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Diabetes Mellitus Type 3C in Pakistan

Abstract

Type 3c diabetes, also known as pancreatogenic diabetes, is a form of diabetes that arises due to pancreatic damage or disease, rather than the autoimmune response seen in type 1 or the insulin resistance seen in type 2. It occurs when the pancreas, specifically the part that produces insulin (endocrine function), is damaged, leading to insufficient insulin production. Common causes include pancreatitis, pancreatic cancer, cystic fibrosis, and hemochromatosis.

Research Article

Maida Ali[1], Memona Ali[2], Maria Ali[3], Maliha Ali[4], Aasma Riazs[5], Dr. Samreen Riaz*[6]

[1]Kinnarid College University, Lahore, Pakistan

[2]Lahore College for Women University, Lahore, Pakistan

[3,4]Riaz Diabetes Research Centre (RDRC), Pakistan

[5]College of Statistical Sciences

[6]University of the Punjab, Lahore Pakistan. Riaz Diabetes Research Centre (RDRC), Pakistan

***Correspondence:** *DSamreen Riaz, University of the Punjab, Lahore, Pakistan. Ambassador For diabetes walk for South East Asia (Intentional Diabetes Federation UK), Riaz Diabetes Research Centre (RDRC), Pakistan. E-mail: diabetologist@barin.net.pk*

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Introduction

Diabetes mellitus is one of the most prevalent metabolic disorders in the world, it is characterized by the 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 [1] Type I and Type II diabetes are considered as the major types of the diabetes to be known by that time and type II Diabetes is more prevalent (>85%) then that of the type I [2] Type I Diabetes is considered to be caused by the deficit insulin secretion from the beta cells of pancreas that actually happens due to the autoimmune devastation of the beta cells. On the other hand, diabetes type II is caused by the two coupled reasons, first one is the resistance to insulin action and second one is the insufficient compensatory insulin secretory response. ”Gestational Diabetes mellitus”(GDM), that is also a situation of glucose intolerance, is known to be recognized during the pregnancy. Except of these above-mentioned types of Diabetes, there are some more specific categories of the diabetes mellitus and the Type 3c Diabetes fall in this category [3-5].

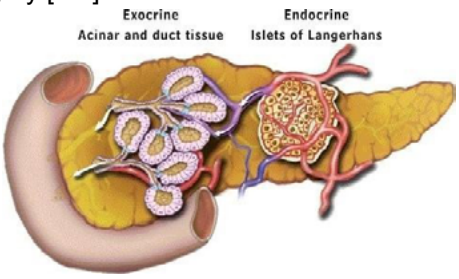


Figure 1. Diagram of the pancreas showing exocrine acinar tissue and ducts, and endocrine Islets of Langerhans involved in hormone secretion.

Among the people who are suffering from the Diabetes mellitus, approximately 2 percent of them have the type 3c diabetes [6-10] Type 3c diabetes might happen due to genetic as well as the non-genetic factors that comprises pancreatic removal, pancreatitis, pancreatic ductal adenocarcinoma, hemochromatosis or cystic fibrosis. One of the most dominating causes of the Type 3c diabetes is chronic pancreatitis. Unfortunately, patients suffering from the type 3c diabetes are not diagnosed properly and timely that is one of the main causes of delay in their required treatment [11-15]

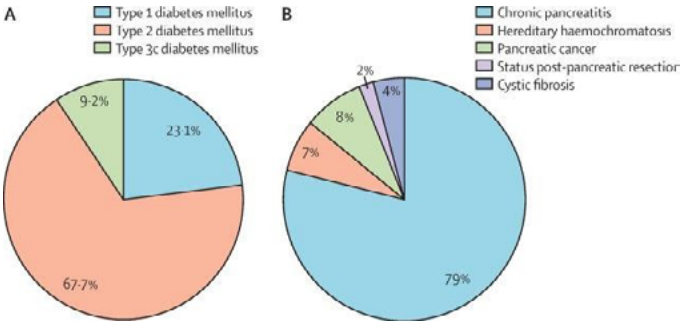
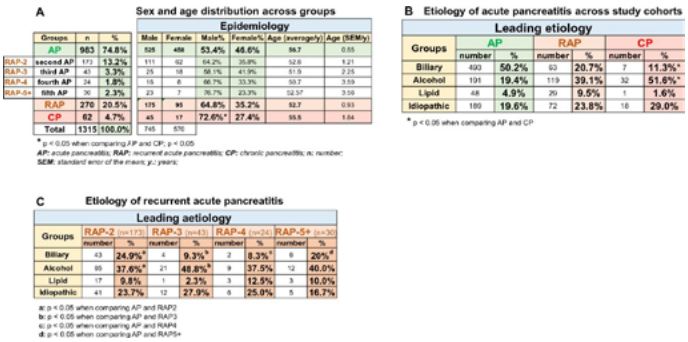


