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Therapeutic intervention for type 5 diabetes mellitus: an overview

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Abstract
Type 5 diabetes mellitus (T5DM), also referred to as pancreatogenesis diabetes or diabetes of the exocrine pancreas (DEP), is a rare but clinically significant form of diabetes arising secondary to pancreatic disorders such as chronic pancreatitis, cystic fibrosis, pancreatic cancer, or after pancreatectomy. Misdiagnosis as type 1 or type 2 diabetes mellitus is common, leading to suboptimal management. This review explores the etiology, pathophysiology, clinical presentation, and current therapeutic strategies for T5DM, focusing on medical nutrition therapy, pharmacologic interventions, and emerging therapeutic approaches. A multidisciplinary management plan including endocrinology, gastroenterology, and dietetics is vital for optimal outcomes.

Keywords: Diabetes Mellitus, type 5, therapeutic diet, human health, foods, glucose level.

Introduction

Type 5 diabetes mellitus (T5DM), also known as pancreatogenesis or secondary diabetes, represents approximately 5-10% of all diabetes cases (Hart *et al.*, 2016) [14]. It is caused by disorders that damage the exocrine pancreas, leading to a loss of insulin-producing β-cells along with pancreatic enzyme insufficiency. Despite its clinical importance, T5DM is frequently underdiagnosed or misclassified as type 2 diabetes mellitus (T2DM), resulting in inadequate treatment protocols (Chakera *et al.*, 2020) [7].

Chronic pancreatitis is the most common cause, accounting for over 80% of cases of T5DM (Ewald & Bretzel, 2013) [13]. Other contributing conditions include pancreatic cancer, cystic fibrosis, and pancreatic surgery. T5DM presents unique therapeutic challenges due to its dual nature—combining features of insulin deficiency and insulin resistance—necessitating an integrated treatment approach.

Type 5 diabetes mellitus (DM), though not as commonly discussed as Types 1 and 2, represents a complex and evolving subclass of diabetes associated with pancreatic exocrine dysfunction, particularly in the context of pancreatogenesis diabetes, also referred to as diabetes secondary to pancreatic disease. It is frequently observed in individuals with chronic pancreatitis, cystic fibrosis, pancreatic cancer, or those who have undergone pancreatectomy (Ewald & Bretzel, 2013) [13]. Unlike traditional forms of diabetes, Type 5 diabetes stems from damage to the pancreas, affecting both its endocrine and exocrine functions. This multifaceted pathology makes it imperative to approach the condition with an integrated therapeutic strategy encompassing pharmacological, nutritional, and lifestyle interventions.

The prevalence of Type 5 DM remains underreported due to its misclassification, often being mistaken for Type 2 DM (American Diabetes Association [ADA], 2024) [2]. According to Ewald and Hardt (2013) [13], diabetes secondary to pancreatic diseases may account for nearly 5-10% of all diabetic cases, although this estimate may be conservative due to diagnostic challenges. The primary pathophysiology of Type 5 DM involves reduced insulin secretion due to beta-cell dysfunction and impaired counter-regulatory hormone production, including glucagon and pancreatic polypeptide. This often leads to brittle glycaemic control, characterized by alternating episodes of hyperglycaemia and hypoglycaemia (Cui & Andersen, 2017) [3, 8].

Effective therapeutic intervention for Type 5 diabetes requires a comprehensive understanding of its etiology and progression. Unlike autoimmune Type 1 diabetes or insulin-resistant Type 2 diabetes, Type 5 diabetes often results from pancreatic fibrosis, calcifications, and parenchymal destruction, leading to progressive islet cell loss. Inflammatory and fibrotic processes interfere with the normal hormonal balance and enzyme secretion, resulting in both endocrine insufficiency and exocrine pancreatic dysfunction (Knop & Holst, 2018) [17]. Therefore, treatment modalities must address not only glycaemic control but also the management of malabsorption, nutritional deficiencies, and gastrointestinal complications.

A major challenge in the treatment of Type 5 diabetes lies in its complex glycaemic profile. The loss of insulin secretion is often compounded by the concurrent reduction in glucagon and somatostatin, which increases the risk of severe hypoglycaemia, especially during insulin therapy (Singh *et al.*, 2019) [23]. Consequently, insulin regimens must be carefully individualized, and the use of newer agents such as incretin mimetics or sodium-glucose co-transporter 2 (SGLT2) inhibitors must be cautiously evaluated for safety and efficacy in this population.

