CHAPTER

163

Pancreatic Diabetes

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INTRODUCTION

Pancreatic or pancreatogenic diabetes is a form of secondary diabetes where pancreatic diseases with exocrine deficiency leads to endocrine dysfunction resulting in defective glucose homeostasis. Though it was felt over last few decades that patient's suffering from diabetes mellitus who have pancreatic diseases like chronic pancreatitis, cystic fibrosis, post pancreatectomy states, pancreatic carcinoma etc. behave in a different manner from that of Type 1 & Type 2 diabetic patients[1], only over last few years it was proved to be a distinct entity needing specific tailored approach. DM due to cystic fibrosis was recognized as a distinct clinical state because the patients have poor nutritional status, severe respiratory inflammatory symptoms, increased mortality rate from respiratory failure.[2] They needed special care in evaluation and treatment. This type of secondary diabetes was called CFRD (cystic fibrosis related diabetes) where exocrine defect altered the pancreatic endocrine system.

The march of events leading to recognition of pancreatic diabetes as a separate entity started with the observation of DM occurring in young population in the tropics where chronic pancreatitis was found to be the main reason. This was initially called Fibro Calculi Pancreatic Diabetes (FCPD). After years of confusion in nomenclature like Tropical diabetes/Malnutrition Related Diabetes (MRDM) it has been finally proven that this entity is a separate one and is now called Pancreatic Diabetes or Type 3c Diabetes. There was a time when the cyanide containing cassava was thought to be the cause of chronic pancreatitis and diabetes. Epidemiological studies had shown that this type of diabetes was common in the countries of tropics where cassava consumption was high in the diet of countries like Brazil, Africa and South India particularly Kerala. Now a days various causes of chronic pancreatitis are incrimated in Pancreatic Diabetes.[3]

Later pancreatic diabetes due to other causes like chronic pancreatitis, pancreatic carcinoma etc. was given separate recognition by ADA & WHO as Type 3C diabetes, in the current classification & criteria for its diagnosis was laid down. (Table 1)

Table 1: Diagnostic criteria for Type 3C DM

Major criteria (all must be fulfilled) :
• Presence of exocrine pancreatic insufficiency (according to monoclonal fecal elastase – 1 or direct function tests). • Pathological pancreatic imaging (by endoscopic ultrasound, MRI or CT). • Absence of Type 1 DM associated autoimmune markers.
Minor criteria :
• Impaired beta cell function (as measured by HOMA – B, C- peptide/ glucose ratio) • No excessive insulin resistance (measured by HOMA- IR) • Impaired incretin (e.g, GIP) or pancreatic polypeptide secretion • Low serum levels of lipid soluble vitamins(A, D, E, K)

Adapted From Ewald and Bretzel[4]

EPIDEMIOLOGY

In the general population prevalence of Type 2 DM is around 8%.[5] As awareness regarding the pancreatic diabetes (Type 3C diabetes) as a separate clinical entity is increasing, western data reveals 10% of the newly diagnosed diabetes belong to Type 3.[6] Though concrete data is not available in Asiatic population the prevalence is more.

Chronic pancreatitis remains the main cause of pancreatic diabetes. Depending on the type of cohort study and duration of study, Type 3C diabetes occurrence varies from 26 to 80 % of chronic pancreatitis patient. In 80% Type 3C diabetes, chronic pancreatitis is the cause in 20% Adolescents and 40 to 55% adults of cystic fibrosis suffer from pancreatic diabetes.[7,8,9,10] There is a high prevalence of calcific pancreatitis in Diabetes in tropics.[3] It was reported that calcific pancreatitis is present in 8% of diabetics in Uganda, 8.9% in Nigeria, 7.5% in Congo and in one study it was seen to be present in 14.8% in Kerala (India).Chronic calcific pancreatitis leading to pancreatic diabetes is seen in 82.2% cases in Nigeria and 90% cases in India. The age of onset of pancreatic diabetes with Tropical Calcific Pancreatitis(TCP) was 12-25 years where as in alcohol induced chronic pancreatitis leading to pancreatic diabetes, the age of onset was 50-60 years.[3]

ETIOLOGY

In the etiology of pancreatic diabetes chronic pancreatitis tops the list. The other causes are listed below[7-11] (Table 2)

PATHOGENESIS

Human Pancreas harbours around 1 million islets of 5-400 micron in diameter. Each islet has around 2000 insulin secreting beta cells, glucagon secreting alpha cells and somatostatin secreting delta cells.[15] Pancreas

