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PANCREATIC TYPE 3C DIABETES MELLITUS: A REVIEW

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ABSTRACT

Pancreatic Type 3c diabetes mellitus (T3cDM) is a less common form of diabetes arising from underlying or preexisting pancreatic conditions, such as chronic pancreatitis, cystic fibrosis, and pancreatic cancer. Unlike type 1 and type 2 diabetes, T3cDM is characterized by the loss of insulin secretion due to pancreatic exocrine dysfunction. This disorder causes structural and functional abnormalities in pancreatic cells, affecting glucose control. Key mechanisms include pancreatic exocrine insufficiency, which impacts enzyme production and nutrition absorption, and disturbance of the enteroinsular axis, which reduces incretin hormone release. Beta cell failure worsens glucose dysregulation. Effective management entails treating exocrine insufficiency with enzyme replacement therapy, optimizing insulin therapy, and making dietary changes to promote nutrition absorption and glucose control.

Keywords: Diabetes, glucose dysregulation, pancreas, pancreatitis

INTRODUCTION

Pancreatic diabetes or type 3c diabetes mellitus (T3cDM) refers to diabetes arising from underlying pancreatic diseases and is marked by pancreatic exocrine insufficiency (PEI) (Johnston *et al.*, 2019) leading to reduced insulin secretion (Hart *et al*., 2016; Rickels *et al*., 2013). Unlike type 1 and type 2 diabetes, T3cDM is characterized by the loss of insulin secretion due to pancreatic exocrine dysfunction. This disorder causes structural and functional abnormalities in pancreatic cells, affecting glucose control. Although the etiology of the various forms of diabetes varies, they are all characterized by a loss or reduction of β-cell activity that results in persistent hyperglycemia.

About 5–10% of Western diabetic populations have T3cDM, with chronic pancreatitis (CP) accounting for the majority of cases (80%) (Ewald and Hardt, 2013). It presents itself as structural and functional loss of glucose-normalizing insulin secretion in the context of exocrine pancreatic dysfunction (Ewald *et al.*, 2012). Other common etiologies of pancreatic diabetes include cystic fibrosis, haemochromatosis, pancreatic cancer, and pancreatectomy (Johnston *et al*., 2019).

Alcoholism, inherited disorders, immunological issues, and trauma can all cause chronic pancreatitis, which commonly develops after acute bouts (Weiss *et al*., 2019).

Diabetes can be a late consequence of chronic pancreatitis or the first clinical indication of chronic pancreatitis (Johnston *et al*., 2019). In about five years, diabetes develops in 33% of people with chronic pancreatitis (Goodarzi *et al*., 2021). Diabetes prevalence is also linked to pancreatic ductal adenocarcinoma (PDAC), the most prevalent kind of pancreatic cancer. Diabetes with recent development may be a sign of pancreatic illness or a sign of an invisible tumour. After a tumour is removed, diabetes associated with PDAC may go away, indicating a relationship between pancreatic cancer and diabetes that goes beyond insulin resistance. Although it is difficult to evaluate, type 2 and type 3c diabetes overlap among PDAC patients and is thought to play a major role in the development of type 3c diabetes cases.

Type 3c diabetes is also linked to other illnesses such as hereditary hemochromatosis and cystic fibrosis (CF). Up to 50% of individuals with cystic fibrosis (CF) have diabetes related to the disease, and pancreatic siderosis caused by the autosomal recessive illness hereditary hemochromatosis causes diabetes, insulin resistance and deficiency (Coderre *et al*., 2021). Pancreatic procedures, which are required for several illnesses, can potentially lead to pancreatogenic diabetes; the degree of tissue loss determines how likely this is to occur.

The present essay covers the physiology of the pancreas, its pathophysiology and management of type 3c diabetes. Online search on relevant published studies in PubMed, Scopus, Embase, ResearchGate, and other research databases was done, covering the period of 2006 – 2025, and 42 articles of them were selected for this review. Keywords search included diabetes mellitus, pancreas, pancreatitis, hyperglycaemia, and type 3c diabetes mellitus.

Physiology of the Pancreas: Exocrine and Endocrine Roles

The pancreas has both endocrine and exocrine activities, which means it secretes hormones and produces enzymes that aid digestion. The exocrine acinar tissue constitutes the greater part of the pancreas from which digestive enzymes such as amylase, lipase, and proteases are synthesized (Valente *et al*., 2024). These enzymes are released into the pancreatic ducts and delivered to the duodenum to aid digestion resulting in the release of nutrients.

