in the setting of pancreatitis irrespective of the timing of diabetes onset (Figure 1). In this review, the DM developing after AP *i.e.*, PPDM-A was focused as a point of discussion.

DIAGNOSTIC CRITERIA OF PPDM-A

The diagnosis of PPDM should be suspected in all patients with a history of pancreatitis and fulfilling the diagnostic criteria for diabetes by the ADA. The diagnosis of PPDM is more of a diagnosis of exclusion, after excluding the more common stress hyperglycemia, type 1 and type 2 diabetes. The diagnosis of PPDM-A is made in patients with first or recurrent episodes of pancreatitis without clinical or imaging features of chronic pancreatitis. Petrov and Yadav[10]



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Figure 1 Spectrum of dysglycemia in pancreatitis. PPDM: Post-pancreatitis diabetes mellitus.

proposed a stepwise and practical algorithm for diagnosing PPDM[10] (Figure 2).

EPIDEMIOLOGY

The global incidence of AP 34 cases/100000 of population based on pooled incidence[10,11]. Of these 6 cases/100000 will develop PPDM-A[10]. The course in AP can be mild, moderately severe, or severe which dictates duration of hospitalization and long-term sequelae. More than 80% of patients have a mild course with a hospitalization required for less than a week, while those with moderate to severe AP experience pancreatic necrosis and a protracted hospital course[12]. Long-term sequelae of AP include exocrine pancreatic insufficiency, complications related to pancreatic necrotic collections, and recurrent attacks of AP in up to 21% patients[13,14].

During hospitalization, hyperglycemia could be seen in up to 51% of patients during AP. Hyperglycemia in the early phase may arise from multiple mechanisms such as uncontrolled pre-existing DM, damage to endocrine pancreas or metabolic stress of critical illness[15]. Hyperglycemia is usually considered as a transient complication of AP. However, two recent meta-analyses have revealed the high incidence of AP related to DM observing that approximately 18%-23% patients of AP will develop DM within three years of discharge[6,16]. However, in longitudinal studies with more than five years of follow-up, the cumulative incidence rate of PPDM-A is up to 40%[16]. Moreover, the precise time of onset of pancreatic endocrine dysfunction cannot be determined. Some studies have demonstrated resolution while others have revealed persistence of endocrine dysfunction[7,17]. To summarize, post pancreatitis endocrine dysfunction is common, however it may be reversible in some cases.

PATHOPHYSIOLOGY

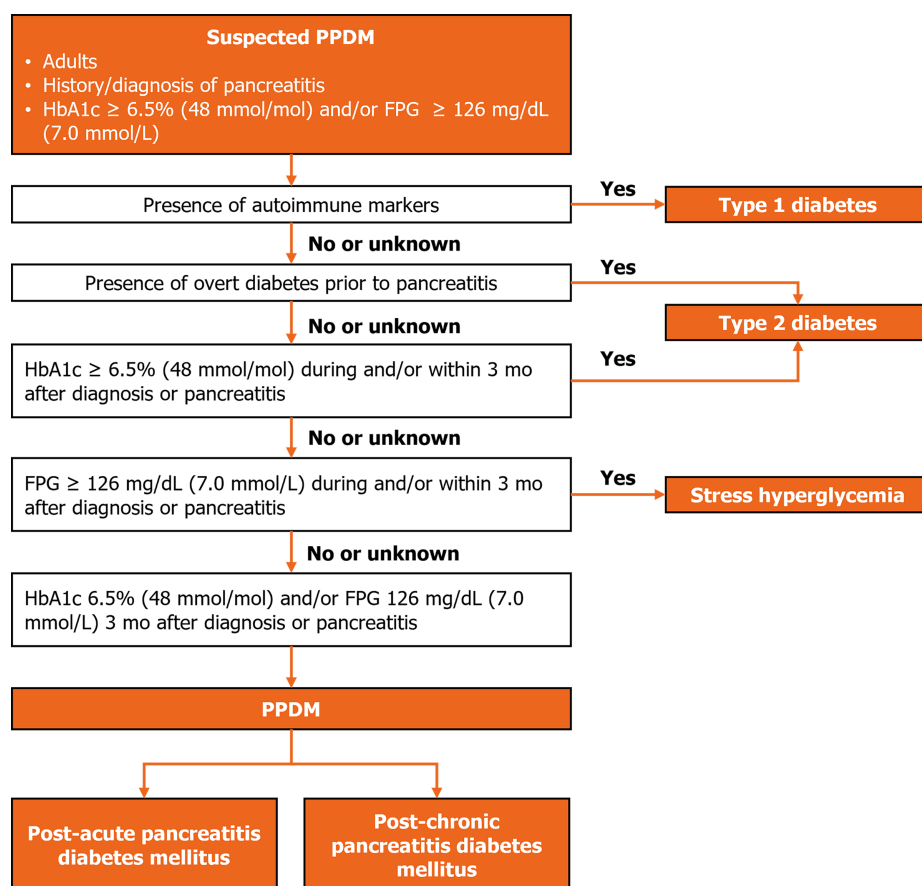
The exact mechanism of PPDM-A is poorly understood. However various mechanisms have been proposed which may lead to diabetes due to loss of islet cell mass, AP induced autoimmunity, alterations in insulin incretin axis and common risk factors. In patients with acute necrotizing pancreatitis, the loss of beta cell of islets of Langerhans leads to insulin deficiency resulting in DM. As a result of pancreatic necrosis, reduction or loss in the production and secretion of insulin as well as other islet hormones is expected. Since, a subset of patients with non-necrotizing AP also develop DM during short-term follow up, the pathophysiology of PPDM seems to be dependent on multiple factors other than immediate loss of islets secondary to necrosis of pancreatitis tissue[16]. It has been observed that the insulin requirements in PPDM-A are akin to type 1 diabetes. Hence, the role of autoimmunity is considered as an important factor in this process. In patients with type 1 diabetes, autoantibodies like glutamic acid decarboxylase (70%-80%), insulin associated antibodies, insulinoma associated autoantigen 2, zinc transporter, and/or tetraspanin 7 cause immune mediated beta cell destruction. There is a possibility that post-pancreatitis there could be immune activation, which though is less clearly defined, which destroys β -cells in pancreas. Some reports have also demonstrated generation of β -cell autoantibody in patients with PPDM-A[18]. However, no available study has evaluated the frequency of autoimmunity following an episode of AP.

