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Detection, Evaluation and Treatment of Diabetes Mellitus in Chronic Pancreatitis: Recommendations from *PancreasFest 2012*

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Abstract

Description—Diabetes and glucose intolerance are common complications of chronic pancreatitis, yet clinical guidance on their detection, classification, and management is lacking.

Methods—A working group reviewed the medical problems, diagnostic methods, and treatment options for chronic pancreatitis-associated diabetes for a consensus meeting at *PancreasFest 2012*.

Guidance Statement 1.1: Diabetes mellitus is common in chronic pancreatitis. While any patient with chronic pancreatitis should be monitored for development of diabetes, those with long-

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Author Contributions:
Developed the concept and the consensus process: M.A.A., R.E.B, L.F. and D.C.W.
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Participated in discussion of statements, reviewed and approved manuscript: All authors and participants.

standing duration of disease, prior partial pancreatectomy, and early onset of calcific disease may be at higher risk. Those patients developing diabetes mellitus are likely to have co-existing pancreatic exocrine insufficiency.

Guidance Statement 1.2: Diabetes occurring secondary to chronic pancreatitis should be recognized as pancreatogenic diabetes (type 3c diabetes).

Guidance Statement 2.1: The initial evaluation should include fasting glucose and HbA1c. These tests should be repeated annually. Impairment in either fasting glucose or HbA1c requires further evaluation.

Guidance Statement 2.2: Impairment in either fasting glucose or HbA1c should be further evaluated by a standard 75 gram oral glucose tolerance test.

Guidance Statement 2.3: An absent pancreatic polypeptide response to mixed-nutrient ingestion is a specific indicator of type 3c diabetes.

Guidance Statement 2.4: Assessment of pancreatic endocrine reserve, and importantly that of functional beta-cell mass, should be performed as part of the evaluation and follow-up for total pancreatectomy with islet autotransplantation (TPIAT).

Guidance Statement 3: Patients with pancreatic diabetes shall be treated with specifically tailored medical nutrition and pharmacologic therapies.

Conclusions—Physicians should evaluate and treat glucose intolerance in patients with pancreatitis.

Rationale

Chronic pancreatitis is a syndrome of pancreatic inflammation with irreversible parenchymal damage and functional changes that is complicated by progressive nutrient maldigestion, glucose intolerance, diabetes mellitus, and metabolic derangements. The complex timing and interactions between nutrient digestion, absorption, and utilization that are normally regulated by the pancreas are variably disrupted with inflammatory and fibrotic injury. Failure to digest nutrients in the proximal gut may result in impaired incretin secretion and thereby diminished insulin release; loss of islet cell mass further contributes to pancreatic endocrine insufficiency. Destruction of islet cells by pancreatic inflammation differs from that in type 1 diabetes by the loss not only of insulin from islet beta cells but also of glucagon and pancreatic polypeptide from islet alpha and PP cells, which can lead to the development of “brittle” disease with large swings in blood sugar that are difficult to control. In addition, patients may have pre-existing risk factors for type 2 diabetes (e.g. insulin resistance, obesity, or dietary habits) that further complicate the optimal regulation of glucose metabolism. As the islet cell loss distinguishes such pancreatogenic diabetes from type 2 diabetes, the diabetes mellitus resulting from recurrent acute or chronic pancreatitis is classified as pancreatogenic diabetes, also known as type 3c diabetes (1-3). Type 3c diabetes may be present in 5-10% of cases of diabetes mellitus, with over 85% of cases related to chronic pancreatitis (3, 4). Despite the metabolic features and clinical considerations related to type 3c diabetes, this condition is not commonly recognized by physicians (3).

