CME

Type 3c: Understanding pancreatogenic diabetes

Jennifer Shurney Vonderau, MMS, PA-C; Chirag S. Desai, MD, FACS

ABSTRACT

Type 3c diabetes, also known as pancreatogenic diabetes, occurs when primary pancreatic disorders damage the pancreatic islets of Langerhans. Although often misdiagnosed as type 2 diabetes, type 3c diabetes is different in cause, clinical presentation, treatment, and prognosis. Patients with type 3c diabetes are more likely to experience complications and death related to hypoglycemic events. This article reviews the causes and management of type 3c diabetes, which is estimated to affect 5% to 10% of all patients with diabetes.

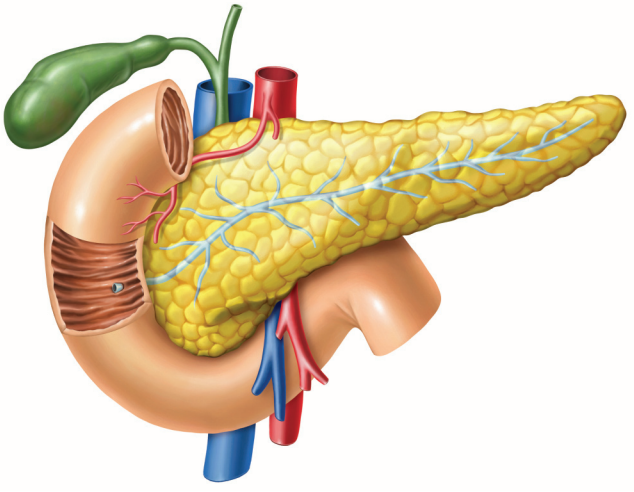
Keywords: type 3c, diabetes, pancreatogenic diabetes, hypoglycemia, islets of Langerhans, exocrine insufficiency

Learning objectives

- Define type 3c (pancreatogenic) diabetes.
- Name the effect of pancreatic diseases on the endocrine hormones produced by the islets of Langerhans.
- Differentiate type 3c diabetes from types 1 and 2 in regard to clinical presentation, diagnosis, and treatment.
- List the diagnostic tests that accurately assess glycemic function for a person with type 3c diabetes.
- Describe the prognosis of type 3c diabetes compared with types 1 and 2.

Diabetes, a group of diseases defined by persistent and recurrent hyperglycemia, affects more than 500 million adults worldwide.[1] The American Diabetes Association (ADA) defines several types of diabetes, all caused by a deficiency of production or function of insulin (or both).[2]

In type 3c diabetes (also known as pancreatogenic diabetes), primary pancreatic disorders damage the pancreatic islets of Langerhans, leading to poor glycemic control. This type has a different cause, pathophysiology, clinical presentation, diagnostic assessment, treatment, and prognosis compared with types 1 and 2 diabetes, but commonly is misdiagnosed as type 2 diabetes.[3]



© ANDREA DANTI/SHUTTERSTOCK.COM

Type 3c often is called *brittle diabetes*, because glucose control is especially challenging absent an appropriate beta cell (insulin) or alpha cell (glucagon) response.[4] Patients with type 3c diabetes are more likely to experience complications and death related to hypoglycemic events, and recognition of type 3c diabetes is critical for appropriate patient care and long-term management.[4,5] In Western populations, type 3c diabetes is estimated to occur in 5% to 10% of all patients with diabetes; however, the true prevalence is relatively unknown, and type 3c diabetes is routinely misclassified or misdiagnosed.[4,6] Considering the frequency with which diabetes is diagnosed in clinical practice, recognition and adequate treatment of type 3c diabetes are paramount to optimal patient care.

PATHOPHYSIOLOGY

The pancreas is a retroperitoneal organ with borders adjacent to the duodenum, vena cava, aorta, and spleen. Its structure comprises the pancreatic parenchyma (head, neck, body, and tail) and the pancreatic duct. The pancreas has exocrine and endocrine functions. The acinar cells produce pancreatic enzymes that aid in digestion. Pancre-

Jennifer Shurney Vonderau is a clinical assistant professor in the PA program at the University of North Carolina at Chapel Hill, N.C. **Chirag S. Desai** is a professor of surgery, surgical director of liver transplant, and director of chronic pancreatitis and autologous islet cell transplant in the Department of Surgery, Division of Abdominal Transplant at the University of North Carolina Medical Center in Chapel Hill. The authors have disclosed no potential conflicts of interest, financial or otherwise.

