IJEAST

INTERNATIONAL JOURNAL
OF ENGINEERING APPLIED SCIENCE
AND TECHNOLOGY

VOLUME : 10 ISSUE : 05 Print / Issue Publication Date: 13-Nov-2025

ISSN : 2455-2143

DOI : 10.33564/IJEAST.2025.v10i05.002

Indexed In

Google SCHOLAR OPEN ACCESS doi Crossref

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International Journal of Engineering Applied Sciences and Technology, 2025
Vol. 10, Issue 05, ISSN No. 2455-2143, Pages 09-30
Published Online September 2025 in IJEAST (http://www.ijeast.com)

SHOULD DIABETIC PATIENTS BE ACTIVELY SCREENED AND TREATED FOR PEI?

Dr. Sarosh Kamal Anwar

Abstract: **Aim: This dissertation aims to review the relationship between endocrine and exocrine pancreas, by doing a systemic review of existing literature and studies and establish the importance and need to screen diabetic patients for Pancreatic Exocrine Insufficiency, in order to avoid complications arising from macro and micronutrient deficiencies and improve glycemic control by using pancreatic enzyme replacement therapy.**

Methods: A thorough search was conducted across various databases including Medline, TRIP database, Cochrane library and Embase that were available on the NHS Wales e-library for health, to review internationally published research articles, based on human studies in the last 20 years, that discussed the prevalence of pancreatic exocrine insufficiency in diabetics, the relationship of PEI with other biochemical parameters, the usefulness of indirect fecal elastase-1 test and the efficacy of treating PEI using pancreatic enzyme supplementation.

Critical Analysis and Discussion: PEI is a frequent cause of mal absorption in diabetic patients presenting with non-specific GI symptoms that confound differential diagnosis because they overlap with othergastrointestinal diseases. Several studies have been done to determine the prevalence of PEI in diabetic patients using both noninvasive and invasive tests. Earlier studies used the gold standard invasive test (pancreozymin-secretin test) to assess exocrine dysfunction revealing an incidence of 52.4%. However, due to the invasive and expensive nature of tests, these studies were limited to a small number of patients. Later on, the inexpensive, non-invasive fecal elastase-1 spot stool test was developed and demonstrated a varying prevalence of PEI : 26-74% in type 1 diabetes and 10-56% in type 2 diabetes. A large retrospective study of 1020 diabeticsshowedthat Type 1 diabeticscollectively had a higher incidence of lower levels of FECs compared to type 2 diabetics. 28.5% of type 1 Diabetics showed severe PEI, 22.6% Mild-moderate insufficiency in comparison to type 2 diabetics, in which 19.9% had severe insufficiency, and 15.5% had mild-moderate insufficiency.The newer fecal elastase-1 test has shown to be more sensitive and specific in diagnosing those with severe PEI but it's sensitivity is reduced for those with mild to moderate PEI. A small study of 33 patients compared indirect and direct methods of assessing pancreatic exocrine function, suggested that clinicians should not use Fecal Elastase-1 test or raised Fecal Fat, as an indicator to start pancreatic enzyme substitution as they are unreliable in diagnosing PEI in type 1 diabetics. Very few studies have explored the therapeutic implications of PERT in diabetic patients, often with conflicting results.In a randomized multicenter double-blind control trial, consisting of type 1 diabetics, no statistically significant beneficial effects of PERT on improvement in glycemic control, insulin response and control of symptoms could be proven.

Conclusion: In conclusion, it is important to raise awareness of PEI amongst diabetics who usually don't volunteer information on their GI symptoms. Similarly, the healthcareprofessionals tend to overlook Type 3c diabetes and PEI is often left untreated. This can result in erratic blood glucose control and increase the risk of long-term complications arising from maldigestion and malnutrition, therefore raising tremendous burden on the NHS. Prevalence studies using fecal elastase-1 stool test have shown that around 40% of diabetics have some degree of pancreatic exocrine insufficiency, of whom one-third suffer from severe insufficiency. Given the cost and non-invasive nature of measuring fecal elastase, it is perhaps worth considering PEI in diabetic patients and actively screening and investigating alldiabetic for gastrointestinal symptoms. There is a definite need for further large scale randomized case-control trials to study the therapeutic implications of PERT in both type 1 and type 2 diabetic patients.

I. INTRODUCTION

What is Pancreatic Exocrine Insufficiency?

Pancreatic Exocrine Insufficiency occurs when the pancreas ability to release pancreatic enzymes is significantly decreased, resulting in enzyme levels that are inadequate to carry out normal digestive processes.[1,2]Pancreatic enzymes released by the pancreatic acinar cellsare essential for thebreakdown of proteins,carbohydrates and especially fats. A deficiency of these enzymes results in malabsorption, vitamin deficiencies, weight loss, malnutrition and its associated complications. Although a diagnosis of PEI is often considered in patients who tend to have pancreatic disease, it is often overlooked in diabetic patients presenting with gastrointestinal symptoms.

International Journal of Engineering Applied Sciences and Technology, 2025
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Prevalence and Etiology of PEI

PEI can occur from both pancreatic and non-pancreatic disorders. Although, the prevalence of PEI in general population is largely unknown,[3] its been reported in healthy individuals at varying frequencies 3.8% to 18.1%.[2] In many cases, PEI is commonly found in association with certain predisposing conditions. [Table 1]

The pancreatic disorders resulting in PEI are chronic pancreatitis, cystic fibrosis, pancreatic cancer and pancreatic resection[Figure 1]. PEI may also be associated with certain gastrointestinal diseases, such as coeliac disease, Inflammatory Bowel Disease or Irritable Bowel Syndrome. The role of diabetes in causing exocrine dysfunction is increasingly gaining awareness and many pathophysiological mechanisms have been hypothesized.

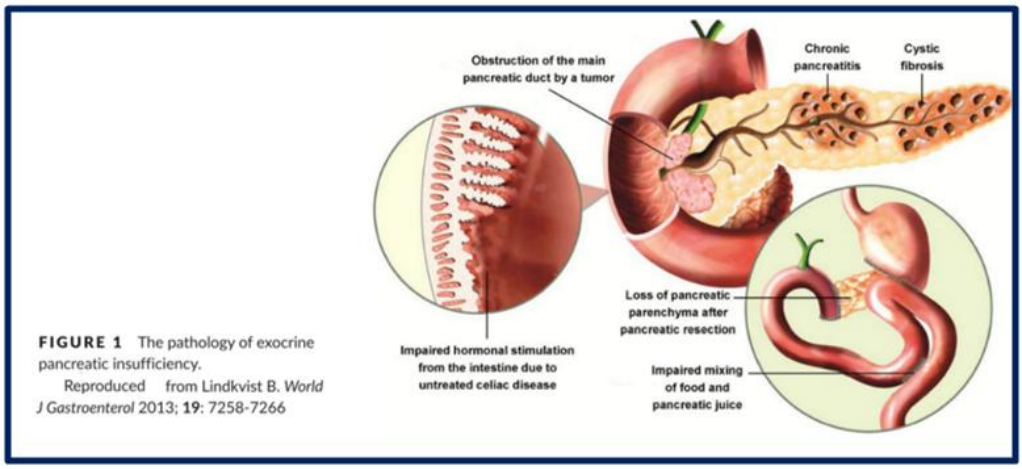

FIGURE 1 The pathology of exocrine pancreatic insufficiency. Reproduced from Lindkvist B. *World J Gastroenterol* 2013; **19**: 7258-7266

TABLE 1: Prevalence of exocrine pancreatic insufficiency in individuals with predisposing conditions

Condition	Estimated prevalence
Chronic pancreatitis	30% in patients with mild disease; 85% with severe disease
Cystic fibrosis	Approximately 85% of newborns
Diabetes	
Type 1	26%-44%
Type 2	12%-20%
HIV/AIDS	26%-45%
Intestinal disorders	
Irritable bowel syndrome	4%-6%
Coeliac disease	12%-30%
Inflammatory bowel disease	19%-30%
Inoperable pancreatic cancer	50%-100%
Surgery	
Distal pancreatectomy	19%-80%
Whipple surgery	56%-98%
Shwachman-Diamond syndrome	82%
Johanson-Blizzard syndrome	High

Adapted from: Othman, MO, Harb, D, Barkin, JA. Introduction and practical approach to exocrine pancreatic insufficiency for the practicing clinician. Int J Clin Pract. 2018; 72:e13066. https://doi.org/10.1111/ijcp.13066

Prevalence of PEI in diabetic patients

Patients with diabetes are rarely enquired about GI symptoms and therefore can miss a diagnosis of PEI. Recent studies have shown that 50% of Type 1 diabetics, and 32 % of Type 2 diabetic patients tend to have PEI to a certain degree.[4]

A few studies have been carried out to determine prevalence of PEI in the diabetic population. These studies can be broadly divided into those that used

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direct pancreatic function tests(pancreozymin-secretin test) and those that used the indirect pancreatic function tests (fecal elastase-1 levels in stool)[Tables 2a and 2b].
Earlier studies used the gold standard invasive test (pancreozymin-secretin test) to asses exocrine dysfunction revealing an incidence of upto53%. However due to the invasive and expensive nature of tests, these studies were limited to a small number of patients.

Later on, the inexpensive, non-invasive fecal elastase-1 spot stool test was developed and demonstrated a heterogeneous prevalence of PEI: 26-74% in type 1 diabetes and 10%-56% inpatients with type 2 diabetes (Table 2b). However, these studies failed to exclude pancreatogenic diabetes (Type 3c diabetes) resulting in a possible bias.

Table 2a
Results of direct pancreatic function tests in patients with diabetes mellitus.

