Indian Journal of Surgical Oncology (June 2021) 12(2):391–396
https://doi.org/10.1007/s13193-021-01315-7

ORIGINAL ARTICLE

Exocrine Pancreatic Insufficiency Following Gastric Resectional Surgery—is Routine Pancreatic Enzyme Replacement Therapy Necessary?

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Received: 9 September 2020 / Accepted: 21 March 2021 / Published online: 5 April 2021

Abstract

The data on exocrine pancreatic insufficiency (EPI) following gastric resectional surgery is variable, ranging from 26% to as high as 100%. This study aimed to document symptomatic EPI following gastric resectional surgery and to objectively document EPI, by fecal elastase (FE) testing. This was a cross-sectional study among patients undergoing gastric resection for adenocarcinoma of the stomach, at the Upper Gastrointestinal Surgical Unit at the Christian Medical College Hospital, Vellore, India. A detailed questionnaire was administered to the patients in the postoperative period, to evaluate clinical symptoms of EPI. Further, study participants were tested for FE pre- and postoperatively. Of the 60 patients in this study, the postoperative questionnaire administered to all patients during follow up. None showed symptoms suggestive of EPI. Pre- and post-operative FE testing were feasible in 27 of the 60 patients, which showed a 33% incidence of EPI. None of the patients had clinical symptoms of EPI, following gastric resectional surgery, on short-term follow-up. However, more than a third of the patients tested developed asymptomatic EPI after gastric resectional surgery, based on FE testing. This may be explained by the fact that in the early postoperative period, EPI following gastric resectional surgery perhaps has a mild, subclinical presentation. Therefore routine pancreatic supplementation after gastric resectional surgery may not be necessary. However, one needs to carefully look for worsening of symptoms of EPI on long-term follow-up, which may necessitate appropriate investigations followed by pancreatic enzyme replacement therapy.

Keywords Gastrectomy · Gastric cancer · Exocrine pancreatic insufficiency · Fecal elastase

Introduction

One of the known causes of troublesome gastrointestinal symptoms following gastric resectional surgery includes exocrine pancreatic insufficiency (EPI), which can lead on to lipid malabsorption, clinically manifesting as steatorrhoea, bloating, weight loss etc. Malnutrition may occur as a consequence of abnormal fat digestion, malabsorption of fat-soluble vitamins as well as decreased circulating lipoproteins and micronutrients [1–3]. Literature supports the presence of EPI following gastric resection surgery and the reported incidence in the published literature varies from about 26 to 100% [4, 5].

The aim of the study was twofold. Firstly, to assess how common the clinical symptoms of EPI were, post gastric resectional surgery. Secondly, to establish the occurrence of EPI more objectively by testing for fecal elastase (FE) in stool samples. Most of the studies on this topic have been from the West and to our knowledge, this study is the first of its kind, reporting the occurrence of EPI, following gastric resectional surgery, from the Indian subcontinent.

Presentation at scientific meeting: IASGCON 2019, AIIMS, New Delhi. (Indian Association of Surgical Gastroenterology)

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Materials and Methods

After obtaining the necessary approval from the Institutional Review Board, the study was conducted prospectively, over a 20-month period, between January 2017 and September 2018, at the Upper Gastrointestinal (GI) Surgery Unit, Christian Medical College Hospital, Vellore, India. Informed consent was obtained from all patients before recruitment. After establishing the diagnosis of gastric cancer, the management plans were finalized in the Upper GI tumour board meetings, as per normal protocol. Upfront surgery was performed in patients who were obstructed or, bleeding or early tumor (< T2, N0). In all other patients, neoadjuvant chemotherapy was administered as per the DOX (Docetaxel, Oxaliplatin, Xeloda ®) or FLOT (5-Fluorouracil, Leucovorin, Oxaliplatin, Taxane) regimens. The standard reconstruction technique following gastric resectional surgery was a Roux en Y reconstruction. A detailed questionnaire was administered to all the 60 patients (in their local language), to assess symptoms of fat malabsorption in the postoperative period. Of these 60 patients, preoperative and postoperative FE testing was feasible in 27 patients. The postoperative testing was performed during the postoperative follow-up when the patient was tolerating orally a normal diet.

Questionnaire Screening

A detailed questionnaire was administered postoperatively, in all the 60 patients to identify the symptoms of EPI in the postoperative period. The questionnaire was administered either in person (at the time of follow-up) or over the phone, by the primary investigator. The questionnaire included questions regarding the symptoms of EPI such as frequency of stools, color and consistency of stools, passage of foul-smelling stools, and other symptoms such as abdomen distension, abdomen pain, bloating, and flatulence.

