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Pancreatogenic (Type 3c) Diabetes

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Version 1.0, September 1, 2015 [DOI: 10.3998/panc.2015.35]

1. Definition

Pancreatogenic diabetes is a form of secondary diabetes, specifically that associated with disease of the exocrine pancreas. The most common disease of the exocrine pancreas associated with the development of diabetes is chronic pancreatitis. Analogous to chronic pancreatitis-associated diabetes is cystic fibrosis-related diabetes (CFRD), in which pancreatic exocrine insufficiency pre-dates the pancreatic endocrine insufficiency responsible for the development of diabetes. Because diabetes in cystic fibrosis is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality from respiratory failure, CFRD has long been recognized as a distinct form of diabetes requiring a specified approach to evaluation and treatment (30) now recognized by the American Diabetes Association (28). While the distinct pathogenesis of diabetes in chronic pancreatitis has also long been appreciated, only recently have guidelines been developed supporting a specified diagnostic and therapeutic algorithm (37). Finally, other less common forms of pancreatogenic diabetes exist, such as that due to pancreatic cancer (18), as well as post-pancreatectomy diabetes, with each requiring individualized approaches to care.

2. Classification

Pancreatogenic diabetes is classified by the American Diabetes Association and by the World Health Organization as type 3c diabetes mellitus (T3cDM) and refers to diabetes due to impairment in pancreatic endocrine function related to pancreatic exocrine damage due to acute, relapsing and chronic pancreatitis (of any etiology), cystic fibrosis, hemochromatosis, pancreatic cancer, and pancreatectomy, and as well rare causes such as neonatal diabetes due to pancreatic agenesis (1). Prevalence data on T3cDM are scarce because of insufficient research in this area and challenges with accurate diabetes classification in clinical practice.

Table 1: Diagnostic Criteria for T3cDM

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 T1DM-associated autoimmune markers.
Minor Criteria:
• Impaired β-cell function (e.g. as measured by HOMA-B, C-peptide/glucose ratio). • No excessive insulin resistance (e.g. as measured by HOMA-IR). • Impaired incretin (e.g. GIP) or pancreatic polypeptide secretion. • Low serum levels of lipid soluble vitamins (A, D, E, or K).

Adapted from Ewald and Bretzel (Ref. 12).

Ewald and colleagues (13) found at an academic referral center in Germany that almost 10% of all diabetes cases could be classified as T3cDM, with chronic pancreatitis being the most common etiology of T3cDM affecting nearly 80% of cases. Most cases of T3cDM were initially misclassified as type 2 diabetes mellitus (T2DM), highlighting an under recognition of the contribution of pancreatic disease to the development of diabetes.

In order to improve recognition of pancreatogenic diabetes, Ewald and Bretzel (12) subsequently proposed diagnostic criteria for T3cDM. As outlined in **Table 1**, the diagnosis of T3cDM requires 1) the presence of pancreatic exocrine insufficiency (according to monoclonal fecal elastase 1 test or direct function tests), 2) evidence of pathological pancreatic imaging (by endoscopic ultrasound, MRI or CT) and 3) the absence of type 1 diabetes mellitus (T1DM)-associated autoantibodies, and may be further supported by evidence of pancreatic polypeptide, incretin or insulin secretory defects in the absence of clinical or biochemical evidence of overt insulin resistance. There is likely a degree of overlap using these criteria in patients with long-standing T1DM or T2DM because established insulin deficiency is also associated with pancreatic atrophy and exocrine insufficiency, and so may be more reliably applied at the presentation of diabetes in order to best diagnose and classify the co-existing exocrine and endocrine diseases to effectively target treatment.

At the presentation of diabetes, discrimination of T3cDM from T2DM is most challenging since T2DM occurs in 8% of the general population, and so is common enough to be present in patients with pancreatic disease. In most cases, the clinical diagnosis of T1DM or T2DM is made by routine endocrinologic evaluation with confirmation by either assessment of T1DM-associated autoantibodies, or documentation of T2DM-associated insulin resistance evidenced by acanthosis nigricans or hyperinsulinemia. When ambiguity remains, consideration of T3cDM should be entertained and may be suggested by a prior (9) or family history of pancreatitis. Completing the evaluation at this point has been made much easier by the availability of fecal elastase-1 as a noninvasive screening test for pancreatic exocrine dysfunction (25), and the improved sensitivity of imaging methods for detecting pancreatic pathology (2). Confirmation of T3cDM can then be made by documentation of an absent pancreatic polypeptide response to mixed-nutrient ingestion, which best discriminates the pathologic islet response from that of T2DM (37).