Figure 2. (A) Distribution of diabetes types: Type 2 (67.7%), Type 1 (23.1%), and Type 3c (9.2%). (B) Causes of Type 3c diabetes: Chronic pancreatitis (79%) is most common, followed by pancreatic cancer (8%), hemochromatosis (7%), cystic fibrosis (4%), and pancreatic resection (2%).

Type 3c Diabetes Mellitus (T3cDM)

Type 3c diabetes mellitus has been designated as the secondary diabetes and usually called as the pancreatogenic diabetes. One can also develop type 3c if he/she has a part or all of the pancreas removed because of any other damage. Some people who take steroids can also develop this type of diabetes. This is also called as steroid-induced diabetes, and is more common in the group of people which are at high risk of type II diabetes.



A Sex and age distribution across groups

			Epidemiology					
Groups	n	%	Male	Female	Male%	Female%	Age (average/y)	Age (SEMy)
AP	983	74.8%	525	458	53.4%	46.6%	59.7	0.55
RAP-2 second AP	173	13.2%	111	62	64.2%	35.8%	52.8	1.21
RAP-3 third AP	43	3.3%	25	18	58.1%	41.9%	51.9	2.25
RAP-4 fourth AP	24	1.8%	16	8	66.7%	33.3%	50.7	3.59
RAP-5+ fifth AP	30	2.3%	23	7	76.7%	23.3%	52.57	3.59
RAP	270	20.5%	175	95	64.8%	35.2%	52.7	0.93
CP	62	4.7%	45	17	72.6%*	27.4%	55.5	1.84
Total	1315	100.0%	745	570				

B Etiology of acute pancreatitis across study cohorts

	Leading etiology					
Groups	AP		RAP		CP	
	number	%	number	%	number	%
Biliary	493	50.2%	63	20.7%	7	11.3%*
Alcohol	191	19.4%	119	39.1%	32	51.6%*
Lipid	48	4.9%	29	9.5%	1	1.6%
Idiopathic	189	19.6%	72	23.8%	18	29.0%

C Etiology of recurrent acute pancreatitis

	Leading aetiology							
Groups	RAP-2 (n=173)		RAP-3 (n=43)		RAP-4 (n=24)		RAP-5+ (n=30)	
	number	%	number	%	number	%	number	%
Biliary	43	24.9%*	4	9.3%*	2	8.3%*	6	20%*
Alcohol	65	37.6%*	21	48.8%*	9	37.5%	12	40.0%
Lipid	17	9.8%	1	2.3%	3	12.5%	3	10.0%
Idiopathic	41	23.7%	12	27.9%	6	25.0%	5	16.7%

Figure 3. Comparison of sex, age, and causes of acute, recurrent, and chronic pancreatitis.

(A) RAP and CP show higher male dominance and younger age.

(B) Biliary cause is most common in AP, while alcohol is predominant in RAP and CP.

(C) In RAP, alcohol-related cases increase with recurrence.

	T1DM	T2DM	T3cDM		
Associated with	Autoimmunity	Obesity	Chronic Pancreatitis	Cystic Fibrosis	Pancreatic Resection
Median age of onset	2nd decade of life	6thdecade of life	5thdecade of life	3rd decade of life	Within 5 yrs of surgery
Pancreatic insufficiency	No	No	Yes	Yes	Yes
Hepatic Insulin Sensitivity	Normal or Decreased	Decreased	Normal or Decreased	?	Normal or Decreased
Peripheral Insulin Sensitivity	Normal or Decreased	Decreased	Normal	?	
Diabetic Ketoacidosis	Yes	No	No	No	No
Hypoglycemia Risk	Increased	Normal	Normal or Decreased	Normal or Decreased	Normal or Decreased
Pancreatic Polypeptide Response	Normal or Decreased	Normal or Decreased	Decreased or Absent	Absent	Absent

Table 1. Clinical Characteristic for Common Forms of Diabetes

Pathogenesis of Type 3c Diabetes mellitus

The pathogenesis of T3cDM is characterized by the declination in the insulin production that might be due to the reduced number of the islet's cells or due to the loss of functionality that is attributed to the fibrosis or sclerosis [16-20]. Basically, the damage of the pancreatic tissue causes the deficiency of insulin and its mechanism can be explained by the functionality dependent interplay between the acinar cells and islets cells.

