Pancreatic Exocrine Insufficiency in Type 1 and 2 Diabetes: Therapeutic Implications

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Abstract
The objective of the present review is to focus on pancreatic exocrine insufficiency that is associated with Type 1 and 2 diabetes, its clinical and therapeutic implications, including the utility and efficacy of pancreatin supplementation. A literature search was conducted on Pubmed / Medline to identify relevant articles using terms pancreatic exocrine insufficiency in diabetes mellitus patients, pathophysiology, prevalence, treatment and management published between 2006-2016 in English language. Meta-analysis has revealed the prevalence of PEI in patients with type-1 and type-2 diabetes mellitus to be 37.7% (CI 27.2-49.5) and 26.2% (CI 19.4-34.3) respectively. Very scanty data are available that evaluates the efficacy of pancreatin in patients with diabetes. In the available studies, pancreatin was found to reduce hypoglycemia in insulin treated patients. Pancreatic exocrine insufficiency in type 1 and 2 diabetes mellitus is not uncommon and correct use of pancreatin may have a positive effect on the glycemic status of the diabetic patients.

Introduction
The pancreas is a major organ that regulates nutrient digestion and absorption in conjunction with other organs. Digestion is mediated largely by the major pancreatic enzymes lipase, amylase and proteases.¹ Reduced secretion of these enzymes from the pancreas, rapid destruction or inadequate contact between food and pancreatic enzymes within the intestine results in nutrient malabsorption. This condition is defined as pancreatic exocrine insufficiency (PEI).² The main clinical consequence of PEI is fat malabsorption and malabsorption, resulting in steatorrhea which is characterized by frothy, foul-smelling and buoyant stools, due to their high fat content. Other non-specific symptoms may include abdominal pain, flatulence, loose bowel movements and weight loss in adults, or lack of weight gain in children.³,⁴ PEI results from several diseases such as chronic pancreatitis, pancreatic cancer, acute pancreatitis with substantial areas of parenchymal necrosis, diabetes, cystic fibrosis, Zollinger Ellison syndrome, to name a few (Table 1).⁵-⁹

In this review, we focus on PEI that result from Type 1 and 2 diabetes, its clinical and therapeutic implications, including the utility and efficacy of pancreatin supplementation. PEI not only affects patients with type 1 diabetes mellitus (T1DM), but is also observed in patients with type 2 diabetes mellitus (T2DM). The reported prevalence of PEI varies widely from 5% to 57% ascertained by fecal elastase-1 excretion in patients with DM.¹⁰ From a recently published meta-analysis, it emerged that one in three patients with DM presented with impaired exocrine function when explored by fecal elastase-1 testing. The weighted prevalence rate of PEI was marginally higher in patients with T1DM (37.7%, CI 27.2-49.5) when compared with that registered in patients with T2DM (26.2%, CI 19.4-34.3).¹⁰ These values are in keeping with the 30-50% prevalence figures in T1DM and the 15-35% values in T2DM reported in studies using direct tests for exocrine function evaluation.¹¹ In a cross sectional study from India that included 89 T1DM and 95 T2DM patients, the prevalence of PEI was observed to be 31.4% in T1DM and 29.4% in T2DM.¹²

Table 1: Etiology of PEI⁵-⁹

<table>
<thead>
<tr>
<th>Pancreatic causes</th>
<th>Non-pancreatic causes</th>
</tr>
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<tbody>
<tr>
<td>Chronic pancreatitis</td>
<td>Celiac disease</td>
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<tr>
<td>Acute pancreatitis</td>
<td>Crohn disease</td>
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<tr>
<td>Pancreatic cancer</td>
<td>Autoimmune pancreatitis</td>
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<tr>
<td>Cystic fibrosis</td>
<td>Zollinger-Ellison syndrome</td>
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<tr>
<td>Obstructions of the pancreatic duct</td>
<td>GI and pancreatic surgical procedures</td>
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<tr>
<td>Diabetes mellitus type 1 and 2</td>
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</table>

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Pathophysiology and Risk Factors of PEI in Diabetes Mellitus

Pathophysiological mechanisms pertaining to PEI in diabetes mellitus are not fully elucidated. However; a number of mechanisms have been proposed by which exocrine dysfunction may occur. Figure 1 describes effect of diabetes on PEI.