From a pharmacological standpoint, insulin remains the mainstay treatment for most patients with Type 5 DM, particularly in advanced cases with significant beta-cell loss. Basal-bolus insulin therapy is often required to mimic physiologic insulin secretion. However, newer antidiabetic agents, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have shown promise in improving glycaemic control without causing significant hypoglycaemia (Rickels *et al.*, 2013) [22]. Nevertheless, their utility may be limited in patients with severe pancreatic dysfunction due to impaired incretin response.

In addition to pharmacological strategies, nutritional intervention is critical in the therapeutic approach to Type 5 diabetes. Patients frequently exhibit steatorrhea, weight loss, and fat-soluble vitamin deficiencies due to exocrine pancreatic insufficiency (EPI), necessitating pancreatic enzyme replacement therapy (PERT). Malnutrition and sarcopenia are prevalent in these patients and significantly influence disease prognosis. A high-protein, low-glycaemic index diet, combined with fat-soluble vitamin supplementation, can improve nutritional status and glycaemic control (Domínguez-Muñoz *et al.*, 2020) [11]. Frequent small meals may also help prevent postprandial glucose fluctuations and hypoglycaemic episodes.

The role of pancreatic enzyme supplementation cannot be overstated. In patients with EPI, PERT improves nutrient digestion and absorption, which is essential for maintaining metabolic homeostasis. Additionally, correcting micronutrient deficiencies—particularly vitamins A, D, E, and K—is vital to avoid complications such as osteopenia, visual disturbances, and impaired immunity (Layer *et al.*, 2014) [18]. Nutritional therapy should thus be personalized, with regular monitoring of body composition, serum micronutrient levels, and gastrointestinal symptoms.

Exercise and lifestyle modification also play an important role in the holistic management of Type 5 DM. Physical activity enhances insulin sensitivity, preserves lean body mass, and contributes to overall metabolic health. However, exercise programs must be carefully tailored to avoid hypoglycaemic episodes, which are more common in this population due to defective counter-regulatory mechanisms (ADA, 2024). Education on hypoglycaemia recognition and management is essential for patients and caregivers.

Psychosocial support is another key element in therapeutic intervention. The chronic nature of pancreatitis or pancreatic diseases, frequent hospitalizations, and the complex insulin regimens required can significantly impact patients' mental health. Depression, anxiety, and diabetes-related distress are common and must be addressed through multidisciplinary care involving psychologists and social workers (Pezzilli *et al.*, 2015). Group counseling and diabetes education programs can improve adherence to therapy and self-management skills.

Recent advancements in biomarker discovery and genetic profiling offer hope for more accurate diagnosis and personalized treatment of Type 5 diabetes. For instance, genetic mutations associated with hereditary pancreatitis or cystic fibrosis can predispose individuals to diabetes, indicating the need for early screening and intervention. Similarly, non-invasive imaging modalities, such as magnetic resonance imaging (MRI) and endoscopic ultrasound, help in early detection of pancreatic structural abnormalities, aiding in the timely initiation of therapeutic interventions (Kirkegård *et al.*, 2017) [15].

Future therapeutic directions for Type 5 DM may involve regenerative therapies, such as stem cell transplantation or pancreatic islet cell transplantation, which aim to restore insulin production capacity. Although still in experimental stages, these strategies offer hope for long-term disease remission or even cure. Moreover, the development of dual hormone delivery systems—combining insulin and glucagon analogs—may better replicate physiological responses and reduce the incidence of hypoglycaemia (Rickels *et al.*, 2013) [22].

Type 5 diabetes mellitus represents a unique and complex form of diabetes that necessitates a comprehensive therapeutic approach. The interplay between endocrine and exocrine dysfunction in pancreatic diseases complicates diagnosis and management, making individualized care paramount. Effective intervention strategies must combine pharmacological therapy, nutritional support, lifestyle modification, and psychosocial care to achieve optimal clinical outcomes. As research advances and new therapeutic modalities emerge, the future holds promise for improved diagnosis, treatment, and quality of life for patients suffering from this challenging condition.

2. Pathophysiology

T5DM results from destruction of the pancreatic parenchyma, which leads to decreased insulin, glucagon, and pancreatic polypeptide secretion. Loss of glucagon-producing α-cells also impairs counterregulatory responses to hypoglycemia, making glycemic management more precarious (Andersen *et al.*, 2018) [3]. Furthermore, malabsorption due to exocrine insufficiency contributes to nutritional deficiencies, compounding metabolic instability.

