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Review Article

Type3c Diabetes Mellitus

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ABSTRACT

Diabetes type 3C is referred to as pancreatogenic diabetes also, which is occurring due to pancreatic cancer, pancreatitis, cystic fibrosis, and also pancreatic disease. In this condition, there is an inconsistent blow from hypoglycemia to hyperglycemia, which occurs due to metabolic abnormalities due to tissue damage in the pancreas. Henceforth, the diagnosis and management of this rare condition is a challenging task for healthcare providers. A group from Germany named Ewald and colleagues has observed that among diabetes patients, 8% of patients suffer from T3cDM having chronic pancreatitis, and the occurrence range varies from 5-8%. Type 3cDM incidence is more in patients with surgical resection, especially in the distal pancreas, the presence of pancreatic calcifications and they are on the verge of developing DM in chronic pancreatitis. Pancreatogenous DM is defined as the development of diabetes mellitus in patients due to exocrine pancreas disease, according to recent literature it's been referred to as type c diabetes. Due to heterogeneity, DM is presently comprised of four types. (1 to 4), depending upon the consumption of tobacco, and often it's linked with alcohol-abusing which is considered to be a predisposition factor in the disorders related to the pancreas. Diabetes type 3C is referred to as pancreatogenic diabetes also, which is occurring due to pancreatic cancer, pancreatitis, cystic fibrosis, and also pancreatic disease. In this condition, there is an inconsistent blow from hypoglycemia to hyperglycemia, which occurs due to metabolic abnormalities due to tissue damage in the pancreas. Henceforth, the diagnosis and management of this rare condition is a challenging task for healthcare providers.

Keywords: Pancreatogenic diabetes, Cystic fibrosis, Pancreatic cancer.

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CLINICAL CASE 1

The patient was admitted ER with an eight-year history of having chronic pancreatitis caused by alcohol of forty-two years old, of bodyweight 61kg than his usual weight of 67kg, and appeared to be weak due to chronic illness. Reported intermittent diarrhea, abdominal pain, poor appetite, flatulence, and cramping. Also, the patient was not advised with PERT (Pancreatic Enzyme Replacement Theory), he was a heavy smoker and abused alcohol.[1]

For constant and chronic pain patient used opiates for a reprieve and minimal intake of diet was poor over a period of years. The patient was also re-educated regarding the proper dietary intake and also, and he was provided with nutrition supplements, the patient went counselling for the proper usage of PERT, and the medication used for pain was also adjusted Upon blood analysis, observed low level of serum was Vitamins (Vit-A, Vit-E, and 25OHD) along with this fasting glucose level was normal and after three days the patient was discharged once and all he was established on the proper PERT, micronutrient supplementation and oral diet. (Type3c again, the patient was re-admitted due to increased thirst, blurred vision, dehydration, and fatigue. Fasting glucose was also found to be upsurged (250 mg/dL), henceforth the patient was diagnosed with new DM, and a reference was made to the endocrinology department for evaluation.[1]

CLINICAL CASE 2

Thirty-seven-year-old female, with body weight, was eighty-eight kgs and a body mass index was 30.4 kg/M^2. With a five-year history of Diabetes Mellitus (T2DM) was referred to the gastroenterology OP clinic with a complaint of diarrhea occurring three to four times per day over six months, along with bloating and flatulence. She was kept on anti-diarrheal medications. Patient-reported that the diarrhea was to occur post-prandially and it was found to be severe after having richer meals. She also reported that after defecating on the toilet pan oil was noticeable which again requires one or more flushes. The previous history of hypertriglyceridemia induced acute pancreatitis, due to this

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patient was hospitalized for up to weeks, she was also been in the critical care unit for one week which required enteral feeding.

Due to oily stools, pancreatitis, and Pancreatic Exocrine Insufficiency (PEI) being doubted, she was prescribed fecal elastase-1. After the test was performed it was found to be 95µg /g indicating PEI to be severe and she was referred to the pancreatologist for further imaging. Type 3c will occur due to pancreas disease. T3cDM is pancreatic or pancreatogenic DM. Whereas, in Europe, nearly two thousand patients were initially categorized under T2DM, but again they were re-categorized to T3CDM. In this category only nearly, 2/3rd patients with this condition were accompanied by chronic pancreatitis.