Insulin stimulates pancreatic acinar cell growth via the insulin-like growth factor 1 receptor i.e. exerting trophic effects on the exocrine pancreas. These trophic and stimulatory insulin effects are lost in diabetes mellitus. In addition to this, morphological distribution of islets throughout the exocrine tissue and the specific blood flow pattern of the insulo-acinar portal system suggest functional interactions between the endocrine and exocrine tissue, i.e. regulation of pancreatic exocrine secretion by stimulatory and inhibitory islet hormones. Furthermore, evidence suggests that increased levels of inhibitory islet hormones such as glucagon and somatostatin further contribute to PEI in DM. Further, PEI may potentially be responsible for variable glycemic control in patients with diabetes. According to a study in T1DM and T2DM patients; the observed decrease in fecal elastase 1 concentrations (FEC) in diabetics was associated with poor glycemic control. Autonomic neuropathy is a frequent complication of long-standing diabetes and pancreatic polypeptide (PP) release has been shown to be a sensitive marker of autonomic neuropathy. Impairment of PP response to a test meal appears to be correlated to the degree of autonomic neuropathy. In a study among T1DM patients, PP plasma levels of basal, cephalic phase and gastric phase, were significantly reduced compared with healthy controls despite the fact that only a minority of patients showed clinical evidence of neuropathy. This may suggest that sub-clinical autonomic neuropathy may impair pancreatic exocrine function in diabetes patients. Apart from this, disturbances of gut hormone release which includes increased basal and post-prandial plasma motilin concentrations and increased post-prandial cholecystokinin (CCK) release marks a potential influence on pancreatic exocrine function in diabetes mellitus.

Auto antibodies originating either from lysis of acinar cells or high circulating glucose concentration are also observed in diabetic patients which might affect acinar cells leading to pancreatic insufficienty. Circulating autoantibodies against pancreatic lipase have been identified in about 75% in T1DM patients and 17% in T2DM patients. Furthermore, gene dysregulation has also been observed as one of the factors leading to PEI in DM patients. In addition, a recent study by Mohaptra S et al observed pancreatic histopathological changes that was marked by mild-to-marked interacinar fibrosis with scant inflammatory infiltrate but hyalinization of arteries and without pancreatic ductal changes, in patients with DM indicating moderate-to-severe subclinical pancreatic fibrosis.

Further, T1DM which is linked to primary autoimmune process and characterized by early occurrence, severe insulin deficiency and long standing disease is more frequently associated with PEI. A large study investigating risk factors for PEI in 195 T1DM patients, demonstrated strong association of PEI and disease duration. Furthermore, in adult T1DM patients, the prevalence of severe (10-30%) and moderate (22-56%) PEI was observed to be higher than in children, possibly suggesting decrease in exocrine pancreatic function with the duration of disease and increase in insulin requirement. Early onset of T2DM,
Diagnosis of PEI in Diabetes Mellitus

It is often difficult to detect PEI in patients with DM in routine clinical practice. Majority of these patients are usually asymptomatic in the early stage of PEI. The classical symptoms of steatorrhea and weight loss only tend to occur in patients with very severe PEI. Therefore, there should be a high index of suspicion for PEI in diabetics. More commonly, patients present with loose bowel movements, abdominal discomfort and flatulence. Patients with diabetes often describe symptoms of fatigue and difficulty controlling blood glucose levels. Although there are many causes of diarrhea in diabetic patients, such as small bowel bacterial overgrowth and diabetic dysautonomia, PEI should be suspected in patients with long standing type 1 and type 2 DM. Other factors that have also been shown to increase the incidence of PEI in diabetic patients include poor glycemic control, insulin dependence, elderly age, presence of microangiopathy and autonomic neuropathy. However, a number of other causes such as gastroparesis, celiac disease, and side effects of blood glucose lowering medications should be excluded before considering PEI.

There are several tests for diagnosing PEI as listed in Table 2. Unfortunately, most of these tests are not performed routinely. The 72 hrs fecal fat estimation test, which is considered the gold standard to detect steatorrhea is seldom performed routinely in laboratories due to the unpleasant nature, and is current restricted only under research setting. The direct tests such as the CCK and secretin stimulation tests, which are highly sensitive, are complicated and require expertise. These tests are also performed under research setting.

Currently the most commonly used test for detecting PEI is the fecal elastase 1 assay. Several studies reported that the prevalence of PEI in DM varied widely from 5% to 57%. One in three patients with DM presented with impaired exocrine function when explored by fecal elastase-1 testing. Of all patients with DM and PEI, half had severe PEI, as identified by FEC <100 μg/g stool. Fecal elastase 1 testing is conducted in a few laboratories across India. The advantage of this test is that a patient need not stop taking pancreatic enzymes before conducting the test. However, one needs to be careful in interpreting the results of Fecal elastase 1 estimation in the presence of diarrheal disease as it might be falsely low. Moreover, sensitivity of fecal elastase has been reported to be lower in diabetes. The 13C-mixed triglyceride breath test is the most recent test for PEI and is a fairly accurate method to evaluate exocrine insufficiency. The additional advantage of this test is that it could also be used to monitor the effect of pancreatic enzyme therapy on fat digestion. This method is simpler than the standard fecal fat test to assess therapy in patients with PEI. Unfortunately, this test is not widely available and is restricted to a few centers in Europe and USA.

