HHS Public Access

Author manuscript

J Dig Dis. Author manuscript; available in PMC 2019 December 13.

Published in final edited form as:

J Dig Dis. 2018 November ; 19(11): 650–656. doi:10.1111/1751-2980.12655.

Enzyme therapy for functional bowel disease-like post-prandial distress

David Y. Graham[1,2], **Gyanprakash A. Ketwaroo**[1,2], **Mary E. Money**[3,4], **Antone R. Opekun**[1,2]

[1]Department of Medicine, Michael E. DeBakey VA Medical Center, Houston, Texas [2]Baylor College of Medicine, Houston, Texas [3]Department of Internal Medicine, University of Maryland School of Medicine, Baltimore, Maryland [4]Department of Internal Medicine, Meritus Medical Center, Hagerstown, Maryland

Abstract

Post-prandial gastrointestinal symptoms such as diarrhea, abdominal distension, flatulence, bloating and a feeling of fullness are common complaints of often unknown etiology and pathogenesis. There is a long history of trials reporting the successful use of products containing a variety of combinations of digestive enzymes including a number of randomized placebo-controlled trials. We provide a narrative review of studies describing the use of multi-digestive enzymes for symptoms consistent with irritable bowel syndrome. We describe clinical trials reported over the past 60 years including double-blinded randomized, placebo-controlled studies and recent trials that focused on post-prandial diarrhea consistent with diarrhea-predominant irritable bowel syndrome. Disaccharidase deficiencies or deficiencies of other carbohydrate digesting enzymes were excluded. Worldwide studies have generally reported success with multi-enzyme preparations although none used a factorial design to identify subgroups or attempted to link specific symptom responses to specific components of therapy. Although there is a long history of the successful use of multi-enzyme preparations for post-prandial symptoms consistent with irritable bowel syndrome, long-term studies using validated scoring systems and factorial designs are needed to confirm the results for specific symptoms and the components of the combination drugs received.

Keywords

diarrhea; digestive enzyme; fecal elastase-1; irritable bowel syndrome; post-prandial distress; therapy

Correspondence David Y. Graham, Michael E. DeBakey Veterans Affairs Medical Center, Room 3A-318B (111D), 2002 Holcombe Boulevard, Houston, TX 77030. dgraham@bcm.edu.

Conflict of interest

Drs. Ketwaroo and Money have no relevant disclosures.

1 | INTRODUCTION

Post-prandial gastrointestinal symptoms or post-prandial distress or diarrhea have long been a cause of suffering and have typically been ascribed to dietary indiscretion such as the type, temperature, volume and rate of food ingestion. This is coupled with the notion that these symptoms are somehow linked to an individual's inability to digest some foods. The concept of poor digestion underlies the widespread use, availability and proliferation of digestive aids such as herbal remedies and liqueurs (e.g., Mirto™, a Sardinian digestive liqueur). People have long sought digestive aids in the belief that they provide as yet unidentified missing ingredients that promote discomfort-free digestion. More recently, the tendency has been to prescribe elimination diets, which have shown some benefits.[1]

Although there are descriptions of pancreatic dysfunction in elderly patients and those with celiac disease, Crohn's disease and diabetes, there are few objective data on the benefits of pancreatic enzymes for treating such patients.[2] Interest has recently been renewed over the use of enzymes with symptoms consistent with meal-associated irritable bowel syndrome, especially those with the diarrhea-predominant irritable bowel syndrome (IBS-D).[3–5]

Here, we review the three groups of patients who may benefit from enzyme therapy, i.e., those with foregut irritable bowel syndrome-like symptoms, those with meal-associated dyspepsia (e.g., abdominal distension, belching, abdominal pain, abdominal distension and epigastric burning) and those with IBS-D-like symptoms. We exclude those with well-recognized conditions such as deficiencies of disaccharidases or other carbohydrate-digesting enzymes (e.g., lactase, trehalase and sucrase-isomaltase) which may have a similar presentation. The role of acquired mucosal disaccharidase deficiencies is still relatively uninvestigated and further studies are warranted.[6,7]

