International Journal of General Medicine

Dovepress
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REVIEW

Glycemic Variability in Pancreatogenic Diabetes Mellitus: characteristics, Risks, Potential Mechanisms, and Treatment Possibilities

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Abstract: In recent years, pancreatogenic diabetes mellitus has garnered significant attention due to its high incidence, complications, and mortality rates. Glycemic variability (GV) can increase the risk of pancreatogenic diabetes mellitus and its associated complications; however, the precise mechanism remains unclear. The effective control of GV is crucial for preventing the onset of pancreatic diabetes mellitus and improving prognosis. Both diet and antidiabetic medications have substantial effects on GV. However, many patients are prescribed suboptimal or even harmful drugs. Therefore, to provide a comprehensive treatment basis for clinicians to prevent and treat pancreatogenic diabetes mellitus, this study aimed to elucidate the relationship between GV and pancreatogenic diabetes mellitus; investigate the potential mechanisms (such as oxidative stress, inflammatory response, insulin resistance, and lipid metabolism disorders); provide lifestyle guidance; and recommend drug selections to reduce the GV in patients with pancreatogenic diabetes mellitus.

Keywords: pancreatogenic diabetes, glucose fluctuation, glycemic variability, therapy, antihyperglycemic drug

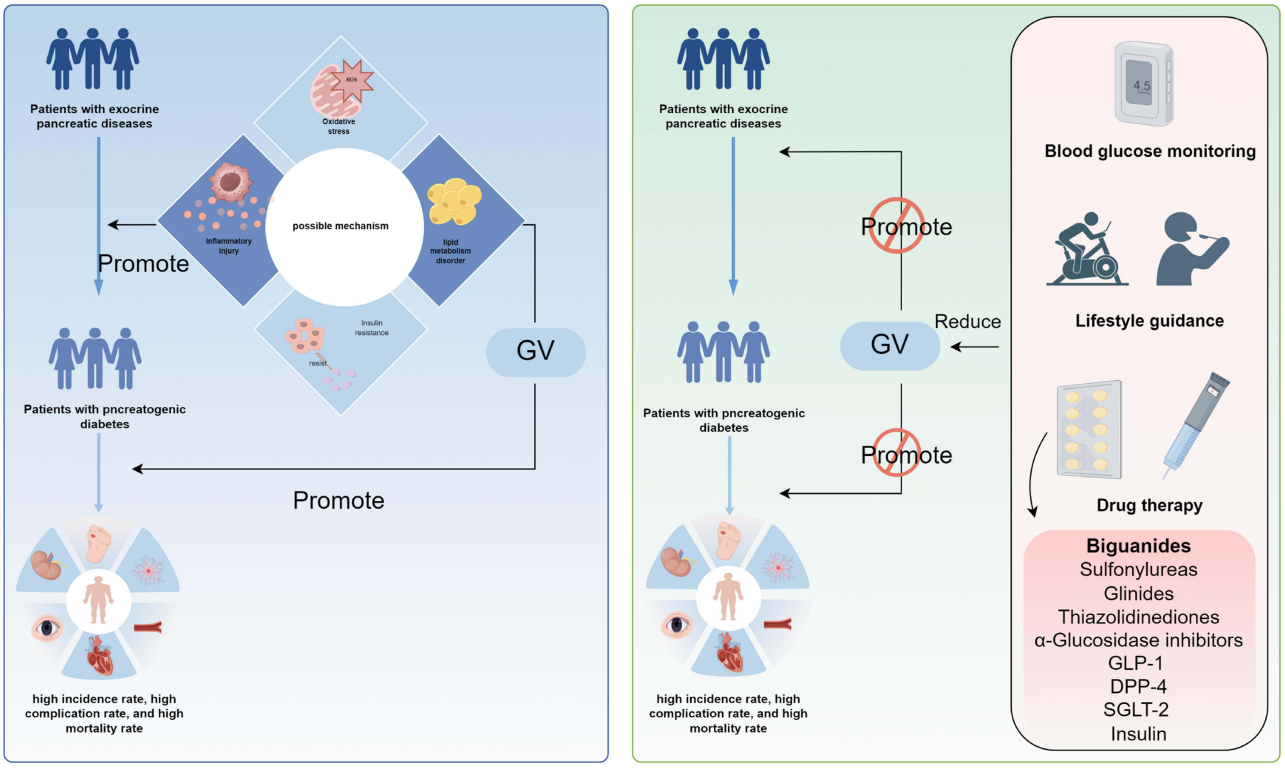
Introduction

Pancreatogenic diabetes mellitus (DM), also known as type 3c DM (T3cDM), is a type of diabetes caused by exocrine pancreatic disease.[1,2] Based on etiology, it can be primarily categorized as post-pancreatitis DM (PPDM, including post-acute pancreatitis DM [PPDM-A] and post-chronic pancreatitis DM [PPDM-C]), pancreatic cancer-related diabetes (PCRD), and cystic fibrosis-related diabetes.[3] Studies have shown that T3cDM has become the second most common type of diabetes in adults after type 2 DM (T2DM), surpassing the prevalence of type 1 diabetes (T1DM).[4,5] 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%.[6] Patients with T3cDM exhibit a worse prognosis than that of individuals with T2DM. Compared with patients with T2DM, these patients have significantly higher risks of pancreatic cancer, hypoglycemia, microvascular and macrovascular complications, and all-cause mortality[7,8] and a shorter life expectancy.[9]

