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Research Status and Advancements in Post-Acute Pancreatitis Diabetes Mellitus

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Abstract: ***Acute pancreatitis (AP), a common cause of acute abdominal pain in gastrointestinal disorders, is characterized by acute non-bacterial inflammation and acinar cell damage within the pancreas. As a heterogeneous disease, acute pancreatitis manifests as a condition with significant variations in presentation and disease progression. Diabetes of the exocrine pancreas (DEP), also termed pancreatogenic diabetes or type 3c diabetes mellitus (T3cDM), constitutes a secondary form of diabetes resulting from various exocrine pancreatic dysfunctions. This review summarizes the definition, diagnostic criteria, epidemiology, pathogenesis, risk factors, and current management strategies for Post-Acute Pancreatitis Diabetes mellitus (PPDM-A). Its objectives are to emphasize the clinical importance of post-discharge management for PPDM-A patients, facilitate effective preventive measures, enable early diagnosis and treatment, Reducing the incidence of PPDM-A and improving patients' quality of life.***

Keywords: Acute pancreatitis, Diabetes, Post-Acute Pancreatitis Diabetes mellitus, Clinical research advancements**.**

1. Introduction

Acute pancreatitis represents a highly prevalent gastrointestinal disorder with a rising global incidence. The disease predominantly manifests local to systemic inflammation-associated responses, featuring complex and variable pathological processes. Early-stage disease assessment poses significant challenges, while late-stage treatment may lead to multiple complications. Studies indicate that approximately 23% of AP patients develop new-onset diabetes post-diagnosis. However, acute pancreatitis history is frequently overlooked in clinical practice, resulting in only half of DEP patients receiving accurate diagnoses, while others are misclassified as type 2 diabetes (T2DM) or type 1 diabetes (T1DM) [1]. Currently, DEP has become the second most common form of adult-onset diabetes after T2DM, with a prevalence surpassing that of T1DM [2]. Nonetheless, PPDM-A remains inadequately recognized and understudied. Thus, this review seeks to provide comprehensive guidance and reference for clinical management.

2. Definition and Diagnostic Criteria for Post-Acute Pancreatitis Diabetes Mellitus

PPDM-A denotes secondary diabetes occurring in individuals without prior diabetes history following the initial episode of acute pancreatitis [3]. Diagnostic criteria recommended by the "Chinese Guidelines for the Diagnosis and Treatment of Acute Pancreatitis" [4] and the American Diabetes Association (ADA) [5] include: (1) Meeting diagnostic criteria for acute pancreatitis; (2) Exclusion of pre-existing T2DM, stress hyperglycemia, and T1DM prior to the first AP episode; (3) HbA1c ≥48 mmol/mol (6.5%), and/or fasting plasma glucose >7 mmol/L (126 mg/dL), with testing performed ≥90 days after AP alleviation. Qian Suwan and Tong Zhihui [6] in China further specify that PPDM-A should be considered in adults with acute pancreatitis history meeting diabetes diagnostic criteria, after excluding transient hyperglycemia within three months post-AP onset.

PPDM-A is frequently misidentified as T2DM, but can be distinguished through clinical features and biochemical markers. PPDM-A exhibits greater glycemic variability and is more difficult to control, accompanied by frequent hypoglycemic episodes and higher insulin requirements [7]. Biochemically, patients demonstrate lower insulin, glucagon, and C-peptide levels compared to other diabetic subtypes [1]. In addition, oxyntomodulin levels (both preprandial and postprandial) in PPDM-A patients are significantly elevated relative to both T2DM patients and healthy subjects, suggesting its potential as a specific biomarker [8]. While autoimmune markers of T1DM can exclude PPDM-A in some cases, whether immune responses triggered by acute pancreatitis contribute to its pathogenesis remains incompletely elucidated [9].

3. Epidemiology of Post-Acute Pancreatitis Diabetes Mellitus

Studies indicate a 17% diabetes incidence following the initial acute pancreatitis episode [10], with affected individuals facing over twice the diabetes risk compared to the general population within five years post-onset [2,11]. Two systematic reviews and meta-analyses [11,12] further report a 23% post-AP diabetes incidence rate, and this incidence has been gradually increasing over time. Notably, patients with alcohol-induced AP exhibit higher diabetes incidence than those with biliary AP. This suggests that chronic alcohol abuse may directly impair pancreatic function while its metabolites indirectly elevate diabetes risk, consistent with findings by Ho et al. [13]. Further studies corroborate the strong association between acute pancreatitis and diabetes. An Australian investigation [14] involving 438 AP patients without prior diabetes history found that 29% developed diabetes post-AP, with 22 cases testing negative for diabetes-associated antibodies, thus meeting PPDM-A diagnostic criteria. Additionally, a five-year follow-up study [10] demonstrated significantly elevated diabetes risk among AP survivors, identifying alcohol-induced pancreatitis and necrotizing pancreatitis as critical predictors. Shen et al. [15]