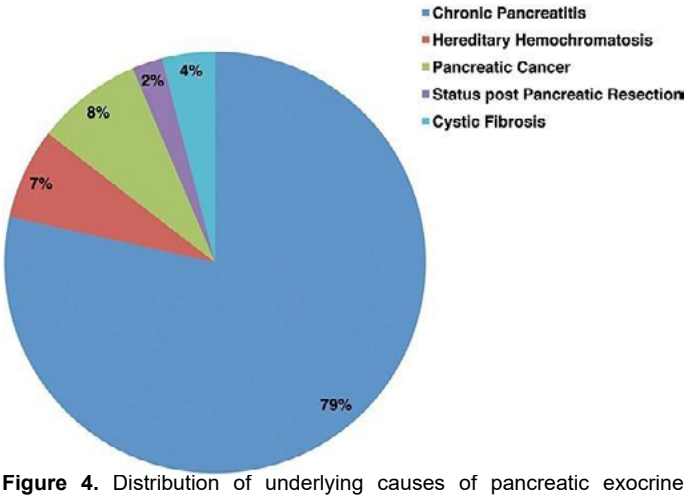


Figure 4. Distribution of underlying causes of pancreatic exocrine insufficiency, with chronic pancreatitis (79%) being the most common, followed by pancreatic cancer (8%), hereditary hemochromatosis (7%), cystic fibrosis (4%), and post-pancreatic resection (2%).

Pancreatic function

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, pancreas is divided into the five regions, it is associated with the gall bladder, duodenum and spleen. It has both the exocrine and the endocrine regions but the maximum region of the pancreas owns exocrine function that is responsible for the formation and release of the digestive enzymes into the duodenum. Acinar cells that make up to 85 percent of the pancreatic cells are devoted for 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 as the islets of langerhans, containing four types of the cells, out of them beta cells (Insulin secreting cells) are in the huge amount. In Type I and Type II Diabetes mellitus, deficient insulin production leads to the hyperglycemia but the digestion of food is unaffected. On the other hand, in Type 3 c Diabetes mellitus, digestion of food also gets effected.

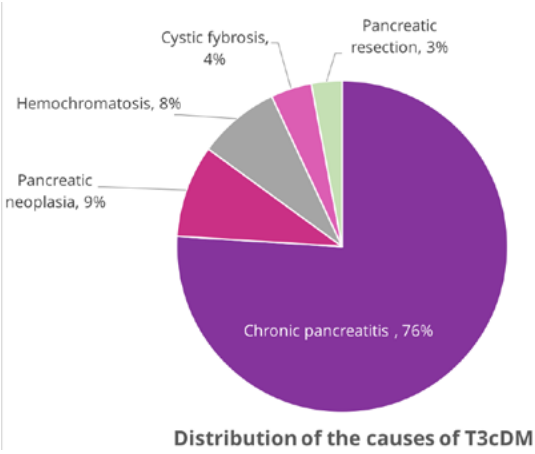


Figure 5. Pie chart illustrating the distribution of etiological factors contributing to Type 3c Diabetes Mellitus (T3cDM). Chronic pancreatitis is the predominant cause, accounting for 76% of cases. Other contributing factors include pancreatic neoplasia (9%), hemochromatosis (8%), cystic fibrosis (4%), and pancreatic resection (3%). This highlights the strong association between chronic pancreatic disorders and the development of T3cDM.

Causes of Type3c Diabetes Mellitus

One of the most frequently recognized causes of the 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 the type 3c diabetes were recorded as: “chronic pancreatitis” (79%), “pancreatic ductal adenocarcinoma” (8%), “haemochromatosis” (7%), “cystic fibrosis” (4%), and previous pancreatectomy (2%), results are also depicted in the Pie Chart. [21-25]

Chronic Pancreatitis and Type 3c Diabetes mellitus

Progressive inflammation in the pancreatic tissue results in the chronic pancreatitis. Genetic and environmental factors both are 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 the Diabetes mellitus [87]. Pancreatitis starts as the pancreatitis and cause the inflammation. On the other hand, reactive oxygen species (ROS) are the triggering factors for the pancreatitis, they are the enhancers of inflammation that have the potential to convert the impaired acinar cell into a manufactory for the cytokines and chemokines [26]. Such type of the inflammatory responses are the instigating factors for the beta cell disruption and resultantly, low levels of insulin and hyperglycemic condition [27-30]. However, there is lack of systematic studies that are capable of examining the main genetic differences between type 3c diabetes secondary to chronic pancreatitis.

