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**Which factors determine exocrine pancreatic dysfunction in diabetes mellitus?**

Altay M. Diabetes mellitus and exocrine pancreas

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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

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**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.

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**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 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.

**REFERENCES**

1 **Lindkvist B**. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol* 2013; **19**: 7258-7266 [PMID: 24259956 DOI: 10.3748/wjg.v19.i42.7258]

2 **Pezzilli R**, Andriulli A, Bassi C, Balzano G, Cantore M, Delle Fave G, Falconi M; Exocrine Pancreatic Insufficiency collaborative (EPIc) Group. Exocrine pancreatic insufficiency in adults: a shared position statement of the Italian Association for the Study of the Pancreas. *World J Gastroenterol* 2013; **19**: 7930-7946 [PMID: 24307787 DOI: 10.3748/wjg.v19.i44.7930]

3 **Yilmaztepe A**, Ulukaya E, Ersoy C, Yilmaz M, Tokullugil HA. Investigation of fecal pancreatic elastase-1 levels in type 2 diabetic patients. *Turk J Gastroenterol* 2005; **16**: 75-80 [PMID: 16252196]

4 **Lindkvist B**, Domínguez-Muñoz JE, Luaces-Regueira M, Castiñeiras-Alvariño M, Nieto-Garcia L, Iglesias-Garcia J. Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. *Pancreatology* 2012; **12**: 305-310 [PMID: 22898630 DOI: 10.1016/j.pan.2012.04.006]

5 **Gullo L**, Costa PL, Fontana G, Labò G. Investigation of exocrine pancreatic function by continuous infusion of caerulein and secretin in normal subjects and in chronic pancreatitis. *Digestion* 1976; **14**: 97-107 [PMID: 950084 DOI: 10.1159/000197914]

6 **Löser C**, Möllgaard A, Fölsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut* 1996; **39**: 580-586 [PMID: 8944569]

7 **Stein J**, Jung M, Sziegoleit A, Zeuzem S, Caspary WF, Lembcke B. Immunoreactive elastase I: clinical evaluation of a new noninvasive test of pancreatic function. *Clin Chem* 1996; **42**: 222-226 [PMID: 8595714]

8 **Molinari I**, Souare K, Lamireau T, Fayon M, Lemieux C, Cassaigne A, Montaudon D. Fecal chymotrypsin and elastase-1 determination on one single stool collected at random: diagnostic value for exocrine pancreatic status. *Clin Biochem* 2004; **37**: 758-763 [PMID: 15329313 DOI: 10.1016/j.clinbiochem.2004.03.010]

9 **Elphick DA**, Kapur K. Comparing the urinary pancreolauryl ratio and faecal elastase-1 as indicators of pancreatic insufficiency in clinical practice. *Pancreatology* 2005; **5**: 196-200 [PMID: 15849489 DOI: 10.1159/000085271]

10 **Lankisch PG**. Secretion and absorption (methods and functions). *Best Pract Res Clin Gastroenterol* 2009; **23**: 325-335 [PMID: 19505662 DOI: 10.1016/j.bpg.2009.03.001]

11 **Zsóri G**, Illés D, Terzin V, Ivány E, Czakó L. Exocrine pancreatic insufficiency in type 1 and type 2 diabetes mellitus: do we need to treat it? A systematic review. *Pancreatology* 2018; : [PMID: 29779830 DOI: 10.1016/j.pan.2018.05.006]

12 **Ewald N**, Bretzel RG, Fantus IG, Hollenhorst M, Kloer HU, Hardt PD; S-2453110 Study Group. Pancreatin therapy in patients with insulin-treated diabetes mellitus and exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations. Results of a prospective multi-centre trial. *Diabetes Metab Res Rev* 2007; **23**: 386-391 [PMID: 17103488 DOI: 10.1002/dmrr.708]

13 **Mohan V**, Poongothai S, Pitchumoni CS. Oral pancreatic enzyme therapy in the control of diabetes mellitus in tropical calculous pancreatitis. *Int J Pancreatol* 1998; **24**: 19-22 [PMID: 9746885 DOI: 10.1007/BF02787526]

