REVIEW ARTICLE

Pancreatic Exocrine Insufficiency after Total Gastrectomy – A Systematic Review

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ABSTRACT

Introduction Pancreatic exocrine insufficiency can cause symptoms of malabsorption after resections of the upper gastrointestinal tract. The pathophysiology is mostly attributed to anatomical alterations causing incomplete digestion, which is termed secondary pancreatic exocrine insufficiency. The aim of this systematic review was to assess the incidence of pancreatic exocrine insufficiency, diagnostic methods available and effects of pancreatic enzyme replacement therapy after total gastrectomy. **Methods** The literature was searched using the Pubmed database for studies on this subject over the past 50 years in accordance with the PRISMA guidelines. **Results** 10 studies were identified and analysed. There is a high incidence of pancreatic exocrine insufficiency in certain post-gastrectomy cohorts, ranging from 47% to 100%. Diagnosis could be assisted with the use of pancreatic exocrine function tests. Indirect tests are preferred in the setting of anatomical changes while non-invasive tests are favoured as they are less difficult to perform. There is recent evidence to suggest an improvement in quality of life with PERT post-gastrectomy, however minimal evidence to suggest a definite improvement in symptoms related to pancreatic exocrine insufficiency. **Conclusion** Pancreatic exocrine insufficiency is an important cause of malabsorption to consider after total gastrectomy. A trial of pancreatic enzyme replacement therapy is reasonable in symptomatic patients post-gastrectomy. High quality studies are warranted to clarify the use of pancreatic exocrine function tests and the effectiveness of PERT in improving outcomes after total gastrectomy.

INTRODUCTION

In 2013, there were 984,000 new cases of stomach cancer worldwide [1,2]. Radical resection with gastrectomy can improve overall survival if the cancer is deemed resectable with curative intent [3,4]. Quality of life after gastrectomy is an important consideration in the long term management of these patients.

Symptoms of malabsorption after resection of the upper gastrointestinal tract are common and can have a significant effect on quality of life [5]. These symptoms include steatorrhoea, weight loss, diarrhoea, bloating and abdominal pain. Overt steatorrhoea only occurs with severe lipid malabsorption, when lipase secretion falls below 10% of normal levels, although lesser levels of lipid malabsorption can still be clinically relevant [6]. Pancreatic exocrine insufficiency (PEI) may contribute to these symptoms, mainly explained by lipid malabsorption [7]. Considering the steady incline in resections of the stomach with increased detection of early-stage cancers, PEI may become a bigger problem in the future. Despite this, the incidence, appropriate diagnostic testing and management of PEI after total gastrectomy are unclear.

As opposed to primary PEI, which results from the loss of functional exocrine pancreatic parenchyma or obstruction of the pancreatic duct, PEI post-gastrectomy is termed secondary PEI, where extra-pancreatic factors impair the final activity of pancreatic enzymes [8,9].

The pathophysiology of PEI post-gastrectomy is attributed to several factors. Firstly, the loss of the gastric reservoir leads to an absence of the initial mechanical digestion of food and faster transit of osmotically active food particles into the small intestine [10]. The less digested food particles are less potent stimulators of cholecystokinin (CCK), resulting in a decrease in endogenous stimulation to release digestive enzymes [6,11,12]. Secondly, loss of duodenal transit of food with reconstructive techniques bypassing the duodenum, such as Billroth-II (B2) and Roux-en Y (RY) reconstructions, leads to less CCK being released in response to the detection of chyme in the duodenum and upper jejunum [13,14]. Thirdly, 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 [15,16]. Finally, truncal vagotomy has been shown to reduce secretin-stimulated pancreatic trypsin and lipase secretion by 50-60% [11,17,18]. This is attributed to the interruption of the cephalic phase of

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pancreatic digestion, during which sensory inputs are transmitted to the exocrine pancreas through the vagus nerve [6].

Since it is difficult to make a clinical diagnosis of PEI due to non-specific symptoms, direct and indirect tests may be used to confirm suspicions of PEI and guide selection of patients who would benefit from treatment [19]. Direct tests measure pancreatic enzyme output while indirect tests assess for secondary effects of pancreatic exocrine function by measuring products of digestion [20, 21].

