World Journal of Gastroenterology

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World J Gastroenterol 2019 June 14; 25(22): 2699-2705

DOI: 10.3748/wjg.v25.i22.2699

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

OPINION REVIEW

Which factors determine exocrine pancreatic dysfunction in diabetes mellitus?

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Author contributions: Only Altay M contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Supported by: no dedicated source of funding.

Conflict-of-interest statement: No potential conflicts of interest.

Manuscript source: Invited manuscript

Received: February 21, 2019
Peer-review started: February 22, 2019
First decision: March 27, 2019
Revised: April 4, 2019
Accepted: April 19, 2019
Article in press: April 20, 2019
Published online: June 14, 2019

P-Reviewer: Vagholkar KR

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Abstract

The exocrine structure is significantly affected by diabetes because of endocrine structure-function disorder within the pancreas. Exocrine pancreatic dysfunction (EPD) is the general name of the malabsorption process resulting from inadequate production, release, decreased activation, and/or insufficient degradation of enzymes required for digestion from pancreatic acinar cells. It is important to diagnose patients early and correctly, since there may be both macro- and micro-nutrient deficiency in EPD. In this paper, EPD, the diabetes-EPD relationship, and the predictive, effective factors affecting the emergence of EPD are briefly explained and summarized with contemporary literature and our experienced based on clinical, lab, and radiological findings.

Key words: Exocrine pancreas; Diabetes mellitus; Fecal elastase; Malabsorption; Chronic complication

Core tip: The early diagnosis of exocrine pancreatic dysfunction cases and initiation of treatment in diabetic patients are important. From this point of view, it is also important to obtain clinical signs and to apply clinical practice to the diagnosis of mild to moderate cases. Direct or indirect exocrine pancreatic dysfunction testing for all diabetic patients is not cost-effective. In this context, we must determine which diabetic patients should be tested.

Citation: Altay M. Which factors determine exocrine pancreatic dysfunction in diabetes mellitus? *World J Gastroenterol* 2019; 25(22): 2699-2705
URL: https://www.wjgnet.com/1007-9327/full/v25/i22/2699.htm
DOI: https://dx.doi.org/10.3748/wjg.v25.i22.2699

S-Editor: Ma RY
L-Editor: Filipodia
E-Editor: Zhang YL

INTRODUCTION

Pancreas secretion has a major impact on the digestion of nutrients, especially fats. Cephalic, gastric, and intestinal phase secretion of pancreatic enzymes is triggered, and the digestion of carbohydrate, protein, and fat occurs during the three main stages of digestion[1]. Exocrine pancreatic dysfunction (EPD) is the general name of the malabsorption process resulting from inadequate production, release, decreased activation, and insufficient enzymatic degradation of enzymes required for digestion from pancreatic acinar cells such as amylase, lipase, and protease[1,2]. Other names for this clinical disorder used in the literature include *pancreatic exocrine insufficiency* and *pancreatic maldigestion*.

Although EPD is used in diagnosing mild to moderate cases, and *pancreatic exocrine insufficiency* is used to refer to clinically more severe cases, in practice the two terms are frequently used interchangeably[1]. It is not possible to give a clear figure about the incidence of EPD in the general population[1]. However, exocrine pancreatic insufficiency in healthy individuals has been reported at different frequencies[3], including 3.8%-18.1%. In many cases, EPD affect the structure and function of the pancreatic gland, such as in chronic pancreatitis, some local or systemic diseases, and surgical intervention. EPD usually occurs when pancreatic enzyme activity falls below 10%. Steatorrhea, weight loss, and abdominal pain alongside bloating are some of the symptoms and findings observed in patients[2]. Furthermore, depending on the degree of malnutrition, more specific symptoms and findings may arise due to the deficiency of albumin and fat-soluble vitamins (A, D, E, K) whose absorption is impaired[4].

Tests used to diagnose EPD can be grouped into two main groups: Direct and indirect tests. Measurements with pancreas aspirates because of secretin and/or secretin-cholecystokinin/cerulein stimulation are examples of direct methods[5]. These are quite sensitive but expensive, time-consuming, and invasive methods. Indirect tests are more widely used in clinical practice. This is because of its easy of application and its being shown to be reliable and sensitive compared to direct tests. Fecal elastase-1 (FE-1) is a non-invasive, inexpensive, and easy-to-use test[6,7]. The human pancreatic FE-1 enzyme is synthesized in acinar cells within the pancreas.