Pancreatic exocrine diseases can impair the pancreatic islet function, leading to the dysregulation of insulin secretion. This impairment can lead to abnormal glucose metabolism, characterized by elevated blood glucose levels and irregular blood glucose fluctuations. Patients with exocrine pancreatic diseases are prone to hypoglycemia due to their specific pathological mechanism, coupled with the destruction of pancreatic islet α-cells, insufficient glucagon secretion, and impaired hypoglycemic antagonistic regulatory mechanism, as well as alcoholism and poor compliance, leading to significant fluctuations in blood glucose levels. Previous studies have reported a significant correlation between abnormal glucose fluctuations and worsening clinical outcomes in hospitalized patients.[10,11] Abnormal glucose fluctuations during the early course of pancreatitis increase the risk of PPDM.[12] In addition, excessive glucose fluctuations increase the risk of complications in patients with DM. Therefore, patients with T3cDM require lifestyle modification and medication

Received: 9 May 2024
Accepted: 3 September 2024
Published: 21 September 2024

Graphical Abstract



treatment to reduce glucose fluctuations before and after disease onset. This study examined the relationship between glucose fluctuations and T3cDM. We also discussed the lifestyle and medication management strategies that can help reduce blood glucose fluctuations in patients with T3cDM. This study aimed to investigate the influence of glucose fluctuations on the development of T3cDM, to prevent the onset and progression of T3cDM, and to enhance the disease prognosis.

Search Strategy

This review utilized the following search terms: (pancreatogenic OR pancreatogenous OR type 3c OR pancreatitis OR post-pancreatitis) AND (diabetes OR diabetes mellitus) AND (glucose fluctuation OR glycemic variability). PubMed, Web of Science, China National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform, and China Biomedical Literature Database were comprehensively searched for relevant literature. The references of selected articles were also reviewed, and other relevant articles were identified. Original articles and those that were highly relevant to the scope of this review were selected.

Blood Glucose Fluctuation

Glycemic management is a key focus in clinical practice and is closely related to the development of various diseases. Glycosylated hemoglobin A1c (HbA1c) is the gold standard for assessing glycemic status.[13] A population-based study in 2021 demonstrated that patients with T3cDM had poorer glycemic control (as evidenced by an elevated HbA1c level) than that of those with T2DM.[14] However, HbA1c does not encompass all components of hyperglycemia and does not reflect fasting, pre-prandial, and post-prandial hyperglycemic and hypoglycemic conditions. Therefore, fluctuations in blood glucose levels were observed. Glycemic fluctuation refers to the instability of blood glucose levels between peaks and troughs, also known as glycemic variability (GV), and is a critical indicator for evaluating blood glucose control.[15]

Over the years, numerous studies have developed various GV parameters to assess short-term and long-term glycemic fluctuations. The coefficient of variation (CV), mean of daily differences (MODD), standard deviation of blood glucose (SDBG), mean amplitude of glycemic excursions (MAGE), and continuous overlapping net glycemic action (CONGA) are commonly used parameters and associated with diabetic complications.[16–19] Controlling glucose fluctuations is critical for reducing adverse clinical outcomes. Research on the effects of abnormal glycemic fluctuations on the human body has gained significant interest and importance.

Relationship between blood glucose fluctuation and pancreatogenic diabetes mellitus and its potential mechanism

