Drug Corner

Clinical Efficacy of Pancreatin Minimicrospheres Supplementation in Patients with Exocrine Pancreatic Insufficiency (EPI) : Real-world Evidence

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Background : Exocrine pancreatic insufficiency (EPI), characterized by reduced secretion or activity of pancreatic enzymes, causes improper absorption of food, excessive fat excretion in the stool, and malnourishment.

Methods : In this observational, real-world evidence study, patients with one or more of the following condition were enrolled: abdominal pain, acidity, diarrhea, nausea, or dyspepsia (as per ROME III criteria). Patients had either been diagnosed with gallstones, hypertriglyceridemia, alcohol consumption or undergone abdominal surgery. Patients were prescribed capsule Enzigest™10000 (pancreatin minimicrospheres) for one month.The severity and frequency of various gastric symptoms was measured at day 0 and day 30.

Results : 540 patients were enrolled with a mean age of 51.6 years. Enzigest significantly reduced the severity of functional dyspepsia by 88.67% ($p<0.001$) as per Rome III Criteria. There is significant improvement in frequency of symptoms (83.80%), abdominal pain severity (81.58%), epigastric pain (83.09%), nausea (84.35%) and vomiting by 89.62% (all $P<0.001$). The overall improvement in symptoms was significant ($p<0.001$). Enzigest was well tolerated.

Conclusion : Enzigest improved abdominal pain, dyspepsia, and acidity in patients with exocrine pancreatic insufficiency due to alcohol consumption, gallstones, hypertriglyceridemia, diuretic (Furosemide or Thiazide) or abdominal surgery. Enzigest containing pancreatin minimicrospheres can be an easy therapeutic option to counteract EPI.

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***Key words* : Abdominal Pain, Dietary Supplement, Dyspepsia, Exocrine Pancreatic Insufficiency (EPI), Pancreatin Minimicrospheres.**

Exocrine Pancreatic Insufficiency (EPI), characterized by reduced secretion or activity of pancreatic enzymes, occurs due to parenchymal dysfunction or ductal obstruction. Pre-existing pancreatic diseases lead to the maldigestion of food and subsequently malabsorption of nutrients[1]. EPI causes improper absorption of food, excessive fat excretion in the stool, and malnourishment[2]. When there is pancreatic enzyme insufficiency, fat is not digested, and it remains in the bloodstream, causing hypertriglyceridemia leading to major cardiovascular disorders[3].

Hypertriglyceridemia is one of the major causes of acute pancreatitis (AP), accounting for 10% of all cases. The precise mechanism by which hypertriglyceridemia causes AP [termed hypertriglyceridemic pancreatitis (HTGP)] is not fully understood. Hypertriglyceridemia [by causing an excess of free fatty acids (FFAs)] and elevated chylomicrons increase plasma viscosity, which may induce ischemia in pancreatic tissue and trigger organ inflammation.

Editor's Comment :

- Exocrine Pancreatic Insufficiency (EPI) is characterized by reduced synthesis or secretion of pancreatic enzymes and bicarbonate.
- Maldigestion of food and subsequent malabsorption of nutrients causes symptoms in patients with EPI.
- Enzigest™ improves abdominal pain, dyspepsia, and acidity in patients with exocrine pancreatic insufficiency due to alcohol consumption, gallstones, hypertriglyceridemia, diuretic (Furosemide or Thiazide) or abdominal surgery.
- Enzigest ™ supplementation can be an easy therapeutic option to counteract EPI.

Chronic Pancreatitis (CP) is the most common pancreatic disease associated with EPI. Clinically significant EPI in CP requires a reduction of almost 90% of pancreatic enzymes and is reported in 60%–90% of CP patients within 10-12 years from diagnosis[4]. The rate of EPI in those with early or idiopathic CP, who are most evaluated at a primary care level, has been reported to be 18.7%[5].

Certain drugs (thiazide diuretics, non-selective beta-blockers, estrogens, tamoxifen, bile-acids resins,

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corticosteroids, protease inhibitors, cyclosporine, retinoids, anti-epileptics and antipsychotics) cause secondary hypertriglyceridemia and acute pancreatitis[6,7].

