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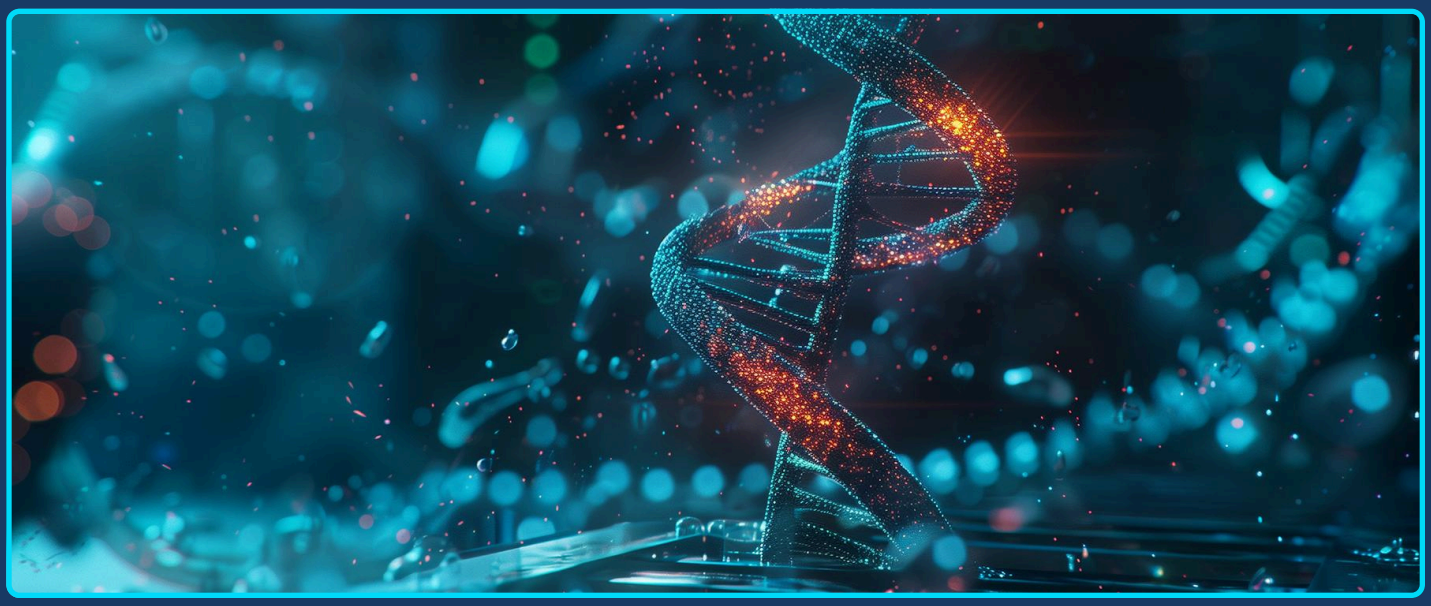

Topic: Gastroenterology and Genetics

Editor: David C Whitcomb MD PhD

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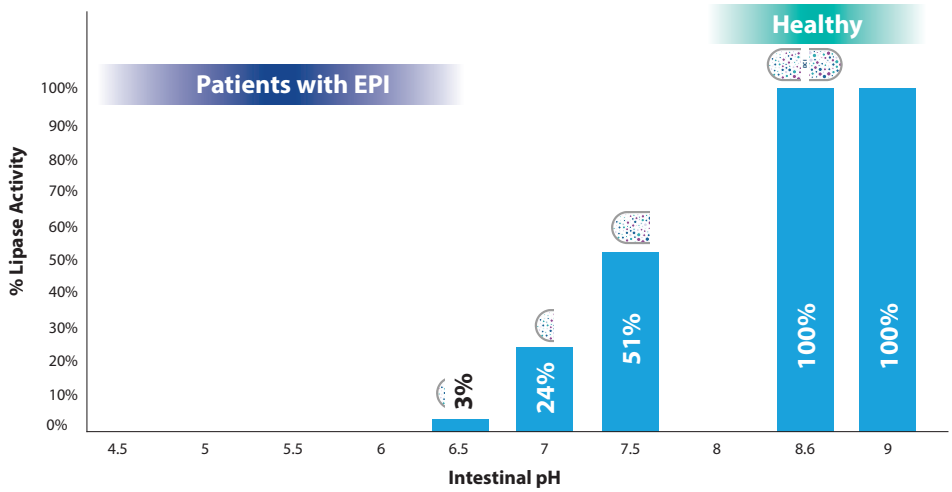

