Review Article

The Role of Enzyme Supplementation in Digestive Disorders

Mario Roxas, ND

Abstract

This article reviews various forms of enzyme supplementation used clinically in digestive and absorption disorders. Enzyme supplementation plays an integral role in the management of various digestive disorders, particularly with regard to exocrine pancreatic insufficiency. However, application of enzymes may also be beneficial for other conditions associated with poor digestion including lactose intolerance. Historically, porcine and bovine pancreatic enzymes have been the preferred form of supplementation for exocrine pancreatic insufficiency. Use of microbe-derived lipase has shown promise with studies indicating benefit similar to pancreatic enzymes, but at a lower dosage concentration and with a broader pH range. Safety and efficacy of enzymes derived from microbial species in the treatment of conditions such as malabsorption and lactose intolerance is promising. Plant-based enzymes, such as bromelain from pineapple, serve as effective digestive aids in the breakdown of proteins. Synergistic effects have been observed using a combination of animal-based enzymes and microbe-derived enzymes or bromelain. (*Altern Med Rev* 2008;13(4):307-314)

Introduction

Animal-based pancreatic enzymes are the accepted form of supplementation for exocrine pancreatic insufficiency, providing benefit to some individuals with gastrointestinal disorders. Studies report microbe-derived lipase has shown promising activity, similar to porcine and bovine pancreatic enzymes. The safety and efficacy of these enzymes in the treatment of malabsorption and lactose intolerance continues to be researched. Advantages of microbe-derived enzymes are that they may be used at a lower dosage and possess a broader pH range of activity than animal-based counterparts. Plant-based enzymes, such as bromelain from pineapple and papain from papaya, have proteolytic activity. Studies combining pancreatic enzymes and fungal enzymes or bromelain have reported synergistic effects.

Digestive enzyme supplementation can aid in the breakdown of fats, proteins, and carbohydrates and may provide benefit in disorders in which compromised digestion may be involved.

The Pancreas: A Review

The pancreas is comprised of an endocrine and an exocrine portion. The endocrine portion consists of the islets of Langerhans, which are responsible for the secretion of insulin, glucagon, and somatostatin. Pancreatic exocrine tissues (the acini) produce digestive enzymes that are mixed with sodium bicarbonate from the ductules connecting the acini to the pancreatic duct. This pancreatic "juice" flows through the pancreatic duct, connecting with the hepatic duct, and ultimately emptying into the duodenum via the sphincter of Oddi.[1] The digestive enzymes in the pancreatic juice break down carbohydrates, proteins, and fats (Table 1). Sodium bicarbonate neutralizes the acidic chyme that will make its way from the stomach to mix with the juice in the duodenum and start the enzyme-activating process.

Problems can occur when there is a dysfunction in the ability of the pancreas to produce enzymes or the body's demand for enzymes exceeds the supply.

Mario Roxas, ND – Technical Advisor, Thorne Research; Associate Editor, *Alternative Medicine Review*; private practice in Sandpoint, Idaho, with an emphasis on clinical nutrition and botanical medicine.
E-mail: m.roxas@comcast.net

Table 1. Pancreatic Enzymes in Digestion

Enzyme	Optimal pH Range	Action
Enterokinase (actually secreted in the small intestine)	5.2-6.0	Transforms trypsinogen into trypsin in duodenum
Proteolytic Enzymes: Trypsinogen (trypsin) Chymotrypsinogen (chymotrypsin) Carboxypolypeptidase Also various elastases and nucleases	7.9-9.7	Trypsin and chymotrypsin break down proteins into polypeptides and dipeptides; carboxypolypeptidase splits peptides into individual amino acids
Amylolytic Enzymes: Pancreatic amylase	6.7-7.2	Hydrolyzes starches, glycogen, and other carbohydrates (other than cellulose) into disaccharides and some trisaccharides
Lipolytic Enzymes: Lipase Phosphalipase A1, A2 Esterase	8.0	Lipase hydrolyzes fats into fatty acids and monoglycerides; phospholipases split fatty acids from phospholipids; esterase hydrolyzes cholesterol esters

This dysfunction can occur for a variety of reasons, including genetic predisposition, illness, injury/trauma, excessive exercise, aging, toxic exposure, or a combination thereof. A deficiency of pancreatic enzymes could potentially contribute to the development of numerous illnesses and degenerative conditions.