Author	Subjects/diabetes type	Methods	Results
Pollard et al., 1943	13	Amylase and lipase after pancreozymin-secretin stimulation	62% reduced
Chey et al., 1963	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	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	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	53 type 2, 4 type 1, 18 controls	Secretin-pancreozymin test	Diabetes: 69% deficient enzyme output; correlation with diabetes control
Lankisch et al., 1982	53 type 1	Secretin-pancreozymin test	Diabetes: 43% impaired function
Bretzke et al., 1984	60 insulin-treated type 2 diabetic patients	Secretin-pancreozymin test	Diabetes: 27% "mild PEI"
El Newihi et al., 1988	10 type 2 diabetic patients with diarrhea and neuropathy	Secretin and CCK test	Enzyme and bicarbonate reduction in all subjects
Hahn et al., 2008	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 2b
Results of indirect pancreatic function tests in patients with diabetes mellitus.

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

Adapted from : Zsori G, et al., Exocrine pancreatic insufficiency in type 1 and type 2 diabetes mellitus: dowe need to treat it? A systematic review, Pancreatology (2018).

Symptoms of PEI: an under-diagnosed condition in diabetics

The symptoms of PEI become evident when pancreatic enzyme activity has dropped below 10%.[5]
The typical symptoms of PEI include abdominal discomfort, bloating, diarrhea, flatulence, steatorrhea and weight loss. These symptoms, however, overlap with other gastrointestinal conditions and therefore PEI may be easily missed or there might be a delay in the diagnosis. The classical symptoms of PEI of steatorrhea (fatty/greasy stools) and weight loss only tend to occur in very severe PEI.[6] Additionally, there is a significant variation in the way PEI presents in different individuals.[7]
In most diabetics, pancreatic exocrine insufficiency is usually mild to moderate and therefore steatorrhea is less of a complaint, and other symptoms like abdominal discomfort and bloating are more common. Patients with diabetes are rarely asked about gastrointestinal symptoms, and if they do

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complain of any GI symptoms, these are more commonly attributed to side effect of anti-diabetic medications, diabetes complications such as gastroparesis and autonomic neuropathy or other GI conditions such as Celiac disease, Small bowel bacterial overgrowth, IBD and IBS, thus rarely considering PEI[Table 3]. This can unfortunately have deleterious outcomes including the potential to miss serious underlying conditions such as pancreatic malignancy and chronic pancreatitis, which may go unrecognized.

Although PEI is often seen in diabetic patients, the percentage of individuals presenting with symptoms differs among research. For instance, in one research comprising of 288 diabetic patients, Cumming et al revealed, that there was at least one PEI symptom present in 24% of diabetic patients, and FE-1 levels were consistent in 50% of these symptomatic patients.[8] This study laid emphasis on investigating diarrhea, bloating and abdominal pain in diabetic patients for diabetes, because steatorrhea and weight-loss were inadequate in demonstrating PEI in diabetics.

A recent audit carried out at Portsmouth analyzed 156 diabetic patients that presented with GI symptoms.[9] Results showed that 22% of patients had an abnormal Bristol Stool Chart rating of type 5-7. Fecal Elastase test for PEI was carried out in 19 patients and 37% of patients who were initially asymptomatic had low levels. These studies suggest that all diabetic patients presenting with gastrointestinal symptomsshould be assessed for Pancreatic exocrine insufficiency as a differential.

Table 3: Common symptoms shared by EPI and other gastrointestinal conditions

Symptom	EPI	Coeliac disease	IBD	SIBO	IBS
Bloating	+	+	+	+	+
Abdominal discomfort/pain	+	+	+	+	+
Voluminous and foul-smelling stools	+	–	–	–	–
Steatorrhoea	+	+	–	+	–
Diarrhoea	+	+	+	+	+
Constipation	–	–	–	–	+
Abnormal stool frequency	+	+	+	+	+
Excess flatulence	+	–	–	+	+
Weight loss	+	+	+	+	–

EPI, exocrine pancreatic insufficiency; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; SIBO, small intestinal bacterial overgrowth. Crohn's disease and ulcerative colitis.

Adapted from: Othman, MO, Harb, D, Barkin, JA. Introduction and practical approach to exocrine pancreatic insufficiency for the practicing clinician. Int J Clin Pract. 2018; 72:e13066. https://doi.org/10.1111/ijcp.13066

II. PATHOPHYSIOLOGIC MECHANISMS OF PEI

Mechanisms of PEI in Diabetes

Recent studies have shown that Diabetes Mellitus can cause structural and functional changes in the pancreas.[10]However, conflicting data exits in literature and research, regarding the connection between diabetes and pancreas exocrine insufficiency. For instance, a large study of 1020 diabetic patients demonstrated a higher frequency of PEI in patients with early onsetdiabetes, longduration of diabetes, insulin use and low BMI with PEI.[11] However, these associations were reported as being weak. Similarly, other studies have demonstrated a relationship between diabetes and FE1, hyperglycemia, high BMI, and low beta cell reserve.[12,13]Several other studies have reported a decrease in pancreatic exocrine secretions in relation to duration of diabetes, glucagon and elevation of somatostatin.[14-17]

On the other hand, in some studies, no correlation was found between exocrine pancreas insufficiency and above mentioned parameters.[18,19] For example, a large scale cohort study analyzing 195 Type 1 DM and 472 Type 2 DM, concluded that there is no relationship between diabetes duration and PEI.[20] A smaller study, followed up diabetic patients over a span of few years, and concluded that there was no relation between PEI and Diabetes, and attributed the mild-moderate PEI to an earlier event. PEI was not shown to progress in these set of patients.[21]

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I. Potential mechanisms that cause PEI in diabetics

Multiple mechanisms have been hypothesized in understanding how diabetes, which is primarily a disease of the endocrine pancreas can have an effect on the pancreatic exocrine function.

1. Insulin hormone has a trophic effect on pancreas acinar cells and its absence may result in atrophy of pancreas.[22,23] This has been demonstrated in some studies using pancreatic imaging with CT and MRI, which showed a reduction in pancreatic volume in diabetic patients.[24,25] In a recent study involving 52 diabetic patients, with an average duration of diabetes of 15 years, pancreatic volume measured by CT was reduced. It also indicated a correlation between this low pancreatic volume with low FE-1 levels and low chymotrypsin activity.[24] However, in clinical practice, using pancreatic imaging techniques in diabetics, to reveal pancreatic volume reduction and consequently PEI, can be very expensive and impractical.
2. Islet cell hormones have a regulatory effect on exocrine tissue, which may be impaired. [27]
3. Diabetic autonomic neuropathy is suggested to be another reason for PEI due to diabetes. A study conducted by Ewald et al was able to establish that FE-1 levels correlated with C-peptide levels and inversely correlated with duration of diabetessuggested that diabetic neuropathy due to chronic diabetes, disrupts the enteropancreatic reflex, thus resulting in exocrine pancreas dysfunction. [13]
4. Micro angiopathic complications related to diabetes have been hypothesized to cause PEI since the 1960s.[26] It is suggested that the impaired blood flow in diabetic angiopathy causes atrophy and fibrosis of the pancreas.
5. Increased levels of glucagon and somatostatin found in diabetics, may suppress exocrine function.[27]
6. Viral infections, autoimmune changes or genetics may play a role in damage to both the exocrine and endocrine tissue simultaneously.[27]
7. Exocrine pancreas diseases, such as Pancreatitis, causes Type 3c diabetes which is often misclassified as type 2 diabetes.[27]

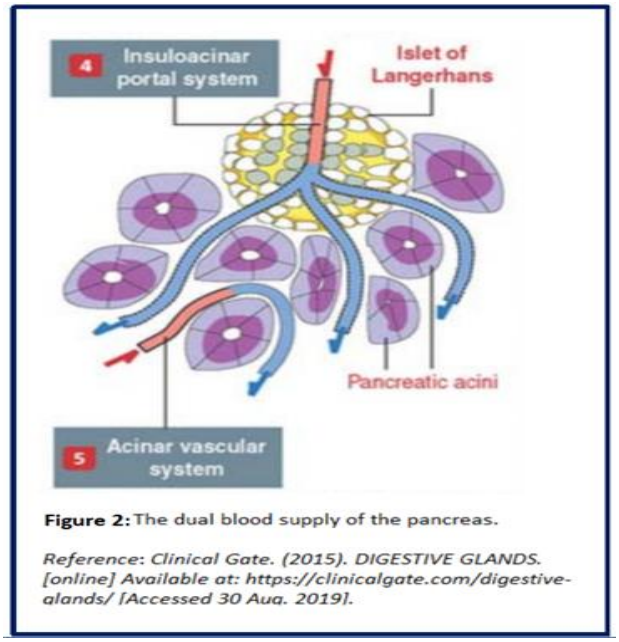

Figure 2: The dual blood supply of the pancreas.

Reference: Clinical Gate. (2015). DIGESTIVE GLANDS. [online] Available at: https://clinicalgate.com/digestive-glands/ [Accessed 30 Aug. 2019].

II. The islet-acinar axis

Traditionally, pancreas has been considered as two distinct organs, however, the endocrine and exocrine parts are interconnected both physiologically and anatomically. Studies have shown, that the pancreatic cells have a dual blood supply system: the Acinar vascular system and the insulo-acinar portal system.[Figure 2] The acinar vascular system is an independent system that supplies the acinar cells. However, an additional network of afferent arterioles supply the islets of Langerhans, which then leave the islets and supply blood to the acini. A scientific research conducted in 1980, to study the islets of Langerhans in rabbits , found that around 77-89% of blood flows directly to the exocrine cells which makes up 98-99% of the organ weight, but around 11–23% of pancreatic blood flow supplies the islets directly [Figure 3].[28] Further electron microscope studies done in humans and other mammals confirmed the presence of an “insulo-acinar portal system’; a microvascular connection linking the exocrine and endocrine portions of the pancreas.[29-31]This explained that a large portion of blood from the islets drained into the exocrine pancreas, and the exocrine pancreas are exposed to

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a high concentration of hormones released by the islets of Langerhans.