3. Epidemiology

While diseases of the pancreas are uncommon, diabetes mellitus is common in patients with pancreatic disease and following pancreatic resection. A consecutive autopsy study documented chronic pancreatic inflammation in 13% of cases, and while few cases carried a clinical diagnosis of chronic pancreatitis, there was a significantly higher incidence of chronic pancreatic inflammation in patients with diabetes (35). In cystic fibrosis, diabetes is present in about 20% of adolescents and 40-50% of adults with the disease, and has been reviewed extensively elsewhere (28). In chronic pancreatitis, diabetes has been observed in 26-80% of patients depending on the cohort studied and duration of follow-up (4, 19, 27, 36, 43).

Chronic pancreatitis is characterized by pancreatic inflammation and fibrosis resulting in a progressive and irreversible destruction of exocrine and endocrine tissue. While toxic insult from alcohol remains the most common etiology of chronic pancreatitis, other etiologies of chronic pancreatitis include obstructive pathology (pancreas divisum, duct scars and groove pancreatitis (4)), autoimmune pancreatitis (type 1 and type II), tropical calcific pancreatitis, hereditary pancreatitis (—i.e. PRSS1 mutations (46)), other genetic pancreatitis (e.g. SPINK1

and/or CFTR mutations (38)), as well as idiopathic causes when no clear etiology is identified. Nevertheless, it is now understood that interactions between genetic, environmental and metabolic factors contribute to the development of recurrent acute and chronic pancreatitis (45).

Chronic pancreatitis results in progressive exocrine and endocrine dysfunction with the development of maldigestion and malabsorption of nutrients resulting in malnutrition, glucose intolerance and eventually overt diabetes as the normal pancreas microarchitecture that maintains the complex interplay of nutrient digestion, absorption and utilization is destroyed by ongoing fibrosis. In fact, while pancreatic exocrine insufficiency typically pre-dates endocrine insufficiency in chronic pancreatitis, there is a significant correlation between measures of pancreatic exocrine and endocrine function (10, 34) evidencing the interrelated pathology in these pancreatic tissue compartments.

The risk for diabetes in patients with chronic pancreatitis increases with longer disease duration, with worsening pancreatic damage, especially early-onset of pancreatic calcification, and with prior distal pancreatectomy (27). In predominantly alcohol-associated chronic pancreatitis the cumulative prevalence of diabetes was 50% and 83% after 10 and 25 years, respectively (27), while in hereditary pancreatitis the cumulative prevalence of diabetes was 5% and 25% by 10 and 25 years from symptom onset, respectively (19). While the progression to endocrine failure appears accelerated with alcohol-associated disease, given a median age of onset ~ 10 years with hereditary pancreatitis, the majority of patients affected develop diabetes by their 5th decade of life (19, 36). Of special consideration is apancreatic diabetes due to partial or total pancreatectomy, which may be indicated in chronic pancreatitis as treatment for intractable pain, biliary obstruction, duodenal stenosis, pancreatic duct stenosis, pancreatic pseudocysts, pancreatic ascites, or pancreatic hemorrhage. Development of surgical diabetes is far more likely with distal vs. proximal pancreatectomy, and of course dependent on the percent of gland removed (27). While surgical drainage per se does not accelerate the progression to diabetes in chronic pancreatitis, pancreaticojejunostomy compromises islet isolation outcomes for auto-transplantation should surgical drainage fail to relieve pain and total pancreatectomy become a consideration (41).