A group from Germany named Ewald and colleagues has observed that among diabetes patients, 8% of patients are found to be suffering from T3cDM having chronic pancreatitis, and the occurrence range varies from 5-8%. Type 3cDM incidence is more in patients with surgical resection, especially in the distal pancreas, the presence of pancreatic calcifications and they are on the verge of developing DM in chronic pancreatitis.[1] Pancreatogenous DM is defined as the development of diabetes mellitus in patients due to exocrine pancreas disease, according to recent literature it's been referred to as type c diabetes.[2] Due to heterogeneity DM is presently comprised of four types (1 to 4), depending upon the consumption of tobacco, and often it's linked with alcohol-abusing which is considered to be a predisposition factor in the disorders related to the pancreas.[3]

RISK FACTORS

Pancreas diseases are uncommon, whereas DM is commonly found in pancreatic patients. Upon autopsy, it has been observed that upon clinical diagnosis of 13% of cases, it was found to be increased incidence of inflammation in the pancreas was seen in patients with DM. Depending on the cohort studies, found that 26-80% of patients with pancreatitis also suffer from diabetes. Insult due to alcohol is the most accepted reason for causing chronic pancreatitis and other motives are due to ducts scar, pancreas divisum, groove pancreatitis, and inherited pancreatitis. Now it has been understood that the reason for chronic and acute pancreatitis is due to metabolic and environmental factors, and genetic factors. Its caused due to the dysfunction of endocrine and exocrine progressively associated with the development of intolerance to glucose, malabsorption, maldigestion, also malnutrition. Acceleration in the endocrine let-down is allied with alcohol.[4] As per, the American Diabetes Association (ADA) they have sorted diabetes causing due to pancreatic trauma, pancreatectomy, cystic fibrosis, chronic pancreatitis, hemochromatosis, malignant and benign disease of the exocrine pancreas, considered as pancreaticogenic disease viz, T3c-DM. (Type3c-5).[5] Type-3c can also be developed by post-pancreatectomy, according to Bretzel and Ewald they anticipated the diagnostic measures i.e., insufficiency of pancreatic exocrine (Levels of faecal elastase-1 is less than 200 µg/g), HbA_{1c} levels are more than 6.5%.[6]

In type3c-DM the upsurge in peripheral insulin sensitivity is observed when its compared to type 2-DM. Intolerance towards glucose is mainly observed due to the islet cell devastation due to inflammation of the pancreas. Improper digestion of nutrients is also the main reason for hampering the incretin secretion and hence diminution in insulin production. As of now, there are no gold-standard methods available for the diagnosis and screening of this newly developing category of diabetes.[7] Chronic pancreatitis is referred to as an inflammatory disease of the pancreas with pain and morphological change observed which is an irreversible and permanent loss of function. This condition is associated with the devastation of healthy pancreas tissues and fibrous scar tissue formation which again causes loss of Exo/endocrine function, abdominal pain, and at last causing malnutrition, and steatorrhea ultimately leading to diabetes.[8]

INDIAN SCENARIO

According to a survey conducted in India in major countries, it has been shown that 12.1% of the prevalence was seen in urban adults. Diabetes onset was ten years before when compared to western countries and which is noted especially in Asian Indians as per the study conducted.[9] The data available in western parts shows that 10% of cases were found to be diabetic to be precisely type3c-DM. There is no solid proof as of now regarding the Asian regions regarding DM.[10,11] The main reason for type3c-DM remains chronic pancreatitis only, 80% of type3c-DM is caused in adults about 40-50%, and 20% of them are seen in adolescents. In one study they found around 14.8% of them found in Kerela. The onset age for type3c-DM is from 12-25 years, but in alcohol-induced pancreatic diabetes is fifty to sixty years.[11]

