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Modern Understanding of the Pathogenesis of Type 3C Diabetes

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Abstract: Type 3c diabetes mellitus (T3cDM), also known as pancreatogenic diabetes, arises due to exocrine pancreatic disorders such as chronic pancreatitis, pancreatic necrosis, or surgery. Recent research highlights the multifactorial nature of T3cDM, involving not only β-cell destruction but also inflammation-driven islet remodeling, immune dysregulation, oxidative and ER stress, fibrosis, and hormonal imbalances. Key molecular mechanisms include activation of inflammasomes (NLRP3), JAK/STAT, and NF-κB pathways, suppression of Nrf2-mediated antioxidant defense, and cytokine-induced β-cell apoptosis. In addition, disturbances in incretin signaling, α- and δ-cell function, and exocrine insufficiency exacerbate metabolic instability. This review synthesizes current data on the morphofunctional alterations and immunometabolic mechanisms underlying T3cDM, underscoring the need for early detection, integrated treatment strategies, and preservation of residual islet function.

Keywords: Type 3c diabetes mellitus, Chronic pancreatitis, β-cell dysfunction, Inflammation, Oxidative stress.

Introduction

Pancreatogenic diabetes mellitus (type 3c diabetes, T3cDM) is a unique form of carbohydrate metabolism disorder that arises as a result of structural and functional damage to the pancreas, primarily in the context of chronic pancreatitis, pancreatic necrosis, and other diseases affecting the exocrine component of the organ. The pathogenesis of T3cDM is based on progressive and combined destruction of both the exocrine and endocrine pancreatic tissues, leading to impaired secretion of insulin, glucagon, and digestive enzymes, as well as disruption of glycemic regulation and malabsorption [8].

Current understanding of the pathogenesis of type 3c diabetes mellitus (T3cDM) has significantly expanded in recent years, moving beyond the classical concept of a simple loss of β-cell mass. Substantial evidence now highlights the involvement of a wide range of pathogenic mechanisms, including chronic inflammation, cytokine dysregulation, activation of both innate and adaptive immunity, mitochondrial dysfunction, endoplasmic reticulum stress (unfolded protein response, UPR), epigenetic modifications, as well as dysfunction of the gut–pancreas axis and alterations in the gut microbiota [14].

Literature analysis

Particular attention is given to the destruction of the islet apparatus under the influence of pro-inflammatory mediators—such as IL-1β, IL-6, and TNF-α—which activate the NLRP3 inflammasome and signaling cascades including JAK/STAT and TLR4/NF-κB, thereby promoting β-cell apoptosis and dysfunction [12].

These findings support the view that type 3c diabetes mellitus (T3cDM) should be regarded as a metabolic and immuno-inflammatory complication of pancreatic diseases, requiring a distinct diagnostic and therapeutic approach.

A key morphofunctional mechanism in the pathogenesis of pancreatogenic diabetes mellitus (type 3c diabetes, T3cDM) is the progressive damage and loss of β-cells in the islets of Langerhans, which are responsible for insulin secretion. These cells are particularly vulnerable to ischemic, inflammatory, and oxidative stress factors arising in the context of chronic pancreatic injury.

In chronic pancreatitis (CP), especially in its calcifying and obstructive forms, there is extensive fibrotic remodeling of pancreatic tissue, accompanied by disruption of organ architecture and vascularization. Studies have shown that patients with these forms of CP exhibit significantly reduced islet capillary perfusion, contributing to β-cell hypoxia and metabolic stress [13].

In the setting of chronic inflammation within the pancreatic tissue, inflammasomes—particularly NLRP3—are activated in response to acinar cell injury and the release of mitochondrial DNA, reactive oxygen species (ROS), and ATP. This activation leads to the maturation of pro-inflammatory cytokines IL-1β and IL-18, which, by interacting with receptors on β-cells, trigger signaling cascades that promote mitochondrial dysfunction, disruption of calcium homeostasis, and activation of caspase-dependent apoptosis [32].