Table 2: Causes of Pancreatic Diabetes
Acute pancreatitis
Relapsing Pancreatitis
Chronic Pancreatitis (Accounting for 80% of Pancreatic Diabetes)
Haemochromatosis
Pancreatic Carcinoma
Pancreatectomy
Rarely Neonatal diabetes (Pancreatic Agenesis)
As chronic pancreatitis is the major cause of pancreatic diabetes the different causes of chronic pancreatitis are given below
Alcohol
Gall stone
Hypertriglyceridemia
Congenital anomalies of pancreatic duct system – Pancreas divisum
Ectopic pancreas
Annular pancreas
Hypertrophic sphincter of oddi
Duct stone
Autoimmune Pancreatitis
Groove Pancreatitis[7]
Tropical calcific pancreatitis[13]
Hereditary Pancreatitis(PRSS1 Mitochondria)
Genetic pancreatitis(SPINK 1 & Chromosome CFTR Mutation)[14]
Mutation of MCP -1 gene
Drugs causing Pancreatitis
Estrogen
Corticosteroids
Thiazides
Incretin based anti diabetic Drugs
Causes of pancreatic calcification
Gall stone pancreatitis
Familial Hyperlipoproteinemia
Hyperparathyroidism
Following pseudocyst of pancreas
Rarely following – Mumps
Miliary TB
Progresive systemic sclerosis
Blaunt trauma to abdomen
Tropical calcific pancreatitis (TCP)
Cystic fibrosis
Schistosomiasis
Hydatid disease

Table 3: Comparison of hormonal and metabolic aspects of pancreatic diabetes, Type-1 DM and Type-2 DM

	Pancreatic diabetes	Type-1 DM	Type-2 DM
Insulin secretion	↓↓	↓↓↓	↓
Insulin sensitivity	0	↓	↓↓
Glucagon secretion	↓↓	↑/↓	↑/↓
Plasma amino acids	↑↑	↑/0	↑/0
Ketosis prone	↑↑	↑↑↑	↑
Glucose counter regulation	↓	0/↓	0/↓
lipids	0	↑	↑↑

↑, Increased; 0, normal; ↓, decreased; IDDM, insulin dependent diabetes mellitus; NIDDM, non – insulin dependent diabetes mellitus; Adapted from Nils Ewald, Philip D Hardt [37]

also contains pancreatic polypeptide secreting pancreatic polypeptide cells. These islets are unevenly scattered throughout the pancreas along with the pancreatic acini. There is paracrine regulation of β-cell by the α-cell secretion. There is also a insulo-acinar axis where the functions of the acini is affected by the islet secretion. Pathogenesis of pancreatic diabetes mostly due to chronic pancreatitis, the tissue injury is thought to occur due to premature activation of pancreatic enzymes. This causes inflammation and auto digestion of the pancreatic tisse leading to tissue loss,replacement fibrosis, septa formation and calcification which leading to exocrine deficiency.[16] The islets resist this auto digestive process to a much greater extent than the acinar cells. Later on the islet cell function decreases and islet atrophy ensues. So exocrine function loss predates endocrine deficiency leading to DM. The exocrine deficiency causes nutrient malabsorption resulting in impaired incretin secretion thereby decreasing the stimulus for insulin secretion. Due to accelerated gastric emptying post prandial rise in glucose level increases. Besides β-cell function loss glucagon secreting alpha cells are also affected but later in the course of the disease. This causes loss of glucagon response to hypoglycemia with wide excursion of glucose level making this type of DM brittle.[17] In type 1 diabetes there is absolute insulin deficiency and in later stage insulin resistance. In Type 2 diabetes tissue sensitivity to insulin decreases whereas in Pancreatic DM tissue sensitivity to insulin is intact.[18] (Table 3)

HISTOPATHOLOGY[3,20,21]

Histopathologic study of pancreas in pancreatic diabetes differs that of from Type 1 and 2 DM. In Type 1 DM auto immune Beta cell specific destruction is seen as insulitis, with infiltration of the lymphocytes in and around islets whereas in Type 2 diabetes islets and pancreas shows

Table 4: Clinical Characteristics for Common Forms of Diabetes

	T1DM	T2DM	T3cDM		
Associated with	Autoimmunity	obesity	Chronic pancreatitis	Cystic fibrosis	Pancreatic resection
Median age of onset	2nd decade of life	6th decade of life	5th decade of life	3rd decade of life	Within 5 years of surgery
Pancreatic insufficiency	No	No	Yes	Yes	Yes
Pain Abdomen	No	No	Yes	Yes	No
Hepatic insulin sensitivity	Normal or decreased	Decreased	Normal or decreased	?	Normal or decreased
Peripheral insulin sensitivity	Normal or decreased	Decreased	Normal	?	Normal
Diabetic ketoacidosis	Yes	No	No	No	No
Hypoglycemia risk	Increased	Normal or increased	Normal or increased	Normal or increased	Normal or increased
Pancreatic polypeptide response	Normal or decreased	Decreased or absent	Decreased or absent	Absent	Absent

Adapted from Gudipaty, Lalitha. Rickels[36]

amyloid deposition. In type 3C Pancreatic diabetes this amyloid deposition is not seen but in CFRD amyloid deposits are present.

