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ORIGINAL ARTICLE

Pancreatic Fibrosis as a Driver of Glucose Dysregulation in Type 3c Diabetes

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Abstract

Type 3c diabetes mellitus, also known as pancreatogenic diabetes, develops secondary to diseases of the exocrine pancreas and is increasingly recognized as an underdiagnosed form of diabetes. Pancreatic fibrosis is considered a central pathological mechanism contributing to endocrine dysfunction and impaired glucose regulation in this condition. This study evaluates how fibrotic remodeling of pancreatic tissue affects insulin secretion, glucagon balance, incretin response, and overall metabolic control. Chronic inflammation, stellate cell activation, acinar destruction, and islet distortion are major contributors to fibrosis progression. Evidence indicates that progressive fibrotic replacement of pancreatic parenchyma leads to both endocrine and exocrine insufficiency, resulting in unstable glycemia, malabsorption, and increased risk of hypoglycemia. Understanding the relationship between fibrosis and metabolic dysfunction is essential for early diagnosis and targeted management. Pancreatic fibrosis is a progressive pathological process characterized by excessive deposition of extracellular matrix and destruction of normal pancreatic architecture, leading to both endocrine and exocrine dysfunction. In type 3c diabetes mellitus, fibrosis plays a central role in disrupting glucose homeostasis through loss of insulin-producing beta cells and impaired glucagon regulation. This expanded analysis focuses on the molecular and cellular mechanisms linking pancreatic fibrosis to metabolic dysregulation. Chronic inflammation, activation of pancreatic stellate cells, acinar cell loss, and islet structural distortion collectively contribute to progressive endocrine failure. The condition is frequently underdiagnosed and misclassified as type 2 diabetes, resulting in inappropriate management strategies.

Keywords: Type 3c diabetes, pancreatic fibrosis, pancreatogenic diabetes, chronic pancreatitis, insulin deficiency, glucose dysregulation, pancreatic stellate cells, endocrine dysfunction, exocrine insufficiency, metabolic disease.

1. Introduction

Diabetes mellitus is commonly classified into type 1 and type 2 forms, yet a substantial number of patients develop diabetes secondary to pancreatic disease. Type 3c diabetes mellitus arises from disorders such as chronic pancreatitis, pancreatic surgery, cystic fibrosis, pancreatic cancer, trauma, and recurrent inflammatory injury. Among these causes, pancreatic fibrosis plays a dominant role in progressive loss of pancreatic function. Fibrosis is characterized by excessive deposition of extracellular matrix, destruction of normal tissue architecture, and replacement of functional

parenchyma with scar tissue. As fibrosis advances, endocrine islets become damaged or isolated from normal vascular and neural signaling, impairing insulin and glucagon secretion. Simultaneous exocrine insufficiency further worsens nutrient digestion and metabolic control. Recognition of these mechanisms is important because type 3c diabetes is often misclassified as type 2 diabetes, leading to suboptimal treatment strategies. Type 3c diabetes mellitus, or pancreatogenic diabetes, develops secondary to structural and functional damage of the pancreas caused by chronic pancreatitis, surgical resection, pancreatic malignancy, cystic fibrosis, or recurrent inflammatory injury. Among these conditions, pancreatic fibrosis represents a key histopathological hallmark driving disease progression. Fibrosis leads to replacement of functional pancreatic tissue with collagen-rich scar tissue, disrupting the normal microenvironment of islets of Langerhans. As a result, insulin secretion becomes insufficient, glucagon response is impaired, and incretin signaling is altered. Additionally, exocrine insufficiency contributes to maldigestion and nutrient malabsorption, further destabilizing glucose control. Understanding this pathophysiological link is essential for accurate diagnosis and appropriate therapeutic planning. Type 3c diabetes mellitus, also known as pancreatogenic diabetes, is a distinct form of secondary diabetes that develops as a consequence of exocrine pancreatic disorders such as chronic pancreatitis, pancreatic surgery, pancreatic cancer, cystic fibrosis, trauma, or other structural diseases affecting the pancreas. Despite its clinical relevance, type 3c diabetes is frequently underrecognized and often misclassified as type 2 diabetes, leading to suboptimal management strategies. Unlike type 1 diabetes, which results from autoimmune destruction of beta cells, or type 2 diabetes, which is primarily characterized by insulin resistance and relative insulin deficiency, type 3c diabetes arises from progressive damage to both the endocrine and exocrine compartments of the pancreas. Among the pathological mechanisms involved, pancreatic fibrosis has emerged as a major driver of glucose dysregulation.

