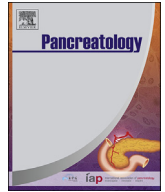




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Exocrine pancreatic insufficiency in type 1 and type 2 diabetes mellitus: do we need to treat it? A systematic review

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ABSTRACT

The exocrine and endocrine pancreata are very closely linked both anatomically and physiologically. Abdominal symptoms such as nausea, bloating, diarrhea, steatorrhea, and weight loss can often occur in diabetic patients. Impairments of the exocrine pancreatic function seem to be a frequent complication of diabetes mellitus; however, they are largely overlooked. The aim of this paper is to provide an overview of the current concepts of exocrine pancreatic insufficiency (PEI) in diabetes mellitus. The prevalence and symptoms of PEI in diabetes mellitus, the pathomechanism, and difficulties of diagnosis and therapy of PEI are summarized in this systematic review.

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Introduction

The exocrine and endocrine pancreata are very closely linked both anatomically and physiologically. Pathological conditions in the exocrine tissue can therefore cause an impairment of endocrine function and vice versa [1]. Pancreatic exocrine insufficiency (PEI) is defined by a deficiency of exocrine pancreatic enzymes resulting in an inability to maintain normal digestion [2]. The primary function of pancreatic enzymes is the hydrolysis of proteins (trypsinogens, proelastase, mesotrypsin), carbohydrates (α -amylase), lipids (lipase) and nucleotids (DNase, RNase). Chronic pancreatitis is the most common etiology of PEI. Gastrointestinal and pancreatic surgical resections, cystic fibrosis, obstruction of the main pancreatic duct (e.g. pancreatic and ampullary tumors), decreased pancreatic stimulation (e.g. celiac disease), or acid-mediated inactivation of pancreatic enzymes (e.g. Zollinger-Ellison syndrome) can lead to PEI [3]. Furthermore, PEI has been demonstrated to be present in a considerable percentage (10–74%) of patients with diabetes mellitus [4,5]. However, the significance of this findings was questioned and it is not clear, whether the presence of diabetes causes any symptoms or requires any treatment [6].

Abdominal symptoms such as nausea, bloating, diarrhea,

steatorrhea, and weight loss can often occur in diabetic patients [4]. These symptoms may be attributed to the side-effects of the metformin they are taking, the autonomic neuropathy on bowel function, small bowel bacterial overgrowth, celiac disease, or PEI. Impairments of the exocrine pancreatic function seem to be a frequent complication of diabetes mellitus; however, they are largely overlooked. Greater knowledge and awareness are required in testing and diagnosing this condition. Previous studies have raised the possibility that the replacement of pancreatic enzymes in exocrine insufficiency improves related symptoms and may aid glucose control.

The aim of this paper is to provide an overview of the current concepts of PEI in diabetes mellitus.

Search strategy

The systematic review was conducted following the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement [7]. A systematic search was performed in 3 databases, Pubmed, Embase and Cochrane Library. The search included the following MESH terms: “diabetes mellitus” AND “pancreatic function” OR “pancreatic exocrine insufficiency” OR “fecal elastase” OR “secretin” OR “cholecystokinin” OR “steatorrhea” or “pancreatic enzyme replacement therapy”. The search was limited to human data and to full text English articles if appropriate. The latest date searched was conducted on the 31 th of January

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Study selection

Selection of the studies was conducted by two investigators (G.Zs. and L.C.) separately. Clinical studies were eligible provided that they reported the data of pancreatic exocrine function in adult patients suffering from type 1 and 2 diabetes mellitus. Publications about type III/C diabetes were excluded. Duplicates, repeated publications, publications available only in abstract form, and review papers were excluded. Moreover, articles with inappropriate study design and patient inclusion criteria were also excluded from this systematic review. Remaining studies were further analyzed in full text. The reference list of obtained articles was also checked for additional articles. If differences were found in the reviewer's judgement, then a committee of three other researchers was invited to draw a conclusion. Database searches yielded altogether 1055 articles (EMBASE: 67; PubMed: 701; Cochrane: 287). The flow-chart diagram (Fig. 1) shows the strategy and results of the study selection.