Fecal Elastase Test

Fecal elastase (FE) testing is an enzyme-linked immunosorbent assay (ELISA) test, with polyclonal antibodies that are directed against species and organ-specific defined peptide sequences of the human pancreatic elastase molecule [6]. Two stool samples were collected for testing, one before and one after the gastric resectional surgery, when the patient was on a normal diet (Fig. 1).

Results

Sixty patients who underwent gastric resectional surgery for adenocarcinoma of the stomach were included, comprising of 39 males and 21 females patients. The mean age was 52 (range 30 to78). Forty-five patients underwent subtotal gastrectomy and the rest 15 patients underwent total gastrectomy. Six of the resections were performed by the minimally invasive technique and the rest were standard open gastric resections. Thirty-nine patients had upfront surgery for gastric adenocarcinoma followed by adjuvant chemotherapy, while 21 patients had perioperative chemotherapy prior to gastrectomy. Pre- and post-operative FE testing were feasible in 27 out of the 60 patients.

Questionnaire Assessment

All the patients were assessed for clinical symptoms of steatorrhoea or lipid malabsorption using a questionnaire in the postoperative period at the time of a routine postoperative out-patient follow-up visit or over the phone, within 3 months. None of the patients in this study had clinically significant steatorrhoea or fat malabsorption based on postoperative questionnaire assessment.

Fecal Elastase Testing

The cut-off value for fecal elastase in the diagnosis of EPI was taken as 200 μg elastase/g feces. The reported sensitivity and specificity of FE testing were both 93% using this value as the cut-off for diagnosing EPI [7, 8]. Patients who had a normal pre-operative FE and subsequently developed an abnormally low value of FE following gastric resectional surgery were considered to have developed EPI following surgery.

Nine patients out of 27 patients had developed abnormally low levels of FE (less than the cut off valve of 200 units) in the post-operative testing as shown in Table 1. Incidence of EPI following gastric resectional surgery in this study was 33.3%. There was no statistical significance between the type of gastrectomy (total vs. subtotal) and the incidence of EPI following gastric resection surgery (p value 0.363).

Timing of Post-Operative Sampling

The time of testing postoperative testing ranged from 14 days to 351 days as shown in Table 2 (mean of 90 days). This varied timing of the post-operative testing was based on the logistics and the availability of the patient for follow-up in our centre, in the postoperative period. However, there was no statistical significance between post-operative elastase results and timing of post-operative sampling by independent sample t test. (p value 0.737).

Discussion

Exocrine pancreatic insufficiency (EPI) is defined as the inability to maintain normal fat digestion due to a reduction or

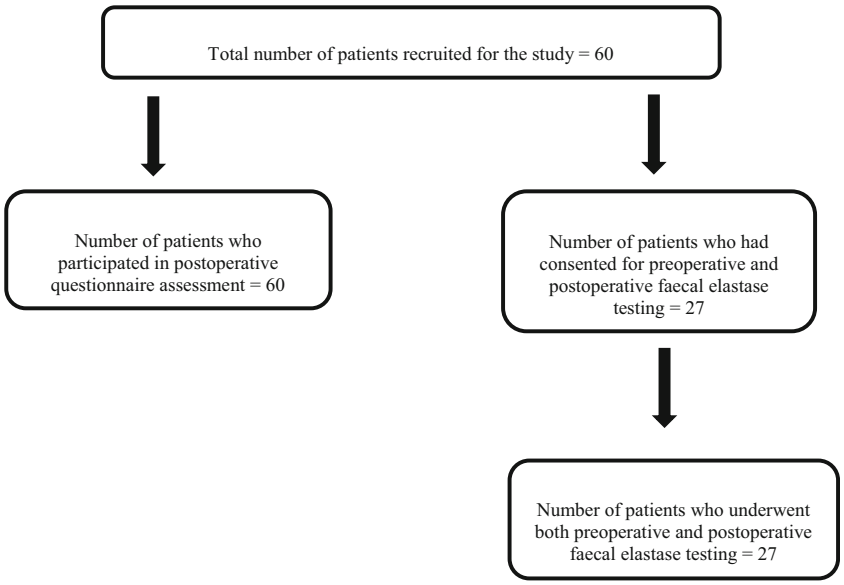

Fig. 1 Study patients' recruitment algorithm. FE = fecal elastase

absence of stimulation, production, or delivery of pancreatic digestive enzymes. This results in malabsorption, eventually leading to malnutrition and a significant drop in the quality of life [9]. Fat malabsorption occurs when the intraduodenal levels of lipase fall below 5–10% of normal enzyme output [10].