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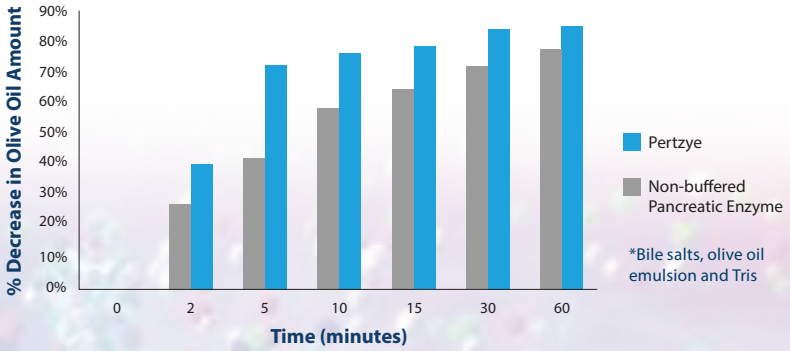

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SMART Medical Review

Type 3c Diabetes: Bridging the Diagnostic and Therapeutic Gap in Pancreatogenic Diabetes

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Abstract: Type 3c diabetes mellitus (T3cDM), also known as pancreatogenic diabetes, arises from diseases affecting the exocrine pancreas and is frequently misclassified as type 1 or type 2 diabetes mellitus. Despite accounting for an estimated 5–10% of diabetes cases in Western populations, T3cDM remains underrecognized in clinical practice. It encompasses a heterogeneous group of conditions, including chronic pancreatitis, pancreatic cancer, cystic fibrosis, and pancreatic surgery, each with distinct implications for metabolic and nutritional management.

The clinical presentation of T3cDM often involves both insulin deficiency and exocrine pancreatic insufficiency, leading to complex challenges in glycemic control and increased risk for micronutrient deficiencies. Misclassification can result in inappropriate treatment strategies and poorer outcomes. Recognizing the unique pathophysiology of T3cDM is essential for tailoring therapy that addresses both endocrine and exocrine dysfunction.

Early diagnosis and a multidisciplinary approach are critical to optimize glucose management, nutritional status, and long-term health outcomes in this population. Greater awareness and clearer diagnostic criteria are needed to ensure patients with T3cDM receive timely and appropriate care.

Key words: *Type 3c diabetes, pancreatogenic diabetes, pancreatic endocrine insufficiency, exocrine pancreatic insufficiency, chronic pancreatitis and diabetes, secondary diabetes mellitus.*

Outline:

1. Overview

Type 3c diabetes (T3cDM), or diabetes due to disease of the exocrine pancreas, is a form of diabetes that arises from pancreatic damage. Though it accounts for 5–10% of diabetes cases in Western populations[(1)], it remains underrecognized and is frequently misclassified as either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus

Abbreviations used in this paper: T3cDM, Type 3c Diabetes Mellitus; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; CP, Chronic Pancreatitis; PEI, Pancreatic exocrine insufficiency; PDAC, Pancreatic Adenocarcinoma; PERT, Pancreatic enzyme replacement therapy; GIP, glucose-dependent insulinotropic polypeptide.

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(T2DM). T3cDM includes a broad spectrum of pancreatic disease with variable presentation and need for individualized treatment. Individuals with exocrine pancreatic insufficiency may have nutritional deficiencies in addition to lack of insulin secretion. Failure to recognize this altered physiology may result in suboptimal glycemic and nutritional management. Therefore, early recognition of T3cDM is critical to safely achieve adequate glucose control and to optimize long-term patient outcomes.