Characteristics of Blood Glucose Fluctuation in Pancreatogenic Diabetes Mellitus

T3cDM has a distinct etiology compared with that of other types of diabetes. The underlying pancreatic inflammation leads to the loss of not only pancreatic β-cells but also α-cells and pancreatic polypeptide (PP) cells. This results in decreased glucagon levels and impaired negative feedback regulation against diabetic hypoglycemia, which contributes to the phenomenon of alternating hyperglycemia and hypoglycemia. Consequently, patients experience significant fluctuations in blood glucose levels, resulting in "fragile diabetes", which is difficult to control.[20] Channaba et al used continuous glucose monitoring (CGM) technology to assess GV in patients with T3cDM and T2DM. Except for the M value, all CGM-derived GV measures (SD, MAGE, CONGA, MODD, and CV percentage (% CV)) were significantly higher in the T3cDM group than in the T2DM group.[21] However, Victoria's (2022) study of glucose variability in patients with T3cDM, T1DM, and T2DM showed that GV was significantly lower in the T3cDM group than in the T1DM group. However, no significant difference was observed between the T3cDM and T2DM groups.[22] This may be due to the diverse causes of T3cDM, which could act as a confounding factor affecting GV. Additionally, the wide range of indicators for assessing GV and the lack of standardization in these measures across the studies may have contributed to the results. Victoria et al used only the % CV to compare the GVs of the study groups, which may have been too restrictive as an observational indicator. Therefore, to gain a more comprehensive and accurate understanding of glucose fluctuations in patients with T3cDM, a more extensive population-based cohort study must be conducted using a diverse set of indicators.

Effect of Blood Glucose Fluctuations on Pancreatogenic Diabetes Mellitus

Both long- and short-term blood glucose fluctuations have significant effects on the occurrence of T3cDM. A cross-sectional study by Channaba examining individuals with chronic pancreatitis observed a significant correlation between substantial long-term glucose fluctuations and the occurrence of diabetes.[21] In addition, patients with good overall long-term glycemic control may still exhibit high GV and are prone to PPDM.[22] In a prospective study of a single-center longitudinal cohort, patients with acute pancreatitis (AP) who had normal but steadily increasing HbA1c levels had a 6% increased risk of developing PPDM with each 1-cm increase in waist circumference compared to patients with AP who had normal and stable HbA1c levels.[23] These studies suggest that abnormal long-term blood glucose fluctuations are closely related to the development of PPDM and may be one of the risk factors for developing PPDM in patients with pancreatitis. The glycemic fluctuation index (GLI) is relevant for evaluating short-term blood glucose fluctuation.[24] In 2022, Bharmal et al found that patients with AP who exhibited fluctuating HbA1c levels had a high incidence of PPDM. Moreover, the GLI had the strongest significant direct correlation with patients who exhibited fluctuating HbA1c levels, which can be used as a predictor of PPDM development in patients with AP. However, the complex calculation of GLI in a hospital setting limits its current use in routine clinical practice, and its accuracy must be verified in a larger population cohort. Nagy et al also demonstrated that increases in peak blood glucose levels at admission and during hospitalization would increase the incidence of short- and long-term complications in patients with AP.[25] In addition, high GV during hospitalization in patients with acute illnesses (including conditions beyond AP) predicts the worsening of HbA1c patterns, new-onset diabetes, and other related complications after discharge from the hospital.[26–28] In conclusion, hyperglycemic variability accelerates the occurrence of new-onset diabetes and contributes to the gradual progression toward overt diabetes after discharge from the hospital. These studies offer valuable insights into the importance of

controlling GV to prevent the development of T3cDM. Nevertheless, most of the existing studies investigated the relationship between abnormal glucose fluctuations and diabetes-related complications, while only a few studies examined the relationship between GV and the development of pancreatic DM. Hence, future studies should explore the predictive role of additional GV indicators in the development of T3cDM.

Possible Mechanisms of Abnormal Glucose Fluctuation on the Development of Pancreatogenic Diabetes

Currently, the precise mechanism by which glucose fluctuation promotes the occurrence of T3cDM remains unknown. It may be associated with oxidative stress (OS) in vivo, the activation of inflammatory response, insulin resistance (IR), and lipid metabolism disorders (Figure 1).

Oxidative Stress

Pancreatic β-cells are extremely susceptible to reactive oxygen species (ROS).[29] Several studies have indicated that OS disrupts the normal β-cell function in the body.[30–33] Patients with exocrine pancreatic diseases inherently experience islet disruption and β-cell dysfunction. OS further exacerbates β-cell damage in these patients and contributes to the development of T3cDM. Fluctuations in blood glucose levels can increase free radical production and activate OS. Fluctuating hyperglycemia is more likely to trigger OS, compared to chronic persistent hyperglycemia.[34] Even after short-term blood glucose fluctuations, the blood glucose levels may return to normal, but the unabated ROS production