Prevalence of exocrine pancreatic insufficiency in diabetes mellitus

There have been numerous reports in recent decades on PEI in patients with diabetes mellitus. In the early studies, pancreatic exocrine function was assessed with the gold-standard method of direct pancreatic function tests (pancreozymin-secretin test). PEI was revealed in 52.4% (18–100%) of the cases (Table 1a) [6,8–15]. However, these studies were only limited to a small number of patients because direct pancreatic function tests are invasive, time-consuming and expensive.

Therefore, a less invasive, cost-effective test was needed to evaluate pancreatic exocrine function in DM. Fecal elastase-1 (FE-1) test measures fecal levels of elastase-1, a proteolytic enzyme produced by pancreatic acinar cells. Fecal level of elastase-1 correlates with the output of other pancreatic enzymes, it is highly stable in

feces and easy to measure [16]. FE-1 demonstrated good sensitivity and specificity in moderate and severe PEI [17,18]. Nowadays, therefore, FE-1 measurement has become a screening tool in determining PEI. The prevalence of PEI has been demonstrated with FE-1 measurement with an average of 40% (26–74%) in type 1 diabetes and with an average of 27% (10–56%) in type 2 diabetes (Table 1b) [4–6,19–32].

The prevalence of PEI in both types of diabetes is very heterogeneous. However, most of these studies did not exclude cases with previous pancreatic disease, thus leading to a possible bias. In two recent studies, the prevalence of PEI in DM was less frequent than in previous studies, probably because pancreatic (type 3c, according to the new classification of American Diabetes Association: type 4 [33]) diabetes was excluded [28,29]. Low FE-1 was measured in only 5.4% of 150 consecutive type 1 and 2 diabetic patients after excluding patients with excessive alcohol consumption, medical history of abdominal surgery, other known reasons for malabsorption, previous pancreatic disease and DM lasting <5 years [28]. In another recent study, PEI was diagnosed with FE-1 measurement in 16.8% of type 2 diabetic patients after excluding patients with an abnormal pancreatic morphology [29]. Indeed, the prevalence of chronic pancreatic diseases among diabetic patients might be high because recent discussions have suggested that pancreatic diabetes (type 4) has been underestimated in the past and that it might cause about 8% of all diabetes cases [34].

Prevalence of morphologic changes of the exocrine pancreas in diabetes mellitus

Several studies have examined the morphologic changes of the exocrine pancreas in DM. In nearly 50% of type 1 DM patients, the pancreas is atrophic and fibrotic, with fatty infiltration and loss of acinar cells on histological examination [35,36]. Reduced pancreas size in patients with DM was demonstrated by abdominal ultrasonography, computed tomography or magnetic resonance imaging (MRI) [37–43]. Ductal changes are detected by endoscopic retrograde cholangiopancreatography in 76% of diabetics.