The remaining component, the endocrine pancreas, is made up of Langerhans islets. Pancreatic islets are highly vascularized, specialized structures that regulate nutrition levels in the bloodstream. They essentially consist of five cell types: α-cells, β-cells, δ-cells, ghrelin cells (γ-cells), and cells that release pancreatic peptide (PP) (Campbell and Newgard, 2021). In humans, β-cells account for over 50% of islet cell mass, while α-cells compose up 35-40%. The remaining cells are somatostatin-secreting δ-cells, γ-cells, and PP-cells that serve as regulatory cells (Cabrera *et al*. 2006, Rorsman and Ashcroft, 2018).

Insulin secretion occurs when β-cell secretory granules fuse with the plasma membrane. Insulin is primarily produced in response to nutrients, particularly glucose; however, other nutrients such as free fatty acids and amino acids can increase glucose-induced insulin production (Fu *et al*., 2013).

Furthermore, a key factor in increasing insulin secretion is the release of gut peptides called incretin hormones following dietary intake (Nauck and Meier, 2018). Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are the two main endogenous incretins that increase glucose-stimulated insulin secretion (GSIS) (Campbell and Drucker, 2013). Incretin hormones, which are released from the intestine in response to glucose and energy intake can, in healthy people, be responsible for up to 50% to 70% of insulin secretion from pancreatic β-cells in

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response to a meal (Chon and Gautier 2016). β-cells releases this synthesized insulin straight into the bloodstream in response to increased dietary nutrients, whereas α-cells release glucagon in response to nutrient-deficient conditions like fasting or starvation.

These hormones are detected in low amounts in the blood while fasting; however, their levels increase quickly after eating, peak after approximately an hour, and then return to baseline within several hours (Nauck and Meier, 2016).

Furthermore, a number of hormones, including growth hormone, melatonin, estrogen, and leptin, also control the release of insulin (Fu *et al*., 2013).

Pathophysiology

Pancreatic type 3c diabetes mellitus, is marked by pancreatic tissue damage that impairs exocrine cells and cell subtypes in the islets of Langerhans (Walling and Freelove, 2017; Hammad *et al.,* 2018; Pham and Forsmark, 2018). T3cDM may arise as a result of damage to various exocrine and endocrine cell types involved in the regulation of glucose metabolism (Wei *et al.,* 2020).

Chronic pancreatitis is often linked to T3cDM as it affects the pancreas both morphologically and physiologically. Chronic pancreatitis (CP) is a multifactorial, fibro-inflammatory condition characterized by widespread replacement of fibrotic tissue brought on by recurrent bouts of pancreatic inflammation. This replacement leads to persistent discomfort and exocrine and endocrine pancreatic insufficiency (Wang *et al.,* 2024). It is extensively defined by the progressive destruction of acinar tissue and its replacement by this inflammatory and fibrotic tissue impacting the physiology of the pancreas as an organ (Sasikala *et al.,* 2012). Apart from CP, most prolonged disorders of the exocrine pancreas led to fibrosis, a process that results in the exocrine tissues being destroyed. Diabetes may appear as a late complication of chronic pancreatitis, or it may be the initial clinical sign of the condition (Johnston *et al.,* 2019).

In chronic pancreatitis, the pancreas responds by producing proinflammatory cytokines, allowing inflammatory cells to infiltrate the organ, and activating pancreatic stellate cells to synthesis extracellular matrix proteins and undergo fibrogenesis. This fibrosis eventually results in the damage of exocrine and endocrine cells (Lin *et al.,* 2015).

The pathophysiology of T3cDM involves multiple factors which include the underlisted:

Pancreatic Exocrine Insufficiency

Damage to the exocrine pancreas, particularly the acinar cells, may decrease digestive enzyme production, limiting nutrition absorption and perhaps reducing incretin hormone output. This decline may cause impaired glucose and lipid metabolism, which manifests as malnutrition in type 3c DM. Loss of digestive enzyme synthesis might increase metabolic abnormalities, adding to the difficulties in regulating blood glucose levels in T3cDM (Ewald and Hardt, 2013). This could lead to a decrease in incretin hormones, as the presence of nutrients stimulates the postprandial release of incretin hormones (GLP-1 and GIP) (Nauck and Meier, 2018)

Enteroinsular Axis: Incretin hormone impairment

Incretin hormones, which are released from the gastrointestinal tract in response to meal consumption, improve glucose-dependent insulin secretion and help maintain glucose homeostasis in healthy people. GLP-1, in particular, protects β-cells by decreasing apoptosis and boosting cell proliferation and neogenesis (Reed *et al*., 2020). However, these protective effects are considerably reduced in persons with diabetes. In Type 3C DM, the role of incretin hormones is lessened due to a disruption in digestion and food uptake caused by damage to the acinar cells, which are responsible for the synthesis of digestive enzymes required to commence the digesting

process. This decrease may contribute to altered glucose and lipid metabolism.

