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Post-acute pancreatitis diabetes. A complication waiting for more recognition and understanding.

Post -acute pancreatitis diabetes

Diego García-Compeán, Alan R Jiménez-Rodríguez, Juan Manuel Muñoz-Ayala, José A González-González, Héctor Jesús Maldonado-Garza, Jesús Zacarías Villarreal-Pérez

Abstract

Post-acute pancreatitis diabetes (PAPD) is the second most common type of diabetes below type II diabetes mellitus (T2DM). Due to the boom in research on this entity carried out during the last decade, its recognition has increased. However, much of the medical community still does not recognize it as a medium and long-term complication of AP. Recent prospective cohort studies show that its incidence is about 23% globally and 34.5% in patients with severe AP. With the overall increase in the incidence of AP this complication will be certainly seen more frequently. Due to its high morbidity, mortality and difficult control, early detection and treatment are essential. However, its risk factors and pathophysiological mechanisms are not clearly defined. Its diagnosis should be made excluding pre-existing diabetes and applying the criteria of the American Diabetes Association after 90 days of resolution of one or more AP episodes.

This review will show the evidence published so far on the incidence and prevalence, risk factors, possible pathophysiological mechanisms, clinical outcomes, clinical characteristics and preventive and corrective management of PAPD. Some important gaps needing to be clarified in forthcoming studies will also be discussed.

Key Words: Acute Pancreatitis; Diabetes Mellitus; Chronic pancreatitis; Post-pancreatitis diabetes; Pancreatogenic diabetes.

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Core Tip: Post-acute pancreatitis diabetes (PAPD) is the second most common type of diabetes below type II diabetes mellitus. Its incidence is about 23% globally and 34.5% in severe AP. With the overall increase in the incidence of AP this complication will also increase. Due to its high mortality, early detection and treatment are essential.

Diagnosis should be made excluding pre-existing diabetes and applying the criteria of the American Diabetes Association after 90 days of resolution of AP episodes. This review will show published evidence on the incidence, risk factors, pathophysiology, clinical outcomes, clinical characteristics and preventive and corrective management of PAPD

INTRODUCTION

Diabetes of the exocrine pancreas (DEP) derives from the dysfunction of the exocrine component of the pancreas. It is the second most type of diabetes after type 2 diabetes mellitus (T2DM) [1]. Its incidence has tripled in the last decade, reaching annual incidence increase of 2.8% [2]. It is associated with higher mortality compared to T2DM [3].

Despite the fact that the relationship between diabetes and diseases of the exocrine pancreas has been known for long time, there have been few advances in the knowledge of the epidemiology and pathophysiological mechanisms of the DEP, which has made it difficult to establish a clear classification of this entity [4].

Terms such as pancreatic, pancreatoprive, pancreatogenic, postpancreatectomy diabetes, and others have been used for this condition. The term "type 3c diabetes" has been attributed to the American Diabetes Association (ADA). The truth is that this nomenclature was not assigned as such to the DEP, but adopted this name because it appeared within the group "other specific types of diabetes" in subsection c of group 3 in the 1998 publication of the ADA on the classification of diabetes. In addition, the use of the term "type 3c diabetes" was not promoted in 2019 guidelines of the ADA [5] . In order to avoid more confusion, the term "diabetes of the exocrine pancreas" has been used more frequently since 2017 [6-8] .There is evidence that an increase in the accumulation of intrapancreatic fat around the pancreatic islets of Langerhans may have pathophysiological role in three of the most frequent types of DEP: post-pancreatitis diabetes (PPD), pancreatic cancer-related diabetes (PCD), and cystic

fibrosis-related diabetes (CFD), but not on T2DM and T1DM [9,10] . However, each of this type of diabetes has different pathophysiology, so it is appropriate to address them separately.

On the other side, the pancreatitis giving rise to diabetes can be acute or chronic, so it is reasonable to make distinction between both: post-acute pancreatitis diabetes (PAPD) and post-chronic pancreatitis diabetes (PCPD). A simplified core classification of DEP is shown in Table 1.

Acute pancreatitis (AP) is one of the most common gastrointestinal causes of hospital admissions worldwide, accounting for more than 275,000 cases per year. The global incidence rate of AP is increasing [11] . Because AP is the most common disease of the exocrine pancreas nowadays, it is probably the most common cause of DEP. However, this complication has been ignored by most physicians who care for patients recovering from AP (1). In the last decade, epidemiological, clinical, and translational research on PAPD has boomed, and some important aspects of this pathology are now more clearly known [12,13] .

