Is Pancreatic Diabetes (Type 3c Diabetes) Underdiagnosed and Misdiagnosed?

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Exocrine pancreatic insufficiency is frequently associated with diabetes, with high prevalence in both insulin-dependent or insulin-independent patients. Exocrine pancreatic failure has often been perceived as a complication of diabetes. In contrast, recent clinical observations lead to the notion that nonendocrine pancreatic disease is a critical factor for development rather than a sequel to diabetes. The incidence of diabetes caused by exocrine pancreatic disease appears to be underestimated and may comprise 8% or more of the general diabetic patient population. Nonendocrine pancreas disease can cause diabetes by multiple mechanisms. Genetic defects have been characterized, resulting in a syndrome of both exocrine and endocrine failure. Regulation of β-cell mass and physiological incretin secretion are directly dependent on normal exocrine function. Algorithms for diagnosis and therapy of diabetes should therefore address both endocrine and exocrine pancreatic function.

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Several pancreatic diseases have been reported as causes of diabetes, with a low incidence of ~0.5–1.15% among all cases of diabetes (1,2). In contrast, exocrine pancreas dysfunction in patients with diabetes has been estimated to be present in up to 50% of subjects in retrospective historical observations in studies with small numbers of patients (3–5). At that time, only invasive diagnostic procedures were available, thus preventing widespread assessment of exocrine pancreas function in patients with diabetes.

Various hypotheses have been put forward to explain the frequent finding of exocrine insufficiency in diabetes: first, dysregulation of exocrine secretion due to diabetic neuropathy (6) and atrophy of exocrine tissue due to lack of local trophic insulin effects (7) or related to local or general vascular damage; second, simultaneous exocrine and endocrine dysfunction as a net result of a common underlying process affecting the whole pancreas, and autoimmune-mediated inflammation induced by the presentation of both β-cell–specific and exocrine tissue antigens (8,9) and genetic defects of exocrine and endocrine cells (10), possibly triggered by previous viral or bacterial infection; and third, a higher prevalence of pancreatic disease with exocrine dysfunction (5) as a cause for diabetes (type 3c in current classifications [11]).

PREVALENCE OF PANCREATIC EXOCRINE INSUFFICIENCY IN PATIENTS WITH DIABETES

In recent years, the evaluation of exocrine pancreatic function has been greatly facilitated by newly available noninvasive stool tests allowing screening of large patient populations. Measurement of fecal elastase-1 concentrations (FECs) by enzyme-linked immunosorbent assay based on monoclonal human specific antibodies has become a standard diagnostic parameter with good correlation to direct tests of pancreatic exocrine function (12) and morphological pancreas alterations (13), albeit limited sensitivity in mild pancreatic exocrine insufficiency.

Exocrine pancreatic function using FEC assessment has been extensively studied in patients with diabetes. Normal exocrine function (FEC >200 μg/g) was observed in ~58% of patients with diabetes (n = 2,001), while pancreatic exocrine insufficiency (pancreatic exocrine insufficiency; FEC <100 μg/g) occurred in 12–20% of patients without insulin therapy, in most cases classified as "type 2," and in 26–44% of patients on subcutaneous insulin therapy, in the majority of cases classified as "type 1" (Table 1) (14–19).

The overall prevalence of ~42% for impaired exocrine pancreatic function in patients with diabetes reported in these studies is in line with previous findings using direct tests of pancreas exocrine function.

MORPHOLOGIC CHANGES OF THE EXOCRINE PANCREAS IN PATIENTS WITH DIABETES

It has been noted that alterations of exocrine pancreatic morphology frequently occur in patients with diabetes. Examinations comprise autopsy studies on macroscopic and histological changes (20–22), ultrasound and computed tomography morphology (23), and imaging of the pancreatic duct system by endoscopic retrograde pancreaticography (24,25). Pathological pancreatic ducts characteristic for chronic pancreatitis (according to the Cambridge classification) have been observed in ~35% of patients previously diagnosed as having type 2 diabetes and up to 50% of patients previously diagnosed as having type 1 diabetes.

