Maldigestion Among Diabetes Patients due to Pancreatic Exocrine Insufficiency (PEI)

An Online Learning Program for Doctors

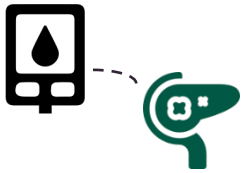
PanCreas EXPERT

An initiative by

RESEARCH SOCIETY FOR THE STUDY OF DIABETES IN INDIA

Learning Objectives

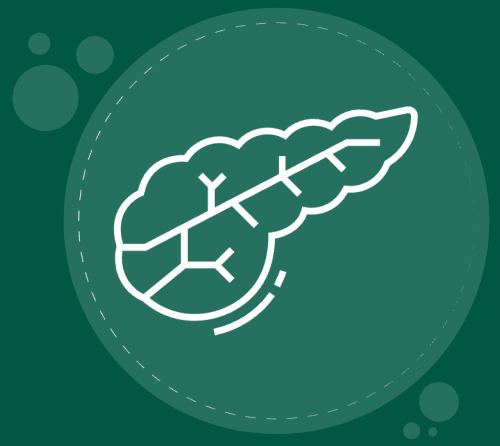
To understand the impact of maldigestion due to pancreatic exocrine insufficiency (PEI) in diabetes patients



To understand the possible mechanisms of pancreatic exocrine insufficiency (PEI) development in diabetes patients

To briefly discuss the signs and symptoms of maldigestion in diabetes patients due to pancreatic exocrine insufficiency (PEI)

To understand the role of pancreatic enzyme replacement therapy (PERT) in the management of maldigestion due to pancreatic exocrine insufficiency (PEI) in diabetes patients



Introduction to Pancreatic Exocrine Insufficiency (PEI)

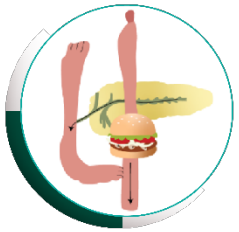
What is Pancreatic Exocrine insufficiency?

Pancreatic exocrine insufficiency (PEI) is defined as a reduction in pancreatic exocrine activity in the intestine to a level that prevents normal digestion.[1]

It is also termed exocrine pancreatic dysfunction or pancreatic maldigestion.[2,3]

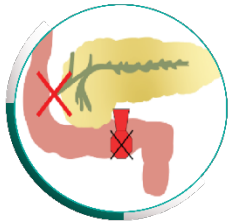
1. Phillips ME, et al. BMJ Open Gastroenterol. 2021;8(1):e000643. **2.** Radlinger B, et al. Curr Diab Rep. 2020;20(6):18. **3.** Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70.

Etiologies of Pancreatic Exocrine Insufficiency



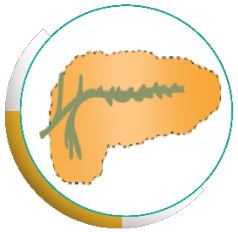
Postcibal gastrointestinal asynchrony

- Diabetes mellitus
- Short bowel syndrome
- Crohn’s disease
- Gastric resections



Inhibition or inactivation of pancreatic secretion

- Obstruction of the pancreatic duct
- Decreased endogenous stimulation (due to conditions such as diabetes mellitus, celiac disease, and Crohn's disease)
- Intraluminal inactivation



Loss of pancreatic parenchyma

- Chronic pancreatitis
- Pancreatic cancer
- Pancreatic resections
- Cystic fibrosis

PEI: Pancreatic exocrine insufficiency.

Kunovský L, et al. J Clin Med. 2021;10(24):5779.

Pancreatic Exocrine Insufficiency (PEI) in Diabetes

Prevalence of Pancreatic Exocrine Insufficiency in Indian Patients With Diabetes (1/2)

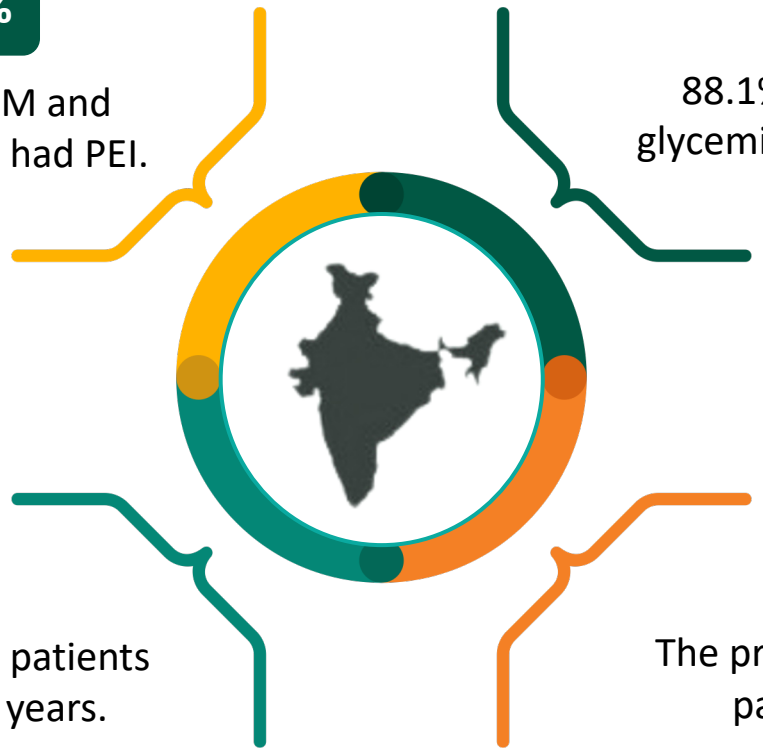
A study was conducted on 300 Indian patients above 18 years of age with T1DM or T2DM for at least 5 years to assess the prevalence of PEI.

PEI: Pancreatic exocrine insufficiency; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.
Data on file: Study.

Prevalence of Pancreatic Exocrine Insufficiency in Indian Patients With Diabetes (2/2)

22.9% & **23.9%**

22.9% of patients with T1DM and **23.9%** of patients with T2DM had PEI.



88.1% of patients with PEI experienced poor glycemic control, indicated by HbA_{1c} levels ≥7.0%.

10 YEARS

The mean duration of diabetes in patients with PEI was approximately 10 years.

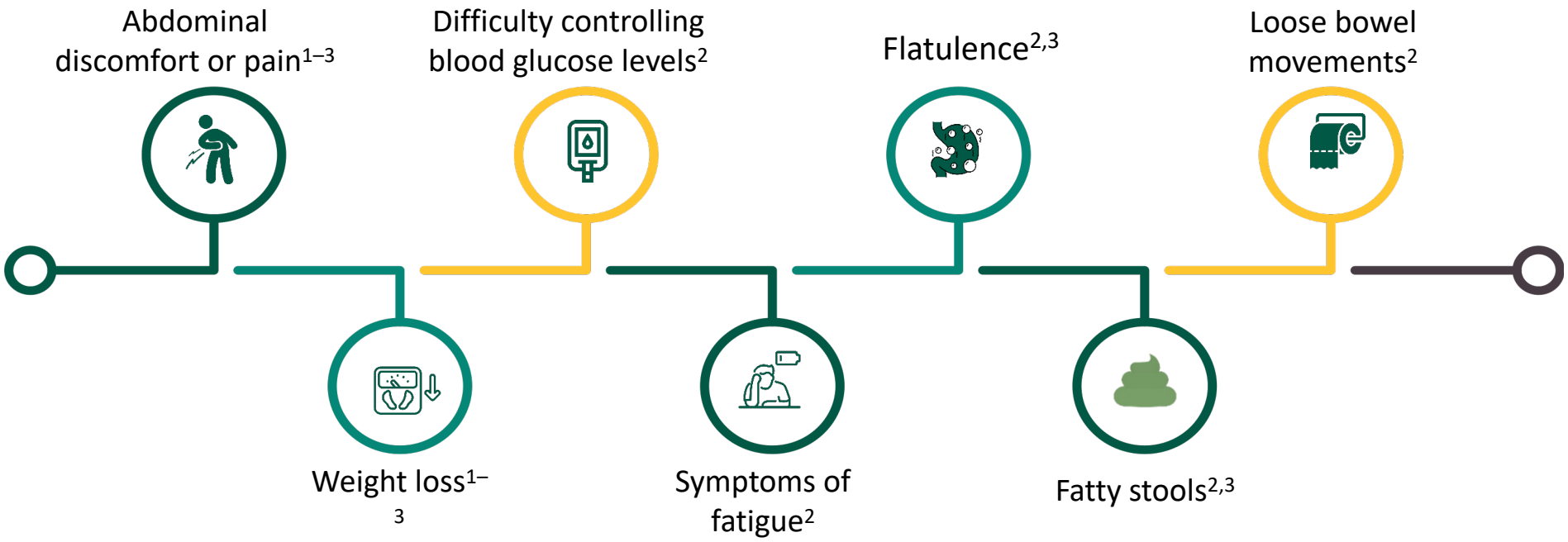
The prevalence of PEI was high among diabetes patients of the age group 41–50 years.

HbA_{1c}: Glycosylated hemoglobin; PEI: Pancreatic exocrine insufficiency; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.
Data on file: Study.

In Patients With Diabetes Mellitus, Pancreatic Exocrine Insufficiency Is More Frequent in Terms of Maldigestion.[1]

Other common symptoms include:

Signs of PEI in diabetes patients



PEI: Pancreatic exocrine insufficiency.

1. Hardt PD, et al. Exp Diabetes Res. 2011;2011:761950. **2.** Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **3.** Radlinger B, et al. Curr Diab Rep. 2020;20(6):18.

Discussion Question

Which of the following causes postcibal gastrointestinal asynchrony, a possible cause of PEI?

- **A** Cystic fibrosis
- **B** Diabetes mellitus
- **C** Pancreatic cancer
- **D** Obstruction of the pancreatic duct

Correct answer

Diabetes mellitus

PEI: Pancreatic exocrine insufficiency.

Kunovský L, et al. J Clin Med. 2021;10(24):5779.