Most of the patients we describe would be classified as having functional bowel syndrome using the Rome IV criteria.[8] With an estimated global prevalence of 11.2%, functional bowel syndromes are common, which results in many patients seeking medical help because of these symptoms.[9] The Rome IV classification defines irritable bowel syndrome as "recurrent abdominal pain, on average, at least 1 day/ week in the last 3 months associated with two or more of the following criteria: related to defecation, associated with a change in frequency of stool, and associated with a change in form (appearance) of stool."[8] The Rome criteria are designed to identify specific subgroups so that those with similar characteristics can be studied. The classification is based on phenotypical criteria and many Rome criteria have been validated with "validated" meaning that when patients with the defined criteria are seen there is a high probability that most practitioners would agree that they had been categorized correctly. Phenotypical criteria lump together conditions based on superficial characteristics without any claim to provide an etiological separation, and thus the diagnosis can never be accurate in the terms of etiology or pathophysiology. One goal of using the Rome criteria is to identify groups of patients with specific characteristics that allow further differentiation, eventually leading to the enteropathogenesis and a specific therapy without excessive and unfruitful diagnostic testing.

Functional bowel diseases can be subdivided into those where symptoms appear to arise from the foregut (the esophagus and stomach, or functional dyspepsia) or hindgut (the small intestine and colon, or irritable bowel syndromes). Most studies on the therapeutic use of enzymes have used combination products that contain pancreatic and other enzymes and digestive aids and have dealt with post-prandial symptoms, including abdominal pain, flatulence, bloating, eructation, feeling of fullness, loss of appetite and diarrhea. Recent studies have focused on post-prandial diarrhea syndromes (see below).

2 | PANCREATIC FUNCTION IN IRRITABLE BOWEL SYNDROME-LIKE CONDITIONS

Unexplained abdominal pain is one reason for referring patients to gastroenterologists. Pain is a symptom of many abdominal diseases, including functional bowel syndromes. One study published in 1991 of 22 patients with endoscopically confirmed functional dyspepsia used Lundh's meal as the pancreatic function test. Six patients had abnormal results.[10] The pain pattern among those with abnormal results differed from the pain of typical irritable bowel syndrome as it was more often described as radiating through to the back and waking them from sleep and less likely to be post-prandial.[10] Distinguishing between pancreatic pain and pain related to irritable bowel syndrome has become easier since the introduction of more accurate tests such as computed tomography or endoscopic ultrasound.[11–13] Currently, assessment for pancreatic disease is often included in the evaluation of those with suspected functional dyspepsia especially if the pain pattern or other features are atypical.

Recent studies of patients with clinical symptoms consistent with IBS-D have suggested that a subset of those might have pancreatic dysfunction, based on the presence of an abnormal level of fecal elastase-1.[3,4] The use of fecal biomarkers in the evaluation of patients with functional bowel disease has resulted in the discovery of abnormal fecal elastase-1 levels in some patients meeting the Rome criteria for IBS-D.[4,14,15] Elastase-1 is produced by the pancreas and appears largely intact in the stool, where it can be easily measured. The normal result of elastase-1 is >200 μ/g feces and levels below 100 μ/g feces are highly suggestive of pancreatic insufficiency. Values between 100 and 200 μ/g feces are considered indeterminate. Because they are concentration-dependent, the results are often inaccurate when unformed stools are tested.[16] Clinical interpretation depends on the pretest probability. A retrospective review of over 3000 patients meeting the Rome III criteria for irritable bowel syndrome found low fecal elastase level, with a frequency of 5% to 13%.[15] Talley et al examined fecal elastase-1 levels in those with IBS-D and found abnormal levels in only 4.6%.[17] A recent review and meta-analysis of fecal elastase testing in the diagnosis of exocrine pancreatic insufficiency concluded that the false-negative rate was 1.1% and the false-positive rate was 11%.[18] In a low pretest probability condition such as IBS-D, most positive tests are likely to be false positive, especially when the stool tested is not formed.[16,18]