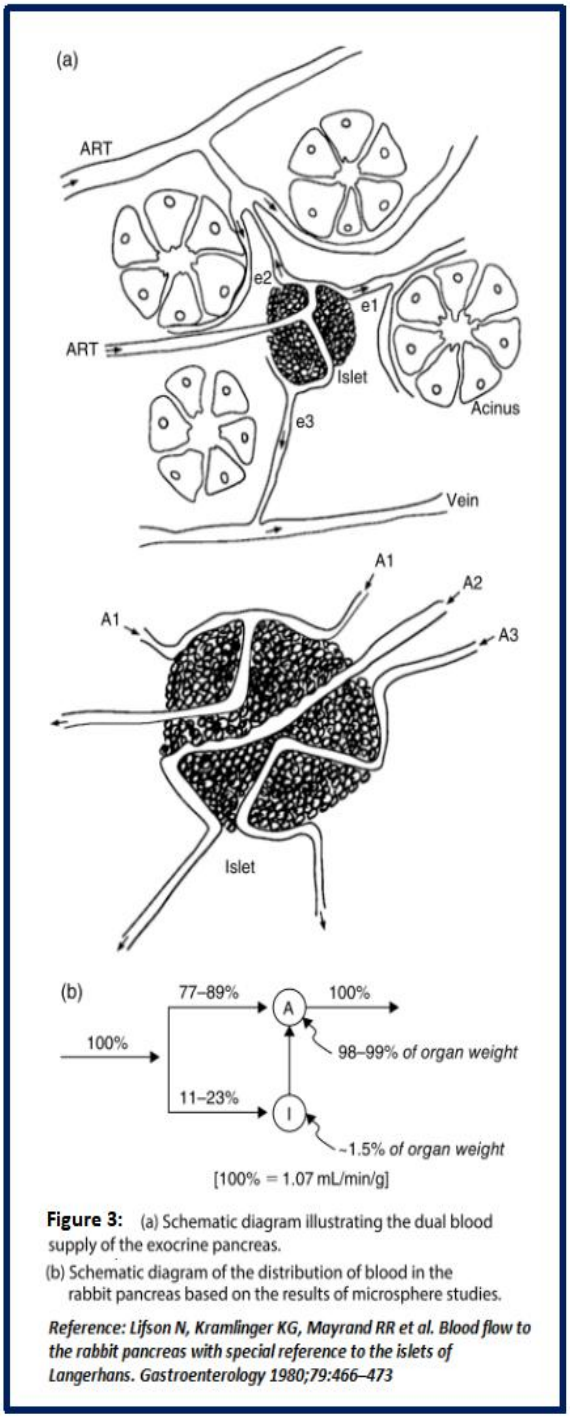

Figure 3: (a) Schematic diagram illustrating the dual blood supply of the exocrine pancreas.
(b) Schematic diagram of the distribution of blood in the rabbit pancreas based on the results of microsphere studies.

Reference: Lifson N, Kramlinger KG, Mayrand RR et al. Blood flow to the rabbit pancreas with special reference to the islets of Langerhans. Gastroenterology 1980;79:466–473

III. Diabetes and Histopathological and structural changes in exocrine pancreas

Several autopsy studies have been conducted on diabetics to investigate the histopathological and structural changes that occur in pancreas of diabetic patients.[32-37] These studies reported that the pancreas of diabetics undergo atrophy, lymphocytic infiltration, calcification, fibrosis resulting in volume reduction and morphological changes.[38]

Ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) done in diabetic patients also demonstrated a decrease in size of pancreas compared to healthy individuals. However, new studies are still needed to investigate the processes that drive these changes in diabetics. It is to be noted that although histopathological structural changes in the exocrine pancreas can be evaluated in diabetic patients, their use in clinical practice is limited.

III. AIMS AND OBJECTIVES

Aim: This dissertation aims to review the relationship between endocrine and exocrine pancreas, by doing a systemic review of existing literature and studies and establish the importance and need to screen diabetic patients for Pancreatic Exocrine Insufficiency, in order to avoid complications arising from macro and micronutrient deficiencies and improve glycemic control by using pancreatic enzyme replacement therapy.

Objectives:

1. To identify studies investigating the prevalence of Pancreatic Exocrine Insufficiency in diabetic patients.
2. To review studies explaining the anatomical and physiologic link between endocrine and exocrine pancreas.
3. To review studies discussing the potential mechanisms of PEI developing in diabetes.
4. To identify studies that investigated the best screening test for PEI and the limitations of the invasive and non-invasive tests.
5. To identify studies investigating the effects of pancreatic enzyme substitution in treating PEI and its effect on other glycemic parameters.
6. To provide a concise overview of PEI in diabetics in order to prevent it from being overlooked.

IV. METHODOLOGY

Review of Electronic Database

A thorough search was conducted using the PICO (patient, intervention, comparison, outcome) method across various databases available on the NHS Wales e-library.The following databases were searched: TRIP (Turning Research into Practice, www.tripdatabase.com), MEDLINE, COCHRANE LIBRARY and EMBASE. In order to expand the outlook of search the following sentences and keywordswere used : “Prevalence of Pancreatic exocrine insufficiency in diabetes” , “efficacy of Pancreatin replacement therapy in diabetics ” , “ Mechanism of pancreatic exocrine insufficiency in diabetic patients”, “role of fecal elastase-1 in detecting pancreatic exocrine insufficiency ”, “Type 3c diabetes prevalence and its association with pancreatic exocrine insufficiency”.The search was limited to articles published over the last 20 years and based on human studies only. The titles and abstracts of the search results were thoroughly screened and those relevant to the dissertation were shortlisted. To cover the scope of the topic; articles were selected that discussed the prevalence of PEI in diabetics, the controversial role of the recommended Fecal elastase-1 test as a screening test, articles discussing Type 3c diabetes which oftenresults in misclassification and underdiagnosis, and finally articles discussing the effects of Pancreatic enzyme replacement therapy in treating PEI.

Other searches

Further searches were conducted to search for papers , recent guidelines and recommendations using Medscape, Dynamed Plus and Upto Date.

Inclusion and Exclusion Criteria:

Inclusion criteria:

1. Internationally published research articles in the English language.
2. Studies based onthe prevalence of pancreatic exocrine insufficiency in diabetic patients
3. Studies based on tests used to diagnose pancreatic exocrine insufficiency.
4. Studies explaining the mechanisms of PEI in diabetic patients.
5. Studies investigating the effects of pancreatic enzyme replacement therapy.

Exclusion criteria:

1. Studies based on research in animals.
2. Case reports, editorials and meta-analysis studies.

CRITICAL ANALYSIS

Critical Analysis

Study 1: High Prevalence of Exocrine Pancreatic Insufficiency in Diabetes mellitus. [39]

Study 2: Pancreatic exocrine insufficiency in type 1 and type 2 diabetics of Indian origin.[45]

Study 3: Low Fecal Elastase 1 Levels Do Not Indicate Exocrine Pancreatic Insufficiency in Type-1 Diabetes Mellitus. [53]

Study 4: Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). [59]

Study 5: 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. [68]

Study 1: **High Prevalence of Exocrine Pancreatic Insufficiency in Diabetes mellitus**[39]

Hardt P, D, Hauenschild A, Nalop J, Marzeion A, M, Jaeger C, Teichmann J, Bretzel R, G, Hollenhorst M, Kloer H, U: High Prevalence of Exocrine Pancreatic Insufficiency in Diabetes mellitus. Pancreatology 2003;3:395-402. doi: 10.1159/000073655

Aim: The study aimed to establish the prevalence of pancreatic exocrine insufficiency in diabetic patients by using Fecal elastase-1 concentrations as a screening tool.
Methods: This observational study was carried out at multiple centers in Germany (Third Medical Department and Policlinic, Giessen University Hospital, Giessen and Hochschulrechenzentrum, Giessen University, Giessen, Germany) where patients with type 1 and type 2 diabetes mellitus, were screened for exocrine dysfunction of the pancreas, using Fecal elastase concentrations in spot stool samples as an indirect test. Fecal elastase concentrations were measured using a commercially available ELISA test kit. FEC >200ug/g were taken as normal, FEC levels between 100-200ug/g and below 100ug/g were categorized as mild-moderate and severe exocrine pancreas insufficiency respectively. The study protocol was in accordance with ethical procedures and approved by the local ethics committee.
A total of 1020 were evaluated, out of which 323 patients had type 1 DM, and 697 patients had type 2DM. Patients with an underlying gastrointestinal or pancreatic condition were excluded from the study. This included, patients with severe diseases, malignancy, any past history of gastrointestinal surgery, proven gastroparesis, a history of alcohol/drug abuse or a known cause of malnutrition and malabsorption. A standard case report form was used to record the clinical parameters of patients such as the duration, type and treatment regimen for diabetes, and gastrointestinal symptoms were recorded using a graded score (Abdominal pain[0=none , 3= severe], stool consistency [0 = hard , 3 = watery), flatulence [0 = none , 3 = severe]).
Statistical analysis was carried out using SPSS for windows 6.13. Parametric x^2 test was used to analyze any differences in prevalence. Correlation analysis between different parameters was done using the Spearman method. Statistical significance was labelled for p values <0.05
Results: Out of the 1020 diabetic patients, 98.5% were Caucasians, 1.34% Oriental, and 0.98% Asians. The mean age at onset and duration of diabetes was 39 years and 11 years, respectively. A normal fecal elastase level was found in 59.3% (602 patients) , a reduced level of fecal elastase between 100-200ug/g was found in 17.8% (181 patients) and 22.9% (232 patients) of the sample showed markedly decreased levels of <100ug/g. These results were further analyzed and grouped according to the type of diabetes. Patients who were diagnosed with type 1 DM, collectively had a higher incidence of lower levels of FECs compared to type 2 diabetics. 28.5% of type 1 Diabetics showed severe PEI, 22.6% Mild-moderate insufficiency in comparison to type 2 diabetics, in which 19.9% had severe insufficiency, and 15.5% had mild-moderate insufficiency. There was no correlation between Fecal elastase levels and age or sex. However, the results showed a correlation between patients with a long duration of diabetes, patients with early-onset diabetes, patients on insulin therapy and those with low MBI with low Fecal elastase concentrations (statistical significance p<0.01). No correlation was demonstrated between symptoms and fecal elastase levels.
Conclusion: This prevalence study used the indirect test of measuring fecal elastase concentrations as a screening test for detecting mild-moderate and severe pancreatic exocrine insufficiency in diabetics,and was able to demonstrate a higher frequency of Pancreatic exocrine insufficiency in both type 1 and type 2 diabetics.

