

A Review of Digestive Enzyme and Probiotic Supplementation for Functional Gastrointestinal Disorders

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Abstract

Functional gastrointestinal disorders (FGIDs) also known as disorders of gut-brain interaction are chronic, recurrent disorders with no identifiable underlying pathology. The FGID with upper abdominal pain and discomfort is the hallmark feature of functional dyspepsia. Around 11-30% prevalence of functional dyspepsia is reported worldwide. One of the unique features of functional dyspepsia is transient deficiency of digestive enzymes in the system. Digestive enzymes are produced and secreted by the gastrointestinal system to break down fats, proteins, and carbohydrates, to accomplish digestion and, afterwards, the absorption of nutrients. Supplementation with digestive enzymes could provide management of disorders caused by impaired digestive function. Various formulations of enzyme supplementation are available commercially in the market, and are currently used in clinical practice for the management of several digestive diseases. Probiotics have multi-faceted role, helping to restore the gut microbiota.

This review elaborates the potential of multi digestive enzymes along with probiotics in the management of digestive diseases and dyspepsia.

Keywords: Digestive enzyme, Probiotics, Functional Dyspepsia, Indigestion.

Conflicts of Interest: None.

Introduction

Digestive symptoms with varying severity ranges around 10-30% in developed countries. Conventional diagnostic procedures fail to detect systemic or metabolic cause of digestive symptoms and disorders, hence these conditions are classified as functional gastrointestinal disorders.^[1] Functional gastrointestinal disorder (FGID) is a term used to describe gastrointestinal (GI) abnormalities and symptoms which are chronic and recurrent, and do not have an identifiable underlying pathology.^[2] Although only about 25% of symptomatic individuals seek medical support, FGIDs represent 40% of diagnosis in gastroenterological setting. To get a proper di-

agnosis of FGIDs is a task. Further, overlaps between syndromes can complicate the interpretation of clinical data and thus the diagnosis.^[1]

The classification of functional disorders according to ROME-III criteria is based on the symptoms of abdominal pain, bowel movement and anorectal disorders for the adult population; whereas for pediatric population, ROME-III classification is based on the age. Functional gastroduodenal disorders are further classified as functional dyspepsia, belching disorders, nausea and vomiting disorders, and rumination syndrome.^[3]

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Functional Dyspepsia

Functional Dyspepsia also known as indigestion can be defined as 'a symptom or set of symptoms that most physicians consider originating from the gastroduodenal area'.^[4] Functional dyspepsia, a condition of impaired digestion is the commonest cause of dyspeptic symptoms across the globe, accounting for more than 70% of the cases of dyspepsia.^[5] The global prevalence of functional dyspepsia varies from 11-30%, and Indian prevalence is reported to be 30.4%.^[6] The symptoms of functional dyspepsia are upper abdominal fullness, heartburn, nausea, belching, or upper abdominal pain. People may also experience feeling full earlier than expected when eating.^[7,8]

The Rome IV criteria in Functional Dyspepsia

The Rome IV criteria defines dyspepsia as any combination of 4 symptoms namely postprandial fullness, early satiety, epigastric pain and epigastric burning. Symptoms are severe enough to interfere with the usual activities and occur at least 3 days per week over 3 months with an onset of at least 6 months in advance. After an accurate history taking and physical examination, in the absence of alarm symptoms and signs patients are diagnosed as being affected by uninvestigated dyspepsia and can be treated empirically.^[1,8]

Digestive enzyme in Human Body

Digestive enzymes are produced and secreted by the gastrointestinal system to degrade fats, proteins,

and carbohydrates, to accomplish the digestion and, afterwards, the absorption of nutrients.^[9]

The following is a table showing the enzyme, source and products of digestion. [Table 1]

Causes of digestive enzyme deficiency

Several factors cause enzyme inadequacy and deficiency, some of which are mentioned as follows:^[10-12]

- 1. Impaired secretion:** Dysfunction of digestive organs, mucosal disease, gastrointestinal surgery and nutritional deficiency can lead to impaired secretion.
- 2. Habits:** Poor eating habits [inadequate chewing food], eating late in the day.
- 3. Dietary choices:** Excessive alcohol, refined carbohydrate and fats, high meat consumption and minimal enzyme rich foods.
- 4. Age:** Aging alters the digestive enzyme secretion with linear decrease after 40 years.