Pathophysiology of Pancreatic Exocrine Insufficiency in Diabetes: A Bird's Eye View

Insulin deficiency	Loss of trophic function
Microangiopathy	Tissue ischemia
Neuropathy	Loss of neuronal signal
Inflammation	Panglandular dysfunction

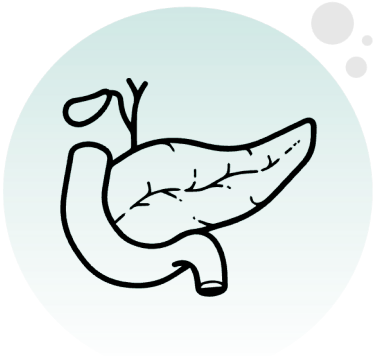
Loss of exocrine pancreatic function

PEI: Pancreatic exocrine insufficiency.

Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70.

Pancreatic Exocrine Insufficiency and Type-1 Diabetes Mellitus

- Link to autoimmunity[1]
- Neural and vascular complications[1]
- Severe insulin deficiency[1]



More frequent association with PEI[1]

PEI seems to occur earlier in T1DM patients, whereas the prevalence of both severe and moderate PEI was found to occur higher in adults than children.[1]

Existing evidence suggests that PEI is a feature of T1DM that has a chronic nature of disease progression and close connection with the impairment of the endocrine components.[1,2]

PEI: Pancreatic exocrine insufficiency; T1DM: Type 1 diabetes mellitus.

1. Piciucchi M, et al. Int J Endocrinol. 2015;2015:595649. **2.** Dozio N, et al. BMJ Open Diabetes Res Care. 2021;9(1):e001158.

Pancreatic Exocrine Insufficiency and Type-2 Diabetes Mellitus

A long, complicated T2DM, with a high degree of microvascular damage, pancreatic fibrosis, and autonomic neuropathy, is associated with PEI occurrence.

The early onset of T2DM and long disease duration, as well as poor glycemic control, seem to be risk factors for the occurrence and severity of PEI.

PEI: Pancreatic exocrine insufficiency; T2DM: Type 2 diabetes mellitus.
Piciucchi M, et al. Int J Endocrinol. 2015;2015:595649.

PEI in Diabetes vs. Diabetes due to PEI: How Do They Differ?

Recent clinical observations showed that nonendocrine pancreatic disease is a critical factor for development rather than a sequel to diabetes.[1]

Nearly half of the patients with this type of diabetes are misdiagnosed as type 1 or 2 as the discrimination of T3cDM from the other two types, especially the T2DM, is highly challenging.[2,3]

This type of diabetes is called T3cDM (or pancreatogenic diabetes) and is a form of secondary diabetes, specifically associated with a disease of the exocrine pancreas.[2]

The major criteria for categorizing T3cDM include PEI, pathological pancreatic imaging, or absence of T1DM-associated auto-antibodies.[4]

PEI: Pancreatic exocrine insufficiency; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; T3cDM: Type 3c diabetes mellitus.

1. Hardt PD, et al. Diabetes Care. 2008;31(Suppl 2):S165–S169. **2.** Pancreatogenic diabetes. Accessed on: 28 February 2022. **3.** Vujasinovic M, et al. World J Gastroenterol. 2014;20(48):18432–18438. **4.** Pancreatogenic type 3c diabetes: Underestimated, underappreciated and poorly managed. Accessed on: 28 February 2022.

Contrasting Characteristics of Types 1, 2, and 3c Diabetes (1/2)

Characteristic	T1DM	T2DM	T3cDM
Hyperglycemia	Severe	Usually, mild	Mild or severe in brittle diabetes
Hypoglycemia	Common	Rare	Common and maybe severe
Insulin levels	Low	High	Low
Glucagon levels	Normal or high	Normal or high	Low
GLP-1 levels	Normal	Low or normal	Normal or high

Adapted from: Pancreatogenic type 3c diabetes: Underestimated, underappreciated and poorly managed. Accessed on: 28 February 2022.

GLP-1: Glucagon-like peptide-1; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; T3cDM: Type 3c diabetes mellitus.
Pancreatogenic type 3c diabetes: Underestimated, underappreciated and poorly managed. Accessed on: 28 February 2022.

Contrasting Characteristics of Types 1, 2, and 3c Diabetes (2/2)

Characteristic	T1DM	T2DM	T3cDM
Pancreatic polypeptide levels	Normal or low	High	Low
Peripheral insulin sensitivity	Normal or increased	Decreased	Increased
Hepatic insulin sensitivity	Normal	Normal or decreased	Decreased
Undernutrition	Uncommon	Rare	Common
Nutrient deficiency	Rare	Rare	Deficiency of fat-soluble vitamins is common

Adapted from: Pancreatogenic type 3c diabetes: Underestimated, underappreciated and poorly managed. Accessed on: 28 February 2022.

T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; T3cDM: Type 3c diabetes mellitus.
Pancreatogenic type 3c diabetes: Underestimated, underappreciated and poorly managed. Accessed on: 28 February 2022.

Discussion Question

Possible mechanism(s) of PEI development in diabetes patients include

- **A** Tissue ischemia
- **B** Loss of neuronal signal
- **C** Loss of trophic effects of insulin
- **D** All the above

Correct answer

All the above

PEI: Pancreatic exocrine insufficiency.

Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70.

Evaluation and Diagnosis of Pancreatic Exocrine Insufficiency (PEI) in Diabetes

Evaluation of Pancreatic Exocrine Insufficiency in Diabetes Patients

Symptoms such as fatty stools and weight loss only tend to occur in people with very severe PEI.[1]

As PEI manifests very frequently as maldigestion in diabetes patients[2], the Bristol stool chart can be used to assess bowel movements. [1]

People reporting abnormal stools (type 5–7) should be screened for PEI.[1]

Differentiation between T2DM-associated PEI and T3cDM can be made by the evaluation of fecal elastase-1 (screens PEI) and an absence of pancreatic polypeptide response to mixed-nutrient ingestion (confirms T3cDM).[3]

Bristol stool chart

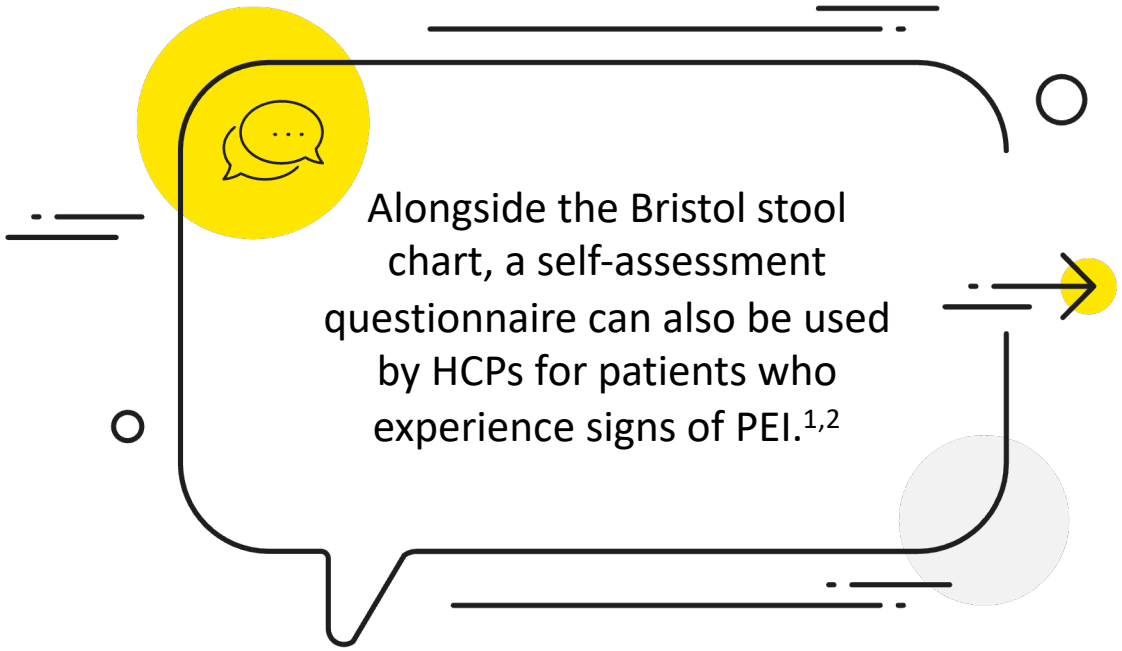
Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely liquid

Adapted from: Cummings M, J Diabetes Nurs. 2014;18:320–333.

PEI: Pancreatic exocrine insufficiency; T2DM: Type 2 diabetes mellitus; T3cDM: Type 3c diabetes mellitus.

1. Cummings M. J Diabetes Nurs. 2014;18:320–333. **2.** Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **3.** Pancreatogenic diabetes. Accessed on: 28 February 2022.

Assessment of Pancreatic Exocrine Insufficiency



Scoring

Domain (mean)	Formula	Please write the patient's score here
Abdominal symptoms (A)	$A = \frac{\text{Sum of scores of items 1 to 7}}{7}$	A =
Bowel movement symptoms (B)	$B = \frac{\text{Sum of scores of items 8 to 13}}{6}$	B =
Total symptom score	$\frac{\textit{(Abdominal symptoms domain score [A] + bowel movement symptoms domain score [B])}}{2}$	(A+B)/2 =
Impacts (C)	$C = \frac{\text{Sum of scores of items 14 to 18}}{5}$	C =
Total summary score (PEI patients only)	$\frac{\textit{(Abdominal symptoms domain score [A] + bowel movement symptoms domain score [B] + impacts domain score [C])}}{3}$	(A+B+C)/3 =

HCPs: Healthcare professionals; PEI: Pancreatic exocrine insufficiency.

1. Johnson CD, et al. Patient. 2017;10(5):615–628.
2. Johnson CD, et al. Pancreatology. 2019;19(1):182–190.

Self-Assessment Questionnaire for Pancreatic Exocrine Insufficiency (1/3)[1,2]

Abdominal symptoms		No not at all	Yes, a little bit	Yes, some	Yes, quite a bit	Yes, a lot	Score
1.	In the past 7 days, did you have **stomach pain?**	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
2.	In the past 7 days, did you **feel** bloated (your stomach feeling **tight** and **full**)?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
3.	In the past 7 days, did your **stomach make noises?**	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
4.	In the past 7 days, did you **pass gas**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
5.	In the past 7 days, when you **passed gas** did it **smell** very **bad**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
6.	In the past 7 days, did you **feel sick** (but didn't actually vomit/throw up)?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
7.	In the past 7 days, did you have a **lack of appetite?**	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
						Sum of abdominal symptom scores:	
						Mean abdominal symptom domain score (A):	

PEI: Pancreatic exocrine insufficiency.

