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REVIEW

Management of pancreatogenic diabetes: challenges and solutions

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Abstract: Pancreatogenic diabetes is an underdiagnosed form of secondary diabetes that is lacking official management guidelines. This paper reviews the recommended management strategies with additional data on the promising novel drugs.

Keywords: T3cDM, pancreatogenic diabetes, diabetes management, brittle diabetes, hypoglycemia

Introduction

Pancreatogenic diabetes is a form of secondary diabetes, classified by the American Diabetes Association (ADA) and the World Health Organization as type 3c diabetes mellitus (T3cDM).[1,2] It refers to diabetes due to diseases of the exocrine pancreas: pancreatitis (acute, relapsing, or chronic pancreatitis of any etiology), pancreatectomy/trauma, neoplasia, cystic fibrosis, hemochromatosis, and fibrocalculous pancreatopathy.[3] With the exception of cancer, damage to the pancreas must be extensive enough for diabetes to occur.[1,2] Rather scarce data on T3cDM suggest that most cases result from chronic pancreatitis, as this condition was identified as the underlying disease in 78.5% of all patients with T3cDM.[4]

In Western populations, T3cDM is estimated to occur in 5%–10% of all diabetic patients, mostly due to chronic pancreatitis.[4–6] True prevalence of T3cDM is unknown – data are scarce, mostly due to challenges with accurate diabetes classification in clinical practice.[4,7–9] Many T3cDM patients are initially misclassified due to underrecognized contribution of pancreatic disease to the development of diabetes. In order to improve diagnosis, diagnostic criteria for T3cDM have been proposed by Ewald and Bretzel which include 1) the presence of pancreatic exocrine insufficiency, 2) evidence of pathological pancreatic imaging, and 3) the absence of type 1 diabetes mellitus (T1DM)-associated autoantibodies.[6] They may be further supported by additional minor criteria, such as an absent pancreatic polypeptide (PP) response to mixed-nutrient ingestion.[6] These criteria may be more reliably applied at the presentation of diabetes due to a degree of overlap in established insulin deficiency (related to pancreatic atrophy and exocrine insufficiency). It is also worth noting that type 2 diabetes mellitus (T2DM) is common enough in the general population to accidentally coexist with exocrine pancreatic disease.[9,10]

Despite the limited data, T3cDM patients appear to share a similar risk for the micro- and macro-vascular complications of diabetes as in T1DM and T2DM.[11,12] Therefore, they should be equally monitored according to guidelines for patients with T1DM

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and T2DM.[13,14] Unlike T1DM and T2DM that increase the risk of pancreatic cancer, T3cDM is an effect and therefore a harbinger of pancreatic cancer in at least 30% of patients.[15]

Pathophysiology

Although classified as a unified group of secondary diabetes, the pathophysiological background of T3cDM differs. Damage to the pancreas disrupts the complex interplay of nutrient digestion, absorption, and utilization at different levels. Endocrine dysfunction represents deficiency of insulin, glucagon, PP, and incretin hormones. Typically, some degree of exocrine dysfunction with maldigestion and malabsorption of nutrients coexists.[5,9,16]

The pathogenesis of T3cDM is ultimately due to decreased insulin secretion; data on hepatic and peripheral tissue insulin sensitivity differ.[9,17–19] Impaired counterregulation due to deficient glucagon secretion, blunted catecholamine response, and impaired activation of hepatic gluconeogenesis result in glycemic instability with hypoglycemic reactions.[20]

Management

Currently, there are no specific guidelines to manage T3cDM as a separate entity. Only two documents exist that can serve as recommendations for T3cDM diabetes management.[13,14] For chronic pancreatitis, recommendations result from a consensus conference of gastroenterologists, endocrinologists, and surgeons with clinical and research expertise in the management of chronic pancreatitis and its complications.[14] For cystic fibrosis patients, a position statement from the ADA is part of clinical care guidelines for cystic fibrosis-related diabetes.[13]

Glycemic control

The current ADA standard of diabetes care does not set specific glycemic targets for T3cDM.[2] Therefore, as with T1DM and T2DM, the primary target is to achieve and maintain the HbA1c <7% in order to minimize the risk of chronic complications.[13,14] Keeping in mind the term "brittle diabetes", it is important to avoid hypoglycemia – blood glucose levels should be slightly above the normal to improve the quality of life.[5,8,20,21]

Lifestyle modifications

Attempts to reduce the toxic and modifiable contributors to chronic pancreatitis such as abstaining from alcohol and smoking cessation are highly recommended as both exacerbate progression of underlying pancreatic inflammation and fibrosis and contribute to pain. Abstaining from alcohol is also helpful for diabetes management, since alcohol acutely inhibits hepatic glucose production and can cause hypoglycemia, especially in the setting of insulin therapy.[9] Due to its vital role in overall health, the guidelines for cystic fibrosis-related T3cDM also recommend moderate aerobic exercise for at least 150 minutes per week.[13]

Nutrition

In chronic pancreatitis-associated diabetes, preventing/treating malnutrition, controlling symptoms of steatorrhea, and minimizing meal-induced hyperglycemia are the primary goals of medical nutritional therapy.[14] Patients should be encouraged to eat meals that are rich in soluble fiber and low in fat. In case of pancreatic exocrine insufficiency (of any degree), concomitant oral enzyme replacement therapy should be prescribed. Oral pancreatic enzyme replacement is particularly important for fat digestion and nutrients absorption. It helps to control symptoms of steatorrhea, protect against fat-soluble vitamin deficiency, and is important for maintaining incretin hormone secretion and thus improving glucose tolerance.[5,9,22–24] Vitamin D deficiency is frequently present in chronic pancreatitis, even in exocrine-sufficient patients.[25] Osteoporosis frequency in these patients is 34%, which is three times higher in comparison to controls.[26]