Tests of pancreatic function other than fecal elastase-1 have been studied in patients with irritable bowel syndrome-like symptoms. One recent study suggested that the postprandial symptoms felt in the lower part of the epigastrium were associated with a urinary test of

pancreatic insufficiency measured by low urinary excretion of para-aminobenzoic acid (PABA).[19] Values below 70% excretion were found in 71.4% of those with post-prandial epigastric fullness, 69.6% of those with epigastric pain and 81.3% of those with diarrhea. No patient had abnormal abdominal X-ray examination, computed tomography or ultrasonography suggestive of chronic pancreatitis. Importantly, there was no control group and the *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid (BT-PABA) test is known to have a high false-positive rate.[20] However, it is interesting that BT-PABA test results have been shown to correlate with cine-dynamic magnetic resonance cholangiopancreatography in relation to the distance and frequency of pancreatic juice discharge (see below).[21]

3 | RESULTS OF ORAL ENZYME THERAPY

Most published studies of post-prandial irritable bowel syndrome-like syndromes have used oral therapy with combination products that contain pancreatic enzymes and other ingredients thought to possibly improve digestion of difficult-to-hydrolyze substances (e.g., hemicellulase and lactase). An example of a typical early study was entitled *"The use of bile acids and pancreatic enzyme substitute in the treatment of 'functional indigestion'"* and involved 32 patients.[22] The digestive aid used contained pancreatic enzymes, bile salts, betaine hydrochloride (a gastric acid supplement) and hemicellulase. The average fecal fat (15.7 g/24 h) and fecal nitrogen excretion (5.6 g/24 h) were considered normal before therapy and were unchanged by therapy. However, 16 (73%) patients reported good to excellent symptomatic results compared with only one of 10 receiving a placebo ($P \leq 0.02$ when analyzed by the Fisher's exact test).[22]

During the 1970s many such studies were published. Most were open-label but a few were placebo-controlled and double-blinded. Overall, they reported treatment success for the wide variety of digestive complaints assessed (reviewed by Graham[23]). Studies continue to be published. A recent example is a post-marketing surveillance study from India with a large sample size including 2125 patients with functional dyspepsia. It was not placebo-controlled. The effect of the multi-enzyme preparation was scored for the reduction of flatulence, bloating, eructation, feeling of fullness, gastroesophageal reflux disease and loss of appetite and as a composite score. The composite symptoms score fell from 6.34 at baseline to 0.57 after 2 weeks of treatment.[24] Another example is a study with a dual-layer tablet, Combizym (Daiichi-Sankyo Europe, Germany), which has an outside layer containing an extract of *Aspergillus oryzae* with cellulase, protease and amylase activity and an inner core of pancreatin.[25] The study was a randomized and placebo-controlled crossover study with 151 patients. The authors reported that the active product was statistically superior to a placebo for abdominal distension, belching, diarrhea, abdominal pain and epigastric burning, but not for constipation. This result was consistent with early studies of the same product.[1,24,26,27] No studies have been performed to identify which components were likely to be responsible for the treatment success.

4 | MEAL-ASSOCIATED DIARRHEA OR IBS-D-LIKE SYNDROMES AND PANCREATIC ENZYME THERAPY

The association of low fecal elastase level and IBS-D-like presentation has prompted therapeutic trials with pancreatic and other enzymes.[4] Leeds et al analyzed 314 patients with the diagnosis of IBS-D and found that 19 (6.1%) had low fecal elastase-1 levels. They found that pancreatic enzyme supplementation with Creon® (Solvay, Brussels, Belgium) resulted in a statistically significant improvement in stool frequency, consistency and reduction of abdominal pain in patients with low fecal elastase level but not in those normal fecal elastase-1 levels.[4] This result suggests that low fecal elastase-1 level in IBS-D may imply a dysfunction in the secretion of pancreatic enzymes. It would be interesting to determine if the reports of abnormal BT-PABA tests and the correlation with cine-dynamic magnetic resonance cholangiopancreatography in relation to the distance and frequency of pancreatic juice discharge also holds true for fecal elastase-1.