4. Clinical Presentation

Because exocrine insufficiency usually pre-dates endocrine insufficiency in chronic pancreatitis, most patients with T3cDM have a known history of pancreatitis with abdominal pain, steatorrhea or maldigestion with nutritional deficiencies and glucose intolerance. Patients may also present with symptoms of maldigestion and/or abdominal pain without a prior diagnosis of chronic pancreatitis, or even may be asymptomatic except for glucose intolerance or diabetes, and only through careful clinical evaluation is pancreatic disease suspected. The alterations in glucose metabolism begin as asymptomatic or mild hyperglycemia early in the course of endocrine insufficiency, and periods of glucose intolerance may only be evident during stress, illness or high dose glucocorticoid treatment. Later in the disease course there is often progression to brittle diabetes characterized by marked glycemic lability and frequent hypoglycemia due to continued loss of not only islet β-cell secretion of insulin but also counterregulatory glucagon secretion from islet α-cells (24) such that replacement doses of insulin unpredictably predispose to hypoglycemia. Unlike T1DM, the β-cell deficit is seldom absolute, and so these patients rarely present with diabetic ketoacidosis **(Table 2)**.

Table 2: 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 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	?	Normal
Diabetic Ketoacidosis	Yes	No	No	No	No
Hypoglycemia Risk	Increased	Normal	Normal or Increased	Normal or Increased	Normal or Increased
Pancreatic Polypeptide Response	Normal or Decreased	Normal or Increased	Decreased or Absent	Absent	Absent

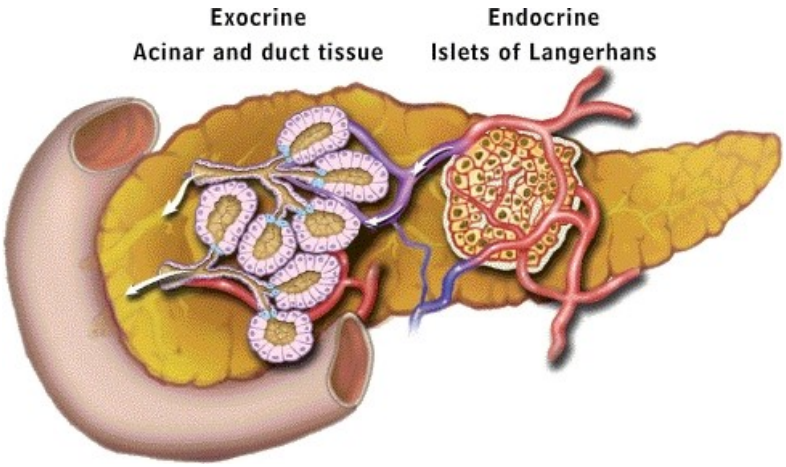

Figure 1: Schematic diagram depicting the arterial supply that allows blood flow from the endocrine pancreas to pass to the exocrine pancreas before entering the general circulation. [Adapted with permission from Gorelick F, Pandol, SJ, Topazian M. *Pancreatic physiology, pathophysiology, acute and chronic pancreatitis*. Gastrointestinal Teaching Project, American Gastroenterologic Association. 2003; Ref. 17].

5. Pathology and Pathogenesis

The pathogenesis of T3cDM is ultimately due to decreased insulin secretion caused by both a reduction in the number of islets and their functional capacity as a consequence of extensive fibrosis and sclerosis (10, 34).The mechanism by which scarring of pancreatic tissue induces insulin deficiency can be explained by the anatomical and functional interplay between the pancreatic islets and acinar tissue.

Islet Architecture

The islets of Langerhans have a distinct arterial blood supply with an insuloacinar portal circulation. The exocrine pancreas receives a large part of its blood flow through the islets and therefore is normally exposed to high concentrations of islet hormones (**Figure 1** (17)). Insulin in particular is essential for the functional efficiency of the acinar tissue (47).