Factor	T3cDM	T1DM	T2DM
Age of Onset	Any age	Childhood/teens (however, must be carefully diagnosed from other forms of childhood from other forms of childhood DM)	Typically, adulthood
Overweight/ Obese	Uncommon (in some cases, despite being overweight muscle depletion is observed)	Rare	Common (known risk factor)
BMI	Normal Reduced range	variable	Usually, high
DM-associated antibodies/ auto-immunity	Absent/ lacking	Present / Present	Rare / absent
Diabetic Ketoacidosis	Rare	Common	Rare
Hyperglycemia	Mild to severe (brittle DM)	Severe	Usually, mild
Hypoglycemia	Common (can be Severe)	Common	rare
Hepatic Insulin Insensitivity	Decreased	Normal	Normal or Decreased

Peripheral Insulin sensitivity	Increased	Normal or Increased	Decreased
Insulin levels	Low	Low	High
Glucagon levels	Low	Normal or high	Normal or high
Pancreatic Polypeptide levels	Low	Normal or Low	High
Malnutrition/ Nutrient deficiency	Common Deficiency of fat-soluble Vitamins (associate with EPI+ poor diet)	Uncommon / rare	Rare / rare
EPI	Can precede and / or is more pronounced in patients with T3cDM often accompanied with metabolic / nutritional derangements	Can be observed in patients having long-standing T1DM	Can be observed in patients having long-standing T2DM
BMD	Risk of having low BDM substantial depending on type of exocrine pancreatic disease	Risk of having BDM	May have low BDM

Table 2. Key clinical and biochemical differences between Type 3c, Type 1, and Type 2. diabetes mellitus

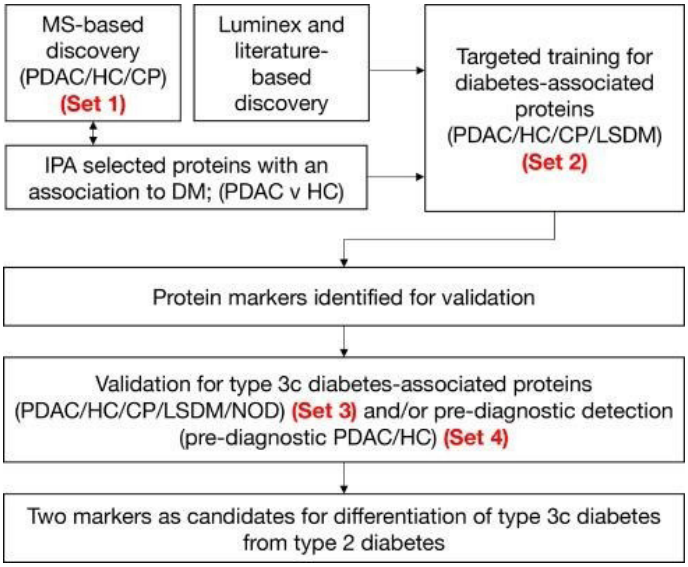


Figure 6. Workflow for identifying and validating protein markers to differentiate Type 3c diabetes from Type 2 diabetes. Protein candidates were discovered (Set 1), refined through targeted training (Set 2), and validated in clinical cohorts (Set 3 & 4), resulting in two markers for distinguishing Type 3c diabetes.

Pancreatic ductal adenocarcinoma and Type 3c Diabetes mellitus

Pancreatic cancer is the leading cause of wide scale deaths around the world and its risk is high in the patients with the new-onset diabetes. Therefore, it is named as pancreatic ductal adenocarcinoma (PDAC)-associated diabetes mellitus (PDAC-DM), a “type 3C diabetes”. The onset of “PDAC-DM” mostly occurs 2–5 years prior to the diagnosis of “PDAC” that’s why its early diagnosis is very significant. However, it is not possible to differentiate PDAC-DM from the other diabetes on the basis of clinical signs and symptoms so, there is the urgent need of the specific markers in the health sector [31-35].

