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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.

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 Cohraine 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 t h 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 meaure [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 heterogenous. 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.

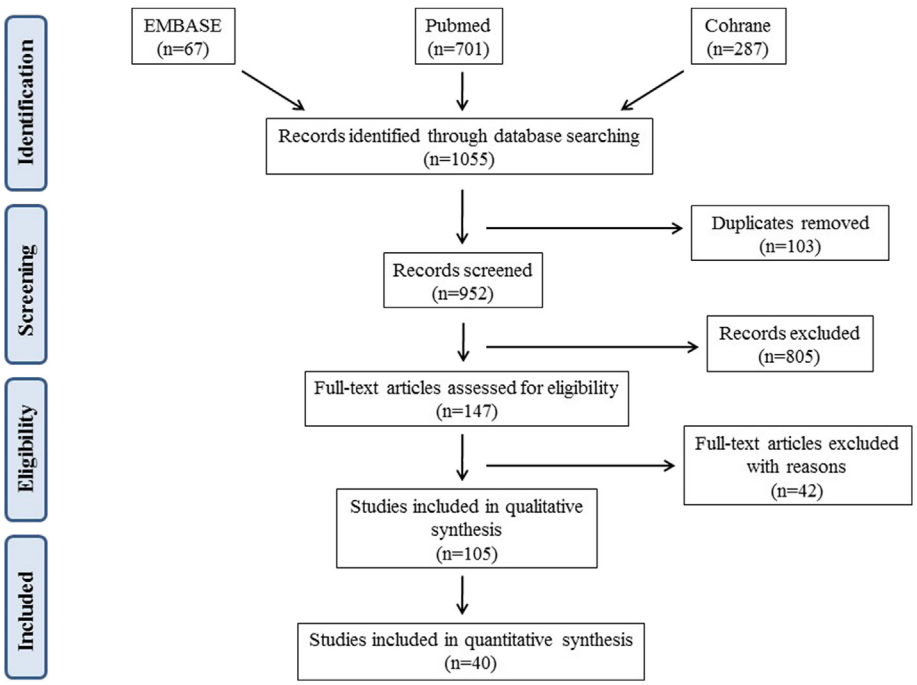

Fig. 1. The flow-chart diagram shows the strategy of the study selection.

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