Critical Analysis:
This observational study was published in 2003 in the journal Pancreatology, which is a peer-reviewed journal. The awareness of Type 3c diabetes has increased in recent yearsestablishing the mechanisms of how primary pancreatic disease such as pancreatitis ,pancreatic cancer can result in diabetes , known as type 3c diabetes.[39] However, very few studies currently exist that investigate how a primary endocrine dysfunction of pancreas, manifesting as diabetes mellitus, can lead to exocrine pancreas dysfunction. This study, therefore aimed to address an important clinical question of determining the prevalence of pancreatic exocrine insufficiency in diabetic patients and was the only study in recent years, that analyzed a large cohort of 1020 patients. The only other study which used a large sample was done in 2001 on 544 patients but it was exclusively for patients with type 2 DM.[40]This study suggested that PEI occurred at a higher frequency in Type 1DM compared to Type 2DM contributing to the hypothesis that an autoimmune disorder in type 1 DM, might play a role in autoantibody induced damage to exocrine pancreas.[39]
Another strength of the study is that , it used the indirect, inexpensive, easily available and time saving spot stool Fecal elastase-1 test for assessing pancreatic dysfunction. Previously, PEI's prevalence amongst diabetics was investigated as early as 1940s using direct tests which were invasive and expensive.[41]Data from this study using the newer Fecal Elastase-1 Elisa test can translate well to the practices in UK, where the test is widely available and cost efficient.
However, It is important to note that although Fecal elastase-1 test has high specificity of 93% for diagnosing PEI,[42]and 100% sensitivity for diagnosing severe PEI (i.e values <100ug/g),[43]however its sensitivity is greatly reduced to upto 63% for diagnosing PEI of mild to moderate severity (FE-1 Values between 100-200ug/g).[43] The study demonstrated that 22.9% of the sampled population had markedly decreased Fecal elastase concentrations and therefore is still a significant number to pick up, and to consider treatment with pancreatic enzyme replacement therapy.
The limitations of the study can be mostly attributed to the study design and sampling techniques. Although the study

mentioned an exclusioncriteriaof not enrolling patients with any previously diagnosed gastrointestinal or pancreatic disease that could alter the fecal elastase levels, it failed to mention how this was ensured. Was the history of previous disorder just asked from patients in Case Report Forms(potential risk for Recall Bias), or all patients had documented absence of any underlying pancreatic disease or malabsorption from other GI conditions (celiac, IBD, etc.) using imaging techniques such as CT and MRI scan? This is important as we know that Type 3c Diabetes(a form of diabetes resulting from primary exocrine pancreas disease) is often a missed diagnosis and is more common than believed so far.[44] Some patients might be asymptomatic for years with underlying chronic pancreaticand therefore the positive screening test result may be wrongly attributed to Type 1 and Type 2DM alone.

Selection bias also exists when comparing the twodiabeticpopulation.The characteristics and clinical findings in the two groups did not demonstrate an ideal match. For instance, 323 patients were type 1DM and 697 were type 2, also the mean duration of diabetes for type 1DM was 16.1 years, compared to 8.7 years of type 2 DM. Can the results of higher frequency of severe insufficiency in type 1DM (28.5%, vs 19.9% in type 2DM) be attributed to the longer duration of diabetes in the type 1 cohort? One of the hypothesis to explain PEI developing in diabetics is that PEI could possibly be due to a complication of chronic diabetes as a result of autonomic neuropathy and angiopathy resulting in atrophy and fibrosis of the pancreas.[13]

The study also failed to describe whether patients enrolled had any clinical symptoms such as diarrhea at the time of screening test. 7% of patients with diarrhea can give false positive test.[42] There has been criticism on using fecal elastase-1 test for diagnosing PEI, because it is likely that those with severe PEI may be symptomatic with steatorrhea and watery stools, resulting in an abnormal test result.

The study showed correlations between low Fecal elastase-1 levels and insulin use, low BMI and duration of diabetes, however also suggested that these associations were weak, and statistical significance could only be attributed to the large sample size.[39] In one of the charts there was 0.9% missing data for type 1 DM, and 0.4% missing data for type 2 DM patients, no reason was mentioned for this. Additionally, there were no healthy controls selected which could have strengthened interpretation of correlations and results.

Despite its limitations, the study was able to demonstrate that pancreatic exocrine insufficiency is quite common in diabetic patients and expressed the need to actively investigate and consider PEI in diabetics.It also demonstrated a weak correlation of PEI with the duration of diabetes and insulin use, raising the importance of testing these group of patients and considering a diagnosis of pancreatic exocrine insufficiency.

Study 2: **Pancreatic exocrine insufficiency in type 1 and type 2 diabetics of Indian origin** [45]

Shivaprasad C, et al., Pancreatic exocrine insufficiency in type 1 and type 2 diabetics of Indian origin, Pancreatology (2015), http://dx.doi.org/10.1016/j.pan.2015.09.018

Aim: This study aimed to investigate the prevalence of pancreatic exocrine insufficiency in both type 1 and type 2 diabetic patients of Indian origin and evaluated the effects of pancreatic exocrine insufficiency on glycemic control and other diabetic metabolic parameters.

Methods: 205 diabetic patients were initially recruited between the years 2012-2014 from two centres in Bangalore (The Bangalore Diabetes Hospital and Vydehi Institute of Medical Sciences and Research Center) and 184 patients who matched the study criteria were selected for the study. Out of the 184 patients, 89 were type 1and 95 wereType 2 diabetics as defined by the American Diabetic Association criteria. Additionally, 95 gender matched healthy controls were also selected. Informed consent was taken and ethics approval was obtained. Exclusion criteria was clearly defined and any patients with the following medical history wereexcluded:-

1. Known cases of pancreatic disease from fibro-calcification
2. Ultrasound/ Abdominal x-ray evidence of pancreatic calcification
3. Any known cause for malabsorption due to pancreatic disease.
4. Past history of Malignancy, gallstones, Gastrointestinal surgery and gastroparesis
5. History of Alcohol abuse.

Patients who fulfilled the criteria were enrolled in the study and a detailed history and examination was performed on all patients. Baseline metabolic parameters(HbA1c, FBS, Hemoglobin, serum albumin, serum calcium), in addition to baselines physical characteristics; like BMI, Weight, Height were also recorded. Detailed history about diabetes was obtained including the onset and duration of diabetes, microvascular & macrovascular complications and treatment regimens. Abdominal X-ray and/or abdominal ultrasound was performed to rule out pancreatic calcification. Finally, Fecal Elastase-1 concentrations were measured using the commercially available ELISA kits from BIOSERVE diagnostics GmbH, Germany. FEC under 200ug/g were considered as diagnostic of pancreatic exocrine insufficiency. FEC below 100 u/g of stool was considered diagnostic of severe PEI. Pearson's correlation was used to study correlation between biochemical and anthropometric parameters and Fecal elastase-1 concentrations. Associations between Fecal elastase-1 levels and various biochemical and anthropometric parameters were calculated using T-test and regression analysis. Statistical significance was defined for P values <0.05.

Results: Results showed that the frequency of severe pancreatic exocrine insufficiency, indicated by FE-1 levels <100ug/g was significantly higher(P<0.05) in Type 1 DM(17.9%) in comparison to Type 2 DM (3.1%). With regards to the symptoms, only 6% of type 1 DM patients reported symptoms vs 4% of Type 2 DM patients. The mean FEC were 249.4 ± 127.3 ug/g(Type 1DM) , 327.3 ± 155.4 ug/g, (Type 2 DM) and 387.24 ± 137.9 ug/g (Control). The prevalence of PEI, as defined by FEC <200ug/g, was found to be 31.4% in Type 1 DM, 29.4% in Type 2DM and only 4.4% in controls.

A negative correlation was reported between FEC and HbA1c (r=-0.321, p=0.01), and between FEC and Fasting Blood sugar (r=-0.194, p=0.001). A positive correlation was observed between BMI and FEC (r=0.24, p=0.004) and between FEC and Hemoglobin (r=0.153, p=0.038). No significant correlation was found between FEC and other biochemical and anthropometric parameters. T-test and step-wise logistic regression after confounding adjustments, was used to analyze any association between FEC and biochemical and anthropometric parameters, but no significant determinants were found to be associated with FEC.

Conclusion: The study reported that approximately one third of Type 1 and Type 2 diabetics have Pancreatic Exocrine Insufficiency which is comparable to other similar studies.[39]Additionally, it was observed that FEC was inversely correlated to both Fasting Blood Sugar and HbA1c. The authors emphasized on the need for further studies to study the impact of PEI on glycemic control and the benefits of enzyme replacement therapy in diabetics with PEI.

Critical Analysis:

This cross-sectional case-control study was conducted recently and was published in a peer-reviewed journal, Pancreatology, in the year 2015. Earlier studies used the direct, invasive secretin-pancreozymin test to demonstrate PEI in diabetics, however, Fecal elastase-1 estimation in stool samples have become the standard and widely adopted as a diagnostic tool for pancreatic exocrine insufficiency. The study used Fecal elastase-1 concentrations to screen patients for PEI , but also recognized the limitation of the polyclonal assay for a tendency to show a higher proportion of false-negative results.[46] Varying estimates of the prevalence of PEI in diabetics have been reported ranging from 19% to 74% in Type 1 DM.[47-49] However, this is the first study to explore prevalence of PEI in diabetic patients of Indian origin. Since a large subset of the UK population consists of Indians, the data from this study is quite useful and relevant to the UK practice.