Cytokines TNF-α and IL-6 also play an additional role by exerting their effects through receptor-mediated activation of the JAK2/STAT3 and NF-κB signaling pathways, thereby enhancing the expression of pro-inflammatory genes, chemokines, and death receptors. IL-1β further inhibits insulin gene transcription and downregulates the expression of key transcription factors essential for β-cell survival, such as PDX-1 and MafA [7].

The particular vulnerability of β-cells is further exacerbated by their inherently low level of antioxidant defense compared to other pancreatic cell types. During increased production of reactive oxygen species (ROS)—arising from both inflammation and mitochondrial dysfunction—oxidative damage to DNA, proteins, and lipids is triggered, ultimately leading to β-cell apoptosis. It has been shown that oxidative stress suppresses the Nrf2 signaling pathway, the key regulator of the cellular antioxidant response, thereby further reducing β-cell resistance to damaging factors [31].

Thus, β-cell dysfunction in type 3c diabetes mellitus (T3cDM) is multifactorial in nature and includes the following mechanisms:

- hypoxia and ischemia resulting from pancreatic fibrosis;
- cytokine-mediated damage (IL-1β, TNF-α, IL-6);
- activation of inflammasomes (particularly NLRP3);
- oxidative stress and suppression of Nrf2 activity;
- impaired expression of insulin-synthesizing and anti-apoptotic transcription factors;
- activation of signaling pathways such as JAK/STAT, NF-κB, and p38 MAPK.

In chronic pancreatitis (CP) and post-necrotic pancreatic remodeling, a sustained activation of the innate immune response is observed, primarily mediated by Toll-like receptor 4 (TLR4), which is expressed on macrophages, acinar cells, and islet cells. Ligand binding of TLR4 by exogenous and endogenous molecules—such as lipopolysaccharides (LPS) and damaged mitochondrial proteins—initiates a signaling cascade involving the activation of transcription factors NF-κB and STAT3, which, in turn, promote the production of pro-inflammatory cytokines including IL-1β, TNF-α, IL-6, and IFN-γ [22].

Cytokines IL-6 and TNF-α, along with IFN-γ, exert direct cytotoxic effects on β-cells by disrupting intracellular calcium homeostasis, inducing endoplasmic reticulum (ER) stress, and

activating the unfolded protein response (UPR), including the PERK–eIF2α, ATF6, and IRE1α–XBP1 branches. These signaling pathways lead to translational inhibition and suppression of insulin secretion, and with prolonged activation, they initiate β-cell apoptosis [9].

In addition, IL-1β and TNF-α are involved in the activation of JNK and p38 MAPK pathways, which further exacerbate the apoptotic response, downregulate the expression of insulin-synthesizing genes (PDX-1, Ins1/2), and impair the regeneration of the β-cell population [6].

In parallel with cytokine-mediated effects, oxidative stress plays a significant role. Under conditions of chronic inflammation, there is excessive generation of reactive oxygen species (ROS), both through the activity of NADPH oxidase in macrophages and acinar cells, and as a result of mitochondrial dysfunction. ROS induce damage to membranes, proteins, and mitochondrial DNA in β-cells, triggering the mitochondrial apoptosis pathway via the release of cytochrome c, apoptosis-inducing factor (AIF), and activation of caspase-9 [20].

The antioxidant defense mechanisms of β-cells are significantly less active compared to other tissues. Studies have shown that the expression levels of superoxide dismutase (SOD), catalase, and glutathione peroxidase are minimal in β-cells. In the context of chronic pancreatitis (CP), there is suppression of Nrf2 expression and its downstream targets, such as HO-1, NQO1, and GCLC, which compromises the cells' ability to neutralize reactive oxygen species (ROS) [31].