The AP and type 2 DM share common risk factors like obesity and hypertriglyceridemia. These factors are independently associated with an increased risk for severe pancreatitis which may partly explain PPDM-A[19,20]. The prevalence of obesity is seen in 42% cases of PPDM-A while in type 2 diabetes obesity is seen in 48% cases supporting the evidence of obesity as a high risk for DM after an episode of AP[21]. Although similar data are not available for hypertriglyceridemia, these factors are likely to contribute towards the development of PPDM-A[22].

Pancreatic exocrine insufficiency may occur in up to 30% of the patients within three years of an episode of AP[23]. In such patients, the incretin-insulin axis is disrupted leading to insufficient incretin hormone production. This leads to reduce secretion of incretin hormones, glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1, and subsequently leads to PPDM-A[24].

NATURAL HISTORY

In the past, several studies ranging from single center studies to systematic reviews and meta-analyses, had looked at the



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Figure 2 Diagnostic algorithm to identify post-pancreatitis diabetes mellitus. PPDM: Post-pancreatitis diabetes mellitus; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c.

development of PPDM-A. A recent systematic review by Zhi *et al*[16] revealed that the incidence of new-onset DM post-AP on follow up was 23% overall. The authors also found that patients with severe pancreatitis had higher incidence of DM as compared to mild AP (39% *vs* 14%). In addition, they found that alcohol related pancreatitis had higher incidence of PPDM-A as compared to biliary pancreatitis (28% *vs* 12%). In a previous systematic review by Das *et al*[6] a similar incidence of PPDM-A was noted. It was also seen that the risk of diabetes increased two-fold at 5 years as compared to 12 mo, on follow up. A few studies have shown higher incidence ranging from 37% to 60.2%[7-10] while others have shown lower incidence, from 10.9% to 22.5%[7,17].

The etiology, severity and degree of pancreatic necrosis are considered important risk factors for development of PPDM-A[16]. In theory, it is believed that the extent of pancreatic necrosis determines the development of PPDM-A, even though some studies have found no association between post-pancreatitis diabetes and severity of pancreatitis[12,13,25-27]. These studies conjecture other mechanisms like autoimmunity and development of insulin resistance leading to PPDM-A. However, most studies have shown a strong association between severity of pancreatitis, extent of pancreatic necrosis and development of diabetes[16,25,27]. Vipperla *et al*[27] considered the risk of new-onset diabetes as determined by severity of AP. They derived the results from the general population and calculated the risk of new-onset diabetes after mild AP as 7%-15% and 30%-50% after severe or necrotizing pancreatitis over a period of 3 to 5 years[27]. The extent of necrosis and number of functionally active beta cells were considered major determinants for development of diabetes. Table 1 summarizes all the studies examined the endocrine insufficiency after AP episodes[8,17,25-60].