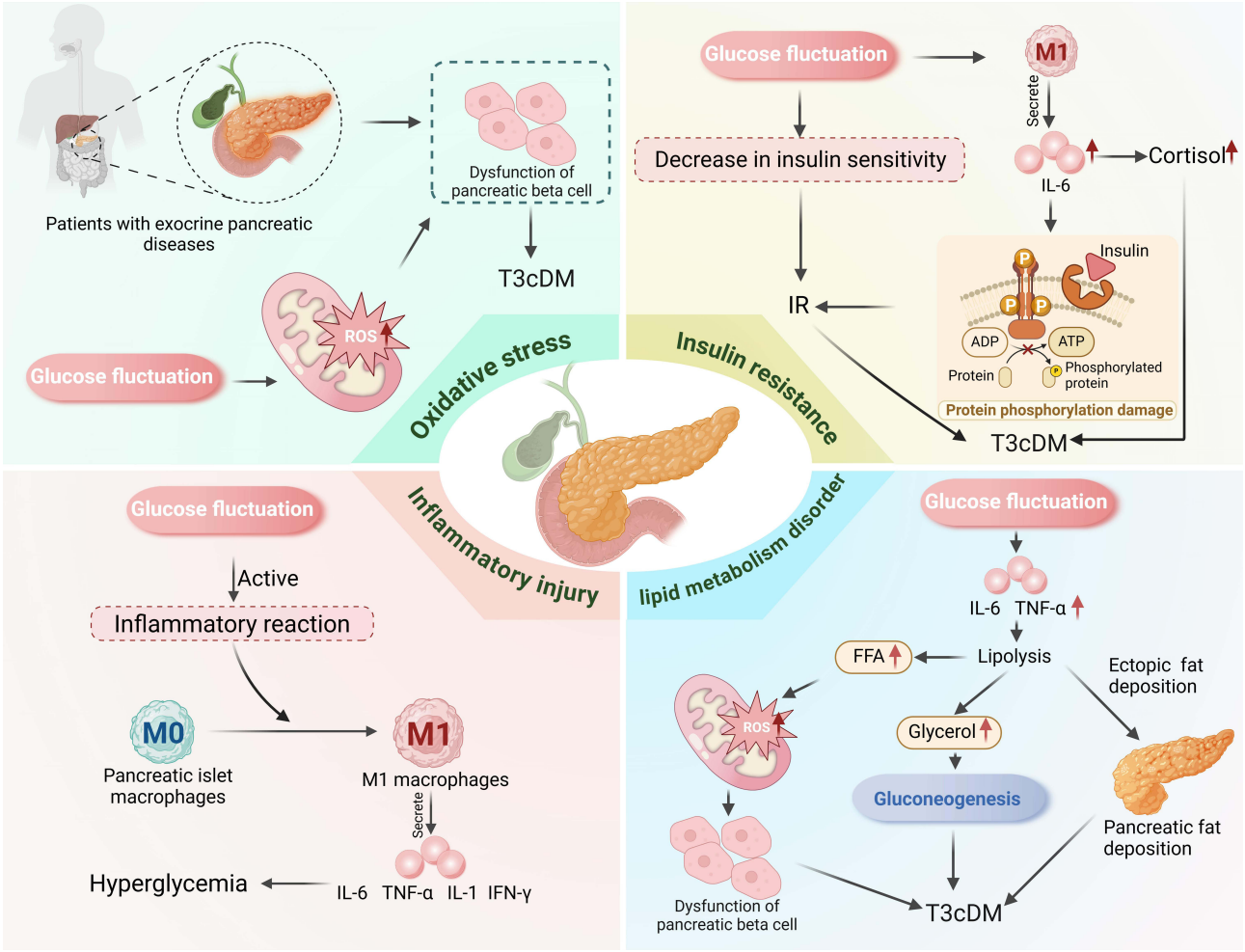


Figure 1 Mechanisms of glycemic variability that can promote the occurrence of pancreatogenic diabetes.

may affect the body.[35] 8-hydroxyl deoxyguanosine (8-OHdG) is a stable and easily detectable biomarker for assessing OS status. Additionally, 8-iso-PGF2α, an arachidonate-like molecule, is commonly used as a biomarker of OS. Zheng et al's study in 2010 found a significant correlation between the MAGE and 8-iso-PGF2α level in plasma. Furthermore, a significant relationship was observed between the mean postprandial glucose drift and plasma 8-OH-dG levels.[36] The study of Xi et al in 2021 further confirmed that in patients with DM, the MAGE level in the high HbA1c group was positively correlated with the 8-OHdG level.[37] These studies indicate that repeated blood glucose fluctuations contribute to the development and progression of diabetes by exacerbating oxidative damage, increasing the level of pro-inflammatory cytokines in healthy individuals, and inducing β -cell dysfunction.

Inflammatory Injury

Abnormal blood glucose fluctuations may increase the risk of T3cDM in patients with pancreatitis by inducing or aggravating inflammatory damage. Abnormal glucose fluctuations can lead to the persistent activation of chronic cellular inflammation throughout the body. This inflammatory environment can prompt the transformation of pancreatic islet macrophages into M1 macrophages, which secrete various cytokines, including interleukin (IL)-6 and tumor necrosis factor-α (TNF-α). Su et al further suggested a close relationship between glucose fluctuations and the production of IL-6 and TNF-α.[38] A prospective longitudinal cohort study identified elevated serum levels of IL-1 and interferon γ (IFN-γ) as significant predictors of prediabetes development (impaired glucose tolerance) in AP (odds ratio = 1.097 and 1.094).[39] In addition, elevated serum IL-6 levels have been linked to the development of chronic hyperglycemia.[40,41] Several studies have also demonstrated that increased levels of circulating IL-6 correlate with post-AP hyperglycemia.[42,43] The Institute of Clinical and Epidemiology of Metabolic, Nutritional, and Pancreatic Diseases (COSMOS) team established IL-6 as the primary cytokine mediator in T3cDM in a cross-sectional study of adults with a history of AP (Project DORADO). In summary, unstable glucose fluctuations may increase the risk of new-onset diabetes by exacerbating the inflammatory response and promoting the production of cytokines.