DOI:10.1097/01.JAA.0000885140.47709.6f

Key points

- Type 3c diabetes is a unique form of diabetes caused by pancreas gland dysfunction.
- Chronic pancreatitis is the most common cause of type 3c diabetes.
- Patients with type 3c diabetes have greater morbidity and mortality because of hypoglycemic events.
- Insulin is the therapy of choice for most patients with type 3c diabetes.

atic insufficiency occurs when production of pancreatic enzymes is impaired.

The endocrine function of the pancreas relies on the islets of Langerhans, which consist of alpha, beta, delta, and polypeptide cells. The alpha cells produce glucagon, a hormone that stimulates gluconeogenesis in response to hypoglycemia, and the beta cells produce the insulin that allows glucose uptake from the peripheral cells. Delta cells inhibit insulin and glucagon release, and pancreatic polypeptide cells play a role in hepatic insulin receptor availability (**Table 1**).[6]

In patients with type 3c diabetes, the pancreatic acinar cells and islets of Langerhans are impaired and/or destroyed by glandular inflammation and fibrosis.[6] Exocrine insufficiency affects nutritional absorption and incretin secretion. The loss of islet group function leads to loss of functional alpha cells and beta cells, resulting in cycles of hypo- and hyperglycemia. Loss of pancreatic polypeptide cells also may lead to hepatic insulin resistance and impaired gluconeogenesis.[6]

CAUSES AND EPIDEMIOLOGY

Chronic pancreatitis is the most common cause of type 3c diabetes.[7] Prevalence of type 3c diabetes in patients with chronic pancreatitis is reported to be up to 70%, and chronic pancreatitis accounts for about 79% of cases of type 3c diabetes.[6,8] Chronic pancreatitis is defined as irreversible physiologic change to the pancreas gland that results in chronic pain and/or opioid reliance, pancreatic insufficiency, dysglycemia, and an increased risk of pancreatic cancer.[7,9,10] Chronic pancreatitis is underrepresented in the primary care population because it is challenging to diagnose and often is mislabeled because of its symptomatology.

Prevalence of chronic pancreatitis is estimated at 5 to 10 per 100,000 adults.[10] The most common causes are alcoholic pancreatitis, hereditary pancreatitis, autoimmune pancreatitis, traumatic pancreatitis, and pancreas divisum.[11] Acute recurrent pancreatitis causes repeated parenchymal trauma and may progress to chronic pancreatitis, and severe episodes of acute pancreatitis may themselves cause substantive islet dysfunction, profound hyperglycemia, and type 3c diabetes.[12]

Patients with chronic pancreatitis often are glucose intolerant, and data suggest that more than 60% of these patients will be diagnosed with diabetes within 5 years of diagnosis.[8]

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer and has a high mortality, with a 5-year survival rate of less than 10%.[7] The understanding of the pathophysiology and relationship between diabetes and PDAC is still evolving. Prolonged type 2 diabetes, especially when concomitant with obesity, is a known risk factor for development of PDAC.[7] The prevalence of diabetes among patients with PDAC supersedes that of the general population. One study found that most patients diagnosed with PDAC had been found to have diabetes less than 2 years earlier.[13] For those patients, the diagnosis of diabetes was made when a pancreatic tumor was radiographically occult. Thus, it is possible to consider new-onset diabetes an impetus to assess for pancreatic disease or cancer.[7]

New-onset diabetes may resolve following PDAC resection.[7,13] This suggests that diabetes diagnosed with PDAC may be caused by pancreatic disease rather than insulin resistance alone. Although it is challenging to assess for the degree of overlap between types 2 and 3c diabetes in patients with PDAC, pancreatic ductal adenocarcinoma is estimated to account for 8% of cases of type 3c diabetes.[6]

Pancreatic exocrine insufficiency is near-universal for patients with cystic fibrosis (CF), a genetic disorder that affects production of sweat, digestive fluids, and mucus. CF-related diabetes is the most common comorbidity of patients with CF, occurring in up to 50% of adults with CF.[14] Type 3c diabetes in patients with CF has a negative effect on overall survival.[14] Patients with CF also may

TABLE 1. Pancreatic hormones[11]