Money et al reported the effect of supplemental enzymes in a 74-year-old woman with a diagnosis of IBS-D in relation to food triggers. The patient had amelioration of her symptoms with the use of pancreatic enzymes (uncoated Viokase; Axcan Pharma, Mont-Saint-Hilaire, Quebec, Canada) by taking one to three capsules as needed before consuming foods recognized to cause post-prandial diarrhea.[5] The patient' s symptoms were clearly related to food triggers (Tables 1 and 2). She had a minimally increased fecal fat (i.e., normal was defined as <7 g/24 h) as her fecal fat excretion during meals with food triggers was 10 g/24 h with IBS-D, 7.5 g/24 h with food triggers and supplemental enzyme use, and 8.8 g/24 h with no food triggers.[5] The authors also performed a pilot study of 49 patients with post-prandial diarrhea with known food triggers who were randomized to placebo or pancrealipase (uncoated Viokase containing lipase 8000 USP, amylase 30 000 USP and protease 30 000 USP; Axcan Pharma).[28] The therapy could be titrated up by the patient from one to three capsules taken before consuming known trigger meals, defined as meals reliably associated with urgent post-prandial diarrhea. Pancreatic enzyme therapy resulted in the significant relief of cramping, bloating, borborygmus, nausea, number of stools and urgency to defecate compared with placebo.[28]

A fecal elastase-1 level of <200 μ/g stool was found in four (6.7%) of 60 stool samples tested. The lowest was 112 μ/g stool. Overall, 61% of the patients ($P = 0.078$) chose pancrelipase as the effective agent. Interestingly, three of the four with low fecal elastase-1 chose the placebo.[28] As previously noted, low fecal elastase-1, especially in low pretest probability groups, has a high false-positive rate (i.e., "in low pretest probability conditions such as irritable bowel syndrome with diarrhea one should expect a high false-positive rate").[18] Possibly, the combination of low fecal elastase-1 and definite food triggers for pain and diarrhea may identify a subgroup of individuals whose pancreatic secretion is adversely affected by food triggers.

Money et al also described their experience with enzyme therapy in a retrospective analysis of 104 patients presenting with irritable bowel syndrome-like symptoms over a 10-year period.[28] For those without obvious pancreatic insufficiency the authors recommended taking one or two capsules of an over the counter vegetal analogue, Essential Enzymes 500

(Source Naturals, Scotts Valley, CA, USA) immediately before each meal. This is an inexpensive combination product containing a vegetal analogue of pancreatin with acid-stable protease (4375 USP units), lipase (375 USP units), a-amylase (2614 USP units), as well as amyloglucosidase, cellulase, hemicellulase and lactase, which clinically seemed to be interchangeable with the original Viokase for the treatment of IBS-D with clear trigger symptoms. There were 86 patients with follow-up data, of whom 71 (82.5%) reported an improvement or elimination of their symptoms. After a median of 3.7 years half patients were still using this enzyme therapy on demand.[28] Subsequently, the authors have continued to suggest this treatment as the first-line therapy for individuals who experience more frequent stools, including diarrhea, after eating, whether pain is present or not and they report substantial improvement for most.

As described above, a number of studies including double-blinded placebo-controlled studies report a beneficial effect of oral enzyme therapy of patients with functional dyspepsia-like and IBS-like presentations. There are a number of important details that are lacking. For example, we lack precise data on which symptoms or group of symptoms are most likely to respond to a particular therapy. This level of detail is needed in order to use a factorial design to tease out the components responsible for treatment success. As noted above, it has been suggested that low fecal elastase may be a biomarker that identifies patients with IBS-D-like conditions who are most likely to respond to enzyme therapy. Also as noted above, an abnormal urinary test of pancreatic insufficiency, the BT-PABA test, correlates with cine-dynamic magnetic resonance cholangiopancreatography in relation to the distance and frequency of pancreatic juice discharge. All biomarkers are plagued by a high proportion of false-positive tests in low pretest probability situations. Their predictive value can be improved by improving the pretest probability by defining the condition more accurately or by showing concordance of two different tests with different mechanisms (e.g., fecal elastase and BT-PABA urine test positivity), or both. There are few data to suggest that significant pancreatic insufficiency with fat malabsorption is a major culprit, as tests for structural pancreatic damage (e.g., using computed tomography) are typically normal. Furthermore, studies claiming treatment success have used small doses of uncoated enzymes where much of the lipase is destroyed in the stomach, or with combination products that contain very little lipase. Overall, these data suggest that disordered regulation or secretion of a pancreatic enzyme could be present and that treatment success is likely to be due to components other than lipase.