Insulin Resistance

IR is currently recognized as the primary mechanism underlying new glucose metabolism disorders after AP.[44] Low PP levels are commonly observed in patients with T3cDM. Recent studies have confirmed that PPs regulate insulin sensitivity in the liver, and a decrease in PP levels increases IR. Homeostatic model assessment of IR (HOMA-IR) is an indicator used to evaluate IR levels. Umapathy et al found that the HOMA-IR value of the DM group after AP was higher than that of the non-DM group during the observation period.[45] Excessive glucose fluctuations can lead to increased IR. In 2003, Li et al confirmed that glucose fluctuation can promote the secretion of insulin resistin by monocytes/macrophages.[32] In 2022, Liu et al showed that glucose fluctuations decreased insulin sensitivity and increased IR.[46] A study investigating islet function and glucose fluctuations observed that HOMA-IR was positively correlated with glucose fluctuation indices (MAGE, LAGE, and SDBG) *(Rs* < 0, p < 0. 05); the severity of IR amplifies glucose fluctuations. However, the causal relationship requires further investigation.[47] In addition, Bharmal et al found that an elevation in IL-6 levels led to an increase in cortisol levels,[48] intermittently regulating human blood glucose concentrations. IL-6 is associated with the occurrence of IR following AP.[43] IL-6 induces IR by impairing the phosphorylation of insulin receptors and insulin receptor substrates. Furthermore, glucose fluctuations can exacerbate chronic inflammation, resulting in increased IL-6 release. This process worsens IR and accelerates the development of T3cDM. This chain reaction highlights the importance of blood glucose stability in preventing diabetes. These findings suggest that managing blood glucose fluctuations may play a vital role in the prevention and treatment of T3cDM.

Lipid Metabolism Disorder

Pendharkar et al found that the levels of lipid metabolism markers were significantly elevated in patients with PPDM-A, indicating the crucial role of lipolysis in the pathogenesis of PPDM.[49] Additionally, chronic inflammatory factors resulting from abnormal blood glucose fluctuations contribute to lipid metabolism in vivo. The pro-inflammatory cytokines IL-6 and TNF-α may drive lipolysis, with disruptions in lipid metabolism further exacerbating glucose metabolism disorders through various complex mechanisms.[50,51]

In addition to the abovementioned mechanisms, autoimmune factors, insulin-incretin axis disorders, intestinal flora disturbances, and intra-pancreatic fat deposition may also contribute to the development of T3cDM.[52] However, the specific mechanism by which blood glucose fluctuations affect the progression of T3cDM has not yet been fully elucidated. Therefore, further research is necessary to identify new targets for its prevention and treatment.

Strategies to Reduce Blood Glucose Fluctuations

Abnormal blood glucose fluctuations not only directly damage the body and increase the risk of complications but also cause unnecessary financial burden. Therefore, reducing blood glucose fluctuations before and after the onset of T3cDM is a critical component of treatment strategies. The international recommendations for controlling blood glucose fluctuations are still limited, with postprandial hyperglycemia and hypoglycemia being the two primary causes of glucose fluctuations.[53] Reducing glucose fluctuations involves three key approaches: reducing fasting blood sugar levels, reducing postprandial blood sugar levels, and reducing hypoglycemic events. Physicians should tailor treatment plans to each patient's condition to ensure individualized care.

Blood Glucose Monitoring

Controlling blood glucose fluctuations and strengthening blood glucose monitoring are integral aspects of treatment. Previous studies have shown that patients who underwent blood glucose monitoring experienced significant improvements in HbA1c levels and significantly lower rates of emergency room visits and hypoglycemia-related hospitalizations, compared to those who did not.[54] A continuous glucose monitoring (CGM) device is a novel monitoring technology. Compared with those who perform self-monitoring of blood glucose (SMBG), patients utilizing CGM devices have lower GV, superior quality of life,[55–60] and fewer hospital admissions for acute diabetic complications such as diabetic ketoacidosis or severe hypoglycemia.[61–63] Nevertheless, the American Diabetes Association's 2019 standards continue to emphasize the importance of SMBG in diabetes management.[64] Similarly, the International Diabetes Federation, American Association of Clinical Endocrinologists, American Association of Endocrinology, and American Diabetes Association recommend SMBG, which is a simpler method than CGM for assessing blood glucose fluctuations.[65,66]

