

REVIEW ARTICLE

Exocrine Pancreatic Insufficiency and Diabetes Mellitus

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ABSTRACT

Gastrointestinal symptoms are common in patients with diabetes mellitus. One possible cause for these symptoms is exocrine pancreatic insufficiency, and although several hypotheses have been proposed to explain the aetiology, the precise pathophysiological mechanisms remain to be elucidated. The prevalence and the clinical importance of exocrine pancreatic insufficiency are debatable. Exocrine pancreatic insufficiency has been confirmed in insulin-dependent and non-insulin-dependent diabetes mellitus and might be related to diabetes mellitus duration. Considering the limitations of the tests, the test and patient selections in different studies have undoubtedly contributed to these conflicting results. Other likely causes are the underestimation of chronic pancreatitis and unrecognised pancreatogenic diabetes (type 3c diabetes mellitus). Because many studies have failed to relate the clinical symptoms of exocrine pancreatic insufficiency to a positive function test (e.g., faecal elastase-1 concentrations), and serum nutritional markers (as signs of malabsorption) were not been determined in all studies, the clinical importance of exocrine pancreatic insufficiency in patients with diabetes mellitus is also controversial. This review presents a critical analysis of the currently published literature on this topic, including the detailed limitations of the specific tests used to confirm exocrine pancreatic insufficiency.

INTRODUCTION

In a large population-based study of upper and lower gastrointestinal symptoms, 40.4% of adult patients with diabetes mellitus (DM) reported having at least one disturbing gastrointestinal symptom (this rate is 33.5% in the corresponding general non-diabetic population) [1]. These symptoms are primarily attributed to irreversible autonomic neuropathy, but studies have demonstrated that this is unlikely to be the only factor. Other possibilities include poor glycaemic control, metabolic derangements secondary to diabetes and exocrine pancreatic insufficiency (EPI), regardless of whether these symptoms are complication or causes of DM [1, 2, 3, 4, 5, 6, 7, 8, 9]. The relationship between EPI and DM is debatable, and the evidence base for a clinical approach in patients with DM needs to be determined.

This review presents a critical analysis of the currently published literature on this topic, including the detailed limitations of the specific tests used to confirm EPI.

METHODS

Search Strategy and Study Selection

We devised a search strategy to identify all published literature on this topic that involved browsing the Medline, Scopus and Embase databases until December 30th 2015 with the aid of the personnel of the University of Ljubljana Central Medical Library. The search strategy included the following key words: exocrine, pancreatic, insufficiency, diabetes, and mellitus. The search was limited to publications in English. The references of the selected studies were also analysed for other relevant articles. The main output was EPI prevalence and its clinical importance in patients with DM.

Data Extraction and Analysis

The authors independently read all of the available articles and abstracts and obtained and pooled the appropriate data. For each eligible study, the following data were extracted: (1) year of publication, (2) country, (3) number of participating centres, (4) methods used to diagnose EPI, (5) number of patients included, (6) patient age, (7) patient gender, (8) EPI prevalence, and (9) the presence of malabsorption and/or other clinical symptoms in patients with EPI.

Search Results

There were 63 papers identified on database searching. Forty-nine papers were excluded due to being review

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Keywords Diabetes Mellitus Exocrine; Pancreatic Function Tests; Pancreatic Insufficiency; Pancreatitis, Chronic

Abbreviations DM diabetes mellitus; EPI exocrine pancreatic insufficiency

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articles and case reports or not being in English language. The final analysis included 14 studies with 3114 patients included. The characteristics of the selected studies and patients are presented in Tables 1 and 2, respectively.

DISCUSSION

The data on EPI prevalence in DM are conflicting, and estimates range from 5 to 100% (Table 1). In general, studies have demonstrated at least some degree of exocrine pancreatic functional impairment in these patients. These impairments range from subclinical exocrine pancreatic dysfunction (disturbances in external secretory function without clinical evidence of disease of the exocrine pancreas) [3, 6, 10] to clinically important EPI [2, 4, 6, 11, 12, 13]. Although subtle changes in exocrine function can be detected in patients with early pancreatic disease, overt steatorrhea does not occur until approximately 90 per cent of the glandular function has been lost [14]. Therefore, it seems logical to expect some degree of correlation with insulin-dependent DM, and most studies have indeed shown impaired exocrine pancreatic function in insulin-dependent DM [5, 6, 7, 8, 13, 15, 16, 17, 18, 19, 20, 21, 22]. Such impairments have also been confirmed in non-insulin-dependent DM [20, 21, 22, 23]. Because DM is a progressive disease, one would similarly expect some degree of correlation with DM duration (at least in type 2 DM), but study data on this subject varies and have confirmed DM duration-independent [13, 18, 19, 24] and -dependent disease [6, 8].