In cystic fibrosis-related T3cDM, similarly, good nutritional status and normal blood glucose levels are the primary goals. Patients are encouraged toward a well-balanced diet with no restriction in caloric intake, no fat, or carbohydrate restriction – all due to increased resting energy expenditure and malabsorption. Fat-soluble vitamins should be routinely supplemented. In contrast to other types of diabetes, there should be no salt and protein restriction in cystic fibrosis-related T3cDM, even in the setting of concomitant arterial hypertension or microvascular complications.[13]

Antihyperglycemic agents

There are no current common guidelines for T3cDM treatment. Although T3cDM represents a unified group of secondary diabetes, the pathophysiological background differs. Therefore, different treatment options should be taken into account and tailored individually.

In chronic pancreatitis-associated diabetes with mild hyperglycemia (HbA1c <8%), oral hypoglycemic agents may be appropriate.[14] Metformin, an insulin sensitizer, should be considered in case of concomitant insulin resistance due to the theoretical rationale in reducing risk of pancreatic

cancer.[5,21,27–29] On the other hand, it is often badly tolerated due to gastrointestinal adverse effects and weight loss, which are undesired in chronic pancreatitis.[9,14] Another group of insulin sensitizers, thiazolidinediones, are generally avoided due to their relation to fluid retention, congestive heart failure, and (particularly undesired) increased risk of fractures.[14,30] Insulin secretagogues (sulfonylureas and glinides) increase the risk of malignancy and can cause hypoglycemia.[5,27,31] If considered, short-acting agents are preferred, especially when meal ingestion is inconsistent.[9,14] Oral hypoglycemic agents are not recommended in cystic fibrosis-related T3cDM, as they are not as effective as insulin in improving nutritional and metabolic outcomes.[13]

Chronic pancreatitis patients with T3cDM not requiring insulin show a parallel to T2DM regarding the pathophysiology of the incretin defect and might benefit from incretin-based antidiabetic therapy.[23] Incretin-based therapies (eg, GLP-1 analogs and DPP-IV inhibitors) enhance insulin secretion, but their use in these patients has been precluded due to association with cases of drug-induced pancreatitis.[9,32,33] Also, GLP-1 analogs have been shown to reduce appetite and food intake leading to weight loss, which is not desired in these patients.[34] Therefore, their use is not recommended until more data become available.[9,14]

There are also no current data available on use of potential sodium–glucose cotransporter 2 inhibitors in T3cDM patients. Although they seem efficient in T2DM management and do not cause hypoglycemia, their main side effect is weight loss, which is unwanted in T3cDM.[35,36]

Insulin increases the risk of malignancy.[5,27,31] But for most T3cDM patients, the principal endocrine defect is insulin deficiency, and therefore, insulin therapy is the preferred treatment.[9] Insulin is the treatment of choice in cystic fibrosis-related T3cDM.[13] In this disease, insulin use is reported to improve outcomes in lung function, pulmonary exacerbation rates, nutritional status, blood glucose control, and decreased mortality.[37–42] Insulin can also be used for other forms of T3cDM, especially for correcting hyperglycemia in chronic acutely ill or hospitalized patients and in severely malnourished patients (to whom the anabolic effects of insulin are particularly beneficial).[9,14] In advanced T3cDM, multidose basal–bolus insulin dosing regimens should follow guidelines for the treatment of T1DM, and include carbohydrate counting for flexible prandial coverage and consideration of continuous subcutaneous insulin infusion or "pump" delivery.[9,13,14] However, in all insulin-based regimens, attention should be drawn to possible hypoglycemias.[36] Deficient counterregulatory glucagon secretion from islet α-cells, combined with blunted catecholamine response and impaired activation of hepatic gluconeogenesis, predisposes to hypoglycemia, which is often unpredictable in replacement doses of insulin.[9,20,43]

Total pancreatectomy with islet autotransplantation

It is a surgical method used in selected patients to treat severe complications (pain) of recurrent acute and chronic pancreatitis or in those with very high risk of pancreatic cancer while reducing the risk of severe diabetes mellitus.[44] It does not serve as a prevention or treatment strategy of T3cDM per se, although it increases chances of good glycemic control.[9] The selection criteria of patients are limitative, and therefore, the number of beneficiaries is very low.[45]

Promising novel drugs

PP has shown great promise as an antidiabetic drug for treatment of T3cDM secondary to chronic pancreatitis.[46–50] It increases the expression of insulin receptors in the liver, thus enabling effective utilization of circulating insulin.[49–52] It improves insulin sensitivity and decreases insulin requirements in T3cDM patients.[49,52] A novel formulation of PP in stabilized phospholipid micelles has been shown to overcome the obstacle of PP's short biological half-life and demonstrate significant antidiabetic activity in a rodent model of pancreatogenic diabetes.[53]

Conclusion

There are no current common guidelines for T3cDM management. Management strategies balance on the edge between optimal glycemic control to minimize the risk of chronic complications and avoiding hypoglycemic reactions but at the same time address malnutrition and disturbing gastrointestinal symptoms of steatorrhea to improve the quality of life.

Disclosure

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