Lifestyle Guidance

People should actively improve their lifestyle, by performing regular physical exercise, increasing dietary fiber intake, and reasonably controlling total calorie intake. Research indicates that moderate-intensity aerobic exercise performed 1 h after meals led to more regular blood glucose patterns and reduced fluctuations in both individuals with normal and abnormal glucose metabolism.[67] Dietary fiber can help maintain gut health and homeostasis, balance glucose metabolism, and decrease IR.[68] Patients with T3cDM should develop a personalized dietary fiber supplementation plan based on the presence or absence of pancreatic exocrine insufficiency. Although no specific nutritional pattern is recommended for patients with T3cDM, current guidelines have affirmed the safety and benefits of a low-carbohydrate diet in improving the levels of HbA1c, triacylglycerol, and other parameters.[69] Patients with T3cDM may adopt this dietary approach under professional guidance.[70] However, the safety and efficacy of this dietary pattern still need to be elucidated further.

Drug Therapy

The selection of medication, dosage, and timing of administration are crucial for managing glucose fluctuations. The complexity of pancreatic origin DM varies according to the extent of insulin deficiency. Currently, no standardized treatment has been established for T3cDM, and drug therapy is primarily empirical (Table 1).

Biguanides

Metformin is currently recommended as the first-line treatment for T3cDM. DM and chronic pancreatitis (CP) are independent risk factors for the development of pancreatic cancer, and their coexistence significantly increases this risk.[71] Cho J et al showed that the risk of pancreatic cancer in patients with T3cDM is seven times higher than that in patients with T2DM,[8] highlighting the value of metformin in preventing the development of pancreatic cancer.[72] Additionally, the COSMOS study demonstrated that patients with T3cDM treated with metformin alone had a significantly lower mortality

Table 1 Summary of the Effects of Hypoglycemic Agents on Glycemic Variability and Treatment in Pancreatogenic Diabetes Mellitus

Pharmacological group	Mechanism of action	Route of administration	Impact on variability	Treatment for T3cDM
Biguanides	Activate the AMPK signaling pathway and reduce insulin resistance	Oral	Neutral	First-line treatment
Sulfonylureas	Promote insulin release from pancreatic β-cells	Oral	Increase	Not recommended for use
Glinides	Promote insulin release from pancreatic β-cells	Oral	Unclear	Not recommended for use
Thiazolidinediones	Increase the sensitivity of target tissues	Oral	Decrease	Need more clinical trials to assess the benefits and risks
α-Glucosidase inhibitors	Prevent glucose absorption in the small intestine through competitive inhibition	Oral	Decrease	Not recommended for use
DPP4 inhibitors	Incretins	Oral	Decrease	Require transparent clinical trials to demonstrate their safety and efficacy in patients with T3cDM
GLP-1 receptor agonists	Incretins	Subcutaneous	Decrease	Require transparent clinical trials that demonstrate its safety and effectiveness in patients with T3cDM
SGLT-2 inhibitors	Inhibit renal glucose and sodium reabsorption by blocking the action of SGLT-2	Oral	Decrease	Not recommended for use in patients with T3cDM until proven safe; more research is needed to explore their benefits and risks in T3cDM
Insulins	Regulate cellular uptake and utilization of glucose	Subcutaneous and intravenous	Decrease	Preferred regimen for patients who cannot achieve adequate blood glucose control with oral medications alone

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; T3cDM, type 3c diabetes mellitus; SGLT-2, sodium-glucose cotransporter-2.

rate than that of with patients with T3cDM who had never used glucose-lowering medications, except those with PCRD. The current recommended dose of metformin for PPDM-A is 1,000 mg/day.[73] A few studies have examined the effect of metformin monotherapy on GV, as most of them compared the effect of metformin in combination with another oral hypoglycemic agent. Takahashi et al compared the effect of metformin monotherapy (1,500 mg) with high-dose (HMET) with that of high-dose metformin (750 mg) combined with linagliptin (LMET + DPP 4) treatment and found no significant difference in GV between the two groups of patients receiving insulin therapy. No significant difference was also noted in the mean glucose level, standard deviation, and mean magnitude of glucose excursion between the two groups. Only the postprandial glucose area under the curve (AUC) 3 h after breakfast ($p = 0.041$) was lower in the LMET + DPP 4 group than in the HMET group.[74] Therefore, although the specific effect of metformin on glycemic fluctuations remains unclear and appears to be neutral, it does not exacerbate GV in patients. Recent studies also suggest that metformin protects β-cell function by inhibiting some harmful effects of pro-inflammatory cytokines.[75] In summary, metformin remains a safe and reliable first-line treatment for patients with T3cDM without undue concern regarding its potential side effects.