1. Johnson CD, et al. Patient. 2017;10(5):615–628.
2. Johnson CD, et al. Pancreatology. 2019;19(1):182–190.

Self-Assessment Questionnaire for Pancreatic Exocrine Insufficiency (2/3)[1,2]

Bowel movement symptoms		No not at all	Yes, a little bit	Yes, some	Yes, quite a bit	Yes, a lot	Score
8.	In the past 7 days, did you have **diarrhea (watery poo)**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
9.	In the past 7 days, did you feel the need to **rush to the toilet** to have a **bowel movement (have a poo)**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
10.	In the past 7 days, did your **poo** look **lighter** or **orange** in color?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
11.	In the past 7 days, when you had a **poo** did it **smell** very **bad**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
12.	In the past 7 days, did you see or have **fat or oil** in your **poo** or on the **toilet paper**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
		No not at all	**Yes, a little bit**	**Yes, moderately**	**Yes, quite a bit**	**Yes, extremely**	**Score**
13.	In the past 7 days, did you feel you needed to be **close to a toilet** because of your **enzyme problems**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
						Sum of bowel movement symptom scores:	
						Mean bowel movement symptom score (B):	
						Mean total symptom score ([A+B]/2):	

PEI: Pancreatic exocrine insufficiency.

1. Johnson CD, et al. Patient. 2017;10(5):615–628.
2. Johnson CD, et al. Pancreatology. 2019;19(1):182–190.

Self-Assessment Questionnaire for Pancreatic Exocrine Insufficiency (3/3)[1,2]

Impacts		No not at all	Yes, a little of the time	Yes, sometimes	Yes, most of the time	Yes, all of the time	Score
14.	In the past 7 days, did you avoid **fatty food**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
15.	In the past 7 days, did your **enzyme problems** affect your ability to **concentrate**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
		No not at all	**Yes, a little bit**	**Yes, moderately**	**Yes, quite a bit**	**Yes, extremely**	**Score**
16.	In the past 7 days, did you feel **embarrassed going to the toilet** because of your **enzyme problems**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
17.	In the past 7 days, did you feel **worried, anxious,** or **stressed** because of your **enzyme problems**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
		No not at all	**Yes, a little of the time**	**Yes, sometimes**	**Yes, most of the time**	**Yes, all of the time**	**Score**
18.	In the past 7 days, did your **enzyme problems** affect your **social activities**?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	
						Sum of impact scores:	
						Mean impact domain score (C):	
						Mean total summary score (PEI patients) ([A+B+C]/3):	

PEI: Pancreatic exocrine insufficiency.

1. Johnson CD, et al. Patient. 2017;10(5):615–628.
2. Johnson CD, et al. Pancreatology. 2019;19(1):182–190.

Diagnostic Tests for Pancreatic Exocrine Insufficiency (1/3)

(i) Direct pancreatic function tests

Test	Advantages	Limitations
72 hours fecal fat estimation/coefficient of fecal absorption	Gold standard	Not pancreas specific
Cholecystokinin/secretin stimulation	Gold standard for the scientific evaluation of pancreatic exocrine function	Invasive and complicated
Endoscopic pancreatic function test	Useful in the investigation of the cause of malabsorptive diarrhea	Time-consuming, issues with quantifying fluid volumes prevent the calculation of enzyme output
Secretin MRCP test	Useful in the evaluation of acute and chronic pancreatitis, used to evaluate neoplasms	Subjective nature of reports, paucity of large trials proving its effect

Adapted from: Talukdar R, J Assoc Physicians India. 2017;65(9):64–70.

MRCP: Magnetic resonance cholangiopancreatography; PEI: Pancreatic exocrine insufficiency.
Talukdar R, J Assoc Physicians India. 2017;65(9):64–70.

Diagnostic Tests for Pancreatic Exocrine Insufficiency (2/3)

(ii) Indirect pancreatic function tests

Test	Advantages	Limitations
Fecal chymotrypsin activity[1]	Good for compliance control, single stool sample	Poor sensitivity in mild PEI, miscalculations can occur as watery stools decrease enzyme activity
Fecal elastase-1 concentration[1]	Single stool sample, PERT can be continued	Poor sensitivity in mild PEI, not suitable if watery stools and small bowel disease are present
^{13}C-mixed triglyceride breath test[1]	Acts for a mild form of PEI, detects fat maldigestion with a sensitivity of >90%	Requires further validation
Blood tests (for magnesium, nutritional markers, bone mineral density, and fat-soluble vitamins)[2]	May hint at the presence of PEI in people with suspected PEI	Not PEI specific

Adapted from: **1.** Talukdar R, J Assoc Physicians India. 2017;65(9):64–70. **2.** Working Party of the Australasian Pancreatic Club, et al. Pancreatology. 2016;16(2):164–180.

PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy.
1. Talukdar R, J Assoc Physicians India. 2017;65(9):64–70. **2.** Working Party of the Australasian Pancreatic Club, et al. Pancreatology. 2016;16(2):164–180.

Diagnostic Tests for Pancreatic Exocrine Insufficiency (3/3)

(iii) Structural imaging

Test	Advantages	Limitations
CT with contrast (first required) ERCP (occasionally required)	Often yields good results; readily available	Some procedures carry a significant measure of risk

Adapted from: Working Party of the Australasian Pancreatic Club, et al. Pancreatology. 2016;16(2):164–180.

CT: Computed tomography; ERCP: Endoscopic retrograde cholangiopancreatography; PEI: Pancreatic exocrine insufficiency.
Working Party of the Australasian Pancreatic Club, et al. Pancreatology. 2016;16(2):164–180.

Sample Patient Cases for the Diagnosis of Pancreatic Exocrine Insufficiency (1/4)

CHIEF COMPLAINTS

- Abdominal pain[1–3]
- Loose bowel movements[1,2]
- Difficulty controlling blood sugar levels[2]
- Pain in the feet, lower legs, and thighs[2]

PROBABLE DIAGNOSES

- Diabetes[2]
- Diabetic neuropathy[2]
- Pancreatic exocrine insufficiency[1–5]

MEDICAL HISTORY

- Shows poor glycemic control ($HbA_{1c} \geq 8.5\%$)[2]
- Has abdominal stool consistency for the past 2 months (type 6 as per the Bristol stool chart)[4]
- Recently diagnosed with magnesium deficiency (<1.3 mg/dL)[5]

MEDICATIONS PRESCRIBED

- Metformin (500 mg orally every 12 hours)[5]
- Premixed insulin injections (at 75/25, mix twice daily)[5]
- Magnesium glycinate (320 mg/day)[5]
- Venlafaxine (25 mg orally thrice daily)[6]
- Pancreatin minimicrospheres (50,000 Ph. Eur. with each of the three main meals/day and 25,000 Ph. Eur. with each of up to three snacks/day)[2]
- Vitamin B supplements (50 mg vitamin B1 daily; 80 mg vitamin B6 daily; and 2.4 mcg vitamin B12 daily)[5]

HbA_{1c}: Glycosylated hemoglobin; PEI: Pancreatic exocrine insufficiency; Ph. Eur.: European Pharmacopoeia.

1. Radlinger B, et al. Curr Diab Rep. 2020;20(6):18. **2.** Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **3.** Hardt PD, et al. Exp Diabetes Res. 2011;2011:761950. **4.** Cummings M. J Diabetes Nurs. 2014;18:320–323. **5.** Phillips ME, et al. BMJ Open Gastroenterol. 2021;8(1):e000643. **6.** Gallagher HC, et al. Cochrane Database Syst Rev. 2015;2015(8):CD011091.

Sample Patient Cases for the Diagnosis of Pancreatic Exocrine Insufficiency (2/4)

CHIEF COMPLAINTS

- Changes in bowel movements for the past 3 months[1,2]
- Several episodes of diarrhea, sometimes with mucus[1,2]
- Severe abdominal cramping and bloating[1–3]
- Paleness in skin[4]

MEDICAL HISTORY

- Had his bariatric surgery 3 months ago[5]
- Has been experiencing watery diarrhea for the past 3 months (type 7 as per the Bristol stool chart)[6]
- Recently diagnosed with iron deficiency (<11 g/dL)[4]

PROBABLE DIAGNOSES

- IBS-D[7]
- Pancreatic exocrine insufficiencyl[1–5]
- Anemia[4]
- Diabetes[1]

MEDICATIONS PRESCRIBED

- Ursodiol (750 mg daily to reduce the risk of developing gallstones during the postsurgical period of rapid weight loss)
- Ferrous fumarate (360 mg/day)[8]
- Loperamide (4 mg after each loose stool to reduce the frequency of diarrhea)[9]
- Pancreatin minimicrospheres (60,000 Ph. Eur. with each of the three main meals/day and 30,000 Ph. Eur. with each of up to three snacks/day)[1]

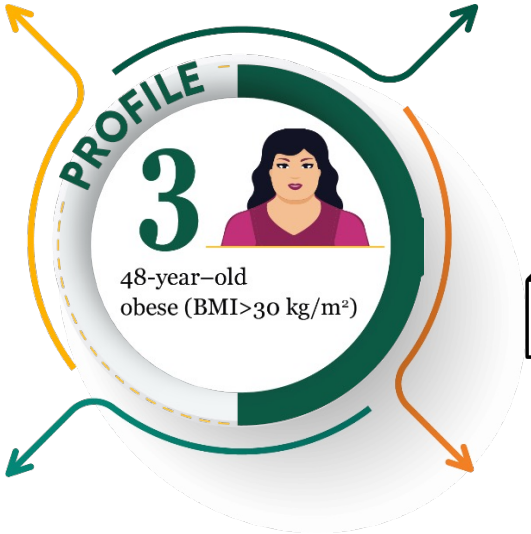
IBS-D: Diarrhea-predominant irritable bowel syndrome; PEI: Pancreatic exocrine insufficiency; Ph. Eur.: European Pharmacopoeia.

1. Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **2.** Radlinger B, et al. Curr Diab Rep. 2020;20(6):18. **3.** Phillips ME, et al. BMJ Open Gastroenterol. 2021;8(1):e000643. **4.** Gowanlock Z, et al. Blood Adv. 2020;4(15):3639–3647. **5.** NCBI bookshelf. Anemia. Accessed on: 21 July 2022. **6.** Cummings M. J Diabetes Nurs. 2014;18:320–323. **7.** UK guidelines. Gastrointestinal disorders in diabetes—Could it be pancreatic exocrine insufficiency? Accessed on: 21 July 2022. **8.** NHS. Ferrous fumarate. Accessed on: 21 July 2022. **9.** NHS. Loperamide. Accessed on: 21 July 2022.

Sample Patient Cases for the Diagnosis of Pancreatic Exocrine Insufficiency (3/4)

CHIEF COMPLAINTS

- Pain and tenderness in the abdomen with flatulence[1,2]
- Changes in bowel habits[1,2]
- Fluctuating blood sugar levels[1]
- Increased thirst and need to urinate[3]
- Severe back pain[4]



MEDICAL HISTORY

- Has diabetes for the past 3 years; although the blood sugar levels were under control, she is currently experiencing recurring hypoglycemic events (with blood sugar levels dropping below 68 mg/dL during each event)[1,5]
- Recently diagnosed with vitamin D deficiency (<13 ng/mL)[6]
- Recently diagnosed with calcium deficiency (<7 mg/dL)[6]

PROBABLE DIAGNOSES

- Hyperparathyroidism[3]
- Osteoporosis[3]
- Pancreatic exocrine insufficiency[1,2]

MEDICATIONS PRESCRIBED/ DIETARY/LSMs RECOMMENDED

- Vitamin D supplements (15 mcg/day)[6]
- Calcium supplements (2500 mg/day)[6]
- Pancreatin minimicrospheres (50,000 Ph. Eur. with each of the three main meals/day and 25,000 Ph. Eur. with each of up to three snacks/day)[1]
- Zoledronic acid (4 mg every 3–4 weeks)[6]
- Ibuprofen (one pill; 300 mg every 4–6 hours)[7]
- Dapagliflozin (5 mg orally once daily)[8*]
- Inclusion of small, nutritious snacks in between meals to keep blood sugar levels constant
- Physical activity as per physiotherapist's advice (including walking outdoors and squats)

*A switch in the patient's antidiabetic medication, i.e. use of dapagliflozin, an SGLT-2 instead of Glucotrol, a sulfonylurea to reduce the risk of hypoglycemia.
BMI: Body mass index; LSM: Lifestyle modification; PEI: Pancreatic exocrine insufficiency; Ph. Eur.: European Pharmacopoeia; SGLT-2: Sodium-glucose Cotransporter-2

1. Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **2.** Radlinger B, et al. Curr Diab Rep. 2020;20(6):18. **3.** NIDDK. Primary hyperparathyroidism. Accessed on: 21 July 2022. **4.** Hopkinsmedicine. Vitamin D and calcium. Accessed on: 21 July 2022. **5.** Foster TP, et al. Endocr Pract. 2020;26(12):1505–1513. **6.** Phillips ME, et al. BMJ Open Gastroenterol. 2021;8(1):e000643. **7.** Harvard Health Publishing. Best bets for back pain. Accessed on: 21 July 2022. **8.** Löhr JM, et al. United European Gastroenterol J. 2017;5(2):153–199.

Sample Patient Cases for the Diagnosis of Pancreatic Exocrine Insufficiency (4/4)

CHIEF COMPLAINTS

- Generalized weakness with dizziness and headache[1]
- Uncontrolled diabetes despite metformin regimen[1]
- An uncomfortable feeling of fullness after eating[2]
- Indigestion[2]
- Skin inflammation[2]

MEDICAL HISTORY

- Lost weight (>5% over the past 7 months)[3]
- Experiences palpitations (>100 heartbeats/minute) [3]
- Has vitamin A deficiency (<0.35 µmol/L)[2]
- Showed a rise in breath hydrogen by 12 ppm above the basal in glucose hydrogen breath test[2]
- Shows poor glycemic control (HbA_{1c}≥7.0%)[1]

PROBABLE DIAGNOSES

- Chronic fatigue syndrome[3]
- SBBO[2]
- Pancreatic exocrine insufficiency[1–3]
- Diabetes[1]

MEDICATIONS PRESCRIBED

- Voglibose (300 mcg three times/day)[1]
- Prandial insulin (started with 0.5 U/kg daily; increased TDD by 2 U/day)[1]
- Cyproheptadine (one tablet; 4 mg 2–3 times a day to reduce dizziness)[4]
- Sotalol (170 mg/day to prevent arrhythmias)[5]
- Rifaximin (550 mg tablet taken orally three times a day for 14 days for SBBO)[2]
- Pancreatin minimicrospheres (70,000 Ph. Eur. with each of the three main meals/day and 35,000 Ph. Eur. with each of up to three snacks/day)[1]
- Vitamin A supplements (700 mcg/day)[2]

HbA_{1c}: Glycosylated hemoglobin; PEI: Pancreatic exocrine insufficiency; Ph. Eur.: European Pharmacopoeia; SBBO: Small bowel bacterial overgrowth; TDD: Total daily dose.

1. Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **2.** Phillips ME, et al. BMJ Open Gastroenterol. 2021;8(1):e000643. **3.** Radlinger B, et al. Curr Diab Rep. 2020;20(6):18. **4.** Medlineplus. Cyproheptadine. Accessed on: 21 July 2022. **5.** NHS. Solatol. Accessed on: 21 July 2022.

Discussion Question

People with severe PEI may experience:

A GERD

B Fatigue

C Fatty stools

D Common abdominal symptoms

Correct answer

Fatty stools

GERD: Gastroesophageal reflux disease; PEI: Pancreatic exocrine insufficiency.

Cummings M. J Diabetes Nurs. 2014;18:320–333.

Management of Pancreatic Exocrine Insufficiency (PEI) in Diabetes

Management of Pancreatic Exocrine Insufficiency: General Considerations

Early diagnosis and initiation of treatment are important to manage PEI in patients with diabetes.[1]

Treatment of PEI should aim not only to alleviate symptoms but also to achieve significant improvements in nutritional parameters.[2]

The mainstay treatment of PEI is pancreatic enzyme replacement therapy.[3] It is usually given as pancreatic enzyme.[4]

PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy.

1. Altay M. World J Gastroenterol. 2019;25(22):2699–2705. **2.** Chaudhary A, et al. Dig Dis. 2020;38(1):53–68. **3.** Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **4.** Foster TP, et al. Endocr Pract. 2020;26(12):1505–1513.

Pancreatic Enzyme Replacement Therapy for Patients With Diabetes

Since there are scant data or guidelines on PERT specifically in patients with diabetes, treatment should be based on the literature pertaining to the treatment of PERT in chronic pancreatitis.[1]

Despite the scant data, pancreatic enzymes have been used for about 150 years in medical practice with the use of a calf pancreatic extract in 1859 for the treatment of a patient with diabetes mellitus.[2]

Recent recommendations also support the use of PERT in patients with diabetes and PEI.[1,3]

PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy.

1. Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **2.** Evidence-based gastroenterology. Principles of enzyme replacement therapy of exocrine pancreatic insufficiency. Accessed on: 21 July 2022. **3.** Rickels MR, et al. Pancreatology. 2013;13(4):336–342.

Characteristics of an Ideal Pancreatin Preparation

The HaPanEU guidelines recommend that enteric-coated microspheres or minimicrospheres of <2 mm in size are the PERT preparations of choice for PEI. An ideal pancreatic enzyme supplement would additionally need to fulfill the following requirements:

A good interspersing capacity to mix well with chyme

Getting emptied from the stomach simultaneously with a meal

Ability to disintegrate rapidly at pH 5.5 in the duodenum and release enzymes

HaPanEU: Harmonizing diagnosis and treatment of chronic pancreatitis across Europe; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme supplementation therapy.

Löhr JM, et al. United European Gastroenterol J. 2017;5(2):153–199.

Comparison of Multiple-Unit Dosage Form and Single-Unit Dosage Form of Pancreatin Preparations

Multiple-Unit Dosage Form*	Single-Unit Dosage Form*
More predictable gastric emptying[1]	Gastric emptying is highly variable[1]
Dissolves within 1–2 min in stomach and releases minimicrospheres; offers sustained enzyme release[2,3]	Releases the enzymes slowly[3]
Helps to achieve increased bioavailability of enzymes[4]	Cannot ensure maximum enzyme utilization[4]
Even distribution within the stomach and thorough mixing with chyme[2,5]	Nonuniform distribution with chyme[5]

*The multiple-unit dosage form refers to pancreatin minimicrospheres and the single-unit dosage form refers to the tablet preparations.

1. Ilhan E, et al. Peertechz J Med Chem Res. 2017;3(1):012–022. **2.** Shrikhande SV, et al. Drug Des Devel Ther. 2021;15:3835–3843. **3.** Al-Hashimi N, et al. Pharmaceutics. 2018;10(4):176. **4.** Pharmaceutical dosage forms: Capsules. Accessed on: 13 July 2022. **5.** Kuhn RJ, et al. J Pediatr Pharmacol Ther. 2007;12(2):115–128.

Pancreatin Preparations in the Market: An Overview

Clinical efficacy of PERT preparations is a function of its physical properties and release kinetics.[1]

Due to the differences in the bioavailability of marketed PERT products, FDA issued a final rule in 1998 that PERT preparations for PEI should be marketed by prescription (rather than OTC) only.[2]

The bioavailability of pancreatic enzymes is dependent on the process used to manufacture the drug products.[2]

Shrikande et al. evaluated the physical properties, in vitro dissolution, and release kinetics of commercially available PERT preparations available in the Indian market.[1]

OTC: Over-the-counter; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy.

1. Shrikhande SV, et al. Drug Des Devel Ther. 2021;15:3835–3843. **2.** Kuhn RJ, et al. J Pediatr Pharmacol Ther. 2007;12(2):115–128.

In Vitro Comparison of Pancreatin Enzyme Preparations Available in the Indian Market (1/2)

(i) Water content

- Presence of water content above 5% in pancreatin preparations leads to lipase degradation and inactivation during product storage.
- This may result in a suboptimal and variable clinical response.
- In this study, only pancreatin preparation C had a water content below 5%.