Chronic pancreatitis was considered a disease of alcoholism until the discovery that smoking, complex genetic genotypes, and other factors accounted for the underlying etiology in over half of all cases of this disease. Severe nutritional and metabolic features often seen in patients with recurrent acute and chronic pancreatitis were not always the consequence of alcoholism, as had been previously thought (5, 6). Furthermore, clinicians caring for these patients may not have been trained in screening for glucose intolerance, optimization of incretin release, or the diagnosis and treatment of type 3c diabetes. Finally,

monitoring islet cell mass is important in the event that total pancreatectomy and islet autotransplantation (TPIAP) is considered as a therapeutic option.

Limited guidelines are available for the detection, evaluation, and treatment of diabetes mellitus in patients with chronic pancreatitis. The Italian consensus guidelines for chronic pancreatitis (7) recommend assessing endocrine function via fasting glucose levels and propose that the treatment of pancreatogenic diabetes does not differ from that of type 1 and type 2 diabetes, although a statement was made against a role for oral hypoglycemic agents.

Guideline Focus

The *PancreasFest* working group framed the development of their discussion questions and guidance statements around three areas of concern: 1) the pathophysiology of diabetes mellitus occurring in the setting of chronic pancreatitis; 2) the distinction of pancreatogenic (type 3c) from type 1 and type 2 diabetes; and 3) the evaluation and management of pancreatogenic diabetes in the context of current endocrine practice.

Target Population

The clinical recommendations guide the evaluation and management of diabetes mellitus and glucose intolerance in adult patients with recurrent acute and chronic pancreatitis.

Guideline Development Process

PancreasFest is an annual meeting that brings together physicians and scientists with interests in the pancreas: pancreatologists, endoscopists, surgeons, radiologists, molecular biologists, geneticists, endocrinologists, epidemiologists, statisticians, systems biologists, and experts in biomarkers (typically 150+ attendees).

At *PancreasFest 2009*, an expert working group convened to identify the most important clinical questions related to diabetes mellitus in chronic pancreatitis and prepared state-of-the-art lectures and case studies for presentation at *PancreasFest 2010*. At *PancreasFest 2011*, the group evaluated the current evidence on diagnosis, classification, and treatment options and developed specific discussion questions and guidance statements.

At *PancreasFest* 2012, the final process was guided by Dr. Frulloni based on the Italian Consensus Guidelines for Chronic Pancreatitis (7). Conference attendees (Appendix) responded to the updated discussion questions and guidance statements and indicated their level of agreement based on a 5-point scale (Table 1) using digital voting devices.

Evidence Review and Grading

Methods of developing consensus were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Grid to reach decisions on clinical practice guidelines (8) and the Surviving Sepsis Campaign report (9).

Evidence and Modification

The discussion questions presented to attendees of *PancreasFest 2012* were followed by one or more guidance statements intended to provide a concise summary and, if indicated, a clinical recommendation. Conference attendees discussed the initial questions and guidance statements of the working group, which were projected for the entire conference to see and revise in real-time. The conference participants then voted on the level of agreement with the statements, with the results tabulated and likewise projected for all to see in real-time. If there less than 80% strong agreement the statement was further discussed and modified in

real time. Following the discussion a second (final) vote was taken and the results were again projected. The working group and audience were also invited to identify areas in which there are insufficient data and where further research is recommended.

Clinical Recommendations

Discussion Question 1.1: In chronic pancreatitis, are there specific risk factors for developing diabetes mellitus?

Guidance Statement 1.1—Diabetes mellitus is common in chronic pancreatitis. While any patient with chronic pancreatitis should be monitored for development of diabetes, those with long-standing duration of disease, prior partial pancreatectomy, and early onset of calcific disease may be at higher risk. Those patients developing diabetes mellitus are likely to have co-existing pancreatic exocrine insufficiency.