14 **Weitgasser R**, Abrahamian H, Clodi M, Fortunat W, Hammer H. [Position paper: Exocrine pancreatic insufficiency and diabetes mellitus]. *Wien Klin Wochenschr* 2012; **124** Suppl 2: 100-103 [PMID: 23250472 DOI: 10.1007/s00508-012-0290-2]

15 **Gilbeau JP**, Poncelet V, Libon E, Derue G, Heller FR. The density, contour, and thickness of the pancreas in diabetics: CT findings in 57 patients. *AJR Am J Roentgenol* 1992; **159**: 527-531 [PMID: 1503017 DOI: 10.2214/ajr.159.3.1503017]

16 **Mohapatra S**, Majumder S, Smyrk TC, Zhang L, Matveyenko A, Kudva YC, Chari ST. Diabetes Mellitus Is Associated With an Exocrine Pancreatopathy: Conclusions From a Review of Literature. *Pancreas* 2016; **45**: 1104-1110 [PMID: 26918874 DOI: 10.1097/MPA.0000000000000609]

17 **Philippe MF**, Benabadji S, Barbot-Trystram L, Vadrot D, Boitard C, Larger E. Pancreatic volume and endocrine and exocrine functions in patients with diabetes. *Pancreas* 2011; **40**: 359-363 [PMID: 21283038 DOI: 10.1097/MPA.0b013e3182072032]

18 **Gaglia JL**, Guimaraes AR, Harisinghani M, Turvey SE, Jackson R, Benoist C, Mathis D, Weissleder R. Noninvasive imaging of pancreatic islet inflammation in type 1A diabetes patients. *J Clin Invest* 2011; **121**: 442-445 [PMID: 21123946 DOI: 10.1172/JCI44339]

19 **Williams AJ**, Thrower SL, Sequeiros IM, Ward A, Bickerton AS, Triay JM, Callaway MP, Dayan CM. Pancreatic volume is reduced in adult patients with recently diagnosed type 1 diabetes. *J Clin Endocrinol Metab* 2012; **97**: E2109-E2113 [PMID: 22879632 DOI: 10.1210/jc.2012-1815]

20 **Waguri M**, Hanafusa T, Itoh N, Miyagawa J, Imagawa A, Kuwajima M, Kono N, Matsuzawa Y. Histopathologic study of the pancreas shows a characteristic lymphocytic infiltration in Japanese patients with IDDM. *Endocr J* 1997; **44**: 23-33 [PMID: 9152611 DOI: 10.1507/endocrj.44.23]

21 **Singh VK**, Haupt ME, Geller DE, Hall JA, Quintana Diez PM. Less common etiologies of exocrine pancreatic insufficiency. *World J Gastroenterol* 2017; **23**: 7059-7076 [PMID: 29093615 DOI: 10.3748/wjg.v23.i39.7059]

22 **Hardt PD**, Hauenschild A, Nalop J, Marzeion AM, Jaeger C, Teichmann J, Bretzel RG, Hollenhorst M, Kloer HU; S2453112/S2453113 Study Group. High prevalence of exocrine pancreatic insufficiency in diabetes mellitus. A multicenter study screening fecal elastase 1 concentrations in 1,021 diabetic patients. *Pancreatology* 2003; **3**: 395-402 [PMID: 14526149 DOI: 10.1159/000073655]

23 **Cavalot F**, Bonomo K, Perna P, Bacillo E, Salacone P, Gallo M, Mattiello L, Trovati M, Gaia E. Pancreatic elastase-1 in stools, a marker of exocrine pancreas function, correlates with both residual beta-cell secretion and metabolic control in type 1 diabetic subjects. *Diabetes Care* 2004; **27**: 2052-2054 [PMID: 15277440 DOI: 10.2337/diacare.27.8.2052]

24 **Ewald N**, Raspe A, Kaufmann C, Bretzel RG, Kloer HU, Hardt PD. Determinants of Exocrine Pancreatic Function as Measured by Fecal Elastase-1 Concentrations (FEC) in Patients with Diabetes mellitus. *Eur J Med Res* 2009; **14**: 118-122 [PMID: 19380282]