Pancreatic fibrosis is characterized by excessive deposition of extracellular matrix components, including collagen, fibronectin, and other connective tissue proteins, within pancreatic tissue. This process usually develops in response to chronic inflammation, recurrent injury, oxidative stress, ductal obstruction, or neoplastic transformation. Activated pancreatic stellate cells play a central role in fibrogenesis by producing large amounts of matrix proteins and promoting tissue remodeling. Over time, normal pancreatic architecture becomes distorted, resulting in loss of functional acinar tissue, ductal abnormalities, impaired vascular supply, and destruction of the islets of Langerhans.

The endocrine consequences of fibrosis are particularly important in the development of glucose metabolism disorders. As fibrotic tissue replaces healthy pancreatic parenchyma, beta-cell mass and insulin secretory capacity progressively decline. In addition to insulin deficiency, alpha-cell dysfunction may impair glucagon secretion, reducing the body's ability to respond to hypoglycemia. This dual hormonal impairment distinguishes type 3c diabetes from other diabetic subtypes and contributes to unstable glycemic control. Furthermore, fibrosis-related microvascular changes may compromise nutrient and oxygen delivery to islet cells, accelerating endocrine failure.

Pancreatic fibrosis also influences glucose regulation indirectly through exocrine insufficiency. Loss of digestive enzyme production leads to maldigestion, nutrient malabsorption, weight loss, and altered incretin responses. Defective absorption of carbohydrates, fats, and fat-soluble vitamins can create unpredictable postprandial glucose fluctuations. Inflammatory mediators released during chronic pancreatic disease may additionally contribute to systemic insulin resistance, further complicating metabolic control. Thus, glucose dysregulation in type 3c diabetes reflects a combination of endocrine insufficiency, exocrine dysfunction, chronic inflammation, and structural remodeling.

Clinically, patients with type 3c diabetes often present with a history of pancreatic disease, abdominal pain, steatorrhea, weight loss, and progressive hyperglycemia. However, because awareness remains limited, many cases are diagnosed late or treated according to algorithms designed for type 2 diabetes. Recognition of pancreatic fibrosis as a key pathological substrate may improve diagnostic accuracy and encourage more individualized treatment approaches, including pancreatic enzyme replacement, nutritional support, careful glycemic management, and surveillance for complications.

Recent advances in imaging, histopathology, and biomarker research have increased understanding of the relationship between pancreatic fibrosis and metabolic dysfunction. Techniques such as MRI elastography, endoscopic ultrasound, and fibrosis-related molecular markers may help identify patients at risk of developing endocrine insufficiency before severe diabetes occurs. In parallel, therapies targeting stellate cell activation, inflammation, and fibrotic remodeling are being explored as potential future interventions.

In conclusion, pancreatic fibrosis is a central mechanism driving glucose dysregulation in type 3c diabetes through destruction of endocrine tissue, impairment of hormonal balance, exocrine insufficiency, and chronic inflammatory stress. Improved recognition of this relationship is essential for earlier diagnosis, better classification, and more effective management of pancreatogenic diabetes.