RISK FACTORS FOR DM AFTER AP

Sex difference

A population-based study from Taiwan confirmed higher risk of PPDM-A in both men and women. The risk was significantly more for males [adjusted hazard ratio (aHR) = 3.21; 95% confidence interval (CI): 2.59-3.98] compared to females (aHR = 1.58, 95%CI: 1.14-2.20)[8]. The COSMOS study also identified higher prevalence of PPDM-A in men (1.32 per 1000 general population) compared to women (0.93 per 1000 general population)[61]. Other population-based studies also demonstrated similar results with higher incidence of PPDM-A among men[62,63].

Table 1 Summaries all the studies examining endocrine insufficiency after episode of acute pancreatitis

Ref.	Study design	Number of patients evaluated for endocrine function	Severity of AP	Etiology of pancreatitis	Follow up period	Test to diagnose endocrine function	Pre-diabetic (%)	Diabetes (%)	Insulin treatment (%)	Comment
Ohlsén <i>et al</i> [28], 1968, Sweden	Prospective case control	23	-	-	Not stated	IV GTT, glucose infusion test	4 (17)	0 (0)	0 (0)	-
Johansen and Ornshtot[29], 1972, Denmark	Prospective cohort	22	-	Alcohol 4 (18%). Biliary 11 (50%). Others 3 (14%). Idiopathic 4 (18%)	24	OGTT	0 (0)	4 (18)	-	-
Olszewski <i>et al</i> [30], 1978, Poland	Prospective case control	25	-	-	12	OGTT, BI	-	7 (28)	-	-
Seligson <i>et al</i> [31], 1982, Sweden	Prospective cohort	9	All severe	-	63	OGTT	3 (33)	2 (22)	-	-
Angelini <i>et al</i> [32], 1984, Italy	Prospective cohort	19	All severe	-	25	OGTT	7 (36)	2 (10.5)	-	-
Eriksson <i>et al</i> [33], 1992, Finland	Prospective cohort	36	Mild: 16 (44%). Severe: 20 (56%)	Alcohol: 28 (78%). Biliary: 2 (6%). Post-ERCP: 2 (6%). Idiopathic: 4 (10%)	74	OGTT	4 (11)	19 (53)	9 (25)	Diabetes was more in surgical necrosectomy compared to conservative approach (100% vs 26%, $P = 0.0004$)
Doepel <i>et al</i> [34], 1993, Finland	Prospective cohort	37	All severe	Alcohol: 28 (76%). Biliary: 3 (8%). Post-ERCP: 2 (5%). Idiopathic: 4 (11%)	74	BG, C-peptide, HbA1c, OGTT	-	20 (54)	9 (45)	Diabetes was more in surgical necrosectomy compared to no necrosectomy (100% vs 29.1%, $P < 0.005$). Diabetes was more common with alcohol related pancreatitis compared to other etiologies (64% vs 22%, $P < 0.05$)
Angelini <i>et al</i> [35], 1993, Italy	Prospective cohort	118	Mild: 35 (30%). Severe: 83 (70%)	-	53	OGTT	-	9 (8)	-	-
Appelros <i>et al</i> [36], 2001, Sweden	Prospective cohort	35	All severe	-	83	Questionnaire, BG, HbA1c	4 (11)	15 (43)	9 (26)	No difference in incidence of diabetes based on etiologies
Malecka-Panas <i>et al</i> [37], 2002, Poland	Prospective cohort	82	Mild: 54 (66%). Severe: 28 (34%)	-	56	OGTT, RIA insulin measurements	2 (2)	15 (16)	6 (7)	-
Ibars <i>et al</i> [17], 2002, Spain	Prospective cohort	55	Mild: 45 (71%). Severe AP 18 (24%)	-	1, 6 and 12	OGTT, arginine test	7 (13)	6 (11)	-	-
Halonon <i>et al</i> [38], 2003, Finland	Prospective cohort	145	All severe	Alcohol: 113 (78%). Others: 32 (22%)	66	Questionnaire	-	68 (47)	-	-
Boreham and	Prospective	23	Mild: 16 (70%).	-	3	FBG	-	4 (17)	1 (4)	-