Sulfonylureas and Glinides

Sulfonylureas and glinides promote insulin release from pancreatic β-cells. Several studies have shown that sulfonylureas increase the risk of hypoglycemia in patients. A European guideline for the management of CP does not recommend the use of sulfonylureas in patients with T3cDM, given the high risk of hypoglycemia.[76] Furthermore, sulfonylureas can

exacerbate glycemic fluctuations. Uemura et al evaluated 123 hospitalized patients with a time in range of (TIR) of >70% to determine the effect of sulfonylureas on the risk of hypoglycemia in patients with reasonable glycemic control. The sulfonylurea group had a higher glycemic standard deviation, % CV, and maximum blood glucose level compared with those in the non-sulfonylurea group, with an increase in % CV of 2.678 ($p = 0.034$). Moreover, the high doses of sulfonylureas were associated with persistent episodes of severe hypoglycemia ($\beta = 0.487$; $p = 0.028$).[77] Glinides are insulin secretagogues with a mechanism similar to that of sulfonylureas but with a faster onset. Both drugs increase insulin secretion, and chronic hyperinsulinemia is a known risk factor for pancreatic cancer.[78] Therefore, insulin secretagogues are not recommended for patients with T3cDM.

Thiazolidinediones

Thiazolidinediones (TZDs) reduce blood glucose levels by enhancing the sensitivity of target tissues to insulin. TZDs can promote fat redistribution by shifting adipose tissues from the visceral tissues to the subcutis, which may help improve peripheral IR. Recent studies have shown that TZDs can enhance hepatic insulin sensitivity,[79] improve GV, and reduce HbA1c levels by 1–1.5%. A 16-week, randomized, open-label study showed that adding pioglitazone to metformin monotherapy in poorly treated patients significantly reduced the HbA1c and mean plasma glucose levels.[80] However, TZDs increase the risk of fracture and heart failure, and patients with exocrine pancreatic dysfunction are at a higher risk of developing osteoporosis.[81] Therefore, more clinical drug trials are needed to assess whether the benefits of TZDs outweigh the risks.

α-Glucosidase Inhibitors

α-Glucosidase inhibitors improve blood glucose levels by preventing glucose absorption from the small intestine through competitive inhibition. In a 12-week study comparing the efficacy of acarbose and metformin in patients with T2DM using premixed insulin, the acarbose group demonstrated significant changes in CV, MAGE, and SD from baseline, compared to the metformin group.[82] However, despite these findings, the use of α-glucosidase inhibitor analogs is not recommended for patients with T3cDM. These inhibitors may exacerbate pancreatic exocrine insufficiency in patients and have significant gastrointestinal adverse effects such as bloating, diarrhea, and abdominal pain.

Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists are both members of the incretin class of drugs. DPP-4 inhibitors reduce the inactivation of GLP-1 by inhibiting the enzyme DPP-4, which deactivates GLP-1, thereby increasing endogenous GLP-1 levels. In addition to their insulin-stimulating effect, GLP-1 receptor agonists promote weight loss[83] and have been approved for this purpose in non-diabetic patients. For patients with T3cDM who have exocrine pancreatic dysfunction and resulting nutritional deficiencies, weight loss may be unnecessary. In 2011, the United States Food and Drug Administration indicated that DPP-4 inhibitors and GLP-1 receptor agonists may increase the risk of pancreatitis and pancreatic cancer.[84] Many subsequent studies have further confirmed that DPP-4 inhibitors are significantly associated with increased risk of pancreatitis.[85,86] In 2020, a meta-analysis of seven randomized controlled studies involving 56,004 patients with T2DM showed no significant increase in the risk of AP or pancreatic cancer in the GLP-1 agonist group compared with the placebo group.[87] However, as patients with overt T3cDM due to CP and pancreatic cancer were often excluded from the study, the validity and reliability of this conclusion for patients with T3cDM remain uncertain. Although both DPP-4 inhibitors and GLP-1 agonists effectively reduce blood glucose fluctuations,[88,89] patients with T3cDM should avoid these agents until definitive clinical trials demonstrate their safety and efficacy in this population.