Taken together, ~40% of all patients with diabetes show alterations of exocrine pancreatic morphology as well as of exocrine function characteristic for chronic pancreatitis.

PREVALENCE OF PANCREATIC DIABETES: THE RECLASSIFICATION STUDY

The frequent association of exocrine and endocrine pancreas disease is consistent with an increased prevalence of pancreatic diabetes (type 3c). In light of this observation, we recently reclassified all patients with diabetes treated at our hospital during a 1-year period (Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel

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Abbreviations: FEC, fecal elastase-1 concentration; GLP, glucagon-like peptide.

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Table 1—*Prevalence of exocrine pancreatic insufficiency as determined by FEC*

	Diabetes type	Number of subjects	Normal function (FEC >200 μg/g) (%)	Insufficiency (FEC <100 μg/g) (%)
Study	1			
Hardt et al. (14)		39	36	44
Hardt et al. (14)	2	77	64	20
Rathmann et al. (15)	2	544	—	11.9
Icks et al. (16)	1	112	—	25.9
Nunes et al. (17)	—	42	64	—
Hardt et al. (18)	1 + 2	1,015	59.3	22.9
Mancilla et al. (19)	1 + 2	72	67	19
Sum/mean	1 + 2	2,001	58	27

RG, Hardt PD, unpublished data), based on standard classification criteria: type 1 diabetes: presence of autoantibodies, early onset, immediate insulin requirement; type 2 diabetes: absence of autoantibodies, no (or late) insulin requirement, insulin resistance; type 3 diabetes: absence of autoantibodies, and both exocrine pancreatic insufficiency and typical morphologic pathology.

Clinical records of 1,922 patients were retrospectively examined for these criteria. Of these, 157 (8%) were reclassified as diabetes type 3c, 227 (12%) as type 1 diabetes, and 1,538 (80%) as type 2 diabetes.

Distribution of exocrine pancreas disease in this population included chronic pancreatitis (76%), hemochromatosis (8%), pancreatic cancer (9%), cystic fibrosis (4%), and previous pancreatic surgery (3%), which is in accordance with other publications.

The rate of 8% of type 3c diabetes might be underestimated, since FEC tests were available for only 307 of the 1,992 total patients, and both pancreas exocrine insufficiency and morphological alterations were seen in 157 of these 307. It is very likely that additional cases of type 3c diabetes are present in the remaining 1,685 patients, further increasing the true prevalence. If confirmed in prospective studies, this observation would significantly change the current notion of diabetes epidemiology.

HOW CAN TYPE 3C DIABETES BE FREQUENT IF PANCREATIC DISEASES ARE UNCOMMON?

— One main argument against the assumption that type 3c diabetes is a frequent problem is the general belief that diseases of the exocrine pancreas are rather scarce. Clinical studies report an incidence of only 0.2–8 in 1,000 people per year for chronic pancreatitis (27). In contrast, several autopsy studies report a prevalence of chronic pancreatitis in 5.3–13% of 394 and 3,821 people, respectively, in selected autopsies (28,29). Interestingly, the clinical diagnosis of chronic pancreatitis had been made in only a minority of those patients (0.5%), and the prevalence of chronic pancreatitis was much higher in patients with known diabetes (11.2–19%) compared with 5.3–7% in nondiabetic patients. These data underscore a significant underestimation of chronic pancreatitis in current medical practice. This might in part be explained by the fact that diagnostic tools have been invasive in the past and have therefore been restricted to a small patient population. Furthermore, clinical symptoms of chronic pancreatitis are unspecific, particularly in an early stage of the disease. We initiated the first population-based study reporting pancreatic insufficiency in 11.5% (914 subjects, age 50–75 years) (30). This number is in accordance with observations from the autopsy studies cited above.

