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**New onset diabetes secondary to acute pancreatitis: An update**

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**Abstract**
Diabetes is a condition of persistent hyperglycemia caused by the endocrine disorder of the pancreas. Therefore, all pancreatic diseases have the risk of diabetes. In particular, more and more attention has been paid recently to new-onset diabetes secondary to acute pancreatitis (AP). The complications of secondary diabetes have caused a lot of trouble for patients and have been paid more and more attention. At present, the pathophysiological mechanism of new-onset diabetes caused by AP is not clear. This review will summarize the current understanding of new-onset diabetes secondary to AP.

**INTRODUCTION**
At present, new-onset diabetes secondary to acute pancreatitis (AP) is considered to be the most common type of pancreatogenic diabetes [1-3]. Structural or functional disorders of blood glucose caused by pancreatogenic factors are the main pathophysiological mechanisms, including acute and chronic pancreatitis, pancreatic trauma, and surgery. The pancreas is the largest endocrine gland of the digestive tract. Although the volume of pancreatic islet B cells is very limited, the insulin secreted by the pancreas plays a key role in maintaining the stability of endocrine blood glucose [4]. In short, any cause of pancreatic damage can lead to diabetes. In recent years, reports on pancreatogenic diabetes are increasing and attracting more and more attention.
AP is a common acute abdomen and the number one cause of acute digestive system hospitalizations in the United States [5, 6]. Most patients with AP are mild and can recover and be discharged after 3 to 5 days of conservative treatment. However, about 20% of patients still develop severe acute pancreatitis (SAP), which leads to systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndromes (MODS), leading to poor prognosis [7, 8]. It has been reported that the risk factors for triggering pancreatic endocrine insufficiency in AP include age (> 45 years), obesity, hypertriglyceridemia, family history of diabetes, and recurrent pancreatitis [9]. But these factors did not affect the severity of endocrine function. In addition, some studies have shown that the severity of AP was not associated with the incidence of new-onset diabetes [10-13]. However, Chinese scholars suggested that pancreatic necrosis (PN) and persistent organ failure (OF) were risk factors for a high incidence of new-onset diabetes secondary to AP [14]. These results suggested that further studies should be conducted to determine the impact of PN on secondary diabetes. There have been few reports on the incidence of new-onset diabetes after pancreatitis, with one meta-analysis showing a prevalence of 23% [15]. Therefore, the current clinical understanding of the characteristics of new-onset diabetes secondary to AP is not exact.

**Diagnostic criteria and definitions**

The diagnostic criteria for pancreatogenic diabetes included: (1) no previous history of diabetes; (2) definite abnormalities of glucose metabolism caused by benign and malignant diseases of the pancreas; (3) the criteria for diabetes diagnosis. Diabetes including impaired glucose tolerance (IGT) was defined according to the 1999 World Health Organization standard. The American Diabetes Association classifies it as Type 3 diabetes [2]. Its main causes include AP, pancreatic cancer, and cystic fibrosis [16, 17]. *Among them*, new-onset diabetes secondary to AP is caused by acute pancreatitis. It occurs based on impaired pancreatic exocrine function. In addition to the similar clinical manifestations, complications, and prognosis of type 2 diabetes, glucose fragility is an obvious clinical characteristic of this disease. Multiple episodes of hypoglycemia can further deteriorate pancreatic islet function and greatly increase the risk of pancreatic
cancer [18-21]. Therefore, standardized and individualized treatment and management of pancreatic diabetes are more necessary.