Pancreatic Enzyme Supplementation

Chymotrypsin, trypsin, pancreatin, and pancrelipase, either individually or in combination, are the key components of most common pancreatic supplements used in health care and are primarily extracted from porcine or bovine sources.[2] Lipase may also be synthesized from microbial sources, such as *Aspergillus oryzae* and *Rhizopus arrhizus*.[3-5]

U.S.Pharmacopoeia (U.S.P.) grade chymotrypsin and trypsin are crystallized from ox pancreas gland extract, pancrelipase is derived from hog pancreas, and pancreatin is extracted from both hog and ox sources.[2]

The activity and concentration of these enzymes are determined by multiple factors, including the animal's species, age and sex, as well as husbandry practices. The physiology of hogs, especially the pancreas, is more similar to humans than any other animal species.[6] Enzymatic activity levels from pork sources are approximately 30- to 50-percent higher than beef sources. While porcine pancreas is particularly rich in amylase and lipase, bovine pancreas is rich in proteolytic enzymes but substantially lower in amylase and lipase. Sow glands are high in lipase, whereas butcher hogs (young male hogs up to 90 kg in weight and six months of age) are high in protease. Enzyme levels in beef cows and bulls differ significantly from those found in steers or heifers.

Plant-Based Enzyme Preparations

As the name implies, plant-based enzyme preparations are derived from plant sources, such as pineapple and papaya. Bromelain is a general name for the family of sulfhydryl-containing, proteolytic enzymes from the pineapple fruit and stem. Bromelain also contains a peroxidase, acid phosphatase, several protease

Table 2. Generally Accepted Industry Methods for Determining Enzymatic Activity of Microbe-Derived Enzymes

Enzyme	Activity Units
Amylase	SKB units (Sandstedt, Keen and Blish, *Cereal Chemistry* 12, 172, 1939); based on the digestion of starch over time
Protease	HUT units (Hemoglobin Units); based on enzymatic hydrolysis of denatured hemoglobin
Lipase	LU (Lipase Units, Food Chemicals Codex (FCC)); based on lipolytic activity utilizing olive oil
Cellulase	GD (Guar Gum or Methylcellulose Hydrolysis); reduced viscosity flow time against hydrolysis
Lactase	FCC units (Food Chemicals Codex). Based on liberation of o-nitrophenol

inhibitors, and organically-bound calcium. Bromelain is commonly used as a supplement to aid digestion of protein. In addition, benefit has been reported with its use in wound debridement[7,8] and as an anti-inflammatory agent, particularly with soft tissue trauma.[9-12]

Different designations are used to indicate the activity of bromelain. Gelatin dissolving units (g.d.u.) and milk clotting units (m.c.u.) are the most commonly used measures of activity. One gram of bromelain standardized to 2,000 m.c.u. would have 1,200 g.d.u. of activity.

Papain is the dried and purified latex from the papaya fruit. It is a complex of several enzymes that have proteolytic, amylolytic, and weak lipolytic activity.[13] Like bromelain, papain is commonly used to aid protein digestion. Benefit has also been reported in symptom relief from episiotomy and treatment of herpes zoster.[13,14]

Microbe-Derived Enzyme Preparations

Microbe-derived enzymes are extracted or synthesized from fungal sources. Examples include lipase from *Aspergillus oryzae* or yeast-based beta-galactosidase (lactase) from *Kluyveromyces lactis*. Their beneficial digestive properties have been known for millennia in Asia and have been exploited in the areas of food production, as well as therapeutic application. For example, *A. oryzae* has traditionally been used in the fermentation process of soybeans to produce soy sauce, tamari, and miso.