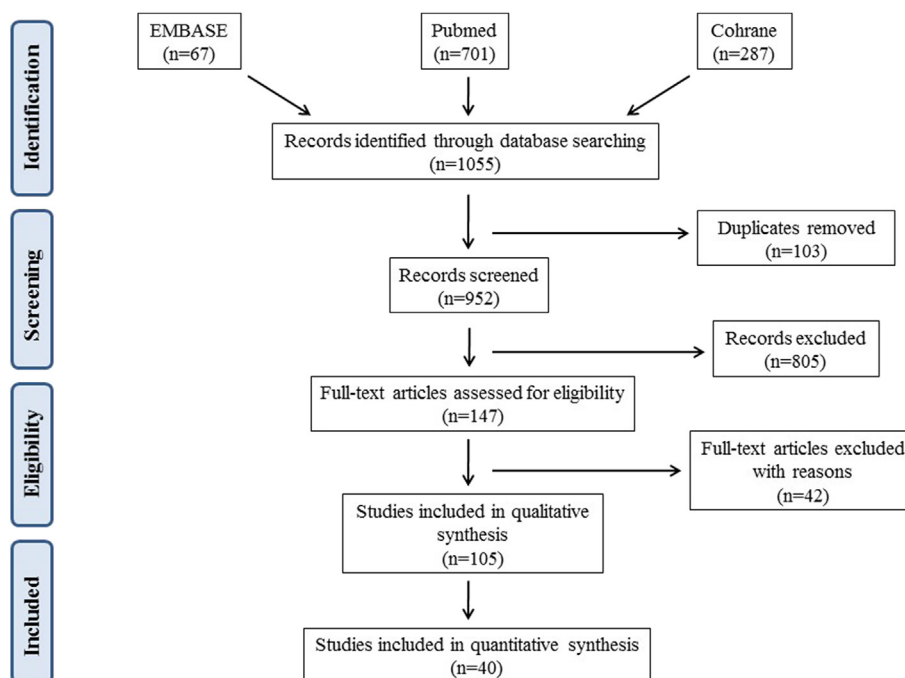


Fig. 1. The flow-chart diagram shows the strategy of the study selection.

Table 1A
Results of direct pancreatic function tests in patients with diabetes mellitus.

Author	Subjects/diabetes type	Methods	Results
Pollard et al., 1943 [8]	13	Amylase and lipase after pancreozymin-secretin stimulation	62% reduced
Chey et al., 1963 [9]	50 diabetic patients; 13 juvenile type	Amylase and lipase after pancreozymin-secretin stimulation	Low amylase output in diabetes: 36%; in juvenile diabetes: 77%
Vacca et al., 1964 [10]	55 diabetic patients (22 insulin-treated)	Diastase and bicarbonate after secretin stimulation; fecal fat	73% abnormal; correlation with age, no correlation with fecal fat
Frier et al., 1976 [11]	20 type 1, 7 type 2, 13 controls	Stimulation with iv secretin and CCK-PZ	PEI: 80% IDDM; correlation with diabetes duration
Harano et al., 1978 [12]	53 type 2, 4 type 1, 18 controls	Secretin-pancreozymin test	Diabetes: 69% deficient enzyme output; correlation with diabetes control
Lankisch et al., 1982 [13]	53 type 1	Secretin-pancreozymin test	Diabetes: 43% impaired function
Bretzke et al., 1984 [14]	60 insulin-treated type 2 diabetic patients	Secretin-pancreozymin test	Diabetes: 27% "mild PEI"
El Newihi et al., 1988 [15]	10 type 2 diabetic patients with diarrhea and neuropathy	Secretin and CCK test	Enzyme and bicarbonate reduction in all subjects
Hahn et al., 2008 [6]	33 type 1	Secretin and CCK test	33% mild enzyme reduction

CCK-PZ: Cholecystokinin-pancreozymin; IDDM: Insulin-dependent diabetes mellitus; PEI: Exocrine pancreatic insufficiency.

Table 1B
Results of indirect pancreatic function tests in patients with diabetes mellitus.

Author	Subjects/diabetes type	Methods	Results
Hardt and Kloer 1998 [19]	128 type 1 and 2	Fecal chymotrypsin	45% < 6 U/l
		Fecal elastase 1	46% < 200 µg/g
Hardt et al., 2000 [5]	39 type 1	Fecal elastase 1	74% < 200 µg/g
	77 type 2		36% < 200 µg/g
Icks et al., 2001 [20]	112 type 1	Fecal elastase 1	54.5% < 200 µg/g
Rathmann et al., 2001 [21]	544 type 2	Fecal elastase 1	30.3% < 200 µg/g
Hardt et al., 2003 [22]	323 type 1	Fecal elastase 1	51% < 200 µg/g
	697 type 2		35% < 200 µg/g
Nunes et al., 2003 [23]	42 type 1 and 2	Fecal elastase 1	36% < 200 µg/g
Cavalot et al., 2004 [24]	66 type 1	Fecal elastase 1	26% < 200 µg/g
Yilmaztepe et al., 2005 [25]	32 type 2	Fecal elastase 1	28% < 200 µg/g
Ewald et al., 2007 [26]	546 type 2	Fecal elastase 1	21.1% < 100 µg/g
Hahn et al., 2008 [6]	33 type 1	Fecal elastase 1	33% < 200 µg/g
Larger et al., 2012 [27]	195 type 1, 472 type 2	Fecal elastase 1	23% < 200 µg/g
Vujasinovic et al., 2013 [28]	50 type 1, 100 type 2	Fecal elastase 1	5.4% < 200 µg/g
Terzin et al., 2014 [29]	101 type 2	Fecal elastase 1	16.8% < 200 µg/g
Cummings et al., 2015 [4]	288 type 2	Fecal elastase 1	10% < 200 µg/g
Shivaprasad et al., 2015 [30]	89 type 1, 95 type 2	Fecal elastase 1	31% < 200 µg/g
Kangrga et al., 2016 [31]	315 type 2	Fecal elastase 1	5.1% < 100 µg/g and 5.1% < 200 µg/g
Oscarsson et al., 2017 [32]	10 type 1, 38 type 2	Fecal elastase 1	33% < 200 µg/g