There are multiple reported cases of Furosemide related pancratitis. Diuretics like Furosemide might impair pancreatic perfusion by diuresis and intravascular volume depletion. The exact mechanism is still unclear, and there are multiple hypotheses including pancreatic exocrine stimulation by furosemide, or hypersensitivity from an immunologic response against a drug-protein[8].

In India, Alcoholic Chronic Pancreatitis (ACP) is the second most common etiology of Chronic Pancreatitis (CP) after Idiopathic Chronic Pancreatitis (ICP)[9,10]. The prevalence of CP is very high in SouthIndia (114-200/1,00,000 population)[11]. The relationship between chronic alcohol consumption and the development of CP is well known. Among patients with alcoholic pancreatitis, the mean duration of alcohol intake is 18±11 years for men and 11±8 years for women[12].

Gastrointestinal (GI) surgery causes structural changes in the GI tract resulting in asynchrony between the release of enzymes and passage of nutrients. Changes in pancreatic enzyme secretion result in the malabsorption of nutrients, fats, and fat-soluble vitamins, leading to primary symptoms[13,14]. About 25% of patients after the Whipple procedure have long-term malabsorption and need supplemental enzymes for life. Other patients may need enzymes for a few months or years after surgery[15]. Some conditions that may cause pancreatic insufficiency include gall stones, blockage or narrowing of the pancreatic or biliary duct (the tubes that carry pancreatic juice or bile), pancreatic or duodenal tumors, cystic fibrosis, or pancreatitis. In India, the prevalence of Gallstone Disease (GSD) is 6.12%, corresponding to a significant burden on the healthcare system and one of the most common reasons for patients with abdominal pain[16]. Patients with biliary pancreatitis have pancreatic enzyme insufficiency[17].

Evidence suggests that Pancreatic Enzyme Replacement Therapy (PERT) improves fat absorption and clinical symptoms, especially pain. The ease of administration and lack of any significant side effects makes PERT the first choice in the medical treatment of pain. Literature suggests that these preparations should contain large amounts of proteases, amylase, and lipases, given four times a day[12].

Materials and Methods

(1) Setting and participants :

This was an observational, real-world evidence study in which treated patients were followed up for a month.Patients were recruited from 40 separate outpatient clinics. Eligible patients were aged more than 18 years, with one or more of the following conditions: abdominal pain, acidity, diarrhea, nausea, or dyspepsia (as per ROME III criteria). Patients had either been diagnosed with gallstones, hypertriglyceridemia, alcohol consumption, diuretic (Furosemide or Thiazide) or undergone abdominal surgery. Exclusion criteria included patients with a history of substance abuse, pregnancy or lactation, any severe disease, or seen unfit for the study. All participants gave written informed consent before the screening.

(2) Study product :

Patients were prescribed Enzigest™10000 (manufactured by Wallace Pharmaceuticals Pvt Ltd), to be taken before every meal for one month**.** Patients were advised not to take other Ayurvedic/herbal/ homeopathic dietary supplements or any alternative therapies during the treatment period. A record of these medications was maintained.

(3) Outcomes and follow-up :

The primary outcome measures included evaluation of symptoms at baseline and after 30 days of treatment. Health-related quality of life (HRQOL) was a secondary outcome measure assessed at the beginning and end of the treatment.

(4) Statistical analysis :

(a) Sample size consideration —

This was the first clinical evidence generation program to evaluate the effectiveness and tolerability of Enzigest™inexocrine Pancreatic Insufficiency (EPI) with no previous data available. A sample size of about 500 participants from 40 centers was considered adequate to address the evaluation objectives.

(b) Effectiveness and tolerability analysis —

Wilcoxon signed Rank Test was used to test the efficacy of parameters. Demographic data were analyzed using descriptive statistics. All tests were carried out at 5% significance.

Results

540 patients were consecutively included in the study. Patient characteristics are summarized in Table 1. The mean age of the patients was 51.6 years.

Enzigest significantly reduced the severity of

functional dyspepsia by 88.67% (p<0.001) as per Rome III Criteria (Fig 1).