Varieties of lipase, amylase, protease, and lactase have been made from microbial species and have been used in the management of enzyme deficiencies. Table 2 provides generally accepted standards for microbe-derived enzyme activity. Benefit has also been reported on the use of fungal-based enzymes in the treatment of chronically obstructed arteries.[15-19]

Clinical Applications

Malabsorption

Enzyme supplementation is an established method to treat a number of digestive conditions. For example, pancreatic enzyme supplementation is the therapy of choice for management of exocrine pancreatic insufficiency (EPI). Abdominal pain, maldigestion, steatorrhea (fat in the stool), and weight loss due to nutrient malabsorption are typical EPI symptoms.

A common cause of EPI is chronic pancreatitis, which can impair the ability of the pancreas to produce the enzymes necessary for proper digestion of nutrients, particularly fats. At least 70 percent of chronic pancreatitis cases stem from chronic alcohol abuse;[20] hence, EPI is often observed in alcoholics.

EPI often occurs in individuals with cystic fibrosis (CF), a genetic disorder that affects approximately 30,000 children and adults in the United States.[21] EPI also occurs in diabetes, which plagues approximately 23.6 million children and adults in the United States alone – almost eight percent of the American population.[22] Of these individuals, it is estimated that 35 percent of type 2 diabetics and 50 percent of type 1 diabetics may suffer from some form of EPI.[23]

Conventionally, porcine lipase is the treatment of choice for pancreatic exocrine insufficiency. The typical recommendation is 25,000-40,000 units of porcine lipase per meal, using pH-sensitive pancreatin microspheres. In case of treatment failure the dose is increased, after ruling out other causes of malabsorption.[24-26]

Concern has been expressed over the necessity of pancreatic enzyme preparations being enteric-coated

or pH-protected to ensure activity in the small intestine. Pancreatic lipase is a relatively fragile enzyme and becomes irreversibly inactivated at a lumen pH<4.0;[27-30] hence, the rationale for an enteric-coating or pH-sensitive medium. However, this can pose its own challenges. Enteric coating is protective as long as the pH in the stomach remains below 5.5; but should stomach pH temporarily rise above 6.0 the coating would disintegrate, making the enzyme vulnerable if the stomach pH fell to 4.0 or lower.[31] To achieve a more consistent alkaline environment, antacids or administration of H2-receptor antagonists are utilized in conjunction with pancreatic enzymes.

One study of six patients with advanced pancreatic insufficiency found that the combination of cimetidine and enteric-coated pancreatin, each given orally after a solid test meal, resulted in reduction in steatorrhea in all patients, with four of the six having complete resolution.[32] However, in the dosage used (30,000 units of pancreatic lipase), the combination of enteric-coated pancreatin and an antacid was no more effective than nonenteric-coated pancreatin alone in decreasing steatorrhea or improving duodenal enzyme delivery. It was concluded that the addition of an antacid may only be helpful in cases of EPI where individuals fail to respond to pancreatic replacement therapy alone.

Unlike pancreatic enzymes, bromelain has a relatively broad pH range in which it can remain effective (4.5-9.8),[33] providing proteolytic activity in the stomach as well as the small intestine. Consequently, bromelain can be used as a supplement in cases of pepsin and/or trypsin deficiencies, for example. Bromelain has been used in combination with pancreatic enzymes to facilitate digestion in cases of exocrine pancreatic insufficiency.[34] A formula consisting of ox bile, pancreatin, and bromelain lowered stool fat excretion in some patients with pancreatic steatorrhoea, and resulted in weight gain, as well as relief from pain, excess flatulence, and diarrhea.[35]

Fungal-derived lipase preparations may be beneficial in the treatment of malabsorption and steatorrhea under a wide variety of conditions.[3,36,37]