Beta Cell Dysfunction:

Beta cell insulin insufficiency in type 3c DM diabetes is a direct result of the disease process or surgical intervention and is more closely associated with the degree of pancreatic damage. Nutrient metabolism is crucial for insulin secretion. As a result, any disturbance in this mechanism has a deleterious impact on insulin secretion. Also altered nutrition metabolism in insulin-sensitive target tissues (liver, adipose tissue, and muscle) can result in hyperglycaemia and lipid levels. This can impact pancreatic β-cell function, insulin resistance, and the development of metabolic syndrome (Newsholme *et al.,* 2014).

Inflammation and Fibrosis

The pancreas in chronic pancreatitis responds by producing proinflammatory cytokines, allowing inflammatory cells to infiltrate the organ, and activating pancreatic stellate cells to synthesis extracellular matrix proteins and undergo fibrogenesis. This fibrosis eventually destroys exocrine and endocrine cell (Lin *et al.,* 2015). Pancreatic stellate cells (PSCs) are pluripotent cells found between pancreatic lobules and acinar. Under normal conditions, PSCs exist in either a resting or active state (Omary *et al*., 2007). Resting PSCs remain quiescent but convert to an activated, myofibroblast-like phenotype in response to damage, such as trauma, inflammation, viral infection, or cancer invasion (Wang *et al*., 2024). The activation leads to increased cell volume, proliferation, and the secretion of extracellular matrix components (collagen, fibronectin, laminin) and cytokines (IL-1, IL-6, TNF-α, TGFβ1), promoting inflammation and tissue remodeling (Apte *et al*., 2011; Erkan *et al*., 2012; Ulmasov *et al.,* 2016). PSCs also have stem cell properties that aid in pancreatic tissue regeneration (Masamune and Shimosegawa, 2013). However, excessive PSC activation leads to excessive extracellular matrix production, disrupting collagen metabolism and causing pancreatic fibrosis, which can progress to chronic pancreatitis and pancreatic cancer (Kong *et al*., 2024).

Diagnosis

Diagnosing and classifying a patient with type 3c diabetes mellitus correctly is not usually an easy task. Patients with diabetes mellitus are already at an increased risk of having acute and/or chronic pancreatitis; nevertheless, long-term patients with type 1 and type 2 diabetes are linked to exocrine pancreatic insufficiency. Independent of their exocrine pancreatic illness, patients with prior episodes of pancreatitis may acquire type 1 or type 2 diabetes (Ewald and Hardt, 2013). In differentiating between the different diabetes types, islet cell antibodies are indicative of type 1 diabetes mellitus, while clinical or biochemical evidence of insulin resistance is indicative of type 2 diabetes mellitus (Ewald and Hardt, 2013).

Owing to the current dearth of widely recognised diagnostic standards, Ewald and Hardt (2013) suggest the subsequent standards for the diagnosis of type 3c diabetes mellitus (Table 1).

Table 1: Proposed diagnostic criteria for type 3c diabetes mellitus

Major criteria (must be present)

- Presence of exocrine pancreatic insufficiency (monoclonal fecal elas tase-1 test or direct function tests)
- Pathological pancreatic imaging (endoscopic ultrasound, MRI, CT)
- Absence of type 1 diabetes mellitus associated autoimmune markers

Minor criteria

- Absent pancreatic polypeptide secretion
- Impaired incretin secretion (*e.g.,* GLP-1)

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- No excessive insulin resistance (*e.g*., HOMA-IR)
- Impaired beta cell function (*e.g*., HOMA-B, C-Peptide/glucose-ratio)
- Low serum levels of lipid soluble vitamins (A, D, E and K)

MRI: Magnetic resonance imaging; CT: Computed tomography; GLP-1: Glucagon-like peptide-1; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-B: Homeostasis model assessment of beta-cell

Management of Type 3C Diabetes Mellitus

The pharmacological drugs commonly used to treat type 3c diabetes mellitus are the same as those used to treat type 2 diabetic mellitus; however, there are currently no widely acknowledged guidelines governing treatment paths for this condition (Rickels *et al* 2013). Metformin is recommended as the first-line oral therapy for type 2 diabetes mellitus (Nathan *et al*., 2009; Moke *et al*., 2023a; Moke *et al*., 2023b; Moke *et al*., 2025), hence, many type 3c diabetes mellitus patients are initially treated with metformin as a drug of first choice. Metformin therapy has been shown to reduce the incidence of pancreatic cancer by up to 70%; however, individuals with type 3c diabetes mellitus due to chronic pancreatitis may benefit from its anti-diabetic and anti-neoplastic properties (Sadeghi *et al*., 2012; Aljofan and Riethmacher, 2019; Goodarzi and Petrov, 2023).

