ANNALS OF MULTIDISCIPLINARY RESEARCH, INNOVATION AND TECHNOLOGY (AMRIT)

(A peer-reviewed open access multidisciplinary journal)

www.adtu.in/amrit

COMMENTARY

# Pancreatogenic Diabetes (Type 3c)

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Article Chronicle: Received: 19/12/2021 Accepted: 31/12/2021 Published Online: 12/01/22

## 1. Introduction and Nomenclature

Type 3c diabetes had been traditionally called 'Pancreatogenic' or 'Pancreatogenous' diabetes mellitus, and defined as diabetes secondary to diseases of the exocrine pancreas. The nomenclature 'Type 3c' is relatively new and appears to have been adopted from the list of the four types of diabetes that was published in the American Diabetes Guidelines until the year 2014.The list contained the term III.C, which indicated diabetes secondary to diseases of the exocrine pancreas and was variably referenced by several authors as Type IIIC diabetes and subsequently Type 3c. The latter term stayed on with greater popularity most likely because of its similarity to and easier distinguishability from the terms Type 1 and Type 2 diabetes. However, since knowledge on Type 3c diabetes is still evolving and there is a lack of global consensus on the definitions and several aspects, the terminologies are likely to change over the coming years.

## 2. Epidemiology

Several exocrine pancreatic diseases have been implicated in the genesis of Type 3c diabetes. Out of these, CP (CP) leads the list with 79%, followed by pancreatic ductal adenocarcinoma (8%), hemochromatosis (7%), cystic fibrosis (4%), and previous pancreatic surgery (2%). Type 3c diabetes has been estimated to constitute 1-9% of all diabetes globally, based on where it has been studied. Estimation of Type 3c diabetes among patients with CP has shown a prevalence of 25-80% across several studies from the west. From our experience in patients with CP from different parts of India, the cumulative incidence of diabetes is 57.9% while the prevalence is 38%. The median (IQR) age of onset of diabetes (majority being Type 3c) in Indian patients with CP is 30.0 (21.0-40.8) years, which is substantially lower than that observed in the west. The most important independent risk factor for development of Type 3c diabetes in the Indian patients is the presence of obstructive pancreatic ductal calculus, which increases the risk of diabetes by over two-folds.

## 3. How Does Type 3c Diabetes Differ From Type 1 and Type 2 Diabetes?

Table 1 shows the salient differences of Type 3c diabetes from Type 1 and Type 2 diabetes.

## 4. Pathogenic Mechanisms of Type 3c Diabetes

The pathogenic mechanisms of development of Type 3c diabetes varies according to the risk factors. The following paragraphs briefly describe the mechanisms for Type 3c diabetes associated with CP and pancreatic cancer.

### 4.1 Chronic Pancreatitis

Several mechanisms have been shown to be operational in the development of diabetes in CP.

**(a) Insulin secretory defect:** During the early stages of CP, due to inflammation of the exocrine and endocrine pancreas, beta cell function gets impaired. Even though the islets remain viable, they do not respond adequately to glucose challenge. We have shown that this secretory defect is due to alteration of the JAK-STAT pathway, which impairs insulin gene expression by exteriorization of the transcription factor pdx from the nucleus to the cytosol. These events are mediated by the secretion of interferon-gamma into the islets as a result of infiltration of Th17 secreting T-helper cells. We had also observed mutations in the BACH 2 gene, which is a master regulator of inflammation. An additional factor that could participate in the beta cell dysfunction in Type 3c diabetes is gut microbial dysbiosis. We and others have shown that the gut microbiota gets disrupted in CP patients with diabetes. There is a reduction in the abundance of the bacteria called *Fecalibacterium praustnizii*, which is known to provide nutri-

Table 1: Salient Differences Between the Three Types of Diabetes

| | Type 1 diabetes | Type 2 diabetes | Type 3c diabetes |
|---|---|---|---|
| Primary pathogenesis | Autoimmunity | Insulin resistance | Pancreatic inflammation |
| Pancreatic exocrine insufficiency | May be present in advanced stages | May be present in advanced stages | Yes |
| Insulin deficiency | Yes | No | Yes |
| Hepatic insulin sensitivity | Normal or decreased | Decreased | Normal or decreased |
| Peripheral insulin sensitivity | Normal or decreased | Decreased | Normal |
| Diabetic ketoacidosis | Yes | No | No |
| Risk of hypoglycaemia | Increased | Normal | Normal or increased |
| Pancreatic polypeptide response | Normal or decreased | Normal or increased | Reduced or absent |

ents to the colonic epithelium and maintain the gut barrier. There is also over expression of lipopolysaccharide (endotoxin) synthetic pathway following which there is translocation of endotoxins into circulation. It has been earlier shown that endotoxins could cause beta cell function via the Toll like receptors 4 with the involvement of the NFkB pathway.