Currently, there is a lack of consensus on the use of pancreatic enzyme replacement therapy (PERT) post-gastrectomy, with some guidelines mandating the commencement of PERT for patients with severe symptoms [19], while others not recommending its routine use due to marginal reported improvements of steatorrhoea or other functional bowel symptoms [22,23].

A systematic review was performed to assess the incidence of PEI, diagnostic methods available and effects of PERT after total gastrectomy.

METHODS

Literature Review

A literature search using the PubMed database was performed for articles published in the English language, during a 51-year period, from January 1968 to January 2019. The search terms used included ‘steatorrhoea’, 'fat malabsorption', ‘exocrine pancreatic insufficiency’, ‘pancreatic function test', ‘gastrectomy’ and 'humans'. These terms were combined using Boolean operators 'AND' and 'OR'. All abstracts were screened and full texts were reviewed. References of papers found on the initial search were also reviewed for further relevant studies.

Selection Criteria

A systematic review was performed in accordance to the PRISMA guidelines for systematic reviews and meta-analysis. 1 author assessed the search findings for potential eligibility. All abstracts were screened and full texts were reviewed. Papers were included for further analysis which discussed incidence or presence of PEI, diagnostic methods available and/or effects of PERT after total gastrectomy. Papers were excluded if they were not published in English, had animals as subjects, described PEI after other pathological processes or surgeries besides total gastrectomy, and if they were case reports, interviews, review articles, editorials or letters. Papers were also excluded if outcomes post-total gastrectomy were analysed in conjunction with outcomes of other surgeries such as partial gastrectomy or oesophagectomy.

Quality Assessment

Observational studies were evaluated according to the Newcastle-Ottowa Scale (NOS), based on patient selection, comparability of study groups and assessment of outcomes, with a maximum score of 9 [24]. The Jadad score was utilised to evaluate randomised controlled trials, based on randomisation, double blinding and flow of patients, with a maximum score of 5 [25].

RESULTS

Data Extraction and Quality Assessment

56 studies were obtained as a result of the search carried out on PubMed. 18 papers were identified from reference lists. 64 studies were excluded. Studies were examined based on their title and abstract. 10 papers were identified for full-text review and deemed suitable for data extraction. Of these papers, 5 discussed presence or incidence of PEI, 7 discussed investigations for PEI and 2 discussed effects of PERT post-total gastrectomy. There were instances where 1 study discussed more than 1 topic. **Figure 1** demonstrates the method of study selection. Based on the quality assessment performed, the average quality of the studies is high, with the observational studies scoring 6 or more on the NOS and the randomised controlled trial scoring a 4 on the Jadad score. Study characteristics of the analysed papers are displayed in **Table 1**.

Incidence of Pancreatic Exocrine Insufficiency

The published literature supports the presence of PEI post-gastrectomy, with an incidence ranging from 47% to 100% **(Table 2)**. The incidence of PEI reached 100% in 1 study cohort of patients who were 3 months post-total gastrectomy with PEI tested using the secretin-cerulein test [26]. Conversely, another study described a significant reduction in, rather than incidence of, pancreatic exocrine function post-gastrectomy, comparing post-operative patients to pre-operative or healthy controls [27].

Investigations of Pancreatic Exocrine Insufficiency

Direct invasive tests measure the secretion of pancreatic enzymes and bicarbonate, classically through the collection of duodenal juices with an oro- or naso-duodenal tube (e.g. secretin caerulein test). They are the most sensitive for detection of PEI.