Prolonged exposure to ROS and pro-inflammatory cytokines also amplifies fibrogenic signaling by activating the TGF-β1/Smad2/3 and PI3K/Akt pathways, which promote the activation of pancreatic stellate cells (PSCs) and increased production of type I and III collagens. This further disrupts tissue microarchitecture and islet vascularization, impairing the functional integrity of β-cells and exacerbating insulin deficiency [1].

Thus, the inflammatory cascade and oxidative stress play a synergistic role in the progressive destruction and dysfunction of β-cells in type 3c diabetes mellitus (T3cDM). The combination of cytokine-induced endoplasmic reticulum stress, inflammasome activation, ROS-mediated damage, and antioxidant depletion leads to irreversible β-cell dysfunction, which underlies the unstable glycemic control characteristic of pancreatogenic diabetes.

Pancreatogenic diabetes mellitus (type 3c diabetes, T3cDM), which develops in the context of chronic pancreatic inflammation, is characterized not only by insulin deficiency but also by a complex disruption in the secretion of other endocrine hormones involved in glucose metabolism. One of the key pathogenic aspects is impairment of the incretin system.

Incretins—primarily glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP)—are synthesized by enteroendocrine cells of the intestine in response to nutrient intake and enhance glucose-dependent insulin secretion by β-cells. In chronic pancreatitis (CP), particularly in the presence of exocrine insufficiency, a reduction in incretin secretion and/or action is observed, leading to decreased β-cell glucose sensitivity and impaired postprandial glycemic control [15].

In patients with type 3c diabetes mellitus (T3cDM), a significant reduction in circulating levels of GLP-1 and GIP has been demonstrated, particularly after food intake. This may be attributed to both impaired nutrient absorption due to malabsorption and altered enteroendocrine regulation [18].

Alongside incretin impairment, dysfunction of δ-cells—which produce somatostatin, a universal inhibitor of hormonal secretion—is also observed. Somatostatin deficiency in chronic pancreatitis (CP) and type 3c diabetes mellitus (T3cDM) leads to impaired inhibition of insulin, glucagon, and pancreatic polypeptide secretion, thereby exacerbating hormonal imbalance [28]. Pancreatic polypeptide (PP), secreted by PP-cells of the pancreas, is also reduced in type 3c diabetes mellitus (T3cDM). PP plays a role in regulating pancreatic exocrine secretion, gastrointestinal motility, and satiety. Its decline in the context of chronic inflammation and fibrosis may be associated with pancreatic tissue degradation and contributes to impaired metabolic adaptation [29]. A particularly important factor in the pathogenesis of type 3c diabetes

mellitus (T3cDM) is the disruption of glucagon secretion by α-cells. In the early stages of the disease, compensatory hyperglucagonemia may occur; however, in the phase of pronounced islet destruction, glucagon secretion becomes suppressed. This creates a predisposition to severe hypoglycemic episodes, especially in the context of insulin therapy, due to impaired counterregulatory glucose control [27].

In T3cDM, a complex multihormonal deficiency develops, involving impaired secretion and action of incretins, deficiency of somatostatin and pancreatic polypeptide, as well as α-cell dysfunction. These alterations contribute to glycemic instability, reduced sensitivity to nutrient intake, and an increased risk of both hyperglycemic and hypoglycemic episodes. Such hormonal disturbances must be taken into account in the diagnosis and treatment of T3cDM, emphasizing the need for integrative approaches aimed not only at insulin replacement, but also at restoring the hormonal homeostasis of the pancreas.

Exocrine pancreatic insufficiency (EPI) is an integral component of the clinical presentation of pancreatogenic diabetes mellitus (T3cDM) and is closely associated with its pathogenesis. EPI is characterized by reduced secretion of key digestive enzymes—lipase, amylase, and proteases—as well as bicarbonates, leading to impaired digestion and absorption of nutrients, particularly fats and fat-soluble vitamins. This process results in malabsorption, steatorrhea, and weight loss, which adversely affect both general metabolic status and the function of β-cells in the islets of Langerhans [5].

