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Review Article

Emerging trends in disturbed function of the pancreas and dyspepsia: an Indian perspective

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ABSTRACT

Disturbed function of the pancreas, especially exocrine pancreatic insufficiency (EPI) results in inadequate synthesis or delivery of the pancreatic enzyme leading to maldigestion. Due to the lack of specific symptoms and overlapping manifestations of EPI, it often goes undiagnosed and untreated. Dyspepsia is another common condition characterized by upper gastrointestinal symptoms caused by a heterogeneous group of disorders. This consensus aims at providing a comprehensive overview of the diagnosis and management of disturbed function of the pancreas and dyspepsia. A total of 95 gastroenterologists participated in expert group meetings organized via virtual focus group discussions. Recent evidence elaborating various aspects like diagnosis and management of EPI and dyspepsia, including the use of pancreatic enzyme replacement therapy (PERT) and issues with compliance were discussed. The experts emphasized that clinical symptoms of maldigestion should not be ignored, and physicians should not wait to diagnose EPI until steatorrhea occurs. Fecal elastase (FE) test and imaging should be performed to confirm diagnosis. If EPI is diagnosed or the patient experiences weight loss or steatorrhea, PERT should be initiated while ensuring compliance. Reducing pill burden, active education, monitoring, and support from healthcare programs may help ensure compliance. EPI is also a cause of dyspepsia. Further, consuming lipid-rich foods worsens symptoms of dyspepsia. First-line treatment includes dietary changes and lifestyle modifications. Digestive enzyme supplements play a significant role in alleviating symptoms of indigestion. Routine enzyme supplementation is beneficial in managing dyspepsia caused by EPI, such as, in patients with EPI due to pancreatitis or diabetes.

Keywords: EPI, Dyspepsia, Compliance, PERT, Pancreas

INTRODUCTION

Disturbed function of the pancreas is defined as inadequate activity or deficiency of the pancreatic enzymes within the intestinal lumen.[1] While pancreatic disturbance can affect both endocrine and exocrine functions, the term pancreatic insufficiency usually refers to exocrine deficiency rather than endocrine deficiency.[2]

EPI results from progressive loss of pancreatic parenchyma resulting in loss of acinar cells that leads to decreased functionality with respect to production and release of pancreatic enzymes. EPI symptoms are not visible in most patients until parenchyma loss causes over 90% of pancreatic function loss. This decrease in pancreatic function leads to malabsorption and impaired digestion of fat and proteins.[3] It results in symptoms varying from mild abdominal discomfort, bloating, cramping and increased flatulence. Patients with severe disturbances have steatorrhea, weight loss.[1] It can occur due to various conditions, like CP pancreatic adenocarcinoma, cystic fibrosis, or pancreatic surgery.[1,4]

An exhaustive assessment is required to identify possible causes of EPI. Underdiagnosis and misdiagnosis of EPI lead to severe nutritional deficiencies, thereby resulting in

generalized malnutrition, excessive weight loss, worsening of underlying disease, and diminished quality of life. Symptoms do not occur until 90% of pancreatic function is lost, and diagnosis based on pancreas function test results in false negatives in the early stages.[3]

Dyspepsia is a widespread condition across the world. It describes a commonly encountered set of upper gastrointestinal symptoms caused by a heterogeneous group of disorders. It is broadly defined as pain or discomfort that is centered in the upper abdomen.[5] Dyspeptic symptoms can have several potential causes, such as peptic ulcer disease, gastroesophageal reflux disease, gastroesophageal malignancy, and functional dyspepsia (FD). Although several advances have been made in this condition, its definition, investigation, and management remain controversial.[6]

Considering the scarcity of information on various aspects of EPI and dyspepsia in India, virtual focus group meetings were conducted with 95 expert gastroenterologists across India. Existing evidence and clinical experience with respect to the diagnosis of EPI, current treatment modalities, and the role of PERT were discussed in detail by the experts, and expert opinions were consolidated and finalized after approval by all participants.