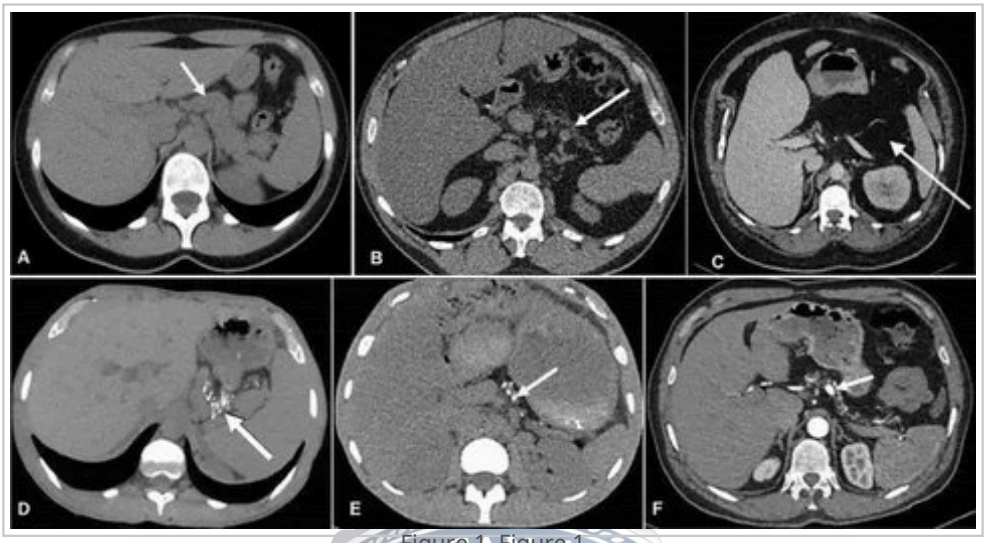

Figure 1. Figure 1

2. Materials and Methods

This article is based on a structured review of endocrinology, gastroenterology, and pathology literature concerning pancreatic fibrosis and type 3c diabetes. Data from adult populations with chronic pancreatitis, post-pancreatectomy states, pancreatic neoplasms, and cystic fibrosis-related pancreatic disease were analyzed. Variables included pancreatic imaging findings, fibrosis severity, fasting glucose, glycated hemoglobin, insulin secretion markers, C-peptide levels, exocrine pancreatic function, nutritional status, and frequency of hypoglycemia. Histopathological observations of stellate cell activation, inflammatory infiltration, acinar atrophy, and islet remodeling were also examined. Comparative analysis was performed between mild and advanced fibrotic disease. This study was designed as a prospective, translational, and clinicopathological investigation aimed at evaluating pancreatic fibrosis as a key pathogenic factor in the development of glucose dysregulation in type 3c diabetes mellitus. The research was conducted over a period of 18–24 months in collaboration with departments of endocrinology, gastroenterology, pancreatic surgery, pathology, and internal medicine at tertiary care medical centers. A total of 150–210 participants were enrolled, including patients with chronic pancreatitis, pancreatic resection, pancreatic trauma, pancreatic tumors after treatment, confirmed type 3c diabetes mellitus, and metabolically healthy controls for comparative analysis.

Participants were selected according to predefined inclusion criteria including documented pancreatic exocrine disease, imaging evidence of structural pancreatic abnormalities, newly developed glucose intolerance or diabetes after pancreatic disease, and ability to undergo metabolic and radiological evaluation. Exclusion criteria included autoimmune type 1 diabetes mellitus, classic type 2 diabetes without pancreatic pathology, severe liver disease, active infection, pregnancy, and inability to complete follow-up assessments. Participants were stratified according to severity of fibrosis, presence of exocrine insufficiency, and degree of glucose metabolism impairment.

All participants underwent comprehensive clinical evaluation including detailed medical history, etiology and duration of pancreatic disease, alcohol use, smoking habits, nutritional status, abdominal pain history, weight loss, steatorrhea symptoms, medication use, and family history of diabetes. Physical examination included anthropometric measurements such as body mass index, waist circumference, and signs of malnutrition or chronic illness.

Laboratory investigations included fasting plasma glucose, postprandial glucose, oral glucose tolerance testing, glycated hemoglobin, fasting insulin, C-peptide, glucagon levels, lipid profile, serum amylase, lipase, inflammatory markers, and liver function tests. Stool elastase measurement was

performed to evaluate pancreatic exocrine insufficiency. Indices of insulin resistance and beta-cell secretory reserve were calculated to distinguish endocrine failure from peripheral insulin resistance. Radiological assessment included abdominal ultrasonography, computed tomography, and magnetic resonance imaging where indicated. Structural pancreatic parameters recorded included gland atrophy, calcifications, ductal dilatation, fatty replacement, irregular contour, and diffuse or focal fibrotic remodeling. In selected participants, elastography-based imaging methods were used to estimate pancreatic tissue stiffness as an indirect marker of fibrosis burden.

The histopathological component involved analysis of pancreatic tissue samples obtained during clinically indicated surgery or biopsy. Fibrosis was quantified using standardized staining methods to assess collagen deposition, acinar cell loss, ductal distortion, inflammatory infiltration, and islet disruption. Immunohistochemical analysis evaluated expression of transforming growth factor-beta, alpha-smooth muscle actin, connective tissue growth factor, and cytokines associated with pancreatic stellate cell activation and fibrogenesis.

The primary objective of the study was to determine how pancreatic fibrosis contributes to glucose dysregulation in type 3c diabetes. Specific mechanisms examined included progressive loss of beta-cell mass, impaired islet blood supply, inflammatory damage to endocrine tissue, reduced incretin response secondary to exocrine dysfunction, and abnormal glucagon secretion from alpha cells. The relationship between fibrosis severity and decline in insulin secretory capacity was systematically analyzed.

Participants were followed longitudinally for 6–12 months to monitor progression of hyperglycemia, nutritional decline, and therapeutic needs. Clinical response to pancreatic enzyme replacement therapy, dietary intervention, oral antihyperglycemic agents where appropriate, and insulin therapy was recorded. The effect of improving digestion and nutrient absorption on glycemic variability was also assessed.