Islets of Langerhans	Hormone produced	Stimulated by	Effects	Contributing mass (per total islets)
Alpha cells	Glucagon	Low blood glucose levels	Increases blood glucose levels	20%
Beta cells	Insulin	Elevated blood glucose levels	Reduces blood glucose levels	75%
Delta cells	Somatostatin	Glucose	Inhibits insulin and glucagon release	4%
Pancreatic polypeptide cells	Pancreatic polypeptide	Meal intake and fasting	Role in appetite	1%

present with other pancreatic disorders, such as pancreatic cystosis, in which most of the pancreatic parenchyma is replaced by cysts. These patients may present with chronic pain and benefit from pancreatic surgery, further increasing their risk of type 3c diabetes.[15] CF-related diabetes is the best recognized cause of type 3c diabetes; however, CF accounts for only 4% of cases of type 3c diabetes overall.[3,6]

Hereditary hemochromatosis is an autosomal recessive condition characterized by the triad of cirrhosis, skin pigmentation, and diabetes.[16] Small but relevant clinical studies estimate the prevalence of diabetes in this population to range from 7% to 40%.[16] The pathophysiology of diabetes in hereditary hemochromatosis is not completely understood and was first attributed to pancreatic siderosis, but it is hypothesized also as secondary to insulin deficiency and insulin resistance.[16,17] Hereditary hemochromatosis is estimated to account for 7% of cases of type 3c diabetes.[6]

SURGICAL PANCREATIC RESECTION

Indications for pancreatic surgery include benign, premalignant, and malignant conditions. The type of surgical resections required for these surgeries varies substantially and may include partial parenchymal resection (such as a Whipple procedure and distal pancreatectomy), ductal drainage procedures, and total pancreatectomy. The degree of pancreatic tissue removed and the type of surgery performed can influence the probability of developing pancreatogenic diabetes, as can a patient's preoperative diabetes status. The incidence of postoperative type 3c diabetes after a Whipple procedure ranges from 20% to 50%.[18] The incidence of type 3c diabetes after distal pancreatectomy is estimated to be up to 60%.[19]

Autologous islet transplant, a surgical procedure in which the pancreas gland, following resection, is digested to isolate the islet cells and then infused into the patient's liver, mitigates the severity of type 3c diabetes and prevents it in up to one-third of patients.[20,21] This procedure is not an option for patients with pancreatic cancer.

Surgical resection of the pancreas is perhaps the most obvious cause of type 3c diabetes, but it accounts for only 2% of cases.[6]

CLINICAL PRESENTATION

Symptoms of pancreatic disease vary widely in severity based on patients' disease type, progression, and treatment. Clinicians managing patients with possible type 3c diabetes should first consider disease cause. Pancreatic insufficiency predates development of type 3c diabetes. These patients may present with nausea, diarrhea, malabsorption, and weight loss.[7,11]

As mentioned above, patients with type 3c diabetes, aside from evidence of pancreatic disease, may present similarly to patients with types 1 or 2 diabetes (**Table 2**). Chronic hyperglycemia may result in weight loss or poor weight gain, as well as increases in appetite, thirst, and urinary frequency. Patients with type 3c diabetes rarely present in a state of ketoacidosis but may present as severely hyperglycemic, depending on the duration of their disease.[6] Symptoms of hypoglycemia in patients with type 3c diabetes may manifest as noncardiogenic syncope, lightheadedness, sweating, confusion, palpitations, hunger, and shaking.

Most presenting symptoms in patients with type 3c diabetes are elicited through thorough history-taking. A physical examination may be normal aside from possible evidence of pancreatic disease.

DIAGNOSIS

The diagnosis of type 3c diabetes is challenging. Assess for evidence of pancreatic disease in any patient with a history of acute pancreatitis, chronic pancreatitis, or chronic abdominal pain. A thorough history and physical examination are paramount for a patient with new dysglycemia. The ADA has various metrics by which a patient may be diagnosed with diabetes, including fasting glucose level, oral glucose tolerance test (OGTT), and/or A1C.[3]

According to the ADA, in addition to standard criteria for diagnosing diabetes, diagnosis of type 3c diabetes requires:

TABLE 2. Diagnostic features of diabetes by type[3,7]