Literature search was performed using PubMed and Google Scholar. After screening, 34 suitable articles were identified and reviewed. This consensus provides a collation of evidence-based literature on accurate diagnosis and management of EPI and dyspepsia along with outcome of focus group meetings of 95 expert gastroenterologists.

UNDERSTANDING DISTURBED FUNCTION OF THE PANCREAS

Overview of pancreatic insufficiency

The pancreas is a gland with an exocrine and endocrine function. Pancreatic enzyme secretion is regulated by two important hormones, secretin and cholecystokinin.[1] Pancreatic dysfunction can affect both endocrine and exocrine functions; however, pancreatic insufficiency specifically refers to exocrine deficiency.[2]

EPI involves reduced or inappropriate activity of pancreatic juices and digestive enzymes, particularly pancreatic lipase, below threshold required for digestive functions.[2,7] It is caused by a variety of factors, such as decreased enzyme secretion in pancreatic diseases, low CCK release in celiac disease/upper gastrointestinal surgery, or anatomical changes after upper gastrointestinal surgery, leading to maldigestion and malabsorption of nutrients.[2,7,8] It clinically manifests as steatorrhea, flatulence, weight loss, and abdominal pain of variable location and severity.[2,7]

Prevalence of EPI in different clinical conditions

Prevalence of EPI in general population is unknown; however, CP is the most common cause of EPI, with prevalence of EPI being 30-90% in patients with CP.[2,7] CP is a progressive inflammatory disease of the pancreas affecting both the exocrine and endocrine functions of the pancreas.[9] Alcohol, tobacco smoking, hypercalcemia, hyperlipidemia, and CRF are toxic-metabolic causes of CP and EPI.[2] Genetic defects, such as cystic fibrosis transmembrane conductance regulator mutations, serine protease inhibitor Kazal-type 1 mutations, serine protease 2 mutations, and hereditary pancreatitis are linked to idiopathic causes.[2,10] Pancreatitis associated with Sjögren's syndrome, primary biliary cirrhosis, and IBD disease are examples of autoimmune causes. Obstructive causes include congenital anomalies of pancreatic ducts, sphincter of Oddi dysfunction, obstruction of the duct by a tumor and post-traumatic pancreatic duct fibrosis.[2] EPI is associated with other pancreatic disorders, such as cystic fibrosis (80%-90%), acute pancreatitis (AP; 20%), autoimmune pancreatitis (30%-60%), Schwachman-diamond syndrome (80%-90%), unresectable pancreatic cancer (20%-60%), pancreaticoduodenectomy (80%-90%), and distal pancreatectomy (20%-50%). Extra-pancreatic disorders, including type 1 diabetes (30%-50%), type 2 diabetes (20%–30%), ulcerative colitis (10%), Crohn's disease (4%), celiac disease (5%-80%), HIV syndrome (10%-50%), and Sjögren's syndrome (10%-30%) are also associated with EPI.[7]

Consensus key point 1

EPI is inability of exocrine pancreatic secretion to maintain normal food digestion. It results in inadequate delivery of pancreatic enzyme into duodenum leading to maldigestion, clinically presents-steatorrhea, weight loss, bloating and other symptoms. CP is most common cause of EPI, may be caused by some auto immune responses, hereditary factors, alcoholism, AP, and other factors.

DIAGNOSTIC CHALLENGES IN INDIA

Current challenges in accurate diagnosis of EPI

Many patients may go undiagnosed and untreated because the symptoms and manifestations of EPI are not specific, and these symptoms may overlap with other common gastrointestinal conditions. Lack of a highly accurate diagnostic test is another obstacle to correct EPI diagnosis. Available diagnostic tests are generally difficult to perform, inaccurate, or non-specific.[11]

Direct and indirect tests

Several tests exist for diagnosing EPI, and they are categorized as direct and indirect. Direct tests assess secretion, whereas indirect tests evaluate quantitative changes in pancreatic secretion to determine impact of exocrine insufficiency (Table 1).[7]

Table 1: Diagnostic tests for EPI.