A crossover, randomized, controlled trial (RCT) compared the efficacy of 400 mg/day (4,800 lipase units) of lipase from *A. oryzae* with 10,000 mg/day (60,000 lipase units) of pancreatin on 11 pancreatectomized dogs.[3] Previously collected pre-operative data served as the control for the experiment. The animals, who varied in weight from 15-21 kg, were placed on a fixed diet that included 46 g/day of fat. Each treatment protocol lasted three weeks; the dogs were weighed and a three-day specimen collection to examine fecal fat excretion and stool volume was taken both at the beginning and end of the trial period. At the end of the study, no significant difference was observed in stool bulk and fecal fat excretion between pancreatin and plant-based lipase treated animals. However, both groups showed a significant reduction in stool bulk and fat excretion compared to the untreated group ($p<0.01$). It is interesting to note the disparity in dosage between the microbe-derived lipase (4,800 lipase units) and the conventional pancreatic preparation (60,000 lipase units) – both yielding essentially similar results.

A human crossover RCT of 17 patients with severe EPI and steatorrhea compared the effects of a nonenteric-coated pancreatic enzyme preparation (360,000 lipase units/day), an enteric-coated pancreatic enzyme preparation (100,000 lipase units/day), and a fungal enzyme preparation (75,000 lipase units/day).[37] The study subjects were divided into two groups based on surgical status – nine subjects had recently undergone Whipple's procedure (bowel resection with partial duodenopancreatectomy) and were in group A, while the remaining nonsurgical subjects were in group B. All three enzyme preparations yielded a significant ($p<0.05$) reduction in the total daily fecal fat excretion. In group A, the average reduction was 58 percent for the enteric-coated preparation (100,000 U lipase/day), 67 percent for the nonenteric-coated preparation (360,000 U lipase/day), and 54 percent for the fungal-based enzyme (75,000 U lipase/day). For group B the average reductions were 58-, 52-, and 46 percent, respectively. All three treatment preparations in both groups yielded significant reduction in total daily stool weight and total daily fecal fat excretion compared to controls. Again, it is interesting to note the disparity in the doses among the three preparations relative to the results. The fungal enzyme preparation produced similar benefit at three-fourths the dose of enteric-coated pancreatic enzyme and one-fifth the dose of the nonenteric-coated pancreatic enzyme preparation.

Lactose Intolerance

Another application for enzyme supplementation is management of lactose intolerance. It is estimated that 75 percent of individuals worldwide experience hypolactasia, or some decrease of lactase activity, especially during adulthood. The frequency of diminished lactase activity varies greatly, from nearly five percent in northern Europe to over 90 percent in parts of Asia and Africa;[38] in the United States, the prevalence is 6-15 percent. Typical symptoms associated with lactose intolerance are diarrhea, bloating, and gas, which can be alleviated with digestive enzyme supplementation.

It is important to note that often lactose intolerance presents with degrees of hypolactasia rather than an all-or-none type of response. Lactose intolerance symptoms are relative to the ability to produce lactase and the amount of lactose in the food consumed.

Lactose intolerance can be the result of damage to the intestinal lining by viral, bacterial, or autoimmune inflammatory responses.[39] Lactose intolerance may also be due to genetic factors resulting in a decrease or total absence of lactase production. A lactase gene has been identified, including a "wild-type" that is characterized by lactase nonpersistence – a physiological decline in intestinal lactase activity that often results in lactose intolerance.[40]

A study conducted on 48 healthy Guatemalan preschool children examined the efficacy of two different microbe-derived beta-galactosidase (lactase) preparations to prevent symptoms of lactose intolerance after consumption of whole cow's milk or milk prehydrolyzed with lactase enzyme.[41] One enzyme preparation was derived from the yeast, *Kluyveromyces lactis* (3,250 neutral lactose units), the other from *Aspergillus oryzae* (6,635 FCC lactose units). Prehydrolyzed milk was used as a standard of reference for effective lactose digestion. Each child, after ingestion of 240 mL whole milk containing 12 g lactose, was tested for degree of lactose via a hydrogen breath test. Although 27 of 48 children could not adequately digest whole milk, when given prehydrolyzed milk with lactase 25 of the 27 lactose-intolerant children showed no signs of maldigestion.