Reported treatment success has often been obtained with combination products that contain enzymes capable of digesting complex carbohydrates and carbohydrate maldigestion and malabsorption are well recognized as irritable bowel syndrome-imitators, such as those seen with fructose malabsorption and starch, sucrose, lactose and trehalose maldigestion.[7,28–31]

Fats and carbohydrates in modern diets have continued to change as highly processed foods occupy an increasing proportion of our diet. For example, trehalose has become an increasing component of the diet, especially in processed and fast foods.[32] The prevalence of trehalase insufficiency is presumed to be low in human beings and their microbiomes have not been subjected to high amounts of it in the past.[33] Major sources of carbohydrates and

fats include high fructose corn syrup and palm oil, which are indigestible and must be highly processed before being added to foods.[34]

5 | RECOMMENDATIONS FOR FUTURE STUDIES

We recommend that future studies attempt to identify specific symptoms or groups of symptoms that respond reliably to specific therapies and can be confirmed in randomized double-blinded trials. Then, factorial designs may be used to isolate and identify the important factors that may be responsible for the relief of a specific symptom or group of symptoms. Similarly, studies of the prevalence of putative biomarkers are of limited value unless they can be reliably linked to a pathophysiological or treatable condition. Fecal elastase-1 is a good example. Data that are typically lacking are whether the stools were formed and whether the abnormal results can be confirmed or correlated with a response to therapy. For example, Leeds et al showed that those with diarrhea and a low fecal elastase-1 level were more likely to respond to enteric-coated pancreatin than patients with a similar presentation and a normal fecal elastase-1 level.[4]

Ran et al tested a combination product containing an extract of *Aspergillus oryzae* with cellulase, protease and amylase activity along with an inner core of pancreatin[25] and found it relieved abdominal distension, belching, diarrhea, abdominal pain and epigastric burning, but not constipation. Studies in which the symptoms are grouped (e.g., abdominal distension and belching only) are needed to define groups for subsequent study. The principle of the Rome criteria is to try to identify precisely subgroups for study and we may possibly start by using the Rome criteria and then proceed, based on factorial design, to allow the generation and testing of hypotheses.

Overall, the data support the notion that patients with a variety of post-prandial abdominal complaints, such as combinations of abdominal distension, belching, diarrhea, abdominal pain, epigastric burning, flatulence, bloating, eructation, a feeling of fullness, loss of appetite and diarrhea, but usually not constipation, often obtain relief using low doses of combination products containing a variety of enzymes, including pancreatin. Similar results have been reported in the USA, Europe, India and China. Many patients in the USA have come to the attention of medical specialists because of diarrhea, some of whom have low fecal elastase-1 level, but objective evidence of pancreatic disease is generally lacking.

Such patients with postprandial abdominal complaints are common and easy to identify but data are lacking as to whether they can be reliably separated into groups with similar features and with similar and different responses to therapy. Studies with probiotics have shown that participants with irritable bowel syndrome have a reduction in some but not all symptoms, including flatulence, abdominal pain and constipation, but excluding bloating.[35] These critical data are missing from the enzyme studies that would allow one to investigate the pathophysiology relief obtained from specific symptoms. Subsequent studies should attempt to identify whether patients fall into separate clusters of symptoms and whether the results are reliably reproducible in double-blind challenges. There are a number of validated forms designed to study the response to therapy in patients with irritable bowel syndrome that may be used.[36–40] Since the regimens typically contain many different components,

such studies should utilize a factorial design to try to identify which component or components may be responsible for treatment success and whether the results are similar for different symptom clusters. Such studies would provide both a scientific basis for these therapies and also insights into the pathophysiology of the conditions leading to causal studies. The problem of post-prandial symptoms is common and the identification of a reliable and successful treatment program would be appreciated by large numbers of individuals.

ACKNOWLEDGMENTS

Dr. Graham received partial research support by the Research Service Department of Veterans Affairs and Public Health Service grant DK56338, which funds the Texas Medical Center, Digestive Diseases Center.

Dr. Graham is a consultant for RedHill Biopharma for novel *H. pylori* therapies and has received research support for the culture of *H. pylori.* He is the principle investigator of an international study of the use of antimycobacterial therapy for Crohn's disease. He is also a consultant for BioGaia in relation to probiotic therapy for *H. pylori* infection and for Takeda in relation to *H. pylori* therapies. Mr. Opekun has received grant support from QOL Medical LLC in relation to disaccharidase therapies.