Diagnostic tests	Benefits	Limitations
Direct function tests		
Fecal fat estimation/CFA	Gold standard for evaluating steatorrhea[7]	-Limited patient compliance[7] -Obtaining a stool sample takes a long time[7] -Not pancreas-specific[12] -Cannot perform PERT simultaneously[12]
Cholecystokinin/secretin stimulation	-High sensitivity (72-94%)[7] -Gold standard for evaluation of pancreatic exocrine function[12]	-Complicated[12] -Invasive[7,12]
Endoscopic pancreatic function test	-Beneficial in diagnosing patients with early CP[12] -Useful in investigating the cause of malabsorptive diarrhea[12]	-Time consuming[12] -Incapable of quantifying fluid volume preventing the calculation of enzyme output[12]
Secretin-enhanced MRCP	-Useful in the evaluation of AP and CP as well as neoplasms[12] -Higher sensitivity and specificity for CP than CT, transabdominal ultrasound, or plain films[9]	-Subjective nature of reports[12] -Lack of data from large trials proving its accuracy[12]
Indirect function tests		
FE-1 concentration	-Reflects pancreatic output level and correlates with output of other pancreatic enzymes, such as lipase, amylase, and trypsin[7] -Single stool sample[12]	-Poor sensitivity in cases of mild EPI, watery stools, and small bowel disease[12]
Fecal chymotrypsin activity	-Requires a single stool sample[12] -Effective for compliance control[12]	-Specificity for EPI lower than FE-1[7] Unsuitable for mild EPI[12] -Require PERT discontinuation before performing the test[12]
^{13}C-mixed triglyceride breath test	-Can measure the most relevant end-effect of exocrine pancreatic function: degradation of triglycerides[13] -Permits monitoring of treatment response[7]	-Non-specific[7] -Low sensitivity for the diagnosis of mild EPI[7] -Relatively time-consuming[7]

Direct function tests

Fecal fat estimation/ CFA

This test involves 72-h fecal fat collection and result expressed as coefficient of fecal absorption (CFA). Normal CFA is ~93% of fat content. This represents gold standard for evaluation of steatorrhea; however, it has several limitations in clinical practice. Firstly, limited patient compliance and obtaining a stool sample takes long time.[7] Further, this test is not pancreas specific and PERT cannot be done simultaneously.[12] Nowadays, it is rarely used in clinical practice.[7]

Cholecystokinin/secretin stimulation

This test is based on stimulating the pancreas with hormonal secretagogues and then collecting duodenal fluid to directly measure its secretory content (enzymes and bicarbonate). Cholecystokinin and secretin have been used to stimulate pancreatic secretion. These tests have a sensitivity of 72%-94% and are the gold standards for evaluation of pancreatic exocrine function. However, they are invasive and complicated.[7,12]

Endoscopic pancreatic function test

In this test, duodenal fluid is collected through the endoscope into a specimen trap in 15-minute aliquots for an hour after the administration of secretin.[7] This test is useful in diagnosing patients with early CP and investigating the cause of malabsorptive diarrhea; however, it is time consuming and does not quantify fluid volume preventing the calculation of enzyme output.[12]

Secretin-enhanced MRCP

Magnetic resonance cholangiopancreatography (MRCP) is a diagnostic imaging technique that can reveal calcifications, pancreatic enlargement, ductal obstruction, or dilation.[9] It is useful in the evaluation of AP and CP as well as neoplasms.[12] MRCP has higher sensitivity and specificity for CP than computed tomography (CT), transabdominal ultrasound, or plain films.[7,9] The

disadvantages of this test are the subjective nature of reports and lack of data from large trials proving its accuracy.[12]