**(b) Hepatic insulin resistance:** This phenomenon is regulated by the pancreatic polypeptide (PP) hormone. PP is responsible for expression of insulin receptors in the liver that results in internalization of insulin into the liver and the downstream metabolic activities. In CP, there is deficiency of PP that results from islet dysfunction and/or apoptosis due to inflammation. This culminates in reduced expression of PP receptors in the liver and thereby hepatic insulin resistance.

**(c) Reduced incretin secretion:** Pancreatic exocrine insufficiency (PEI) is an integral component of CP. Due to PEI there will be nutrient maldigestion which was shown to result in impaired late phase of insulin secretory responseto glucose-dependent insulinotropic polypeptide (GIP). However, whether altered GIP secretion is a cause or effect of Type 3c diabetes is still under evaluation.

**(d) Destruction of islets:** Islet loss occurs as CP progresses over time due to the inflammation and progressive fibrosis. It also results from total or partial pancreatectomy, in which case Type 3c diabetes would develop much earlier.

### 4.2 Pancreatic Cancer

The association between Pancreatic Ductal Adenocarcinoma (PDAC) and diabetes has long been recognized. This can be looked from two perspectives. Firstly, meta-analyses have shown that patients with long-standing (>5yrs duration) diabetes has a 1.5-2.0 folds increase the risk of developing PDAC. This association has been attributed to insulin resistance and an increase in insulin, which has growth promoting action, in the pancreatic microenvironment. Secondly, PDAC could result in new-onset diabetes,which have been demonstrated in a series of elegant epidemiological, clinical and experimental studies.The data in support of this are: a) more than 80% patients with PDAC develop glucose intolerance and approximately 66% develop frank diabetes; b) over 80% of patients with PDAC who develop diabetes have new-onset diabetes, detected 24-36 months before the diagnosis of PDAC, thereby demonstrating a temporal relationship; and, c) resection of PDAC has been shown to improve or resolve the new-onset diabetes in these patients, but not the long-standing one, thereby implying a potential paraneoplastic mechanism. Following are a few of the proposed mechanisms of PDAC induced diabetes:

**(a) Beta cell dysfunction:** While insulin resistance could be associated with PDAC induced Type 3c diabetes, insulin secretory defect have emerged as a more profound mechanism to this effect. Proteomic studies have demonstrated an increased secretion of peptide hormone adrenomedullin from pancreatic cancer cells. Based on further studies, it has been proposed that the adrenomedullin is packaged into exosomes that deliver the hormone to the beta cells. Once inside the beta cells, adrenomedullin impairs the secretion of insulin thereby leading to glucose intolerance and diabetes, thereby making PDAC induces diabetes an exosomopathy. Earlier, adrenomedullin was also shown to contribute to the aggressiveness of PDAC.

**(b) Adipokine:** Neutrophil gelatinase associated lipocalin (NGAL) is a potential adipokine that could be associated with diabetes in PDAC. This adpokine is also elevated in obesity and is responsible for glucose metabolism and insulin sensitivity.

**(c) Immunological markers:** A few immune markers that have been proposed to be associated with diabetes in PDAC includes calprotectin (S100 A8/A9), vanin 1 and matrix metalloproteinase (MMP) 9. However, further studies will be required before a causal or biomarker role could be ascribed to these molecules.

## 5. Complications of Type 3c Diabetes

Even though not studied widely in a systematic manner, the complication of Type 3c diabetes are similar to those with Type 1 and 2 diabetes. Patients should be monitored for the development of the key micro and macrovascular complications just in the same manner as done for Type 1 and Type 2 diabetes. Similar cardiovascular risk reduction guidelines should also be followed.