CLINICAL FEATURES (TABLE 4)

Pancreatic diabetes patients usually have history of pancreatitis in past, pain abdomen, dyspepsia, steatorrhea and symptoms of malabsorption. Due to defect in fat soluble vitamins (A,D,E,K) absorption patients may show features of these vitamin deficiency states. Initially overt diabetes or hyperglycemia may not be present but only occurs during periods of stress, illness, surgery, high dose corticosteroids. As beta cell deficiency progress, these patients develop overt diabetes. Patients with chronic calcific pancreatitis may present with features of malabsorption and failure to thrive or with chronic abdominal pain of chronic pancreatitis or with osmotic features of DM. Very often they present with features of malabsorption and DM. In patients presenting with DM, the abdominal pain is less perceived due to autonomic neuropathy. Pancreatic diabetic patients do not develop DKA as the beta cell deficiency is seldom absolute and therefore were classified as ketosis resistant DM in the young in the older classification. Brittle Diabetes is another feature of Pancreatic Diabetes.[22]

DIAGNOSIS

The diagnosis of pancreatic diabetes mellitus is entertained when

1. Patients of diabetes mellitus have abdominal symptoms and features of malabsorption.
2. Wherever ambiguity regarding typing of diabetes mellitus as type 1 and type 2 arises, possibility of pancreatic diabetes mellitus should be thought of.

Conventionally typing of diabetes is confirmed by presence of Type 1 associated autoantibodies and Type 2 diabetes by presence of insulin resistance. In Type 3C or pancreatic diabetes investigation for exocrine and endocrine deficiencies should be done.

1. OGTT fasting blood glucose > 126 mg/dl and HbA1c > 6.5 % gives the diagnosis of pancreatic diabetes. If the FBG is between 100- 125 mg/dl or HbA1c 5.7- 6.5 %, this state is called IFG (impaired fasting glucose). If the 2 hr PPBG > 200 mg/dl, then it can be taken as diabetes and if it lies between 140-200 mg/dl it is called as prediabetes.[12]
2. Exclusion of Type 1 diabetes is done by estimation of GAD antibodies, antibodies against islet cell antigen and insulin. Exclusion of Type 2 diabetes is done by estimation of fasting serum insulin which remains high in Type 2 diabetes reflecting insulin resistance.[23]
3. For exocrine deficiency in pancreatic diabetes, fecal elastase – 1 estimation remains a conventional noninvasive measure.[24] The PP (polypeptide) respone to 12 ounce of boost high protein supplemented with pancreatic enzymes is estimated[23]. In normal population the PP response increases 4 to 6 fold over the basal value whereas in pancreatic diabetes less than doubling over the basal value is the rule.[25]
4. Pancreatic imaging is a must in cases of pancreatic diabetes to establish the cause. Once evidence of calcification in the pancreatic duct is established in USG of abdomen,the above mentioned tests are inconsequences.

COMPLICATIONS

The complication of pancreatic diabetes follows the similar risk pattern as that of Type 2 diabetes mellitus with micro and macrovascular complications(e.g., CVD). These patients may show brittle diabetes with wide excursion of glucose level and frequent hypoglycemia. Nutritional deficiencies like decreased vitamin-D levels predispose them to osteoporosis.[23]

Diabetic ketoacidosis (DKA) is less in pancreatic diabetes.[33-35] Another important aspect of pancreatic diabetes is that it is the harbinger of pancreatic carcinoma, hence Type 3C Diabetes is considered as a premalignant condition.[26-28]

MANAGEMENT

In the management of pancreatic DM the aim is to control the hyperglycemia (HbA1c <7%), care of exocrine deficiency like managing malnutrition and abdominal symptoms and sometimes giving special care to brittle diabetics. Management of pancreatic diabetes is problematic because of both carbohydrate and lipid malabsorption, irregular pattern of eating habits due to abdominal symptoms and loss of glucagon response to hypoglycemia.