Indirect function tests

FE-1 concentration

FE-1 determination is the most employed indirect test for exocrine pancreatic function. It reflects the pancreatic output level and correlates with the output of other pancreatic enzymes such as lipase, amylase, and trypsin. It is highly stable in feces for up to 1 week at room temperature and for 1 month when stored at 4°C, making conservation simpler. A concentration of <200 µg/g in the feces is considered abnormal.[7] It requires a single stool sample. It has poor sensitivity in cases of mild EPI, watery stools, and small bowel disease.[12]

Fecal chymotrypsin activity

Chymotrypsin is an enzymatic product of pancreatic secretion, which can be dosed in fecal samples and used in the diagnosis of EPI.[7] It requires a single stool sample and is effective for compliance control. However, the specificity of fecal chymotrypsin for EPI is lower than FE-1 and is unsuitable for mild EPI. PERT must be discontinued before performing this test.[12]

^{13}C-mixed triglyceride breath test

Breath tests involve the oral administration of a ^{13}C-marked test meal and evaluation of the degradation of triglycerides. The degradation of triglycerides denotes the end-effect of exocrine function.[7,13] Subjects with EPI have decreased lipase activity, which can be detected as a decreased recovery of $^{13}CO_2$ in exhaled air.[13] The main limitations of the test are that it is non-specific and has low sensitivity for the diagnosis of mild EPI. Furthermore, it is relatively time-consuming, requires specific instruments and reagents, and is only available in a few referral centers. Yet, it has the advantage of being modified by PERT, thus permitting monitoring response to treatment.[7]

Differential diagnosis of EPI

The first step in an investigation is to thoroughly review the patient's symptoms and acquire pertinent background information. These findings determine proper order for further investigations. Patient's medical history, results of the physical examination, lab testing, imaging and trials of various conservative treatments are then used to rule out a number of diseases. Finally, direct pancreatic function testing, if available, may be used to confirm EPI.[14]

Consensus key point 2

Early diagnosis of EPI is critical. Clinical symptoms of maldigestion must not be ignored, and the treating physician should not wait to diagnose the condition until steatorrhea occurs. Experts recommend evaluating symptoms of maldigestion, nutritional status, and performing a pancreatic function test. Typically, EPI patients present with symptoms, and thus an FE-1 test should be performed for confirmation because it is an outpatient procedure. None of the experts recommended secretin stimulation or a chymotrypsin test. Experts also recommended performing at least one imaging modality, either ultrasonography or CT depending on the level of suspicion. CFA is the gold standard for diagnosing fat maldigestion and is calculated based on 72-hour fecal fat. Experts reached the consensus that there should be easier and cheaper methods for diagnosing EPI. A carbon 13 (^{13}C)-mixed triglyceride (^{13}C-MTG) breath test is an accurate and easy alternative to stool tests in diagnosing EPI with maldigestion.

CURRENT TREATMENT REGIMES USED IN INDIA

Clinical management of EPI

The primary goal of EPI treatment is restoring the normal digestion process to maintain adequate nutrition and quality of life.[2,15] It is also imperative to treat symptoms related to EPI and stop disease progression.[15] The fundamental elements of current EPI management in adults include PERT; lifestyle modifications, such as alcohol abstinence and smoking cessation; antacid trial in patients who continue experiencing EPI symptoms despite high doses of PERT; diet adjustments, such as small frequent meals, normal fat intake, and vitamin supplementation; and follow-up of patients focusing on nutritional deficiencies, symptoms of maldigestion, treatment of any causative diseases and ensuring treatment compliance.[2,15]

PERT

PERT continues to remain the mainstay of EPI treatment. It involves delivering pancreatic extracts, which are a combination of lipase, amylase, and protease, into the duodenum in the form of encapsulated preparations, restoring nutrient digestion and preventing malabsorption.[2,15] The preparations are ingested with a meal and mixed with the chyme intra-gastrically; however, an enteric coating protects them against acid degradation and they are released with the chyme from the stomach into the duodenum, where the pH-sensitive coating dissolves in the alkaline environment, releasing enzymes at the optimal time for digestion and absorption.[15]