reported a 2.54-fold increased risk of PPDM-A in AP patients versus the general population (95% CI: 2.13-3.04), while Lee et al. [16] observed a 2.1-fold higher diabetes incidence compared to controls (95% CI: 1.92-2.41). These findings collectively reinforce the significant link between acute pancreatitis and subsequent diabetes risk.

Additionally, multiple studies indicate [17-19] an overall PPDM-A incidence of 27.8% (range: 8%-54%), rising to 38.4% (range: 16%-54%) in patients with severe acute pancreatitis (SAP). The cumulative diabetes incidence reached 41% in studies with a minimum 5-year follow-up. Nevertheless, the exact post-AP onset timing remains undefined [15]. A recent prospective investigation [20] documented diabetes incidence rates of 3%; 7%; 9%; and 11% at 6, 12, 18, and 24 months post-AP, this finding suggests that the incidence of diabetes mellitus demonstrates progressive temporal escalation after acute pancreatitis.

4. Pathogenesis of Post-Acute Pancreatitis Diabetes Mellitus

4.1 Pancreatic Necrosis

The pathogenesis of Post-Acute Pancreatitis Diabetes Mellitus involves intricate mechanisms, with pancreatic necrosis identified as a critical pathological factor. Tu et al. [18] conducted follow-up assessments of endocrine and exocrine functions in AP patients, revealing a 59.25% combined incidence of diabetes and impaired glucose tolerance, higher than pancreatic exocrine insufficiency. Studies demonstrate that >50% pancreatic necrosis extent, walled-off necrosis, and insulin resistance constitute independent risk factors for new-onset diabetes. Pancreatic necrosis directly damages β-cells, triggering insulin resistance and ultimately promoting diabetes development. A meta-analysis [12] indicated markedly higher diabetes incidence in AP patients with pancreatic necrosis versus those without (37% vs. 11%). Additional studies [18] confirm pancreatic necrosis as a key risk factor for PPDM-A, with β-cell injury being pivotal to disease progression. Furthermore, Pendharkar et al. [21] observed significantly elevated fasting/postprandial insulin levels yet reduced insulin sensitivity in PPDM-A patients, indicating that β-cell compensatory effects proved insufficient to meet insulin demands, thereby exacerbating diabetes pathogenesis. Collectively, these findings demonstrate that pancreatic necrosis not only disrupts endocrine function but also promotes diabetes through insulin resistance.

4.2 Metabolic Dysregulation

Metabolic disorders play a critical role in PPDM-A pathogenesis, with dyslipidemia constituting a key pathological mechanism. Studies confirm elevated glycerol and triglyceride levels strongly correlate with PPDM-A development, indicating that lipolysis plays a critical role in its pathogenesis [22,23]. Furthermore, Ko et al. [24] demonstrated that pancreatic fat accumulation inversely associates with insulin sensitivity exclusively in PPDM-A patients—a phenomenon absent in T2DM or healthy controls. Singh et al. [25] The study further confirms that significantly increased pancreatic fat deposition tightly linked to insulin resistance in PPDM-A Furthermore, Patients exhibit higher visceral adipose tissue mass and elevated visceral-to-subcutaneous fat ratios than non-diabetic AP patients or healthy controls [26]. Acute-phase elevations in C-reactive protein and biliary pancreatitis etiology notably associate with increased visceral/pancreatic fat deposition. These collective findings highlight the pivotal role of ectopic pancreatic and visceral fat accumulation in PPDM-A progression.

Obesity, as another critical metabolic disorder, not only correlates strongly with PPDM-A but also represents a shared risk factor for both T2DM and acute pancreatitis [27,28]. Pre-existing metabolic abnormalities before AP onset significantly elevate diabetes risk and may accelerate disease progression. These dysmetabolic factors independently associate with clinical severity in acute pancreatitis [29,30], further elucidating mechanisms underlying elevated PPDM-A risk. Although the precise pathogenesis of visceral adiposity remains incompletely defined, studies suggest that ectopic peripancreatic fat accumulation surrounding the islets of Langerhans likely plays a central role in the pathophysiology of both acute and chronic PPDM-A. Crucially, insulin resistance serves as a pivotal mechanism bridging obesity to PPDM-A development [26].