Ammori[39], 2003, United Kingdom	cohort		Severe: 7 (30%)								
Szentkereszty <i>et al</i> [40], 2004, Hungary	Prospective cohort	22	All severe	-	38	Questionnaire	-	3 (14)	-	-	
Sabater <i>et al</i> [41], 2004, Spain	Prospective cohort	27	All severe	-	12	Cardinal symptoms identification, 2 basal BG, OGTT in patients with lower BG	-	-	4 (15)	-	
Hochman <i>et al</i> [42], 2006, Canada	Prospective cohort	25	All severe	Alcohol: 4 (16%). Biliary: 12 (48%). HTG: 2 (8%). Idiopathic: 7 (28%)	24 and 36	Questionnaire	-	8 (19)	5 (20)	-	
Symersky <i>et al</i> [43], 2006, Netherland	Prospective cohort	34	Mild: 22 (65%). Severe: 12 (35%)	-	55	OGTT	-	-	3 (9)		Endocrine insufficiency develops independent of severity of AP
Kaya <i>et al</i> [44], 2007, Turkey	Prospective cohort	112	Mild: 136 (68%). Severe: 63 (32%)	-	12	OGTT	27 (24)	13 (21)	-		No association between endocrine insufficiency and necrosis or disease severity
Yasuda <i>et al</i> [45], 2008, Japan	Prospective cohort	41	All severe	-	56	FBG	-	16 (39)	4 (9)		No difference in etiology, presence of necrosis or alcohol intake among development of diabetes <i>vs</i> no diabetes
Pelli <i>et al</i> [46], 2009, Finland	Prospective cohort	46	Mild: 41 (76%). Severe: 13 (24%)	-	23 (median)	FBG, plasma HbA, OGTT	12 (20.1)	5 (10.8)	-	-	
Gupta <i>et al</i> [47], 2009, India	Prospective cohort	30	All severe	Alcohol: 10 (33.3%). Biliary: 12 (40%). Alcohol + biliary 3 (10%). Idiopathic 5 (16.6%)	31	FBG, postprandial sugar level, OGTT, fasting serum C-peptide	6 (20)	6 (20)	6 (100)		No effect of etiology of pancreatitis on the incidence of endocrine insufficiency
Andersson <i>et al</i> [48], 2010, Sweden	Prospective cohort	39	Mild: 26 (65%). Severe: 14 (35%)	-	45	FBG, C-peptide, insulin, OGTT	13 (33)	9 (23)	-	-	
Uomo <i>et al</i> [49], 2010, Italy	Prospective cohort	38	All severe	Alcohol 0 (0%). Others: 38 (100%)	179	FBG, OGTT	-	6 (16)	-		No relationship between extent of pancreatic necrosis and endocrine insufficiency
Wu <i>et al</i> [50], 2011, China	Prospective case control	59	Mild: 24 (41%). Severe: 35 (59%)	Gallstone 42 (71%). Hyperlipemia 7 (12%). Alcoholic 7 (12%). Idiopathic 3 (5%)	42	FBG, HbA1c, FBI, C-peptide, HOMA	14 (23.7)	5 (8)	-		Possible risk factors for endocrine dysfunction were pancreatic surgery, pancreatic necrosis, family history of diabetes, obesity, alcohol abuse, smoking and hyperlipidemia
Garip <i>et al</i> [51], 2013, Turkey	Retrospective cohort	96	-	-	32	OGTT	5 (5.2)	33 (43)	-		Severe disease and necrosis was associated with development of new onset diabetes
Vujasinovic <i>et al</i> [52], 2014, Slovenia	Retrospective cohort	100	Mild: 67 (67%). Moderate: 15 (15%). Severe: 18 (18%)	Alcohol: 42 (42%). Biliary: 36 (36%). Idiopathic: 12 (12%). Others: 10 (10%)	32	OGTT, HbA1c	-	14 (14)	-		Severe disease was associated with development of diabetes