Pathophysiology of EPI Following Gastric Resectional Surgery

Several factors contribute to the pathogenesis of EPI following gastric resectional surgery. Firstly, the absence of antro-fundic and duodeno-fundic reflexes following gastric resection surgery results in a decrease in the neurally stimulated pancreatic secretion [11]. Secondly, reconstructive techniques bypassing the duodenum, such as Billroth-II (B2) and Roux-en Y (RY) reconstruction leads to the loss of duodenal transit of food which in turn leads to decreased Cholecystokinin [12, 13]. Thirdly, a rapid upper intestinal transit time contributes to EPI. The loss of gastric reservoir hinders mechanical digestion of food and rapid transit of food into the small bowel [14]. The release of pancreatic enzymes is not coordinated with the intestinal transit of food and inadequate mixing occurs (post-cibal asynchrony) leading to ineffective digestion [9, 15]. And finally, denervation of the pancreas during lymph nodal dissection and vagotomy, inherent to gastric resections, has also been attributed to cause EPI [16–18]. All these theories, individually and in combination, may contribute to the occurrence of EPI [11, 16–19].

Tests of Pancreatic Function

The tests of pancreatic exocrine function can be classified as *direct* or *indirect*. Direct tests are based on the measurement of secreted enzymes and bicarbonate whereas indirect tests assess the effect of pancreatic secretion on various enzymes or nutrients and the consequences of EPI. The tests may be further referred to as *invasive* or *non-invasive*, depending on the ease of administration to the patient.

The direct tests invasive tests are performed by stimulation of the pancreas using hormonal secretagogues, after which duodenal fluid is collected with the help of an upper GI endoscopy, to directly quantify pancreatic secretory content, e.g., secretin stimulation test, secretin-cholecystokinin test, secretin-cerulein test, and the Lundh test meal. The direct, non-invasive tests include serum trypsin assay, fecal chymotrypsin, and amino acid consumption tests [20].

The indirect tests include triglyceride breath test, dual-label Schilling test, Betiromide test, fecal elastase test (FE), and the 72-h fecal fat analysis tests. The 72-h fecal fat analysis is considered the gold standard test for fat malabsorption and is expressed as the coefficient of fat absorption [19, 21]. But this test is quite cumbersome and logistically difficult to implement on a routine basis. The alternative indirect test, the FE testing is much simpler, non-invasive, and is shown to be comparable to the secretin test at detecting EPI. Hence, FE testing is preferred over the 72-h fecal fat analysis test and was used in this study [7, 22]. Carbon-13 triglyceride breath test is another indirect test to consider in detecting EPI, with a reported sensitivity of 100% and specificity of 92%, using direct secretin test as the reference standard [23].

Currently, there is no literature comparing the accuracy of Carbon-13 triglyceride breath test and FE test with the 72-h fecal fat estimation in diagnosing EPI following gastric resection surgery [24]. The choice of test for detecting EPI following gastric resection surgery is center-dependent, taking into account the availability, limitations in the ease of administration of the test along with other pros and cons of the test. We

Table 1 Fecal elastase test results of study patients

Patient	Type	Histopathological stage*	Time of testing	Pre-op FE value	Post-op FE value	EPI
Patient 1	Subtotal	pT4aN3b	>3 months	439	99	Yes
Patient 2	Subtotal	pT3N1	>3 months	271	255	No
Patient 3	Total	ypT3N2	<3 months	261	468	No
Patient 4	Subtotal	pT4aN3b	<3 months	264	182	Yes
Patient 5	Subtotal	pT4aN3a	<3 months	365	113	Yes
Patient 6	Subtotal	pT3N1	<3 months	528	585	No
Patient 7	Subtotal	ypT0N0	<3 months	308	18	Yes
Patient 8	Subtotal	pT3N1	<3 months	298	74	Yes
Patient 9	Total	pT4aN1	<3 months	531	452	No
Patient 10	Subtotal	pT3N3a	>3 months	549	203	No
Patient 11	Subtotal	pT4aN3a	<3 months	429	359	No
Patient 12	Subtotal	pT4aN2	>3 months	449	279	No
Patient 13	Subtotal	pT4aN1	>3 months	635	206	No
Patient 14	Subtotal	pT4aN3a	<3 months	646	623	No
Patient 15	Total	ypT3N2	<3 months	626	521	No
Patient 16	Total	ypT4aN0	<3 months	581	431	No
Patient 17	Total	ypT3N3	<3 months	554	369	No
Patient 18	Subtotal	pT4aN1	<3 months	520	413	No
Patient 19	Total	ypT0N0	<3 months	317	124	Yes
Patient 20	Subtotal	pT3N2	>3 months	559	158	Yes
Patient 21	Subtotal	pT1N1	>3 months	537	201	No
Patient 22	Subtotal	ypT2N0	>3 months	221	447	No
Patient 23	Subtotal	ypT4aN3a	<3 months	386	357	No
Patient 24	Subtotal	pT2N2	<3 months	549	308	No
Patient 25	Subtotal	pT2N1	<3 months	448	156	Yes
Patient 26	Subtotal	pT3N2	<3 months	291	55	Yes
Patient 27	Total	ypT4aN3a	<3 months	200	394	No

FE fecal elastase, *EPI* exocrine pancreatic insufficiency

*Post-resection histopathology–pTN for patients who underwent upfront surgery and ypTN for patients who had neoadjuvant chemotherapy

did not have Carbon-13 triglyceride breath testing at our centre and hence FE testing was used in the study.