Diabetes was diagnosed by typical diabetes symptoms with any of the following parameters (table 1 and table 2):

Pathophysiology of new-onset diabetes secondary to AP

The main functions of the pancreas include exocrine and endocrine parts. The exocrine part consists of the acinar and duct, secreting pancreatic juice containing a large amount of bicarbonate and a variety of digestive enzymes, involved in the digestion of food. The endocrine part of the pancreas, namely the islet, is composed of A, B, D, and PP cells, which can secrete insulin, glucagon, somatostatin, and pancreatic polypeptide correspondingly. The pancreas as a whole cannot be separated from its exocrine and endocrine functions. The exocrine and endocrine secretory parts of the pancreas interact and influence each other in pancreatic physiology and disease. AP is often accompanied by elevated blood glucose [22], which may be related to the following factors: (1) Under stress, insulin can reverse regulate the secretion of the hormone, while insulin secretion is relatively reduced, which leads to the enhancement of lipolysis and proteolysis, and the increase of liver glucose production; (2) Acute inflammation of the pancreas, pancreatic tissue swelling, ischemia, microcirculation disorders, affect the secretion and excretion of insulin, when a large number of pancreatic cells necrosis in a short period time, can lead to a serious shortage of endogenous insulin secretion; (3) Sympathetic nervous system excitatory catecholamine secretion increases, accelerates liver glycogen decomposition and inhibits pancreatic B cell secretion, increases blood glucose and further aggravates endogenous insulin secretion deficiency; (4) AP may be accompanied by insulin resistance. This high blood glucose state is AP glands, exocrine function in the performance of the different degree of damage, AP early hyperglycemia, and the correlation between the severity of AP has been recognized and valued. However, in the past, blood glucose metabolism disorder was considered a transient manifestation of the disease, so the monitoring and management of blood glucose after discharge did not receive enough attention.
In AP, there is usually simultaneous pancreatic and exocrine dysfunction, and the disorder of blood glucose metabolism, as a common clinical manifestation of AP in the early stage, has gradually attracted attention. However, the pathophysiology of onset diabetes secondary to AP remains unclear [23]. But its occurrence may be related to some factors of AP, including islet cell damage associated with AP, pancreatic autoimmunity induced by AP, and insulin secretion disorder induced by the inflammatory response, etc. At present, basic and clinical studies on the pathogenesis of diabetes are still insufficient. Defining mechanisms is essential to guide clinical interventions.

It is important to emphasize that diabetes and hyperglycemia levels themselves can increase the severity of acute pancreatitis, mortality, and complications, and in turn increase the severity of diabetes [24, 25]. However, higher body mass index and other factors are often closely associated with the development of diabetes [26]. Therefore, attention should be paid to the risk of new-onset diabetes in patients with acute pancreatitis caused by weight and other related indicators.

**Management of new-onset diabetes secondary to AP**

Currently, there is no detailed standard for the management of new-onset diabetes secondary to AP. However, as a special type of diabetes, in addition to its general clinical manifestations, complications, and prognosis, blood glucose fragility is a significant clinical feature of new-onset diabetes secondary to AP. Such fluctuations in blood glucose can lead to dysfunction in the pancreas, further increasing the risk of pancreatic cancer [19, 20]. Therefore, it is necessary to pay attention to the changes in blood glucose in time and select an individualized treatment plan.

Based on the current clinical data, the management of new-onset diabetes secondary to AP mainly includes prevention, screening, and treatment. From a prevention perspective, it is important to guide the population to avoid risk factors or lifestyles that contribute to AP and diabetes, such as timely control of obesity and hyperlipidemia. In terms of treatment, despite the lack of clinical trial evidence and relevant evidence-based guidelines, type 2 diabetes-based control strategies can still be used for new-onset diabetes secondary to AP. It is important to clarify the pathogenesis and inducement of
diabetes secondary to AP for precise treatment. As for follow-up screening, given the potential risk of pancreatic cancer after new-onset diabetes secondary to AP, regular follow-up is necessary for standard assessment of pancreatic endocrine function.

CONCLUSION
New onset diabetes secondary to AP is increasingly recognized as a sequela of acute pancreatitis. The few studies to date show that the severity of AP does not indicate the risk of developing secondary diabetes. Further elucidation of the risk factors and pathogenesis of new-onset diabetes secondary to AP will facilitate more effective early treatment. Early warning, screening, and follow-up findings will benefit new-onset diabetes secondary to AP patients. At the same time, worldwide evidence-based studies will help to enrich the in-depth understanding of the disease.