Funding information

National Institute of Diabetes and Digestive and Kidney Diseases, Grant/Award Number: DK56338

REFERENCES

1. Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology. 2014;146:67–75.e5. [PubMed: 24076059]
2. Singh VK, Haupt ME, Geller DE, Hall JA, Quintana Diez PM. Less common etiologies of exocrine pancreatic insufficiency. World J Gastroenterol. 2017;23:7059–7076. [PubMed: 29093615]
3. Kellow JE. IBS: do we need to exclude exocrine pancreatic insufficiency in IBS? Nat Rev Gastroenterol Hepatol. 2010;7:479–480. [PubMed: 20811362]
4. Leeds JS, Hopper AD, Sidhu R, et al. Some patients with irritable bowel syndrome may have exocrine pancreatic insufficiency. Clin Gastroenterol Hepatol. 2010;8:433–438. [PubMed: 19835990]
5. Money ME, Hofmann AF, Hagey LR, Walkowiak J, Talley NJ. Treatment of irritable bowel syndrome-diarrhea with pancrealipase or colesevelam and association with steatorrhea. Pancreas. 2009;38:232–233. [PubMed: 19238028]
6. Opekun AR, Balesh AM, Shelby HT. Use of the biphasic ^{13}C-sucrose/glucose breath test to assess sucrose maldigestion in adults with functional bowel disorders. Biomed Res Int. 2016;2016:7952891.
7. Henstrom M, Diekmann L, Bonssslio F, et al. Functional variants in the sucrose—isomaltase gene associate with increased risk of irritable bowel syndrome. Gut. 2018;67:263–270. [PubMed: 27872184]
8. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology. 2016;150: 1262–1279.e2.
9. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012;10: 712–721.e4. [PubMed: 22426087]
10. Smith RC, Talley NJ, Dent OF, Jones M, Waller SL. Exocrine pancreatic function and chronic unexplained dyspepsia. A case-control study. Int J Pancreatol. 1991;8:253–262. [PubMed: 2051063]
11. Anaizi A, Hart PA, Conwell DL. Diagnosing chronic pancreatitis. Dig Dis Sci. 2017;62:1713–1720. [PubMed: 28315036]