Level of Agreement: A 58%; B 42%; C 0%; D 0%; E 0%

Evidence—Diabetes mellitus has been observed in 26-80% of patients with chronic pancreatitis, depending on the cohort and duration of follow up (10-12). There is a clear increase in diabetes prevalence with longer duration of disease. Median age of diabetes onset in hereditary pancreatitis ranges from 38-53 years and does not vary by mutation status (11, 12). Risk factors for progression to diabetes mellitus identified in one large cohort of patients with primarily alcohol-related chronic pancreatitis included early onset of pancreatic calcifications and prior distal pancreatectomy (2-3 fold elevated risk) (13). Since type 2 diabetes can co-exist with pancreatic diabetes, canonical risk factors for type 2 diabetes (e.g., family history, overweight/obesity, increasing age and high risk ethnicity) may also play a role in earlier development of diabetes mellitus in chronic pancreatitis.

Diabetes mellitus in chronic pancreatitis occurs due to islet/beta cell loss mediated by fibro-inflammatory destruction of the pancreatic parenchyma. Thus, it is not surprising that pancreatic exocrine and endocrine deficiencies are correlated, with a linear relationship among stimulated protease (chymotrypsin), amylase, and bicarbonate production with basal and stimulated insulin and C-peptide (14, 15). In contrast to other forms of diabetes mellitus, subjects with diabetes due to chronic pancreatitis are highly likely to have abnormal exocrine function on pancreazymin/secretin testing. In one study, nearly all patients with chronic pancreatitis-related diabetes had an abnormal response to exocrine pancreatic function tests (16). Cystic fibrosis-related diabetes is a condition analogous to diabetes due to chronic pancreatitis, in that both disorders result from progressive fibrosis of the pancreas. C-peptide and glucagon secretory responses are impaired in exocrine-insufficient cystic fibrosis patients, compared with those who are exocrine sufficient (17).

Discussion Question 1.2: How should diabetes mellitus in the setting of chronic pancreatitis be classified?

Guidance Statement 1.2—Diabetes occurring secondary to chronic pancreatitis should be recognized as pancreatogenic diabetes (type 3c diabetes).

Level of Agreement: A 44%; B 36%; C 11%; D 3%; E 6%

Evidence—The most common forms of diabetes mellitus in the U.S. are type 2 diabetes (accounting for 90% of diabetic cases) and type 1 diabetes (accounting for ~10% of diabetic cases). Pancreatogenic diabetes, or type 3c diabetes, has traditionally been recognized as a cause in only 0.5% of patients with diabetes, although it has been proposed that up to 8% of diabetes in some centers may be due to pancreatic disease (18). Type 3 diabetes refers to specific types of diabetes other than type 1 or type 2 (19) and is further categorized by the

American Diabetes Association to include diseases of the exocrine pancreas (i.e., type 3c) (2). Because low fecal elastase has been observed in type 1 and type 2 diabetes, the presence of exocrine insufficiency alone may not justify a diagnose pancreatogenic diabetes (18, 20).

However, when diabetes mellitus occurs in patients with an existing diagnosis of chronic pancreatitis, the proper classification in most cases is pancreatogenic diabetes. Positive islet antibodies in a patient with chronic pancreatitis suggest type 1 diabetes, particularly if diabetes onset is in childhood or is associated with severe hyperglycemia and ketosis. Because type 2 diabetes occurs in 8% of the general population, it is possible to have type 2 diabetes superimposed on pancreatogenic diabetes. Unfortunately, current ICD-9 codes do not distinguish pancreatogenic diabetes from other forms of diabetes mellitus — particularly type 2 — which may cause confusion among care providers. Common diabetes mellitus ICD-9 codes include: 250.00 type 2 diabetes; 250.00 diabetes mellitus associated with pancreatic disease; 250.01 type 1 diabetes mellitus; 249.00 secondary diabetes; and 251.3 diabetes mellitus secondary to pancreatectomy.

Discussion Question 2.1: How should patients with chronic pancreatitis be evaluated for increased risk or the presence of diabetes?

Guidance Statement 2.1—The initial evaluation should include fasting glucose and HbA1c. These tests should be repeated annually. Impairment in either fasting glucose or HbA1c requires further evaluation.