The measurement of FE-1 in spot stool has been the gold standard test for the measurement of indirect pancreatic functions in recent years[8,9]. Enzyme-linked immunosorbent assay (ELISA) is used for this measurement. Patients with FE-1 levels above 200 μg/g are considered normal, those that fell between 100-200 μg/g are considered to have mild to moderate pancreas insufficiency, and those below 100 μg/g are considered to have severe pancreas insufficiency[10].

The specificity of FE-1 in demonstrating exocrine pancreatic insufficiency is 90% in cases with severe insufficiency, and the sensitivity is 100%; whereas in cases with mild to moderate pancreatic insufficiency, the sensitivity decreases to 65%[6,7]. In the treatment of EPD patients, a change in lifestyle (*i.e.*, smoking and alcohol abstinence), appropriate diet regimen (*i.e.*, frequent but small amount of nutrition, normal intake of fat, intake of fat-soluble vitamins with diet), pancreatic enzyme replacement therapy (PERT) and, if necessary, proton pump inhibitors are recommended. PERT is provided by taking pancreatic enzymes in an encapsulated microgranule or minimicrosphere structure with one's main meals and snacks. The main goal of the treatment is to decrease the morbidity and mortality associated with the disease by ensuring normal digestion and by decreasing steatorrhea and other symptoms.

DIABETES AND EPD

In pancreatic related diseases, it is not uncommon to observe endocrine and exocrine disorders that co-exist or that cause an association between anatomic and functional aspects. Studies have shown that a significant proportion of diabetic patients have EPD. EPD is known to be present in 40% (26-74) of Type 1 diabetes mellitus (DM) patients and 27% (10-56) of Type 2 DM patients[11]. EPD is present in almost all patients with pancreatogenic diabetes, also known as Type 3 c diabetes. EPD is mild to moderate in most diabetic patients. Therefore, complaints such as abdominal discomfort, bloating and abdominal pain are more prominent in patients than in steatorrhea. PERT in diabetic patients is recommended when the FE-1 level is below 100 μg/g. Some studies have reported that symptoms have regressed when pancreatic extracts are provided with meals (40000-50000 U lipase), and that even glucose is better controlled, thus reducing insulin requirements[12]. However, the opposite results have also been reported[13,14].

There are numerous radiological, histopathological and autopsy reports showing how the pancreatic structure of diabetic patients is affected[15-20]. In these studies, the

general findings in the pancreas of diabetic patients include atrophy, lubrication, lymphocyte infiltration, calcification, different degrees of fibrosis, and consequential volume reduction, lobulation, and morphological changes[21]. Studies using ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) showed that diabetic patients had smaller pancreases than healthy controls. Unfortunately, there is no adequate or clear data about what kind of process these effects have and what the determining factors are. Studies aimed at investigating the pathological and clinical features of this process have increased over the past two decades. In a significant number of these studies, it has been shown that there is a relationship between long duration of diabetes, insulin use, and low body mass index (BMI) and EPD[22]. Other studies have shown that that there is a relationship between high BMI, low beta cell reserve, and hyperglycemia and FE-1 in diabetic patients[23,24]. However, in some studies measuring fecal fat excretion, no correlation between these parameters and EPD was found[25,26]. In other studies, the duration of diabetes, glucagon, and somatostatin elevation, as well as exocrine secretions from the pancreas have been shown to be significantly reduced[27-30].

There are five major theories proposed to explain the cause of EPD in diabetes patients. The first theory is that pancreatic islet cell hormones have regulatory properties for exocrine tissue functions, and that the stimulating-inhibitory islet cell hormone balance changes in diabetic patients[31,32]. The second theory is that insulin is effective in trophic pancreatic acinar cells, and therefore that pancreatic acinar atrophy may develop as a result of insulin deficiency[31,33]. Third is the theory that it may be associated with a decrease in the enteropancreatic reflex and exocrine functions due to autonomic neuropathy and gastroparesis as a complication of diabetes[24,34]. The fourth hypothesis is autoimmunity, whereby antibodies against islet cells may cross-react against the acinar cell, or that antibodies against exocrine pancreatic tissue (such as anti-cytokeratin antibodies) may cause pancreatic insufficiency[35-37]. The fifth hypothesis is that due to microvascular complications, blood supply to the pancreas is impaired and fibrosis develops, thereby resulting in exocrine pancreatic insufficiency[38,39].

