

Alterations in Exocrine Pancreatic Function in Diabetes Mellitus

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1. Introduction

Despite being described anatomically almost 2,000 years ago the physiological function of the pancreas and its role in diseases remained more or less unknown until the 19th century. Performing pancreatectomies in dogs, *von Mehring* and *Minkowski* realised that the animals developed diabetes that could be cured by pancreas transplantation (26). Ever since these studies it has been accepted that pancreatic diseases or diseases involving the exocrine pancreas can induce diabetes mellitus. The American Diabetes Association (ADA) diabetes classification published in 1998 therefore includes pancreatic diabetes as “type 3c” that can be caused by pancreatic neoplasms, acute or chronic pancreatitis, hemochromatosis, cystic fibrosis or pancreatic surgery (37). When the role of insulin was established in the early 20st century, physicians were aware that patients with diabetes mellitus – most of them having type 1 diabetes at the time – also suffered from malnutrition. While prior to the discovery of insulin this malnutrition was a consequence of failure of nutrient storage rather than digestion, physicians nonetheless suspected that the digestive function of the pancreas might be reduced in patients with diabetes mellitus and several groups started to investigate exocrine pancreatic function in

diabetes mellitus once pancreatic function tests became available.

2. Studies of Exocrine Pancreatic Function in Diabetes Mellitus

Direct function tests

The first exocrine pancreatic function tests available in specialized centres were direct function tests using cholecystokinin (CCK) and/or secretin stimulation to measure pancreatic enzyme output in duodenal juice. Despite being rather invasive and complicated, these tests remained the gold standard for scientific evaluation of exocrine pancreatic function until today. *Pollard et al.* reported as early as 1943 that the secretin stimulated lipase and amylase output in a small series of patients with diabetes mellitus was reduced in 62% of all cases (31). Several studies in the 1970s and up to today reported similar findings (**Table 1**). On average, pancreatic exocrine insufficiency (PEI) was described in 67% of the patients investigated with direct function tests, most of them being classified as insulin dependent diabetes mellitus (“IDDM”) or type 1 diabetes where absolute insulin deficiency leads to pancreas gland atrophy.

Table 1: Overview of studies assessing exocrine pancreatic function in diabetes mellitus by direct function tests.

Author	Year	Subjects	Methods	Results
Pollard H et al. (31)	1943	13	Amylase and lipase after pancreozymin-secretin stimulation	62% reduced
Chey WY et al. (5)	1963	50 diabetic patients; 13 juvenile type	Amylase and lipase after pancreozymin-secretin stimulation	Low amylase output in diabetes 36%; In juvenile diabetes : 77%
Vacca JB et al. (38)	1964	55 diabetic patients (22 insulin treated)	Diastase and bicarbonate after secretin stimulation; fecal fat	73% abnormal
Frier BM et al. (10)	1976	20 IDDM, 7 NIDDM, 13 controls	Stimulation with iv secretin and CCK-PZ	PEI: 80% IDDM
Harano Y et al. (12)	1978	53 NIDDM, 4 IDDM, 18 controls	Secretin-pancreozymin test	Diabetes: 69% deficient enzyme output
Lankisch PG et al. (22)	1982	53 IDDM	Secretin-pancreozymin test	43% impaired function
Bretzke G et al. (3)	1984	60 insulin-treated type 2 diabetic patients	Secretin-pancreozymin test	„mild PEI“ in 27%
EiNehwihi H et al. (7)	1988	10 type 2 diabetic patients with diarrhea and neuropathy	Secretin and CCK test	Enzyme and bicarbonate reduction in all subjects
Semakula C et al. (34)	1996	307 IDDM, 303 non-diabetic siblings, 207 controls	Serum amylase and lipase	Reduced enzyme levels in 18% IDDM, 6% siblings and 2% controls

Indirect function tests

Later on, when indirect function tests became available, fecal chymotrypsin activity and fecal elastase 1 concentrations (FEC) were used to measure exocrine pancreatic function. Since these tests did not depend on specialized centers, it was possible to involve larger series of patients with diabetes mellitus. The largest trial was carried out as a multi-center trial in Germany and included 323 patients classified as “type 1 diabetes mellitus” and 697 patients classified as “type 2” diabetes mellitus. The prevalence of exocrine pancreatic insufficiency (FEC < 200

µg/g) was reported to be 51% and 35% respectively (15). Other studies reported very similar results – an overview of the available studies is given in **Table 2**. While the relevance of these findings is still under debate, it can be summarized that the coincidence of exocrine and endocrine pancreatic insufficiency has been accepted to be very frequent. Furthermore it has been shown in autopsy studies and imaging studies that pancreas anatomy frequently shows alterations in patients with diabetes mellitus (16).