Parameter	Type 1	Type 2	Type 3c
A1C	>6.5%	>6.5%	>6.5%
Fasting glucose	>126 mg/dL	>126 mg/dL	>126 mg/dL
Fasting C-peptide (0.5 to 2.0 ng/mL)	Very low: <0.2 ng/mL	Normal to high	Low to normal
Ketoacidosis	Common	Rare	Rare
Hypoglycemia (glucose <69 mg/dL)	Common	Rare	Frequent
Islet autoantibodies	Positive	Negative	Negative
Exocrine insufficiency (fecal elastase <200 mcg/g)	Negative	Negative	Positive
CGM	Hyperglycemia and reactive hypoglycemia	Hyperglycemia	Alternate hyperglycemia and hypoglycemia

- presence of pancreatic insufficiency
- evidence of pathologic pancreatic imaging
- absence of type 1 diabetes-associated autoimmune markers.[3,7]

Additional or minor criteria include impaired beta-cell function, absence of insulin resistance, impaired incretin secretion, and low serum concentration of lipid-soluble vitamins (A, D, E, and K).[6] Type 1 diabetes autoimmune markers, which commonly include islet cell antibodies, GAD-65 antibodies, and insulin antibodies, are negative.[21]

Pancreatic insufficiency is considered through history-taking (steatorrhea and diarrhea) and diagnosed with a fecal elastase. MRI of the abdomen is the preferred imaging to diagnose pancreatic disease such as chronic pancreatitis and pancreatic cancer. CT of the abdomen is also highly sensitive for identifying abnormal pancreatic parenchyma or masses. Islet-specific autoantibodies can be studied through serum to assess for autoimmune type 1 diabetes.

Evaluate the glycemic control of patients with type 3c diabetes with a variety of diagnostic methods. Insulin production, representing beta-cell function, can be assessed by fasting C-peptide and stimulated C-peptide (C-peptide response to arginine or glucagon bolus), because C-peptide is produced in equimolar quantities to endogenous insulin but is more stable in the serum.[22]

A1C can be used to provide a global understanding of average glucose level, although it will not provide a good representation of the severity of blood glucose variability. For patients with CF, guidelines state that A1C cannot be used as a diagnostic tool for CF-related type 3c diabetes.[14]

OGTTs and mixed-meal glucose tolerance tests assess beta-cell function and insulin resistance. The OGTT is the screening and diagnostic test of choice for type 3c diabetes in patients with CF.[14]

Alpha cell dysfunction manifests as impaired glucagon production, but there is substantial heterogeneity of glucagon in the serum, and glucagon levels cannot be accurately assessed by serum studies. Continuous glucose monitoring (CGM) can be used to provide highly accurate, ongoing surveillance of glucose levels and can be clinically useful in identifying periods of hyperglycemia and hypoglycemia. CGM also is being studied as a predictor of islet function following pancreatic surgery and autologous islet transplant.[23]

TREATMENT

Insulin is the most often recommended therapy for patients with type 3c diabetes, and it is the most useful therapy for type 2 diabetes associated with advanced chronic pancreatitis. Use strict caution when dosing and monitoring patients using insulin therapy because of the risk of hypoglycemia due to the impaired glucagon function inherent to type 3c diabetes.

Treatment of type 3c diabetes also should include treatment of pancreatic exocrine insufficiency with pancreatic enzyme replacement to improve absorption of fats and fat-soluble vitamins. Pancreatic insufficiency causes malabsorption of nutrients, and replacement with pancreatic enzymes can improve nutrient absorption and incretin secretion, which ultimately improves glycemic control.[4,6]

For patients with CF, type 3c diabetes should be managed by a multidisciplinary team with expertise in both types of diabetes.[14] Insulin is the only recommended medical therapy for patients with type 3c diabetes and CF; however, evidence regarding superiority of any specific insulin regimen is lacking.[14]

Metformin therapy can be considered, especially in patients with types 2 and 3c diabetes; this drug may protect against development of pancreatic ductal adenocarcinoma.[6]

Overall, no evidence-based treatment exists for type 3c diabetes that is uniquely distinguished from types 1 and 2 diabetes, and treatment should be based on the disease's cause and pathophysiology.[6]

IMPORTANT CONSIDERATIONS IN PROGNOSIS

The ADA does not classify specific targets for glycemic control for patients with type 3c diabetes, nor does it define a safe value for A1C. The ADA defines stages of hypoglycemia that may be especially important to identify in a patient with type 3c diabetes:

- Level 1 is defined as glucose between 54 and 69 mg/dL
- Level 2 is defined as glucose less than 54 mg/dL
- Level 3 (severe hypoglycemia) is defined as glucose less than 54 mg/dL requiring assistance.[3] Patient-reported severe hypoglycemic events are associated with a 3.4-fold increase in 5-year mortality.[5]

