Digestive and Liver Disease xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Pancreatic enzyme replacement therapy after gastric resection: An update

Filippo Antonini [a,*], Stefano Crippa [b], Massimo Falconi [b], Giampiero Macarri [a], Raffaele Pezzilli [c]

[a] Department of Gastroenterology, A. Murri Hospital, Polytechnic University of Marche, Fermo, Italy
[b] Division of Pancreatic Surgery, Pancreas Translational and Clinical Research Center, San Raffaele Scientific Institute, Vita e Salute University, Milan, Italy
[c] Department of Digestive Diseases and Internal Medicine, Sant'Orsola-Malpighi Hospital, Bologna, Italy

ARTICLE INFO

Article history:
Received 24 June 2017
Received in revised form 7 October 2017
Accepted 24 October 2017
Available online xxx

Keywords:
Exocrine pancreatic insufficiency
Gastrectomy
Pancreatic enzyme
Surgery

ABSTRACT

Exocrine pancreatic insufficiency (EPI) is one of the possible mechanisms of fat maldigestion following gastric surgery, together with reduced food intake, loss of gastric reservoir, small bowel bacterial overgrowth and rapid small bowel transit. Oral pancreatic enzyme replacement therapy (PERT) is the mainstay of treatment for EPI. The efficacy and safety of pancreatic enzyme substitution in patients following gastric resection remains unclear. This review article summarizes relevant studies addressing PERT after gastric resection.

1. Introduction

The exocrine pancreas plays a key role in the digestive function by delivering a juice consisting of several pancreatic enzymes and sodium bicarbonate, the latter useful for increasing the pH of the intestinal lumen, thus optimizing the work of pancreatic enzymes [1–3]. Main pancreatic digestive enzymes are amylase, protease, and lipase that, under normal physiological conditions, digest the macronutrients present in the chyme [2]. While starch digestion begins in the mouth and protein digestion begins in the stomach, most of lipid digestion and absorption starts in the duodenum where triglycerides are broken down into fatty acids and monoglycerides, which are then solubilized by bile salts [2,4].

Exocrine pancreatic insufficiency (EPI) is a condition characterized by the inability to properly digest food due to a reduction or absence of stimulation, production, or delivery of pancreatic digestive enzymes to the bowel lumen, resulting in maldigestion, malabsorption and, ultimately, malnutrition. As pancreatic lipase accounts for up to 90% of fat digestion, the hallmark of EPI is maldigestion of fat rather than proteins or carbohydrates [5]. This condition may go undiagnosed because symptoms of EPI are not specific and can often be misdiagnosed as gastrointestinal functional disorders. Indeed, fat maldigestion and specific consequences, such as steatorrhoea, only occur when lipase output decreases below 10% of normal level [5]. Clinical pictures of EPI vary along with the severity of the underlying disease. The main clinical signs are steatorrhoea and weight loss, but the most common symptoms include abdominal discomfort, bloating, flatulence and diarrhea. Other conditions such as deficiency of fat-soluble vitamins (A, D, E, K), bone loss and compromised immunity can be associated [3].

The etiology of EPI includes both pancreatic and extrapancreatic causes (Table 1). Up to 90% of patients who have had total or subtotal gastrectomy may develop a postoperative maldigestion syndrome with subsequent weight loss and abdominal discomfort that significantly affects their quality of life [6–9]. Moreover, chronic malnutrition in cancer patients can negatively affect their response to postoperative chemotherapy and increase the incidence of treatment-related side-effects that can lead to treatment interruption, thus impairing quality of life [10,11]. The etiology of malnutrition following gastric resection is multifactorial and EPI is one of the possible mechanisms of fat maldigestion. Oral pancreatic enzyme replacement therapy (PERT) is the mainstay of treatment for EPI. The efficacy and safety of pancreatic enzyme substitution in patients following gastric resection remains unclear.

This review article summarizes relevant studies addressing PERT after gastric resection.

* Corresponding author at: UOC Gastroenterologia ed Endoscopia Digestiva, Università Politecnica delle Marche, Ospedale "A.Murri", 63900 Fermo, Italy.
E-mail address: filippo.antonini@sanita.marche.it (F. Antonini).

https://doi.org/10.1016/j.dld.2017.10.025
1590-8658/

Table 1
Pancreatic and extrapancreatic causes of exocrine pancreatic insufficiency.