PANCREAS DEVELOPMENT: TRANSDUCTION AND TRANSDIFFERENTIATION OF ISLET CELLS

— It has been shown that the β-cell mass is not a fixed cell population, but is subject to a permanent reconstitution (31). Increase in β-cell mass can occur through various mechanisms: *1*) increased β-cell replication, *2*) β-cell size increase, *3*) reduced β-cell death rate, and *4*) differentiation from β-cell precursor cells. There is evidence that islet cell formation can originate from ductal epithelial tissue. β-Cell neogenesis from a pancreatic precursor cell pool was found in several models of experimental pancreas lesions (32). In addition, data from animal models suggest transdifferentiation of β-cells from precursor ductal cells. Moreover, soluble growth and regeneration factors (e.g., islet neogenesis-associated protein [INGAP], gastrin, and epithelial growth factor [EGF]) have been shown to (trans)-differentiate β-cells from acinar and ductal pancreatic cells in rodents and humans. Rat and human ductal epithelial cells, possibly containing endocrine pancreatic precursor cells, proliferate and transdifferentiate under specific culture conditions in vitro (33). Similarly, transduction of endocrine transcription factors for β-cell development (e.g., Ngn-3, PDX-1) can drive ductal cells toward β-cell phenotypes (34). Currently, transdifferentiation cannot be dissected from propagation and differentiation of precursors versus dedifferentiation or "lineage switching" from differentiated nonendocrine pancreas cells. However, in light of the association between pancreas exocrine and endocrine deficiency, the concept of "shared injury" and common origin of exocrine and endocrine pancreatic precursor cells deserves greater attention.

DIABETES AND PANCREATIC EXOCRINE DYSFUNCTION DUE TO MUTATIONS IN THE CARBOXYL-ESTER LIPASE

— It has been speculated for several years that genetic factors might contribute to exocrine dysfunction in diabetes. Only recently, a relevant mutation has been uncovered in two Norwegian families with diabetes and exocrine pancreas dysfunction (10). Affected members of this family presented with a type of diabetes characterized by primary β-cell failure and simultaneous pancreatic exocrine dysfunction. Genomic screening has linked diabetes to chromosome 9q34. Using fecal elastase deficiency as a marker of pancreatic exocrine dysfunction further refined the critical chromosomal region to 1.16 Mb. A heterozygous frame-shift mutation was identified in exon 11 of the carboxyl-ester lipase (CEL) gene. This enzyme is a major component of pancreatic juice and is responsible for the duodenal hydrolysis of cholesterol esters and other complex lipids. The in vitro catalytic activities of wild-type and mutant carboxyl-ester lipases were similar. In contrast, the mutant enzyme was significantly less stable compared with wild-type CEL. A

polygenic role for this region is likely, since common insertions were associated with exocrine dysfunction in other diabetic patients. To further explore early pathological events in this condition, radiological examinations of the pancreas were performed in nondiabetic children carrying genetic mutations with signs of exocrine dysfunction. Development of diabetes was preceded by pancreas lipomatosis. These findings link diabetes to the disrupted function of a lipase in the pancreatic acinar cells and imply that fatty replacement of the normal pancreas structure contributes to development of pancreatic disease development. A number of studies have been initiated to further investigate the quantitative relevance of this genetic mutation.

THE ROLE OF INCRETIN HORMONES

— The gut hormones glucose-dependent insulinotrophic polypeptide (GIP) and glucagon-like peptide (GLP)-1 are secreted in response to nutrient digestion and absorption. GIP is known to stimulate insulin secretion and to retard gastric emptying. GLP-1 stimulates insulin and suppresses glucagon secretion, reduces appetite, and likewise decelerates gastric emptying (35,36). Furthermore, it was shown to stimulate β-cell neogenesis, growth, and differentiation in rodents and tissue culture and to inhibit β-cell apoptosis in vitro. GLP-1 can normalize plasma glucose levels in type 2 diabetes. The hormone is rapidly inactivated by proteolysis (dipeptidyl peptidase IV [DPP IV]) and eliminated through the kidney. Therefore, agents interacting with GLP-1 receptors either found in nature or developed by intentional modification of GLP-1 as "incretin mimetics" have been developed as antidiabetic agents (37). It is currently unclear whether long-term use of such agents will prevent or slow down the continuous decline in β-cell function and mass associated with progression of type 2 diabetes. Animal experiments show an increase in β-cell mass within weeks of treatment with dipeptidyl peptidase IV inhibitors and enhanced β-cell preservation (38).