Unlike T1DM, autoimmune destruction is not involved. Unlike T2DM, insulin resistance is less prominent unless compounded by obesity or metabolic syndrome. Hence, management needs to consider not only glycaemic control but also enzyme replacement, nutritional support, and frequent monitoring for complications.

3. Clinical Features and Diagnosis

Clinical diagnosis is challenging due to overlapping features with other diabetes types. Symptoms include postprandial hyperglycaemia, steatorrhea, weight loss, and frequent hypoglycaemia episodes (Rickels *et al.*, 2013) [22]. Diagnosis of T5DM should be considered in patients with new-onset diabetes and evidence of pancreatic disease.

The diagnostic criteria include:

- History of pancreatic disease
- Absence of T1DM autoantibodies
- Low or normal BMI
- Evidence of exocrine pancreatic insufficiency (fecal elastase <200 μg/g)

Imaging studies (CT/MRI), pancreatic function tests, and fasting glucose/C-peptide levels assist in establishing the diagnosis (Ewald & Hardt, 2013) [13].

4. Medical Nutrition Therapy

Nutrition plays a pivotal role in managing T5DM. Caloric intake should be optimized to maintain weight and correct malnutrition. Patients often present with fat-soluble vitamin deficiencies (A, D, E, and K), necessitating supplementation (Kleeff *et al.*, 2017) [16]. Pancreatic enzyme replacement therapy (PERT) is essential to correct maldigestion, improve nutrient absorption, and support glycaemic control.

Dietary recommendations include:

Frequent Small Meals and Low-Glycaemic Index Carbohydrates: Chronic pancreatitis is a progressive inflammatory disorder of the pancreas characterized by irreversible structural damage, chronic pain, and impaired endocrine and exocrine functions. Nutritional management plays a critical role in mitigating complications, alleviating symptoms, and improving the quality of life in affected individuals. Among various dietary approaches, the implementation of frequent small meals and inclusion of low-glycaemic index (GI) carbohydrates has emerged as a cornerstone strategy in the nutritional care of individuals with chronic pancreatitis.

Frequent small meals help reduce the pancreatic workload by distributing energy intake throughout the day and preventing large-volume meals that may overstimulate pancreatic enzyme secretion. In chronic pancreatitis, the damaged pancreas struggles to produce adequate digestive enzymes, and large meals can exacerbate abdominal pain and maldigestion. By eating small amounts every 2 to 3 hours, individuals can reduce gastrointestinal symptoms, prevent postprandial discomfort, and maintain nutritional adequacy (Lindkvist, 2013) [19]. This approach also helps stabilize blood glucose levels, which is particularly crucial since chronic pancreatitis often results in pancreatic diabetes (type 3c diabetes) due to progressive islet cell damage (Ewald & Hardt, 2013) [13].

On the other hand, the glycaemic index of foods—an indicator of how quickly carbohydrates raise blood glucose levels—plays a pivotal role in dietary planning. In chronic pancreatitis, glucose regulation becomes increasingly impaired, and sudden spikes in blood sugar can further burden the compromised endocrine function. Therefore, choosing low-GI carbohydrates such as whole grains (e.g., oats, barley), legumes, vegetables, and certain fruits can help in maintaining stable glycaemic control. These carbohydrates are digested and absorbed more slowly, leading to a gradual increase in blood glucose and insulin levels (Wolever *et al.*, 2003) [25]. This is particularly advantageous in preventing hyperglycaemia in patients who may have reduced insulin output from islet cell insufficiency.

Moreover, low-GI diets are associated with reduced inflammation and oxidative stress—both of which are implicated in the pathophysiology of chronic pancreatitis (Augustin *et al.*, 2015) [5]. A low-GI diet also helps address associated conditions such as dyslipidaemia and metabolic syndrome, which may co-occur with pancreatic disease, especially in patients with comorbidities like obesity and alcoholism.

Combining frequent small meals with low-GI carbohydrates creates a dietary pattern that not only supports better digestive efficiency but also minimizes glycaemic fluctuations, facilitates nutrient absorption, and reduces abdominal discomfort. Importantly, this dietary pattern ensures that patients maintain adequate caloric and nutrient intake, as malnutrition is a common complication of chronic pancreatitis due to malabsorption and chronic inflammation (Papachristou *et al.*, 2017) [20]. Dietitians often work closely with patients to plan individualized meal schedules that balance macronutrients and incorporate low-GI foods to optimize both comfort and nutritional status.