Management of PEI in Diabetes Mellitus

The mainstay of treatment of PEI in diabetes is pancreatic enzyme replacement therapy (PERT). Since there are scant data or guidelines on PERT specifically in patients with diabetes, treatment should be based on literature pertaining to treatment of PERT in chronic pancreatitis. Several pancreatic enzyme preparations have been tested and used extensively for treating PEI associated with pancreatic diseases. Recent recommendations support the use of PERT in patients with diabetes and PEI. Table 3 shows various pancreatic enzyme preparations that have been approved by the US FDA.
For optimal digestive action, a pancreatic enzyme preparation should survive the acidic milieu, get released into the duodenum along with chyme, and contain the correct dose of lipase, which is the most crucial component of the preparation. Use of enteric-coated technology to coat the enzyme preparation protects them for gastric acid mediated degradation. The HP55 coating dissolves at a pH >5.5 to release the lipase, amylase and protease in the duodenum. Use of enzymes in the minimicrosphere formulation enables entry of the enzyme spheres into the duodenum along with the solid food chyme. In the stomach, solid food usually gets broken down into sizes of 2mm or less by the antral contractions before moving through the pyloric channel into the first part of the duodenum. Studies have demonstrated that the size of the particles affect the synchronous delivery of enzymes with chyme to the duodenum, with particles of size 1.0-1.2mm being associated with 25% higher efficacy. In theory, along with delivering adequate amounts of lipase to the duodenum at the same time as the ingested food, the minimicrosphere technology allows for a more adequate mixture of enzyme with the postprandial chyme. The third crucial component of pancreatic enzyme preparation is the dose of lipase. The intestine has brush border aminopeptidases and carboxypeptidases that could aid in protein digestion, along with pancreatic enzymes. Furthermore, gastric acid itself initiates protein digestion in the stomach. Furthermore, the gastrointestinal (GI) tract contains more of salivary amylase than pancreatic amylase; and in the event of PEI the concentration of salivary amylase has been shown to increase. Therefore, strict dosage criterion may not be mandatory for amylase and protease concentrations in pancreatic enzyme preparations. On the other hand, lipase is the most vulnerable among the supplemented pancreatic enzyme, with survival of as low as 1% of the enzyme during intestinal transit in the absence of substrate, i.e. fat in the diet. Therefore, a high concentration of lipase in the pancreatic enzyme supplement is mandatory to achieve the optimal dose. The pancreas has a huge reserve of enzymes, and it has been shown that only 10% of the total daily lipase output (which is 6,00,000U) is required for fat digestion. Therefore, the daily dose of at least 20,000U per meal of lipase is mandatory for fat digestion. Thus, an ideal pancreatic enzyme supplement preparation should be an enteric-coated minimicrosphere with at least 20,000U of lipase; and optimal action could be achieved by taking the preparation along with or immediately after food intake. In our experience, for Indian patient’s intake along with food provides the best compliance. Since the initial response of PEI to PERT could be erratic, supplementation should usually be started with a higher dose of 25000 to 40000U of lipase with each major meal, which could then be titrated up or down based on patient’s response. Factors such as the size of the patient, size of the meals and nutrition status could also aid in determining the starting and maintenance doses of PERT.

Another important aspect to note is that for PERT to be effective, the diet with nutrients, especially fat, will be needed in the enzyme, especially lipase, ineffective. Furthermore, even though it is generally believed that PERT aids in micronutrient digestion, there are several micronutrients, for e.g. vitamins B1-B5, vitamin C, zinc, copper, iodine, biotin and to a certain extent folate, which do not require pancreatic enzymes for digestion, and therefore should be supplemented especially in the presence of features of malnutrition.