Ho <i>et al</i> [53], 2015, Taiwan	Retrospective population-based database study	12284	Mild: 11519 (93.8%). Severe: 665 (6.2%)	Biliary: 6556 (53.3%). Alcohol: 5728 (46.7%)	-	ICD-9-CM code for diabetes	-	618 (5)	-	Alcohol associated AP and ≥ 2 admissions for AP were predictors of new onset diabetes mellitus
Chandrasekaran <i>et al</i> [54], 2015, India	Prospective cohort study	35	All severe	Alcohol: 19. Gallstone: 11. Idiopathic: 5	26.6	OGTT	-	17 (48.5)	12 (34.3)	-
Winter Gasparoto <i>et al</i> [55], 2015	Retrospective cohort study	16	-	Biliary: 10 (62.5%). Alcohol: 4 (25.0%). HTG: 2 (12.5%)	34.8	OGTT, C-peptide, HOMA (homeostasis model assessment)	7 (43.7)	5 (31)	-	-
Yuan <i>et al</i> [56], 2017, China	Retrospective cohort study	310	Mild: 261 (84.19). Moderate: 39 (12.58). Severe: 10 (3.23)	Biliary: 153 (49.35). Hyperlipidemia: 32 (10.32). Alcohol: 15 (4.84). Others: 110 (35.48)	-	FBG	34 (11)	35 (11.3)	-	Hyperlipidemia and fatty liver were predictors of abnormal FBG. Abnormal FBG was not different between alcohol and biliary pancreatitis
Lee <i>et al</i> [8], 2016, Taiwan	Retrospective population-based database study	3187	Mild: 2932 (92%). Severe: 255 (8%)	-	-	ICD-9-CM code for diabetes	-	324	-	-
Umapathy <i>et al</i> [57], 2016, United States	Retrospective cohort study	73	-	-	3 yr (median)	-	-	33 (45)	-	Risk of endocrine insufficiency was associated with extent of necrosis 2/3 rd develop diabetes during index admission
Vipperla <i>et al</i> [27], 2016, United States	Retrospective cohort study	101	-	-	34.5	WHO criteria of OGTT	-	28 (28)	-	Risk of diabetes increased with severity of disease
Nikkola <i>et al</i> [58], 2017, Finland	Prospective cohort study	47	-	-	126	FBG, OGTT	13 (27.6)	7 (15)	7 (15)	Pancreatogenic diabetes develops in recurrent AP only
Tu <i>et al</i> [26], 2017, China	Prospective cohort study	113	Mild: 10 (8.8%). Moderate: 12 (10.6%). Severe: 91 (80.6%)	Alcohol: 3 (2.7%). Biliary: 65 (57.5%). Hyper TG: 39 (34.5%). Others 6 (5.3%)	42.9	FBG, OGTT	33 (29.2)	34 (30.1)	-	Extent of pancreatic necrosis > 50%, walled-off necrosis and insulin resistance were independent risk factors for new onset diabetes after AP
Tu <i>et al</i> [25], 2018, China	Prospective cohort study	256	Mild: 54 (21.1%). Moderate: 42 (16.4%). Severe: 160 (62.5%)	Alcohol: 7 (2.7%). Gallstone: 147 (57.5%). Hyperlipemia: 88 (34.5%). Others: 14 (5.3%)	42.9	FBG, OGTT	-	154 (60.2)	-	Incidence of pancreatic necrosis was higher in diabetics (64.7% and 53.0%, $P = 0.06$). Necrotic debridement (PCD or surgical necrosectomy) were higher in diabetes (66.3% vs 33.7%, $P = 0.02$)
Phillips <i>et al</i> [59], 2020, United States	Prospective cohort study	186	Mild: 120 (64.5%). Moderate: 40 (21.5%). Severe: 26 (14.0%)	Alcohol: 17 (9.1%). Biliary: 84 (45.2). Idiopathic 26 (16.1%). Post-ERCP 23 (12.4%). Other 17 (9.1%). Hyper TG 15 (8.1%)	12	Questionnaire	-	9 (4.8)	-	-
Man <i>et al</i> [60], 2022, Romania	Prospective cohort study	329	Mild: 117 (35.6%). Moderate: 167 (50.8%). Severe: 45 (13.7%)	Alcohol: 87 (26.4%). Biliary: 217 (66.7%)	1, 3 and 12 mo	FBG, OGTT, HbA1c	-	29 (8.8)	-	Obesity and pancreatic necrosis > 50% were risk factors for new onset diabetes

AP: Acute pancreatitis; GTT: Gestational trophoblastic tumours; OGTT: Oral glucose tolerance test; BI: Blood insulin; ERCP: Endoscopic retrograde cholangiopancreatography; BG: Blood glucose; HbA1c: Hemoglobin A1c; Hemoglobin A1c; RIA: Radioimmunoassay; FBG: Fasting blood glucose; HTG: Hypertriglyceridemia; FBI: Fasting blood insulin; HOMA: Homeostatic model assessment; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; WHO: World Health Organization; TG: Triglycerides.

Age

The risk of PPDM-A is also age dependent, with increased risk of PPDM-A among younger population. A United Kingdom population-based study showed that individuals aged 30-39 [odds ratio (OR): 1.68; 95%CI: 1.20-2.35] and 20-29 (OR = 4.25, 95%CI: 2.58-7.01) and a history of disease of exocrine pancreas had a higher risk of newly diagnosed diabetes compared with general population[62]. Individual with age group between 40-59 years has similar risk of developing PPDM and type 2 DM while those with age 60-79 years had increased risk of type 2 DM than PPDM. Bendor *et al*[61] in a population-based study also noted that individuals with age < 40 years and a history of AP had higher risk of developing DM [adjusted OR (aOR) = 4.65, 95%CI: 2.48-8.72] compared to the general population.