## 6. Diagnosis

A set of major and minor diagnostic criteria for Type 3c was proposed by Ewald and Breztel in 2013 (Table 2). However, these factors could also be observed in advanced Type 1 and Type 2 diabetes. For instance, pancreatic exocrine insufficiency and pancreatic atrophy on morphology can also be seen in Type 1 and Type 2 diabetes. Therefore, these diagnostic criteria have not gained popularity.

Table 2: Proposed Diagnostic Criteria of Type 3c Diabetes

| **Major criteria (all must be present)** |
|---|
| Presence of pancreatic exocrine insufficiency (according to monoclonal fecal elastase 1 or direct function tests) |
| Pathological pancreatic imaging (By endoscopic ultrasound, MRI or CT) |
| Absence of Type 1 diabetes-associated autoimmune markers |
| **Minor criteria** |
| Impaired beta-cell function (eg. As measured by HOMA-B, C-peptide/glucose ratio) |
| No excessive insulin resistance (eg. As measured by HOMA-IR) |
| Impaired incretin (eg. GIP) or pancreatic polypeptide secretion |
| Low serum lipid soluble vitamins (A, D, E, and K) |

Initial diagnostic evaluation for Type 3c diabetes is similar to that of Type 1 and Type 2 diabetes based on the ADA criteria. What becomes important is to differentiate Type 3c diabetes from Type 1 and Type 2. Onset of diabetes on the background of clinical and imaging evidence of florid CP would highly suggest a diagnosis of Type 3c diabetes. However, in younger patients with diabetes but ambiguous signs of CP, islet autoantibodies need to be evaluated to rule out Type 1 diabetes. Similarly, in overweight or obese patients with CP and diabetes, presence of hyperinsulinemia or high C-peptide would rule out Type 2 diabetes. In the presence of further ambiguities, the diagnosis of Type 3c diabetes can be clinched by the pancreatic polypeptide response to mixed nutrient. In this test, 12 ounces of the Boost High Protein diet or equivalent, which represents mixed-nutrient, is administered along with standard doses of pancreatic enzymes. In a healthy person, there will be a 4-6 folds elevation of pancreatic polypeptide, while in patients with CP and Type 3c diabetes the elevation will be less than twice the basal level. On the other hand, in early Type 1 diabetes, there will be a normally elevated pancreatic polypeptide response and in early Type 2 diabetes, both the basal and stimulated response of the hormone will be elevated.

## 7. Treatment Outlines

Currently there are no data based on randomized controlled trial that addressed the efficacy of anti-diabetic agents in Type 3c diabetes in patients with CP and PDAC. However, the goal of treatment of Type 3c diabetes in CP is similar to that for Type 1 and 2 diabetes, i.e. glycaemic control and prevention of long-term complications. Pharmacotherapy for Type 3c diabetes resulting from CP was earlier invariably initiated with insulin based on the notion that there is islet destruction and loss of insulin secretion. However, with the current understanding that in the early stages there is not much islet destruction, initial first line of medication, especially if the hyperglycaemia is mild (HbA1c <8.0%) is metformin. Insulin can be started if response to metformin is suboptimal or if the patient has severe hyperglycaemia. The role of incretin based therapies, which is otherwise popular in the treatment of Type 2 diabetes, is unclear in Type 3c diabetes especially because it is avoided in CP due to an increase risk of acute pancreatitis. However, recent observations have ruled out the risk of acute pancreatitis with the use of incretin-based therapy. Thiazolidinediones increases hepatic and peripheral insulin sensitivity and could be beneficial in Type 3c diabetes, especially in the early stages, but should be used with caution due to its effect on bone health, since patients with CP are a higher risk of osteoporosis due to pancreatic exocrine insufficiency. In contrast to CP, since the life expectancy in PDAC is relatively shorter, the primary goal of treatment of Type 3c diabetes is prevention of short-term metabolic complications rather than long-term complications. Metformin is an ideal first choice in for these patients. Insulin is used as a second line while incretin-based therapies as best avoided due to the increased but controversial risk of PDAC. Besides specific antidiabetic drugs or insulin, other general measures such a diet and lifestyle modifications hold good also for Type 3c diabetes. Furthermore, in patients with CP, alcohol cessation is important not only for its beneficial action against inflammation, but also in preventing hypoglycaemic episodes after insulin therapy (since alcohol acutely inhibits hepatic glucose production). These patients should also receive appropriate doses of pancreatic enzyme replacement since other than improving nutrient digestion; the enzymes have also been shown to improve in cretin secretion.

## Further Readings

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