The human pancreas harbored around ten lakhs (One million) of 5–400-micron diameter of islets. One islet has an average of about 2000 insulin-secreting beta-cells, somatostatin-secreting delta cells, and glucagon-secreting alpha cells. Pancreas also has pancreatic polypeptide-secreting cells. They are present in the pancreas invariably also with pancreatic acini. In the axis named insulo-acinar, the islet secretions affect the functions of acini. Tissue injury When enzymes get prematurely activated, it causes tissue injury, leading to auto digestion and inflammation of pancreas tissue, calcification, septa formation, fibrosis replacement, loss, and finally, exocrine deficiency.[11]

Pancreatic resection comprehends a wide range of techniques, including distal pancreatectomy, enucleation procedures, and pancreaticoduodenectomy procedures. Pancreatic resection is done for the neoplastic lesions for managing chronic pancreatitis, and malignant, benign, and premalignant lesions. Survival post-pancreatectomy has executed to malignant disease, and also need to understand the effect of T3cDM are increased in the patients in post-pancreatectomy. In distal pancreatectomy

assumed more likely resulting in the deficit of glucagon and hypoglycemia because of islets locations more particularly in alpha cells. Specifically, post pancreatectomy DM the deficiency of endocrine is correlated to the area where the pancreas has been resected. Duodenum and pylorus resection shows an effect on glycemic control and the action of incretin, in patients who are undergoing the procedure of pancreaticoduodenectomy has observed an upsurge of secretion of FLP-1, reduced GIP levels, and decreased production of insulin. It is all possible ways that affect the health of the patient in the incidence of pancreatitis (Chronic) and more likely giving a way to develop DM.[8]

In T3c-DM histopathological studies propose that the pancreas differs from the type-2 and 1, in this condition of pancreatic diabetes the deposition of Cystic Fibrosis-Related Diabetes (CFRD) amyloid has been seen. Occurrence of T3c-DM is seen usually at the age of 59 years i.e., in males, and Body Mass Index (BMI) is found to be 29.2 kg/m^2. T3cDM is occurring due to the influence of the exocrine pancreas which is leading to hyperglycemia, studies show that the development of this condition is due to pancreatitis in patients. A study was conducted on 2966 individuals and it was found that the patients with acute pancreatitis were at the verge of risk to develop this condition 2.5 times more than the patient without acute pancreatitis.[12]

Additive effect to endocrine effect, chronic pancreatitis will lead to the incomplete or whole devastation of pancreatic tissues which in turn leads to the loss of bicarbonate and enzymes that helps in digesting (Digestive enzymes). In pancreatic cancer or Pancreatic Ductal Adenocarcinoma (PDAC), inflammation of the fibrous pancreas is the second risk factor that causes T3DM. This condition is associated with immunopathogenesis, insulin resistance, deficiency, genetic association, and decreased incretin effects, these are five major functional changes that occur in this condition. Blood flows via capillaries through the endocrine pancreas and to the exocrine pancreas which is surrounded by the islets, this system provides endocrine hormones in high concentration i.e., glucagon, somatostatin, insulin, and amylin. The acinar cells encompassed the insulin receptors, which regulate the synthesis of digestive enzymes in the exocrine pancreas. Scar in the pancreas tissues will lead to insulin deficiency and, in turn, to the interplay b/w the acinar tissues and the pancreatic islets. The main mechanism behind T3cDM is fibrosis and the inflammation of the pancreas which progressively leads to the devastation of islets. Beta cell destruction is due to stressful inflammation and cytokines.[12]

Diagnosis

Includes the measurement of the fasting blood glucose and glycated hemoglobin (A1c/HbA_{1c}) and is done yearly for individuals with pancreatitis. The American Diabetes Association (ADA) stated the diagnostic conditions for DM, i.e., plasma glucose level >126 mg/dL (>7mmol/L) (Fasting), or HbA_{1c} >48mmol/L (About 6.5%), and low insulin levels. Parallelly there will be a decrease in hepatic insulin sensitivity and shows an increase in peripheral insulin sensitivity. Hepatic glucose formation and impaired sensitivity to insulin in the hepatic is observed due to a decrease in the pancreatic polypeptide secretion. Henceforth, T3cDM is associated with a pancreatic disease, along with the swing of the glucose level in the blood from hypo to hyperglycemia, again which is a major challenge for management. Ewald and Hardt proposed the guideline for the diagnosis by minor and major criteria (Table 3).[12]