The secretin caerulein test has been utilised to assess the incidence and extent of PEI where duodenal continuity was preserved with gastrectomy. It is the gold standard for measurement of pancreatic secretion and is most sensitive for detection of mild PEI. Gullo *et al.* compared the secretion of bicarbonate and lipase between 12 patients post-total gastrectomy and jejunal interposition or oesophago-duodenostomy and controls. The reduction of lipase output compared to controls was 38.7%, and the reduction of bicarbonate output was 47.9%. 67% were found to have steatorrhoea [27]. Freiss *et al.* compared secretions of pancreatic enzymes in 15 patients before and after total gastrectomy with jejunal pouch interposition [26]. All demonstrated a decrease in pancreatic enzyme secretion, with a reduction of bicarbonate output of 92%. Lipase output was not measured. In both studies, subjects maintained enzyme output volumes of at least 10% of pre-operative or control values [26,27]. Gullo *et al.* demonstrated a lack of correlation in lipase outputs and the presence of steatorrhoea (8 out of 12 patients), suggesting

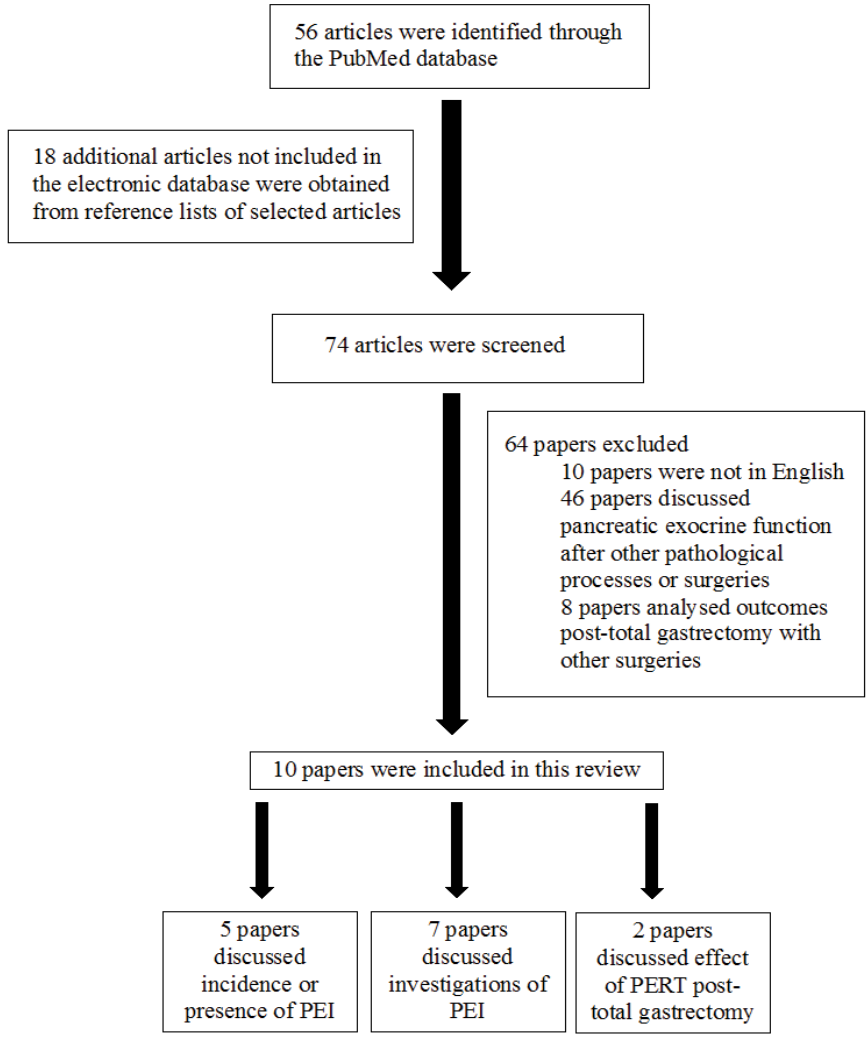

Figure 1. Method of study selection in the systematic review of pancreatic exocrine insufficiency post-total gastrectomy.

Table 1. Study characteristics of 10 papers included in the final review.