Moreover, dysfunction of the entero-pancreatic axis significantly contributes to PPDM-A pathogenesis. Research indicates [31,32] that abnormalities in nutrient digestion, absorption, and metabolic utilization mediated by this axis which regulates glucose homeostasis may occur in PPDM-A patients. Oxyntomodulin and glicentin demonstrate strong correlations with PPDM-A, with reduced levels of these proglucagon-derived peptides reflecting the extent of exocrine pancreatic impairment [32]. Further studies reveal [8] significantly lower fasting and postprandial oxyntomodulin levels in PPDM-A patients compared to healthy controls and T2DM subjects, suggesting its potential as a biomarker for distinguishing PPDM-A from T2DM, However, larger studies are still needed to validate it.

Regarding iron metabolism, PPDM-A patients exhibit distinct dysregulation characterized by elevated circulating hepcidin levels and reduced Ferritin levels [33]. Increased hepcidin likely reflects suppressed intestinal iron absorption, indicating hepcidin may exert protective effects by restricting dietary iron uptake, thereby participating in PPDM-A pathophysiology.

4.3 IL-6

Proinflammatory cytokines play a pivotal role in PPDM-A pathogenesis and progression. Interleukin-6 (IL-6) constitutes a key inflammatory mediator that disrupts glucose metabolism by inducing insulin resistance. IL-6 impairs insulin signaling primarily by nterfering with phosphorylation of insulin receptors and insulin receptor substrate-1 (IRS-1) [34], ultimately leading to insulin resistance [34].

This mechanism offers potential therapeutic targets for PPDM-A prevention and early intervention. Clinical studies consistently demonstrate acute-phase IL-6 elevation in acute pancreatitis, with levels correlating positively with disease

severity [35,36]. Unlike TNF-α, IL-6 does not enhance pS-612 phosphorylation in IRS-1 but still modulates insulin signaling pathways through gene transcription regulation. The IL-6-insulin resistance link is well-established, with adipose tissue in insulin-resistant individuals exhibiting significantly increased IL-6 expression (approximately 15-fold), paralleling upregulation of TNF-α and IL-8 [37]. further indicate that IL-6 is not only independently involved in insulin resistance, but may also act synergistically with other inflammatory mediators to collectively promote insulin resistance and elevate diabetes risk. Moreover, persistent IL-6 elevation during AP reflects localized and systemic inflammation, wherein chronic inflammatory states may drive PPDM-A onset and progression via insulin resistance mechanisms [34,39].

5. Risk Factors

Significant progress has been made in research on risk factors for PPDM-A, aiming to identify high-risk populations for early prediction and intervention, thereby reducing PPDM-A incidence and improving patients' quality of life.

Multiple studies [40] indicate that males have higher PPDM-A risk than females, with young adults under 45—especially males—facing the highest susceptibility (adjusted HR: 7.46; 95% CI: 5.12-10.87). Advanced age, metabolic syndrome (such as hypertension, obesity, hyperlipidemia), and multiple comorbidities are also critical risk factors [41]. Analysis of Taiwan's population database further confirms [15] significantly elevated diabetes risk in male AP patients versus females (HR 3.21 vs. 1.58, P=0. 0004). Ho et al. [42] similarly identified alcohol-induced AP, AP readmission, the male sex, and younger age as significant predictors of new-onset diabetes (P<0.001). A large New Zealand study found that PPDM patients had comparable vascular and non-vascular non-cancer mortality risks to T2DM or T1DM patients, but significantly higher cancer mortality risk (adjusted HR 1.32-1.65), particularly among females (P=0.003-0.006). PPDM patients had substantially shorter life expectancy before age 64 than T2DM and T1DM patients. Cho et al. [41] further demonstrated the incidence of pancreatic cancer in patients with PPDM, post-T2DM pancreatitis, pancreatitis alone and T2DM alone was 3.1%, 2.3%, 2.0% and 0.6%, respectively. The PPDM showing the highest risk (HR 6.94; 95% CI 4.09-11.0). Another large New Zealand study [43] confirmed the risk of vascular and nonvascular noncancer death in patients with PPDM was similar to that of T2DM or T1DM, but significantly elevated cancer mortality in PPDM (adjusted HR 1.32-1.65) with higher female susceptibility (P=0.003-0.006). besides, PPDM patients also showed reduced life expectancy before age 64 compared to T2DM/T1DM patients. Cho et al. [44] additionally reported pancreatic cancer incidences of 3.1% in PPDM, 2.3% in post-T2DM pancreatitis, 2.0% in pancreatitis alone, and 0.6% in T2DM alone, confirming the highest risk in PPDM patients (HR 6.94; 95% CI 4.09-11.0).