Treatment of Functional Dyspepsia

For the management of functional dyspepsia, medical treatment is recommended as a supportive measure. The duration of treatment is limited (e.g., a period of 8–12 weeks) in the absence of casual therapy and is always oriented on the principal symptoms, particularly since the placebo success rate can be very high, up to 60%.^[13]

The following categories of evidence-based treatment are mentioned as follows:

Table 1: Digestive enzymes in human body

Enzyme	Produced By	Site of Action	Role
Carbohydrate Digestion			
Salivary amylase	Salivary glands	Mouth	Breakdown starch to maltose
Pancreatic amylase	Pancreas	Small intestine	Breakdown starch to maltose
Maltase	Small intestine	Small intestine	Breakdown maltose to glucose
Lactase	Small intestine	Small intestine	Breakdown lactose to glucose and galactose
Protein Digestion			
Pepsin	Gastric glands	Stomach	Breakdown protein to peptides
Trypsin	Pancreas	Small intestine	Breakdown protein to peptides
Peptidase	Small intestine	Small intestine	Breakdown peptide to amino acids
Nucleic Acid Digestion			
Nuclease	Pancreas	Small intestine	Breakdown RNA and DNA to nucleotides
	Small intestine	Small intestine	Breakdown nucleotide to nitrogen base, sugar and phosphate
Fat Digestion			
Lipase	Pancreas	Small intestine	Breakdown fat droplet to monoglycerides and fatty acids

- **Acid suppression agents:** Proton pump inhibitors are logical as there is evidence that there is impaired duodenal clearance and increased duodenal sensitivity to acid (exogenously administered) in dyspeptic patients.^[14]
- **Prokinetic agents:** These can accelerate gastric emptying and enhance gastric accommodation. Examples include cisapride, mosapride and domperidone. Older agents like cisapride are no longer preferred due to their QT prolongation adverse effect.^[15]
- **Helicobacter pylori eradication:** A meta-analysis found that H. pylori eradication caused the reduction of peptic ulcers and symptomatic relief. But it did not improve the quality of life of patients with functional dyspepsia and led to adverse events.^[16]
- **Antidepressants:** Studies have also shown that antidepressants are particularly effective against dyspepsia symptoms when the predominant complaints are abdominal and/or mental comorbidity.^[11]
- **Digestive enzymes:** Studies have shown that the pancreatic enzyme supplementation in functional dyspepsia is beneficial and significantly reduces the symptoms of flatulence, bloating, belching, fullness and post-prandial distress. The rationale for digestive enzymes is that carbohydrates, proteins and fats are initially converted to smaller units by various digestive enzymes and are then assimilated. By aiding the digestive process, the dyspeptic symptoms would be ameliorated. Hence, to assist the adequate digestion of every nutrient, a combination of different enzymes must be supplemented.^[10]

Digestive enzyme supplementation

Digestive enzyme supplementation is a necessity

in an individual with enzyme deficiency leading to functional dyspepsia and GI disorder. The required digestive enzymes as a supplementation are as follows (Table 2):

Breakdown of carbohydrates and proteins

Alpha amylase hydrolysis, alpha-linked polysaccharides from starch, glycogen to glucose and glucoamylase hydrolyses, the non-reducing end of starch to yield glucose. Whereas glycolipids and glycoproteins is hydrolysed by alpha galactosidase. Lactase is an essential enzyme that hydrolyse lactose (milk sugar) and aids in the complete digestion of whole milk. Lactase is effective in person with lactose intolerance symptoms. Invertase hydrolysis converts sucrose into fructose and glucose. Cellulose is an important structural component of the primary cell wall of green plants used as a vegetative food. Cellulase hydrolyse cellulose polysaccharide into glucose and oligosaccharides which further gets hydrolysed by amylases. Papain (Proteolytic enzyme) extracted from papaya fruit also serves as a supplement for breakdown of protein into peptides and amino acids. The digestive enzyme supplementation, when indicated, may provide a reliable help as an adjuvant treatment of several disorders characterized by an impairment of digestive functions.^[9]

Oral digestive enzymes and probiotics for treating dyspepsia

Digestive enzymes are often prescribed to patients with various dyspeptic complaints. Studies exhibit the favourable role of oral digestive enzyme supplementation in patients with complaint of functional dyspepsia due to inadequate digestive enzymes. A study pointed the role of pancreatic enzyme supplementation in functional dyspepsia where the therapy significantly reduced the symptoms of flatulence, bloating, belching, fullness and post-prandial distress.^[17,18]

Table 2: Advantages of digestive enzymes preparation over antacids

Antacid	Digestive enzyme
Antacid reduces digestion	Digestive enzyme increases digestive power
Antacid is unnatural and not part of the metabolism	Matches the natural metabolism
Provides temporary relief	Lasting solution for GI problems
Some disturb the synthesis of gastric acid	Does not interfere with the internal metabolism
Blocks the absorption of nutrients and drugs	Helps in complete absorption of nutrients
Decreases the anti-microbial activity of stomach	Promotes the anti-microbial activity of stomach
Calcium base leads to several disorders like renal failure, hypercalcemia and alkalosis	Calcium not present
Side-effects include constipation, dizziness, loss of appetite, unpleasant taste, nausea, increased thirst	Well tolerated with minimum side effects