Therefore, several hypotheses have been proposed to explain the aetiology of EPI in patients with DM (regardless of the type of DM):

- a) The lack of insulin (which has a trophic effect on pancreatic acinar tissue) causes pancreatic atrophy [25],
- b) Langerhans islet hormones (which are impaired in DM) have regulatory functions on the exocrine tissue, and this tissue is thus also impaired [26],

- c) Autonomic neuropathy leads to impaired enteropancreatic reflexes and thus to EPI [2],
- d) Diabetic angiopathy causes arterial lesions that lead to pancreatic fibrosis and exocrine atrophy [27, 28],
- e) Elevated contra-insulatory hormones (e.g., glucagon and somatostatin) cause pancreatic atrophy [29, 30, 31, 32],
- f) Diabetic acidosis induces mild pancreatitis [33],
- g) The exocrine and the endocrine function of the pancreas might be affected by a common immunological process [34].

Numerous studies have provided support for at least one of these hypotheses, but none have provided a satisfactory explanation of the majority of EPI cases. Not all insulin-dependent DM patients suffer from EPI; thus, the lack of insulin cannot be the only cause. Because EPI has been found to occur independently of DM duration, diabetic angiopathy and neuropathy (the latter two are chronic microvascular complications of DM), these are also unlikely to be leading causes. These conclusions are also supported by a summary of the morphological data that have been gathered via pancreatic imaging [2, 3, 4, 15, 18]. In recent years, a growing body of data has suggested that primary injuries to the exocrine pancreas lead to subsequent pancreatogenic DM, and this topic will be discussed later [35, 36, 37].

It has been hypothesized that pancreatic steatosis may play an important role in patients with type 2 DM due to the damage of the islet pancreatic cells [38]. That hypothesis was not confirmed in study on 101 patients with type 2 DM in whom abdominal ultrasound (US) and computed tomography (CT) were performed to detect the morphological features of pancreas [24]. There was no correlation between the occurrence of pancreatic steatosis nor pancreatic atrophy and a decreased faecal elastase-1 (FE1) level.

Table 1. Characteristics of the included studies.

Study	Year	Country	Number of Participating Centres	Method Used To Diagnose EPI	Prevalence of EPI (%)
Chey [11]	1963	USA	1	secretin-pancreozymin test	37.5
Lankisch [16]	1982	Germany	1	secretin-pancreozymin test	43
el Newihi [2]	1988	USA	1	secretin and cholecystokinin test	100 (in all patients enzyme and bicarbonate reductions were found)
Hardt [4]	2000	Germany	1	faecal elastase 1	56.7 in type 1 DM 35.0 in type 2 DM
Icks [12]	2001	Germany	3	faecal elastase 1	45.5
Rathmann [21]	2001	Germany England	41 general practices	faecal elastase 1	30.3
Hardt [5]	2003	Germany	10	faecal elastase 1	51.1 in type 1 DM 35.4 in type 2 DM
Nunes [23]	2003	Portugal	1	faecal elastase 1	36
Cavalot [6]	2004	Italy	1	faecal elastase 1	56.7
Yilmaztepe [19]	2005	Turkey	1	faecal elastase 1	28.1
Larger [22]	2012	France	1	faecal elastase 1 and chymotrypsin	34-39% in type 1 DM 20% in type 2 DM
Vujasinovic [13]	2013	Slovenia	1	faecal elastase 1	5.4
Terzin [24]	2014	Hungary	1	faecal elastase 1	16.8
Shivaprasad [65]	2015	India	2	faecal elastase 1	31.4 in type 1 DM 29.4 in type 2 DM

Assuming there is a common underlying mechanism, it will be difficult to definitively identify because there are over 20 tests that are used to assess pancreatic exocrine function. Moreover, only a few of these tests are clinically available [39], and each has specific limitations. Together, these factors lead to variable diagnostic confirmation. In the last 20 years, non-invasive methods have become gold standards for EPI detection. The commonly used exocrine pancreatic function tests (PFT) tests are presented below.

