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Pancreatic enzyme replacement therapy in chronic pancreatitis

E.C.M. Sikkens, MD *, D.L. Cahen, MD, PhD [1], E.J. Kuipers, Md, PhD, Professor [2], M.J. Bruno, MD, PhD, Professor [3]

Department of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

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Exocrine pancreatic insufficiency (EPI) is a serious condition which occurs in several diseases including chronic pancreatitis (CP), cystic fibrosis, pancreatic cancer, and as a result of pancreatic surgery. The lack or absence of pancreatic enzymes leads to an inadequate absorption of fat, proteins, and carbohydrates, causing steatorrhoea and creathorrhea which results in abdominal discomfort, weight loss, and nutritional deficiencies. To avoid malnutrition related morbidity and mortality, it is pivotal to commence pancreatic enzyme replacement therapy (PERT) as soon as EPI is diagnosed. Factors as early acidic inactivation of ingested enzymes, under dosage, and patient incompliance may prevent normalisation of nutrient absorption, in particular of fat digestion. This review focuses on the current status of how to diagnose and treat EPI.

Exocrine pancreatic insufficiency and chronic pancreatitis

In EPI the pancreas is unable to deliver sufficient amounts of pancreatic enzymes to the small intestine to digest intraluminal nutrients. EPI may occur due to loss of functional parenchyma (atrophy), blockage of the pancreatic duct, or postprandial asynchrony. Besides CP, other conditions that can result in loss of parenchyma are severe acute pancreatitis (which can cause transient EPI), pancreatic resection, and cystic fibrosis (CF). Chronic obstruction of the main pancreatic duct can be

* Corresponding author. Tel.: +31 (10) 70 31073.
E-mail addresses: e.sikkens@erasmusmc.nl (E.C.M. Sikkens), d.cahen@erasmusmc.nl (D.L. Cahen), e.j.kuipers@erasmusmc.nl (E.J. Kuipers), m.bruno@erasmusmc.nl (M.J. Bruno).
[1] Tel.: +31 (10) 70 35946.
[2] Tel.: +31 (10) 70 34681.
[3] Tel.: +31 (10) 70 35946; fax: +31 (10) 70 34682.

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caused by strictures or ductal stones in CP, or obstruction due to a malignancy. Postprandial asynchrony is the disjunction between gastric emptying of a meal and the delivery of pancreatic enzymes into the small intestine, which can occur as a result of gastric surgery, short bowel syndrome, Crohn's disease, and diabetes mellitus [1,2].

In CP, the progression to gland failure depends on the underlying cause of the disease [3]. Patients with alcoholic pancreatitis for instance, develop exocrine insufficiency after a median of ten years while in patients with idiopathic CP this may take up to 20 to 25 years to occur [4]. Furthermore, in autoimmune pancreatitis, EPI is one of the presenting symptoms in over 75% of patients [5,6].

Pancreatic secretion

The pancreas plays a crucial role in the digestive system. The gland produces pancreatic juice that consists of a mixture of more than two dozen digestive enzymes in the pre-activated form, called zymogens. Zymogens are produced by acinar cells and mixed with a bicarbonate rich fluid that is produced by pancreatic ducts cells [1,7]. Trypsinogen is the most important zymogen because it becomes trypsin, the key enzyme that activates all other zymogens. Trypsin, chymotrypsin, amylase and lipase are responsible for the majority of the enzyme activity derived from the pancreas [7]. Lipase is one of the most important enzymes because it plays a leading role in the digestion of fat, which is the highest dietary source of calories. There are three types of lipase: lingual, gastric and pancreatic. Approximately 10–30% of the lipolytic activity can be attributed to gastric and lingual lipase [8,9]. This explains the residual fat digestion and absorption in pancreatectomized individuals.

After exocrine pancreatic enzymes are secreted in the duodenum, they move to the ileum and during this intestinal transit the intraluminal activity of the enzymes diminishes due to irreversible proteolytic and acidic degradation. There is a considerable variability in the intraluminal stability of the different pancreatic enzymes [10,11]. Lipase is the most susceptible to acidic and proteolytic degeneration and is therefore available for a shorter period during small intestinal transit in patients with EPI as well as in healthy people [11–13]. In healthy people, 74% of the amylase activity, 22% of the trypsin activity and just 1% of the lipase activity survive intestinal transit [11]. The digestion and absorption of lipids takes place between the pylorus and the ligament of Treitz [12,14,15]. Digestion in the jejunum and the ileum is less efficient. In meals with a high concentration of fat the physiologic malabsorption of several grams of fat occurs. A fecal fat excretion of up to 7 g/d can therefore be considered normal.

Pathophysiology

The pancreas has a large functional reserve and clinically evident EPI occurs only when 90% of the function is lost and the secretion of pancreatic enzymes is less than 10% of normal [11,16]. Because of a decrease in lipase, trypsin and amylase activity, maldigestion of fat, proteins and carbohydrates occurs. Malabsorption of fat precedes malabsorption of proteins and carbohydrates and is clinically more apparent [11,17,18]. The decrease in pancreatic lipolytic activity cannot be compensated effectively by other mechanisms. As a consequence, the increased presence of lipids and other nutrients in the distal small bowel causes significant alterations in gut motility leading to accelerated gastric emptying and intestinal transit. This results in a marked decrease in the time available for digestion and absorption of nutrients, which contributes to the malabsorption [14,15,19–21]. Furthermore, in diabetic patients, autonomic neuropathy may further accelerate the early arrival of chyme to the cecum as well [22].

There is one additional factor that may contribute to impaired lipolysis. In EPI the secretion of bicarbonate by the pancreas is considerably diminished. Normally, bicarbonate protects pancreatic enzymes from denaturation by gastric acid. Due to the low bicarbonate secretion, the intraduodenal pH may drop below 4 late postprandially which negatively affects lipase activity [23]. Another effect of the diminished bicarbonate secretion is that bile salts may precipitate which leads to a decrease in postprandial duodenal lipid solubilisation [24].