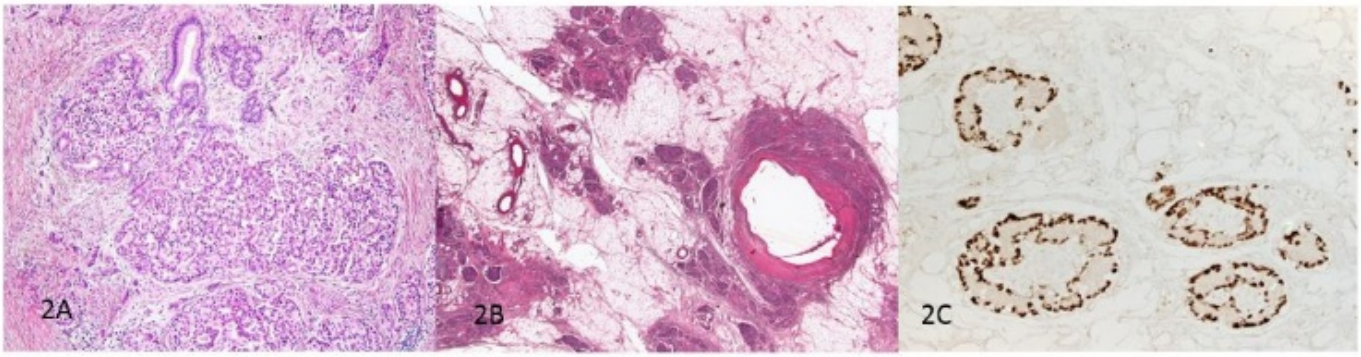

Figure 2: Histopathology of the pancreas in alcoholic chronic pancreatitis (2A). The exocrine parenchyma is replaced by sclerotic tissue containing islet aggregates typically found in chronic pancreatitis. Histopathology of the pancreas in cystic fibrosis (2B). Note the extensive fibrosis of the pancreatic parenchyma. This is from a 41 year-old patient with advanced cystic fibrosis and diabetes. Histopathology of the pancreas in cystic fibrosis-related diabetes with glucagon staining (2C). Note the extensive fibrosis and amyloidosis within the islet. [Images Courtsey of G. Kloppel]

In chronic pancreatitis, replacement of the pancreatic parenchyma containing pancreatic acini, ducts, and nerve bundles by connective tissue is characterized by increases in collagen fibers in perisinusoidal spaces with progressive scarring leading to loss of vascularity (21). The pancreatic islets are distributed throughout the exocrine tissue and can be highly variable with occasional nesidioblastic processes but receive decreased blood flow with overall reduced granular content and eventual ischemic atrophy **(Figure 2A).**

Similarly, in patients with pancreatic insufficient cystic fibrosis there is extensive fibrosis of the pancreatic parenchyma with islands of residual exocrine tissue and islets that are intact **(Figure 2B)**.These pathologies are distinct from that seen in the pancreas of T1DM which is primarily characterized by insulitis, an autoimmune mediated β-cell specific destruction with an infiltration of lymphocytes in or around the islets (14). Histologically, T2DM islets are characterized by amyloid deposition (15) which is not present in chronic pancreatitis, but interestingly is found in islets associated with CFRD **(Figure 2C)**.

β-Cell Function

In chronic pancreatitis, tests of insulin secretion after maximal β-cell stimulation with combined oral glucose, intravenous glucagon, and intravenous tolbutamide have demonstrated a decreased β-cell secretory capacity even in patients with normal oral glucose tolerance, and with progression to diabetes, that the β-cell secretory capacity becomes markedly reduced (10). Importantly, tissue sensitivity to insulin is not overtly impaired in chronic pancreatitis regardless of glucose intolerance or overt diabetes (48). This not only is distinctive from T2DM, but also T1DM whereby absolute insulin deficiency is associated with the development of insulin resistance (32).

α-Cell Function

Because β-cell function inversely regulates α-cell function via paracrine mechanisms within the islet, the initial defects in insulin secretion seen in chronic pancreatitis are associated with increases in glucagon secretion that may contribute to early impairment in glucose tolerance (23), and correlates with an increase in the numbers of islet α-cells observed pathologically (21). However, with progressive islet damage during the course of T3cDM diabetes, glucagon secretion becomes impaired (24), which may contribute to the development of brittle diabetes late in the disease.

Pancreatic Polypeptide (PP)-Cell Function

PP-secreting cells, which are localized at the periphery of the pancreatic islets and also are

scattered between the acini and in the epithelium lining the pancreatic ducts, are universally diminished in function during the course of chronic pancreatitis. In fact, defects in PP function are observed early in the course of chronic pancreatitis (42), with markedly impaired responses present by the time oral glucose tolerance becomes impaired (40). In cystic fibrosis, PP function is essentially absent in exocrine-insufficient patients with or without current CFRD (29, 33). This suggests that PP deficiency may be an early marker for the development of endocrine dysfunction in patients with exocrine insufficiency (37). In advanced chronic pancreatitic with established PP deficiency and T3cDM, isolated hepatic insulin resistance has been observed that may be normalized by infusion of PP (6).