Malabsorption of fats and fat-soluble vitamins (A, D, E, K), as well as trace elements such as zinc and magnesium, plays an important role in the deterioration of β-cell function. Zinc is involved in the stabilization of insulin crystals within secretory granules, while magnesium is essential for post-receptor insulin signal transduction. Deficiencies in these micronutrients are associated with impaired insulin secretion, reduced glucose sensitivity, and activation of oxidative stress [3].

Moreover, impaired nutrient absorption alters the enteroendocrine response. In the setting of exocrine pancreatic insufficiency (EPI), the secretion of incretins (GLP-1 and GIP) is reduced, which limits glucose-dependent insulin stimulation and exacerbates hyperglycemia [17].

A direct correlation has also been established between the severity of exocrine pancreatic insufficiency (EPI) and the extent of endocrine dysfunction. A large cohort study demonstrated that patients with chronic pancreatitis and fecal elastase-1 levels below 100 μg/g had a significantly higher incidence of type 3c diabetes mellitus (T3cDM) compared to those with preserved exocrine function [16].

An additional contributing factor is the alteration of gastrointestinal motility and changes in the composition of the gut microbiota in the context of exocrine pancreatic insufficiency (EPI). These changes can enhance inflammation, disrupt intestinal barrier function, and promote the activation of systemic inflammatory responses, which in turn exert further detrimental effects on insulin secretion [4].

Exocrine pancreatic insufficiency (EPI) is not an isolated phenomenon; rather, it has both direct and indirect effects on glucose metabolism in type 3c diabetes mellitus (T3cDM). Through nutrient deficiencies, impaired incretin response, and systemic inflammation, EPI exacerbates β-cell dysfunction and contributes to the progression of diabetes. This highlights the need for a comprehensive approach to diagnosis and treatment, including enzyme replacement therapy and nutritional support to correct EPI.

Pancreatogenic diabetes mellitus (T3cDM) may develop not only in the context of chronic pancreatitis but also as a long-term consequence of severe acute pancreatitis (AP), particularly when associated with pancreatic necrosis. Several clinical studies have shown that up to 23–40% of patients who experience severe AP develop persistent disturbances in glucose metabolism within 3 to 5 years, eventually leading to the full clinical manifestation of T3cDM [19].

A key pathogenic mechanism is the massive death of acinar cells with involvement of the islet apparatus in the inflammatory and necrotic process. Infiltration of the islets by neutrophils, macrophages, and activated T-lymphocytes leads to β-cell destruction already during the acute phase of inflammation. One of the central molecular mechanisms is the so-called cytokine storm that accompanies severe acute pancreatitis (AP). Elevated levels of pro-inflammatory mediators—including TNF-α, IL-1β, IL-6, and IFN-γ—activate signaling cascades that induce the expression of Fas and FasL, caspase activation, and β-cell apoptosis [2].

In the context of pancreatic necrosis, the damage is not limited to the islet epithelium—local microvascular disruption also occurs, leading to islet ischemia and the activation of oxidative stress. The level of reactive oxygen species (ROS) increases, activating NF-κB and MAPK pathways, thereby intensifying cell death and suppressing reparative processes [10].

Even after the clinical resolution of an acute episode of acute pancreatitis (AP), the risk of metabolic disturbances remains high. In the long-term phase, post-necrotic fibrosis develops, accompanied by the replacement of functional islets with connective tissue, impairment of capillary blood flow, and reduced proliferative activity of the remaining β-cells. These changes contribute to the development of persistent hyperglycemia, which subsequently progresses to the chronic form of type 3c diabetes mellitus (T3cDM) [30].

In addition to β-cell loss, damage to α- and δ-cells may also occur, disrupting the regulation of glucagon and somatostatin. This impairs glucose counterregulation and increases the risk of hypoglycemic episodes, particularly in patients receiving insulin therapy [26].