25 **Hahn JU**, Kerner W, Maisonneuve P, Lowenfels AB, Lankisch PG. Low fecal elastase 1 levels do not indicate exocrine pancreatic insufficiency in type-1 diabetes mellitus. *Pancreas* 2008; **36**: 274-278 [PMID: 18362841 DOI: 10.1097/MPA.0b013e3181656f8]

26 **Hardt PD**, Hauenschild A, Jaeger C, Teichmann J, Bretzel RG, Kloer HU; S2453112/S2453113 Study Group. High prevalence of steatorrhea in 101 diabetic patients likely to suffer from exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations: a prospective multicenter study. *Dig Dis Sci* 2003; **48**: 1688-1692 [PMID: 14560984 DOI: 10.1023/A:1025422423435]

27 **Ferrer R**, Medrano J, Diego M, Calpena R, Graells L, Moltó M, Pérez T, Pérez F, Salido G. Effect of exogenous insulin and glucagon on exocrine pancreatic secretion in rats in vivo. *Int J Pancreatol* 2000; **28**: 67-75 [PMID: 11185712 DOI: 10.1385/IJGC:28:1:67]

28 **Unger RH**, Aguilar-Parada E, Müller WA, Eisentraut AM. Studies of pancreatic alpha cell function in normal and diabetic subjects. *J Clin Invest* 1970; **49**: 837-848 [PMID: 4986215 DOI: 10.1172/JCI106297]

29 **Liu Z**, Kim W, Chen Z, Shin YK, Carlson OD, Fiori JL, Xin L, Napora JK, Short R, Odetunde JO, Lao Q, Egan JM. Insulin and glucagon regulate pancreatic α-cell proliferation. *PLoS One* 2011; **6**: e16096 [PMID: 21283589 DOI: 10.1371/journal.pone.0016096]

30 **Gyr K**, Beglinger C, Köhler E, Trautzl U, Keller U, Bloom SR. Circulating somatostatin. Physiological regulator of pancreatic function? *J Clin Invest* 1987; **79**: 1595-1600 [PMID: 2884233 DOI: 10.1172/JCI112994]

31 **Williams JA**, Goldfine ID. The insulin-pancreatic acinar axis. *Diabetes* 1985; **34**: 980-986 [PMID: 2412919]

32 **Hardt PD**, Ewald N. Exocrine pancreatic insufficiency in diabetes mellitus: a complication of diabetic neuropathy or a different type of diabetes? *Exp Diabetes Res* 2011; **2011**: 761950 [PMID: 21822421 DOI: 10.1155/2011/761950]

33 **Korc M**. Islet growth factors: curing diabetes and preventing chronic pancreatitis? *J Clin Invest* 1993; **92**: 1113-1114 [PMID: 8376573]

34 **el Newihi H**, Dooley CP, Saad C, Staples J, Zeidler A, Valenzuela JE. Impaired exocrine pancreatic function in diabetics with diarrhea and peripheral neuropathy. *Dig Dis Sci* 1988; **33**: 705-710 [PMID: 2897272]

35 **Nakajima K**, Oshida H, Muneyuki T, Kakei M. Pancrelipase: an evidence-based review of its use for treating pancreatic exocrine insufficiency. *Core Evid* 2012; **7**: 77-91 [PMID: 22936895 DOI: 10.2147/CE.S26705]

36 **Kobayashi T**, Nakanishi K, Kajio H, Morinaga S, Sugimoto T, Murase T, Kosaka K. Pancreatic cytokeratin: an antigen of pancreatic exocrine cell autoantibodies in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1990; **33**: 363-370 [PMID: 1696227]

37 **Mally MI**, Cirulli V, Hayek A, Otonkoski T. ICA69 is expressed equally in the human endocrine and exocrine pancreas. *Diabetologia* 1996; **39**: 474-480 [PMID: 8777998]

38 **Czakó L**, Hegyi P, Rakonczay Z Jr, Wittmann T, Otsuki M. Interactions between the endocrine and exocrine pancreas and their clinical relevance. *Pancreatology* 2009; **9**: 351-359 [PMID: 19454837 DOI: 10.1159/000181169]