In this review, the evidences published so far on the incidence, risk factors, possible pathophysiology, clinical outcomes, clinical characteristics, and management of PAPD will be discussed. However, the knowledge of a large part of these aspects is still incomplete, so some important gaps will be pointed out which will have to be clarified in future research studies.

EPIDEMIOLOGY

AP is an inflammatory disease of the exocrine pancreas whose global incidence is 34/100,000 inhabitants per year, with some geographical differences [14]. This condition has mortality rate from 1 to 2/100,000 person-years [15]. Biliary lithiasis, alcohol abuse, endoscopic retrograde cholangiopancreatography (ERCP), hypertriglyceridemia, and some drugs are the most common causes. On the other hand, 80% of patients have mild pancreatitis associated with few complications and short hospital stay. However, up to 20% of patients may have severe or necrotizing pancreatitis, giving rise to local and systemic complications, increased mortality and long hospital stay [16].

Studies in general population have shown that an episode of AP confers at least twice the risk of subsequent diabetes compared with controls [1]. Two meta-analyses published in 2014 and 2019 [17.18] , (with 31 studies and 13,894 adult patients with no history of DM or prediabetes), evaluated the prevalence of diabetes after one or more episodes of AP. Only 3 were case-control and 28 were non-comparative prospective cohort studies. The cumulative pooled incidence for diabetes was 23% (95%, CI 16-31%). The diabetes incidence was higher in the populations that had severe AP than in those with mild AP (39 vs. 14%). The case-control studies and 12 cohort studies had significant methodological shortcomings (few patients, short follow-up or deficient methods for defining diabetes). In the 16 remaining best-quality studies, an overall incidence of PAPD of 27.8% (range 8 to 54%), and of 38.4% (range 16-54%), only in the severe forms, was found. The cumulative incidence of diabetes reached up to 41% in studies with at least 5 years of follow-up [19-34] (Table 2). The wide range in diabetes incidence of these studies may be due to differences in methodological design, patient selection, and diabetes diagnostic methods.

The time at which diabetes appears after AP is unknown [35] . A recent prospective study, which assessed the course of glycemia over months, reported that the proportion of patients who developed diabetes after an AP episode was 3% at 6 mo, 7% at 12 mo, 9% at 18 mo, and 11% at 24 mo [36]. (Figure 1)

RISK FACTORS AND PREDICTORS

Some authors have not found association between the severity of AP and the incidence of PAPD [37-39], while others have found strong relationship [28.40-43]. A higher prevalence of PAPD was found in patients with severe AP than with mild AP in the most recent meta-analysis [18]. In another study, intensive care stay during the AP episode was associated with higher risk of developing diabetes in the 2 years after discharge [44]. The differences in the prevalence of PAPD in the severe forms shown in these studies could be explained, by the different definitions of severity and the diversity of scales used for assessing severity, such as Ranson, APACHE II, BISAP, or the Atlanta classification [45]. It seems that the strongest risk factors in the development of PAPD are pancreatic

necrosis and recurrent episodes of AP [40,46]. For recurrent AP, one study evaluated computed tomography evidence of pancreatic volume loss in patients with a single episode of AP compared with recurrent pancreatitis. The investigators found that total pancreatic volume was significantly reduced in those with recurrent AP and these patients also had a strong association with endocrine and exocrine insufficiency [46]. Diabetes in patients with severe and recurrent AP may be due to structural damage of the β cells of the pancreatic islets. Nevertheless, it is important to highlight that the increased risk of diabetes also in patients with mild AP (without necrosis) suggests that there could be other mechanisms involved in its pathophysiology.

Other studies have shown that advanced age and male gender are significant risk factors [47]. Additionally, the alcoholic etiology of pancreatitis seems to increase this incidence [18]. On the other hand, some parameters of metabolic dysfunction, such as obesity and dyslipidemia, could be important risk factors, including genetic factors, particularly in patients with family history of DM.

In total, PAPD risk factors have been poorly or incompletely studied, mostly in retrospective studies with unclear defining parameters. However, the definition of risk factors is important to predict the incidence of diabetes in order to adopt an effective screening strategy of diabetes in patients who recover from AP, particularly in the mild form which is the most frequently seen. Specially designed prospective studies are required in order to clear this issue.