Nutritional management

Pancreas Fest Working Group they were the first to provide the context for the diagnosis and management of T3cDM in chronic pancreatitis. The individuals are treated with precise medical nutrition and the main aim is to treat or prevent malnutrition, reduce the minimize the hyperglycemia induced by the meals, and treat steatorrhea. Andersen and Cui proposed a treatment, like modifying the lifestyle which is responsible for malignancy, hyperglycemia, restricted carbohydrate intake, and abstinence from smoking and alcohol. Duggan *et al.* provided in detail dietary management, educating the individuals regarding hypoglycemia treatment and symptoms and preventing the hypoglycemic events. Regular blood level monitoring, with self-monitored insulin regimens. ADA has not provided any specific guidelines for T3cDM, but they provided the management of symptoms, regimen monitoring, and monitoring is not necessary for patients who are taking hypoglycemic agents. They provided a specified meal plan with a limited amount of carbohydrates and starch.[1]

Glycemic control

Currently, there are no standard drugs or therapy are available for treating or targeting specifically glycemic. Henceforth, along with T1 and T2DM the major prime target is to maintain less than 7% of HbA_{1c} to avoid the complication and keep in mind to avoid hypoglycemia, it's important to keep the blood glucose level slightly above normal conditions. Diagnostic criteria for the Type3c DM is given in (Table 1) and Features of T1, 2 and 3c DM is given in (Table 2).[12,13]

Table 1: Diagnostic criteria for the Type3c DM: As per Ewald and Bretzel.[13]

Major Criteria	Minor Criteria
Absence of Type-1 DM-associated autoimmune disease.	Decreased serum levels of lipid-soluble Vitamins (A, D, E, K).
Pancreatic imaging	No excessive insulin resistance.
Presence of exocrine pancreatic insufficiency.	Pancreatic polypeptide secretion/ Impaired incretin
	Impaired beta cell function.

Table 2: Features of T1,2 and 3c DM (Type3c 12).[12]

	T1DM	T2DM	T3DM
Onset age	**Adolescent**	**Adult**	**Adult/Childhood**
Risk factors	Standard of living, Less exposure to UV-B, Reduced levels of VitD, Environmental influences Inherited.	Gestational diabetes, Genetic dispositions, Increased carbohydrate.	Acute pancreatitis, Chronic pancreatitis, Pancreatic cancer, Cystic fibrosis.
Symptoms	Ketoacidosis, Hyperglycemia, Common hypoglycemia, Decreased concentration of insulin.	Resistance to insulin, Decreased concentration of insulin in later stage, Decreased sensitivity to insulin (Hepatic and Peripheral).	Deficit of pancreatic enzyme, Maldigestion, Swings b/w hypo and hyperglycemia, Steatorrhea (Occasionally), Impairment in glucose tolerance.
Etiology	Annihilation of beta cells and autoimmune disorder.	Decreased glucose transporter expression in insulin-sensitive tissues, Diminishing of signaling pathways, Later, deficiency of insulin due to beta cell damage.	Decreased insulin receptors, GLUT-2, Initially exocrine pancreatic cell and beta cell damage, Insufficient pancreatic enzyme, Due to scar in islets causes lowers the levels of incretin.
Management	Insulin	GLP-1 analogues, Insulin, SGLT-2 inhibitors, Sulphonylureas, Thiazolidinediones, Biguanides, DPP-4 inhibitors.	Pancreatic insufficiency management, Supplementation (Vit-D), PERT (Pancreatic enzyme replacement therapy).

Table 3: Ewald and Hardt guidelines for the diagnosis of T3c.[12]

Major criteria	Minor criteria
Pancreatic imaging.	Blighted secretion of incretin.
Privation of T1DM-linked auto-antibodies.	Absence of insulin resistance.
Pancreatin exocrine insufficiency.	Impaired beta cell functioning, low serum levels of fat-soluble Vitamins.