Interestingly, these ductal changes do not correlate with DM type, DM duration or age (Table 2) [35–48].

Pathophysiology

The mechanism of exocrine pancreatic insufficiency in diabetes is multifactorial (Fig. 2). Pancreas atrophy is a related event in DM and plays a central role in the development of PEI. (1) Insulin has a trophic effect on pancreatic acinar tissue through the insulin-acinar portal system, so its decreased locally high level could lead to pancreatic atrophy [49]. Moreover, decreased pancreatic volume and PEI were shown to correlate in patients with DM [43,50,51]. (2) Acute hyperglycemia was demonstrated to inhibit basal and cholecystokinin-stimulated pancreatic enzyme secretion with an insulin-independent mechanism [52]. (3) Pancreatic stellate cells (PSCs) play a pivotal role in pancreatic fibrosis. Hyperglycemia was demonstrated to promote proliferation and activation of PSCs and to stimulate collagen production of PSCs via the protein kinase seC-p38 mitogen-activated protein kinase pathway, resulting in pancreatic fibrosis [53]. (4) The islet hormones (e.g. glucagon and somatostatin) can regulate exocrine tissue, so the lack of these hormones causes dysregulation of enzyme synthesis and resultant exocrine insufficiency. (5) Diabetic microangiopathy leads to insufficient perfusion through local microangiopathy, resulting in

ischemia of the exocrine pancreas, which could lead to pancreatic fibrosis, atrophy and PEI [29]. (6) Autonomic neuropathy may give rise to impaired enteropathic reflexes and PEI [27,54,55]. Moreover, (7) viral infections [56], (8) autoimmunity [57], or (9) genetic changes, as single-base deletion in the variable number of tandem repeats containing exon 11 of the carboxyl ester lipase gene [58] could increase simultaneous damage to exocrine and endocrine tissue.

The higher prevalence of PEI in type 1 diabetes can be explained by the more severe insulin deficiency, longer disease duration, and higher rate of microvascular complications characterized by type 1 DM.

The correlation between diabetes duration and the prevalence of PEI is contradictory. Previous studies have described an association or at least a weak correlation between low FE-1 level in type 2 DM and age of onset of diabetes, relatively long diabetes duration, and relatively high glycosylated hemoglobin (HbA1c) concentration, suggesting that exocrine dysfunction is a long-term complication of diabetes [22,59]. However, studies have demonstrated that there is no relationship between fecal elastase concentration and diabetes duration [60]. Otherwise, an inverse correlation was described between diabetes duration and HbA1c levels, and a positive correlation was reported between C-peptide and FE-1 levels [59]. A long-term follow-up study suggested that a mild to

Table 2
The prevalence of morphologic changes of the exocrine pancreas in diabetes mellitus.