2. Background

The acronym, Type 3c diabetes, was adopted when the American Diabetes Association listed pancreatogenic diabetes under Category III, other specific types, in the 1997 paper on the diagnosis and classification of diabetes.[2] This classification of diabetes mellitus by the American Diabetes Association and World Health Organization has continued and now defines diabetes mellitus related to disease of the exocrine pancreas as pancreatogenic diabetes or T3cDM but does not offer specific diagnostic criteria or make treatment recommendations. (see Table 1) T3cDM has become the second most common type of diabetes in adults after T2DM, surpassing the prevalence of T1DM.[3] The projected incidence of T3cDM is expected to reach 16 individuals per 100,000 by 2050, indicating an average annual growth rate of approximately 3%.[4]

Table 1. Comparative Features of Type 1, Type 2, and Type 3c Diabetes Mellitus

Feature	Type 1 Diabetes (T1DM)	Type 2 Diabetes (T2DM)	Type 3c Diabetes (T3cDM)
Onset	Rapid in younger patients, slower in older patients	Gradual; may be preceded by pre-diabetes	Variable: post-pancreatic injury (though this history could be remote)
Age	Often children/young adults but can be diagnosed at any age	Gradual, typically in older adults with rising incidence in younger people with obesity	Any age. frequently misdiagnosed as T2DM
Etiology	Autoimmune β-cell destruction	Insulin resistance + β-cell dysfunction	Endocrine and Exocrine pancreatic disease or injury
Autoantibodies	GAD65, IA-2, ZnT8 (positive)	Negative	Negative (Autoantibody positivity in type 3c is rare, but when present can be transient (due to islet antigen release) or persistent in the setting of ongoing islet inflammation)[26]
C-peptide	Low/undetectable	Normal or high (early), low (late)	Low or variable
Insulin Resistance	Not central	Key feature	Controversial (mild/absent with reports of hepatic insulin resistance)
Ketoacidosis Risk	High	Rare	Rare
Exocrine Dysfunction	Absent	Absent	Present
Common Causes	Genetic predisposition, viral triggers	Obesity, lifestyle, genetics	Chronic pancreatitis, surgery, cystic fibrosis, hemochromatosis, pancreatic cancer
Diagnosis	Autoantibodies frequently positive.	In setting of obesity and metabolic syndrome	History of pancreatic disease, abnormal findings on pancreatic imaging, evidence of exocrine pancreatic insufficiency.
Management	Lifelong insulin therapy	Lifestyle modifications, non-insulin diabetes medications ± insulin	Insulin often needed ± enzyme replacement therapy. Monitor brittle glucose control.