Although these theories have been proposed and are supported by evidence, they may not be sufficient to identify the cause of EPD on a case-by-case basis. However, for example, in a case of EPD in the early stage of newly diagnosed type 2 diabetes, no evidence to support these five hypotheses may be detected.

The early diagnosis of EPD cases and initiation of treatment are important. From this point of view, it is also important to obtain clinical clues and to apply clinical practice to the diagnosis of mild to moderate cases. Direct or indirect EPD testing for all diabetic patients is not cost-effective. In this context, we need to know which diabetic patients should be tested. Factors that show or suggest the presence of EPD in diabetic patients are given in Table 1. Typically, Types 1, 2, or even 3 DM is included in the studies, and many studies have reported that the factors that determine EPD are independent of the type of diabetes. However, different interpretations were made in the subgroup analysis conducted in certain studies. For example, Larger *et al*[40] reported that EPD is associated with vasculopathy in patients with Type 2 DM, and this relationship is not reported in Type 1 DM. In the following, the determinant or diagnostic factors of EPD in diabetic patients were discussed individually. However, it is important to note that the number of studies related to some factors is very low (*e.g.*, histopathological findings, symptoms and clinical findings). In many studies, patient characteristics are heterogeneous, and study designs and methodologies are different. Furthermore, the prospective controlled study is almost negligible. For these reasons, it is very difficult to comment on the degree of sensitivity and specificity of the aforementioned factors according to the current data.

Changes in the histopathological structure of the pancreas

It has long been known that the exocrine pancreas can change structurally and functionally in diabetic patients[16]. Moreover, these ultrastructural disorders have been diagnosed in the majority of patients without evidence of chronic pancreatitis. In the exocrine pancreas of patients with Types 1 and 2 diabetes, fibrosis was found to be significantly different compared to healthy controls, and ductal structure was preserved[16]. In a Japanese study, lymphocytic infiltration was observed in the pancreas of approximately half of patients with Type 1 diabetes[20]. In an autopsy study conducted in Denmark, diabetes was found to be more frequent among patients with chronic mild inflammation[41]. Although it may seem possible to histopathologically evaluate whether the exocrine structure of the pancreas is affected in diabetic patients, it cannot be used in daily practice.

Duration of diabetes

In some studies examining the relationship between EPD and diabetes, hypotheses

Table 1 Possible factors affecting exocrine pancreatic dysfunction in diabetes

Changes in the histopathological structure of the pancreas
Duration of diabetes
Poorly controlled diabetes
Symptoms
Laboratory findings
Macrovascular complications
Microangiopathic complications
Pancreas atrophy-volume change

have been established surrounding the fact EPD has a long-term complication of diabetes and correlations have been found between these two conditions[22,24]. In our study, we found that the relationship with low FE-1 levels increased as the duration of diabetes increased[42]. However, several studies together suggest that there is no relation between diabetes duration and EPD[40,43]. For example, Larger *et al*[40] concluded that in a cohort study of 667 diabetic patients (195 Type 1 DM, 472 Type 2 DM), there was no relationship between EPD and the duration of diabetes. In a small number of studies, diabetic patients were followed up over several years, whereupon it was reported that mild to moderate EPD had been present since the beginning of diabetes and had not progressed, and that the results of the tests did not show any relationship with the duration of diabetes[44].

Poorly controlled diabetes

There are studies showing that poor levels of blood glucose regulation correlate with low levels of FE-1[23,24]. In a study of 307 diabetes patients with FE-1 levels, Ewald *et al*[24] revealed that there is an inverse relationship between HbA1c level and FE-1 level. In the same study, the authors reported that EPD is a chronic complication of diabetes because of the duration of diabetes and cited a correlation with C-peptide. In a recent study, Prasanna Kumar *et al*[45] reported that fasting blood glucose, satiety blood glucose, and HbA1c levels are correlated to FE-1 levels in diabetic patients. However, as in our study[42], it is not possible to say that EPD is directly related to poorly controlled diabetes given that there are studies with conflicting results[40,44].