Authors	Date	Type of study	Relevant topic(s) discussed	Number of patients	Age, years (mean (range))	Men, %	Time postoperatively assessed, months (median (range))	Quality according to NOS scale or Jadad score
Gullo *et al.*	1979	Prospective observational	Incidence of PEI, investigations of PEI	12	42 (29-74)	50	10 (7-76)	8
Armbrecht *et al.*	1987	Prospective observational	Incidence of PEI	12	79 (63-83)	67	20 (90-135)	6
Armbrecht *et al.*	1988	Double-blind cross-over	Investigations of PEI, effects of PERT	15	64 (47-83)	66	20 (4-156)	7
Walther *et al.*	1989	Prospective observational	Incidence of PEI	11	53-77	64	1 and 6 (-)	6
Bragelmann *et al.*	1996	Prospective observational	Incidence of PEI	174	58 (-)	64	19** (16-54)	6
Freiss *et al.*	1996	Prospective observational	Incidence of PEI, investigations of PEI	15	62* (-)	80	3 (-)	7
Bragelmann *et al.*	1999	Randomised controlled trial	Investigations of PEI, effects of PERT	52	57* (50-65)	73	13 (placebo) 4 (intervention)	4
Takase *et al.*	2003	Prospective observational	Investigations of PEI	40	65 (48-77)	Not available	Dec-36	7
Heneghan *et al.*	2015	Prospective observational	Investigations of PEI	66	63 (54-72)	67	23 (18-28)	9
Borbely *et al.*	2016	Prospective observational	Investigations of PEI	188	41 (30-52)	23	12.5 (3-96)	9

*Median instead of mean, **Mean instead of median, NOS newcastle-ottawa assessment scale, PEI pancreatic enzyme insufficiency
PERT pancreatic enzyme replacement therapy

Table 2. Published literature on the incidence or presence of pancreatic exocrine insufficiency post-total gastrectomy [26,27,48,49].

Author, Country	Year	Number of patients (method of reconstruction)	Test	Results
Gullo *et al.*, Italy	1979	12 (10 jejunal interposition, 2 oesophago-duodenostomy_	Secretin caerulein test, clinical assessment	Bicarbonate and lipase significantly lower as compared to healthy controls. 67% clinical steatorrhoea.
Bragelmann *et al.*, Germany & Netherlands	1996	174 (26 continuous duodenal passage, 115 without continuous duodenal passage, 22 other, 11 unknown)	72-hour FF test, within 1 year post-op	47% severe steatorrhoea (faecal fat ≥ 14 g/day).
Freiss *et al.*, Germany	1996	15 (jejunal pouch interposition)	Secretin –caerulein test, 3 months post-op	100% PEI. Significant reduction in pancreatic juice volume, trypsin, chymotrypsin, amylase and bicarbonate secretion as compared to pre-operative levels (no measurement of lipase output).
Walther *et al.*, Sweden	1989	11 (RY)	^{14}C triolein breath test, measure peak expiratory $^{14}CO_2$ (per hour), 1 and 6 months post-op	82% PEI at 1 and 6 months. Significant reduction compared with pre-op.
Armbrecht *et al.*, Sweden	1987	12 (RY)	72-hour FF test, median of 19.5 months post-op	92% had values reflecting steatorrhoea.

FF faecal-fat, RY roux-en y reconstruction

Table 3. Published literature assessing the use of pancreatic enzyme replacement therapy post-gastrectomy [29, 39].

Author, Country	Year	Cohort	PERT used	Results
Bragelmann *et al.*, Germany	1999	52 total gastrectomy (34 RY, 10 Longmire reconstruction, 1 Siewert-Peiper reconstruction, 2 Schloffer reconstruction,3 oesophago-jejunostomy, 2 unknown)	9 sachets of pancrelipase per day. 1-2 sachets were consumed with each meal. Each sachet contains 36,000 U of lipase, 27,000 U of amylase and 2,400 U of protease)	No significant improvement in specific symptoms and no significant decrease in median faecal fat excretion with PERT. Patients felt significantly better overall with PERT.
Armbrecht *et al.*, Germany	1988	15 total gastrectomy (100% RY)	3.6 g of pancrelipase capsules per day with meals. Each capsule contains 300 mg of pancrelipase (10,000 U of lipase, 10,000 U of amylase, 650 U of protease)	Patients with high-degree steatorrhoea (i.e. free and esterified fatty acids >350 mmol/72 hours) had a significant reduction in median faecal fat excretion with PERT.