Initiation of PERT in EPI

Several conditions may require the initiation of PERT, including but not limited to cystic fibrosis, pancreatic cancer, AP, CP, and pancreatic surgery.[13,16] PERT is unquestionably indicated in EPI in cases of steatorrhea.[13] Study results show that PERT can only be implemented when a person loses >15 g of fat on a normal 100-g diet or

when they lose weight continuously despite the fecal output of <15 g/day. If the weight is maintained, PERT need not be initiated.[16]

Strategy for dosage and timing of PERT

According to the Australasian Pancreatic Club guidelines, adults should initiate PERT with 25,000-40,000 units of lipase taken with each meal. If the initial dose does not produce a sufficient response, then the dose should be titrated up to a maximum of 75,000-80,000 units of lipase per meal. PERT dosage must be adjusted to each patient's requirements to achieve the lowest effective dose while avoiding the gastrointestinal side effects of higher enzyme doses and treatment burden. The highest recommended dose of PERT is 10,000 units of lipase/kg/day because extremely high doses have been linked to fibrosing colonopathy.[15] These supplements need to be administered such that they are consumed both early and late in the meal.[11]

Benefits and application of PERT

PERT improved CFA significantly compared to baseline and placebo in a study involving 511 patients with CP. It improved the coefficient of nitrogen absorption (CNA) while decreasing faecal fat excretion, faecal nitrogen excretion, faecal weight, and abdominal pain with no significant side effects. Furthermore, it was found to improve gastrointestinal symptoms and quality of life while increasing serum nutritional parameters.[17]

Furthermore, PERT treatment improved CFA and CNA in another study involving 54 patients with EPI due to CP. Significant improvements in body weight and numerical increases in body mass index (BMI) indicated improvements in nutritional status.[4]

Management of EPI after extensive surgery

EPI is an often-underestimated complication following pancreatic surgery. Untreated EPI after surgery may result in significant morbidity related to gastrointestinal symptomatology, malnutrition, and decreased quality of life, eventually leading to a lower long-term survival rate. PERT after gastrointestinal and pancreatic surgery is shown to improve nutritional status and EPI symptoms.[4]

Several studies have reported improvement in malabsorption and nutritional status with PERT after pancreatic and gastrointestinal surgery. PERT has been shown to improve CFA, CNA, body weight, and BMI after gastrointestinal surgery. It also resulted in improved nutritional status and digestive function in patients who had undergone pancreaticoduodenectomy.[4]

Consensus key point 3

Every patient presents with varied symptoms and degree of damage to the pancreas. Experts recommend initiating PERT if EPI is diagnosed based on clinical symptoms or if the patient experiences weight loss or steatorrhea. A normal diet and PERT are recommended for patients with pancreas enlargement; however, if the symptoms do not resolve or the patient does not respond to treatment, a fat-free diet is recommended.

The experts recommend that without evidence of fat maldigestion, PERT should not be considered in patients. PERT is indicated in patients with CP and EPI. Further, patients with acute severe necrotizing pancreatitis can be supplemented for at least six months. AP is mostly temporary and the pancreas function is not affected; there is no indication for using PERT in such cases.

Experts recommended that pancreatic enzyme supplements can be consumed 20 to 30 minutes after a meal. Experts recommend starting with a dose of 30,000 units with each major meal and between 10,000 and 20,000 units of lipase for snacks, which is sufficient, especially in the Indian context where the snack is not very calorie dense. However, the experts opined that patients should not be insisted to take PERT with snacks because there is a lack of adherence to PERT, and thus compliance is lost. Furthermore, it has been observed in studies that low-dose PERT containing 4000-5000 IU lipase is also beneficial in patients with mild to moderate EPI due to CP.[18,19] In case of insufficient response to PERT, the pancreatin dose should be doubled or tripled, and/or a proton pump inhibitor (PPI) should be administered.

