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Advances in the Study of Pancreatic Exocrine Diabetes Mellitus

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Abstract: ***Pancreatogenic diabetes, also known as type 3c diabetes mellitus, is a distinct form of diabetes caused by disorders of the exocrine pancreas. In recent years, significant advances have been made in understanding its pathogenesis, diagnosis, and therapeutic strategies. However, clinical diagnosis remains challenging, as the condition is often misdiagnosed as type 2 diabetes mellitus, leading to inappropriate treatment and poor prognosis. Currently, diagnosis relies on clinical history, imaging studies, and evaluation of pancreatic exocrine function. Compared with the more prevalent type 2 diabetes, patients with pancreatogenic diabetes face greater difficulty in glycemic control, more frequent episodes of hypoglycemia, higher insulin requirements, and more complex treatment regimens. Management requires a comprehensive approach to address both exocrine insufficiency and hyperglycemia. Pancreatic enzyme replacement therapy can improve nutrient absorption, while insulin and oral hypoglycemic agents remain the mainstays of glucose control.***

Keywords: Pancreatogenic diabetes, Type 3c diabetes mellitus, Chronic pancreatitis, Pancreatic enzyme replacement therapy.

1. Introduction

Diabetes of the exocrine pancreas (DEP), formerly known as type 3c diabetes mellitus (T3cDM) or pancreatogenic diabetes, is a distinct subtype of diabetes that arises secondary to disorders affecting the exocrine pancreas. In 2020, the American Diabetes Association (ADA) officially updated its clinical classification guidelines, adopting the term DEP in place of T3cDM—a milestone in the etiological classification of diabetes [1]. DEP is characterized by impaired insulin secretion and regulation due to structural and functional loss within the pancreatic islets, occurring in the context of exocrine pancreatic dysfunction [2]. Unlike type 1 or type 2 diabetes, DEP is frequently misdiagnosed as type 2 diabetes, leading to inappropriate treatment and suboptimal outcomes. Although its prevalence is significantly higher than that of type 1 diabetes, it remains markedly lower than that of type 2. Due to widespread misdiagnosis, the global prevalence of DEP remains unclear. Retrospective cohort studies have estimated its incidence to be approximately 2.6 per 100, 000 annually—surpassing that of type 1 diabetes [3].

DEP is often referred to as “brittle diabetes” due to the lack of sufficient β-cell (insulin) and α-cell (glucagon) responses, making glycemic control particularly difficult. Patients are more susceptible to hypoglycemia-related complications and mortality [4]. In China, research on DEP remains limited. Therefore, deepening our understanding of this condition is vital for elucidating its underlying mechanisms, improving clinical management, and enhancing patient outcomes and quality of life. Once accurately diagnosed, individuals with DEP may benefit from targeted lifestyle recommendations, pancreatic enzyme replacement therapy (PERT), metformin therapy, and appropriately titrated insulin regimens — measures essential for achieving optimal outcomes in this unique form of diabetes.

2. Diagnostic Methods

At present, there is no universally recognized diagnostic criterion for Diabetes Exocrine Pancreatic (DEP). The diagnosis of DEP is based on the standard diagnostic criteria for diabetes. The most widely accepted diagnostic criteria were proposed by Ewald and Bretzel [5]: The main criteria include (all must be met): (1) Evidence of exocrine pancreatic dysfunction (fecal elastase-1 < 200μg/g or abnormal direct function tests); (2) Abnormal pancreatic imaging (endoscopic ultrasound, magnetic resonance imaging, and computed tomography); (3) Absence of autoantibodies associated with type 1 diabetes mellitus (glutamate decarboxylase antibody, islet cell antigen, or insulin antibody). Secondary criteria include: (1) Impaired function of pancreatic β-cells; (2) No peripheral insulin resistance; (3) Reduced secretion of incretin hormones [GLP-1 and/or pancreatic polypeptide]; (4) Decreased serum levels of fat-soluble vitamins A, D, E, and K.

Despite the existence of these criteria, the diagnosis of DEP still presents numerous challenges, making it difficult to establish a definitive diagnosis and apply across all clinical settings. For instance, reduced exocrine function is also observed in long-standing type 1 and type 2 diabetes. Moreover, patients with diabetes have an inherently increased risk of developing acute and chronic pancreatitis as well as pancreatic cancer. Additionally, those with a history of pancreatitis may concurrently develop type 1 or type 2 diabetes, independent of their exocrine dysfunction. The high prevalence of type 2 diabetes can complicate classification further, potentially overlapping with DEP [6].

3. Etiology and Pathogenesis

3.1 Common Causes

The various etiologies of Diabetes Exocrine Pancreatic (DEP) include pancreatitis, both acute and chronic, which are the most common causes leading to DEP. Even a single episode of pancreatitis can lead to post-pancreatitis diabetes, with the risk of diabetes increasing with recurrent episodes. The 2024 guidelines suggest that patients should undergo diabetes

screening within 3-6 months after an acute pancreatitis attack, followed by annual screenings thereafter. Patients with chronic pancreatitis should be screened annually. Other less common causes of pancreatic disease include surgical removal of the pancreas, pancreatic cancer, cystic fibrosis, hemochromatosis, and congenital absence of the pancreas, among others (refer to Table 1 below for details).