Level of Agreement: A 83%; B 14%; C 3%; D 0%; E 0%

Evidence—As defined by the American Diabetes Association (2), impairment in fasting glucose (100-125 mg/dl) or HbA1c (5.7-6.4%) constitutes categories of increased risk for diabetes (pre-diabetes). A fasting glucose ≥ 126 mg/dl or HbA1c ≥ 6.5% may already indicate the presence of diabetes. In the absence of unequivocal hyperglycemia (random glucose ≥ 200 mg/dl), results should be confirmed by repeat testing unless both tests support the diagnosis (Table 2).

Discussion Question 2.2: What further evaluation is recommended when the initial screening tests suggest glucose intolerance?

Guidance Statement 2.2—Impairment in either fasting glucose or HbA1c should be further evaluated by a standard 75 gram oral glucose tolerance test.

Level of Agreement: A 69%; B 19%; C 6%; D 3%; E 3%

Evidence—Serum glucose should be measured after fasting at both one and two hours following glucose ingestion. Per the American Diabetes Association (2), a diagnosis of diabetes mellitus should be made by a two-hour glucose measurement of ≥ 200 mg/dl, and an impaired glucose tolerance is defined by a two-hour glucose of 140-199 mg/dl, which is consistent with pre-diabetes (Table 2). 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 beta cell function in patients with pancreatic disease (21). If insulin resistance associated with type 2 diabetes is suspected, a fasting serum insulin level may be helpful to document hyperinsulinemia.

Discussion Question 2.3: How can diabetes due to chronic pancreatitis be distinguished from type 1 and type 2 diabetes?

Guidance Statement 2.3—An absent pancreatic polypeptide response to mixed-nutrient ingestion is a specific indicator of pancreatogenic diabetes.

Level of Agreement: A 39%; B 33%; C 20%; D 7%; E 2%

Evidence—The presence of islet antibodies (e.g., against glutamine acid decarboxylase, islet cell antigen, or insulin) is consistent with type 1 diabetes, and the presence of clinical or biochemical evidence of insulin resistance (e.g., acanthosis nigricans or hyperinsulinemia) is associated with type 2 diabetes. However, if ambiguity remains, confirmation of pancreatogenic diabetes can be established by measurement of the pancreatic polypeptide (PP) response to insulin-induced hypoglycemia, secretin infusion, or mixed-nutrient ingestion (Table 3). Mixed-nutrient ingestion can be standardized to 12 ounces of Boost® or equivalent and administered with prescribed pancreatic enzymes; definitive criteria for the assessment of the PP response to nutrients have yet to be established, but non-diabetic subjects demonstrate a 4-6 fold increase (basal and stimulated values are elevated in the elderly), whereas patients with severe chronic pancreatitis demonstrate less than a doubling of their low basal values (1). Therefore, an absent PP response distinguishes pancreatogenic from early type 1 diabetes in which PP levels may be elevated (22, 23) and may distinguish pancreatogenic from type 2 diabetes, which is characterized by elevated levels of PP (24, 25). In cystic fibrosis, the PP response to a mixed-nutrient meal (26) and to hypoglycemia (17) is essentially absent in exocrine-insufficient individuals with or without current cystic fibrosis-related diabetes. While this suggests that an absent PP response may be an early marker for endocrine impairment in patients with exocrine insufficiency, it is not yet known if measuring this response leads to earlier identification of impaired glucose homeostasis compared with measures of fasting glucose, HbA1c, and oral glucose tolerance, as discussed above. Both type 1 and type 3c diabetes are associated with insulin deficiency due to beta-cell loss (see Table 3). Although a deficiency in PP responsiveness suggests exocrine pancreatic disease, this conclusion should be supported by other historical and investigative evidence to confirm a diagnosis of type 3c diabetes.

Discussion Question 2.4: When should assessment of pancreatic endocrine reserve be performed in chronic pancreatitis?

Guidance Statement 2.4—Assessment of pancreatic endocrine reserve, and importantly that of functional beta-cell mass, should be performed as part of the evaluation and followup for TPIAT.