There is significant improvement in frequency of symptoms (83.80%), abdominal pain severity (81.58%), epigastric pain (83.09%), nausea (84.35%), and vomiting by 89.62% (all P<0.001) as shown in Fig 2. The effectiveness data of Enzigest is shown in Table 2. Improvement in sickness (86.41%), loss of appetite (80.57), and retrosternal discomfort (85.38%) were observed after treatment with Enzigest. The reduction in diarrhea, bowel movement per day, and pain/cramping in the abdomen with bowel movement after treatment were 94.28%, 31.57%, and 78.33%, respectively (all p<0.001) as shown in Fig 3. The overall improvement in symptoms was significant (p<0.001) (Fig 4). No major adverse events were observed in the follow-up period in the study population.

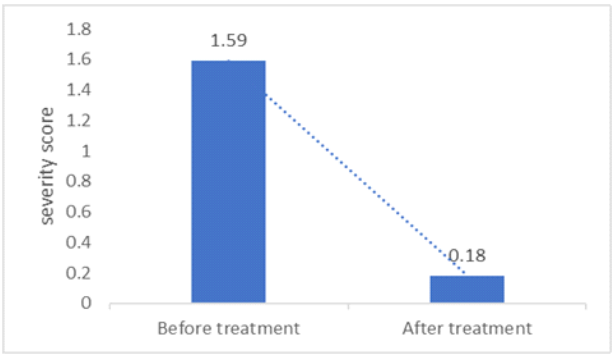

Fig 1 — Severity of functional dyspepsia

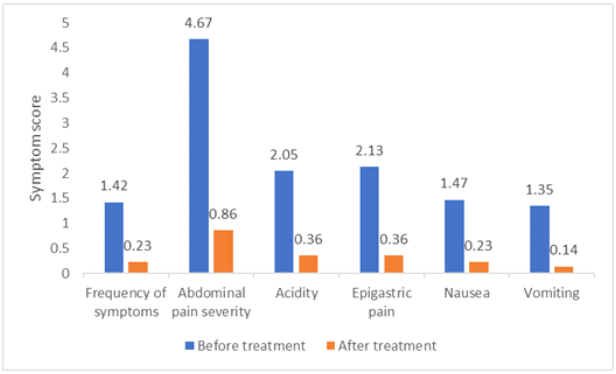

Fig 2 — Symptomatic improvement

Table 1 — *Baseline demographic details*

Parameter	n (%)
Sex :	
Male	369 (68.33%)
Female	170 (31.48%)
Gall stones	210 (38.89%)
Alcohol consumption	212 (39.26%)
Abdominal pain	474 (87.78%)
Acidity	451 (83.52%)
Diarrhea	119 (22.04%)
Nausea	358 (66.30%)
Dyspepsia-as per Rome III Criteria	271 (50.19%)