12. Trikudanathan G, Vega-Peralta J, Malli A, et al. Diagnostic performance of endoscopic ultrasound (EUS) for non-calcific chronic pancreatitis (NCCP) based on histopathology. Am J Gastroenterol. 2016;111:568–574. [PubMed: 26952577]
13. Dimastromatteo J, Brentnall T, Kelly KA. Imaging in pancreatic disease. Nat Rev Gastroenterol Hepatol. 2017;14:97–109. [PubMed: 27826137]
14. Parsons K, Goepp J, Dechairo B, et al. Novel testing enhances irritable bowel syndrome medical management: the IMMINENT study. Glob Adv Health Med. 2014;3:25–32.
15. Emmanuel A, Landis D, Peucker M, Hungin AP. Faecal biomarker patterns in patients with symptoms of irritable bowel syndrome. Frontline Gastroenterol. 2016;7:275–282. [PubMed: 27761231]
16. Struyvenberg MR, Martin CR, Freedman SD. Practical guide to exocrine pancreatic insufficiency - breaking the myths. BMC Med. 2017;15:29. [PubMed: 28183317]
17. Talley NJ, Holtmann G, Nguyen QN, et al. Undiagnosed pancreatic exocrine insufficiency and chronic pancreatitis in functional GI disorder patients with diarrhea or abdominal pain. J Gastroenterol Hepatol. 2017;32:1813–1817. [PubMed: 28332731]
18. Vanga RR, Tansel A, Sidiq S, El-Serag HB, Othman MO. Diagnostic performance of measurement of fecal elastase-1 in detection of exocrine pancreatic insufficiency: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018;16:1220–1228.e4. [PubMed: 29374614]
19. Fujikawa Y, Tominaga K, Tanaka F, et al. Postprandial symptoms felt at the lower part of the epigastrium and a possible association of pancreatic exocrine dysfunction with the pathogenesis of functional dyspepsia. Intern Med. 2017;56:1629–1635. [PubMed: 28674349]
20. Kitagawa M, Naruse S, Ishiguro H, Nakae Y, Kondo T, Hayakawa T. Evaluating exocrine function tests for diagnosing chronic pancreatitis. Pancreas. 1997;15:402–408. [PubMed: 9361095]
21. Yasokawa K, Ito K, Tamada T, et al. Noninvasive investigation of exocrine pancreatic function: feasibility of cine dynamic MRCP with a spatially selective inversion-recovery pulse. J Magn Reson Imaging. 2015;42: 1266–1271. [PubMed: 25847877]
22. Rider JA. The use of bile acids and pancreatic enzyme substitutes in the treatment of ‘functional indigestion’. Am J Gastroenterol. 1960;33:734–739.
23. Graham DY. Enzyme therapy of digestive disorders In: Holcenberg JS, Roberts J, eds. Enzymes as Drugs. New York, NY: Wiley; 1981:331–351.
24. Khandke DA, Jain SK, Shirsath PA. Post-marketing surveillance study to assess the efficacy and tolerability of Al5zyme — a multienzyme preparation in patients with functional dyspepsia. Ind Med Gaz. 2013;181–191.
25. Ran ZH, Yuan YZ, Li ZS, et al. The efficacy of Combizym in the treatment of Chinese patients with dyspepsia: a multicenter, randomized, placebo-controlled and cross-over study: Shanghai Combizym Clinical Cooperative Group. JDigDis. 2009;10:41–48.
26. Kataria MS, Bhaskarrao D. A clinical double-blind trial with a broad spectrum digestive enzyme product (‘Combizym’) in geriatric practice. Br J Clin Pract. 1969;23:15–17. [PubMed: 4884205]
27. Moosauer M. High-dose enzyme-substitution therapy in digestive disorders. Fortschr Med. 1976;94:1815–1817. (in German). [PubMed: 1002087]
28. Money ME, Camilleri M. Review: management of postprandial diarrhea syndrome. Am J Med. 2012;125:538–544. [PubMed: 22624684]
29. Cohen SA. The clinical consequences of sucrase-isomaltase deficiency. Mol Cell Pediatr. 2016;3:5. [PubMed: 26857124]
30. Ford AC, Vandvik PO. Irritable bowel syndrome: dietary interventions. BMJ Clin Evid. 2015;2015:0410.
31. Robayo-Torres CC, Baker SS, Chumpitazi BP, Lecea CE, Nichols BL Jr, Opekun AR. Poor starch digestion in children with CSID and recurrent abdominal pain. J Pediatr Gastroenterol Nutr. 2012;55 suppl 2:S32–S34. [PubMed: 23103649]
32. Richards AB, Krakowka S, Dexter LB, et al. Trehalose: a review of properties, history of use and human tolerance, and results of multiple safety studies. Food Chem Toxicol. 2002;40:871–898. [PubMed: 12065209]
33. Bergoz R, Vallotton MC, Loizeau E. Trehalase deficiency. Prevalence and relation to single-cell protein food. Ann Nutr Metab. 1982;26:291–295. [PubMed: 7137952]

34. Crister G. Fat Land. New York, NY: Mariner Books; 2003.
35. Liu Y, Tran DQ, Rhoads JM. Probiotics in disease prevention and treatment. J Clin Pharma. 2018; [Epub ahead of print].
36. Rabeneck L. Measuring dyspepsia-related health in randomized trials: the severity of dyspepsia assessment (SODA) and its use in treatment with NSAIDs and COX-2-specific inhibitors. Rheumatology (Oxford). 2003; 42 suppl 3:iii32–iii39. [PubMed: 14585916]
37. El-Omar EM, Banerjee S, Wirz A, McColl KE. The Glasgow dyspepsia severity score—a tool for the global measurement of dyspepsia. Eur J Gastroenterol Hepatol. 1996;8:967–971. [PubMed: 8930560]
38. Leidy NK, Farup C, Rentz AM, Ganoczy D, Koch KL. Patient-based assessment in dyspepsia: development and validation of Dyspepsia Symptom Severity Index (DSSI). DigDis Sci. 2000;45:1172–1179.
39. Hu WH, Lam KF, Wong YH, et al. The Hong Kong index of dyspepsia: a validated symptom severity questionnaire for patients with dyspepsia. J Gastroenterol Hepatol. 2002;17:545–551. [PubMed: 12084027]
40. De Luca L, Zagari RM, Pozzato P, et al. Measuring dyspepsia: a new severity index validated in Bologna. Dig Liver Dis. 2004;36:806–810. [PubMed: 15646426]