Sodium-Glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter protein 2 (SGLT-2) inhibitors lower blood glucose levels by blocking glucose and sodium reabsorption in the renal tubular cells, which decreases the renal glucose threshold and increases urinary glucose excretion. However, the effect of SGLT-2 inhibitors on glucose fluctuation remains controversial. Lee et al showed that SGLT-2 inhibitors reduced the blood glucose levels but did not affect the GV.[90] Meanwhile, the study by Luo et al demonstrated that patients treated with SGLT-2 inhibitors (dapagliflozin) showed significant reductions in HbA1c, fasting

blood glucose, mean blood glucose (MBG), MAGE, time out of range (>10 mmol/L), hyperglycemic index, glycemic management index, and incremental AUC (>10) of blood glucose levels above 10 mmol/L. Conversely, the TIR (3.9–10 mmol/L) increased, and insulin requirements decreased.[91] However, the glucose-lowering mechanism of SGLT-2 inhibitors can lead to nutrient loss, which is closely associated with diabetic ketoacidosis. Considering that the majority of patients with T3cDM are insulin deficient, experts recommend against the use of such drugs in those with T3cDM until their safety is confirmed.[76] In addition to their glucose-lowering effect, SGLT-2 inhibitors offer several benefits, such as the prevention of cardiovascular events and the protection of renal function.[92] Hence, further studies are needed to evaluate the overall risk-benefit profile of SGLT-2 inhibitors in patients with T3cDM.

Insulin

T3cDM is caused by exocrine pancreatic dysfunction and reduces the body's sensitivity to hyperglycemia, making oral medications ineffective in controlling blood glucose. Consequently, insulin therapy remains the preferred treatment for these patients. Several studies indicate that insulin is used earlier and more frequently in patients with T3cDM than in those with T2DM.[14,93] However, despite the higher rates of insulin use, glycemic control remains poor in patients with T3cDM. Patients with T3cDM typically have higher HbA1c levels and more hypoglycemic episodes than those in patients with T2DM.[93] This finding indicates that hyperglycemia in patients with T3cDM is more severe and persistent than in those with T2DM, making it more difficult to achieve successful treatment. Currently, the recommendations for insulin administration in patients with T3cDM should follow the practices used in T1DM management, and the dose should be adequately adjusted in overweight patients.[94] Basal insulin-like insulins can provide more stable and prolonged glycemic control by mimicking endogenous insulin secretion during pre-prandial and overnight fasting periods, thereby reducing fluctuations in blood glucose levels and GV.[95] A 2015 meta-analysis of seven clinical trials suggested that degludec insulin was associated with lower nighttime hypoglycemia and MBG levels, compared to glargine insulin.[96] A 2022 randomized controlled study found that degludec insulin provided a longer TIR than that by glargine 100 units, but not longer than that with glargine 300 units.[97] However, no significant differences were found between glargine and degludec insulin levels in other GV measures (eg SD, MAGE, and CV).[97,98] The abovementioned studies were conducted in patients with T2DM, highlighting the need for additional clinical trials to determine the most effective long-acting insulin for patients with T3cDM. Furthermore, different insulin administration methods provide various benefits for T3cDM. In a study of 39 patients with T3cDM, the insulin pump continuous subcutaneous insulin infusion approach was more effective in reducing HbA1C levels (8.1% vs 7.3%, $p = 0.16$). Compared with those using the single or multiple daily injections approach, these patients had a lower incidence of severe hypoglycemia.[99] However, caution should be observed when using insulin in patients with PPDM-A, as prolonged insulin therapy following an initial episode of AP (compared with not using insulin) may increase the risk of progression to recurrent pancreatitis.[100]

Future Prospects

T3cDM differs from T2DM in the following aspects: its insidious onset, high misdiagnosis rate, and poor prognosis. Currently, no standardized treatment guidelines exist, making the early identification of risk factors for disease onset and effective intervention crucial. Several studies have shown that abnormal glucose fluctuations increase the risk of developing T3cDM. However, only a few prospective studies on blood glucose fluctuations and T3cDM have been conducted; moreover, the pathological mechanism of T3cDM has not been fully clarified, warranting further investigation. In addition, glucose-lowering drugs have a significant effect on glucose fluctuations. However, the current pharmacological treatment of T3cDM is often suboptimal or potentially harmful, with no standardized approach to drug selection. Therefore, further studies are needed to evaluate the risks and benefits of classical and novel medications for T3cDM. In addition, the non-glycemic effects of these drugs should be considered as part of the overall therapeutic regimen. This approach aims to provide practical solutions for the prevention and treatment of T3cDM, thereby improving prognosis and enhancing the health and well-being of patients.

Conclusion

GV is a significant risk factor for the development of T3cDM and is closely associated with the development of many diabetic complications. Reducing GV is crucial for preventing T3cDM and improving patient prognosis. Clinicians can reduce the incidence of GV by encouraging effective self-monitoring and promoting healthy lifestyle changes. In terms of drug therapy, patients with T3cDM exhibit considerable variability and present significant treatment challenges. Currently, most treatments are empirical. Metformin and insulin are recommended as first-line options owing to their safety, effectiveness, benefits, and ability to reduce GV. Further studies on other classical and novel hypoglycemic drugs are needed to evaluate their safety and effectiveness and to provide additional evidence-based guidance for clinical treatment.

Disclosure

The authors report no conflicts of interest in this work.

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