Level of Agreement: A 45%; B 20%; C 10%; D 18%; E 8%

Evidence—Functional beta-cell mass can be estimated from serum C-peptide levels determined during either oral glucose tolerance (14) or mixed-nutrient meal testing (Table 3). Beta-cell secretory capacity may be more accurately measured by the insulin or C-peptide response to glucose-potentiated arginine testing (27), but such testing is not routinely available.

Discussion Question 3: What steps should be taken to optimize treatment of diabetes mellitus in patients with chronic pancreatitis?

Guidance Statement 3—Patients with pancreatic diabetes shall be treated with specifically tailored medical nutrition and pharmacologic therapies.

Level of Agreement: A 85%; B 10%; C 3%; D 0%; E 3%

Evidence—In the setting of chronic pancreatitis and diabetes, the primary goals of medical nutrition therapy are to prevent or treat malnutrition, control symptoms of steatorrhea, and minimize meal-induced hyperglycemia. Oral pancreatic enzyme replacement improves fat absorption in patients with pancreatic exocrine insufficiency and can help control symptoms of steatorrhea. However, many patients with chronic pancreatitis manifest some degree of fat malabsorption, regardless of the presence of symptoms. Fecal elastase C-1 levels and

fecal fat collections can confirm the presence of pancreatic exocrine insufficiency (28). In addition, the release of intestinal-derived incretin hormones that augment glucose-dependent insulin secretion is impaired in patients with pancreatic exocrine insufficiency. Replacement with oral pancreatic enzymes restores incretin hormone secretion, which is associated with improved insulin secretion and glucose tolerance during meal ingestion (29, 30). Oral pancreatic enzyme replacement also protects against the loss of fat-soluble vitamins A, D, E, and K. Maintaining vitamin D levels is essential to prevent metabolic bone disease and osteoporosis.

The most common issues with pancreatic enzyme replacement include inappropriate dosing and timing of enzymes, misdistribution of calories across meals, lack of acid suppression therapy, not taking enzymes with snacks, and, less commonly, associated bacterial overgrowth (31-33). A reduction in fat intake may reduce the symptoms of steatorrhea, but the reduction in fat can result in greater carbohydrate intake, which in turn can exacerbate hyperglycemia, necessitating adjustments in diabetes medications. Alcohol abstinence can help with diabetes management, since alcohol temporarily impairs hepatic glucose production and can cause hypoglycemia, especially in the setting of insulin therapy. Alcohol abstinence is particularly important for patients with alcoholic pancreatitis, as alcohol exacerbates the progression of exocrine pancreatic insufficiency and causes pain.

No study has yet compared the long-term relative efficacy and safety of different hypoglycemic agents in chronic pancreatitis. Therefore, therapy is dictated by patient phenotype and an understanding of the pathophysiology of hyperglycemia in chronic pancreatitis. Since the principal endocrine defect is insulin deficiency, insulin therapy is the preferred treatment for most patients. The degree of insulin deficiency varies with disease severity and duration. Controlling mild hyperglycemia with oral hypoglycemic agents early in the disease history may be a valid approach. During acute episodes of pancreatitis, oral agents should be avoided, since they are usually not effective and may be unsafe. In advanced pancreatogenic diabetes, insulin replacement therapy is the only effective treatment option, and patients should be treated using general insulin dosing and regimen guidelines for type 1 diabetes. In pancreatogenic diabetes, blood glucose control may be labile due to loss of the glucagon response to hypoglycemia, carbohydrate malabsorption, and/or inconsistent eating patterns due to pain and/or nausea. Insulin pump therapy should be considered for patients who are sufficiently motivated to provide adequate prandial coverage of multiple small meals.

