Type 3c Diabetes. A New Challenge of 2021 to Diabetologists

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Abstract
The patients with chronic pancreatitis or with their pancreas being removed are observed with a high percentage of Diabetes Type 3c, yet they are mostly confused with type 1 or type 2 diabetes. Chronic pancreatitis is the leading cause of Type 3c DM along with hemochromatosis and adenocarcinoma etc. The pancreatic tissue abnormality and loss of islet’s cells result in the declination in insulin production and hyperglycemic conditions with clinical presentation of abdominal pain, bloating, steatorrhea or maldigestion, and glucose intolerance sometimes in association with PEI. True diagnosis for Type 3c must include pathological pancreatic imaging, and the patient should be checked for PEI as the absence of pancreatic enzyme is another true indicator of type 3c. The DM insulin replacement therapy is preferred for treating Type 3c DM to achieve optimal glucose concentration in blood.

Introduction
Diabetes mellitus is one of the most prevalent metabolic disorders in the world; it is characterized by high blood glucose levels (hyperglycemia) due to the defects in the action of insulin, secretion of insulin or may be due to both of them [80]. Type I and Type II diabetes are considered as the major types of diabetes to be known by that time and type II Diabetes is more prevalent (>85%) then that of type I [81]. Type I Diabetes is considered to be caused by the deficit insulin secretion from the beta cells of the pancreas that actually happens due to the autoimmune devastation of the beta cells. On the other hand, diabetes type II is caused by two coupled reasons, the first one is the resistance to insulin action, and the second one is the insufficient compensatory insulin secretory response. “Gestational Diabetes mellitus” (GDM), which is also a situation of glucose intolerance, is known to be recognized during pregnancy. Except for these above-mentioned types of Diabetes, there are some more specific categories of diabetes mellitus, and Type 3c Diabetes falls in this category [82]. Among the people suffering from Diabetes mellitus, approximately 2 percent of them have type 3c diabetes [83]. Type 3c diabetes might happen due to genetic and non-genetic factors that comprise pancreatic removal, pancreatitis, pancreatic ductal adenocarcinoma, hemochromatosis, or cystic fibrosis. One of the most dominating causes of Type 3c diabetes is chronic pancreatitis. Unfortunately, patients who have type 3c diabetes are not diagnosed properly and timely, which is one of the main causes of delay in their required treatment [84].

Type 3c Diabetes Mellitus (T3cDM)
Type 3c diabetes mellitus has been designated as secondary diabetes and usually called the pancreatogenic diabetes. One can also develop type 3c if they have a part or all of the pancreases removed because of any other damage. Some people who take steroids can also develop this type of diabetes. This is also called steroid-induced diabetes and is more common in people at high risk of type II diabetes.

Pathogenesis of Type 3c Diabetes mellitus
The declaration characterizes the pathogenesis of T3cDM in insulin production that might be due to the reduced number of the islet’s cells or due to the loss of functionality attributed to fibrosis or sclerosis [85]. Basically, the pancreatic tissue damage causes the deficiency of insulin, and its mechanism can be explained by the functionality-dependent interpaly between the acinar cells and islets cells.

Pancreatic Function
The pancreas holds two significant functions in the human body, firstly, it controls the blood glucose levels, and secondly, it assists in the digestion of the food. Anatomically, the pancreas is divided into five regions associated with the gall bladder, duodenum, and spleen. It has both the exocrine and the endocrine regions. Still, the maximum region of the pancreas owns an exocrine function responsible for the formation and release of the digestive enzymes into the duodenum. Acinar cells that makeup to 85 percent of the pancreatic cells is devoted to synthesizing the enzymes for carbohydrates, lipids,
and protein digestion. The main enzyme contributors include amylases, lipases and trypsin, and zymogens (proelastase, trypsinogen, chymotrypsinogen procarboxypeptidase). Endocrine secretory tissues residing in the pancreas are called the islets of Langerhans, containing four types of cells. The beta cells (Insulin secreting cells) are in a huge amount. In Type I and Type II Diabetes mellitus, deficient insulin production leads to hyperglycemia, but the digestion of food is unaffected. On the other hand, in Type 3c Diabetes mellitus, digestion of food also gets affected.