Finally, there is a known relationship between chronic pancreatitis, diabetes, and development of pancreatic cancer, with further risk for patients with a history of hereditary pancreatitis.[6,7]

CONCLUSION

Type 3c diabetes is a complication of pancreatic disease that may be overlooked or misunderstood and frequently is misdiagnosed. Accurate history-taking and use of appropriate diagnostic studies can help clinicians identify patients with type 3c diabetes and provide appropriate care that can result in improved patient outcomes. **JAAPA**

Earn Category I CME Credit by reading both CME articles in this issue, reviewing the post-test, then taking the online test at http://cme.aapa.org. Successful completion is defined as a cumulative score of at least 70% correct. This material has been reviewed and is approved for 1 hour of clinical Category I (Preapproved) CME credit by the AAPA. The term of approval is for 1 year from the publication date of November 2022.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 10th ed. https://diabetesatlas.org/atlas/tenth-edition. Accessed August 17, 2022.
2. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. *Diabetes Care*. 2021;44(suppl 1):S15-S33.

3. American Diabetes Association. Understanding A1C: diagnosis. www.diabetes.org/a1c/diagnosis. Accessed July 27, 2022.
4. Makuc J. Management of pancreatogenic diabetes: challenges and solutions. *Diabetes Metab Syndr Obes*. 2016;9:311-315.
5. McCoy RG, Van Houten HK, Ziegenfuss JY, et al. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care*. 2012;35(9):1897-1901.
6. Hart PA, Bellin MD, Andersen DK, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol*. 2016;1(3):226-237.
7. Andersen DK, Korc M, Petersen GM, et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. *Diabetes*. 2017;66(5):1103-1110.
8. Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol*. 2013;19(42):7276-7281.
9. Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatology*. 2016;16(2):218-224.
10. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013;144(6):1252-1261.
11. Goldman L, Schafer AI. *Goldman-Cecil Medicine*. 25th ed. Philadelphia, PA: Elsevier Saunders; 2015.
12. Bellin MD, Lowe M, Zimmerman MB, et al. Diabetes mellitus in children with acute recurrent and chronic pancreatitis: data from the INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE cohort. *J Pediatr Gastroenterol Nutr*. 2019;69(5):599-606.
13. Pannala R, Leirness JB, Bamlet WR, et al. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology*. 2008;134(4):981-987.
14. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;33(12):2697-2708.
15. Desai CS, Vonderau JS, McCall R, et al. Pancreatic cystosis in patients with cystic fibrosis: a qualitative systematic review. *Pancreatology*. 2018;18(7):700-704.
16. McClain DA, Abraham D, Rogers J, et al. High prevalence of abnormal glucose homeostasis secondary to decreased insulin secretion in individuals with hereditary haemochromatosis. *Diabetologia*. 2006;49(7):1661-1669.
17. Barton JC, Acton RT. Diabetes in HFE hemochromatosis. *J Diabetes Res*. 2017;2017:9826930.
18. Kahl S, Malfertheiner P. Exocrine and endocrine pancreatic insufficiency after pancreatic surgery. *Best Pract Res Clin Gastroenterol*. 2004;18(5):947-955.
19. Maeda H, Hanazaki K. Pancreatogenic diabetes after pancreatic resection. *Pancreatology*. 2011;11(2):268-276.
20. Baldwin XL, Williams BM, Schrope B, Desai CS. What is new with total pancreatectomy and autologous islet cell transplantation? Review of current progress in the field. *J Clin Med*. 2021;10(10):2123.
21. Al-Sofiani ME, Quartuccio M, Hall E, Kalyani RR. Glycemic outcomes of islet autotransplantation. *Curr Diab Rep*. 2018;18(11):116.
22. McEachron KR, Skube ME, Yang Y, et al. Utility of arginine stimulation testing in preoperative assessment of children undergoing total pancreatectomy with islet autotransplantation. *Clin Transplant*. 2019;33(8):e13647.
23. Vonderau JS, Williams BM, DeCherney S, et al. Use of continuous glucose monitoring for evaluation of hypoglycemia pre- and post-operatively for patients undergoing total pancreatectomy with autologous islet cell transplant. *Clin Transplant*. 2021;35(11):e14450.