Oral treatment with insulin segretagogues (glinides and sulfonylurea) may also be tried in early type 3c diabetes mellitus; however, thiazolidines should be avoided due to prominent side effects (e.g., fluid retention, congestive heart disease, and bone fractures) (Ewald and Hardt, 2013).

Although the pathophysiology of type 3c DM denotes a reduction in incretin hormones, incretin-based therapies are not advised, as therapies like sitagliptin, may increase β-cell mass and cause significant growth in the exocrine pancreas through increased cell proliferation and α-cell hyperplasia, which could lead to the development of endocrine tumors (Butler *et al.,* 2013).

Table 2: Management regimen for type 3c diabetes mellitus

Regimen	Treatment of choice	Side effects
1.) Management of Hyperglycemia	**Oral Hypoglycemics:** a.) **<u>Metformin</u>**: Metformin belongs to the class of anti-diabetic drugs called "Biguanides" and is used in the mild stage of hyperglycemia (Rickels *et al.,* 2013) **MOA**: • Metformin can reduce blood glucose levels, by increasing glucose utilization by the peripheral tissues, by increasing glucose uptake, it also decreases gluconeogenesis. • It has been shown that metformin does not cause hypoglycemia. • Another important consideration of metformin use is that it is contraindicated in patients who are alcoholic or susceptible to metabolic acidosis. However, as long as the use of metformin is not contraindicated and is tolerable in terms of side effects, it can be regarded as primary therapy for hyperglycemia in patients with T3cDM. (Bhattamisra *et al*., 2019)	• Headache • Anorexia • Nausea and vomiting

	b.) **Sulfonylureas**. **MOA**: • Sulfonylureas work by stimulating the pancreas to produce and release more insulin. They bind to specific receptors on the beta cells in the pancreas, leading to an increase in insulin secretion. This helps lower blood sugar levels by enhancing the body's insulin response, aiding in the uptake of glucose by cells for energy or storage.	• Hypoglycemia • Headache • GI disturbances • Weight gain • Sensitivity reactions
	c.) **Thiazolidinediones (TZDs)** Thiazolidinediones also improve insulin sensitivity but are associated with an increased risk of fluid retention, congestive heart failure, and fractures (Rickels *et al*., 2013)	•
2.) Treatment of Exocrine Insufficiency	• Pancreatic enzyme replacement therapy is one of the sought treatment for exocrine insufficiency and it is one of the most used treatments for pancreatic diabetic patients (Alexandre-Heymann *et al*., 2024). • Pancreatic enzyme replacement therapy is shown to decrease fat malabsorption, hence reverting steatorrhea (Nofal *et al*., 2018). It helps with difficulty in protein and lipase digestion, which when handled could in turn lead to the expression of incretin hormones. The pancreatic enzyme is administered alongside each meal of a diabetic patient. • Another treatment is insulin replacement therapy. This treatment will help reduce insulin deficiency and resistance as a means to curb the blood glucose level (Rahman *et al*., 2021).	
3.) Dietary / Nutrition management:	• Dietary advice involves the consumption of meals rich in soluble fiber and low fat. Regular fat-soluble vitamin supplementation is recommended (Makuc, 2016). • It is important to keep track of blood sugar levels, maintain regular eating times, avoid missing meals, and reduce intake of high-sugar foods and alcohol.	

MOA – Mechanisms of action

CONCLUSION

Type 3c diabetes mellitus (T3cDM) is a complex form of diabetes resulting from pancreatic disease, characterized by both exocrine and endocrine dysfunction. A comprehensive strategy is needed for effective treatment, including insulin medication, pancreatic enzyme replacement, and dietary changes to improve nutritional status and glucose control. Continued research into the pathophysiology and management of T3cDM is essential for improving diagnosis, treatment outcomes, and quality of life for affected individuals. Improved awareness among medical personnel is essential for timely identification and effective intervention, which in turn improves patient outcomes and management.

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