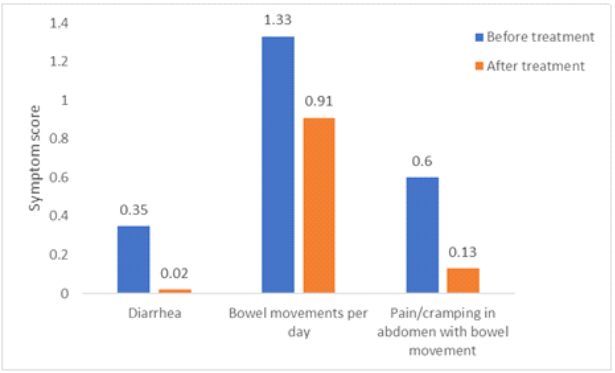

Fig 3 — Reduction in diarrhea

Table 2 — *Change in outcome measures*

Parameter	Before treatment (mean ± SD)	After treatment (mean ± SD)	% change	p value
Severity of functional dyspepsia	1.59±0.72	0.18±0.40	88.67%	<0.001
Frequency of symptoms	1.42±0.87	0.23±0.79	83.80%	<0.001
Abdominal pain severity	4.67±2.36	0.86±1.06	81.58%	<0.001
Overall assessment	0.79±0.71	1.86±1.01	135.44%	<0.001
Epigastric pain	2.13±1.05	0.36±0.57	83.09%	<0.001
Early satiety	1.53±1.09	0.31±0.48	79.73 %	<0.001
Nausea	1.47±0.97	0.23±0.46	84.35%	<0.001
Vomiting	1.35±1.01	0.14±0.37	89.62%	<0.001
Acidity	2.05±1.16	0.36±0.56	82.43%	<0.001
Sickness	1.62±1.08	0.22±0.50	86.41%	<0.001
Loss of appetite	1.75±1.22	0.34±0.61	80.57%	<0.001
Retrosternal discomfort	1.71±1.22	0.25±0.48	85.38%	<0.001
Diarrhea	0.35±0.55	0.02±0.14	94.28%	<0.001
Bowel movements per day	1.33±1.19	0.91±0.60	31.57%	<0.001
Pain/cramping in the abdomen with bowel movement	0.60±0.53	0.13±0.44	78.33%	<0.001

Discussion

To the best of our knowledge, no other study has evaluated the effect of pancreatic enzyme supplementation in a real-world setting. The current study showed that Enzigest, a pancreatic enzyme supplement, is effective in abdominal pain, dyspepsia, and acidity in patients with EPI due to various clinical conditions. Furthermore, it has excellent tolerability, as suggested by the lack of adverse events in the study population.

The management of CP involves managing pain and steatorrhea[8]. Clinical studies support the efficacy and safety of different pancreatic enzyme formulations, including enteric-coated minimicrospheres

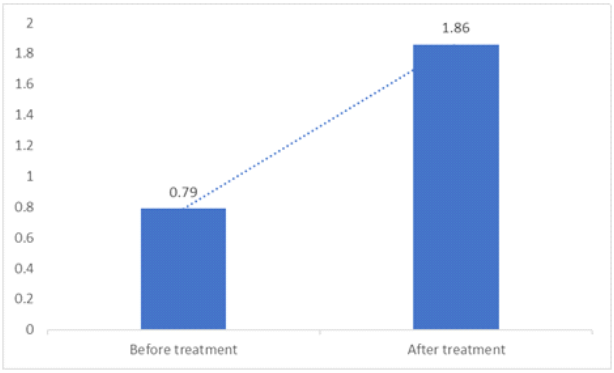

Fig 4 — Overall assessment

(MMS) containing protease, amylase & lipase[18-20]. Literature suggests that most CP patients can be managed with pancreatic enzyme supplementation[21]. According to a survey conducted in the Asia-Pacific region, most experts used pancreatic enzyme supplementation in clinical practice along with analgesics for pain relief[11]. Pancreatic enzymes enteric-coated MMS for one year significantly improved fat absorption, nitrogen absorption, and nutritional parameters, improvements in clinical symptoms, and favorable safety and tolerability profile in patients with PEI due to CP[22].

In our study Enzigest significantly reduced the severity of functional dyspepsia (88.51%), frequency of symptoms (84.01%), abdominal pain severity (81.6%), epigastric pain (83.3%), nausea (84.66%), and vomiting (89.47%). In few randomized, double-blind, placebo-controlled studies, PERT supplementation significantly increased fat absorption up to 88.6% and protein absorption up to 87.2% ($P<0.001$)[23].

PERT is the standard of care for PEI, whatever its etiology, and effectively improves maldigestion and the clinical symptoms associated with PEI. Pancreatic enzyme preparations are a life-saving substitution for a pivotal physiological function of the entire organism with exocrine pancreatic insufficiency. Pancreatic enzyme preparations, generically called pancreatin, are not alike. Instead, they present a wide variety of pancreatin compositions[24].

Lipase supplementation improves fat digestion and absorption, resulting in lesser steatorrhea and clinical improvement[25]. The proteases in the pancreatic enzyme supplement are hypothesized to inhibit overstimulation of duodenal Cholecystokinin (CCK) receptors, thereby reducing pain.