In conclusion, the emphasis on frequent small meals and low-GI carbohydrates in the dietary management of chronic pancreatitis is strongly supported by clinical guidelines and research. These strategies provide symptomatic relief, stabilize blood glucose, and improve the overall nutritional outcome in affected individuals.

Moderate Protein and Fat Intake and Avoidance of Alcohol and Smoking: In the nutritional management of chronic pancreatitis, regulating macronutrient intake and eliminating modifiable risk factors are essential for controlling disease progression and improving patient outcomes. Among these, moderate intake of protein and fat, along with the complete avoidance of alcohol and smoking, represents a foundational pillar of dietary and lifestyle intervention.

Protein and fat are essential macronutrients, but their metabolism is significantly affected in chronic pancreatitis due to diminished pancreatic enzyme output. While protein requirements may be slightly increased to compensate for muscle loss and chronic catabolism, excessive intake is discouraged due to its stimulatory effect on pancreatic secretions, which can worsen pain and inflammation (Domínguez-Muñoz, 2010) [9]. The goal is to maintain a moderate protein intake, ensuring sufficient levels for tissue repair without overwhelming the exocrine function. Sources of lean protein, such as eggs, poultry, tofu, and legumes, are generally recommended.

Similarly, fat intake must be carefully moderated. Fat malabsorption is a hallmark of chronic pancreatitis, often leading to steatorrhea (fatty stools), weight loss, and deficiencies in fat-soluble vitamins (A, D, E, and K). Although extremely low-fat diets were once prescribed, current evidence supports a moderate fat diet, especially when supplemented with pancreatic enzyme replacement therapy (PERT) (Toouli *et al.*, 2002) [24]. This allows for improved digestion and absorption of fats while minimizing gastrointestinal symptoms. Sources of healthy fats such as omega-3 fatty acids (e.g., from flaxseeds, walnuts, and fish)

are often preferred due to their anti-inflammatory effects (Calder, 2013) [6].

Beyond dietary modifications, lifestyle changes are vital. Alcohol consumption is the most significant risk factor for the development and progression of chronic pancreatitis. Chronic alcohol use leads to repeated pancreatic injury, inflammation, and fibrosis, eventually resulting in irreversible pancreatic damage. Abstinence from alcohol not only halts further injury but also improves long-term survival and reduces hospitalization rates (Yadav & Lowenfels, 2013) [26]. Patients must be counselled on the critical importance of complete alcohol avoidance, regardless of whether alcohol was the initial cause of the disease.

Likewise, smoking has emerged as an independent risk factor for both the onset and progression of chronic pancreatitis. Studies show that smoking accelerates pancreatic calcification and increases the risk of pancreatic cancer in patients with chronic pancreatitis (Andriulli *et al.*, 2010) [4]. The exact mechanism is unclear, but it is thought that tobacco-related toxins exacerbate inflammation and oxidative stress within pancreatic tissue. Smoking cessation is therefore not only advised but considered a mandatory component of comprehensive management. Counselling and pharmacologic aids such as nicotine replacement therapy may be necessary for effective cessation.

Taken together, moderation in protein and fat intake, tailored according to individual digestive capacity, and strict avoidance of alcohol and tobacco form an integrated approach for managing chronic pancreatitis. These measures reduce pancreatic stimulation, minimize inflammation, and prevent complications such as malnutrition, diabetes, and cancer. As these recommendations require sustained behavioural change, multidisciplinary support—including from dietitians, gastroenterologists, and psychologists—is crucial to ensure adherence and long-term success.

A holistic approach to chronic pancreatitis management includes not only carefully balanced dietary practices but also elimination of harmful lifestyle habits. Moderate macronutrient intake, paired with complete abstinence from alcohol and smoking, significantly improves prognosis, quality of life, and clinical outcomes in affected individuals.