Recurrent attacks of AP

Evidence suggests that the probability of diabetes increases with the number of AP episodes. Lee *et al*[8] in a population-based study analyzed 12284 individuals with initial attack of AP. They found that two or more recurrent attacks of pancreatitis significantly increased the risk of PPDM-A (OR = 1.94, 95%CI: 1.48-2.40). Similarly, COSMOS study found that one recurrence of pancreatitis was not associated with the increased risk of PPDM-A (aHR = 0.93, 95%CI: 0.56-1.52) [61]. However, two (aHR = 1.9, 95%CI: 1.04-3.76) and more recurrences (aHR = 2.77, 95%CI: 1.34-5.72) were associated with significantly increased risk of PPDM-A.

Exocrine pancreatic dysfunction

A number of studies suggest that patients with DM have increased prevalence of exocrine pancreatic insufficiency. However, the reverse was not discovered until recently. Cho *et al*[64] in a national population-based study investigated patients of pancreatitis, both acute and chronic, without a history of both DM and exocrine pancreatic insufficiency. Study revealed that exocrine pancreatic dysfunction was associated with higher risk of PPDM-A (aHR = 2.51, 95%CI: 1.38-4.58). This association was independent of severity and etiology of AP.

Other factors

A number of other factors are shown to be associated with increased risk of PPDM-A. Deposition of intra-pancreatic fat after an episode of pancreatitis is a risk factor for PPDM, independent of obesity or visceral fat[65]. Yuan *et al*[56] identified the presence of hyperlipidemia and fatty liver as predictors of follow-up abnormal fasting blood sugar on Kaplan-Meier analysis with 2.52- and 1.87-fold increased risk, respectively, compared to absence of these conditions.

Etiology of pancreatitis as a risk factor for development of diabetes has been evaluated by a number of studies. Doepel *et al*[34] in a small study identified alcohol as the risk factor for the development of diabetes after severe pancreatitis. Subsequent population-based study by Ho *et al*[53] also found a similar association with alcohol oriented pancreatitis and risk of PPDM-A. Though a number of studies have not found such association with etiology of pancreatitis and risk of PPDM-A[56], a meta-analysis with meta-regression found no evidence to suggest a differential effect of alcohol or gallstone etiology on the risk of PPDM-A[6].

Severity of AP has long been considered as a risk factor of development of PPDM-A. Das *et al*[6] in a meta-analysis identified minimal effect of severity of pancreatitis on the development of PPDM-A. Subsequently, large population-based study by Lee *et al*[8] showed that risk of PPDM-A did not change significantly for mild (aHR = 2.10, 95%CI: 1.92-2.41) and severe disease (aHR = 2.22; 95%CI: 1.50-3.29). These findings were further confirmed in a large population-based study by Shen *et al*[7]. Though, severity of AP has no effect of PPDM-A, the amount of necrosis and requirement of surgical necrosectomy have been identified as predictors of PPDM-A in a number of studies[25-27].

CONCOMITANT ENDOCRINE AND EXOCRINE INSUFFICIENCY

Incidence of endocrine insufficiency varies from 4.8% to 60.2% after the initial episode of AP. Similarly, exocrine insufficiency develops in 0% to 35%[26,49]. Literature on the development of both exocrine and endocrine insufficiency after episodes of AP is limited. Ho *et al*[53] in a nationwide cohort study identified that 3% patients develop both exocrine and endocrine insufficiency after an initial episode of AP. The incidence of both exocrine and endocrine insufficiency was less than the individual endocrine (5%) or exocrine insufficiency (45.7%) after the first episode of AP. The study identified that alcohol-associated AP (OR = 1.804; 95%CI: 1.345-2.263; $P < 0.001$), and ≥ 2 readmissions for AP (OR = 3.190; 95%CI: 2.317-4.063; $P < 0.001$) were independent predictors for development of both exocrine and endocrine insufficiencies after AP. These risks were similar to the risk factors for development of individual endocrine or exocrine insufficiency[53].

Uomo *et al*[49] during long term follow up of AP patients managed non-surgically, found that exocrine insufficiency was temporary in patients with endocrine insufficiency. Huang *et al*[66] also found in the meta-analysis that exocrine insufficiency decreases from 62% to 35% during follow up after AP. These differences in incidences of exocrine insufficiency could be multifactorial and driven by the symptomatic nature, test used for screening, level of pancreatic necrosis during the episode of AP, pancreatic resection during necrosectomy *etc*.