3. Etiologies and Pathophysiology

The pathophysiology of T3cDM is characterized by a multifactorial process resulting from diseases that damage the exocrine pancreas, including chronic pancreatitis, pancreatic ductal adenocarcinoma, cystic fibrosis, hemochromatosis, genetic syndromes, and surgical resection. These etiologies lead to a combination of insulin deficiency (due to destruction or dysfunction of pancreatic islets), glucagon deficiency, and pancreatic exocrine insufficiency. Pancreatitis is the leading cause of pancreatogenic diabetes, accounting for 80% of cases in adults. Of these cases, 80% are due to acute pancreatitis and 20% are due to chronic pancreatitis (CP), including autoimmune and necrotizing pancreatitis. (see Table 2) Acute pancreatitis is associated with a rapid onset of diabetes, often within months to years after the initial episode. The primary mechanism is inflammatory destruction of pancreatic islet cells, which may be exacerbated by severe disease, necrosis, or organ failure.[5] In contrast, chronic pancreatitis leads to diabetes through progressive, irreversible fibrosis and destruction of both exocrine and endocrine pancreatic tissue. The risk of diabetes increases with disease duration and severity, with up to 30–75% of adults affected over time.[6] In terms of risk factors, T3cDM risk was elevated not only by pancreatitis-related factors such as advanced morphological changes, exocrine insufficiency, and prior pancreatic surgery, but also by traditional type 2 diabetes risk factors including obesity and family history.[7] Additionally, intrapancreatic inflammation disrupts β-cell function early in CP with studies showing elevated islet levels of IFN γ and Th1/Th17 infiltration impairing insulin gene transcription through JAK STAT signaling and promoting β-cell dysfunction before overt fibrosis or mass loss occurs.[8] Complementing this, experimental data demonstrate that proinflammatory cytokines such as IL 1β, IL 6, and TNF α cause β-cell dedifferentiation and impaired insulin secretion.[9] Pancreatic adenocarcinoma (PDAC) accounts for about 18% of cases of T3cDM, and genetic causes such as cystic fibrosis[10], hemochromatosis and enzyme mutations account for a much smaller percentage.[11] In all of these types of pancreatic disease, progressive loss of acinar and islet cell mass is common leading to insulin and pancreatic enzyme deficiencies over time. Reduction in islet cell mass in T3cDM confers unique physiologic changes compared to loss of beta cells which is typical in T1DM and long-standing T2DM. Unlike other forms of T3cDM, diabetes secondary to PDAC appears to result primarily from paraneoplastic effects, with tumor-derived mediators and inflammatory signaling pathways contributing to β-cell dysfunction and insulin resistance, rather than pancreatic destruction per se.[12] In addition to insulin deficiency, loss of alpha cells reduces glucagon secretion which increases susceptibility to hypoglycemia. On the other hand, pancreatic polypeptide deficiency is a common finding in T3cDM, leading to persistent hepatic glucose production, reduced hepatic insulin receptor expression, and consequently increased hepatic insulin resistance.[13] Loss of islet cells, in particular insulin secretion from beta cells, reduces trophic influences on neighboring acinar cells and is one factor in the progression of pancreatic exocrine insufficiency. Inflammation and ductal obstruction are other factors. Emerging evidence suggests that islet autoimmunity may contribute to β-cell dysfunction in a subset of patients with pancreatitis-related diabetes. In a recent multicenter cohort of 927 individuals with acute, recurrent acute, or chronic pancreatitis, 5.5% were positive for at least one islet autoantibody and 3.2% for two or more, after excluding insulin autoantibody reactivity.[14]

Table 2. Etiologies of Type 3c Diabetes Mellitus by Prevalence

Etiology	% Prevalence
Acute/Recurrent/Chronic Pancreatitis	~40–70%
Pancreatectomy	~20%
Pancreatic Cancer	~10%
Cystic Fibrosis	<5%
Hemochromatosis	Rare
Trauma	Rare

4. Genetics and Biomarkers

T3cDM is not a primary genetic disorder with no established genetic risk factors or loci, however, genetic predisposition to the underlying pancreatic diseases may indirectly increase risk. Furthermore, Genetic studies have identified mutations in Serine Protease 1 – Trypsin 1 (PRSS1), Serine Protease Inhibitor Kazal Type 1 (SPINK1), Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), Chymotrypsin C (CTRC), and Calcium-Sensing Receptor (CASR) as contributing factors to the development of chronic pancreatitis and increased risk of pancreatic cancer.[11] On the other hand, many biomarkers have been identified and evaluated in patients with T3cDM to see if they provide guidance in distinguishing this diagnosis from other types of diabetes. A T3cDM index proposed by Juza et al. demonstrated high sensitivity and specificity for identifying T3cDM. This index incorporates fasting insulin, BMI, adrenomedullin, and eGFR; and is significantly lower in patients with T3cDM.[15] Patients with CP or pancreatic cancer exhibit lower levels of C-peptide and insulin, elevated adiponectin concentrations,[16,17] and diminished pancreatic polypeptide responses compared to those with T2DM.[18] In pancreatic cancer–associated diabetes, inflammatory mediators such as metalloproteinase-9 (MMP9) and calprotectin (S100A8/A9) are implicated in β-cell dysfunction and have been proposed as biomarkers to distinguish this form of diabetes from T2DM.[13]