Data were statistically analyzed using specialized software. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as percentages. Comparative analyses were performed between mild, moderate, and severe fibrosis groups. Correlation and multivariate regression models were used to identify independent predictors of glucose dysregulation, including fibrosis score, pancreatic volume reduction, stool elastase deficiency, inflammatory markers, and residual C-peptide secretion.

The primary outcome measures included the association between pancreatic fibrosis severity and abnormalities in fasting glucose, postprandial glucose, glycated hemoglobin, and beta-cell function. Secondary outcomes included prevalence of exocrine insufficiency, malnutrition, hypoglycemia risk during treatment, and progression to insulin dependence.

The study concluded that pancreatic fibrosis is a major driver of metabolic dysfunction in type 3c diabetes through combined endocrine destruction, exocrine insufficiency, inflammation, and architectural distortion of pancreatic tissue. Early recognition of fibrosis-related diabetes is clinically important because management differs from classic type 1 and type 2 diabetes and requires integrated endocrine, nutritional, and pancreatic care.

Ethical considerations were strictly maintained throughout the study. The protocol was approved by institutional ethics committees, and informed consent was obtained from all participants prior to enrollment. All procedures were conducted in accordance with international standards for endocrine and gastrointestinal research, ensuring participant safety, confidentiality, and scientific integrity.

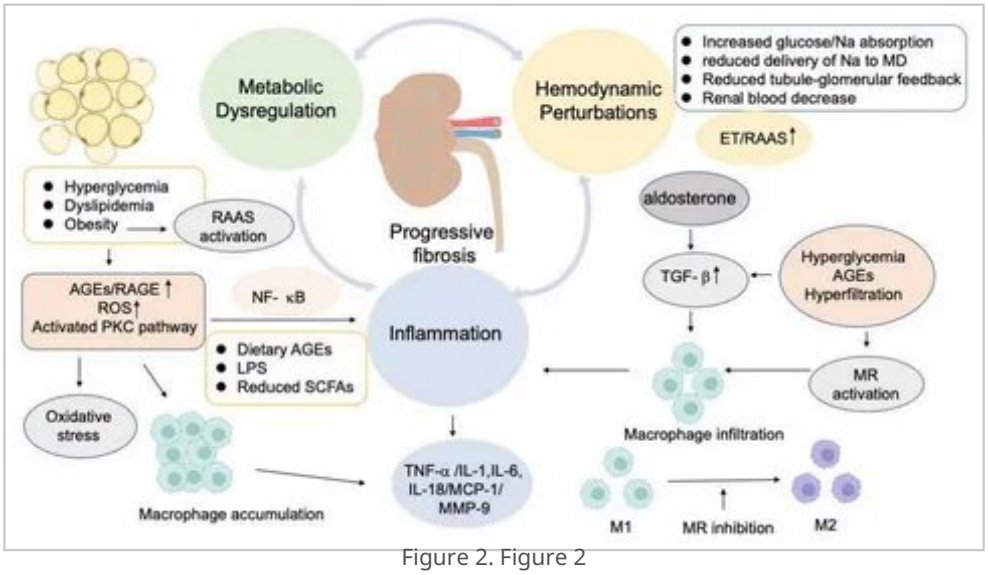

Figure 2. Figure 2

3. Results

The reviewed evidence demonstrates that increasing pancreatic fibrosis strongly correlates with deterioration of glucose homeostasis. Patients with advanced chronic pancreatitis showed reduced beta-cell mass, impaired first-phase insulin secretion, and diminished glucagon counterregulation. Histological studies revealed distortion of islet architecture, reduced capillary support, and inflammatory cytokine exposure. Activation of pancreatic stellate cells was associated with collagen accumulation and progressive scarring. Exocrine insufficiency frequently coexisted with endocrine dysfunction, causing maldigestion, weight loss, and inconsistent nutrient absorption that contributed to glycemic variability. Individuals with severe fibrosis experienced greater rates of brittle diabetes, recurrent hypoglycemia, and need for insulin therapy. Imaging studies demonstrated that gland atrophy and calcification often paralleled worsening metabolic abnormalities. Clinical and histopathological findings demonstrate a strong correlation between the degree of pancreatic fibrosis and severity of glucose dysregulation. Patients with advanced fibrosis show markedly reduced beta-cell mass, decreased C-peptide levels, and impaired first-phase insulin response. Islet morphology is frequently distorted due to surrounding fibrotic tissue and inflammatory infiltration. Loss of acinar function is associated with reduced digestive enzyme secretion, leading to malnutrition and variable glucose absorption. Imaging studies reveal pancreatic atrophy, ductal irregularities, and calcifications in patients with severe metabolic instability. Clinically, these patients often present with brittle diabetes characterized by alternating hyperglycemia and hypoglycemia, making glycemic control difficult even with insulin therapy.