Till date no definite therapeutic guidelines have been established. So the consensus follows the treatment guidelines for Type 2 DM with modification when needed. In view of the pathological changes in exocrine as well as endocrine pancreas, insulin secretagogues or drugs enhancing innate insulin secretion have very little role to play. Similarly, the quantum of tissue insulin resistance being negligible, role of insulin sensitizers is also very limited.

The mainstay of management is insulin therapy. Due to deficiency of exocrine pancreatic enzymes, supplementation with enzymes like lipase along with other nutritional supplements,fat soluble vitamin supplements like vit. A,D,E,K should be done in patients with FCPD. Lifestyle modifications like cessation of smoking, abstinence from alcohol and low fat diet is helpful.

Surgical treatment is often given to patients of FCPD through the PEUSTOW'S procedure where the pancreatic duct is opened up longitudinally, then stones removed and pancreaticojejunostomy is performed. The residual β-cell and exocrine pancreatic mass is salvaged.Nesidioblastosis i.e regeneration of β-cell have occurred in some cases after surgical procedure. Endoscopic intervention can also be attempted in cases where there is primarily narrowing of the pancreatic duct in the head region. This procedure is performed with the help of ECLT (Extra Corporeal Lithotripsy) which can pulverise the stone, especially in case of a large stone in head region of pancreatic duct. Total pancreatectomy with islet autotransplantation (TPIAT) is considered in pancreatic DM with pancreatic cancer.[30]

CONCLUSION

Pancreatic diabetes (Type 3C diabetes) is a separate entity for which diagnostic criteria and treatment modalities are different. 5 to 10% of the newly diagnosed diabetes are now Type 3 diabetes. Chronic pancreatitis remains the major cause of pancreatic diabetes. Exocrine deficiency often predates pancreatic diabetes. Defective pancreatic polypeptide response is the early marker of pancreatic diabetes.[32] Some of the pancreatic diabetes patients are brittle. Chronic pancreatitis and pancreatic diabetes are considered to be premalignant condition for pancreatic carcinoma.

REFERENCES

1. Hart PA, Chari ST. Diabetes mellitus as a result of pancreatic cancer. Pancreapedia: Exocrine Panaceas Knowledge Base. DOI: 10.3998/panc.2015.34, 2015.
2. Moran A, Hardin D, Rodman D, Allen HF, Beall RJ, Borowitz D, et al. Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report. *Diabetes Res Clin Pract* 1999; 45:61-73. PMID: 10499886.
3. P.J. Gee Varghese, Annie Abraham. Calcific Pancreatitis And Diabetes In The Tropics, Second Edition, Published by Dr. P.J. Gee Varghese, Cochin, India, 1995
4. Ewald N, Bretzel RG. Diabetes mellitus secondary to pancreatic diseases (Type 3c) - Are we neglecting an important disease? *Eur J Intern Med* 2013; 24:203-206. PMID: 23375619.
5. Hardt PD, Brendel MD, Kloer HU, Bretzel RG. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? Diabetes Care 2008; 31(Suppl 2):S165–S169.
6. Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel RG, Hardt PD. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). *Diabetes Metab Res Rev* 2012; 28:338-342. PMID: 22121010.
7. Bertin C, Pelletier AL, Vullierme MP, Bienvenu T, Rebours V, Hentic O, et al. Pancreas Divisum Is Not a Cause of Pancreatitis by Itself But Acts as a Partner of Genetic Mutations. *Am J Gastroenterol* 2012; 107:311-317. PMID: 22158025.
8. Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe.*Clin Gastroenterol Hepatol* 2004; 2:252-261. PMID: 15017610.
9. Malka D, Hammel P, Sauvanet A, Rufat P, O'Toole D, Bardet P, et al. Risk factors for diabetes mellitus in chronic pancreatitis. *Gastroenterology* 2000; 119:1324-1332. PMID: 11054391.
10. Rebours V, Boutron-Ruault MC, Schnee M, Ferec C, Le MC, Hentic O, et al. The natural history of hereditary pancreatitis: a national series. *Gut* 2009; 58:97-103. PMID: 18755888.
11. Wakasugi H, Funakoshi A, Iguchi H. Clinical assessment of pancreatic diabetes caused by chronic pancreatitis. *J Gastroenterol* 1998; 33:254-259. PMID: 9605958.
12. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012; 35:S64-S71. PMID: 22187472.
13. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis

is caused by a mutation in the cationic trypsinogen gene. *Nat Genet* 1996; 14:141-145. PMID: 8841182.