Hydrogen Breath Test

What is the hydrogen breath test?

The hydrogen breath test measures the amount of breath hydrogen and is used to diagnose digestive disorders, such as lactose intolerance. Colonic anaerobic bacteria produce hydrogen when exposed to unabsorbed sugars and other carbohydrates. It is common for a small amount of hydrogen to be produced from the limited amount of unabsorbed food that normally reaches the colon. However, large amounts of hydrogen can be produced when digestion is compromised, for example when inadequately digested food passes through the small intestine, resulting in more unabsorbed sugars and carbohydrates reaching the colon. High hydrogen output can also occur when colonic bacteria move back into the small intestine. In this instance, bacteria are exposed to unabsorbed food that has not been fully digested. Some of the hydrogen produced is absorbed into the bloodstream and travels to the lungs where the hydrogen is released and exhaled in the breath. Hydrogen breath testing is used to identify inadequate digestion of dietary sugars, including lactose, sucrose, fructose, and sorbitol. The second condition for which breath testing is used is for diagnosing bacterial overgrowth of the small bowel, a condition in which larger-than-normal numbers of colonic bacteria are present in the small intestine. The third condition for which breath testing is used is for diagnosing rapid passage of food through the small intestine. All three conditions may cause abdominal pain, bloating and distention, flatulence, and diarrhea.

How does hydrogen breath testing work?

A baseline breath hydrogen level is established by blowing into a balloon-type apparatus. The individual is then given pure lactose (typically 20-25 g) and readings taken every 15, 30, or 60 minutes for the next two to three hours. If hydrogen levels rise more than 20 ppm above the lowest preceding value within the test period, the patient is typically diagnosed as lactose intolerant, meaning they are not breaking down lactose. Methane output may also be measured. If the patient produces methane ≥12 ppm above the lowest preceding value, then they are considered to have malabsorption. If the patient produces both hydrogen and methane, then the values are typically added together and the mean of the numbers is used to determine whether the test is positive, usually at least 15 ppm above the lowest preceding value.

Lactose as a Supplement Diluent

Lactose is used as a diluent in numerous pharmaceutical and nutritional preparations, including in bromelain, papain, pepsin, and pancreatin. The U.S. Pharmacopoeia states that each milligram of National Formulary (N.F.) or U.S.P. pepsin should digest between 3,000 and 3,500 times its weight of coagulated egg albumin. When a pepsin with higher digestive activity is used it is mixed with lactose to reduce its digestive potency to the official standard.* Lactose is also the primary substance used to dilute U.S.P. pancreatin. Each milligram of U.S.P. pancreatin is standardized to contain no less than 25 U.S.P. units of amylase activity, 2.0 U.S.P. units of lipase activity, and 25 U.S.P. units of protease. Both pepsin and pancreatin preparations of higher digestive power are labeled as a whole number multiple (e.g., 2X, 3X).* Manufacturer analysis of raw pancreatin indicates the pure product displays not less than 9X of the U.S.P. value. Thus, one gram of pure pancreatin contains approximately 235,000-275,000 units of amylase activity, 220,000-270,000 units of protease activity, and 18,000-40,000 units of lipase activity.

**The United States Pharmacopeia* (22nd revision), The National Formulary (17th ed), United States Pharmacopeial Convention, Inc.: Rockville, MD;1990.

The 27 lactose-intolerant children were then given the enzyme preparations with whole milk. Both *K. lactis*- and *A. oryzae*-derived enzymes significantly reduced hydrogen breath excretion ($p<0.05$); the *K. lactis* preparation was 82 percent as effective, while the *A. oryzae* preparation was equally effective as the prehydrolyzed milk.

A crossover RCT was performed on 50 healthy adults who each ingested 360 mL cow's milk in one of three forms: intact milk, prehydrolyzed milk, and milk to which 1 g of *K. lactis*-derived enzyme (LactAid) was added before consumption.[42] Using breath hydrogen excretion testing, 25 subjects had incomplete carbohydrate digestion with intact milk. Adding enzyme five minutes before consumption yielded a 62-percent reduction in breath hydrogen excretion and symptoms of intolerance were significantly reduced.