Table 1: Classification of Diabetes Exocrine Pancreatic (DEP) Adapted from Hart et al. [7]

Classification	Causes
No Islets Present	Total Pancreatectomy
	Pancreatic Dysplasia
Partial Loss of Functional Islets	Chronic Pancreatitis
	Partial Pancreatectomy
	Severe Acute Pancreatitis
	Cystic Fibrosis
	Hemochromatosis
Paraneoplasmic	Pancreatic Ductal Adenocarcinoma
Classification	Transient Hyperglycemia due to Acute Pancreatitis

3.2 Pathogenesis

3.2.1 Islet Dysfunction and Insufficient Insulin Secretion

In the pathogenesis of DEP, immune-mediated islet dysfunction plays a central role. In the context of chronic pancreatitis and pancreatic cancer, high levels of cytokines and a stressful inflammatory environment cause dysfunction of pancreatic β-cells. A large number of inflammatory cells, such as lymphocytes, macrophages, and neutrophils, infiltrate the islet tissue. After aggregation within the islets, these cells release a series of cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interferon-γ (IFN-γ). The continuous production of these inflammatory cytokines forms a vicious cycle that continuously destroys islet function. Subsequently, pancreatic stellate cells are activated and interact with various immune cells, further exacerbating the fibrosis of pancreatic tissue. Due to severe fibrosis of the pancreatic parenchyma, functional pancreatic tissue such as acini, ducts, and nerve bundles are eventually replaced by connective tissue, losing vascular and secretory functions, thereby promoting the onset of diabetes [8].

3.2.2 Insulin Resistance

Insulin resistance is a prominent feature of diabetes [9] and may also be a factor in secondary diabetes after pancreatitis [10-11]. Studies [12] have confirmed that patients with DEP exhibit hepatic insulin resistance, with an insufficient response to pancreatic polypeptide playing a key role. Pancreatic polypeptide has been identified as a glucose-regulating hormone that regulates hepatic insulin sensitivity and can reverse the reduction of insulin receptors in pancreatitis [13]. It is secreted by the PP cells of the gut pancreas after a mixed meal, enhancing the action of insulin on hepatic glucose metabolism. The absence of PP cells leads to hepatic insulin resistance due to a decrease in the availability of hepatic insulin receptors. In the context of insufficient insulin secretion, this leads to hyperglycemia and diabetes. Therefore, administering pancreatic polypeptide to patients with pancreatitis who lack it can reverse hepatic insulin resistance [14]. It is worth noting that the administration of PP has been shown to improve glucose homeostasis, and conservative surgery that preserves the head of the pancreas seems to reduce the incidence of postoperative diabetes [15].

3.2.3 Reduced Proinsulin Effect—Decrease in Incretin Hormones

When pancreatic function is impaired, it leads to malabsorption of nutrients, which in turn affects the secretion of incretin hormones. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are hormones released during the digestion and absorption of nutrients in the gut. GLP-1 regulates insulin secretion, delays gastric emptying, stimulates the release of insulin, inhibits the secretion of glucagon, reduces appetite, and slows gastric emptying [16]. Additionally, GLP-1 promotes the growth, differentiation, and protection of pancreatic β-cells [17-18].

When pancreatic function is compromised, the secretion of digestive enzymes decreases, and nutrients such as fats, proteins, and carbohydrates are not fully digested and absorbed. The transport and metabolism of undigested nutrients in the gut are altered, leading to a decrease in the release of incretin hormones. The glucose-dependent stimulatory effect on insulin secretion is weakened, glucose regulation is impaired, postprandial insulin secretion is correspondingly reduced, and postprandial hyperglycemia is more likely to occur.

3.2.4 Disruption of the Gut Microbiota

Pancreatic diseases such as chronic pancreatitis can cause damage to the intestinal mucosal barrier, leading to changes in the gut microbiota. The gut microbiome participates in metabolic and inflammatory responses in the body [19]. Studies [20] have found that various physical and chemical factors and pathogenic agents that cause pancreatic damage and inflammatory responses during pancreatitis lead to impaired integrity of the intestinal mucosal barrier, thereby promoting changes in the gut microbiota. When the gut microbiota is disrupted, the number of beneficial bacteria such as Bifidobacterium and Lactobacillus decreases, while the number of conditional pathogens such as Enterobacteriaceae increases. Changes in the gut ecology and bacterial metabolism can, in turn, affect diabetes and human metabolism [21]. These abnormal bacteria produce a large number of harmful metabolic products, further exacerbating intestinal and systemic inflammatory responses. The inflammatory state, in turn, affects pancreatic function, creating a vicious cycle. Additionally, changes in the gut microbiota can affect the secretion and metabolism of gut hormones, disrupting the normal signaling of the gut-pancreas axis, leading to abnormal insulin secretion and glucose regulation, and promoting the onset and progression of pancreas-derived diabetes.