Direct pancreatic function tests (DPFTs) involve the collection and analysis duodenal fluid after the administration of a meal (Lund test) or hormonal secretagogues (cholecystokinin and secretin). The identity of the test that offers the best sensitivity for the detection of early pancreatic functional impairment remains unknown [40, 41, 42]. DPFTs are performed in only a few specialised centres due to their invasiveness, expense and requirements for special technical equipment trained personal [39].

Faecal fat quantification is still considered to be the gold standard for the diagnosis of EPI but has many disadvantages that limit its clinical applicability (e.g., the collection of stool over 3 days is required, which is unpleasant and cumbersome for patients and laboratory staff) [43].

Indirect pancreatic function tests (IPFTs) measure the consequences of EPI that result from a lack of enzymes [39, 42]. FE1 and chymotrypsin were used in the first IPFT studies. Using direct pancreatic function tests as reference standards, FE1 has approximately 100% sensitivity for severe, 77-100% for moderate and 0-63% sensitively for mild EPI with approximately 93% specificity. These studies also suggest the greater sensitivity and specificity of FE1 compared to faecal chymotrypsin [44, 45, 46, 47]. IPFTs are very simple, easier to perform and less expensive than DPFTs. The measurement of FE1 is currently the preferred PFT and can be recommended as the first step in pancreatic function diagnostics [48]. The ¹³C-mixed triglyceride (C-MTG) breath test is a simple and accurate non-invasive oral method for detecting EPI and is easily applicable in clinical routines. This test is not only useful for detecting EPI but also for controlling the efficacy of therapy in these patients [43]. Unfortunately, the ¹³C-MTG breath test remains unavailable in many countries, and the costs of the substrates, the high time expenditure and the lack of standardisation continue to limit the clinical utilisation of this test [49].

Secretin-enhanced diffusion-weighted magnetic resonance cholangiopancreatography imaging (sMRCP) might also be used to quantify pancreatic exocrine function [50]. The duodenal filling evaluated with sMRI is significantly reduced in patients with EPI compared to the healthy population and correlates with the measurements of direct intubation tests [51]. The main advantage of sMRCP over other function tests is that it is a non-invasive technique (with the exception of the need to administer intravenous secretin) that provides both functional and

morphological dynamic information [43]. Quantification of exocrine function was reviewed in many studies and the results were well correlated with severity of pancreatitis [52, 53].

Considering the variations and limitations of all mentioned tests, test selection has undoubtedly contributed to the variations in the EPI prevalence results. Another likely cause of this variation is the underestimation of DM secondary to pancreatic diseases, which is classified as type 3c DM (T3cDM) in the current classification of DM and accounts for 5-10% of the Western diabetic population [35, 54, 55]. Data has shown that nearly half of T3cDM patients are misdiagnosed as type 1 or type 2 DM. The most common cause of T3cDM is chronic pancreatitis (CP), which is found in 78.5% of T3cDM cases [35, 36, 37]. In the majority of studies on this topic CP was not excluded by radiologic or endoscopic testing because T3cDM diagnosis in general clinical practice is primarily based on the particular clinical and laboratory features of T3cDM that differ from other types of DM. A body mass index <25 kg/m² or the absence of a family history of diabetes might rise the suspicion of T3cDM. Clinical features, such as "brittle diabetes" due to problems with hypoglycaemia [56, 57] and serologic markers (e.g., postprandial pancreatic polypeptide deficiency) [56] also seem useful. Factors that influence the risk of type 2 DM can also impact the occurrence of type 3cDM in CP and both, type 2 DM and type 3cDM can co-exist [58]. Unfortunately, most studies on the risk of DM in CP do not discern the type of DM [35]. The proper diagnosis of type 3cDM and distinction from other forms of DM is a big challenge for the clinicians. Absence of pancreatic polypeptide response to mix-nutrition ingestion seems to be specific diagnostic criteria of type 3cDM [58].

Furthermore, there is another connection between CP and DM - both are risk factors for the development of pancreatic cancer (PC). Their combined presence increases the risk for the disease by 33-fold. New-onset T3cDM occurs in 30% of PC patients [55]. Completing the circle, PC can hinder pancreatic exocrine secretions from reaching the gut by obstructing the pancreatic duct and thus cause EPI [59]. Notably, the treatment for T3cDM should differ from that for other types of DM because insulin, insulin secretagogues and incretin-based treatments should be used with caution due to the high risk of PC [55, 58, 60, 61, 62, 63]. Metformin should be the drug of choice due to its anti-diabetic and anti-neoplastic actions [55, 58, 60, 63, 64]. PC should always be tested, searched for and excluded in these patients.