The main strengths of this study lie in the study design and methodology. The study selected a comparable sample size of both Type 1 DM and Type 2 DM patients. A healthy gender matched control group was also selected for comparison. Additionally, steps were taken to ensure that patients with underlying GI and Pancreatic disease that could alter the FEC were excluded, by performing ultrasound and abdominal x-rays on all patients to identify pancreatic calcifications. However, a systemic review and meta-analysis comparing imaging modalities (CT, MRI, Endoscopic Ultrasound, Abdominal Ultrasound) concluded that abdominal ultrasound had the lowest accuracy in diagnosing chronic pancreatitis.[50] Thus, the choice of modalities chosen to exclude underlying pancreatic might not be sensitive enough to confidently exclude underlying pancreatic disease causing Type 3C diabetes, an underdiagnosed and often missed condition.

The study, however, is not without weaknesses. Data was not shared on whether the two diabetics groups matched the duration of diabetes. This is important as it has been suggested by some studies that PEI could be a complication of long standingdiabetes and therefore it is difficult to comment on the higher prevalence of PEI in T1D vs T2D. Furthermore, it was not mentioned, how the Fecal elastase-1 measurements related with symptomatic patients, because diarrhea (a common symptom of exocrine insufficiency) can give false positive results in 7% thus reducing the sensitivity of the test.[42]

Despite the weaknesses, the study was able to produce prevalence data comparable to other studies. For instance, in a study involving 195 Type 1 Diabetics, 34% were reported to have PEI.[47]A study involving 1020 reported comparable results of combined Type 1 and Type 2 PEI prevalence of 51%. In another large study of 544 Type 2 DM patients, 30 % were reported to have Pancreatic exocrine insufficiency.[51] This study concluded that an inverse relation exists between FEC and HbA1c levels, which was also demonstrated by Terzin et al, showing that low Fecal elastase-1 levels correlated with higher HbA1c.[52]

Finally, the study raised an important clinical question, as to whether screening for PEI should only be offered to patients with GI symptoms? It was found that only 6% of T1D and 4% of T2D reported any symptoms, thus emphasizing the importance of asymptomatic PEI and the need to perform FE-1 test at an earlier stagebefore symptoms develop.

Study 3: Low Fecal Elastase 1 Levels Do Not Indicate Exocrine Pancreatic Insufficiency in Type-1 Diabetes Mellitus [53]

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(3):274-8.

Aim: Measuring low fecal elastase-1 concentrations in stool have become increasingly popular over the past few years to diagnose pancreatic exocrine insufficiency and have replaced the invasive and costly secretin-pancreozymin test to assess pancreatic function.[54,55] The indirect FE-1 test has been used to claim increased frequency of PEI in diabetics with upto 40% of the patients requiring pancreatic enzyme

substitution. This high reported frequency could affect the increasing diabetic population worldwide, and have a serious impact on health care costs. The objective of this study was to evaluate the results of gold standard secretin-cerulein test performed on Type 1 diabetics, and compare the results with indirect tests; fecal elastase 1 and fecal fat estimations.

Methods: 93 consecutive type 1 diabetics who attended the Clinic for Diabetes and Metabolic Diseases in Karlsburg, Germany were initially offered the pancreatic exocrine function evaluation, however only 33 agreed to take part in the research. Type 1 Diabetes was diagnosed using clinical history (ketosis, age, polyuria, polydipsia, onset and duration, insulin regimen) and antibody test was used for those with atypical symptoms to confirm diagnosis.Glycemic control, frequency of mild/severe hypoglycemic episodes, Diabetic Ketoacidosis events and self measured pre-meals glucose levels were recorded. Patients with glucose levels within normal range and mild hypoglycemic episodes were deemed stable. Whereas, patients with repeated episodes of hypoglycemia or DKA events were labelled as having labile diabetes. Additionally, patients were evaluated for other micro and macrovascular diabetic complications such as diabetic neuropathy, retinopathy and nephropathy. Patients with past history of acute pancreatitis, gastrointestinal surgery, hyperthyroidism or inflammatory bowel disease were excluded from the study. 1 patient had been previously diagnosed with celiac disease, and antibodies were found in 4 additional patients, indicating latent celiac disease. Ethical approval was obtained from ethics committee of the Ernst Moritz Arndt University, Greifswald, Germany.

A Secretin-cerulein test was performed along with fecal weight and FEC measurement on the selected 33 patients. A Normal SCT was defined as fluid secretion > 67 mL/30 min, bicarbonate concentration >70mmol/l, bicarbonate output >6.5mmol/30min after secretin administration; and amylase output >12,000 U/30 min, lipase > 21,000 U/30 min after cerulein administration. For fecal fat analysis, patients had to collect stool for 72 hours at home and analysis was done using Van de Kamer method (reference levels: fecal weight, G200 g/d; fecal fat, G7 g/d)[56]Fecal elastase 1 was measured in stool using two methods; monoclonal antibodies (ScheboTech, Wettenberg, Germany); and polyclonal antibodies (Bioserv Diagnostics, Rostock, Germany). Pancreatic exocrine Insufficiency was defined as FE-1 levels <200 ug/g according to kit manufacturers. The result of each test, was unknown to the individuals performing the 3 tests.

Student T-test was used to compare continuous variables, Kruskal-Wallis test for ordinal variables, and Fisher exact test for categorical variables. Negative predictive value, positive predictive value, sensitivity and specificity were calculated for SCT, FE-1 and Fecal Fat tests.

Results: Out of 33 patients, 17 were men and 16 women. Fecal elastase 1 concentration using monoclonal antibodies was found to be abnormal in 45.5% (15 patients) patients and normal in 54.5% (18 patients). SCT was also found to be normal in 13 of these 18 patients but abnormal in the remaining 5 patients. SCT was also abnormal in 6 of the 15 patients with an abnormal FE-1 test result, but normal in the remaining 9 patients. Thus, normal and abnormal fecal elastase 1 test results were confirmed by the SCT in 57.6% (19 patients) and not confirmed in 42.4%(14 patients). Fecal elastase 1 levels using polyclonal antibodies were normal in 72.7% (24 patients)and abnormal in 27.3%(9 patients). Out of 24 patients with a normal test result, the SCT was also normal in 17 patients, but abnormal in the remaining 7 patients. Out of the 9 patients with an abnormal test result, the SCT was normal in 5 but abnormal in the remaining 4 patients. Thus, normal and abnormal fecal elastase 1 test results were confirmed by the SCT in 63.6% (21 patients) and not confirmed in 36.4%(12 patients).

Data was found to be low for sensitivity, specificity, PPV and NPV, for Fecal-elastase 1 estimations (using both monoclonal and polyclonal antibodies) in predicting steatorrhea and SCT results. No significant correlation was demonstrated between fecal elastase 1 levels and increased steatorrhea episodes.

A significant correlation was found between fecal fat concentration and fecal weight (P = 0.0022). Fecal fat excretion was normal in 33.3% (11 patients) and abnormal in 66.7% (22 patients). Steatorrhea was mild to moderate (7-10 g/d) in 7 patients, it was severe (9-0 g/d) in 15 patients. Overall, 12 (54.5%) out of 22 patients with steatorrhea had diarrhea as a symptom. Patients with steatorrhea were more likely to also have labile diabetes. (P = 0.03)

No significant correlation was found between the SCT and Fecal elastase -1 levels with gender, age, age at onset of diabetes, diabetes duration, alcohol use, HbA1C, or complications like retinopathy, nephropathy, and neuropathy. The only exceptions were BMI which was found to be significantly higher in patients with normal SCT (p=0.02) and nephropathy, which was significantly higher in patients with decreased fecal elastase 1 levels (P = 0.002).

Conclusion: In summary, the study demonstrated that only 11 out of 33 patients had abnormal SCT results. These patients only had mild-moderate PEI, and In the 4 patients with steatorrhea and decreased lipase output , lipase secretion was not less than 10% of normal, which according to research is when steatorrhea due to pancreatic disease usually manifests itself.[57] Maldigestion resulting in steatorrhea has many other causes including bacterial overgrowth, cirrhosis, biliary obstruction and celiac sprue. In this study, patients with inflammatory bowel disease and hyperthyroidism had been excluded and no correlation was found between steatorrhea and celiac disease, and patients with inflammatory bowel disease and hyperthyroidism had been excluded. Additionally, no other signs and symptoms

were present for other rare causes. Thus, the author suggested that steatorrhea in these patients was not pancreatogenic and was attributed to bacterial overgrowth. The study concluded, that neither Fecal elastase-1 , nor fecal fat estimations, could be used reliably for a diagnosis of pancreatic exocrine insufficiency in patients with type 1 diabetes and therefore should not be used as a tool to guide expensive treatment with pancreatic enzyme replacement.

Critical Analysis:

This article was published in 2008 in the official journal of the International Association of Pancreataology (IAP) and the European Pancreatic Club (EPC) called Pancreatology. All articles in the journal are peer-reviewed. The objective of the study was to compare the results of fecal fat analysis and Fecal Elastase-1 test, both indirect tests used to diagnose Pancreatic exocrine insufficiency in a cohort of type 1 diabetics, with the direct, invasive, gold standard Secretin-Cerulein Test. The worldwide prevalence of diabetes as reported by IDF, is 8.8% and is expected to rise to 9.9% by the year 2045.[58] In UK alone, 3.8 million people have been diagnosed with diabetes. Studies in the past using indirect test have reported a prevalence of PEI of upto 51% in type 1 diabetics and 32% in type 2 diabetics (Hardt and Ewald, 2011) with upto 40% requiring pancreatic enzymes substitution.[54,55]Thus, this study proposed an important question; whether Fecal Elastase-1 is a reliable test in accurately diagnosing patients with PEI that would require Pancreatic Enzyme Replacement therapy, which would ultimately increase health care costs.

The strength of this study was in comparing data from both indirect and direct tests, which has not been done before. With the ease in availability of Fecal Elastase-1 test and the non-invasive characteristic of the test, it has has been widely adopted as the first-line screening test for PEI. This is stressed upon by the fact, that out of the 93 patients that were initially selected, 60 patients refused to take part in the study. Some of the reasons listed were social problems, long distance to the hospital, and reluctance to take time off from work. 4 patients were unable to swallow the endoscopy tube needed to carry out SCT. These are some major disadvantages of using invasive tests and therefore emphasize the need for an alternative noninvasive but reliable test for diagnosing pancreatic exocrine insufficiency. To ensure blinding, the measurements of the SCT and fecal fat analysis were not known to those measuring fecal elastase 1, and vice versa. This eliminated any bias from the investigator and those carrying out the laboratory analysis.