Recurrent acute pancreatitis and pancreatic necrosis are established as significant risk factors for PPDM-A. Patients with recurrent AP face substantially elevated PPDM-A risk (OR: 1.94; 95% CI: 1.48-2.40; P<0.001) [42], while pancreatic necrosis may promote diabetes via cumulative tissue damage and β-cell destruction [45,46]. Evidence conflicts regarding AP severity as an independent risk factor. some studies [41,47] suggest higher PPDM-A risk in severe AP, whereas others [15,16] report no significant association. Recent meta-analysis indicates a markedly higher post-AP diabetes incidence in severe AP (39%) versus mild AP (14%) [12], supported by Firkins et al. [41] who attribute this to Large-scale studies suggest that more severe AP may lead to more β-cell loss [48,49], which supports this conclusion. Additionally, patients requiring intensive care during AP hospitalization show significantly increased diabetes risk within two years post-discharge [50]. These discrepancies may reflect heterogeneity in severity definitions (such as Ranson score, APACHE II, BISAP, Atlanta classification) [51].

In summary, PPDM-A development results from multifactorial interplay. Clinically established risk factors include sex, age, recurrent acute pancreatitis, disease severity, and pancreatic necrosis. Moreover, PPDM-A not only increases the risk of diabetes, but also significantly correlates with compromised long-term prognosis, including heightened cancer incidence and reduced life expectancy. Based on current evidence, we recommend strengthening early identification of high-risk populations in clinical practice, implementing dynamic surveillance, and adopting multidisciplinary interventions. These strategies aim to improve early diagnosis rates, optimize therapeutic outcomes, mitigate complication risks, and enhance patients' overall survival quality.

6. Management of Post-Acute Pancreatitis Diabetes

Current evidence on treating PAPD (Post-Acute Pancreatitis Diabetes) remains scarce. Although theoretical frameworks may inform therapeutic decisions, However, it needs to be understood that treatments will need to be refined. This refinement will be based on the results of future well-designed treatment studies. A dual preventive-corrective approach is advocated. Preventive management focuses on reducing diabetes, this goal can be achieved by identifying known risk factors and clinical and biochemical predictive markers. from this, it can be seen that Pancreatic necrosis and recurrent acute pancreatitis (AP) represent the most robust risk factors. Early aggressive interventions, including cholecystectomy for biliary AP, alcohol cessation, and optimized AP management may yield beneficial effects for these patients, though validation through well-designed trials is needed. Corrective management follows American Diabetes Association (ADA) guidelines for T2DM and T1DM, with necessary adaptations. Notably, these patients exhibit fragile glycemic stability, necessitating insulin therapy in most cases. Population-based studies reveal significantly higher insulin usage among PAPD patients versus T2DM controls within five years (20.9% vs. 4.1%), alongside poorer glycemic control (defined as HbA1c ≥7%) [2].

7. Summary and Perspectives

Post-Acute Pancreatitis Diabetes Mellitus (PPDM-A) development closely correlates with pancreatic function impairment, particularly pancreatic necrosis and recurrent

acute pancreatitis episodes as key risk factors. Current evidence indicates increasing PPDM-A incidence, showing an upward trend over time and being closely associated with etiologies like alcohol-induced pancreatitis and severe acute pancreatitis. Although diagnostic criteria for PPDM-A are progressively being clarified, significant challenges remain in early detection and therapeutic intervention.

Current treatment of PPDM-A primarily relies on a preventive-corrective dual approach. preventive management, through early control of acute pancreatitis particularly in high-risk patients, may effectively reduce diabetes incidence. Corrective management depends on insulin therapy and precise glycemic fluctuation control. Nevertheless, despite proposed treatment protocols, empirical evidence remains lacking for clinical applications, we offer individualized treatment plans for patients at different stages of the disease.

Future research should focus on elucidating PPDM-A pathogenesis, exploring more effective therapeutics, particularly targeting pancreatic β-cell protection and insulin resistance mechanisms, and conducting large-scale, multicenter clinical trials to Exploring the efficacy of different interventions, Remains an urgent current scientific issue. Furthermore, advances in molecular biology coupled with precision medicine may offer novel strategies for early diagnosis and individualized therapy in PPDM-A.

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