5. Clinical Manifestations, Diagnostic Criteria and Challenges

Clinical presentation of T3cDM can range from mild glucose intolerance to brittle diabetes, marked by frequent hypoglycemia due to paradoxical insulin sensitivity and impaired hepatic glucose regulation.[19] The risk of severe hypoglycemia in patients with CP related diabetes is fivefold higher compared with that of patients with T2DM. Up to 85% of patients with pancreatic cancer develop glucose abnormalities 1–2 years prior to diagnosis.[15]

The diagnosis of T3cDM is based on hyperglycemia plus evidence of pancreatic disease, but exact criteria are lacking. Diabetes is diagnosed using the usual glucose criteria,[2] however, further evaluation to assess both endocrine and exocrine pancreatic function is needed to fully characterize the severity of T3cDM.[20] Ewald and Bretzel proposed using imaging evidence of pancreatic pathology together with evidence of pancreatic exocrine insufficiency and absence of autoimmune markers suggestive of T1DM to diagnose T3cDM, though these criteria are not widely accepted. (see Table 3)

Pancreatic exocrine insufficiency (PEI) should be suspected in patients with an underlying pancreatic disease in addition to steatorrhea, weight loss, bloating, excessive flatulence, fat-soluble vitamin deficiencies, and protein-calorie malnutrition. Pancreatic function tests are objective, however, fecal elastase test is the most appropriate initial and diagnostic test.[21] Pancreatic endocrine dysfunction is characterized by low C-peptide, low or absent glucagon and pancreatic polypeptide levels.[13] T3cDM can be superimposed on long-standing T1DM, as up to 5% of these patients show pancreatic atrophy on imaging and may have findings of pancreatic exocrine insufficiency.[22] Pancreatitis can worsen insulin deficiency in individuals with a history of T2DM which also presents a diagnostic challenge.

Table 3. Tools and Tests to Aid in Diagnosing T3cDM

Tool/Test	Purpose	Notes
Detailed History	Identify potential patients with T3cDM	Examples include lack of metabolic syndrome, lower BMI, history of intermittent and unexplained abdominal pain, abdominal trauma or surgery, cholelithiasis, pancreatitis, alcohol and tobacco use
Fecal Elastase-1	Assesses pancreatic exocrine output	<100 µg/g indicative of PEI, >100 and <200 µg/g is intermediate
Serum lipase	Assess exocrine pancreatic mass	<20 units/L is suggestive of low pancreatic mass
Fat soluble vitamin levels	Assess exocrine pancreatic function	Fasting vitamin levels (vitamins A, D, E, K)
Postprandial C-Peptide, Insulin	Assess endogenous insulin secretion	Often low in T3cDM
Autoantibodies (GAD65, IA2, ZNT8)	Rule out Type 1 diabetes	Strongly positive levels indicate T1DM
CT/MRI/EUS	Evaluate pancreatic structure	Look for calcification, atrophy, inflammation, narrow pancreatic duct, cysts or masses
HbA1c, OGTT	Diagnose hyperglycemia	OGTT may show delayed insulin peak
Pancreatic Enzyme Trial	Therapeutic test	Improves glucose control, gastrointestinal symptoms and nutrition