PERT must be individualized after extensive surgery. In case of major surgery or reduction in the length of the gastrointestinal tract, which causes malabsorption, patients are recommended for pancreatic enzyme supplementation as well as dietary modifications such as reduced intake of high-fat diet.

OVERCOMING THE "COMPLIANCE" HURDLE

Importance of patient monitoring and patient compliance

Patients who fail to improve with PERT should be carefully reassessed for compliance with treatment and the accurate timing of doses in relation to meals. One of the factors that leads to non-compliance is pill burden. Prescribing higher-strength capsules when higher doses are required helps reduce the pill burden and improve patient compliance.[1]

According to a study by Barkin et al in pancreatic cancer patients, inappropriate administration and use by both healthcare professionals and patients as well as inconsistent timing of PERT prescriptions were some factors adding to the compliance burden. An increase in patient and provider education programs on PERT usage and administration was considered necessary for compliance.[20]

Another study by Kim et al reported that poor compliance was significantly associated with weight loss. Further, 30% of patients in the treatment arm were non-compliant with PERT, indicating a problem with the prescribed treatment and tolerability issues with PERT. A rigorous education program prior to the start of PERT and re-education during therapy may help improve compliance.[21]

Non-compliance to PERT in EPI management has also been associated with higher utilization and healthcare costs.[22] Kamat et al studied the direct cost required for the non-surgical management of CP. Drugs were responsible for 54% of the total cost, and PERT contributed to 72% of the cost of drug therapy. Further, 7.7% of participants were non-compliant with PERT due to its high cost and affordability issues.[23]

Step-wise optimization of PERT

Patients may have varying degrees of residual pancreatic secretion and gastric lipase production. Several factors determine the response to treatment including the degree of residual pancreatic function, anatomy, and the size and fat content of meals. Because of differences in residual pancreatic secretion and gastric lipase production, therapy must be tailored to the individual patient, based on the severity of symptoms and response to treatment.

Optimization of PERT involves assessing compliance and reinforcing the importance of daily dosing with all meals and snacks, increasing the dose of PERT, attempting concomitant PPI or H2-receptor antagonist (H2RA) therapy, and switching formulation. Ruling out alternative causes for steatorrhea when patients fail to respond to PERT is important. The most common reason for failure is inadequate dosage. Either the patient requires more enzyme or the timing of delivery is off, resulting in inadequate mixing of enzymes with chyme in the duodenum. In patients who have been compliant to the initially prescribed PERT dosage, the first step would be to double the dose of the enzyme. The addition of acid suppression with PPIs or H2RAs is a reasonable next step in patients with a suboptimal response. On occasion, changing formulations may improve symptoms if dosage increases and acid suppression fails to improve symptoms.[1]

Consensus key point 4

Experts believe that non-compliance is the result of increased pill burden. Patients less than 20 years of age with tropical pancreatitis or hereditary pancreatitis, may require a higher dose due to the severe course of the disease. Likewise, patients undergoing pancreaticoduodenectomy might be prescribed higher doses. Thus, increased doses require a greater number of pills to be taken, leading to reduced adherence. Lack of proper communication regarding the timing of the doses, affordability and lack of support from healthcare programs are also factors contributing to non-compliance. According to experts, there are several healthcare programs in India; however, none of these programs create patient awareness and make the drug affordable.

Active education and monitoring before starting pancreatic enzymes and during follow-up would improve compliance. Furthermore, adjusting doses according to patient response and reducing pill burden by giving higher doses in a single pill as well as the timing of doses in relation to the meal would also improve compliance.

Compliance can be monitored by answering a questionnaire about the patient's complaints and the status of symptom resolution. Treatment optimization should begin with doubling the enzyme dose for patients who do not show improvement in symptoms despite taking PERT as advised.