Primary pancreatic disease	Extrapancreatic diseases
Pancreatitis (acute and chronic)	Diabetes mellitus
Pancreatic cancer	Coeliac disease
Pancreatic surgery	Gastric surgery
Pancreatic agenesia	Bariatric surgery
Cystic fibrosis	Peri-ampullary tumors
Congenital disorders (pancreatic hypoplasia, isolated lipase-colipase deficiency, Shwachman–Diamond syndrome, Johanson–Blizzard syndrome)	Extrapancreatic neuroendocrine tumors (gastrinoma, somatostatinoma)
Pancreatic lipomatosis or atrophy	Inflammatory bowel disease

2. Search of literature

A computer-assisted search on three databases such as PubMed, Scopus and Web of Science (WoS) was carried out to identify relevant studies in English literature. The search was performed from January 1990 to April 2016 and was carried out using MESH terms for PubMed (Postgastrectomy Syndromes, Gastrectomy, Maldigestion, Malabsorption) and key words for Scopus and WoS (Gastrectomy, Maldigestion, Malabsorption). Two authors independently assessed the papers against the study's eligibility criteria. Study inclusion criteria were: (1) prospective design; (2) complete data on PERT after gastric resection. Review articles, letters to editors and papers not containing original data were excluded. In these three databases 94 full text papers were identified but most of them (n = 92) were not fit for the study as they did not include complete and original data. Only two randomized controlled trials met the criteria and were included in this review [12,13]. Finally, references included in the selected papers were also checked to find more papers in scope with the study.

3. Pathophysiology of exocrine pancreatic insufficiency secondary to gastric resection

Gastric resection can cause a multifactorial maldigestion syndrome characterized by diarrhea, flatulence, anorexia, weight loss and fatty stools, irrespective of the type of gastrectomy procedure [14,15]. EPI is one of the possible mechanisms of maldigestion following gastric surgery, together with reduced food intake, loss of gastric reservoir, small bowel bacterial overgrowth (SIBO) and rapid small bowel transit [16–18]. Integrity of the gastro–pancreatico–duodenal complex is crucial for a correct process of digestion of food.

Pancreatic secretion is a complex process regulated by both neural and endocrine controls. It is divided into the cephalic, gastric, and intestinal phases. In the gastric phase, when the meal enters the stomach, fundus relaxation triggers a vagal reflex (neurally mediated post-prandial stimulation of exocrine pancreatic secretion) that causes secretion of pancreatic enzymes [19]. The fundus relaxation due to the presence of nutrients in the gastric antrum (antro-fundic reflex) and the inhibition of antral motility induced by the presence of nutrients within the duodenal lumen (duodenogastric reflex) together regulate gastric emptying. Moreover, small particles of nutrients reach the duodenum in a slow and progressive manner. The passage of gastric chyme into the duodenum stimulates the intestinal phase that accounts for 70%–80% of pancreatic secretion and is mostly regulated by the release of secretin and cholecystokinin [20].

The main cause of maldigestion following gastric resection is the asynchrony between delivery of the pancreatic enzymes and the food particles, caused by anatomic alterations [3]. Indeed, patients with a preserved duodenal passage after surgery, as it happens in a Billroth I reconstruction, showed better results in the absorption of medium-chain triglycerides. Moreover, they have improved nutritional parameters and an overall better physiological state [21–23].

Table 2
Main hypothesized mechanisms affecting exocrine pancreatic function after gastric surgery.

- Alterations of gastric relaxation due to the absence of neural gastric reflexes [19]
- Absence of neural gastric stimulation responsible for pancreatic secretion caused by the lack of fundus relaxation [19]
- Rapid gastric emptying and asynchrony between gastric emptying and bilio-pancreatic secretion due to new tracts of various reconstructions [23]
- Bacterial overgrowth after gastrectomy [17]
- Extensive denervation of the pancreas due to lymph node dissection and truncal vagotomy [18]

Another possible explanation of post-gastrectomy maldigestion is a deficiency of gastric lipase that can account for 10–30% of triacylglycerol hydrolysis occurring in the gastrointestinal tract of adult patients [24].

Table 2 summarizes the mechanisms that can be considered responsible for EPI after gastric surgery.

4. Pancreatic enzyme replacement therapy after gastric resection

Oral PERT is the mainstay of treatment for EPI [25,26]. The exogenous pancreatic enzyme products used for PERT are extracts from swine pancreas. Although they contain all pancreatic enzymes (mainly amylase, proteases and lipase), it is lipase that plays the most important role in therapy. The goal of the treatment is to replicate the physiological process that allows an adequate concentration of active pancreatic enzymes in the duodenum along with the presence of nutrients [4,27]. When a sufficient enzyme concentration is delivered into the duodenal lumen, fat absorption is enhanced. For this reason, pancreatic extracts should be ingested during the meal [4,27]. A variety of formulations containing pancreatic enzymes have been developed in an attempt to avoid gastric inactivation and enable delivery to the duodenum where lipid digestion is physiologic [2]. Encapsulated enteric-coated microspheres and mini-microspheres with a pH sensitive coating are considered the enzyme treatment of choice by all major current European national consensus guidelines [28–30]. The correct amount of oral lipase replacement dose should be adjusted according to dietary fat content, EPI severity, body weight, clinical symptoms, and stool fat content and should not be less than 40,000–50,000 U of lipase per meal [31]. Several days should be allowed between dose adjustments to give sufficient time for the enzymes to work [32].

Maldigestion following gastric surgery can lead to malnutrition: this is considered as one of the major complications after gastric cancer surgery [33]. Therapeutic efficacy is associated not only with

Please cite this article in press as: Antonini F, et al. Pancreatic enzyme replacement therapy after gastric resection: An update. Dig Liver Dis (2017), https://doi.org/10.1016/j.dld.2017.10.025