Incidence of EPI Following Gastric Resectional Surgery

The reported incidence of EPI after gastric resectional surgery is variable, ranging between 26 and 100% in the available literature. Friess et al. reported a 100% incidence of EPI, measured using the secretin-cerulein test, 3 months following total gastrectomy [25]. Büchler et al. measured the incidence of EPI after distal gastric resections and found the incidence of EPI to between 47–64% after Billroth-I surgery and 64–70% after Billroth-II surgery using pancreolauryl test [26]. A much lower incidence of EPI of 26.8% of patients at 6 months and 44% at 18–24 months was reported using FE testing by Heneghan et al. [5]. Heptner et al. reported EPI after gastric resectional surgery in only 30% of patients, even though the pancreolauryl test was abnormal in 90% of these patients [27].

Production of major pancreatic proteases trypsin and chymotrypsin decreased by 89% and 91%, respectively, in 3 months following gastric resectional surgery for gastric cancer along with lower levels of pancreatic polypeptides and gastrin levels [25].

Treatment of EPI

Treatment for EPI includes dietary management, lifestyle changes, and pancreatic enzyme replacement therapy (PERT) [28]. Dietary modification like low-fat diet and lifestyle modifications including a decrease in alcohol consumption and smoking cessation helps in tackling EPI. Two studies have documented an improvement in clinical symptoms and quality of life, with enzyme supplementation following total gastrectomy [29, 30]. PERT is initiated in starting doses of at least 30–40,000 IU with each meal and 15–20,000 IU with snacks [31].

Table 2 Timing of post-operative fecal elastase testing

Time of fecal elastase testing from surgery	Number of patients
<=1 month	13
>1 month to <=3 months	3
>3 months to <=6 months	6
>6 months	5
Total	27

Comparison Between our Data and Available Literature

In this study, the incidence of EPI following gastric resection surgery, (based on FE testing) was 33.3%, which is much less compared to some of the available literature [25, 26]. Besides, the post-operative questionnaire did not reveal symptoms of EPI in any patient indicating that if present, the EPI may be subclinical, bearing in mind there may be regional variations depending on the diet. As mentioned earlier, the available literature is entirely from the West and there is currently no available data from the East. To our knowledge, this is the first study of this kind, from the Indian subcontinent.

One of the potential limitations of the study is the short term follow-up (mean follow-up 90 days). A limitation in the use of FE is that it can be low in patients with diabetics, inflammatory bowel disease or chronic pancreatitis and hence FE test needs to be interpreted with caution in this subgroup [32, 33]. The fact that one-third of patients have subclinical EPI in this short-term follow-up reinforces the need for adequate and thorough symptomatic assessment of EPI, which may become apparent on a longer-term follow-up. Selective testing for pancreatic insufficiency testing by FE testing may be warranted if patients do exhibit symptoms, on such long-term follow-up.

Conclusions

None of the patients had clinical symptoms of EPI, following gastric resectional surgery, on short-term follow-up. However, more than a third of the patients tested, developed asymptomatic EPI after gastric resectional surgery, based on FE testing. Routine testing for EPI and/or oral pancreatic enzyme supplementation may not be necessary for all patients undergoing gastric resectional surgery. However, one needs to remember to look out for EPI on long-term follow-up, which when clinically appropriate, can be managed with appropriate PERT.

Acknowledgements We would like to thank Dr. Sam Marconi David, Assistant Professor, Department of Community Health, Christian Medical College, Vellore and Mrs. Grace Rebekah, lecturer, Department of Biostatistics, Christian Medical College, Vellore, for assisting with the data analysis. No external funding was used for the study.

Authors' Contributions RPS, MY, and IS have contributed in the conception and design of the study. RPS, SDC, and KAB have contributed in acquisition of data and analysis. RPS, MY, SDC, KAB, and IS contributed in the interpretation of acquired data. RPS drafted the article. MY, SDC, KAB, and IS contributed in revising it critically for important intellectual content. All authors read and approved the final version for publication.

Funding This study was funded by the Internal Fluid research grant, Christian Medical College, Vellore, India-632004. No external funding was used in the study.

Availability of Data and Materials The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Code Availability Not applicable.

Declarations

Ethics Approval and Consent to Participate The questionnaire and methodology for this study were approved by the Institutional Review Board, Christian Medical College, Vellore, India-632004.

Competing Interests The authors have no relevant financial or non-financial interests to disclose.

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