Table 2: Overview of studies assessing exocrine pancreatic function in diabetes mellitus by indirect function tests

Author	Year	Subjects	Methods	Results
Hardt PD et al. (17)	2000	39 type 1	Fecal elastase 1	74% < 200 µg/g
		77 type 2	Fecal elastase 1	36% < 200 µg/g
Icks A et al. (18)	2001	112 type 1	Fecal elastase 1	54,5% < 200 µg/g
Rathmann W et al. (32)	2001	544 type 2	Fecal elastase 1	30,3% < 200 µg/g
Hardt PD et al. (15)	2003	323 type 1	Fecal elastase 1	51% < 200 µg/g
		697 type 2	Fecal elastase 1	35% < 200 µg/g
Nunes AC et al. (28)	2003	42 type 1+2	Fecal elastase 1	36% < 200 µg/g
Yilmaztepe A et al. (41)	2005	32 type 2	Fecal elastase 1	28% < 200 µg/g
Cavalot F et al. (4)	2006	66 type 1	Fecal elastase 1	26% < 200 µg/g
Mancilla AC et al. (24)	2006	67 type 2	Fecal elastase	33% < 200 µg/g
Larger E et al. (23)	2012	195 type 1	Fecal elastase 1	34% < 200 µg/g
			Fecal chymotrypsin	39% < 6 U/g
		472 type 2	Fecal elastase 1	20% < 200 µg/g
			Fecal chymotrypsin	20% < 6 U/g
Vujasinovic M et al. (39)	2013	50 type 1	Fecal elastase 1	6% < 200 µg/g
		150 type 2	Fecal elastase 1	5% < 200 µg/g
Terzin V et al. (36)	2014	101 type 2	Fecal elastase 1	17% < 200 µg/g

Several national and international associations have discussed and published special considerations concerning exocrine insufficiency in diabetes mellitus and type 3c diabetes mellitus (1, 13, 33, 40).

3. Fat Excretion in Diabetes Mellitus

Fat digestion in patients with diabetes mellitus and low fecal elastase 1 levels have been studied by at least two different centers. *Hardt et al.* reported that about 60% of the patients (type 1 or type 2) with FEC < 100 µg/g had steatorrhea (14) and *Cavalot et al.* reported that 29% of type 1 patients had steatorrhea. In this study there was a significant inverse correlation between FEC and the amount of fat excretion (4). Despite this surprising finding (steatorrhea is believed to exist only if pancreatic lipase secretion is below 10% of normal activity) it did not receive much attention.

This neglect might be explained by the fact that most diabetic patients do not report classical symptoms of exocrine insufficiency – unless they are asked about it. If asked, they report a slightly increased number of stools, bloating and loose stools as compared to patients without PEI. Major pain episodes are rare.

4. Pathophysiological Concepts

A number of different pathophysiological concepts that try to explain pancreatic exocrine insufficiency in diabetes mellitus have been discussed in the past (1):

- A lack of local insulin levels (as in type 1 diabetes) might cause an atrophy of acinar tissue since insulin is a relevant local trophic factor (insulin-acinar portal system)

- Regulatory functions of other islet hormones on exocrine tissue might be impaired in diabetes mellitus or suppress exocrine function (glucagon, pancreatic polypeptide, somatostatin etc.)
- Diabetic autonomic neuropathy may cause problems in the enteropancreatic interaction and may result in exocrine pancreatic dysfunction
- Diabetic angiopathy may cause pancreatic fibrosis and atrophy
- Simultaneous damage of exocrine and endocrine pancreatic tissue may result from:
 - infections (e.g. viral infections)
 - autoimmunity (e.g. autoimmune pancreatitis)
 - genetic mutations (e.g. CEL mutation)
- Pancreatic diabetes (type 3c) might be more common than previously believed
- Beta-cell regeneration from exocrine and ductal tissue might be altered in pancreatic diseases
- Inflammatory alterations and/or altered cytokine expression (e.g. TGF β 1, TGF α , TNF α , etc.) in metabolic syndrome and obesity may lead to the described comorbidity

When taking into consideration that in most studies the finding of PEI did not depend on the duration of diabetes mellitus, it seems rather unlikely that PEI is a complication of diabetes mellitus. There are other findings – e.g. some type 1 diabetes patients do not suffer from PEI despite complete lack of local insulin – suggesting that type 3c diabetes might be underdiagnosed and much more frequent than previously believed (9).