Das *et al*[6] in a meta-analysis evaluated the concomitant development of exocrine and endocrine insufficiency after AP. The pooled prevalence of exocrine and endocrine insufficiency after AP was 29% and 43%, respectively. The prevalence of concomitant pancreatic exocrine insufficiency in newly developed prediabetes/DM was 40%. To summarize, the initial exocrine insufficiency after AP being transient recovers in a majority of patients and concomitant endocrine and exocrine insufficiency develops in 3%-17%.

BIDIRECTIONAL RELATIONSHIP BETWEEN AP AND DIABETES: DM AS A CAUSE OF AP

It is well established that AP can lead to DM, however the reverse is less well studied. Epidemiological studies have reported increased incidence of AP in patients with DM. A United States insurance claims database reported 2.83-fold increased risk of AP in diabetic cohort compared to non-diabetic counterpart[67]. In Taiwan, Lee *et al*[8] reported 1.95-fold higher incidence of AP in diabetics compared to non-diabetics. Same study also reported even higher HR in those who had a history of hyperglycemic episodes so there might be a severity-response relationship[8]. Another study from the United Kingdom reported 1.49-fold higher incidence of AP in patients with type 2 DM[68]. Proposed pathophysiology of increased incidence of AP in DM includes: (1) Chronic hyperglycemia leads to formation of reactive oxygen species, lipid peroxidation and may result in episodes of pancreatitis; (2) Association of comorbid risk factors like obesity, hypertriglyceridemia and gall stone disease which may independently precipitate pancreatitis; (3) Enhanced ryanodine receptor function leading to alteration in calcium metabolism; (4) Certain medications [dipeptidyl peptidase-4 (DPP-4) inhibitors] may enhance AP risk when used for the treatment[8].

Another study has reported structural changes in pancreas in patients with diabetes. Authors found reduced weight and volume of pancreas in patients with type 1 DM, when fibrosis without significant inflammation and ductal changes were observed in autopsy reports. Fecal elastase levels were low in these patients but there were no symptoms of pancreatitis. There were no significant changes in patients with type 2 DM. This study highlighted the complex interplay between exocrine and endocrine pancreas[69]. These studies suggest a bidirectional relationship between DM and AP. More studies are needed for a better understanding of this complex interplay between exocrine and endocrine pancreas.

MANAGEMENT OF PPDM-A

Screening for diabetes after AP

Currently there are no evidence-based guidelines for screening of diabetes after AP. Though diabetes can develop more frequently after necrotizing pancreatitis requiring necrosectomy, it can also develop even after an episode of mild pancreatitis. So, screening for diabetes should be done in every patient of AP even in the absence of robust risk factors for the development of the same.

One more dilemma is the timing and frequency of screening tests. A proposed approach is of frequent screening for the first year (HbA1c in 6 mo intervals) after hospital discharge. Subsequent, screening should be done on annual basis[70]. The rationale of frequent screening for the first year is based on the observation of new-onset of pre-diabetes or diabetes in 20% of the patient within 6 mo of an episode of AP[70]. However, further population-based studies regarding actual prevalence, time course of NODAP, cost and effectiveness of screening tests are needed for definite recommendation of screening in these patients.

Medical management

There are no evidence-based guidelines available regarding the treatment of PPDM-A in the absence of clinical trials. Current treatment is typically adapted using a similar paradigm as used in type 2 DM, however, PPDM-A is more difficult to control than type 2 DM. A large United Kingdom based study showed that mean HbA1c level was significantly higher at the time of diagnosis in patients with PPDM-A compared to type 2 DM ($8.3\% \pm 2.4\%$ vs $7.9\% \pm 2\%$; $P = 0.002$)[62]. The difference of mean HbA1c level remained statistically significant at 1 year ($7.1\% \pm 1.5\%$ vs $6.8\% \pm 1.2\%$, $P < 0.001$) and at 5 years (7.6 ± 1.7 vs 7.2 ± 1.4 , $P < 0.001$) of follow-up. The proportion of patients with poor glycemic control (defined with HbA1c $\geq 7\%$) was higher at 1 year (aOR = 1.3) and at 5 years (aOR = 1.7) compared to type 2 DM. Same study also reported that a higher number of patients were on insulin therapy for glycemic control after 5 years of diagnosis in the PPDM-A group (20.1%) compared to type 2 DM (4.1%)[62]. In the absence of defined guidelines and prospective studies, metformin is most commonly used as a first line therapy in PPDM-A as in type 2 DM. Metformin is associated with reduced risk of hypoglycemia which is one of the main concerns in patients with PPDM-A[71].