The American Diabetes Association-European Association for the Study of Diabetes consensus group recommends metformin as a first-line oral therapy for type 2 diabetes because insulin resistance is a prominent feature (34). In diabetes due to chronic pancreatitis, when hyperglycemia is mild (HbA1c < 8.0%) and concomitant insulin resistance is suspected, therapy with the insulin sensitizer metformin should be considered in the absence of contraindications and if tolerated. The main side effects of metformin include nausea, abdominal discomfort, diarrhea, and weight loss (35) — symptoms that patients with chronic pancreatitis are less likely to tolerate. However, observational studies in type 2 diabetes suggest that metformin may confer protection against pancreatic cancer, providing a theoretical rationale for using this drug. Thiazolidinediones also improve insulin sensitivity but are associated with increased risk of fluid retention, congestive heart failure, and fractures (36). The latter is of particular concern, since patients with chronic pancreatitis are at increased risk for osteoporosis. Given that treatment alternatives are available, the use of thiazolidinediones should generally be avoided in pancreatogenic diabetes.

In early diabetes due to chronic pancreatitis (HbA1c < 8.0%), therapy with insulin secretagogues (sulfonylurea and glinides) may also be considered. Because secretagogues

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 require further study. GLP-1 analogues have a high frequency of gastrointestinal side effects (e.g., nausea, delayed gastric emptying, weight loss) (37), symptoms that patients with chronic pancreatitis routinely experience. Both GLP-1 analogues and DPP-IV inhibitors have been associated with cases of drug-induced pancreatitis (38-40). Until more data are available, incretin-based therapies should be avoided in pancreatogenic diabetes.

As with type 1 and type 2 diabetes, those affected with diabetes due to chronic pancreatitis are at risk for microvascular complications (41). Patients should be monitored for the development of retinopathy, nephropathy, and neuropathy using the same guidelines as for patients with type 1 and type 2 diabetes.

Research Recommendations

The systematic review of glucose intolerance and diabetes mellitus in the setting of pancreatitis revealed knowledge gaps in definition and detection (Guidance Statements 1.1 – 1.2), diagnosis (Guidance Statements 2.1 – 2.4), and treatment (Guidance Statement 3). Further research in the following specific areas was recommended to provide stronger levels of evidence in areas of uncertainty or lower levels of agreement.

Guidance Statement 1.1

Further refinement of risk stratification is needed for diabetes that could influence clinical decision making, such as, for example, earlier consideration of TPIAT prior to loss of islet function. Areas for investigation include the molecular genetics of recurrent acute or chronic pancreatitis, their relationship with type 2 diabetes susceptibility alleles, and canonical risk factors for type 2 diabetes.

Guidance Statement 1.2

During the discussion, it was recognized that while pathophysiologic defects that distinguish between pancreatogenic (type 3c), type 1, and type 2 diabetes have been described, further research is needed to determine whether metabolic tests of islet cell hormone secretion and action or other biomarkers can better distinguish among these three forms of diabetes, and whether treatment based on proper classification improves clinical outcomes.

Guidance Statement 2.1

Additional research is needed to determine whether earlier case identification can result in improved long-term glycemic control and a consequent reduction in diabetes-associated complications.

Guidance Statement 2.2

Further research is needed into whether the one-hour glucose level during a standard 75 gram oral glucose tolerance test can improve risk stratification and, if so, using what criteria. In addition, investigation into the potential role for simultaneous measurement of C-peptide and insulin during the oral glucose tolerance in assessing insulin secretion and sensitivity, respectively, is warranted to evaluate the discriminatory value of this test for identifying impaired beta-cell function or insulin resistance.

Guidance Statement 2.3

Further research is needed to better define the PP response compared with measures of fasting glucose, HbA1c, and oral glucose tolerance in the determination of risk for progression to pancreatogenic diabetes.

Guidance Statement 2.4

Future research is needed to determine whether the insulin or C-peptide response to glucose-potentiated arginine testing is predictive of islet yield and metabolic functional outcomes when assessed prior to TPIAT.