(ii) Lipase activity

- The USP guidelines specify that each capsule of PERT preparations should contain between 90% and 165% of the labeled lipase.[2]
- In this study, pancreatin preparation C met the label claim for lipase activity, having the highest value of 120%, showing the presence of adequate lipase.[1]

(iii) Particle size distribution

- Particle size and size distribution of PERT preparations impact their clinical efficacy.[1]
- PERT preparations with a smaller particle size have been associated with higher lipolytic activity and more rapid onset of action.[1]
- The HaPanEU guidelines recommend that enteric-coated microspheres or minimicrospheres of <2 mm in size are the PERT preparations of choice for PEI.[3]
- In this study, 50% of the pellets of preparation C were smaller than 1.6 mm and all the pellets from this preparation had a wider size distribution with pellets as small as 1–1.1 mm.[1]

HaPanEU: Harmonizing diagnosis and treatment of chronic pancreatitis across Europe; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy; USP: United States Pharmacopeia.

1. Shrikhande SV, et al. Drug Des Devel Ther. 2021;15:3835–3843. **2.** Case CL, et al. Pancreas. 2005;30(2):180–183. **3.** Löhr JM, et al. United European Gastroenterol J. 2017;5(2):153–199.

In Vitro Comparison of Pancreatin Enzyme Preparations Available in the Indian Market (2/2)

(iv) Enzyme release at pH 5/pH 6

- Ideally, PERT preparations should resist low pH (pH 1–5) to avoid the deactivation of the enzymes in the stomach and release the enzymes only once they enter the duodenum together with the chyme, where the pH is the most conducive to enzymatic activity (pH 5.5).
- In this study, pancreatin preparation C did not show any release of lipase at pH 5 whereas an immediate release happened at pH 6.

(v) Dissolution

- Although the pH of pure gastric secretions is pH 1–2, pH of the stomach can temporarily rise to pH 5 due to the buffering capacity of the stomach and the volume of food ingested, and then decrease below 4 due to gastric acid secretion.
- These alterations in pH can lead to inactivation of the enzymes released by PERT preparations. Hence, the release kinetics of these preparations at pH 5–6 is important in predicting their ability to deliver enzymes in the duodenum.
- In this study, after an initial incubation in simulated gastric fluid (pH 1) for 2 hours, more than 90% of the pellets of preparation C dissolved within 20 minutes in phosphate buffer at pH 6, showing a good dissolution profile.

PERT: Pancreatic enzyme replacement therapy.

Shrikhande SV, et al. Drug Des Devel Ther. 2021;15:3835–3843.

In Vitro Comparison of Pancreatin Enzyme Preparations Available in the Indian Market: Conclusion

CONCLUSION

Considerable differences in the physical and in vitro release behavior are present between the PERT preparations available in the Indian market.

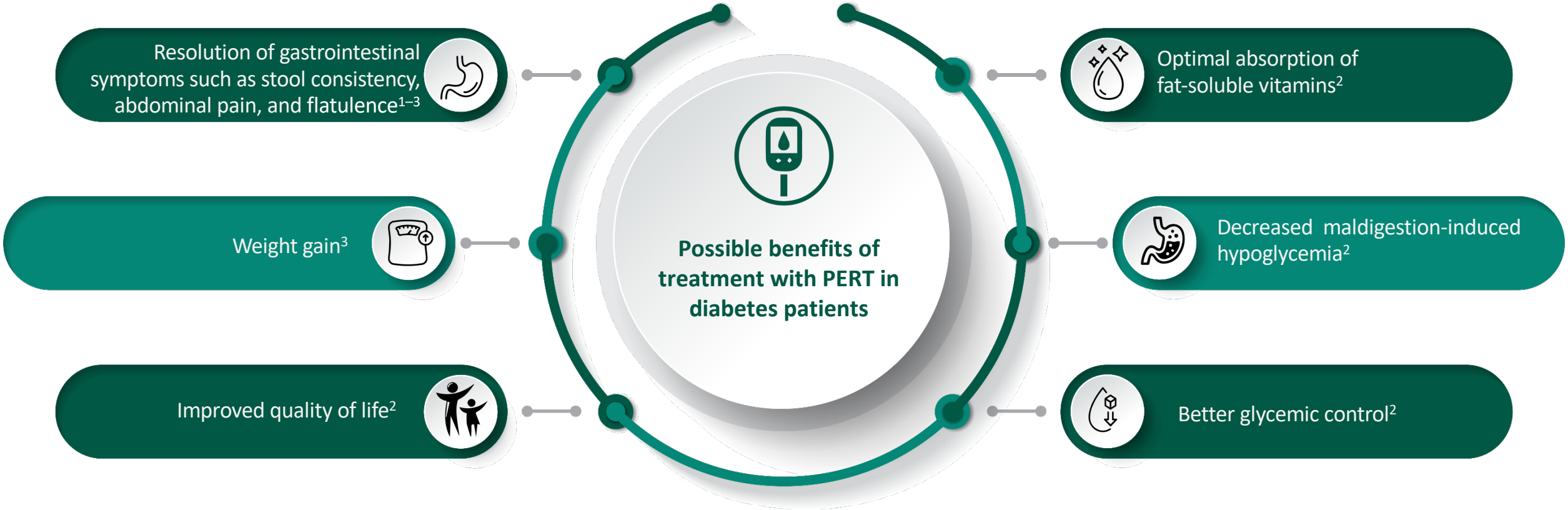
The PERT preparations tested in this study differed significantly from their label claims in terms of their lipase activity, water content, and in vitro dissolution behaviors.

As PERT products differ in their in vitro characteristics and adherence to label claim, caution should be taken when replacing or “switching” between products.

PERT: Pancreatic enzyme replacement therapy.

Shrikhande SV, et al. Drug Des Devel Ther. 2021;15:3835–3843.

Benefits of Pancreatin Usage in Diabetes Patients



PERT: Pancreatic enzyme replacement therapy.

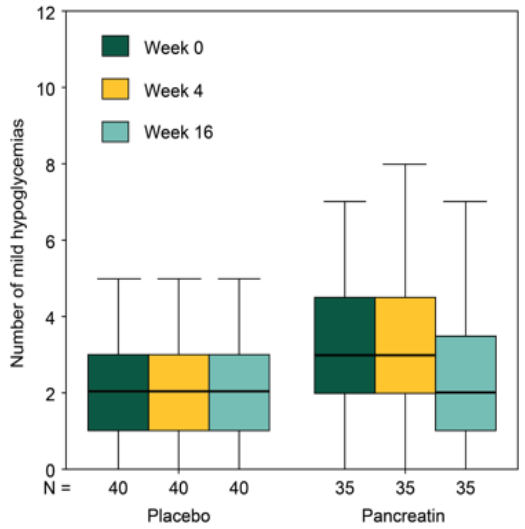
1. Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **2.** Foster TP, et al. Endocr Pract. 2020;26(12):1505–1513. **3.** Ramesh H, et al. Pancreatotomy. 2013;13(2):133–139.

Efficacy of Pancreatic Enzyme Replacement Therapy in Patients With Diabetes (1/5)

(i) Ewald et al. 2007

- Patients with diabetes mellitus requiring insulin treatment received 10,000 FIP units pancreatin or placebo (four capsules, thrice a day) with their main meals. Additional 10,000 units (two capsules) were allowed, if necessary.
- Vitamin D levels increased in the pancreatin group during the observational period.
- A reduction in mild and moderate hypoglycemia was observed in the pancreatin group at week 16.
- **Conclusion:** Pancreatin therapy can be used safely in patients with diabetes mellitus and PEI and helps to improve hypoglycemia.

Events of mild and moderate hypoglycemia reported during the observational period



Vitamin levels reported during the observational period

Vitamin D (nmol/L)					
Treatment		Week 0	Week 4	Week 10	Week 16
Placebo	Mean	60.20	55.63	61.78	62.70
	Standard deviation	24.09	22.84	26.13	26.25
Pancreatin	Mean	54.10	52.03	56.63	59.42
	Standard deviation	19.44	20.14	18.35	24.35

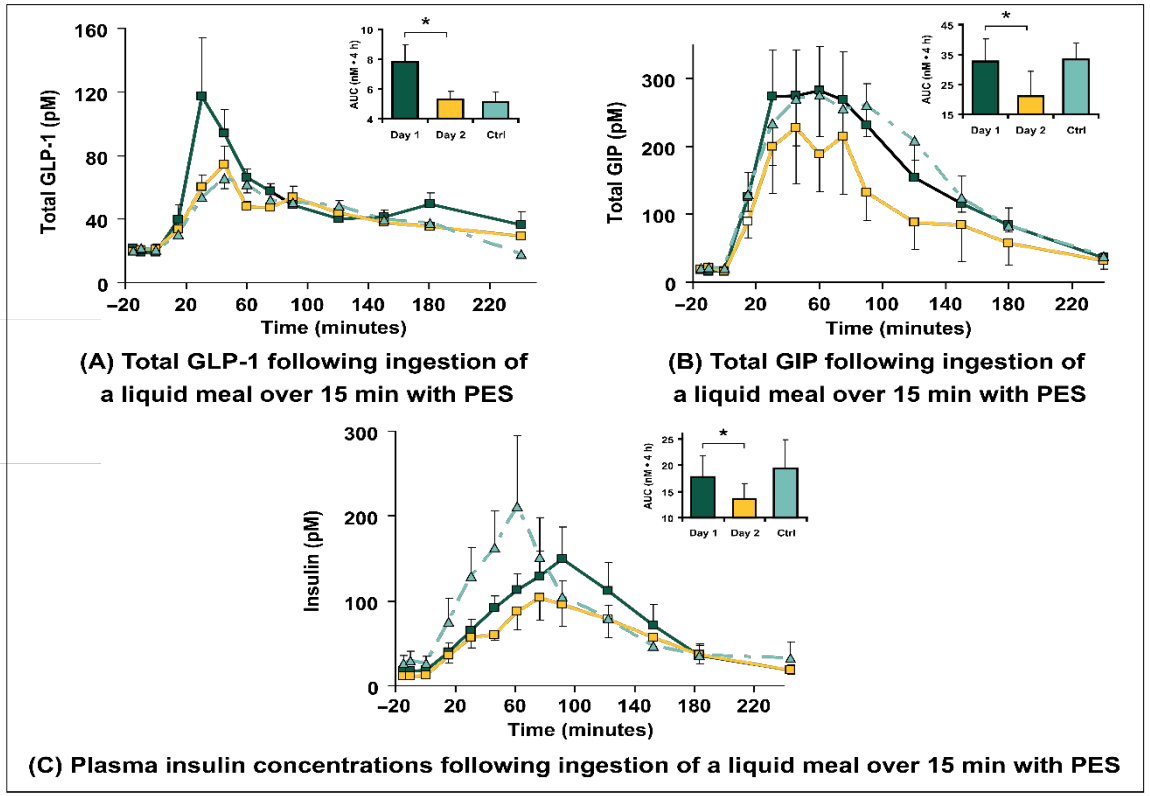
Adapted from: Ewald N, et al. Diabetes Metab Res Rev. 2007;23:386–391.