**Causes of Type 3c Diabetes Mellitus**

One of the most frequently recognized causes of Type 3c diabetes mellitus is chronic pancreatitis. The most commonly identified cause of type 3c diabetes is chronic pancreatitis. According to a single-center review, causes of type 3c diabetes were recorded as: “chronic pancreatitis” (79%), “pancreatic ductal adenocarcinoma” (8%), “hemochromatosis” (7%), “cystic fibrosis” (4%), and previous pancreatectomy (2%), results are also depicted in the Pie Chart. [86]

**Chronic Pancreatitis and Type 3c Diabetes mellitus**

Progressive inflammation in the pancreatic tissue results in chronic pancreatitis. Genetic and environmental factors are both considered as its cause. It is characterized by the gradual devastation of the pancreatic secretory parenchyma and results in the replacement with the fibrous cells. This condition leads to Diabetes mellitus [87]. On the other hand, reactive oxygen species (ROS) are the triggering factors for pancreatitis; they are the enhancers of inflammation that can convert the impaired acinar cell into a manufactory for the cytokines and chemokines [88]. Such types of inflammatory responses are the instigating factors for the beta-cell disruption and, resultanty, low levels of insulin and hyperglycemic condition [89]. However, there is a lack of systematic studies that can examine the main genetic differences between type 3c diabetes secondary to chronic pancreatitis.

**Pancreatic ductal adenocarcinoma and Type 3c Diabetes mellitus**

Pancreatic cancer is the leading cause of wide-scale deaths worldwide, and its risk is high in patients with new-onset diabetes. Therefore, it is named pancreatic ductal adenocarcinoma (PDAC)-associated diabetes mellitus (PDAC-DM), a “type 3C diabetes”. The onset of “PDAC-DM” mostly occurs 2–5 years before diagnosing “PDAC,” which’s why its early diagnosis is very significant. However, it is not possible to differentiate PDAC-DM from other diabetes based on clinical signs and symptoms. There is an urgent need for specific markers in the health sector [90].

**Cystic fibrosis and type 3c Diabetes mellitus**

Cystic fibrosis diabetes is the most apparent form of diabetes in people with cystic fibrosis. Although it possesses characteristics of both type 1 and type 2, it is a quite different condition. Type 3c diabetes develops mainly due to the damage of the pancreas that can happen because of a few typical reasons. Although it is much different from other types, you can still get the wrong diagnosis of diabetes type 2 because Type 3c isn’t well diagnosed. Becoming unable to get the right diagnosis can be tough to deal with it emotionally. You may feel angry for not having the right treatment, or maybe you could just get ruined by the whole process. Thus, make sure you find the right person to communicate with.

**Clinical Presentation of Type 3c Diabetes Mellitus:**

Many patients suffering from type 3c Diabetes mellitus have some history of pancreatitis along with abdominal pain, steatorrhea, or maldigestion with nutritional deficiencies and glucose intolerance. Patients may also flex the symptoms of mal-digestion or abdominal pain without any diagnosis of chronic pancreatitis, or even maybe asymptomatic except for glucose intolerance. Only through careful clinical evaluation is pancreatic disease suspected [91].
### Table 1: General Comparison of Three DM Types

<table>
<thead>
<tr>
<th>S r No.</th>
<th>T1DM</th>
<th>T2DM</th>
<th>T3eDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Association of DM with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Obesity</td>
<td>Chronic Pancreatitis</td>
<td>Cystic Fibrosis</td>
</tr>
<tr>
<td>2. Average age of onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd decade of life</td>
<td>6th decade of life</td>
<td>5th decade of life</td>
<td>3rd decade of life</td>
</tr>
<tr>
<td>3. Pancreatic enzyme insufficiency PCE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Hepatic IS (Insulin Sensitivity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal or decreased</td>
<td>Decreased</td>
<td>Normal or decreased</td>
<td>?</td>
</tr>
<tr>
<td>5. Peripheral IS (Insulin Sensitivity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal or decreased</td>
<td>Decreased</td>
<td>Normal</td>
<td>?</td>
</tr>
<tr>
<td>6. Hypoglycemia Risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>Normal or increased</td>
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</tbody>
</table>

### Symptoms of Diabetes Type 3c
Diabetes type 3c is a complex situation in which this is very difficult to diagnose the problem. In specific, several symptoms are associated with PEI (Pancreatic exocrine insufficiency). In this disease, the pancreas is not functional anymore, and it does not provide the body with the essential enzymes required for appropriate digestion. This is mainly due to chronic pancreatitis and cystic fibrosis. That is the reason why the symptoms of Diabetes type 3c are usually linked with digestive tract symptoms. The major symptoms include [72]:
- Diarrhea
- Abdominal bloating
- Eating issues