RY roux-en y reconstruction, U units

that such mild to moderate reductions of enzyme output may not cause steatorrhoea [27].

Non-invasive tests (direct or indirect) have been favoured more recently in testing for PEI after gastrectomy, especially since invasive tests are difficult following anatomical alterations. Direct non-invasive tests measure pancreatic enzymes through serum or stool sampling (e.g. faecal elastase (FE) test). Indirect non-invasive tests measure fat or synthetic substrates in the stool, blood, urine or breath to assess for consequences of ineffective digestion (e.g. 72-hour faecal-fat (FF) test, Carbon-13 triglyceride breath test (13C-TG-BT)) [20,21].

Faecal fat excretion can be quantified in patients post-gastrectomy using the 72-hour FF test. It is the gold standard test for quantification of faecal fat. Steatorrhoea is deemed present, and PEI is diagnosed, when 7 g or more of faecal fat is excreted in stool over 24 hours, where 100 g of fat is consumed daily for at least 2 days before, and for the 3 days during, the collection of stool [7]. It has been utilised in studies not only to assess for fat malabsorption where PEI is suspected, but also to assess response to PERT post-gastrectomy. In 1988, Armbrecht utilised the 72-hour FF test to evaluate the effects of PERT on faecal fat excretion after total gastrectomy with RY anastomosis. All patients had varying magnitudes of steatorrhoea [28]. A decade later, Bragelmann *et al.* tested the same hypothesis in participants who had faecal fat of ≥ 14 g per day. At that time, the FE test had not been described. Other tests such as the N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) test, the pancreolauryl test and the faecal chymotrypsin test were considered of low specificity [29]. However, the 72-hour FF test may not be sensitive enough to detect mild deterioration of pancreatic function, where faecal fat is not detected in stool [30]. It also cannot be used to distinguish pancreatic and non-pancreatic causes of steatorrhoea, and hence is limited to testing with a trial of PERT, where malabsorption can only be attributed to PEI where there is a response to PERT.

Despite the 72-hour FF test being considered gold standard for quantification of faecal fat, the FE test and the 13C-TG-BT have been used more commonly to demonstrate PEI post-gastrectomy due to their less cumbersome application [31].

Dominguez-Munoz *et al.* recommend the FE test as a first line test for pancreatic function [30]. FE is an enzyme produced by pancreatic acinar cells which binds to bile salts and passes through the gut with minimal degradation. It can be measured by means of monoclonal and polyclonal enzyme-linked immunosorbent assays (ELISAs). Attention should be paid to methodology, given that the polyclonal assay produces higher levels of FE [30]. With the direct secretin-caerulin test as a reference standard assessing patients with both primary and secondary PEI, sensitivity and specificity for severe PEI are 100% and 93%, and for

mild PEI 93% and 65% respectively [32]. The FE test can be used to grade the severity of PEI based on quantification of FE. Heneghan *et al.* utilised the FE test to identify PEI post-oesophagectomy and gastrectomy. He calculated the correlation coefficient between grades of FE and % change in weight or symptoms of malabsorption [5]. The FE test has been utilized by Borbly *et al.* to detect PEI after primary RY reconstruction as a bariatric surgical procedure. The FE test was favoured in this setting as it is not affected by anatomical alterations, or the effects of PERT (as the test only detects human elastase), or the change in taste and dietary tolerance in post-gastric surgery patients (which would be a limitation if an unpalatable or poorly tolerated test diet was required) [32].