CLINICAL CONSEQUENCES OF EXOCRINE PANCREATIC INSUFFICIENCY IN PATIENTS WITH DIABETES

— Chronic pancreatitis without major clinical symptoms is present in a high percentage of patients with diabetes. Contrary to common belief, that chronic pancreatitis in these patients is generally alcohol induced, we suggest other critical factors be considered, such as genetic changes (10), autoimmunity toward exocrine antigens (8,9), and chronic inflammation associated with gallstone disease and consequent obstructive pancreatitis (39,40). There is clearly a lack of prospective studies to characterize the pathophysiological relevance of these conditions. To prevent progression of chronic pancreatitis to overt exocrine and endocrine function, screening programs to detect pancreas disease at an early stage should be considered.

Patients with diabetes and pancreatic exocrine insufficiency as measured by FEC develop overt steatorrhea in ~60% of the cases (41). Even in patients considered to have normal exocrine function by FEC, steatorrhea can sometimes be present (42). Fecal fat excretion is of high relevance for clinical symptoms (meteorism, abdominal pain, diarrhea) and qualitative or even quantitative malnutrition (e.g., deficiency of fat-soluble vitamins).

In patients with diabetes and pancreatic exocrine insufficiency, meteorism and stool texture correlate with steatorrhea, whereas abdominal pain and stool frequency do not. In an intervention study using exocrine pancreatic enzyme replacement therapy, steatorrhea was reverted, while no statistically significant effect on gastrointestinal symptoms was detected (Hardt PD, Hauenchild A, Jaeger C, Teichmann J, Bretzel RG, Kloer HU, unpublished data).

To date, there is only limited information available on the impact of chronic pancreatitis on qualitative malnutrition. High rates of exocrine pancreas dysfunction have been reported in patients with osteoporosis and vitamin D deficiency (43). However, in another study in diabetic patients with reduced FEC, levels of fat-soluble vitamins remained within normal levels during a 16-week follow-up in both enzyme replacement and placebo group (43a).

The influence of pancreas enzyme replacement therapy on glucose metabolism in insulin-treated patients with exocrine insufficiency remains controversial. Whereas improved blood glucose control and reduced A1C were reported in one study (44), others found no effect (45,46).

In addition, chronic pancreatitis and exocrine dysfunction have been associated with impairments of the incretin system. It has been previously demonstrated that glucose-dependent insulinotrophic polypeptide secretion is reduced in patients with steatorrhea due to alcoholic pancreatitis and can be normalized by enzyme replacement therapy (47). To our knowledge, no studies have been performed on the effect of exocrine pancreas enzyme substitution on incretin function in patients with chronic pancreatitis and type 3c diabetes.

CONCLUSIONS

— Pancreatic exocrine insufficiency, as determined by both direct and indirect function tests, is very frequent in patients with diabetes and is often associated with steatorrhea. It not only affects patients with type 1 diabetes (up to 50%), but is also observed in type 2 diabetic patients. In addition to impaired exocrine function, pancreatic morphological changes are present in up to 40% of the cases. Several hypotheses have been generated to interpret these findings and are consistent with the explanation that type 3c diabetes is indeed more common than previously believed. It might affect at least 8% of all patients with diabetes. Of particular interest is the presence of genetic mutations that can induce both exocrine and endocrine failure, which has recently been demonstrated for the CEL gene. Furthermore, it has been suggested that β-cell regeneration is disturbed in pancreatic diseases, which could explain reduced β-cell mass and diabetes in chronic pancreatitis. Incretin secretion is impaired in steatorrhea, since the extent of incretin secretion depends on regular digestion of nutrients. The implications of the above-described findings deserve more attention, since they are likely to change the clinical workup of patients with diabetes or impaired glucose tolerance and could change the current paradigm of diabetes epidemiology. Diagnostic and screening strategies must be adapted to detect exocrine diseases at earlier stages and possibly to stop progression to overt exocrine and endocrine pancreas insufficiency. In patients with steatorrhea, pancreatic enzyme replacement therapy is warranted for treating symptoms and preventing qualitative malnutrition. Furthermore, it seems very likely that pancreatic enzyme replacement therapy will augment incretin secretion and thus become a valuable treatment modality.

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