Author	Year	Subjects	Methods	Results
Blumenthal HT et al. [44]	1963	3821 autopsy cases	Morphology	Prevalence of pancreatitis: - In diabetics: 11.2%; - In non-diabetics: 5.3%
Putzke HP et al. [45]	1986	100 diabetic and 100 non-diabetic autopsy cases	Histopathology	Lipomatosis: - In diabetics: 75%; - In controls: 60%
Gilbeau JP et al. [37]	1992	20 type 1, 37 type 2	CT scans	Pronounced lobulation, small size compared to controls
Alzaid A et al. [39]	1993	14 type 1, 43 type 2	Ultrasound	Small size compared to controls; type1<type2<controls
Nakanishi K et al. [40]	1994	36 type 1, 43 type 2	ERCP	Changes like CP: - type 1: 40% - type 2: 9%
Klöppel G et al. [36]	1996	type 1	Histology	Fibrosis, atrophy, fatty infiltration
Foulis AK et al. [35]	1997	type 1	Histology	Fibrosis, atrophy, fatty infiltration
Altobelli E et al. [38]	1998	60 type 1	Ultrasound	Small size compared to controls; dependent on duration
Hardt PD et al. [41]	2002	38 type 1, 118 type 2	ERCP	Changes like CP: type 1 > type 2, up to 75%
Williams et al. [47]	2007	12 male patients with type 1 and 12 healthy controls	MRI	Pancreatic volume showed a 48% reduction in long-standing type 1 diabetes as compared with age-matched normal subjects.
Bilgin M et al. [42]	2009	82 type 1 and type 2	MRI/MRCP	Changes like CP
Philippe et al. [43]	2011	24 type 1 and 28 type 2	CT scans	The pancreatic volume, 42 cm (25–57 cm), was decreased in most patients
Williams et al. [48]	2012	20 male recent-onset type 1 diabetes patients and 24 male healthy controls	MRI	Pancreatic volume is reduced by 26% in type 1 diabetes
Burute N et al. [46]	2014	32 type 2 and 50 normoglycemic individuals	MRI	Patients with type 2 DM had significantly lower pancreatic volume than normoglycemic individuals (p < 0.001)

ERCP: endoscopic retrograde cholangiopancreatography; CP: chronic pancreatitis; CT: computed tomography; MRI: Magnetic Resonance Imaging; MRCP: Magnetic Resonance Cholangiopancreatography.

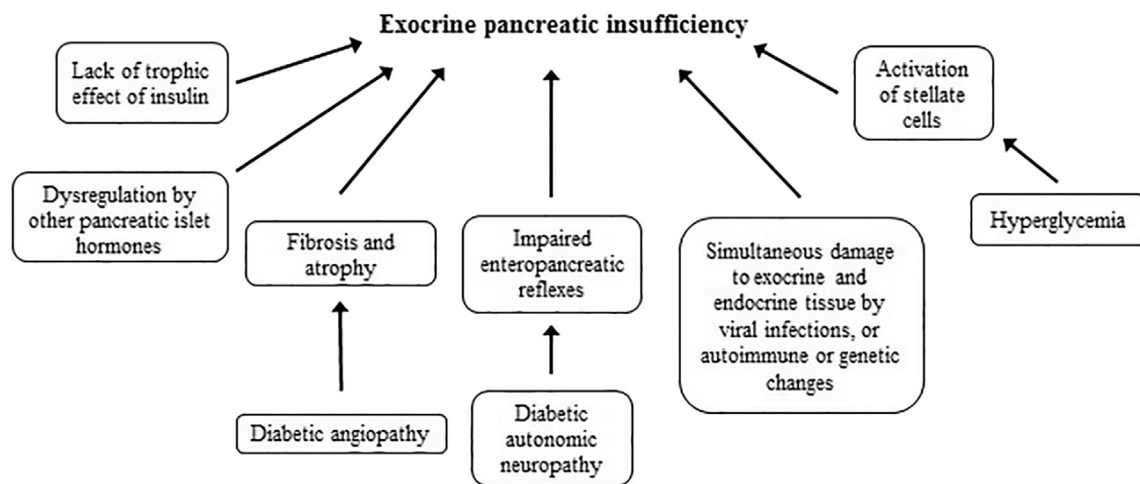


Fig. 2. The mechanism of exocrine pancreatic insufficiency in diabetes mellitus.

moderate exocrine pancreatic insufficiency is due to an early event in the course of DM and does not progress [61].

Nowadays the role of signaling proteins in pancreatic inflammation and diabetes induced pancreatic insufficiency is getting more attention. In a previous study the levels of total PKB, p70S6K, 4 E-BP1, ERK1/2, and NF-kappaB in the diabetic pancreas compared to control were significant decreased, however, the phosphorylation of p70S6K1, 4 E-BP1, ERK1/2, and protein ubiquitination were increased significantly compared to control group [62]. Presumable, that these factors are liable for decreased enzyme synthesis and pancreatic atrophy.