The 13C-TG-BT is an indirect test to consider. It measures $13CO_2$ excreted in the breath over 6-8 hours as an indirect measure of lipolysis of 13C-labelled fat by pancreatic lipase within the small intestine. Between the various types of 13C-TG-BT, testing with the Carbon-13 mixed triglyceride may be preferred over medium chain triglycerides as the mixed triglyceride mixture contains naturally occurring long-chain fatty acids, which is more consistent with the normal constituents of food [33]. A sensitivity of 100% and specificity of 92% have been reported for detecting PEI in patients with a clinical suspicion of PEI, with the direct secretin test as a reference standard [34]. Due to the strong correlation between duodenal lipase activity and $13CO_2$ excretion, the 13C-TG-BT has been utilized in studies to compare maldigestion between various reconstructive techniques post-gastrectomy. Takase *et al.* used the 13C-trioctanoin breath test to compare fat digestion and absorption between the Billroth-I, double-tract and RY reconstructions post-total gastrectomy. He concluded that reconstruction techniques that included duodenal transit had better absorption of triglycerides. As the 13C-TG-BT permits the measurement of the rate of excretion of $13CO_2$, this allows the rate of fat absorption of various reconstructive techniques to be compared [13].

Currently, there are no studies available comparing the accuracy of the FE test and 13C-TG-BT test with the 72 hour FF test for diagnosing PEI post-gastrectomy. There are several small studies assessing patients with chronic pancreatitis. In these studies, the 72 hour FF test is deemed the gold standard for diagnosing PEI and is used as a reference standard to calculate sensitivity and specificity. A high sensitivity but low specificity has been demonstrated for the FE test in 2 studies with the definition of low FE <200 μg, implying that FE is not accurate in differentiating patients with or without steatorrhoea [35,36]. On the contrary, Symersky *et al.* demonstrated a low sensitivity of 68% for detecting PEI using the FE test in patients with chronic pancreatitis, with a definition of low FE <218 μg [37]. As for the 13C-TG-BT test, Dominguez-Munoz *et al.* demonstrated a high sensitivity and specificity of 92.9% and 91.7%. The definition of PEI was <29% of the total cumulative recovery rate (CRR) of $13CO_2$ over 6 hours [38].

Testing for PEI remains contentious and choice of test for PEI remains centre-dependent, with varying pros and cons of each test specific to testing of PEI after gastrectomy. Anatomical alterations, dietary intolerances, as well as the diagnostic accuracy of the test, should be considered when selecting the most appropriate test.

Effects of Pancreatic Enzyme Replacement Therapy after Total Gastrectomy

Pancreatic enzyme replacement therapy (PERT) is the main treatment for pancreatic exocrine insufficiency. It has been reported as safe with few side effects at low to moderate doses. The most concerning side effect of fibrosing colonopathy is largely associated with high-dose enzyme therapy (>50,000 IU/kg daily) [7]. PERT consists of amylase, lipase and protease derived from pig pancreatic parenchyma. Guidelines recommend 25,000 to 40,000 units of lipase with each meal, with 10,000 units consumed with each snack [19]. Pancrelipase usually comes encapsulated, protected from acid degradation, with microgranules releasing enzymes when the pH-sensitive coating dissolves in an alkaline environment where digestion and absorption is optimal. Granules and powder preparations are recommended for those with accelerated gastric emptying. As the relationship between PERT dosage and response to therapy is non-linear, PERT dosages should be individualised, with the aim of using the lowest effective dose to suppress symptoms. This helps to avoid gastrointestinal complications associated with higher enzyme doses and reduces treatment burden [9,19]. The administration of PERT is usually accompanied by education about dietary intake and nutritional supplementation for optimisation of digestion and nutrition. The published literature assessing the use of PERT post-total gastectomy are summarised in **Table 3**.

2 trials have been conducted over the last 3 decades assessing the use of PERT after total gastrectomy. In both studies, patients experienced symptoms of malabsorption, however PEI was not formally tested. A double-blind, cross-over trial comparing PERT and placebo was conducted by Armbrecht *et al.* 15 patients post-total gastrectomy with RY reconstruction for gastric cancer with varying magnitudes of steatorrhoea underwent a 7-day intervention period, followed by a 7-day placebo period. Faecal fat was analysed from collected stool from day 4 to day 6, with 200 ml of dairy cream ingested from day 2 to day 6. A significant reduction in median faecal fat excretion with PERT was observed in those with high-degree steatorrhoea (i.e. fatty acids >350mmol/72hours). An improvement in stool consistency was observed with PERT. There was no influence of PERT on pain, vomiting, nausea, bloating or dumping [39]. Bragelmann *et al.* performed a multi-centred, double-blinded, randomised controlled trial on 52 patients with a faecal fat output of ≥ 14 g per day after total gastrectomy for gastric cancer, comparing PERT and placebo. Drug intervention lasted for 14 days. The test diet consisted of 48% fat, 17% protein and 35% carbohydrates. Individual nutritional intake was