14. Schneider A, LaRusch J, Sun XM, Aloe A, Lamb J, Hawes R, et al. Combined Bicarbonate Conductance-Impairing Variants in CFTR and SPINK1 Variants Are Associated With Chronic Pancreatitis in Patients Without Cystic Fibrosis. *Gastroenterology* 2011; 140:162-171. PMID: 20977904.
15. Meier JJ, Butler PC. Insulin secretion. In: DeGroot LJ, Jameson JL, editors. Endocrinology, 5th ed. Philadelphia: Elsevier Saunders; 2005. pp. 961–973.
16. Schrader H, Menge BA, Schneider S, *et al.* Reduced pancreatic volume and beta-cell area in patients with chronic pancreatitis. Gastroenterology 2009; 136:513–522.
17. Larsen S, Hilsted J, Tronier B, Worning H. Pancreatic hormone secretion in chronic pancreatitis without residual beta-cell function. *Acta Endocrinol (Copenh)* 1988; 118:357-364. PMID: 2899369.
18. Yasuda H, Harano Y, Ohgaku S, Kosugi K, Suzuki M, Hidaka H, et al. Insulin Sensitivity in Pancreatitis, Liver-Diseases, Steroid Treatment and Hyperthyroidism Assessed by Glucose, Insulin and Somatostatin Infusion. *Horm Metab Res* 1984; 16:3-6. PMID: 6141989
19. Gorelick F, Pandol SJ, Topazian M. Pancreatic physiology, pathophysiology, acute and chronic pancreatitis. Gastrointestinal Teaching Project, American Gastroenterological Association. 2003.
20. Gepts W. Pathologic Anatomy of Pancreas in Juvenile Diabetes Mellitus. *Diabetes* 1965; 14:619-&. PMID: 5318831.
21. Gepts W, Veld PAI. Islet Morphological-Changes. *Diabetes Metab Rev* 1987; 3:859-872. PMID: 3315523.
22. Nosadini R, Delprato S, Tiengo A, Duner E, Toffolo G, Cobelli C, et al. Insulin Sensitivity, Binding, and Kinetics in Pancreatogenic and Type-I Diabetes. *Diabetes* 1982; 31:346-355. PMID: 6759250.
23. Rickels MR, Bellin M, Toledo FGS, Robertson RP, Andersen DK, Chari ST, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis:. Recommendations from Pancreas Fest 2012. *Pancreatology* 2013; 13:336-342. PMID: 23890130.
24. Loser C, Mollgaard A, Folsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut* 1996; 39:580-586. PMID: 8944569.
25. Cui YF, Andersen DK. Pancreatogenic Diabetes: Special Considerations for Management. *Pancreatology* 2011; 11:279-294. PMID: 21757968.
26. Ben Q, Xu M, Ning X, *et al.* Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. Eur J Cancer 2011; 47:1928–1937.
27. Li D, Tang H, Hassan MM, *et al.* Diabetes and risk of pancreatic cancer: a pooled analysis of three large case-control studies. *Cancer Causes Control* 2011; 22:189–197.
28. Solanki NS, Barreto SG, Saccone GT. Acute pancreatitis due to diabetes: the role of hyperglycaemia and insulin resistance. *Pancreatology* 2012; 12:234–239.
29. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32:193-203. PMID: 18945920.
30. Bellin MD, Freeman ML, Gelrud A, Slivka A, Clavel A, Humar A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: Recommendations from PancreasFest. *Pancreatology* 2014; 14:27-35. PMID: 24555976.
31. Sikkens ECM, Cahen DL, Koch AD, Braat H, Poley JW, Kuipers EJ, et al. The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. *Pancreatology* 2013; 13:238-242. PMID: 23719594.
32. Valenzuela JE, Taylor IL, Walsh JH. Pancreatic polypeptide response in patients with chronic pancreatitis. *Dig Dis Sci* 1979; 24:862-864. PMID: 520107.
33. Ebert R, Creutzfeldt W. Reversal of impaired GIP and insulin secretion in patients with pancreatogenic steatorrhea following enzyme substitution. *Diabetologia* 1980; 19:198–204. [PubMed]
34. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; 26 Suppl 1:S5–S20.[PubMed]
35. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011; 34 Suppl 1:S62–S69. [PMC free article] [PubMed]
36. Gudipaty, Lalitha. Rickels, Michael R. (2015). Pancreatogenic (Type 3c) Diabetes. *Pancreapedia: Exocrine Pancreas Knowledge Base*, DOI: 10.3998/panc.2015.35
37. Nils Ewald, Philip D Hardt. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. 2013; 19:7276–7281.
38. Juris J. Meier; Arnd Giese. diabetes associated with pancreatic diseases. *Curr Opin Gastroenterol* 2015; 31:400-406.