Metformin is also associated with reduced risk of pancreatic neoplasia with anti-neoplastic properties. Even in patients with established pancreatic carcinoma, metformin is associated with better surgical and overall clinical outcomes[72-75]. As pancreatic carcinoma is also one of the dreaded long-term complications of chronic pancreatitis, these added benefits of metformin make its usually first line therapy in the management of PPDM. However, some gastro-intestinal side effects like nausea, diarrhea and weight loss might become more prominent in some patients with pancreatitis resulting in poor tolerability[71]. Incretins based therapy (glucagon like peptide 1 receptor agonists and DPP-4 inhibitors) have also been tried in PPDM-A, however, incretins can precipitate AP and they are more likely to be associated with gastro-intestinal side effects so preferably avoided in the treatment of PPDM-A[76,77]. Additional post-marketing surveillance studies are needed to confirm the safety of these medications in this setting.

Sulphonylureas are again not good choice because of poor beta cell reserve in PPDM-A. Thiazolidinediones are generally avoided given the risk of fluid overload, and risk of fracture, however this is an insulin sensitizing drug and can actually improve glycemic variability in patients on insulin injection[78]. Sodium-glucose cotransporter-2 inhibitors use in PPDM-A is limited due to the associated muscle/weight loss, which may be undesirable in already malnourished patients. In a nutshell, most oral antidiabetic drugs are recommended in mild PPDM-A with HbA1c $< 8\%$. Despite the use of oral anti-diabetic agents, most patients require insulin at the onset or later, given the progressive nature of the disease. Insulin being an anabolic hormone, is associated with weight gain, a beneficial effect to combat malnutrition. Basal bolus regime, similar to being used in type 1 DM, are frequently used in PPDM-A according to pre-meal glucose levels and carbohydrate intake. Some patients require basal only, basal plus oral antidiabetic drugs or basal plus regimes. In the presence of associated alpha cell injury and blunted glucagon response to hypoglycemia, careful titration of insulin dose is required to prevent hypoglycemic episodes. Due to the complex issues in the management of hyper- and hypoglycemia in patients with PPDM-A, it is also called 'brittle diabetes'. Frequent blood glucose monitoring is the cornerstone of management.

Additionally, treatment of concurrent pancreatic exocrine dysfunction which can occur in up-to one third of patients as a sequel of AP, might also be associated with better glycemic control as shown in patients with chronic pancreatitis, by stimulating the incretin hormone response[79].

KNOWLEDGE GAPS AND FUTURE STUDIES

The pathophysiology of PPDM-A is incompletely understood. Currently the diagnosis of PPDM-A is mainly based on the chronological sequence of pancreatitis diagnosed before the onset of diabetes. Comparative studies of more common subtypes of diabetes like type 1 and type 2 diabetes are lacking. Large prospective epidemiological studies focusing on incidence, risk factors and natural history as well as studies focusing on tailored approaches for diagnosing, screening, preventive and treatment strategies are lacking. Studies with continuous glucose monitoring while using oral anti diabetic drugs and/or insulin can give insights into glycemic management in such patients. Randomized trials comparing insulin vs oral antidiabetic drugs in AP are warranted but may not be ethically viable.

To address these knowledge gaps, the National Institute of Diabetes and Digestive and Kidney Diseases of the United States recently formed a collaborative network referred as Type 1 Diabetes after Acute Pancreatitis Consortium. The objective of this consortium is to conduct large prospective observational studies to focus on pathophysiology, incidence, natural history and identification of risk factors. One such trial is Diabetes RElated to Acute Pancreatitis and its Mechanisms, NCT05197920. Animal models should also be developed to accurately replicate AP related diabetes, to better characterize the pathophysiology of the disease and provide a platform to investigate potential therapeutic interventions. Also, interdisciplinary and collaborative work is needed to address the screening, preventive and treatment approaches.

CONCLUSION

PPDM-A is increasingly being recognized as a long-term sequel of diseases of exocrine pancreas after the episodes of AP. This is a distinct clinical entity as mechanisms and natural history are different from type 1 and type 2 DM. As there is necrosis and fibrosis involving both the exocrine and endocrine pancreas; concomitant exocrine dysfunction is common. There is involvement of all the subtypes of islet cells of Langerhans which explains the brittle nature of diabetes. The

pathophysiology is poorly understood, large prospective cohort and animal studies are needed for better understanding. Also, interdisciplinary and collaborative work is needed to address screening, preventive and treatment approaches.

FOOTNOTES

Author contributions: Manrai M, Singh AK, Birda CL, and Shah J wrote the manuscript; Singh AK and Birda CL prepared the research data; Dutta A, Bhadada SK and Kochhar R contributed to the discussion; and all authors reviewed and approved the final version.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Chen YX

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