**Characteristics of an Ideal Pancreatic Enzyme Preparation**

For optimal digestive action, a pancreatic enzyme preparation should survive the gastric acidic milieu, get released into the duodenum along with chyme, and contain the correct dose of lipase, which is the most crucial component of the preparation. Use of enteric-coated technology to coat the enzyme preparation protects them for gastric acid mediated degradation. The HP55 coating dissolves at a pH >5.5 to release the lipase, amylase and protease in the duodenum. Use of enzymes in the minimicrosphere formulation enables entry of the enzyme spheres into the duodenum along with the solid food chyme. In the stomach, solid food usually gets broken down into sizes of 2mm or less by the antral contractions before moving through the pyloric channel into the first part of the duodenum. Studies have demonstrated that the size of the particles affect the synchronous delivery of enzymes with chyme to the duodenum, with particles of size 1.0-1.2mm being associated with 25% higher efficacy. In theory, along with delivering adequate amounts of lipase to the duodenum at the same time as the ingested food, the minimicrosphere technology allows for a more adequate mixture of enzyme with the postprandial chyme. The third crucial component of pancreatic enzyme preparation is the dose of lipase. The intestine has brush border aminopeptidases and carboxypeptidases that could aid in protein digestion, along with pancreatic enzymes. Furthermore, gastric acid itself initiates protein digestion in the stomach. Furthermore, the gastrointestinal (GI) tract contains more of salivary amylase than pancreatic amylase; and in the event of PEI the concentration of salivary amylase has been shown to increase. Therefore, strict dosage criterion may not be mandatory for amylase and protease concentrations in pancreatic enzyme preparations. On the other hand, lipase is the most vulnerable among the supplemented pancreatic enzyme, with survival of as low as 1% of the enzyme during intestinal transit in the absence of substrate, i.e. fat in the diet. Therefore, a high concentration of lipase in the pancreatic enzyme supplement is mandatory to achieve the optimal dose. The pancreas has a huge reserve of enzymes, and it has been shown that only 10% of the total daily lipase output (which is 6,00,000U) is required for fat digestion. Therefore, the daily dose of at least 20,000U per meal of lipase is mandatory for fat digestion. Thus, an ideal pancreatic enzyme supplement preparation should be an enteric-coated minimicrosphere with at least 20,000U of lipase; and optimal action could be achieved by taking the preparation along with or immediately after food intake. In our experience, for Indian patient’s intake along with food provides the best compliance. Since the initial response of PEI to PERT could be erratic, supplementation should usually be started with a higher dose of 25000 to 40000U of lipase with each major meal, which could then be titrated up or down based on patient’s response. Factors such as the size of the patient, size of the meals and nutrition status could also aid in determining the starting and maintenance doses of PERT.

**Another important aspect in achieving the best possible response to PERT is provision of adequate nutrition.** Enzymes require substrate to work. Therefore, depletion of the diet with nutrients, especially fat, will render the enzyme, especially lipase, ineffective. Furthermore, even though it is generally believed that PERT aids in micronutrient digestion, there are several micronutrients, for e.g. vitamins B1-B5, vitamin C, zinc, copper, iodine, biotin and to a certain extent folate, which do not require pancreatic enzymes for digestion, and therefore should be supplemented especially in the presence of features of malnutrition.

**Efficacy Studies Pertaining to Pancreatin**

Efficacy of PERT may be influenced by denaturation of lipase by gastric acid, improper timing of enzymes in duodenum, coexisting small-intestinal mucosal disease, rapid intestinal transit and effects of diabetes. Even though data on efficacy of pancreatic supplementation in PEI associated with CP and cystic fibrosis abounds the literature, there are very limited studies on diabetes. Table 4 shows the studies that had evaluated the
efficacy of pancreatin in patients with diabetes.56-58

A double-blind, randomized placebo-controlled trial among insulin treated patients receiving either Creon or placebo observed reduction in mild to moderate hypoglycemia in Creon group.56 Furthermore, a study conducted to evaluate the effect of Creon on insulin secretion in CP with secondary DM and PEI patients observed an increase in total plasma insulin and total insulin secretion after Creon administration along with an increase in the total glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP) response. These findings suggest that the secretion of GLP-1 and GIP is under influence of the digestion and absorption of nutrients in the small intestine. These incretin hormones are responsible for 70% of insulin secretion following oral ingestion of glucose. Thus, pancreatic enzyme supplementation may be associated with rise in insulin levels through increase in incretin hormone response by improving digestion of nutrients.57 A recent double-blind, randomized placebo-controlled trial of Creon in patients having PEI with or without diabetes mellitus reported Creon to improve fat and protein absorption in both the groups as compared to placebo. The mean change from baseline in coefficient of fat absorption (CFA) (36% vs. 7.5%, P<0.0001) and coefficient of nitrogen absorption (CNA) (33.4% vs. 3.7%, P=0.0002) in DM group was significantly greater with pancrelipase than with placebo (p<0.00001).