5. Clinical Relevance

The clinical relevance of PEI in diabetes mellitus is still under debate. Nevertheless, the high prevalence of coexisting pathological findings in endocrine and exocrine pancreas has stimulated several national and international expert committees to discuss and publish guidelines on PEI in diabetes mellitus and diagnosis and management of diabetes mellitus in pancreatic diseases. These guidelines try to summarize the current knowledge. So far, they have proposed the evaluation of exocrine function in patients with known diabetes mellitus and symptoms suggestive of PEI. Furthermore treatment of PEI, if present, is suggested. However, before reasonable advice can be given, there is still need for prospective trials to determine the true prevalence of type 3c diabetes mellitus and its clinical relevance.

Impact on qualitative nutrition

The maldigestion due to PEI can lead to a relevant qualitative malnutrition concerning e.g. the absorption of fat-soluble vitamins (A, D, E, and K), especially vitamin D. A significant correlation of low fecal elastase 1 levels and low vitamin D levels has been demonstrated e.g. in osteoporosis and alterations of bone metabolism have been shown in patients with PEI (25, 35). A recent German study of 248 patients with PEI due to different reasons (e.g. chronic pancreatitis, pancreatic carcinoma, etc.) showed vitamin D deficiency in 93% of those patients. Supplementation with high doses of vitamin D resulted in normalization of serum concentrations (19). Considering the important role of vitamin D in the regulation of the immune system, the possible role of vitamin D deficiency in the pathogenesis of type 1 diabetes and the highly interesting association of low vitamin D levels and poor glycemic control, qualitative malnutrition of vitamin D in patients with PEI and diabetes mellitus may be of great clinical importance. Measuring serum 25-hydroxyvitamin D levels and

supplementing patients with low levels should therefore be considered in these patients. However, up to date randomized, controlled trials are still missing and are strongly encouraged.

Impact on glycemic control

Since the secretion of incretins (regarded as a major factor regulating insulin secretion and action) largely depends on normal fat and protein digestion, PEI might play a critical role in quite a number of patients. As early as in 1980, exocrine pancreatic insufficiency has been shown to prevent the normal release of GIP in response to oral feeding and that this effect can be abolished by enzyme replacement therapy (6). Other recent studies emphasize the important role of unimpaired fat hydrolysis in regulating GLP-1 secretion (2) and document a reversal of impaired GLP-1 secretion by pancreatic enzyme supplementation in patients with exocrine pancreatic insufficiency due to cystic fibrosis (21).

Since the incretin axis has become a major target in modern diabetology, it is of utmost importance to learn about the clinical implications of exocrine pancreatic insufficiency in diabetic patients.

However, there are hardly any studies addressing the impact of PEI on glycemic control in diabetes mellitus. This is rather astonishing considering the fact, that due to the above described reasons one would expect a rather important impact of restoring proper fat digestion in those patients.

Most studies address glycemic control in patients with type 3c diabetes mellitus due to chronic pancreatitis or cystic fibrosis (11, 27, 29, 30). Even those studies show very inconsistent results. Some report more stable glucose control, some less stable control, and some no impact of enzyme replacement therapy on glycemic control. To our knowledge there is only one study so far addressing the impact of pancreatic enzyme replacement therapy on glycemic control in patients with diabetes mellitus and PEI. In this multicenter study no positive effect on HbA1c, C-peptide levels or blood glucose levels could be

found. There was a slight trend towards fewer hypoglycemic episodes in the pancreatic enzyme treated group, yet it was not statistically significant (8). Yet, taking a closer look at the study, one must admit that it bears several flaws. The study included insulin dependent diabetes mellitus patients and did not differentiate between type 1, type 2 or type 3c diabetes mellitus. Furthermore the follow up of 16 weeks was rather short.

Several studies describe a major impact of an adequately restored fat digestion on incretin action and therefore on glycemic control (2, 6, 20, 21). Thus, a well-designed randomized controlled trial on pancreatic enzyme replacement therapy in patients with diabetes mellitus and PEI is urgently needed. One might speculate that pancreatic enzyme replacement therapy would be a beneficial therapeutic option concerning glucose control.

6. Summary

It is evident that there is a frequent comorbidity of endocrine and exocrine pancreatic pathology. Alterations in exocrine pancreatic function in diabetes mellitus can be found quite frequently. Although there are many interesting pathophysiological concepts trying to explain those consistent findings, none of the raised hypotheses have been proven so far. Probably several of the described pathophysiological hypotheses contribute to the phenomenon to a certain degree.

The relevance of the finding of a frequent comorbidity of exocrine and endocrine pancreatic disease is still under controversial debate. Unfortunately randomized controlled trials are very rare in this research area. A very interesting field might be the qualitative malnutrition (e.g. vitamin D, lipid digestion) in these patients and the impact it might have on diabetes mellitus. Furthermore the impact of fat and protein maldigestion (and therefore impaired incretin secretion) on glycemic control is unclear due to the lack of larger clinical studies.

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