The weakness of the study was the small sample size of only 33 patients. Patients were selected from a referral center for diabetes, and therefore did not represent the general population. There was no randomization done and no controls were chosen for accurate comparison of data. While exclusion criteria was briefly mentioned, the methods to ensure patients did not have underlying pancreatic disease by performing imaging studies were not discussed. Although all patients were tested for transglutimnase antibodies for celiac disease, yielding 5 abnormal results, these patients were not excluded from the study. This was a major selection bias, because the results of the screening tests for PEI in diabetics couldn't be explained by diabetes alone, as it included patients with celiac disease.

Additionally, it was not mentioned whether patients were enquired about GI symptoms before testing, because diarrhea can result in inaccurate fecal elastase-1 estimations. No P-value for statistical significance was mentioned for comparing data of the three tests. Therefore, the claim by the author, that Fecal elastase-1 is not appropriate for accurately diagnosing PEI cannot be regarded as evidence-based. The author made another claim that the most likely explanation for fatty stools in type 1 DM, was due to bacterial overgrowth. The reasoning behind this was, that they had already excluded patients with hyperthyroidism, inflammatory Bowel disease, GI surgery, and no correlation was found between celiac disease and patients with steatorrhea in their study, and that signs and symptoms to suggest other rarer causes of malabsorption were absent. However, this was not supported by performing Hydrogen breath test on patients to diagnose bacterial overgrowth, nor were other tests done to confirm the absence of other GI diseases. Thus, the study failed to give an explanation for steatorrhea in the type 1 diabetics.

Finally, the study recommended that clinicians should not use Fecal Elastase-1 test or raised Fecal Fat, as an indicator to start pancreatic enzyme substitution as they are unreliable in diagnosing PEI in type 1 diabetics, and therefore "this may also be true in type 2 diabetics". The study did not recruit any type 2 diabetics or controls and therefore failed to back up the advice with statistically significant evidence.

Although the reliability of fecal elastae-1 test in diagnosing PEI has often been debated and conflicting literature exists against it, studies such as this one have not been able to conclusively demonstrate disadvantage of using fecal elastase-1 test. For instance, other studies have shown that Fecal elastase test has high specificity of 93% for diagnosing PEI [42], and 100% sensitivity for diagnosing severe PEI (i.e values <100ug/g).[43]The current Australian and UK clinical guidelines also recommend using fecal elastase-1 as the initial screening test in diagnosing pancreatic exocrine insufficiency.

Study 4: Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c)[59]

Ewald, N. , Kaufmann, C. , Raspe, A. , Kloer, H. U., Bretzel, R. G. and Hardt, P. D. (2012), Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). Diabetes Metab Res Rev, 28: 338-342. doi:10.1002/dmrr.2260

Aim: According to the American Diabetes Association, the current classification of diabetes consists of Diabetes type 1

-type 4.[60] However, despite the awareness of the more common type 1 and type 2 diabetes mellitus, type 3c diabetes due to pancreatic disease is rarely thought of in everyday clinical practice. Hardly any data exists investigating the prevalence of type 3c diabetes. The objective of this study was to investigate the prevalence of diabetes due to pancreatic disease and analyze the different characteristics and parameters of patients suffering from it.

Methods: This was a retrospective study, that analyzed the records of 1868 diabetic patients who had been admitted in The University Hospital Gissen in Germany, over a period of 24 months (1st Jan 2003- 31st December 2004). Standardized data forms were used to document parameters such as age, sex, MBI, HbA1c, diabetes duration and therapy, and clinical symptoms and complications related to GI tract and diabetes. Patient records were also checked for results from imaging procedures including MRI, Ultrasound, CT , and ERCP.

On the basis of available parameters, all patients were reclassified according to the American Diabetes Association's classification of Diabetes Mellitus.[60]Patients with Autoimmune antibodies for diabetes and insulin dependency at diagnosis, were labelled as Type 1. Absence of autoantibodies, BMI above 25kg/m^2 and residual C-peptide levels in patients were classified as type 2. Finally, patients with FE-1 concentration below 200ug/g, absence of autoantibodies, and pathologic findings on imaging were diagnosed as type 3c diabetes.

Adherence to Good Clinical Practice guidelines and Declaration of Helsinki principles was ensured for the study. Statistical analysis was carried out using SPSS V11.5. Correlations were investigated using Pearson test or Spearman's rho test. Correlation of HbA1c, BMI, age, amongst the three diabetic groups was done using Dunnet's T2 test.

Results: Prior to reclassification, out of 1869 patients, 23.3% (436 patients) were diagnosed with T1DM, 69.5% (1298 patients) with T2DM, 6.3% (117 patients) were diagnosed with Type 3c diabetes and 0.9% (17 patients) were unclassified. Reclassification was done according to the ADA criteria, and 23.1% (431 patients) were classified as having T1DM, 677% (1265 patients) with T2DM, and 9.2% (172 patients) were classified as Type 3c Diabetes. It was found that from the newly classified type 3c group of 172 patients, 6.4% (11 patients) were initially misdiagnosed as T1DM, 40.1% (69 patients) were initially misclassified as T2DM, 51.2%(88 patients) were correctly diagnosed as Type 3c DM and 2.3% (4 patients) who were not classified initially, were reclassified as Type 3c.

The underlying cause for type 3c diabetes in the 172 patients was assessed. The most common cause identified was chronic pancreatitis 78.5% (135 patients), followed by pancreatic cancer 8.1% (14 patients), Hereditary Hemochromatosis 7% (12 patients), Cystic fibrosis 4.1% (7 patients) and post pancreatic resection for various reasons 2.3% (4 patients).

The anthropometric and metabolic parameters between the three groups was also compared. Concerning age, there was a significant difference between type 1 and type 2 ($p < 0.001$) and between type 1 and type 3c ($p < 0.001$). Concerning sex, type 3c diabetes was more common in males 60.5% than females 39.5% ($p=0.014$). However, no relevant and significant difference was reported for type 1 and type 2.BMI comparison of type 1 (mean BMI 25 kg/m 2) and type 2 (mean BMI 30.3 kg/m2) showed a significant difference ($p< 0.001$). Similarly, a significant difference was noted between type 2 and type 3c patients (mean BMI 26.6 kg/m2) ($p < 0.001$) and between type 1 and type 3c patients ($p=0.020$).

The mean HbA1c values were 7.7%, 7.5% and 7.8% for type 1, type 2 and type 3c patients, respectively. These values did not show any statistically significant difference.

Conclusion: This retrospective study showed that the prevalence of type 3c diabetes was approximately 9% which was underestimated initially in diabetic patients treated at a tertiary care hospital over a period of 2 years . The study also showed that type 3c diabetes had a significantly lower BMI compared to other types, which may be explained by malnutrition from exocrine insufficiency. Type 3c diabetic patients were older compared to type 1 (type 1 is mostly diagnosed at a younger age). However, age and absence of autoantibodies, could not be used to differentiate type 2 and type 3c patients, resulting in type 3c patients often misdiagnosed as being type 2. The most common pancreatic disorder amongst type 3c patients was chronic pancreatitis (78.5%). Previous studies have shown that there is a significant underestimation of chronic pancreatitis in medical practice.[61,62] Additionally due to the invasive nature of diagnostic tools and unspecific nature of symptoms, chronic pancreatitis is often underestimated and therefore type 3c diabetes is generally rarely considered by clinicians.

The authors concluded that diabetes mellitus secondary to exocrine pancreatic diseases is often misclassified and under-diagnosed and should not be ignored when diagnosing patients with diabetes, as it would change the clinical workup and therapeutic options available for patients. For instance, PERT is needed to prevent nutritional deficiencies (Vitamin D deficiency and its complications) and may augment GLP secretion thus improving glucose metabolism.[63,64]

Critical Analysis:

This study was published in an online-only journal called Diabetes/Metabolism Research and Reviews in the year 2011. The impact factor of this journal is 4.758. Impact factor was conceptually developed in the 1960 and has been accepted as a quantitative measurement for journal quality.[65]A retrospective analysis was done collecting data

of 1869 patients diagnosed with diabetes mellitus, who received treatment at a tertiary care hospital. The objective of the study was clearly defined: to investigate the prevalence of patients with type 3c diabetes, a type of diabetes resulting from exocrine pancreas disease. The large sample size of 1869 adds to the strength of the study. The study is also a pioneer in investigating the misclassification of diabetes types by healthcare professionals using the American Diabetes Association classification of diabetes.

The study was not without weaknesses. For instance, no inclusion and exclusion criteria were mentioned. It was also not discussed how and if, any randomization was done. The study tried to reclassify patients into 3 groups, type 1, type 2 and type 3c DM according to the American Diabetes Association criteria, however, it did not discuss whether the sample collected included patients belonging to other diabetes types , such as type 3 from other causes and type 4 or how other types were excluded. The study was conducted at a centre that specialized in diabetology, gastroenterology and pancreatology, and is therefore prone to Selection bias. This would have probably contributed to an overestimation of prevalence of Type 3c DM patients because patients with pancreatic disease are more likely to be hospitalized. The data was collected from only one centre, and therefore limits the interpretation of prevalence results, for which a cross-sectional analysis from multiple centre is a suitable design method. Furthermore, it is unlikely that all diabetic patients had been tested for fecalelastase-1 levels and imaging studies were done to exclude pancreatic disease. Therefore, due to the retrospective nature of the study, how the reclassification based on these parameters was done is unclear.

Despite the limitations, the study concluded that a large population of diabetic patients have type 3c diabetes (9.2%)These results are close to a previous study consisting of 1922 patients, which reported a type 3c prevalence of 8%.[66]

A failure to recognise the right diagnosis can result in suboptimal treatment and lower quality care. This study was pivotal in recognising pancreatogenic diabetes often being misdiagnosed as type 2 diabetes, which could place a tremendous burden on the NHS by putting diabetic patients at short and long term risks due to inadequate treatment.