It is important to note that in some cases, post-necrotic type 3c diabetes mellitus (T3cDM) may develop even in the absence of overt clinical signs of chronic pancreatitis. This necessitates clinical vigilance and regular monitoring of glucose metabolism following episodes of severe acute pancreatitis (AP), particularly in necrotizing forms, prolonged inflammation, or infected pancreatic necrosis.

The development of T3cDM after AP is a clinically significant complication driven by a combination of islet necrosis, inflammatory signaling, vascular injury, and fibrotic tissue remodeling. These mechanisms highlight the need for a multidisciplinary approach to patient rehabilitation and the development of preventive strategies, including the early use of anti-cytokine and antioxidant therapies during the inflammatory phase.

The morphological structure of the pancreas in pancreatogenic diabetes mellitus (type 3c diabetes, T3cDM) undergoes complex changes that reflect the interplay of inflammatory, necrotic, fibrotic, and endocrine processes characteristic of chronic pancreatitis (CP) and post-necrotic states. Recent studies confirm that T3cDM is associated with marked destructive and degenerative transformations in both the exocrine and endocrine compartments of the pancreas, primarily affecting the islets of Langerhans.

One of the key morphological features is a significant reduction in the volume and density of the islets of Langerhans. According to immunohistochemical studies, β-cell mass in patients with T3cDM may be reduced by 50–80% compared to controls, particularly in cases of long-standing CP with calcifying changes [11].

Against the background of prolonged inflammation and fibrosis, diffuse sclerotic changes are observed in pancreatic tissue, characterized by the deposition of type I and III collagen, marked interstitial and periductal fibrosis, and replacement of normal acinar epithelium with connective tissue elements. These processes disrupt the tissue architecture, destroy the capillary network, and cause islet ischemia, thereby exacerbating the loss of endocrine function [25].

Immunophenotyping reveals active infiltration of the islets by macrophages and T-lymphocytes, particularly $CD68^+$ and $CD3^+$ cells, accompanied by increased expression of pro-inflammatory cytokines (TNF-α, IL-1β) and fibrogenic factors such as TGF-β1, indicating an ongoing inflammatory and remodeling process [33].

Histological examination of pancreatic tissue in patients with type 3c diabetes mellitus (T3cDM) often reveals macro- and microcalcifications, areas of fatty infiltration (steatosis), cystic changes, and intraparenchymal pseudocysts. These findings reflect the consequences of recurrent inflammatory episodes, necrosis, and impaired drainage of the pancreatic ducts [24].

One of the specific findings in patients with type 3c diabetes mellitus (T3cDM) is an altered ratio of cellular populations within the islets of Langerhans. Several studies have reported a disproportionate shift toward δ- and α-cells, with a relative increase in their proportion and a decrease in β-cells. This imbalance affects the homeostasis of insulin, glucagon, and somatostatin, further contributing to metabolic destabilization and predisposing to hypoglycemic episodes in the later stages of the disease [21].

It should also be noted that morphological changes in the pancreas in type 3c diabetes mellitus (T3cDM) are often accompanied by a reduced number of insulin-positive cells, impaired expression of glucose transporters (GLUT2), and diminished expression of β-cell proliferation markers such as Ki67. These findings indicate a decreased regenerative capacity of the islets and exhaustion of the functional reserve of the pancreas [23].

Conclusions

Thus, the morphological changes observed in type 3c diabetes mellitus (T3cDM) reflect the consequences of prolonged inflammation, fibrosis, vascular disturbances, and immune-mediated injury, leading to structural destruction and functional exhaustion of the endocrine component of the pancreas. These findings emphasize the importance of early diagnosis of T3cDM and the implementation of comprehensive therapy aimed not only at glycemic control but also at anti-inflammatory and antifibrotic interventions, with the goal of preserving residual β-cell mass and slowing the progression of morphological deterioration.

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