In an RCT, 18 children (mean age 11 years) with lactose intolerance were given oral lactase tablets or placebo immediately after ingesting a lactose challenge solution.[43] Breath samples were taken for hydrogen analysis at 30-minute intervals for two hours, and clinical symptoms were monitored. Hydrogen production was significantly greater in the placebo group (maximum hydrogen excretion = 60 ppm) compared to the lactase group (maximum hydrogen excretion = 7 ppm). The increase in hydrogen excretion also correlated with increased physiological symptoms, including abdominal pain (89 percent), bloating (83 percent), and flatulence (44 percent). The results suggest concurrent ingestion of lactase enzyme tablets with lactose can significantly reduce breath hydrogen excretion and lactase deficiency symptoms.

The rationale for comparing the efficacy of enzyme tablets to prehydrolyzed milk is because prehydrolyzed milk requires refrigeration, which may not be readily available in developing countries. Lactase enzymes in pill form offer an added benefit because the individual can take the enzyme as needed with fresh whole milk.

Celiac Disease

Proteolytic enzymes such as papain are effective in some cases of gluten intolerance. Celiac disease is a digestive malabsorption disorder associated with an allergic response to foods containing gluten, a protein found in some grains, including wheat, rye, and barley. In one case study, oral papain was administered to an adult male celiac patient suffering from intestinal malabsorption who had partial atrophy of the intestinal wall.[44] Prior to therapy he was placed on a gluten-free diet, resulting in weight gain and symptom improvement; however, steatorrhea persisted. The patient began taking 1,800 mg of an enteric-coated papain enzyme tablet with each meal and was able to tolerate some gluten. After one month on this protocol, the patient no longer experienced loose stools and absorption normalized.

Toxicity and Side Effects

In general, enzyme side effects are few. Complications typically arise from either excessive dosing or allergic reaction to porcine substances, Aspergillus spp, or pineapple. In the case of excessive dosing, transient gastrointestinal upset may result. To avoid hypersensitivity reactions, it is best to confirm a patient is not allergic

Table 3. General Comparison of Amylase, Protease, and Lipase from Microbe-Derived Enzymes and Pancreatin

Enzyme	Microbe-derived	Pancreatin
Amylase	100 SKB	≈89 USP units
Protease	500 HUT	≈197 USP units
Lipase	100 LU	≈80 USP units

to the given enzyme source prior to use. Hyperuricosuria (excess uric acid in the urine) and hyperuricemia (excess uric acid in the blood) are associated with extremely high doses of exogenous pancreatic enzymes.[6]

Dosage Recommendations

Bromelain

As with any enzyme preparation, potency is a key factor in determining proper dosage. It is recommended to use bromelain with an enzymatic activity of at least 2,000 m.c.u/g (or 1,200 g.d.u./g) activity. Typical daily dosages range from 200-2,000 mg/day and most research has utilized four divided doses.[45] When used other than as a digestive aid, it has been suggested to ingest bromelain between meals, although research is unavailable to confirm enhanced efficacy of this approach.

Pancreatic and Microbe-derived Enzymes

For general malabsorption disorders the recommendation for enzyme supplementation ranges from 25,000-40,000 units of porcine lipase per meal, which is equivalent to 18,750-30,000 units of fungal-based lipase per meal. It is difficult to provide a dosage range, however, for either animal-based or microbe-derived enzymes due to variance in application, enzyme type, enzymatic activity, preparation strength, and patient requirements. Table 3 compares enzymatic activity of pancreatic and fungal-based enzymes.

Conclusion

Enzyme therapy provides safe treatment for digestive malabsorption disorders, such as exocrine pancreatic insufficiency and lactose intolerance. Animal-based enzymes serve as an established standard of care. The growing study of plant-based and microbe-derived enzymes offers great promise in advancing the benefits of digestive enzyme therapy.

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