MANAGEMENT OF DYSPEPSIA

Overview of dyspepsia

Dyspepsia is a common complaint in clinical settings, although several patients do not seek medical attention.[5] Patients with dyspepsia are designated as having "uninvestigated dyspepsia" when they first present for an evaluation. Organic factors can cause dyspepsia; however, the majority of patients experience FD.[24]

FD is characterized by the presence of symptoms believed to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease. Symptoms of FD can be caused by several pathophysiologic mechanisms, such as delayed gastric emptying, impaired gastric accommodation to a meal, and hypersensitivity to gastric distention, *Helicobacter pylori* infection, altered duodenal response to lipids or acid, abnormal duodenojejunal motility, or central nervous system dysfunction.[25] Characteristic symptoms include epigastric pain, epigastric burning, postprandial fullness, or early satiety, present for at least six months.[26] Risk factors for FD include age, gender, dietary factors, smoking, alcohol consumption, use of non-steroidal anti-inflammatory drugs (NSAIDs), and psychological factors.[24]

Dietary factors are the leading causes of dyspepsia. Overeating, spicy and fatty foods, citrus juices, carbonated beverages, caffeine, and alcohol all contribute to heartburn, which is an important symptom of indigestion.[27] Asian diet is slightly different from the Western diet in terms of the addition of some ingredients like chilli in variable amounts in different Asian countries. However, the reasons for the impact of chilli on GI symptoms remain unclear.[28] Further, consuming lipid-rich foods worsens indigestion. Symptoms of indigestion, such as nausea, bloating, pain, and fullness during stomach distension are all caused by lipids.[29]

The modulatory function of fat on gastrointestinal sensitivity may be mediated in part by cholecystokinin

release.[1,30] Fat-induced cholecystokinin release prevents postprandial gastric emptying by modulating stomach motility. Similarly, fat hydrolysis by-products reduce postprandial gastric acid secretion, possibly by regulating cholecystokinin release. This fat-induced cholecystokinin release may play a significant role in the pathophysiology of FD in addition to its effects on upper gastrointestinal function, such as gastric emptying, stimulation of pancreaticobiliary secretion, and gastric acid secretion.[30]

Diabetes is another factor that often results in indigestion due to decreased gastrointestinal motility and decreased pancreatic enzyme secretion.[31] Dyspepsia is expected to occur in CP.[32] Indigestion is caused by anatomical and physiological alterations brought on by gastrointestinal and pancreatic surgery due to an imbalance between the gastric emptying of nutrients and biliopancreatic secretion.[33]

Diagnosis of dyspepsia

The initial assessment of a patient with dyspepsia begins with the recording of a thorough medical history and physical examination. However, the presence of alarm symptoms may indicate advanced disease. Examples of alarm symptoms include unexplained weight loss, recurrent vomiting, progressive dysphagia, odynophagia, gastrointestinal blood loss, and a family history of upper gastrointestinal cancer. An upper endoscopy is advised for every patient exhibiting alarm symptoms. Although the diagnostic yield is low, endoscopic evaluation for new onset dyspepsia in individuals over 50 years of age is recommended.[25]

Treatment algorithm for patients with dyspepsia

Dyspepsia management involves a combination of pharmacological and non-pharmacological therapies. Non-pharmacological therapy includes the consumption of small and frequent meals, and avoiding alcohol and NSAIDs. Pharmacological therapy includes PPIs, H2RAs, prokinetics and antidepressants.[25]

Numerous guidelines recommend *H. pylori* testing and treatment as the first step in the care of young patients with uninvestigated dyspepsia. Such recommendations are mostly based on the knowledge that *H. pylori* plays a role in peptic ulcer disease as well as evaluations of the cost-effectiveness of non-invasive versus invasive therapeutic techniques. In the test-and-treat strategy for *H. pylori*, patients with uninvestigated dyspepsia younger than 45 to 50 years and not exhibiting any warning signs are noninvasively tested for *H. pylori* and treated with antibiotics in case of an infection. In patients with uninvestigated dyspepsia, empirical therapy with a PPI, H2RA, or prokinetic agent has also been used as an initial management option.[5]