In the other side, some biological markers with the aim of predicting the development of PAPD have been investigated. One study found that elevated plasma levels of Interleukin-1β and interferon γ in individuals with AP and normal glycemia may predict the onset of de novo diabetes during follow-up [48]. Another study found that elevated basal insulin and glucagon plasma levels were associated with de novo diabetes post AP (OR: 1.99 and 3.44 respectively) [49]. Another prospective, longitudinal cohort study found that the variability of glucose plasma levels in the early stages of AP may predict the development of diabetes at 2-year follow-up [50]. Although the results of

these studies may appear promising, the research on this field is still very limited and these findings need to be validated before being used in clinical practice.

PATHOPHYSIOLOGY

The pathophysiologic relationship between AP and diabetes seems to be bidirectional [51]. On the one hand, patients with T1DM and T2DM have higher risk of developing AP, as demonstrated in a meta-analysis with 5.7 million participants and 14,124 cases. Patients with diabetes had higher risk of AP than individuals without diabetes (HR: 1.74) [52]. Likewise, other studies have reported that patients with diabetes develop more severe AP [42].

Despite it is accepted that AP can give rise to diabetes, the pathophysiological mechanisms are still unknown. In necrotizing AP, diabetes may be attributed to structural damage of pancreatic parenchyma. However, in the mild AP the involved mechanisms are less clear. Overall, it has been hypothesized that the pathophysiology of PAPD may be multifactorial, involving diverse mechanisms that could have effect at different levels of the glucose metabolism regulation pathways. It may be possible that one or more of these mechanisms may predominate in the different diabetes phenotypes. According to some evidence collected so far, some of the possible mechanisms are discussed in the following sections. (Figure 2)

(a) Pancreatic necrosis

This complication of AP has already been discussed previously in the above sections [28,40-42,53.54]. In a recent meta-analysis, patients who displayed pancreatic necrosis during the AP attack(s) had a higher frequency of diabetes than those without necrosis (37 vs. 11%) [18]. In other series, the incidence exceeds 50% of the cases [29]. Notwithstanding, the relation between diabetes incidence and the extension and site of necrosis has not been completely defined. In a recent study with 109 patients with AP the incidence of de novo diabetes in patients with pancreatic necrosis demonstrated by contrasted CT scan was higher (66.6%) than in those without necrosis (27.8%). However, no relationship was found between diabetes incidence and necrosis rate or site of necrosis (head, body or tail of pancreas) [26] This may be explained because diabetes may be due, in addition

to destruction of β cells of the pancreas, to insulin resistance. And also, because β cells are located homogeneously in the different segments of the pancreas.

Pancreatic necrosis may also induce exocrine pancreas insufficiency (EPI). From 15 to 30% of patients who have an episode of AP may have chronic pancreatitis after 3 years of follow-up [47].

(b) Autoimmunity against β cells and other components of Langerhans islets.

It has been speculated that the local and systemic inflammatory response occurring in AP patients may result in post-translational modifications of endogenous islet cell proteins, such as insulin, nucleic acids, and other proteins. Such modified neoepitopes may act as autoantigens, inducing an autoimmune response against components of the Langerhans islet [55]. To date, the frequency of autoimmunity during and after an AP episode has not been evaluated, particularly in patients who develop de novo diabetes.

(c) Metabolic dysregulation

Obesity and hypertriglyceridemia are risk factors for the development of both T2DM and AP [56,57]. Their presence prior to AP may result in greater risk of developing diabetes and may accelerate the onset of this condition. Both factors are independently associated with increased risk of clinical severity of AP, which could explain the risk of diabetes [58,59]. In fact, hypertriglyceridemia is one of the most frequent causes of AP, only below biliary and alcoholic etiology. The impact that visceral obesity may have is unknown. However, there is evidence that increased accumulation of intrapancreatic fat around the islets of Langerhans may have pathophysiological role in acute and chronic post-pancreatitis diabetes (PPD) [9,10]. Insulin resistance may be the mechanism in these patients [60] .

(d) Local and systemic inflammatory response

During the course of AP, serum interleukin-6 (IL-6) levels increase as a consequence of the local and systemic inflammatory response. It has been hypothesized that this and other cytokines could favor the development of chronic hyperglycemia [61]. Multiple studies have found that the role of IL-6 on impaired glucose metabolism is primarily through insulin resistance [62,63].