quantified by a dietician. Faecal fat was analysed during the last 72 hours of the controlled diet periods. There was no improvement in specific symptoms including bowel habit and no significant decrease in median faecal fat output with PERT compared to placebo. However, an overall improvement of quality of life was reported (p=0.006). It is noted that the diet utilised in this study contained a high proportion of fat (48%). The reason for the high fat content diet was to ensure a fat intake sufficient for a fat balance study – faecal assimilation was calculated as the proportion of fat excreted in relation to intake [29,40].

The overall evidence suggests that benefits can be seen with PERT when trialled in patients suffering from symptoms of malabsorption post-total gastrectomy. If symptoms of malabsorption persist after upper gastrointestinal resection despite treatment with PERT, testing for bile acid malabsorption (BAM) and small intestinal bacterial overgrowth (SIBO) could be performed. A SeHCAT [tauroselcholic (selenium-75) acid] retention study can test for BAM while hydrogen breath testing can test for SIBO [5]. Loco-regional recurrence should be ruled out, especially if weight loss persists despite treatment with PERT [41].

PERT is usually administered in combination with dietary education regarding meal size and frequency, nutritional supplementation and fat requirements. PEI may result in malabsorption of fat-soluble vitamins (including vitamins A, D, E and K), water-soluble vitamins (such as vitamin B12 and folate) and trace elements (such as iron) [6,42]. This is of concern, given that pathologically low levels of micronutrients may not be clinically apparent but may lead to later complications [19]. The advised time of screening for vitamin deficiencies post upper gastrointestinal surgery is not clearly established. Early screening of micronutrient deficiencies should be considered, given that vitamin E deficiency can begin within 6 months after gastrectomy for cancer. Vitamin E deficiency has been associated with development of peripheral neuropathy, with resolution of symptoms after oral supplementation [43]. Replacement of these dietary elements would aim to prevent complications of malabsorption.

DISCUSSION

Review of the literature identified a high incidence of PEI in total gastrectomy cohorts, ranging from 47 to 100%. Given the variety of tests used and varying timings post resection in these studies, the true incidence of PEI post-total gastrectomy cannot be determined. Fortunately, PEI decreases in the long-term, due to compensatory mechanisms by the intact and hypertrophied pancreas, as well as extrapancreatic mechanisms occurring such as the upregulation of gastric lipase [14,44].

Friess *et al.* demonstrated that PEI can be detected as early as 3 months post-gastrectomy. Incidence and severity of PEI post-gastrectomy may be affected by the type of reconstruction (duodenal passage of food preserved or bypassed). Total gastrectomy with duodenal bypass reconstructive techniques (e.g. RY reconstruction) are associated with greater risks of PEI [13]. Recognising PEI as a cause of malabsorption and raising suspicions early is important as it is treatable.

Functional tests could be used to guide the need for a trial of PERT where symptoms are equivocal. The FE test has been used in studies where certain patients are already taking PERT or where patients are unable to adhere to a test diet. Notably, where surgical diversion of bowel has occurred, the FE test can yield false-negative results. The threshold to commence PERT in such cases should be reassessed, especially when the suspicions of PEI are high [30]. Additionally, the FE test should not be utilised in isolation to diagnose PEI. It has a potential for false positives, especially in patients with diabetes, coeliac disease and irritable bowel syndrome [45]. As compared to the FE test, the 13C-TG-BT does not require stool or urine collection. Moreover, it has been shown to be more accurate compared to the FE test for symptoms of malabsorption in patients following pancreatic surgery (62% *vs*. 88%) [33]. However, it is expensive, not widely available at this time and there is insufficient evidence in the literature to support its routine use. Despite this, the 13C-TG-BT has been used in studies where reconstructive techniques are compared with regards to fat digestion and absorption.