In the case of FD, testing and treating for *H. pylori* is always the first step. Following that, the treatment is a two-step process. A PPI or H2RA is used as first-line therapy for at least four weeks. If symptoms persist, tricyclic antidepressants or prokinetic agents are used. Psychotherapy, herbal supplementation, lifestyle modification, dietary interventions, acupuncture, and electrical stimulation are examples of adjunctive or alternative non-pharmacologic therapies.[34]

Consensus key point 5

According to experts, lipids are a major trigger for indigestion symptoms, which are common after the intake of fatty and spicy food. Indigestion or dyspepsia can be diagnosed mainly by medical history evaluation and physical examination. Laboratory tests and upper gastrointestinal endoscopy may be performed at the specialist level. Dietary modifications and lifestyle changes are first-line treatment options in FD. Apart from these, acid suppressants in combination with prokinetics are commonly used as first-line therapy for indigestion symptoms; however, these may be usually ineffective. Activated dimethicone (simethicone) or alpha-galactosidase act as anti-flatulent agents and are used for the management of bloating.

ROLE OF PANCREATIC ENZYMES IN THE MANAGEMENT OF DYSPEPSIA

Digestive enzymes are often prescribed to patients with various dyspeptic complaints in addition to consuming adequate amounts of raw foods. The main digestive enzymes are amylases, proteases, and lipases, which are used to digest carbohydrates, proteins, and fats, respectively. Thus, symptoms of dyspepsia would be lessened by assisting in digestion.[35]

Lipids are triggers for indigestion and associated symptoms, so it is imperative that the enzyme supplement preparation should have lipase as it is the only enzyme that can digest lipids.[27,35] Several preparations available in the Indian market do not meet the label claim for lipase enzymes. Thus, these preparations may not reduce symptoms of indigestion effectively.[36] To manage these patients holistically, it is crucial to choose the right blend of enzymes and choose one that contains all the necessary enzymes for digestion.[37]

Animals, plants and microorganisms are capable of producing lipases. However, microbial lipases are gaining more attention due to their wide range of catalytic activities, high yields, simplicity of genetic manipulation, consistency of supply due to lack of seasonal fluctuations, the rapid growth of microorganisms on inexpensive media, greater stability than the corresponding plant and animal enzymes, and feasibility and safety of production.[35]

According to a study, pancreatic enzyme supplements can significantly lessen the symptoms of flatulence, bloating, belching, fullness and postprandial distress in people with FD.[35] Another study revealed that pancreatic supplements

resulted in fewer postprandial symptoms related to high-fat meals in healthy subjects, suggesting that enzyme supplementation may be beneficial in reducing FD and associated symptomatic responses.[38]

Consensus key point 6

Digestive enzyme supplements play a significant role in alleviating the symptoms of indigestion. Patients with pancreatic enzyme deficiency as a cause of dyspepsia, such as those with pancreatitis or diabetes, can benefit from enzyme supplementation. Lipase-containing preparations should be chosen to provide holistic indigestion management.

CONCLUSION

EPI is observed in different pancreatic conditions, after pancreatic surgery as well as dyspepsia. This consensus article highlights the current diagnostic and treatment modalities for disturbed pancreatic function and dyspepsia in India, along with the role of conventional treatment and PERT. Despite the wide application of PERT, patient compliance remains a problem; therefore, current strategies need optimization. Therefore, experts believe that if EPI is diagnosed or the patient experiences weight loss or steatorrhea, PERT should be initiated while ensuring compliance. Furthermore, digestive enzyme supplements also play a significant role in alleviating symptoms of indigestion. Routine enzyme supplementation is beneficial in managing dyspepsia caused by EPI, such as, in patients with EPI due to pancreatitis or diabetes.

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