(e) Disturbance of the gut-pancreas axis

It has been suggested that of some of the pancreatic and intestine functional interconnections involved in the digestion, absorption, and utilization of nutrients which regulate glucose homeostasis may be disturbed in PAPD [53]. This assertion is based on the fact that 15 to 30% of patients who have AP show chronic pancreatitis 3 years after the acute episode [47,64]. The most common endocrine dysfunction results from decreased levels of insulin, glucagon, and pancreatic polypeptide (PP) [65]. Impaired secretion of enteral glucoregulatory hormones (incretins secreted by intestinal epithelium cells), such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) may also be observed. These peptides are associated with increased insulin secretion, glucagon secretion modulation and reduction of hepatic and peripheral insulin resistance [66]. It is important to underline that the reduction of glucagon secretion is the cause of severe hypoglycemia due to the loss of its counter-regulatory effect [67]. Therefore, the combined hormonal abnormalities that occur in PAPD result in a severely disrupted endocrine environment that is different from the pattern of abnormalities seen in T1DM or T2DM. Hence the need to understand and recognize these entities separately.

In summary, it is essential to determine the relative contribution of each of these pathophysiological mechanisms involved in PAPD, as well as their interrelationship with the possible genetic predispositions. In order to clarify this important issue, both clinical and basic studies in experimental models of PAPD are needed due to the difficulty in obtaining tissue samples from human beings.

DIAGNOSIS

For stablishing the diagnosis of PAPD it is important to rule out preexisting diabetes (mainly T2DM) which sometimes is difficult. The diagnostic criteria for PAPD proposed some years ago that included the demonstration of exocrine pancreatic insufficiency (EPI) as well as the absence of autoantibodies directed against β cells of the pancreas are not currently valid [68,69] because only 30% of patients show evidence of EPI 3 years after AP [64,70]. In addition, patients who develop EPI have increased risk of diabetes [71],

so it should be considered as a risk factor and not as its defining characteristic. On the other hand, early and intermediate stages of EPI are difficult to demonstrate as functional tests and sophisticated imaging techniques are often not available in real life practice and are costly. In total, the term PAPD should be reserved specifically to de novo diabetes in individuals after AP with or without morphological or functional evidence of chronic pancreatitis and without the need to demonstrate the absence of anti- β cell antibodies.

The diagnosis of diabetes should be established based on the criteria recommended by the ADA: glycosylated hemoglobin (HbA1c) ≥ 48 mm/mol or 6.5% and/or fasting glucose > 7 mmmol/L or 126 mg/dL [72], which must be performed more than 90 days after AP resolution. This is important because HbA1c levels reflect the mean plasma glucose concentration in the previous 8-12 wk and also due to the stress hyperglycemia that can occur before this period. It has been shown that the oral glucose tolerance test (OGTT) is better for detecting early-stage diabetes as it is not affected by stress and does not require 90 days to give reliable results.

Some clinical characteristics and biochemical markers can help to differentiate PAPD from T2DM. PAPD has greater glycemic variability and more difficult control, showing frequent hypoglycemic episodes and more insulin requirements [73]. From the biochemical point of view, PAPD patients have lower baseline and stimulated levels of insulin, glucagon and C-peptide [1]. Besides, pre and postprandial serum levels of oxyntomodulin, (an intestinal peptide derived from proglucagon that participates in the regulation of the pancreatic exocrine function), have been found to be significantly higher in patients with PAPD compared to T2DM and healthy controls. This opens the possibility of being used as a specific biomarker [74]. For some, the presence of diagnostic autoimmune markers for T1DM (i.e., islet cell antibodies or antibodies against glutamic acid decarboxylase, insulin, tyrosine phosphatase-like proteins, or zinc transporter) [75], rules out the diagnosis of PAPD. However, as already mentioned, an autoimmune component triggered by neoepitopes induced by the systemic inflammatory response of AP at the level of the β cells has not been ruled out as

pathophysiological mechanism of PAPD in some patients [55]. Finally, it is also important to identify overlapping causes of DEP such as pancreatic surgery, cystic fibrosis, toxic pancreatic medications, hemochromatosis, and pancreatic cancer.