Although this study's main objective was to investigate the prevalence of Type 3c diabetes, it should be noted that individuals with longstanding Type 1 and Type 2 DM are at higher risk of developing acute and chronic pancreatitis , and with it pancreatic exocrine insufficiency, suggesting a bidirectional causality.[67] This means, that GI complains in all diabetic patients should be investigated for PEI, which could uncover an underlying disease of the exocrine pancreas (Type 3c diabetes) or a complication of long-standing diabetes.

Study 5: 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-centretrial[68]

Ewald, N. ,Bretzel, R. G., Fantus, I. G., Hollenhorst, M. , Kloer, H. U. and Hardt, P. D. (2007), 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., 23: 386-391.

Aim: Patients with Fecal elastase-1 levels below 100ug/g are defined as having severe exocrine pancreas insufficiency and steatorrhea is present in 60% of these patients, indicating the need for pancreatic enzyme substitution.[19] This study aimed to investigate the effect of pancreatic enzyme replacement therapy (PERT) on diabetic patients that were on insulin therapy and evaluate the effects of PERT on glucose metabolism and treatment of diabetes.

Methods: This was a randomized double-blinded control trial conducted at multiple centres (14 centres). An informed consent was taken and 546 diabetic patients that were on insulin treatment were screened for severe PEI(<100ug/g), using the commercially available fecalelastase-1 ELISA kit (Schebo Biotech, Giessen, Germany. 115 patients(21.1%) had an FEC<100ug/g, out of which 95 entered the study and 80 patients were further randomized to receive either placebo (41 patients) or Pancreatin enzyme(Creon)(39 patients) in a double-blind manner. Pancreatin was to be taken thrice a day with meals (4 capsules of either placebo or 4 capsules each of 10000 FIP units pancreatin) . Additionally, 2 capsules of 10000 FIP units pancreatin or placebo were allowed with each extra snack.

Patients were observed for 4 months (16 weeks) during which clinical symptoms and parameters of diabetes therapy and glucose metabolism were recorded including HbA1c, Fasting blood glucose, 1 and 2 h glucose. Clinical symptoms [abdominal pain (0 = none , 3 = severe), flatulence (0 = none − 3 = severe),stool consistency (1 = hard , 4 = watery)] were assessed by investigator at 0,1,2,5,10 and 16 weeks , along with diabetes history (onset, duration, dose of insulin, hypoglycemic episodes) , recorded on a standard case report form. Additionally, physical examination, vital signs, adverse event reports, as well as blood, biochemistry and urine analysis data was recorded on standard forms. Statistical analysis was done using SAS and SPSS for windows 11.5.1. P values <0.05 were considered statistically significant. The Ethics committee of each centre approved the study design.

Patients with proven gastroparesis or diarrhea, history of drug or alcohol abuse, any severe disease, any malignancy, history of gastrointestinal surgery, or any diagnosed cause for maldigestion or malabsorption were excluded from the trial.

Results: 546 diabetic patients that were on insulin treatment were screened for severe PEI (<100ug/g), using fecal elastase-1 test. 115 patients (21.1%) had an FEC<100ug/g, out of which 95 entered the study and 80 patients were further randomized to receive either placebo (41 patients) or Pancreatin enzyme (Creon) (39 patients). In the pancreatin group, there were 26 male, 13 females, mean age 45.3 years, and mean BMI 26.4kg/m^2, and in the placebo group there were 25 males, 16 females, mean age 43.2 years and mean BMI 25.3kg/m^2 . Insulin requirement was measured at 0, 4 and 16 weeks, but did not change significantly between the two groups. There was a slight increase in HbA1c in both groups, however, no significant difference was observed. Similarly, 2h glucose measurements following 75g oral glucose load did not show any important differences between the groups. There was no difference observed in clinical symptoms during the observation period. Although Vitamin A levels remained unchanged, there was an elevation of Vitamin E levels in the both groups, and an increase in Vitamin D levels in the pancreatin group. At the beginning of the study, the pancreatin group had more episodes of mild to moderate hypoglycaemia, however, throughout the 16 weeks observation period, no significant difference was observed between the two groups in the number of mild or moderate hypoglycaemic episodes. At end of 4 months, both groups were equal ($p > 0.05$), indicating a reduction in hypoglycaemic episodes in the pancreatin group. Adverse events from treatment were reported in 33 patients (84.6%) of the pancreatin group, and in 35 patients (85.4%) of the control group. The most common side effects reported were headache, diarrhea, pain, dyspepsia and infection. On physical examination and laboratory evaluations, no safety difference was found between the two groups.

Conclusion: In summary, the study was unable to demonstrate any benefits on glucose metabolism parameters by using pancreatin enzyme replacement therapy (PERT). By the end of 16 weeks observation period, both the placebo and pancreatin group showed no significant difference in FBS, HbA1c, 2h- postprandial glucose levels and other clinical symptoms and side effects. There were more hypoglycaemic episodes at baseline in the treatment group, and a reduction was observed in the same group making both the control and pancreatin groups equal in number of hypoglycaemic episodes ($p>0.05$) at the end of the trial. The authors, therefore, concluded that PERT was associated with amore stable control of insulin therapy. Finally, it was suggested that pancreatin enzyme replacement therapy could be safely used in type 1 patients and similar studies evaluating effects of PERT on glucose metabolism in type 2 diabetics are required.

Critical Analysis:

This study was published online in Wiley Inter Science (www.interscience.wiley.com) in the year 2006. All research articles submitted to Wiley are reviewed by at least two qualified experts. The trial aimed to evaluate the effects of pancreatin therapy in patients with insulin-treated diabetes with pancreatic exocrine insufficiency diagnosed by low levels of fecal elastase-1 concentration in stool. A study published in Lancet revealed that exocrine dysfunction of pancreas may also influence glucose metabolism, due to the close morphological and functional link between exocrine and endocrine pancreas.[69] FE-1 levels <100ug/g are associated with steatorrhea in about 60% ,which is an indicator of qualitative and quantitative fat malabsorption.[19] Steatorrhea not only results in complications from deficiency of fat soluble Vitamin D (for eg. Osteoporosis), but absence of free fatty acids (FFA) has an effect on beta cell contributing to development of diabetes mellitus.[19,70] Additionally, its been known that malabsorption resulting from PEI, disrupts the nutrient-induced release of insulin-tropic polypeptide (GIP) , thus worsening glucose tolerance and increasing blood glucose levels. This response is known as the incretin effect of fat and has been shown to be reversible with pancreatic enzyme replacement therapy.[71] A large number of diabetic patients seem to have severe PEI, requiring treatment with Pancreatin enzyme replacement therapy but very few studies have been done on this topic, often with contradictory results.[72-74]This particular trial, is the first and only randomized control trial in recent years that aimed to address the usefulness of pancreatic enzyme substitution in diabetics with severe PEI, and its possible advantageous effects on glucose metabolism and symptom control. Currently, newer studies addressing role of PERT in treating diabetics patients for PEI are under the process of recruitment.

In this randomized , prospective, case-control trial patients were recruited from multiple centres (14 centres). The fact that multiple centres were chosen allows for greater variation and generalizability. Solvay Pharmaceuticals in Germany, provided material support and technical help in the study, which may reduce the credibility of results interpretation as it has been known that trials funded by pharmaceutical companies describe favourable outcomes for the sponsor.[75,76] Although 546 patients were initially recruited, only 80 patients were included in the study, therefore the small sample size may not be an accurate representation of a larger population. It has been known that smaller trials provide less precise data on the effects of treatment compared to larger trials.[77]Although the study was regarded as being double-blinded, no further explanation was given as to who was blinded and how this was achieved. Similarly, the method of randomization for the placebo and treatment group was not shared. Data on the anthropometric and biochemical parameters of the two groups was not available, and so it is difficult to comment on whether the results from the two groups are comparable. The exclusion criteria was mentioned but the methods to

International Journal of Engineering Applied Sciences and Technology, 2025
Vol. 10, Issue 05, ISSN No. 2455-2143, Pages 09-30
Published Online September 2025 in IJEAST (http://www.ijeast.com)

ensure people were accurately excluded, for eg. by imaging studies and blood tests, was not available, resulting inthe potential for Selection bias.

Interestingly, the author claimed that a reduction in hypoglycemic episodes was observed in the pancreatin group. This was rationalized by the fact that both groups were equal in hypoglycemic episodes at the end of the trial ($p>0.05$), compared to the beginning of the trial, when the pancreatin group had more episodes of hypoglycemia. However, this observation was not statistically significant ($P > 0.05$). Furthermore, the p-value for differences in hypoglycemic episodes at the start of trialwas not given. It seems the authors tried to highlight a great advantageous effect of using PERT without any statistical evidence. Similarly, an increase in Vitamin D levels in the pancreatin group was observed, but no p value was reported.

In this study the adverse events were comparable ; 84.6% in the pancreatin group and 85.4% in the placebo group. It is essential to consider the safety of a particular treatment while evaluating the efficacy of treatment.[78] Thus, the study proved that it is safe to use PERT in diabetics. The most common side effects reported were headache, diarrhea, pain, dyspepsia and infection.

A possible reason for lack of effective response from PERT, might be from the dosage of Pancreatin selected for the treatment group. With every 300-600kcal meal, the healthy pancreas normally secretes around 720000 lipase units.[79] The current guidelines suggest the starting dose of PERT around 50000 units.[80] This dose can be uptitrated depending on the type of meal eaten, specially if it contains more fat content, such as, fried foods, cheese, pastry etc. An additional 25000 units is recommended with each extra snack. In this trial, the dose of pancreatin might be inadequate to demonstrate an effective response (4 capsules of 10000 units were used for each main meal, and an additional 2 capsules with each snack). The study design also did not ensure whether both the placebo and treatment groups, received the same meals.The dietary habits of the patients were also not considered, and therefore patients who only ate vegan food, might have shown variable clinical response.