39 **Vesterhus M**, Raeder H, Johansson S, Molven A, Njølstad PR. Pancreatic exocrine dysfunction in maturity-onset diabetes of the young type 3. *Diabetes Care* 2008; **31**: 306-310 [PMID: 17989309 DOI: 10.2337/dc07-1002]

40 **Larger E**, Philippe MF, Barbot-Trystram L, Radu A, Rotariu M, Nobécourt E, Boitard C. Pancreatic exocrine function in patients with diabetes. *Diabet Med* 2012; **29**: 1047-1054 [PMID: 22273174 DOI: 10.1111/j.1464-5491.2012.03597.x]

41 **Olsen TS**. The incidence and clinical relevance of chronic inflammation in the pancreas in autopsy material. *Acta Pathol Microbiol Scand A* 1978; **86A**: 361-365 [PMID: 716898]

42 **Aksöz Z**, Beyan E, Yıldırım AM, Karadağ İ, Ertuğrul DT, Altay M. Exocrine pancreatic function is also impairing in diabetic patients. 17th ed. National Congrees of Internal Medicine, Oct 14-18 2015 Antalya, Turkey, (OP) 112-113

43 **Rathmann W**, Haastert B, Oscarsson J, Berglind N, Wareham NJ. Inverse association of HbA1c with faecal elastase 1 in people without diabetes. *Pancreatology* 2015; **15**: 620-625 [PMID: 26601880 DOI: 10.1016/j.pan.2015.09.014]

44 **Creutzfeldt W**, Gleichmann D, Otto J, Stöckmann F, Maisonneuve P, Lankisch PG. Follow-up of exocrine pancreatic function in type-1 diabetes mellitus. *Digestion* 2005; **72**: 71-75 [PMID: 16113545 DOI: 10.1159/000087660]

45 **Prasanna Kumar HR**, Gowdappa HB, Hosmani T, Urs T. Exocrine Dysfunction Correlates with Endocrinal Impairment of Pancreas in Type 2 Diabetes Mellitus. *Indian J Endocrinol Metab* 2018; **22**: 121-125 [PMID: 29535950 DOI: 10.4103/ijem.IJEM\_139\_17]

46 **Cummings MH**, Chong L, Hunter V, Kar PS, Meeking DR, Cranston ICP. Gastrointestinal symptoms and pancreatic exocrine insufficiency in type 1 and 2 diabetes. *Practical Diabetes* 2015; **32**: 54-588 [DOI: 10.1002/pdi.1924]

47 **Boneu B**, Fernandez F. The role of the hematocrit in bleeding. *Transfus Med Rev* 1987; **1**: 182-185 [PMID: 2980277 DOI: 10.1016/j.pan.2018.05.483]

48 **Terzin V**, Várkonyi T, Szabolcs A, Lengyel C, Takács T, Zsóri G, Stájer A, Palkó A, Wittmann T, Pálinkás A, Czakó L. Prevalence of exocrine pancreatic insufficiency in type 2 diabetes mellitus with poor glycemic control. *Pancreatology* 2014; **14**: 356-360 [PMID: 25278304 DOI: 10.1016/j.pan.2014.07.004]

49 **Lazarus SS**, Volk BW. Pancreas in maturity-onset diabetes. Pathogenetic considerations. *Arch Pathol* 1961; **71**: 44-59 [PMID: 13759774]

50 **Rathmann W**, Haastert B, Icks A, Giani G, Hennings S, Mitchell J, Curran S, Wareham NJ. Low faecal elastase 1 concentrations in type 2 diabetes mellitus. *Scand J Gastroenterol* 2001; **36**: 1056-1061 [PMID: 11589378 DOI: 10.1080/003655201750422657]

51 **Goda K**, Sasaki E, Nagata K, Fukai M, Ohsawa N, Hahafusa T. Pancreatic volume in type 1 and type 2 diabetes mellitus. *Acta Diabetol* 2001; **38**: 145-149 [PMID: 11827436]

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**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 |