3.2.5 Other Factors

For example, genetic factors also play an important role in the pathogenesis of DEP. Mutations in certain genetic genes related to chronic pancreatitis and pancreatic cancer significantly increase the risk of DEP. Specific genes for chronic pancreatitis that have been identified in related studies include PRSS1, SPINK1, CFTR, CTRC, and CASR [22].

4. Treatment Strategies

Currently, there are no established, systematic guidelines for the treatment of diabetes of the exocrine pancreas (DEP), which has hindered its effective clinical management. In practice, DEP is often misdiagnosed as type 2 diabetes mellitus, leading to suboptimal treatment and poor outcomes. A mechanism-based approach targeting the core features of DEP may offer better control. Management typically involves addressing exocrine insufficiency, achieving glycemic control, providing nutritional support, and implementing lifestyle interventions [23].

4.1 Pancreatic Enzyme Replacement Therapy (PERT)

Exocrine pancreatic dysfunction in DEP is commonly treated with pancreatic enzyme replacement therapy (PERT), administered at mealtimes and monitored for effectiveness. Oral pancreatic enzymes improve fat absorption, reduce steatorrhea, enhance absorption of fat-soluble vitamins, and stimulate incretin release via increased exposure to intestinal amino and fatty acids. This, in turn, can boost postprandial insulin secretion and reduce post-meal blood glucose spikes. However, improved nutrient absorption from enzyme supplementation may raise blood glucose levels, requiring dietary adjustments. Though no universal consensus exists regarding PERT dosage, it is generally accepted that PERT should be limited to the early refeeding stage after acute pancreatitis and discontinued once pancreatic function recovers [24].

A crossover study involving five non-diabetic cystic fibrosis patients demonstrated that PERT reduced postprandial glucose peaks (8.2 vs. 13.7 mmol/L) and helped normalize GLP-1 secretion and gastric emptying after a high-fat, high-carbohydrate meal [25].

4.2 Glycemic Management

Metformin and insulin are the most frequently used agents in DEP, in line with several recent expert recommendations [26-28]. Metformin, an insulin sensitizer, reduces hepatic glucose output and improves peripheral insulin sensitivity, making it a first-line agent in type 2 diabetes. Additionally, studies suggest metformin may prolong survival in non-metastatic pancreatic cancer patients with concurrent diabetes [29]. It has also been associated with a reduced risk of pancreatic ductal adenocarcinoma in case-control studies (odds ratio 0.38) [30] and in meta-analyses of retrospective observational studies (relative risk 0.63) [31].

Because DEP is a progressive condition, long-term monotherapy may not suffice. Over time, glycated hemoglobin levels (HbA1c) in DEP patients tend to exceed those in type 2 diabetes [32], necessitating combination regimens. However, high-quality evidence comparing various glucose-lowering strategies in DEP is lacking [33]. Other agents used for type 2 diabetes, such as thiazolidinediones, α-glucosidase inhibitors, and sulfonylureas, may be prescribed in select cases but are generally not first-line options due to side effects [34].

GLP-1 receptor agonists and DPP-4 inhibitors are typically avoided in DEP due to their potential association with pancreatitis and pancreatic cancer. Nonetheless, their cardiovascular benefits—especially in terms of anti-atherosclerotic effects—raise questions about their selective use in DEP patients with comorbid cardiovascular disease, a topic requiring further clinical investigation.

Current guidelines suggest insulin as a first-line therapy for diabetes secondary to pancreatitis [35], as it addresses the primary deficit of insulin secretion. Compared with type 2 diabetes, insulin is required earlier and at higher doses in DEP [36]. However, long-term insulin use is linked to increased hypoglycemia risk, and studies have shown no significant improvement in long-term survival outcomes [37].

4.3 Nutritional Support and Lifestyle Modification

As with other forms of diabetes, lifestyle changes should begin early—ideally when impaired fasting glucose is first detected. Core strategies include regular monitoring of fasting glucose and HbA1c, smoking and alcohol cessation, weight control, and dietary adjustment [38]. Smoking and alcohol use accelerate the progression of DEP and increase the risk of hypoglycemia, making patient education in cessation a key component of care [39]. According to diabetes guidelines, a weight reduction greater than 5% significantly improves glycemic control in type 2 diabetes [40], a principle that may also apply to patients with pancreatic fat infiltration in DEP. Most individuals with DEP exhibit some degree of exocrine insufficiency and fat malabsorption. Therefore, screening for deficiencies in fat-soluble vitamins A, D, E, and K is important for ensuring adequate nutrition and assessing PERT efficacy [41]. When more than 90% of exocrine function is lost, malabsorption of fats and proteins becomes clinically significant. Both PERT and vitamin D supplementation are essential for nutritional and skeletal health.

Duggan et al. [42] observed that patients with chronic pancreatitis, especially those with late-stage disease and steatorrhea, have a markedly increased risk of bone loss and even osteoporosis. As such, timely vitamin D supplementation is recommended to prevent metabolic bone disease.

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