### Safety Profile of Pancreatin Enzyme Preparation

In general, PERT is regarded as well-tolerated with few side effects, and some adverse events are comparable to those with placebo. Supplemental enzymes act within the lumen of the intestine, and this is considered an intraluminal and not a systemic therapy. Most common side effects of pancreatin preparations are, abdominal pain, nausea, vomiting, constipation, and diarrhea.59 Table 4 depicts studies that evaluated the safety of pancreatin in patients with diabetes.

### Summary

In this manuscript we have addressed the issue of PEI in patients with type 1 and 2 diabetes. Even though not often considered in assessment of diabetes in routine clinical practice, PEI in DM is not uncommon as evidence data from India and the west suggests. Several tests to detect PEI have been developed, of which the fecal elastase and 13C-mixed triglyceride breath tests are used in clinical practice. In India, only fecal elastase test is available in very

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### Table 4: Efficacy and safety of pancreatin (Creon)56-58

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Treatment arms</th>
<th>Efficacy results</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewald et al, 2007</td>
<td>Prospective multicentre placebo trial</td>
<td>Creon vs. placebo</td>
<td>An increase in vitamin D levels in the pancreatin group and an increase in vitamin E levels in both groups during the observational period. Reduction in mild and moderate hypoglycemia in the treatment group at week 16.</td>
<td>Treatment emergent adverse events (TEAE) occurred were similar in both the groups. Most frequent adverse events were headache, infection, diarrhea, and dyspepsia. No description regarding adverse events.</td>
</tr>
<tr>
<td>Knop et al, 2007</td>
<td>Open-label trial</td>
<td>Creon vs. standard meal</td>
<td>The total GLP-1 (7.8±1.2 vs. 5.3±0.6 nM, P=0.01) and total GIP (375±77 vs. 270±84 pM, P=0.04) increased along with increased plasma insulin and total insulin secretion after Creon administration.</td>
<td>Most patients in DM group experienced no TEAEs. However, one patient with DM in the Creon arm reported abnormal feces, frequent bowel movements, and inadequate control of DM. Hypoglycemia and hyperglycemia occurred in one patient.</td>
</tr>
<tr>
<td>Whitecomb et al, 2016</td>
<td>Post hoc analysis of a RCT</td>
<td>Pancrelipase vs. placebo</td>
<td>Change in CFA from baseline in diabetes mellitus (DM) patients was 36% (18.6%) for Creon and 7.3% (12.3%) for placebo (p&lt;0.0001). Change in CNA from baseline in DM patients was 33.4% (30.5%) for Creon and 3.7% (29%) for placebo (p=0.0002). The mean change from baseline in CFA and CNA in DM group was significantly greater with pancrelipase than with placebo (p&lt;0.0001).</td>
<td>Most frequent adverse events were headache, infection, diarrhea, and dyspepsia.</td>
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### Table 5: Salient points on the management of PEI49,55,60

- Patients with diabetes mellitus have an increased risk of developing PEI due to pancreatic acinar atrophy.
- Symptoms of PEI do not manifest until duodenal lipase levels fall below 5-10% of normal postprandial levels.
- Clinical consequence of PEI is fat maldigestion, resulting in steatorrhoea and weight loss.
- Upon clinical suspicion, a pancreatic function test should be performed for identifying subclinical PEI.
- Pancreatic enzyme replacement therapy is the main pharmacological treatment for PEI.
- Lowest recommended dose of PERT is 25,000-40,000 units of lipase per meal, then titrated upwards according to clinical response. Maximum recommended dose of PERT in adults is 75,000-80,000 units of lipase per meal. In infants and children, the maximum recommended dose is 10,000 units of lipase per kilogram per day. For snacks, PERT can be used in half the dose for main meals.
- Pancreatic enzymes are most effective when given with meal, rather than before or after it.
- A dietician experienced in treating PEI should be involved in patient management.
- Routine nutritional assessment of patients with PEI is essential due to the potential impact of malabsorption on nutritional status and quality of life.
- PERT helps to maintain weight and improve overall quality of life.
- Supplementation with fat-soluble vitamins is also appropriate.
few select centers, while the breath test is not available. Therefore, a high index of clinical suspicion is prudent to identify diabetic patients with PEI. This is important because PEI could be managed adequately with the correct use of pancreatin and studies have shown that pancreatin supplementation could also have a positive effect on the glycemic status of the diabetic patients. Even though there are no specific guidelines for management of PEI in diabetes, the principles of treatment are the same; and guidelines meant for management of PEI in chronic pancreatitis should hold good for diabetic patients also. Table 5 presents salient points on the management of PEI, that has been taken from the Romanian, Australasian, and Spanish guidelines.49,55,60

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Conflict of Interest

Rupjyoti Talukdar and D. Nageshwar Reddy declare that they have no conflict of interest.

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