Nutrition

In T3cDM, nutrition therapy aims to treat malnutrition, reduce the hyperglycemia induced by the meal, and control the symptoms of steatorrhea. The individual should be given meals that are encompassed with low fat and rich in soluble fiber. In the case of exocrine deficiency, oral enzyme therapy has been suggested. This therapy helps in nutrient absorption and fat digestion, and parallelly helps protect against fat-soluble vitamin deficiency, controls steatorrhea, helps maintain incretin secretion, and improves glucose tolerance. In chronic pancreatitis condition, Vit-D dearth and 34% of osteoporosis are seen. The screening and Diagnosis of type 3C-DM is depicted in (Figure 1).[13]

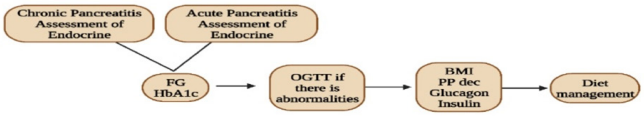

Figure 1: Screening and Diagnosis Type3c-DM.[13]

Drugs for Hyperglycemicagents

Currently, there are no well-established protocols or guidelines for the management of T3cDM, this condition points towards secondary diabetes, but only pathological condition differs. In the case of CP-associated diabetes for treating hyperglycemia (HbA1c <8%), hypoglycaemic agents are chosen. The insulin sensitizers are chosen in case of insulin resistance and metformin as a hypoglycaemic agent. Patients suffering from CP and T3cDM those are not required insulin sensitizers. The use of DPP-IV inhibitors and the GLP-1 analogs. Usage of GLP-1 analogs has not been recommended until further more data is available, because they decrease food consumption and appetite ultimately leading to a weight loss of an individual which is not encouraged in the patients. The usage of SGLT-2 inhibitors is also not clear, but the have shown encouraging results in T2DM, the main drawback of

this class of drugs are, they causes weight loss of patients which is not recommended for T3cDM patients.[12]

Novel drugs

Pancreatic polypeptide usage has emerged with promising results as an antidiabetic drug for treating T3cDM secondary to chronic pancreatitis, in the liver, it upsurges the expression of insulin receptors which activates the proper circulation of insulin. They improve insulin sensitivity in T3cDM patients. A new formulation of PP is the stabilized micelles of phospholipids to overcome the problem of the short biological half-life of pancreatic polypeptide. They have exhibited a good significant antidiabetic activity in the pancreatogenic diabetes rodent model.[12]

CONCLUSION

One of the most prevalent metabolic illnesses is diabetes, which develops for a variety of reasons including genetic, environmental, and lifestyle factors. Several epidemiological research show that smoking cigarettes is harmful. T3cDM is a form of diabetes that encompasses exocrine pancreas disorders such chronic pancreatitis. People may receive the wrong diagnosis, usually T2DM, as a result of a lack of knowledge about this disorder. In order to minimise hypoglycemia, reduce hyperglycemia, prevent malnutrition, treat PEI, and reduce the risk of complications related to diabetes, regular dietary evaluation and monitoring should be a part of the nutritional management of T3cDM.

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ABBREVIATIONS

PERT: Pancreatic Enzyme Replacement Therapy; **DM:** Diabetes Mellitus; **OP:** OutPatient; **PEI:** Pancreatic exocrine insufficiency; **ADA:** American Diabetes Association; CFRD: Cystic fibrosis-related diabetes; **BMI:** Body Mass Index; **PADC:** Pancreatic ductal adenocarcinoma; **CP:** Chronic Pancreatitis; **PP:** Polypeptide.

Author Contribution

AHR, YMT, VJ, PH and RUR made significant contribution to the work reported, whether that is in the conception, execution, or the acquisition, analysis, or interpretation of data, or all the areas; took part in drafting, revising, or critically reviewing the article; and gave final approval of the version to be published. All have read and agreed to the published version of the manuscript.

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