Symptoms of PEI in diabetes

The main clinical symptoms of PEI are due to the maldigestion and malabsorption of fat, including steatorrhea, abdominal pain,

flatulence, bloating and weight loss [4]. As a consequence of malnutrition, PEI is associated with low serum levels of micronutrients, lipid soluble vitamins (vitamins A, D, E, and K), trace elements, albumin, prealbumin and lipoproteins [2,29,63–74]. The low level of serum vitamin D leads to osteoporosis and an increased risk of fractures [75]. Protein-energy malnutrition and malabsorption of vitamin D and other micronutrients may result in a higher risk of infection due to their associated effects on innate and adaptive immune responses [76].

Although PEI seems to be frequent in DM, data on the occurrence of the symptoms of PEI in diabetes are limited. Gastrointestinal (GI) symptoms are common (27–87%) in patients with type 1 and type 2 DM [77–79]. In a recent study by Cummings et al. [4], 24% of diabetic patients had one or more GI symptoms consistent with a diagnosis of PEI (Bristol stool type 5–7, steatorrhea or weight loss). Among these patients, 42% had a low FE-1, indicating PEI. It

can be concluded that FE-1 screening is beneficial in patients with GI symptoms, suggesting the presence of PEI. Furthermore, steatorrhea was a poor marker of PEI in diabetes in this study, since only the minority of patients with steatorrhea had a low fecal elastase level. One would logically expect that diabetic patients with PEI experience weight loss, lower body weight and BMI. However, there were no significant differences in BMI between diabetic patients with a decreased or normal PE-1 concentration [4,29]. Inconsistent with these findings, the size of the pancreas did not correlate with BMI among diabetic patients in another study [37]. Furthermore, PEI detected by low FE-1 concentrations is frequent even in obese diabetic patients [23,80], and diabetic individuals with excess weight (BMI >25) may be at increased risk for PEI [25].

Diagnosis of PEI

PEI is suggested by clinical symptoms or poor glycemic control despite an adequate diet, antidiabetic therapy and patient adherence [24,29]. Determination of FE-1 is the most convenient way to diagnose PEI. Decreased FE-1 concentration has previously been demonstrated to be a sensitive method in moderate and severe PEI (sensitivity: 87% and 95%, respectively) and correlated significantly with the direct pancreatic function test, fat digestion, and the Cambridge severity classification of chronic pancreatitis [81–83]. FE-1 concentration correlates with the severity of PEI: a level of less than 200 µg/g stool indicates moderate PEI, while a level of less than 100 µg/g stool indicates severe PEI [84]. FE-1 is not sufficiently sensitive in mild PEI, but if FE-1 level is decreased, there is a strong chance of revealing changes in the pancreatic duct system and steatorrhea [83,85].

PEI can also be diagnosed with a ¹³C mixed triglyceride breath test by measuring the concentration of ¹³CO₂ in expired air after administering the radiolabeled test meal containing a known amount of fat [86]. Its accuracy is similar to FE-1 in diagnosing PEI [87].

Coefficient of fat absorption (CFA) is another gold standard test for PEI [88], although it has not been evaluated in DM. During the 72-h stool collection period, the patient consumes 100 g of fat per day. Fat malabsorption is diagnosed at >7 g of fat/100 g of stool/day, with severe steatorrhea at ≥15 g/day. However, the diet is cumbersome, the 3-day stool collection is inconvenient for both patients and laboratory staff, and therefore CFA is not used in daily clinical practice. It is utilized to evaluate the effectiveness of pancreatic enzyme replacement therapy (PERT) in PEI [89].

Direct pancreatic function tests are considered the gold standard in diagnosing PEI, and they definitely have advantages over indirect tests. However, direct tests are rather time-consuming and expensive to perform, very inconvenient for patients, and only available in a few academic centers.