In summary, the diagnosis of PAPD, should be based on the exclusion of any type of preexisting diabetes before AP and on identification of diabetes ninety days after AP based on the ADA criteria. For now, screening for PAPD should be performed in all patients who have had at least one episode of AP. The knowledge of the risk factors will contribute to selecting patients for screening in the future. Although there is no consensus on the frequency of screening, it is recommended to be carried out every 6 mo the first year and every year thereafter. Figure 3 shows a simplified PAPD diagnostic algorithm.

COMPLICATIONS

It has been demonstrated that PAPD has higher short- and long-term morbidity and mortality than T2DM.[3] A recent population-based study of 139,843 individuals showed that those with PAPD had significantly higher risk of pancreatic cancer than those with T2DM or those with no history of pancreatitis (adjusted RR: 6.94; $P < 0.05$) [76] . It is important to underline that in patients recovering from AP, diabetes may be the clinical manifestation of pancreatic cancer, so early detection strategies for these neoplasms should be applied. Another recent study with 10,549 individuals showed that patients with PAPD, compared to T2DM, had higher all-cause mortality (RR: 1.13), cancer (RR: 1.14), infections (RR: 2.52), and gastrointestinal disease (RR: 2.56). Likewise, the risk of rehospitalizations was significantly higher, which represented greater economic burden [77].

MANAGEMENT

The data so far available regarding the treatment of PAPD are very scarce, however, some rationale may be useful to guide treatment decisions with the understanding that refinement will be required based on the results of well-conducted future therapeutic studies. The management of PAPD should ideally be preventive and corrective.

Preventive management aims to reduce the incidence of diabetes which would be achieved if the risk factors and predictive clinical and biochemical markers were clearly known. It seems that pancreatic necrosis and recurrent episodes of AP are the most solid risk factors. Possibly in patients with these complications a more aggressive and earlier management of AP, the performance of early cholecystectomy in biliary AP and stopping alcohol consumption could have some beneficial impact. In this context, well-conducted studies are required in order to demonstrate this issue.

For corrective management it is suggested to apply the ADA recommendations for the treatment of T2DM and T1DM with some nuances [78]. It is important to be aware of the fragile stability of glycemia of these patients. This leads that a large part of patients be treated with insulin. In a large population-based study, higher proportion of patients with PAPD were already on insulin therapy within 5 years compared to T2DM (20.9% *vs* 4.1% respectively), and had poorer glycemic control (defined as HBA1c ≥7%) [1].

It is important to remember that about 30% of patients with AP develop EPI [70]. At this point, one study reported increased postprandial responses of GLP-1 and GIP in patients with chronic pancreatitis and EPI following pancreatic enzyme substitution (PES). Concurrently, both plasma insulin, plasma C-peptide, and total insulin secretion increased after PES. These results suggest that secretion of GLP-1 and GIP is under influence of the digestion and absorption of nutrients in the small intestine and that PES increased insulin secretion [66]. Concomitant improvement of glycemic control was not assessed in diabetic patients from this study. As a result of these findings, the assessment of therapeutic effects of PES from the early stages of diabetes development may be warranted.

Finally, the management of PAPD is complex and requires a common approach, preferably by a medical team that includes gastroenterologists, endocrinologists, primary care physicians, nutritionists, and behavioral health specialists.

CONCLUSION

PAPD is currently the second most common type of diabetes. It is increasingly known as a result of the recently published research around this entity. However, much of the medical community still ignores its existence. With the increasing global incidence of AP, the frequency of this type of diabetes will certainly increase.

Due to its high morbidity, mortality and difficult treatment, its recognition as a complication of AP is of paramount importance. Pancreatic necrosis and recurrence seem to be the strongest risk factors. Its pathophysiological mechanisms and other risk factors are not yet clearly known. The diagnosis should be based on the exclusion of any type of preexisting diabetes and on identification of diabetes ninety days after AP based on the ADA criteria. Screening for diabetes should be performed in all patients who have had at least one episode of AP. Management is not yet standardized.

It was recently announced the launch of a multicenter clinical study designed to understand the frequency and phenotypes of this type of diabetes. This study has been called DREAM (Diabetes RElated to Acute Pancreatitis and its Mechanisms) and is supported by The National Institute of Diabetes and Digestive and Kidney Diseases [79]. In this research project, it is planned to study risk factors and some of the mechanisms possibly involved in the pathophysiology of PAPD [80-82].

Certainly, the results of this and other similar forthcoming studies will contribute to the clarification of some important gaps that still persist in the knowledge of PAPD making possible a more effective screening and better preventive and corrective management.

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