FIP: International Pharmaceutical Federation; PEI: Pancreatic enzyme insufficiency; PERT: Pancreatic enzyme replacement therapy.
Ewald N, et al. Diabetes Metab Res Rev. 2007;23:386–391.

Efficacy of Pancreatic Enzyme Replacement Therapy in Patients With Diabetes (2/5)

(ii) Knop et al. 2007

- Patients received two capsules of PES with the first sip of the meal.
- 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 PES administration.
- **Conclusion:** Therapy with PES results in an increased secretion of incretin hormones and thereby helps to improve glucose tolerance.



(A) Total GLP-1 following ingestion of a liquid meal over 15 min with PES

(B) Total GIP following ingestion of a liquid meal over 15 min with PES

(C) Plasma insulin concentrations following ingestion of a liquid meal over 15 min with PES

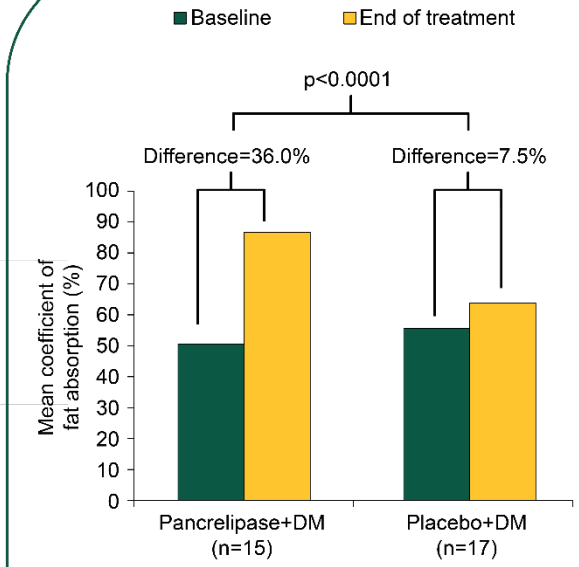
Adapted from: Knop FK, et al. Am J Physiol Endocrinol Metab. 2007;292:E324–E330.

DM: Diabetes mellitus; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy; PES: Pancreatic enzyme supplement.
Knop FK, et al. Am J Physiol Endocrinol Metab. 2007;292:E324–E330.

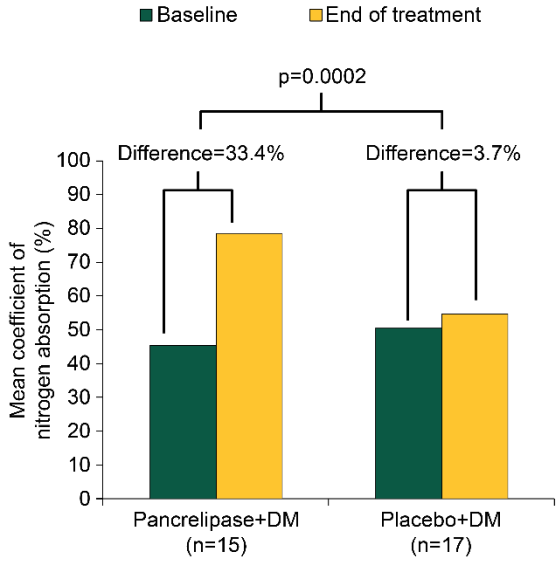
Efficacy of Pancreatic Enzyme Replacement Therapy in Patients With Diabetes (3/5)

(iii) Whitcomb et al. 2016

- Patients received pancrelipase or placebo for 7 days after a 5-day placebo run-in period (baseline).
- Mean changes in nutrient absorption were greater with pancrelipase vs. placebo in patients with DM (CFA, 36.0% vs. 7.5%, p<0.0001; CNA, 33.4% vs. 3.7%, p=0.0002).
- **Conclusion:** Pancrelipase therapy improved fat and protein absorption in patients with PEI due to chronic pancreatitis or pancreatectomy with or without DM.



Mean CFA: pancrelipase + DM versus placebo + DM (efficacy population)



Mean CNA: pancrelipase + DM versus placebo + DM (efficacy population)

Adapted from: Whitcomb DC, et al. Pancreas. 2016;45:676–686.

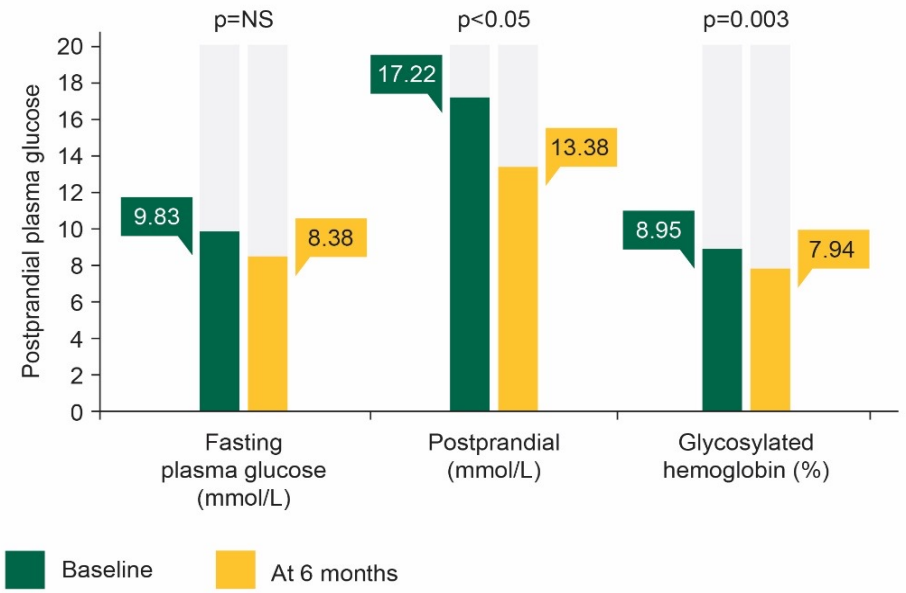
CFA: Coefficient of fat absorption; CNA: Coefficient of nitrogen absorption; DM: Diabetes mellitus; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy.
Whitcomb DC, et al. Pancreas. 2016;45:676–686.

Efficacy of Pancreatic Enzyme Replacement Therapy in Patients With Diabetes (4/5)

(iv) Mohan et al. 1998

- A total of 40 patients with fibrocalcific pancreatic diabetes received pancreatic enzyme supplements with a dosage of one tablet, three times a day. Each tablet of pancreatic enzyme supplement provides 300 mg pancreatin enzymes (8000 FIP U lipase, 9000 U amylase, and 450 U protease).
- Treatment with pancreatic enzyme supplements over 6 months significantly reduced postprandial plasma glucose level ($p<0.05$) and glycosylated hemoglobin ($p=0.003$).
- **Conclusion:** Treatment with PES helps to achieve better control of diabetes, improvement in nutrition, and overall improvement in quality of life in patients with diabetes.

Reduction in postprandial plasma glucose and HbA_{1c} at baseline vs. 6 months treatment with PES (total dose 8000 lipase units)



Adapted from: Mohan V, et al. Int J Pancreatol. 1998.

FIP: International Pharmaceutical Federation; $HbA1_c$: Glycosylated hemoglobin; NS: Not significant; PERT: Pancreatic enzyme replacement therapy; PES: Pancreatic enzyme supplement.

Mohan V, et al. Int J Pancreatol. 1998;24(1):19–22.

Efficacy of Pancreatic Enzyme Replacement Therapy in Patients With Diabetes (5/5)

(v) Ramesh et al. 2013

- In this study, 48 patients with PEI due to CP completed treatment with pancreatin at a dosage of 80,000 Ph. Eur. lipase units with each of the three main meals/day and 40,000 with each of up to three snacks/day.
- Significant improvements were observed in the patients treated with pancreatin from baseline to the end of OLE in mean±SD coefficient of fat absorption (CFA: 22.7%±12.2%), coefficient of nitrogen absorption (CNA: 6.5%±7.9%), and most nutritional laboratory parameters tested ($p \leq 0.001$).
- **Conclusion:** In patients with PEI due to CP, treatment with pancreatin for 1 year was associated with significant improvements in clinical symptoms, and a favorable safety and tolerability profile.

Changes from baseline to the end of OLE in CFA, CNA, and stool characteristics (OLE FA sample)

	Change from baseline		p-value*
	n	Mean±SD	
CFA (%)	47	22.7±12.2	0.001
CNA (%)	42	6.5±7.9	0.001
Stool fat content (g/day)	47	–25.1±14.4	0.001
Stool nitrogen content (g/day)	42	–0.5±0.5	0.001
Stool weight (g/day)	47	–349±213	0.001
*p-value for change from baseline to end of OLE (Wilcoxon's signed rank test).			

Adapted from: Ramesh H, et al. Pancreatotomy. 2013;13(2):133–139.

CP: Chronic pancreatitis; FA: Full analysis; OLE: Open-label extension; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy; Ph. Eur.: European Pharmacopoeia; SD: Standard deviation.
Ramesh H, et al. Pancreatotomy. 2013;13(2):133–139.