Guidance Statement 3

Additional studies should examine the efficacy, safety, and tolerability of metformin compared with sulfonylurea therapy early in the course of pancreatogenic diabetes. Furthermore, studies are needed to evaluate the long-term glycemic control and rate of diabetes-associated complications of early insulin compared with oral therapy for pancreatogenic diabetes.

Summary

These statements represent the most current, clinically relevant recommendations on the evaluation and treatment of glucose intolerance and diabetes mellitus in patients with recurrent acute and chronic pancreatitis. Type 3c pancreatitis may also occur with other disorders such as hemochromatosis and pancreatic cancer, which were not addressed by the working group. There was strong consensus (≥90% agreement, as indicated by A or B in Table 1) that a large portion of patients with chronic pancreatitis are likely to eventually develop diabetes mellitus; that diabetes mellitus often co-exists with exocrine insufficiency; that fasting glucose and HbA1c should be measured annually; that abnormal findings should be further evaluated with a 75 gram oral glucose tolerance test; and that diabetes should be treated with specifically tailored medical nutrition and pharmacologic therapies. There was weaker consensus (<90% but >50% agreement) that diabetes secondary to chronic pancreatitis should be recognized as pancreatogenic diabetes; that absent pancreatic polypeptide responses to mixed nutrient ingestion is a specific indicator of pancratogenic diabetes; and that pancreatic endocrine reserve should be part of the evaluation for TPIAT. No statements received less than 50% agreement.

Taken together, the response to these statements highlight the need to include specific testing for and treatment of diabetes in patients with chronic pancreatitis and that more research and education are needed to provide guidance in addressing pancreatogenic diabetes as distinct from type 1 and type 2 diabetes and in the evaluation of patients who are potential candidates for TPIAT.

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Table 1

Voting Options

For each statement the audience was asked to vote on their level of agreement using the following options:

A:	Strong positive	(definitely)
B:	Weak positive	(probably)
C:	Uncertain or equivocal	(=)
D:	Weak negative	(probably not)
E:	Strong negative	(definitely not)

Table 2

American Diabetes Association criteria for defining increased risk (impaired) and diagnosis of diabetes (2).

	Normal	Impaired[b]	Diabetes[c]
HbA1c (%)	< 5.7	5.7 – 6.4	≥ 6.5
Fasting Glucose (mg/dl)	< 100	100 – 125	≥ 126
2-hour Glucose (mg/dl)[a]	< 140	140 – 199	≥ 200
Random Glucose (mg/dl)			≥ 200[b]

[a] During a 75 gram oral glucose tolerance test.

[b] Any measure of impaired glycemia is consistent with increased risk for diabetes, or prediabetes, although the risk is continuous throughout the ranges becoming disproportionately greater at the higher ends of each range.

[c] Any one measure of diabetic glycemia requires confirmation by repeat testing, unless two or more different measures indicate diabetic glycemia, in which case the diagnosis of diabetes is confirmed.

[d] Sufficient for a diagnosis of diabetes when accompanied by classic symptoms (polyuria and polydipsia) of hyperglycemia.

Table 3

Islet cell hormonal responses to mixed-nutrient meal[a] testing (17, 22, 30)

	Type 1 Diabetes	Type 2 Diabetes	Type 3c Diabetes
C-peptide	Normal[b], low or absent	Elevated[c] or normal[b]	Normal[b], low or absent
Insulin	Normal[b], low or absent	Elevated[c] or normal[b]	Normal[b], low, or absent
Glucagon	Normal[b] or elevated	Normal[b] or elevated	Normal[b], low, or absent
Pancreatic Polypeptide	Normal or low	Normal or elevated	Low or Absent

[a] Can be standardized to 12 ounces of Boost® or equivalent and administered with prescribed pancreatic enzymes.

[b] Values in the normal range are inappropriate in the context of elevated glucose and indicate an impairment in beta-cell mass or function.

[c] Elevated levels were calculated by comparing area under the curve for serum c-peptide and insulin responses to a liquid test meal for cases and controls.