A conclusion cannot be drawn about the sensitivity and specificity of both tests compared to the 72 hour FF test due to the lack of evidence in the literature. Inconsistences in results have been reported for the FE test in chronic pancreatitis, most likely due to the different cut-offs used for defining PEI.

Both the FE test and the 13C-TG-BT are highly sensitive and specific for severe PEI when compared to the direct invasive tests, but less sensitive and specific for mild PEI, which are the cohort with less obvious symptoms of PEI and hence more relevant for testing. Direct invasive tests, such as the secretin cerulein test, are most sensitive for detection of early or mild PEI. However the clinical relevance of early or mild PEI is questionable, given that it may not translate into steatorrhoea [27]. Arguably, other symptoms may develop which are as or more debilitating compared to steatorrhoea. Additionally, pathologically low levels of micronutrients, such as fat-soluble and water-soluble vitamins, may be present in mild PEI and should be screened [19,46].

The lack of concensus reached by guidelines on the commencement of PERT can be explained by the limited number of high quality trials assessing the potential benefits of PERT post-total gastrectomy [47-49]. The available evidence shows that PERT improves health outcomes and quality of life post-total gastrectomy. However, effects of PERT on symptoms of malabsorption is discordant. Conflicting results could be due to the difference in pancreatic enzyme dosages, proportion of patients with RY reconstruction (and hence duodenal bypass) and proportion of fat in the test diet. Studies were

limited by the small sample sizes and short periods of observation during intervention only.

Based on the available evidence, we conclude that PERT should be trialled in patients suffering from symptoms of malabsorption post-total gastrectomy, especially where symptoms are affecting their quality of life. Weighing risks and benefits, the threshold to commence PERT should be low, given limited ease of testing, chances of false negative results (especially with mild PEI) as well as the negligible side effects with low to moderate doses of PERT [7,9]. However there is a need to consider medication-related burden and efforts needed to optimise therapy.

This systematic review analysed papers from the last 51 years that studied incidence of PEI, diagnostic methods available and effects of pancreatic enzyme replacement therapy (PERT) after total gastrectomy. The studies included in the review mainly focused on PEI as a sequela of gastric resection, with clearly defined outcomes suggestive of PEI. The quality of the included studies were assessed as displayed in **Table 1**, and demonstrated the average study quality was high. Performance and detection bias would be minimal in the 2 randomised controlled trials assessing the use of PERT post-total gastrectomy due to blinding. Selection bias could be present in the cohort studies assessing incidence of PEI, however the cohorts were adequately described. Attrition bias was not detected in the studies reviewed. Limitations include the heterogenous nature of studies from varying institutions with their own standards of testing for PEI as well as different duration of time between surgery and measurement of pancreatic exocrine function. The quantity and formulation of PERT utilised in each randomised controlled trial were different, which may have affected outcomes of interest such as symptoms and quality of life. This heterogeneity made a meta-analysis inappropriate in this review. High quality studies, as well as recent studies within the last decade, were scarce. However, this review aims to provide an insight into evidence of PEI post-total gastrectomy, options available for testing and studies of efficacy of PERT to date.

CONCLUSION

Pancreatic exocrine insufficiency is an underdiagnosed condition post-total gastrectomy. It is an issue of concern, given the reported high incidence in the literature and its potential to affect quality of life. The faecal elastase test and Carbon-13 mixed triglyceride breath test can be considered to assist with diagnosis and guide the trial of pancreatic enzyme replacement therapy, especially where symptoms are equivocal. Pancreatic enzyme replacement therapy should be trialled in patients post-total gastrectomy when patients are symptomatic and when no other treatable causes of malabsorption are present. High quality trials examining pancreatic exocrine insufficiency post-total gastrectomy are warranted, especially in relation to the use of pancreatic exocrine function tests and pancreatic enzyme replacement therapy in improving outcomes.

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Conflicts of Interest

The authors report no conflict of interest.

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