TABLE 1

Symptom checklists used by Mary Money, MD to identify patients with food triggers

1a. **Questionnaire for increased bowel movements association with eating.**

1. Do most of your bowel movements occur when you have **not** eaten or have been fasting?

   a._____yes

   b._____no

2. Why do you think you have frequent bowel movements? (check all that apply).

   a._____ not sure

   b._____with eating

   c._____stressful situations

   d._____other_____

3. What percentage of the increased bowel movement episodes that you have **each week** is due to *only* **stress**?

   a. _____not applicable, I do not have bowel movements due to stress.

   b. _____not applicable, I do not have episodes associated with stress weekly

   c. _____less than 25%

   d. _____at least 25% but less than 50%

   e. _____at least 50% but less than 75%

   f. _____more than 75%

4. Do you have to eat a certain type of meal or food to have an episode of increased bowel movements or does this happen with anything that you eat? (Check all that apply).

   a. _____not applicable, the increased bowel movements do not occur after eating.

   b. _____it happens every time that I eat.

   c. _____it happens only sporadically when I eat.

   d. _____I do not know when it will occur with eating.

   e. _____I frequently can guess when it might occur if I eat a particular substance or meal that acts like a laxative.

5. During an average week, how many episodes of increased bowel movements occur?

   a. _____fewer than 1

   b. _____1–2 usually

   c. _____3–4 usually

   d. _____5 or more usually

6. During an **average week**, how **many** episodes of increased bowel movements after **eating** (versus stress) do you typically experience?

   a. _____fewer than 1

b. _____1–2 usually

c. _____3–4 usually

d. _____5 or more usually

7. Are you able to **identify certain foods** that cause you to have increased bowel movements?

a. _____yes

b. _____no

8. Please list the worse food triggers below:

Worse triggers: _____

_____

_____

TABLE 2

Check list for identifying potential food triggers

Fruits

	Apples or pears
	Apricots
	Bananas
	Black berries
	Cantaloupe
	Honey Dew Melon
	Oranges
	Pears
	Peaches
	Plums
	Prunes
	Other fruits (please specify):

Vegetables

	Beans (pinto, baked, black, etc)
	Asparagus
	Broccoli
	Brussels sprouts
	Cabbage
	Carrots
	Cauliflower
	Corn
	Cucumber
	Egg plant
	Green beans
	Lima Beans
	Lentils
	Lettuce (Please specify type): _____
	Mushrooms
	Peas
	Peppers (green/red/ NOT hot)
	Spinach
	Sweet potatoes
	Tomatoes
	White potatoes
	Winter Squash
	Yellow summer squash
	Zucchini
	Other vegetables (please specify):

Spices or Seasonings

	Garlic
	Black pepper
	Cinnamon
	Onion
	MSG
	Hot peppers
	Mustard
	Ketchup
	Steak sauces
	Soy sauce
	Teriyaki Sauce

Dairy

	Milk
	Yogurt
	Ice cream
	Cottage cheese
	Hard cheese
	Butter
	Margarine
	Cream (in coffee)
	sour cream
	Other diary (please specify):

Beverages

	Coffee (not decaffeinated)
	Tea
	Cola or other soft drinks (pop)
	Diet cola or other diet soft drinks
	Beer
	Wine
	Liquor
	Orange Juice

Restaurant Dining

	Chinese or Japanese food
	Creamed Dishes
	Italian food other than pizza
	Mexican food
	Cajun or other spicy, barbecued food
	Any Restaurant Meal

Meats and Eggs

	Fried chicken
	Grilled chicken
	Hamburgers
	Hot dogs
	Processed meats (usage, salami, bologna, etc.)
	Bacon
	Beef, pork or lamb
	Fish
	Seafood, (crabs, mussels, etc)
	Eggs
	Tuna Fish

Miscellaneous

	Pop corn
	Rice
	Pasta
	French fries
	Pizza
	Nuts
	Peanut butter
	Potato chips

Other Triggers:

(please specify):