Entero-Insular Axis

In patients with pancreatic exocrine insufficiency, maldigestion and consequent malabsorption of nutrients impairs enteral secretion of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are both important for augmenting glucose-dependent insulin secretion. Oral pancreatic enzyme replacement not only improves in particular fat digestion and absorption that can control symptoms of steatorrhea, but also improves incretin and insulin secretion, and consequently glucose tolerance during meal ingestion (11, 22). Whether overall decreased exposure to the tropic effect of incretin hormones contributes to the progressive islet failure in T3cDM is not known.

6. Diagnosis

In patients with chronic pancreatitis, the initial evaluation should include fasting glucose and HbA_{1c}, with impairment in either further evaluated by a standard 75 g oral glucose tolerance test (OGTT) (37). Impairment in fasting glucose (100-125 mg/dl) or HbA_{1c} (5.7-6.4%) constitutes increased risk for diabetes, a condition known as pre-diabetes, while a fasting glucose ≥126 mg/dl or HbA_{1c} ≥6.5% may already indicate the presence of diabetes (1). In the absence of unequivocal hyperglycemia (random glucose ≥200 mg/dl), such results should be confirmed by repeat testing unless both support the diagnosis.

The OGTT is the most sensitive test for making a diagnosis of diabetes, and involves measurement of serum glucose fasting and at both one and two hours following glucose ingestion. A diagnosis of diabetes is made by a two-hour glucose measurement ≥200 mg/dl, and impaired glucose tolerance is defined by a two-hour glucose of 140-199 mg/dl, also consistent with pre-diabetes (1). While there are no standard criteria for interpreting the one-hour glucose test, a level ≥200 mg/dl likely represents an early indication of impaired β-cell function in patients with pancreatic disease (5, 30). If insulin resistance associated with T2DM is suspected, a fasting serum insulin level can be helpful to document hyperinsulinemia (37).

When suspected, the presence of islet autoantibodies (e.g. against glutamic acid decarboxylase, islet cell antigen, or insulin) may confirm T1DM, and the presence of clinical or biochemical evidence of insulin resistance (e.g. acanthosis nigricans or hyperinsulinemia) can confirm T2DM. However, if uncertainty remains, T3cDM can be established by measurement of the PP response to mixed-nutrient ingestion. Mixed-nutrient ingestion can be standardized to 12 ounces of Boost High Protein® or equivalent and administered with prescribed pancreatic enzymes (37). While definitive criteria for the assessment of the PP response to nutrients have yet to be established, non-diabetic subjects demonstrate a 4-6 fold increase over basal levels, whereas patients with chronic pancreatitis-associated diabetes demonstrate less than a doubling of their basal values (8). This is in distinction from early T1DM in which PP levels may increase normally (24), and early T2DM

which is characterized by elevated basal and stimulated levels of PP (16).

In patients without a clinical diagnosis of chronic pancreatitis, unless the presentation is classic for T1DM or T2DM, the evaluation should consider any personal or family history of pancreatitis (9), as well as any current symptoms of maldigestion and/or abdominal pain as possibly related to T3cDM. In addition to considering pancreatic endocrine function testing as above, the diagnosis will require evidence of pancreatic exocrine dysfunction, with fecal elastase-1 serving as a noninvasive screening test (25), and some form of sensitive imaging for detecting pancreatic pathology (2). When weight loss exists, and especially if out-of-proportion for the severity of the presenting diabetes, pancreatic imaging is essential for possible early detection of pancreatic cancer (18).

7. Complications

While limited data exist, patients with T3cDM appear to share a similar risk for the micro- and macro-vascular complications of diabetes as seen in T1DM and T2DM (7, 43). Thus, patients should be monitored for the development of retinopathy, nephropathy, neuropathy, and follow the same cardiovascular disease risk reduction guidelines as for patients with T1DM and T2DM (37).

8. Management

Control of hyperglycemia to achieve and maintain the HbA_{1c} <7% remains the primary target for the management of T3cDM as with T1DM and T2DM in order to minimize the risk of micro- and possibility macrovascular complications. Currently, there are no randomized controlled trial data available to direct the development of guidelines specific to T3cDM. Therefore, the recommendations detailed below are based on guidelines developed as part of a consensus conference of gastroenterologists, endocrinologists, and surgeons with clinical and research expertise in the management of chronic pancreatitis and its complications (37).