### Hypoglycemia Risk
- Bloating and abdominal pain
- Nausea
- General fatigue

These symptoms are usually accompanied by several conditions like patients with a history of pancreatic disorders, an instance of weight loss, and severe pain. [73]

### Diagnosis of Diabetes Type 3c
Diagnosis of Diabetes type 3c is too complicated, and that’s why it renders it undiagnosed and maltreated in most cases. A few reasons for its being difficult to diagnose are the high variability of glucose levels in the blood, i.e., it sometimes becomes too high and sometimes too low. That’s why it some-
times sounds like Diabetes type 1 and hyperglycemia, and sometimes it seems to be hyperglycemic. Now, after a long run of research, there has been set a few standard steps to follow when diagnosing for Diabetes [73] which are:

1. Check for pancreatic exocrine insufficiency
2. Perform pathological pancreatic imaging
3. Check for Diabetes type 1-associated auto-antibodies

Based on these criteria, there can be several ways to check for type 3c and rule out the other types; for example, the absence of pancreatic enzymes in the body after glucose or mixed meal can be a true sign of type 3c. [73] HbA1c was initially thought to be a screening test for DM type 3c, but there is a much lower connection between A1c and insulin tolerance levels. That’s why HbA1c can’t be used as a standard technique to diagnose DM type 3c [76]. It is simply conclusive that the major relation of diabetes type 3c is with PEI and pancreatic disorders, so diagnosing in-depth for the problems associated with pancreatic problems is the major gateway to diagnose type 3c [74].

General overview of the differential criteria between T2 and T3c DM
Type 3c is characterized by a deficiency of PP (pancreatic polypeptide), whereas type 2 contains high levels of nutrient-stimulated pancreatic polypeptide, i.e., PP. Different criteria on which Type 2 DM and Type 3c DM can be categorized, including pathological imaging, i.e., endoscopy, MRI and ultrasound, etc. The absence of some autoimmune markers associated with Type 1 DM is another basis of differentiation between these two. Some minor criteria include identifying B-cell functionality, IR (Insulin Resistance), Abnormalities of incretin secretion, and low levels of fat-soluble vitamins (A, D, E, K). However, Type 3c and Type 2 DM still overlap at many points, which will need more research to differentiate the different types of diabetes [79].

Management of Diabetes Type 3c
Management of Diabetes type 3c is not a much-researched field due to fewer reported and diagnosed cases [76]. Management is based upon the cause of particular type 3c diabetes. Usually, it is suggested that the patients get some knowledge and awareness about diabetes management in sessions about the diabetes awareness programs and seminars [76]. The basic need is to maintain a little greater than the normal level of glucose in the body, i.e., to avoid hypoglycemia [78]. On the other hand, it is suggested that patients with a history of chronic pancreatitis take a rich diet in dietary fiber and lack fat. In this way, they can avoid the symptoms of steatorrhea, and they must also need to prevent hyperglycemia through diet. [78] Thus, it can be said that the only way to manage this least researched form of diabetes is to use a multi-dimensional approach in which both nutritional and therapeutic parameters are taken underuse. [77] And to minimize the serious complications, strategic management should be balanced to maintain maximum glycemic control. Other healthy improvisions can also be helpful to prevent hyperglycemia [78].

Treatment of Diabetes Type 3c
About 75% of type 3c diabetes result from chronic pancreatitis, which ultimately increases the risk of the development of carcinoma in the pancreas. Treatment with insulin or insulin secretagogue can readily increase the risk of malignancy due to their hypoglycemic activity, whereas metformin could be beneficial in reducing it. However, in advanced type 3c, DM insulin replacement therapy is preferred, which helps the patients achieve optimal glucose concentration in blood by mimicking the physiological delivery of insulin in a very comprehensive approach.[79]

Conclusion
Type 3c DM is getting prevalent today due to a lack of diagnostic sense in the people as it is always confused with Diabetes type 1 and type 2. Type 3c DM is majorly caused by chronic pancreatitis, adenocarcinoma, hemochromatosis, or pancreatic removal. So, patients with these problems should be identified in their medical histories and distinguished from other diabetic patients.
Conflict of Interest

The authors declare that the publication of this article has no conflict of interest.

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