Probiotics are live microorganisms, when provided in adequate amount leads to better gastrointestinal health. Probiotics supplements are shown to improve the Functional Gastrointestinal Disorders which includes abdominal pain, dysbiosis, dyspepsia, etc. Probiotics have a multifaceted role in restoring and maintaining the normal flora of the gut.^[19] Probiotics may restore the composition of the gut microbiome and introduce beneficial functions to gut microbial communities, resulting in amelioration or prevention of gut inflammation and other intestinal or systemic disease phenotypes.^[20]

The rationale for prescription of digestive enzymes is that enzymes breakdown carbohydrates, proteins and fats into smaller sub-units, in order to facilitate their absorption and utilization by the body. Addition of probiotics supplementation aids in restoring the gut flora. Thus, the combination of digestive enzyme and probiotics would facilitate in relieving GI discomfort, indigestions and thereby may even prevent IBS.^[21,22]

Rationale for Digestive Enzymes and Probiotics : Companions in Digestion

Digestive enzyme supplementation are from the natural source and required by the body to metabolize and digest complex food to prevent indigestion and for better GI health. Some conditions (such as diarrhoea, constipation, dyspepsia, etc.) can change the normal balance of bacteria (flora) found in the stomach and intestines. For better improvement of digestion and restoring normal gut flora; probiotics are beneficial. Digestive enzymes and probiotics are essential for normal digestive function. The addition of probiotics to enzymes helps promote a healthy intestinal tract environment. Combination of digestive enzymes and probiotics exhibits beneficial action in metabolism and utilization of nutrients. Probiotics with digestive enzymes have been used to prevent bowel symptoms (such as gas, bloating, abdominal discomfort, etc.) and to treat lactose intolerance. Thus, the combination of digestive enzyme and probiotics would help in digestion and restore the normal flora which in turn would also aid digestion. Together, the combination would be useful in relieving GI discomfort as seen in dyspepsia, constipation, diarrhoea, lactose intolerance, etc. and thereby may even prevent IBS.^[9]

Clinical evidence

Wealth of evidence exists for digestive enzymes and probiotics, but the exact dose, combination, duration of therapy, etc. needs to be explored further by the scientific community.

The study by Pawar D (2001) evaluated the efficacy and safety of fungal diastase and papain in patients (n = 100) of non-ulcer dyspepsia. Efficacy and tolerability were assessed at baseline, at day 7 and at day 14 of treatment. End of the 14 day treatment exhibit significant improvement in frequency and severity of all symptoms of indigestion (fullness, belching, bloating, flatulence and postprandial distress). Physician rated excellent (67%) and good efficacy (29%) whereas patients rated excellent (65%) and good tolerability (27%) in resolution of symptoms of functional dyspepsia. The combination was well tolerated with minor adverse effects (nausea and skin problems).^[23]

A post-marketing surveillance study by Khandke D *et al* (2013) evaluated the efficacy and tolerability of a multienzyme preparation containing amylase, protease, lipase, lactase and alpha-galactosidase. The multienzyme preparation was given for 14 days. Treatment was associated with a significant reduction in frequency and severity of every abdominal symptom (flatulence, bloating, belching, dyspepsia, feeling of fullness, abdominal discomfort, heart burn and anorexia) (p <0.0001). In the overall assessment by physicians 55% rated the preparation as excellent and 41% as good. Assessment by patients in terms of tolerability and effectiveness was also carried out with 51% rated the preparation as excellent and 44% rated it as good.^[24]

Ahyani T (2016) conducted a randomized study 116 patients who fulfilled the Rome III criteria for functional dyspepsia. Patients received either *Lactobacillus* probiotics or placebo for 2 weeks. The probiotics group had significantly reduced frequency of pain (P=0.0001), but no significant differences in pain severity (P=0.08) or pain duration (P=0.091) compared to placebo after the end of 2 weeks study period. In conclusion, authors found no significant differences in recovery from functional dyspepsia but the probiotics group has significantly reduced frequency of pain compared to that of the placebo group.^[25]

Conclusion

FGIDs represent 40% of diagnosis in gastroenterological settings. Meticulous history taking, judicious investigations, evidence-based medications based on symptomatology and an empathetic approach to the patient is the key to managing FGID patients. Incomplete digestion often results in digestive problems such as bloating, diarrhoea, stomach pain and cramps. For smooth digestion gut needs three essential ingredients: digestive enzymes, probiotics and the

prebiotics that feed them. Clinical studies elucidate that digestive enzymes and probiotics are essential for normal digestive function. The addition of probiotics to enzymes help in digestion and restoring the normal flora of the gut and promote a healthy intestinal tract environment. Together, the combination would be useful in relieving GI discomfort as seen in dyspepsia, constipation, diarrhoea, lactose intolerance, etc. and thereby may even prevent IBS.

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