Symptoms

Common symptoms in diabetic patients include abdominal discomfort, pain, weight loss, diarrhea, bloating, and gas. Although EPD is frequently seen in diabetic patients, the proportion of symptomatic patients varies among studies. For example, Cummings *et al*[46] reported in one study involving 288 diabetic patients that at least one gastrointestinal symptom of EPD was present in 24% of diabetic patients, and that in half of these symptomatic cases, FE-1 levels were consistent with EPD. In this study, steatorrhea and weight loss were found to be insufficient in terms of showing EPD in diabetic patients, and it was emphasized that complaints such as diarrhea, abdominal pain and gas should be researched in greater detail. Recently, Lindkvist *et al*[47] reported that diarrheal-related symptoms and digestive-related symptoms were similar to those with normal FE-1 levels in patients with low FE-1 levels in a multicenter study involving 315 Type 2 DM patients. In other studies, it was found that there was no relationship between weight loss or BMI and EPD, and that EPD could be more frequent in obese patients[3,48]. In our study, we found significantly higher rates of abdominal distention and weight loss in diabetic patients than in the control group[42]. In addition, we found that the only factors that predicted EPD in diabetic patients were abdominal pain and distension[42]. These studies demonstrate that EPD should be suspected in patients with GI symptoms and EPD should be considered in the differential diagnosis.

Microangiopathic complications

The hypothesis that EPD is the result of a complication associated with microangiopathy has been investigated since the 1960s[49]. However, the results of the study were found to be contradictory. Ewald *et al*[24] showed an inverse correlation between the duration of diabetes and the FE-1 levels, and even a correlation between the C peptide level and FE-1. They suggested that this was due to diabetic neuropathy due to prolonged diabetes duration. The disruption of enteropancreatic reflex due to autonomic neuropathy or changes in gastrointestinal peptide levels has also been suggested to disrupt exocrine pancreatic function[34]. On the contrary, there are studies whereby no relationship between diabetic neuropathy and FE-1 levels were found[45,50].

Recently, Prasanna Kumar *et al*[45] reported a relationship between FE-1 levels and diabetic retinopathy in type 2 DM patients. In our study, we found significantly lower levels of FE-1 in diabetic patients with retinopathy than in non-diabetic patients. We also found a correlation between the presence of retinopathy and low Fe-1 levels[42]. In the same study, we could not find any relationship between FE-1 and other microvascular complications (neuropathy and nephropathy). The relationship between microangiopathy and EPD is interesting and requires more research.

Macrovascular complications

There are few studies investigating the relationship between EPD and major arterial complications. Prasanna Kumar *et al*[45] found a relationship between low FE-1 levels and the absence of peripheral pulse in diabetic patients. Larger *et al*[40] found a relationship between low-FE-1 and vascular disease in type 2 DM patients. We cannot say that there is a clear relationship between the macrovascular complications brought about by diabetes and EPD because of the low number of studies and because of the inability to show the same correlation in patients with type 1 DM.

Pancreas atrophy-volume change

Reduced insulin levels are expected to have a trophic effect on pancreatic acinar cells, resulting in decreased pancreas size. Indeed, studies have shown that there is a relationship between EPD and decreased pancreatic volume in diabetic patients[17,51]. In the first studies on this subject, ultrasonography was used, and in more recent years, pancreatic imaging with CT and MRI has become more widely used. In a recent study, the CT-measured pancreatic volumes of diabetic patients were found to be smaller, and that the low-volume and low-FE-1 concentration and low chymotrypsin activity were shown to be related[17]. Despite these findings, it is not a practical and inexpensive method to reveal volume reduction, which is a result of pancreas atrophy by imaging methods in a patient with diabetes to demonstrate the presence of EPD.

Lab findings

Because of the pathophysiology of EPD, lab findings related to micronutrient and fat-soluble vitamin levels can be seen[4,40]. For example, vitamin D, albumin, and calcium levels may be reflected in the lab findings. However, these nonspecific findings can be seen at different levels related to the degree of malabsorption. Direct and indirect tests used in the diagnosis of EPD are tests with quite high sensitivity and specificity. The purpose of this review is not to discuss diagnostic tests.

CONCLUSION

No specific data are available yet, with the exception of lab tests, that demonstrate the presence of EPD in a patient with diabetes, or to suggest the development of EPD. However, EPD should be considered in patients with long-term diabetes diagnosis, in the presence of poor blood glucose control with incidence of pancreatic atrophy, and when there are also gastrointestinal symptoms such as abdominal distension, abdominal pain, and diarrhea. Lab tests involving the use of indirect methods should be performed to develop a diagnosis and treatment plan.

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