On the other hand, incretin based treatment could prevent or slow-down the decline in β -cell function and mass associated with progression of type 2 DM as suggested by animal experiments [66]. The incretins, gut-derived peptide hormones, released soon after lipid and carbohydrate ingestion, stimulate insulin production - the incretine effect [67]. Deregulation of this secretion affects altered insulin response in type 2 DM [68]. Malabsorption

Table 2. Clinical and demographic features of the patients included in the studies.

Study	Total Patients Included (N)	Type of DM	Male Patients (%)	Mean Patient's Age (Years)	Malabsorption In Patients With EPI	Clinical Symptoms In Patients With EPI
Chey [11]	48	IDDM	44	49.6	NA	without clinical evidence of disease
Lankisch [16]	53	IDDM	NA	29.3	NA	NA
el Newihi [2]	10	IDDM and NIDDM type 2	20	56.9	NA	steatorrhea in 20.0% of patients
Hardt [4]	114	IDDM and NIDDM 31 type 1 83 type 2	type 1: 67.7 type 2: 55.4	60	NA	no correlations between clinical symptoms and FEC
Icks [12]	112	IDDM type 1	51	37	NA	no correlations between clinical symptoms and FEC
Rathmann [21]	544	IDDM and NIDDM type 2	64	63	NA	diarrhea in 2.8% of diabetic patients
Hardt [5]	1020	IDDM 323 type 1 697 type 2	type 1: 67.3 type 2: 68.7	type 1: 41.6 type 2: 53.8	NA	no correlations between clinical symptoms and FEC
Nunes [23]	42	IDDM and NIDDM type 2	NA	NA	NA	steatorrhea in 1/3 of obese diabetic patients
Cavalot [6]	37	IDDM type 1	43.2	34	NA	19.0 % of patients with low FEC had steatorrhea
Yilmaztepe [19]	32	IDDM type 2	46.9	58	NA	NA
Larger [22]	667	IDDM type 1 and type 2 NIDDM Type 2	59.00%	57	NA	NA
Vujasinovic [13]	150	IDDM type 1: 50 type 2: 50 NIDDM type 2: 50	48	59	62.50%	37.5% of patients with low FEC had one or more clinical symptom
Terzin [24]	101	IDDM type 2:62 NIDDM type2:39	46.5	60.3	NA	NA
Shivaprasad [65]	184	IDDM type 1: 89 DM type 2: 95	NA	12.6 in patients with DM type 1 and 50.2 in patients with DM type 2	NA	6.0% of patients with IDDM type 1 and 4.0% of patients with DM type 2

due to EPI also results in impaired incretin secretion and the consequent insulin response [69].

These intertwined and somewhat contradictory data raise questions concerning clinical management: should we actively look for EPI in DM patients and should we treat it? The main clinical consequence of EPI is malnutrition, resulting from maldigestion and poor absorption of nutrients. The presence of nutritional deficiencies can be used to estimate the probability of EPI in patients with DM but the evidences supporting the routine use of nutritional parameters for such purpose are currently very sparse [70]. It is also unclear whether this would have any impact on patient management. As oral pancreatic exocrine replacement therapy (PERT) is the cornerstone for patients with confirmed EPI and malnutrition [70]. It should be noted that some studies found no clinical symptoms of EPI in DM patients and no correlation between clinical symptoms and FE1 concentrations (**Table 2**). Limited randomised controlled trial data do not support treating patients with PERT simply on the basis of very low faecal elastase levels [71]. Further studies with carefully chosen endpoints are needed to be more definitive on this topic.

CONCLUSIONS

The prevalence and the clinical importance of EPI in patients with DM are debatable specifically because of study designs that include different methodologies and the underestimation of CP in unrecognised T3cDM.

Adequately powered, well-designed studies that include appropriate diagnostic methods (especially the 13C-MTG breath test and sMRCP) for EPI combined with malabsorption statuses (determined by serum nutritional markers) are required in patients with DM.

Competing Interest

MV received lecture fee; other two authors have no competing interests.

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