Lifestyle Modifications

Attempts to reduce the toxic and modifiable contributors to chronic pancreatitis such as abstaining from alcohol and smoking cessation are highly recommended as both exacerbate progression of underlying pancreatic inflammation and fibrosis and contribute to pain. Alcohol abstinence is also helpful for diabetes management, since alcohol acutely inhibits hepatic glucose production and can cause hypoglycemia, especially in the setting of insulin therapy. Medical nutritional therapy should include advice regarding eating meals rich in soluble fiber and low in fat, and in patients with any degree of pancreatic exocrine insufficiency, together with oral enzyme replacement. Oral pancreatic enzyme replacement is particularly important for fat digestion and absorption, and so helps to control symptoms of steatorrhea and protect against fat soluble vitamin deficiency. Maintaining sufficient levels of vitamin D is essential to prevent the development of metabolic bone disease and osteoporosis (39). As already discussed, treatment with pancreatic enzymes is also important for maintaining incretin hormone secretion in patients with exocrine insufficiency where their use is associated with better glucose tolerance during meal ingestion.

Anti-Hyperglyemic Agents

Since the principal endocrine defect is insulin deficiency, insulin therapy is the preferred treatment for most patients, and especially to correct hyperglycemia for CFRD, for acutely ill or hospitalized patients, and for severely malnourished patients wherein the anabolic effects of insulin are particularly beneficial. In advanced T3cDM, multi-dose basal-bolus insulin dosing and regimens should follow guidelines for the treatment of T1DM, and include carbohydrate counting for flexible prandial coverage and consideration of continuous subcutaneous insulin infusion or “pump” delivery.

In chronic pancreatitis-associated diabetes, when hyperglycemia is mild (HbA_{1c} <8%) oral hypoglycemic agents may be appropriate. When concomitant insulin resistance is suspected or evidenced, therapy with the insulin sensitizer metformin should be considered. Metformin is recommended as first-line oral therapy for T2DM (31), a population in which metformin may reduce the risk of pancreatic cancer, and so has a theoretical rationale in chronic pancreatitis if tolerable due to common gastrointestinal adverse effects and weight loss. Therapy with insulin secretagogues (sulfonylureas and glinides) may also be considered, but because these drugs can cause hypoglycemia, short-acting agents are preferred when meal ingestion is inconsistent. Incretin-based therapies (e.g. GLP-1 analogues and DPP-IV inhibitors) also enhance insulin secretion, but have been associated with cases of drug-induced pancreatitis (2) precluding their use in T3cDM until more data become available.

Total Pancreatectomy with Islet Autotransplantation (TPIAT)

TPIAT is considered as definitive treatment of recurrent acute or chronic pancreatitis for the primary indication of providing pain relief, with hoped for withdrawal of narcotics and amelioration from recurrent hospitalizations to treat pain exacerbations (3). It is important to appreciate that the objective of the islet autotransplant is prevention or amelioration of surgical diabetes, and while the chances of achieving good glycemic control increase with exclusion of pre-existing T3cDM, this procedure does not prevent nor is a treatment for T3cDM. Assessment of pancreatic endocrine reserve, and importantly that of functional β-cell mass, should be performed as part of the evaluation and follow-up for TPIAT (37). Functional β-cell mass can be best estimated clinically from serum C-peptide levels determined during either oral glucose tolerance (34) or mixed-nutrient meal (26) testing. Whether or not patients with pre-existing T3cDM who exhibit preserved β-cell secretory reserve benefit sufficiently from amelioration of post-pancreatectomy diabetes to justify the added risks of islet autotransplantation requires further study.

9. Acknowledgments

This work was supported in part by the Joanne and Raymond Welsh Research Fellowship (L.G.), the Cystic Fibrosis Foundation (M.R.R.), and Public Health Service research grant R01 DK97830 (M.R.R.).

All of the histology slides presented in **Figure 2** are a generous contribution from Dr. Günter Klöppel, Consultant and Professor Emeritus, Department of Pathology, Center for Pancreatic and Endocrine Tumors, Technical University of Munich, Ismaningerstr 22, 81675 Munich, Germany.

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