Finally, the trial was unable to demonstrate statistically significant beneficial effects of PERT on patients with type 1 diabetes, both in terms of symptom control and improvement in glycemic control and insulin response.

V. DISCUSSION

The pancreas has traditionally been considered as two distinct organs, however, the endocrine and exocrine parts are interconnected both physiologically and anatomically. Studies have shown,that a network of afferent arterioles supply the islets of Langerhans, blood then leaves the islets anddrains into the acini.Electron microscope studies done in humans and other mammals confirmed the presence of an “insulo-acinar portal system’; a microvascular connection linking the exocrine and endocrine portions of the pancreas.[29-31]This indicated that a large portion of blood from the islets drains into the exocrine pancreas, and the exocrine pancreas are exposed to a high concentration of hormones released by the islets of Langerhans. Multipleresearchers studied the relationship between endocrine and exocrine pancreas and many mechanisms have been hypothesized in which the endocrine dysfunction of pancreas manifesting as diabetes can lead to exocrine dysfunction and insufficiency. Diabetic patients often suffer from persistent gastrointestinal symptoms, but do not discuss their symptoms with endocrinologists. The lack of awareness of the relationship between endocrine and exocrine dysfunction, further contributes to PEI being unrecognized and untreated. This dissertation aimed to review the pathophysiology and relationship between the exocrine and endocrine pancreas, the prevalence of PEI in diabetics and explored the evidence on the impact of PEI and its treatment with pancreatic enzyme replacement therapy (PERT) on glycemic control.

Diabetes can cause inflammation of the pancreas, pancreatic fibrosis and atrophy due to the loss of trophic action of islet hormones on pancreatic tissue, resulting in decreased capacity of the pancreas for adequate pancreatic enzyme secretion. PEI and other forms exocrine dysfunction may occur in about half of type 1 diabetics and almost a third of those diagnosed with type 2 diabetes.[81]A few studies have been carried out to determine the prevalence of PEI in the diabetic population often with varying results. A large observational study consisting of 1020 patients reported that around 22.9% of diabetics had severe PEI.[39] The study also showed a correlation between long duration of diabetes and PEI, contributing to the hypothesis that PEI may result as a complication of diabetes from autonomic neuropathy and angiopathy.

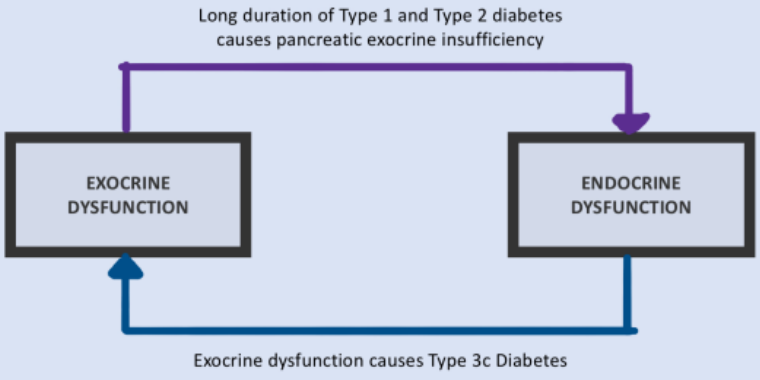

Figure 4: Pancreatic exocrine and endocrine functions are interdependent

International Journal of Engineering Applied Sciences and Technology, 2025
Vol. 10, Issue 05, ISSN No. 2455-2143, Pages 09-30
Published Online September 2025 in IJEAST (http://www.ijeast.com)

The traditional view of the pancreas is now obsolete, and it is now widely accepted that pancreatic exocrine and endocrine functions are mutually dependent (Figure 4). On one hand, insulin has an influence on the proper functioning of the exocrine tissue, whereas a primary exocrine dysfunction (for eg. from chronic pancreatitis, malignancy, cystic fibrosis) causes nutrient maldigestion and malabsorption, impaired incretin secretion and diminished insulin release from the islets, manifesting as Type 3c diabetes (pancreatogenic diabetes). Pancreatitis may be subclinical and type 3c diabetes is often misdiagnosed as type 2 diabetes. A reclassification study consisting of 1868 diabetic patients, found that a large population of diabetic patients have type 3c diabetes (9.2%) and that approximately 40% of type 3c patients were misclassified as type 2 DM.[59] These results are close to a previous study consisting of 1922 patients, which reported a type 3c prevalence of 8% .[66] Thus, the bidirectional causality of PEI suggests that it is not a condition to be overlooked in diabetics and maybe more common than we think.

The diagnosis of PEI can be challenging because the symptoms only manifest when the pancreatic exocrine function has dropped below 10% .[5]The typical symptoms of PEI such as abdominal discomfort, bloating, diarrhea, flatulence, steatorrhea and weight loss, overlap with other gastrointestinal conditions and therefore PEI may be easily missed or there might be a delay in the diagnosis. Furthermore, the classical symptoms of PEI of steatorrhea (fatty/greasy stools) and weight loss only tend to occur in very severe PEI.[6]Fecal elastase -1 test is an indirect test that has been widely accepted as a noninvasive, cheaper alternative to the direct invasive tests for diagnosing PEI. Fecal elastase test has high specificity of 93% for diagnosing PEI [42], and 100% sensitivity for diagnosing severe PEI (i.e values <100ug/g).[43]However, its sensitivity is greatly reduced to upto 63% for diagnosing PEI of mild to moderate severity (FE-1 Values between 100-200ug/g).[43] To add to the challenge, the test can be false positive in 7% of those with loose stool, making the interpretation of results difficult. [41]A small study of 33 patients compared indirect and direct methods of assessing pancreatic exocrine function, suggested that clinicians should not use Fecal Elastase-1 test or raised Fecal Fat, as an indicator to start pancreatic enzyme substitution as they are unreliable in diagnosing PEI in type 1 diabetics, and therefore “this may also be true in type 2 diabetics”. The study did not recruit any type 2 diabetics or controls and failed to back up the advice with statistically significant evidence.

PEI should be investigated in diabetics when diabetic complications (gastroparesis), side effects of anti-diabetic medications (metformin), and other causes of gastrointestinal symptoms (IBS, IBD, celiac disease) have been excluded. PEI should also be suspected in those with recurrent unexplained hypoglycemia and erratic blood glucose levels known as “brittle diabetes”. There is growing awareness that malabsorption from PEI, may disrupt the intestinal-islet incretin axis, resulting in poor glycemic control. Additionally, PEI can result in fat-soluble vitamins deficiency which can be associated with serious health problems. These complications may consist of immune deficiency (Vitamin A), Osteopenia/Osteoporosis (Vitamin D), neurological disorders (Vitamin E) and blood coagulation disorders (Vitamin K).

The main goals of treatment of PEI are to restore nutritional status, relieve the maldigestion/malabsorption symptoms and to reduce the risk of long-term complications by replacing the missing enzymes. Pancreatic enzyme replacement treatment (PERT) involves taking pancreatin enzyme in the form of enteric-coated capsules with each meal and snacks, to mimic the normal physiologic response of healthy exocrine pancreas. Very few studies have explored the therapeutic implications of PERT in diabetic patients, often with conflicting results. For instance, in one study of 40 diabetic patients with tropical calculous pancreatitis who were treated with PERT, a drop of 11mmol/mol (1%) in mean HbA1c was reported after six months [82]The UK prospective diabetes study (UKPDS) has shown that reducing HbA1c by 1% is associated with significant long-term benefits such as a 37% reduction in the risk of microvascular complications, a 43% decreased risk of peripheral vascular disease, and a 14% decrease in the risk of heart attack.[83] However, in a randomized

multicentre double-blind control trial, consisting of type 1 diabetics, no statistically significant beneficial effects of PERT on improvement in glycemic control, insulin response and control of symptoms could be proven. The study, however, showed a rise in Vitamin D levels compared to the placebo group and no difference in adverse events between the placebo and treatment group.[68]

VI. RECOMMENDATION AND CONCLUSION

In conclusion, contradictory data currently exists concerning the prevalence of pancreatic exocrine insufficiency in diabetes and its management which raises the question: Should diabetic patients be actively screened for PEI and should it be treated?. The main concerns regarding PEI arethe maldigestion and malnutrition and the consequences of nutritional deficiencies that result from it.

It is important to raise awareness of PEI amongst diabetics who usually don't tend to volunteer information on their GI symptoms. Similarly, the healthcare professionals, tend to overlook Type 3c diabetes and PEI is often left untreated. This can result in erratic blood glucose control ("Brittle Diabetes") and increase the risk of long-term complications arising from maldigestion and malnutrition, therefore raising tremendous burden on the NHS.

Prevalence studies using fecal elastase-1 stool test have shown that around 40% of diabetics have some degree of pancreatic exocrine insufficiency, of whom one-third suffer from severe insufficiency. Given the cost and non-invasive nature of measuring fecal elastase, it is perhaps worth considering PEI in diabetic patients and actively screening and investigating diabetics for gastrointestinal symptomsespecially those with abnormal nutritional parameters.

There is a definite need for further large scale randomized case-control trials with robust designmethods and carefully chosen endpoints, to study the therapeutic implications of PERT in both type 1 and type 2 diabetic patients.

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ABBREVIATIONS

ADA	American Diabetes Association
ANOVA	Analysis of variance
BMI	Body mass index
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DPP4	Dipeptidyl peptidase-4
ELISA	Enzyme linked immunosorbent assay

FE-1	Fecal elastase -1
FEC	Fecal elastase concentration
FFA	Free fatty acids
GAD	Glutamic acid decarboxylase
GLP-1	Glucagon like peptide-1
HbA1c	Glycosylated haemoglobin
ID	Insulin dependent
NID	Non-insulin dependent
NPV	Negative predictive value
PEI	Pancreatic exocrine insufficiency
PERT	Pancreatic enzyme replacement therapy
PPV	Positive predictive value
SCT	Secretin-cerulein test
SGLT-2	Sodium glucose co-transporter-2
T1DM, T1D	Type 1 Diabetes Mellitus
T2DM,T2D	Type 2 Diabetes Mellitus

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