Therapy

PERT is applied in PEI to prevent the symptoms of malabsorption, such as steatorrhea, and to provide physiologic nutrition by correcting maldigestion. Only a very limited number of publications have investigated the effectiveness of PERT in PEI associated with diabetes, and the results are contradictory. Three small trials studied the efficacy of PERT in patients with diabetes mellitus secondary to chronic pancreatitis [90,91]. Treatment with PERT demonstrated a significant reduction in post-prandial plasma glucose and glycosylated hemoglobin at 6 months versus baseline values in patients with diabetes due to tropical calculous pancreatitis [92]. In contrast, PERT did not improve mean glucose values; it produced potentially life-threatening disturbances in glucose control among insulin-dependent diabetic patients due to chronic

pancreatitis [93]. However, a recent double-blind, randomized, placebo-controlled trial of PERT in patients with PEI due to chronic pancreatitis demonstrated that the efficacy outcomes and adverse event profile for PERT were comparable between patients with and without diabetes [94]. A larger multicenter, double-blind, randomized, placebo-controlled trial demonstrated that PERT was safe, but has no effect on glycemic control in insulin-treated diabetic patients with FE-1 <100 µg/g [26]. Reduction in mild to moderate hypoglycemic episodes was revealed after 16 weeks of treatment with four capsules of 10 000 FIP units of pancreatin with main meals and two capsules of 10 000 FIP units of pancreatin with snacks, suggesting a more stable control of insulin therapy. However, this study might be criticized. First, patients were selected according to the presence of PEI irrespective of PEI-related symptoms. Second, the applied dose of pancreatin might be low. Recent guidelines [93–96] recommend a starting dose of PERT to be 50 000 IU lipase per main meal and 25 000 IU per snack, and this may be titrated up according to symptoms. However, recent evidence suggests that even this dose of PERT may not be sufficient to normalize nutrition [94,97].

Nutrient-induced glucose-dependent insulinotropic polypeptide (GIP) response is diminished in patients with PEI [98]. PERT has been demonstrated to reverse an impaired GIP response and therefore to restore the incretin effect of fat [98]. This effect of PERT may be beneficial in the glycemic control of diabetic patients with PEI.

However, while diabetic patients with reduced FE-1 may not complain about PEI-related gastrointestinal symptoms, they still might suffer from qualitative fat maldigestion, for example, lack of vitamin D, as has been proposed recently [99]. Furthermore, patients with diabetes mellitus have an increased risk of bone fractures [100]. PERT has been demonstrated to increase serum vitamin D level in diabetic patients with PEI, an effect which would be beneficial to reducing the increased risk of bone fracture [26].

However, there are several limitations to this systematic review. Firstly, the prevalence of PEI in both types of diabetes is very heterogenous, ranging between 5.1 and 80%. Secondly, studies applied the gold standard direct pancreatic function test in the measurement of PEI are limited to a small number of patients because of the invasive nature of the test. Thirdly, most of these studies did not exclude cases with previous pancreatic disease, thus leading to a possible bias. Fourth, PEI seems to be frequent in DM, data on the occurrence of the symptoms of PEI in diabetes are limited. Furthermore, only a very limited number of publications have investigated the effectiveness of PERT in PEI associated with diabetes, and the results are contradictory.

Conclusion

The currently available evidence is limited to answering the question of whether PERT is efficacious in glycemic control in patients with diabetes and PEI. Without doubt, there is a need for further randomized clinical trials in the field. For the moment, we can only suggest searching for PEI in diabetic patients by looking for abdominal symptoms that may be related to PEI and by analyzing serum nutritional factors and vitamin D level. If the test is positive, a trial of PERT is recommended. The response of abdominal symptoms, serum nutritional factors and parameters of glucose metabolism should be followed. In the case of positive response, long-term PERT is suggested.

Abbreviations

DM	Diabetes mellitus
PEI	Exocrine pancreatic insufficiency

FE-1	Fecal elastase-1
HbA1c	Glycosylated hemoglobin
FIP	International Pharmaceutical Federation
SCT	Secretin-cerulein test
PSCs	Pancreatic stellate cells
GI	Gastrointestinal
PERT	Pancreatic enzyme replacement therapy
GPI	glucose-dependent insulinotropic polypeptide
MRI	Magnetic Resonance Imaging
CFA	Coefficient of fat absorption

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