In this study, the effectiveness data of Enzigest demonstrated improvement in sickness, loss of appetite, and retrosternal discomfort. A meta-analysis concluded that PERT significantly increased the Coefficient of Fat Absorption (CFA) ($p<0.001$). Furthermore, the subgroup analysis indicated that standard forms of PERT displayed higher effectiveness. PERT is effective and tolerable in patients with EPI, especially using standard administration of PERT[2]. Although lower in incidence, chronic pancreatitis significantly reduces patients' quality of life. Alcohol consumption has increased in India due to rapid urbanization and increased affluence. This increase would increase the burden of alcohol-related pancreatitis and associated enzyme insufficiency in India[26].

CP ultimately leads to exocrine pancreatic insufficiency and progressive endocrine failure resulting in diabetes. The spectrum of chronic pancreatitis in India is changing, with increased occurrence in older patients, the incidence of milder diseases, including milder diabetes, increasing longevity, and increasing association with alcoholism and smoking[27].

The improvement in abdominal pain observed in this study most likely reflects an improvement in pain associated with PEI-related maldigestion rather than the characteristic severe abdominal pain often experienced by patients with CP. Pancreatic enzymes allow patients with pancreatic insufficiency to eat a regular diet and prevent the deleterious effects of continued nutrient malabsorption and malnutrition. Moreover, PERT could prevent the long-term complications of malabsorption such as cerebellar ataxia, increased prothrombin time and osteoporosis, and increased morbidity and mortality related to malnutrition[2].

After curing acute pancreatitis, management of exocrine insufficiency is a significant clinical challenge. Evidence suggests that oral pancreatic enzyme supplementation has a positive effect on managing AP and the global health status (less weight loss, less flatulence, improved quality of life). A double-blind, placebo-controlled, randomized study showed that oral pancreatic enzyme supplementation could be added to the treatment regimen of patients in a refeeding status after severe acute pancreatitis. Among 56 patients, 20 showed low faecal elastase values indicating pancreatic exocrine insufficiency after acute pancreatitis. The median time to recovery from exocrine pancreatic insufficiency was 14 days in the enzyme supplementation group and 23 days in the placebo group. Overall, the patients receiving enzyme supplementation had a better quality of life[28]. Enzyme supplementation positively affects the course of acute

pancreatitis if administered during the early refeeding phase after acute pancreatitis.

Many patients with pancreatic disease undergo cholecystectomy as part of the management of gallstone disease, which is associated with a risk of Bile Acid Malabsorption (BAM). Pancreatic enzyme supplementation could also help manage BAM, commonly called bile acid diarrhea[29]. Some patients develop transient pancreatic insufficiency following an episode of severe AP, and some authors recommend using PERT during the recovery phase[30]. In one retrospective study, 45% of patients with hypertriglyceridemia and pancreatitis had received oral pancreatic enzyme replacement therapy[31].

In our study, 38.89% of patients were diagnosed with cholelithiasis. Similarly, in Yan *et al*, 25% of patients with cholelithiasis had impaired pancreatic exocrine function[32]. Another study on gallstone patients found a high prevalence of pathological changes in exocrine pancreatic function based on faecal elastase-1 concentrations. Literature suggests that gallstones might cause chronic pancreatitis, as they cause acute pancreatitis[33]. Pancreatic enzyme supplementation should be prescribed for patients with symptoms of pancreatic exocrine insufficiency[34].

The treatment of EPI focuses on the management of symptoms. Patients are advised to follow a healthy low-fat diet, Pancreatic Enzyme Replacement Therapy (PERT), and vitamin and mineral supplementation[35]. The enzymes from the enteric-coated preparations are generally released more distally in the jejunum and ileum. Thus, enteric-coated enzyme preparations don't require co-prescription of a proton pump inhibitor or H2 receptor blocker, unlike non-enteric preparations[36].

This study has some limitations. Firstly, since this was an open-label, real-world evidence generation program, lacking a control group. It may be helpful to design a study that will take biochemical parameters and objective assessments into consideration. Further studies are encouraged to gather data from a larger sample size.

Conclusion

The novelty of this study is the demonstration that pancreatic enzyme supplementation improves abdominal pain, dyspepsia, and acidity in patients with exocrine pancreatic insufficiency due to alcohol consumption, gallstones, hypertriglyceridemia, diuretic (Furosemide or Thiazide) or abdominal surgery. The results obtained from this study show that supplementation with Enzigest can be an easy therapeutic option to counteract EPI.

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