6. Precision Management Strategies

Comprehensive management of individuals with T3cDM involves controlling hyperglycemia, addressing exocrine insufficiency, and preventing or correcting nutritional deficiencies. Clinically significant protein and fat malabsorption typically does not manifest until more than 90% of pancreatic exocrine function is lost; however, clinical studies suggest that many patients with chronic pancreatic disease experience some degree of malabsorption even before reaching this threshold.[23] Pancreatic enzyme replacement (PERT) is recommended when exocrine function is found to be deficient and when patients have symptoms of fat malabsorption and rapid gut transit. Some patients may require PERT, while others may need dietary counseling and selective vitamin replacement, the most common being vitamin D supplementation.[24] When PEI with symptoms is identified, clinical evidence supports 40,000–50,000 lipase units per meal, titrated to symptom relief.[20,25] Notably, PERT restores the diminished incretin response, specifically glucose-dependent insulinotropic polypeptide (GIP), in patients with PEI, thereby helping to optimize blood glucose control. Randomized controlled trials in cystic fibrosis and chronic pancreatitis populations demonstrate that PERT normalizes postprandial GIP and GLP-1 secretion, slows gastric emptying, and attenuates postprandial

hyperglycemia, even when insulin secretion is unchanged. The mechanism is attributed to improved nutrient breakdown and absorption, which restores physiological incretin release and enhances the enteroinsular axis.[26,27] Ongoing monitoring of nutritional status and vitamin levels is needed to prevent protein-calorie and micronutrient malnutrition.[28]

7. Diabetes Treatment

Specific guidance for therapy order in T3cDM is limited, and recommendations are largely extrapolated from type 2 diabetes guidelines. Individuals with T3cDM have commonly been excluded from major diabetes drug trials.[29] Treatment of diabetes depends on the degree of insulin deficiency. In cases of mild hyperglycemia with features of insulin resistance, metformin is a reasonable first choice. Alternatively, insulin is preferred in cases of severe hyperglycemia and in patients with severe malnutrition (given its anabolic effects).[30] In addition to Metformin's glucose-lowering effect, a meta-analysis of 12 observational studies showed that metformin reduced the risk of pancreatic cancer in individuals with diabetes.[20] Moreover, one study reported a 32% reduction in mortality risk among patients with diabetes treated with metformin, although further studies are needed to validate these findings.[31] Thiazolidinediones and short-acting sulfonylureas may help, though their safety and efficacy in pancreatic disease remains unconfirmed. Experts have recommended against use of thiazolidinediones given their association with bone fractures and while individuals with chronic pancreatitis have an increased risk of osteoporosis.[30] Sulfonylureas are not considered optimal treatment given their risk of hypoglycemia.[29] Dipeptidyl-peptidase 4 inhibitors require intact beta cells for efficacy, and safety is unclear due to conflicting data on cancer and pancreatitis risk. Glucagon-like Peptide 1 receptor agonist product labels advise against use in patients with a history of pancreatitis, however, evidence from Juel et al. supports the cautious use of lixisenatide after total pancreatectomy to manage postprandial hyperglycemia, highlighting an extrapancreatic mechanism of action.[32] Insulin is often required due to loss of beta cells and the resulting insulin deficiency. In many cases, low doses of insulin may be sufficient due to high peripheral insulin sensitivity, especially in patients with PEI. Patients with low muscle mass and protein-calorie malnutrition, whether due to malabsorption or inflammation or both, typically have low basal insulin requirements and need relatively higher pre-meal doses. Overall insulin doses may be lower in those with evidence of malnutrition such as low body mass index, especially in those with total pancreatectomy or pancreatic atrophy. Insulin pumps with automated insulin delivery have not been tested in this population but are used to provide insulin in an individualized manner and to prevent hypoglycemia. Matching pre-meal insulin doses with food intake and enzyme replacement require diabetes education and close glucose monitoring.[33]

Nutritional support is critical. Patients with PEI are often counseled to follow a low-fat diet to reduce gut transit time and symptomatic diarrhea. Diets may be higher in easily digestible carbohydrates to provide caloric support, but this can contribute to higher post-prandial glucose excursions and need for relatively more prandial insulin compared to basal insulin.