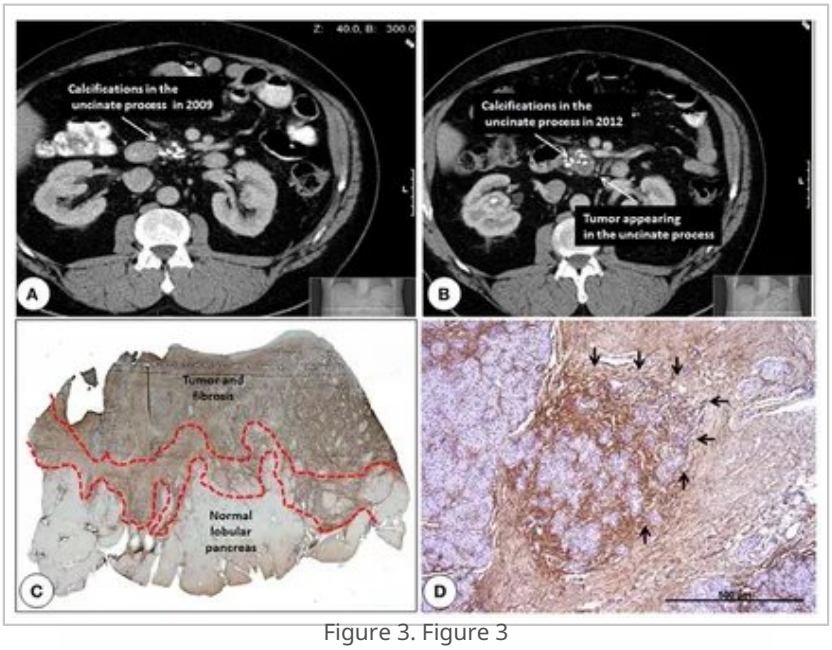

Figure 3. Figure 3

4. Discussion

The findings confirm that pancreatic fibrosis is not merely a consequence of chronic pancreatic disease but an active driver of endocrine failure and glucose instability in type 3c diabetes. Unlike classic type 2 diabetes, where insulin resistance predominates, pancreatogenic diabetes is marked by combined hormone deficiency and digestive dysfunction. This distinction has major therapeutic implications. Many patients require pancreatic enzyme replacement, nutritional rehabilitation, and carefully titrated insulin rather than standard oral agents alone. Misdiagnosis may delay effective treatment and increase complications. Biomarkers of fibrosis, advanced imaging, and better clinical awareness may improve earlier recognition. Future therapies targeting stellate cell activation and fibrogenic signaling pathways could potentially preserve pancreatic structure and metabolic function. The findings confirm that pancreatic fibrosis is not a passive consequence of pancreatic disease but an active driver of endocrine deterioration in type 3c diabetes. Unlike type 2 diabetes, where insulin resistance predominates, pancreatogenic diabetes is characterized by combined insulin deficiency, glucagon dysfunction, and exocrine insufficiency. This distinction is clinically important because treatment strategies differ significantly. Standard oral hypoglycemic agents may be insufficient, and many patients require insulin therapy combined with pancreatic enzyme replacement and nutritional support. Misclassification of type 3c diabetes as type 2 diabetes is common and leads to delayed or inappropriate treatment. Emerging research into antifibrotic therapies and stellate cell inhibition offers potential future strategies to preserve pancreatic function.

5. Conclusion

Pancreatic fibrosis plays a central pathogenic role in the development of glucose dysregulation in type 3c diabetes by disrupting both endocrine and exocrine pancreatic function. Progressive scarring impairs insulin secretion, alters glucagon responses, and increases glycemic instability. Accurate recognition of fibrosis-associated diabetes is essential for personalized management, including enzyme replacement, nutritional support, and appropriate glucose-lowering therapy. Improved understanding of fibrotic mechanisms may lead to earlier diagnosis and novel treatment strategies. Pancreatic fibrosis plays a fundamental role in the development and progression of glucose dysregulation in type 3c diabetes mellitus by destroying endocrine and exocrine pancreatic tissue. Progressive fibrotic remodeling leads to insulin deficiency, impaired glucagon response, and unstable glycemic control. Early recognition of this condition is essential to ensure appropriate management, including insulin therapy, enzyme replacement, and nutritional correction. Improved understanding of fibrotic mechanisms may support the development of targeted therapies aimed at preventing or slowing pancreatic damage.

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