Cystic fibrosis and type3c 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, but it is a quite different condition. Type 3c diabetes develops mainly due to the damage of pancreas that can happen because of a few typical reasons. Although it is much different from other types, still you can get a wrong diagnosis of diabetes type 2 because Type 3c isn’t well diagnosed. Becoming unable to get the right diagnosis can be really hard 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:

Large no of patients suffering from the 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 maldigestion or abdominal pain without any diagnosis of chronic pancreatitis, or even may be asymptomatic except for glucose intolerance, and only through careful clinical evaluation is pancreatic disease suspected [36-40].

Symptoms of Diabetes Type 3c

Diabetes type 3c is a complex situation in which this is very difficult to diagnose that actually what the problem is. In specific, there are a number of symptoms that are associated with PEI (Pancreatic exocrine insufficiency). In this disease, the pancreas is not functional anymore and it does not provide the body with essential enzyme 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 [41]:

- Diarrhea
- Abdominal bloating
- Eating issues
- Bloating and abdominal pain
- Nausea
- General fatigue

These symptoms are usually accompanied by a number of conditions like the patients with a history pancreatic disorders, an instance of weight loss and a severe pain. [42-45]

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 of the cases. A few reasons of its being difficult to diagnose is high variability of glucose level in the blood i.e., it sometimes becomes too high and sometimes become too low. That's why it sometimes 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 [46] 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 a number of ways to check for type 3c and rule out the other types, for example absence of pancreatic enzymes in body after a glucose or mixed meal can be a true sign of type 3c. [47] 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 [48]. 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 of 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 deficiency of PP (pancreatic polypeptide) whereas type 2 contains high levels of nutrient stimulated pancreatic polypeptide i.e., PP. There are different criteria on which Type 2 DM and Type 3c DM can be categorized, which includes the pathological imagining i.e., endoscopy, MRI and ultrasound etc. Absence of some autoimmune markers associated with Type 1 DM is another basis of differentiation between these two. Some minor criteria include the identification of 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 overlaps at many points, which will need more research work to further differentiate the different types of diabetes [49-55].

Management of Diabetes Type 3c

Management of Diabetes type 3c is not a much-researched field due to less reported and diagnosed cases [56]. Management is based upon the cause of particular type 3c diabetes. Usually, it is suggested for the patients to get some knowledge and awareness about the diabetes management in sessions about the diabetes awareness programs and seminars [57-60]. Primarily the basic need is to maintain a little greater than the normal level of glucose in body i.e., to avoid hypoglycemia. [78] On the other hand it is suggested for the patients with a history of chronic pancreatitis to take a diet that is rich in dietary fiber and lacks fat. In this way they can avoid the symptoms of steatorrhea, and they must also need to prevent hyperglycemia through diet. [61] 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 under use. [62] And to minimize the serious complications, strategic management should be balanced to maintain the maximum glycemic control. Other healthy improvisions can also be helpful to prevent hyperglycemia. [63-70]

Treatment of Diabetes Type 3c

About 75% of the type 3c diabetes result from the chronic pancreatitis which ultimately increases the risk of 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. [71-83]

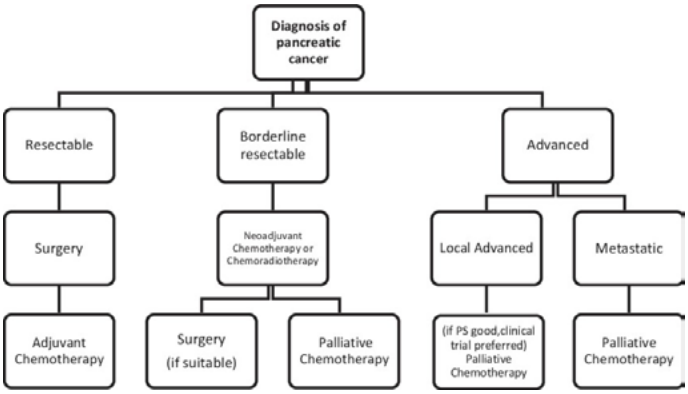


Figure 7. Management of pancreatic cancer by stage

Conclusion

Diabetes mellitus is a particularly heterogeneous and multifactorial metabolic disorder that is characterized by a combination of insulin insufficiency and insulin resistance. The prevalence of diabetes mellitus has risen exponentially over the last three decades, with resultant increase in morbidity and mortality mainly due to its complications. There is need of Increases awareness of these complications among patients and populations, this facilitate early detection and prevention of these diseases. The earlier diagnosis, timely appropriate treatment may help in avoiding severe, irreversible disability and deformity, which can be done with the tool of patient education and conducting seminar to increase awareness.

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