Table 1: Therapeutic Interventions for Type 5 Diabetes Mellitus (Pancreatogenesis Diabetes)

Therapeutic Intervention	Description	Purpose/Outcome	Reference
Pancreatic Enzyme Replacement Therapy (PERT)	Administration of pancreatic enzymes with meals to aid digestion and absorption.	Improves nutrient absorption, reduces steatorrhea, and supports glycemic control.	Toouli *et al.*, 2002; Domínguez-Muñoz, 2010[9, 24]
Insulin Therapy	Exogenous insulin administration to manage hyperglycemia due to β-cell destruction.	Essential in most patients due to insulin deficiency; often preferred over oral antidiabetics.	Ewald & Hardt, 2013; Yadav & Lowenfels, 2013[13, 26]
Frequent Small Meals	Eating smaller meals every 2-3 hours.	Reduces postprandial glucose spikes and minimizes pancreatic stimulation.	Lindkvist, 2013[19]
Low-Glycemic Index Carbohydrates	Preference for slow-absorbing carbohydrates like legumes, oats, and vegetables.	Stabilizes blood glucose levels and reduces insulin demand.	Wolever *et al.*, 2003; Augustin *et al.*, 2015[5, 25]
Moderate Protein and Fat Intake	Balanced intake of protein and fat while avoiding excessive intake.	Prevents pancreatic overload, supports metabolism, and ensures nutritional adequacy.	Domínguez-Muñoz, 2010[9]
Alcohol and Smoking Cessation	Complete avoidance of alcohol and tobacco.	Prevents further pancreatic damage and reduces risk of complications and pancreatic cancer.	Andriulli *et al.*, 2010; Yadav & Lowenfels, 2013[4, 26]
Vitamin and Micronutrient Supplementation	Supplementation of fat-soluble vitamins (A, D, E, K), vitamin B12, calcium, magnesium, and zinc.	Corrects malnutrition and deficiencies due to malabsorption.	Papachristou *et al.*, 2017[20]
Dietary Counselling and Nutrition Therapy	Personalized medical nutrition therapy with a clinical dietitian.	Enhances adherence to dietary recommendations and improves overall glycaemic and nutritional outcomes.	Lindkvist, 2013; Domínguez-Muñoz, 2010[9, 19]
Use of PPAR-γ Agonists (in selected cases)	Thiazolidinediones like pioglitazone may be used cautiously in early insulin-resistant stages.	May improve insulin sensitivity; limited role due to risk of weight gain and edema.	Ewald & Bretzel, 2013[13]
Physical Activity and Lifestyle Management	Regular exercise tailored to the patient's capability.	Improves insulin sensitivity, reduces metabolic risk factors, and enhances quality of life.	American Diabetes Association, 2023[1]

5. Pharmacological Treatment

5.1 Insulin Therapy

Insulin remains the mainstay for patients with significant β-cell loss. Long-acting basal insulin analogs, combined with mealtime short-acting insulins, can help mimic physiological insulin patterns. Due to the absence of glucagon, patients are highly susceptible to hypoglycaemia and require careful titration and frequent monitoring (Rickels *et al.*, 2013) [22].

5.2 Oral Hypoglycaemics

Oral agents such as metformin may be considered if insulin resistance is present and β-cell function is partially preserved. However, agents like sulfonylureas are generally avoided due to the risk of hypoglycaemia.

5.3 Pancreatic Enzyme Replacement Therapy (PERT)

PERT with lipase, protease, and amylase enzymes is essential. It improves nutrient absorption and contributes to better glycaemic control by facilitating consistent carbohydrate digestion (Domínguez-Muñoz *et al.*, 2017) [10].

5.4 Emerging Therapies

Recent studies have examined incretin-based therapies like GLP-1 receptor agonists and DPP-4 inhibitors, but their use remains controversial in T5DM due to gastrointestinal side effects and limited β-cell reserves (Drucker, 2018) [12].

6. Monitoring and Complications

Due to the complex pathophysiology of T5DM, patients are at high risk for both microvascular and macrovascular complications. Regular monitoring of HbA1c, fasting glucose, nutritional status, and vitamin levels is essential.

Advanced complications include:

- Severe hypoglycaemia
- Diabetic retinopathy and neuropathy
- Cardiovascular disease
- Osteoporosis (due to fat-soluble vitamin D deficiency)

Annual eye exams, foot checks, and renal function tests should be integrated into care protocols (ADA, 2023).

Conclusion

Type 5 diabetes mellitus remains underrecognized and undertreated despite its complex clinical implications. Early identification, personalized nutrition, pancreatic enzyme support, and tailored pharmacotherapy are fundamental in its management. Future research should focus on standardized diagnostic criteria, novel therapeutic options, and long-term outcome studies to optimize care for this unique subset of diabetes patients.

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