Hypoglycemia prophylaxis is best managed with continuous glucose monitoring for early warning of impending low glucose. Patients should be instructed to treat hypoglycemia with glucose, either in tablet or liquid form (such as Gatorade) rather than with more complex carbohydrate sources. Diabetic ketoacidosis is uncommon in T3cDM due to loss of glucagon; however, it can occur in the most insulin-deficient patients.[34]

8. Diagnostic Tools and Clinical Algorithms

Diagnostic precision is critical for guiding appropriate therapeutic strategies, which often require multi-specialty care from dietitians, gastroenterologists and endocrinologists.[24]

Stepwise Diagnostic Algorithm

A structured diagnostic framework is essential to accurately identify T3cDM and distinguish it from T1DM or T2DM. The recommended stepwise approach includes (see Table 3):

1. Identify patients with new-onset diabetes mellitus, or existing diabetes who lack metabolic syndrome characteristics and T1DM antibodies.
2. Evaluate for Pancreatic Disease History:
    - Chronic or recurrent pancreatitis
    - Pancreatic surgery (e.g., Whipple procedure)
    - Pancreatic malignancy
    - Genetic cause of pancreatic disease
    - Pancreatic abnormalities or atrophy on imaging
3. Assess Exocrine Pancreatic Function:
    - Fecal elastase-1, done on solid or semi-solid stool specimen, that is < 100 μg/g indicates exocrine insufficiency, >100 and <200 μg/g is intermediate.
    - Low serum lipase (<20 units/L has 69% sensitivity and 69% specificity; <10 units/L has 33% sensitivity and 96% specificity for PEI) in patients with pancreatic calcifications indicates advanced chronic pancreatitis with glandular atrophy.[35]
4. Rule Out Type 1 Diabetes Mellitus:
    - Negative beta cell autoantibodies including glutamic acid decarboxylase 65 (GAD65), antityrosine phosphatase antibody (IA2), zinc transporter antibody (ZnT8)
    - Low or inappropriately normal C-peptide in the context of dysglycemia

5. Confirm Diagnosis:
    - Presence of major criteria—diagnosis of diabetes and history of pancreatic pathology make the diagnosis
    - Presence of pancreatic exocrine insufficiency and severe insulin deficiency without autoimmunity indicates severe T3cDM

9. Future Directions

Advancing the diagnosis and treatment T3cDM requires targeted research and system-level changes. Future work should prioritize the development of clinical guidelines that distinguish T3cDM from other diabetes subtypes and accommodate its unique pathophysiology. Prospective, multicenter trials are necessary to evaluate the long-term safety and effectiveness of pharmacologic agents, especially insulin and metformin, in both chronic pancreatitis and pancreatic cancer contexts.[18]

Precision diagnostics, including the T3cDM index proposed by Juza et al, require further validation across diverse patient populations. Large-scale cohorts like the UK Biobank and NIH's All of Us Research Program offer valuable platforms for identifying genetic markers and environmental contributors to T3cDM.[36] The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) continues to elucidate the natural history of pancreatogenic diabetes and may inform strategies for earlier intervention. Additionally, integrating omics approaches—genomics, proteomics, and metabolomics—could lead to more accurate disease phenotyping and inform individualized care. Digital innovations such as continuous glucose monitoring (CGM), automated insulin delivery, artificial intelligence (AI)-based decision support, and mobile health platforms should be explored for their potential to improve glycemic control and patient engagement. Finally, interdisciplinary care models involving endocrinologists, gastroenterologists, dietitians, and mental health professionals are essential to managing the multifaceted needs of this patient population.

10. Conclusion

T3cDM is a distinct and underappreciated diabetes subtype requiring nuanced management. Misclassification as T1DM or T2DM compromises outcomes. Accurate diagnosis through clinical, biochemical, and imaging criteria, combined with targeted therapy including insulin, metformin, PERT, and nutritional support, can improve prognosis and quality of life. Ongoing research and awareness are essential for optimizing care and preventing complications in these patients.

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Huda Al-Bahadili led the writing and drafting of the manuscript. All other authors contributed equally to reviewing, editing, and providing critical feedback on the content.

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