Revisiting the Patients' Cases: Clinical Improvements Posttreatment (1/4)

CHIEF COMPLAINTS

- Abdominal pain[1–3]
- Loose bowel movements[1,2]
- Difficulty controlling blood sugar levels[2]
- Pain in the feet, lower legs, and thighs[2]

MEDICAL HISTORY

- Shows poor glycemic control ($HbA_{1c} \geq 8.5\%$)[2]
- Has abdominal stool consistency for the past 2 months (type 6 as per the Bristol stool chart)[4]
- Recently diagnosed with magnesium deficiency (<1.3 mg/dL)[5]

PROBABLE DIAGNOSES

- Diabetes[2]
- Diabetic neuropathy[2]
- Pancreatic exocrine insufficiency[1–5]

MEDICATIONS PRESCRIBED

- Metformin (500 mg orally every 12 hours)[5]
- Premixed insulin injections (at 75/25, mix twice daily)[5]
- Magnesium glycinate (320 mg/day)[5]
- Venlafaxine (25 mg orally thrice daily)[6]
- Pancreatin minimicrospheres (50,000 Ph. Eur. with each of the three main meals/day and 25,000 Ph. Eur. with each of up to three snacks/day)[2]
- Vitamin B supplements (50 mg vitamin B1 daily; 80 mg vitamin B6 daily; and 2.4 mcg vitamin B12 daily)[5]

POSTTREATMENT FOLLOW-UP

At 3 months:

- Improved stool consistency[2]
- Reduction in neuropathic pain[6]

At 6 months:

- Improved blood sugar levels[2,5]
- Better absorption of micronutrients[2,5]
- Further improvements in stool consistency[2]

HbA_{1c}: Glycosylated hemoglobin; PEI: Pancreatic exocrine insufficiency; Ph. Eur.: European Pharmacopoeia.

1. Radlinger B, et al. Curr Diab Rep. 2020;20(6):18. **2.** Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **3.** Hardt PD, et al. Exp Diabetes Res. 2011;2011:761950. **4.** Cummings M. J Diabetes Nurs. 2014;18:320–323. **5.** Phillips ME, et al. BMJ Open Gastroenterol. 2021;8(1):e000643. **6.** Gallagher HC, et al. Cochrane Database Syst Rev. 2015;2015(8):CD011091.

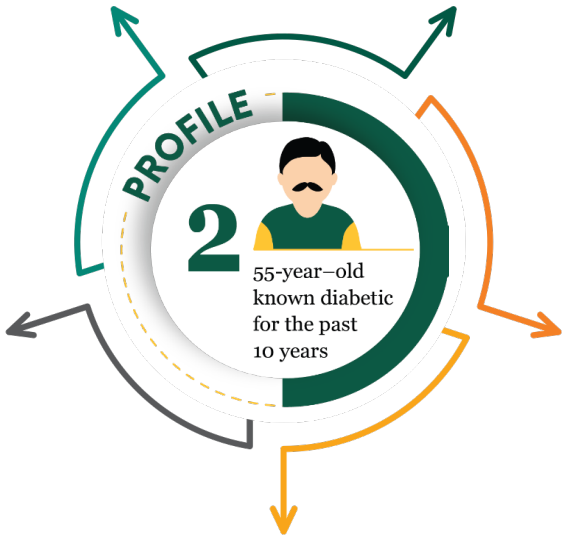
Revisiting the Patients' Cases: Clinical Improvements Posttreatment (2/4)

CHIEF COMPLAINTS

- Changes in bowel movements for the past 3 months[1,2]
- Several episodes of diarrhea, sometimes with mucus[1,2]
- Severe abdominal cramping and bloating[1–3]
- Paleness in skin[4]

MEDICAL HISTORY

- Had his bariatric surgery 3 months ago[5]
- Has been experiencing watery diarrhea for the past 3 months (type 7 as per the Bristol stool chart)[6]
- Recently diagnosed with iron deficiency (<11 g/dL)[4]



PROBABLE DIAGNOSES

- IBS-D[7]
- Pancreatic exocrine insufficiency[1–5]
- Anemia[4]
- Diabetes[1]

MEDICATIONS PRESCRIBED

- Ursodiol (750 mg daily to reduce the risk of developing gallstones during the postsurgical period of rapid weight loss)
- Ferrous fumarate (360 mg/day)[8]
- Loperamide (4 mg after each loose stool to reduce the frequency of diarrhea)[9]
- Pancreatin minimicrospheres (60,000 Ph. Eur. with each of the three main meals/day and 30,000 Ph. Eur. with each of up to three snacks/day)[1]

POSTTREATMENT FOLLOW-UP

At 3 months:

- Improved stool consistency and reduction in diarrhea[1,9]
- Less severe abdominal symptoms[1]

At 6 months:

- Better iron absorption[1,8]
- Significant reduction in anemia symptoms[1,8]

IBS-D: Diarrhea-predominant irritable bowel syndrome; PEI: Pancreatic exocrine insufficiency; Ph. Eur.: European Pharmacopoeia.

1. Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **2.** Radlinger B, et al. Curr Diab Rep. 2020;20(6):18. **3.** Phillips ME, et al. BMJ Open Gastroenterol. 2021;8(1):e000643. **4.** Gowanlock Z, et al. Blood Adv. 2020;4(15):3639–3647. **5.** NCBI bookshelf. Anemia. Accessed on: 21 July 2022. **6.** Cummings M. J Diabetes Nurs. 2014;18:320–323. **7.** UK guidelines. Gastrointestinal disorders in diabetes—Could it be pancreatic exocrine insufficiency? Accessed on: 21 July 2022. **8.** NHS. Ferrous fumarate. Accessed on: 21 July 2022. **9.** NHS. Loperamide. Accessed on: 21 July 2022.

Revisiting the Patients' Cases: Clinical Improvements Posttreatment (3/4)

CHIEF COMPLAINTS

- Pain and tenderness in the abdomen with flatulence[1,2]
- Changes in bowel habits[1,2]
- Fluctuating blood sugar levels[1]
- Increased thirst and need to urinate[3]
- Severe back pain[4]

MEDICAL HISTORY

- Has diabetes for the past 3 years; although the blood sugar levels were under control, she is currently experiencing recurring hypoglycemic events (with blood sugar levels dropping below 68 mg/dL during each event)[1,5]
- Recently diagnosed with vitamin D deficiency (<13 ng/mL)[6]
- Recently diagnosed with calcium deficiency (<7 mg/dL)[6]

PROBABLE DIAGNOSES

- Hyperparathyroidism[3]
- Osteoporosis[3]
- Pancreatic exocrine insufficiency[1,2]

MEDICATIONS PRESCRIBED/ DIETARY/LSMs RECOMMENDED

- Vitamin D supplements (15 mcg/day)[6]
- Calcium supplements (2500 mg/day)[6]
- Pancreatin minimicrospheres (50,000 Ph. Eur. with each of the three main meals/day and 25,000 Ph. Eur. with each of up to three snacks/day)[1]
- Zoledronic acid (4 mg every 3–4 weeks)[6]
- Ibuprofen (one pill; 300 mg every 4–6 hours)[7]
- Dapagliflozin (5 mg orally once daily)[8*]
- Inclusion of small, nutritious snacks in between meals to keep blood sugar levels constant
- Physical activity as per physiotherapist's advice (including walking outdoors and squats)

POSTTREATMENT FOLLOW-UP

At 3 months:

- Ability to manage hypoglycemia[1,5,8]
- Improved micronutrient status[1,6]

At 6 months:

- Decreased abdominal symptoms[1]
- Reduction in back pain[7]
- Improvements in bone mineral density[1,6]

*A switch in the patient's antidiabetic medication, i.e. use of dapagliflozin, an SGLT-2 instead of Glucotrol, a sulfonylurea to reduce the risk of hypoglycemia.
BMI: Body mass index; LSM: Lifestyle modification; PEI: Pancreatic exocrine insufficiency; Ph. Eur.: European Pharmacopoeia; SGLT-2: Sodium-glucose Cotransporter-2

1. Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **2.** Radlinger B, et al. Curr Diab Rep. 2020;20(6):18. **3.** NIDDK. Primary hyperparathyroidism. Accessed on: 21 July 2022. **4.** Hopkinsmedicine. Vitamin D and calcium. Accessed on: 21 July 2022. **5.** Foster TP, et al. Endocr Pract. 2020;26(12):1505–1513. **6.** Phillips ME, et al. BMJ Open Gastroenterol. 2021;8(1):e000643. **7.** Harvard Health Publishing. Best bets for back pain. Accessed on: 21 July 2022. **8.** Löhr JM, et al. United European Gastroenterol J. 2017;5(2):153–199.

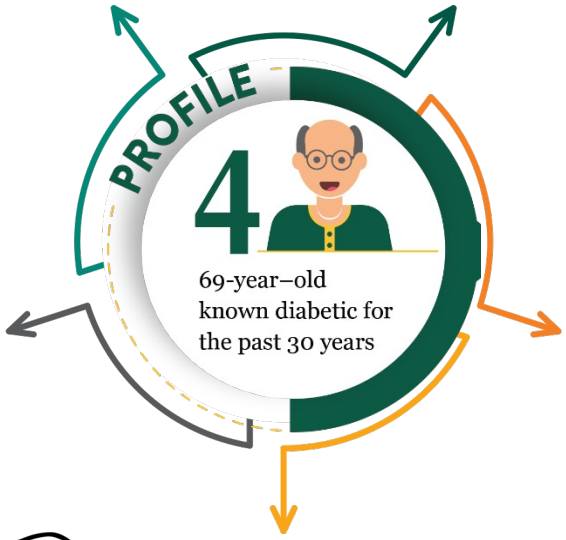
Revisiting the Patients' Cases: Clinical Improvements Posttreatment (4/4)

CHIEF COMPLAINTS

- Generalized weakness with dizziness and headache[1]
- Uncontrolled diabetes despite metformin regimen[1]
- An uncomfortable feeling of fullness after eating[2]
- Indigestion[2]
- Skin inflammation[2]

MEDICAL HISTORY

- Lost weight (>5% over the past 7 months)[3]
- Experiences palpitations (>100 heartbeats/minute) [3]
- Has vitamin A deficiency (<0.35 µmol/L)[2]
- Showed a rise in breath hydrogen by 12 ppm above the basal in glucose hydrogen breath test[2]
- Shows poor glycemic control ($HbA_{1c} \geq 7.0\%$)[1]



PROBABLE DIAGNOSES

- Chronic fatigue syndrome[3]
- SBBO[2]
- Pancreatic exocrine insufficiency [1–3]
- Diabetes[1]

MEDICATIONS PRESCRIBED/

- Voglibose (300 mcg three times/day)[1]
- Prandial insulin (started with 0.5 U/kg daily; increased TDD by 2 U/day)[1]
- Cyproheptadine (one tablet; 4 mg 2–3 times a day to reduce dizziness)[4]
- Sotalol (170 mg/day to prevent arrhythmias)[5]
- Rifaximin (550 mg tablet taken orally three times a day for 14 days for SBBO)[2]
- Pancreatin minimicrospheres (70,000 Ph. Eur. with each of the three main meals/day and 35,000 Ph. Eur. with each of up to three snacks/day)[1]
- Vitamin A supplements (700 mcg/day)[2]

POSTTREATMENT FOLLOW-UP

At 3 months:

- Better nutritional status[1,2]
- Improvements in postprandial abdominal symptoms[1]

At 6 months:

- Ability to maintain blood sugar levels and BMI[1]
- Stable heartbeat rate with a decrease in dizziness and headache[1,4,5]
- Improved energy levels[1]

BMI: Body mass index; HbA_{1c}: Glycosylated hemoglobin; PEI: Pancreatic exocrine insufficiency; Ph. Eur.: European Pharmacopoeia; SBBO: Small bowel bacterial overgrowth; TDD: total daily dose.

1. Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **2.** Phillips ME, et al. BMJ Open Gastroenterol. 2021;8(1):e000643. **3.** Radlinger B, et al. Curr Diab Rep. 2020;20(6):18. **4.** Medlineplus. Cyproheptadine. Accessed on: 21 July 2022. **5.** NHS. Solatol. Accessed on: 21 July 2022.

Tolerability of Pancreatic Enzyme Replacement Therapy in Patients With Diabetes

The long-term tolerability of pancreatin in patients with PEI due to CP or PS is supported by a 6-month and 51-week double-blinded studies.[1,2]

In the 6-month study, the majority (63%) of all TEAEs recorded in this study were observed to be mild and the number of TEAEs judged by the investigator to be possibly or probably related to treatment medication was low (7.8%). The delayed-release pancreatin capsules were also shown to be well-tolerated over 6 months, with a good tolerability profile.[1]

Furthermore, treatment with pancreatin for up to 1 year was well-tolerated, with a favorable tolerability profile. The overall rate of TEAEs observed was found to be acceptable given the long duration of the trial and the general health of the study participants.[2]

CP: Chronic pancreatitis; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme supplementation therapy; PS: Pancreatic surgery; TEAEs: Treatment-emergent adverse events.

1. Gubergrits N, et al. Aliment Pharmacol Ther. 2011;33(10):1152–1161. **2.** Ramesh H, et al. Pancreatotomy. 2013;13(2):133–139.

Dosage Considerations for Pancreatin Preparations

10%

The recommended initial dosage of pancreatin is about 10% of the physiologically secreted dosage of lipase into the duodenum after a normal meal.

Pancreatin preparations should be taken along with meals and snacks.

A minimum lipase dose of 40,000–50,000 Ph. Eur. U is recommended with main meals and half of that dose with snacks.

PERT: Pancreatic enzyme replacement therapy; Ph. Eur. U: European Pharmacopoeia unit.

Löhr JM, et al. United European Gastroenterol J. 2017;5(2):153–199.

Usage of Pancreatin Preparations in Special Population

(i) Use in pregnancy and breastfeeding

It is important that adequate PERT is maintained during pregnancy as a continuous supply of nutrients is required for the brain and retinol development of fetus.[1]

Although there is inadequate human data, PERT is unlikely to cause any harm to the fetus/infant and can be used safely during pregnancy and breastfeeding, because of the minimal maternal systemic absorption.[1,2]

(ii) Use in patients with renal impairment

Porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels.[2]

Thus, caution should be exercised when prescribing PERT to patients with gout, renal impairment, or hyperuricemia.[2]

PERT: Pancreatic enzyme replacement therapy.

1. Phillips ME, et al. BMJ Open Gastroenterol. 2021;8(1):e000643. **2.** NCBI. Pancrelipase. Accessed on: 13 July 2022.

Monitoring Patients on Pancreatic Enzyme Replacement Therapy

Regular monitoring of blood glucose levels and glycemic responses is recommended while taking PERT.[1]

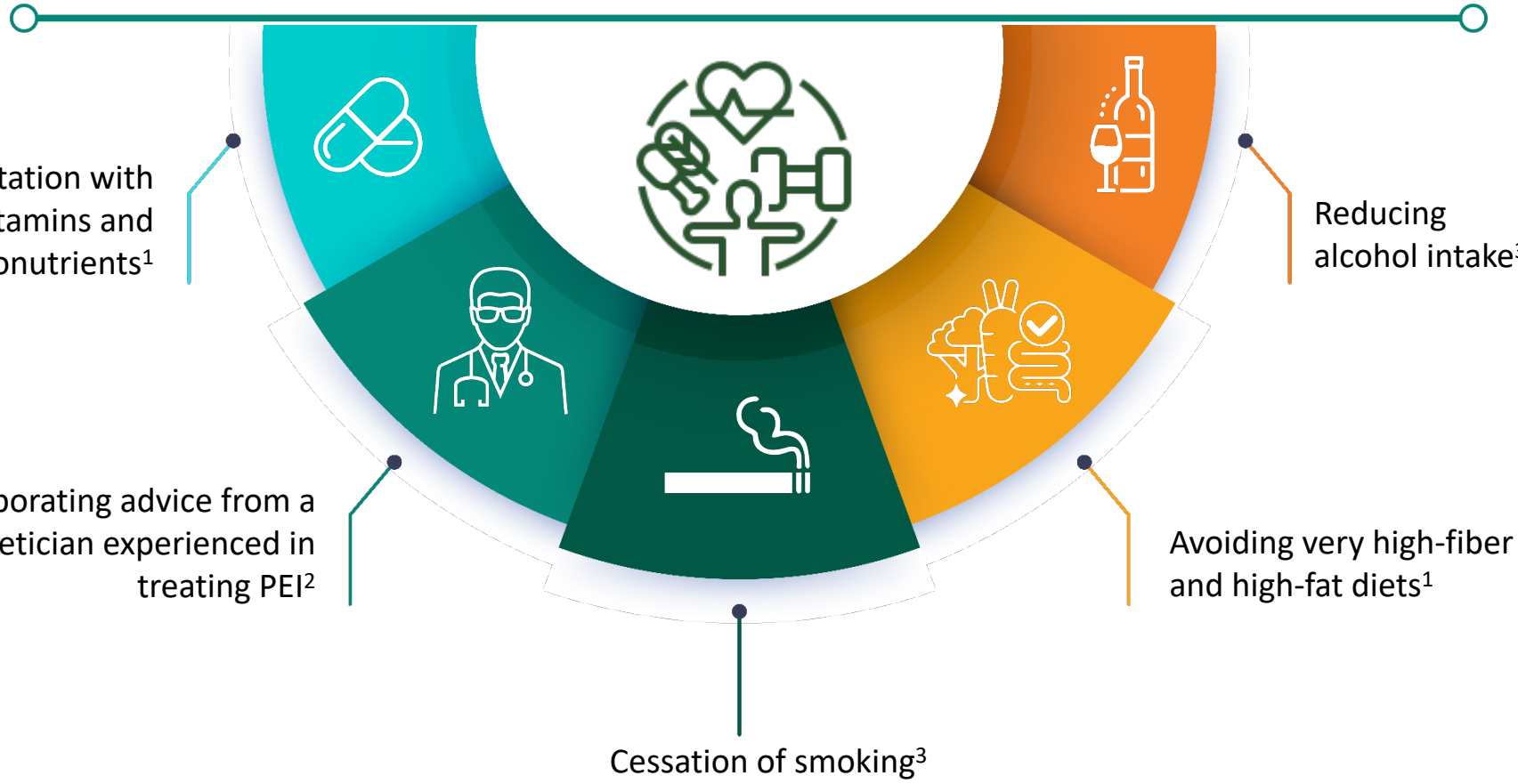
Doses of antidiabetic therapy, including sulfonylureas and insulin, may need adjusting while taking PERT.[1]

International guidelines for the management of PEI in diabetes recommend continuing PERT with increased dosages[1] and considering the diagnosis of associated chronic pancreatitis or other pancreatic diseases in case PEI symptoms are not controlled.[2]

PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy.

1. Gastrointestinal disorders in diabetes—Could it be pancreatic exocrine insufficiency? Accessed on: 28 February 2022. **2.** Pezzilli R, et al. World J Gastroenterol. 2013;19(44):7930–7946.

Recommended Dietary and Lifestyle Modifications for the Management of Pancreatic Exocrine Insufficiency



PEI: Pancreatic exocrine insufficiency.

1. Radlinger B, et al. Curr Diab Rep. 2020;20(6):18. **2.** Talukdar R, et al. J Assoc Physicians India. 2017;65(9):64–70. **3.** Gastrointestinal disorders in diabetes—Could it be pancreatic exocrine insufficiency? Accessed on: 28 February 2022.

Discussion Question

Which one of the following makes PERT a better therapeutic choice for PEI in patients with diabetes?

A PERT helps with the optimal absorption of fat-soluble vitamins

B PERT relieves gastrointestinal symptoms related to PEI

C PERT helps maintain a better glycemic control

D PERT helps manage weight

Correct answer

PERT helps maintain a better glycemic control

PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy.

Foster TP, et al. Endocr Pract. 2020;26(12):1505–1513.

Key Takeaways

PEI manifests more commonly as maldigestion in patients with diabetes mellitus.

Nearly one-fourth of diabetes patients in India have PEI.

PERT is the cornerstone of PEI management and is an effective and well-tolerated treatment option for patients with diabetes.

The HaPanEU guidelines recommend that enteric-coated microspheres or minimicrospheres of <2 mm in size are the PERT preparations of choice for PEI.

Patients with PEI should take pancreatin with every meal and snack and the required pancreatin dose for a main meal (breakfast, lunch, or dinner) ranges from about 25,000 to 80,000 Ph. Eur. U of lipase, and half of the individual dose for snacks.

Regular monitoring of blood glucose levels and glycemic responses are recommended while taking PERT.

HaPanEU: Harmonizing diagnosis and treatment of chronic pancreatitis across Europe; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy; Ph. Eur. U: European Pharmacopoeia unit.

Thank you!

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