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Review: Management of Postprandial Diarrhea Syndrome

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ABSTRACT

Unexpected, urgent, sometimes painful bowel movements after eating are common complaints among adults. Without a clear etiology, if pain is present and resolves with the movements, this is usually labeled "irritable bowel syndrome-diarrhea" based solely on symptoms. If this symptom-based approach is applied exclusively, it may lead physicians not to consider treatable conditions: celiac disease, or maldigestion due to bile acid malabsorption, pancreatic exocrine insufficiency, or an a-glucosidase (sucrase, glucoamylase, maltase, or isomaltase) deficiency. These conditions can be misdiagnosed as irritable bowel syndrome-diarrhea (or functional diarrhea, if pain is not present). Limited testing is currently available to confirm these conditions (antibody screens for celiac disease; fecal fat as a surrogate marker for pancreatic function). Therefore, empirical treatment with alpha amylase, pancreatic enzymes, or a bile acid-binding agent may simultaneously treat these patients and serve as a surrogate diagnostic test. This review will summarize the current evidence for bile acid malabsorption, and deficiencies of pancreatic enzymes or a-glucosidases as potential causes for postprandial diarrhea, and provide an algorithm for treatment options.

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KEYWORDS: Bile acid malabsorption; Disaccharidase deficiency; Functional diarrhea; Glucosidase deficiency; Glucosidase inhibition; Irritable bowel syndrome; Maldigestion; Pancreatic insufficiency; Postprandial diarrhea; Trigger foods

Currently, the diagnosis of irritable bowel syndrome is based predominantly upon symptoms listed in **Table 1**, recurrent abdominal pain coinciding with changes in stool frequency or consistency. The symptom-based diagnosis stems from validation studies that contrasted symptoms with "organic" diseases. For example, in the classical paper of Manning et al,[1] there was a comparison of the symptoms of 32 irritable bowel syndrome patients and 33 with organic diseases: 13 duodenal ulcer; 5 inflammatory bowel disease; 4 gastroesophageal reflux; 2 gastric ulcer, gallstones, and carcinoma of the colon respectively; and 5 miscellaneous gastrointestinal disorders. Primary care physicians have been advised to make a positive, symptom-based diagnosis of irritable bowel syndrome,[2] although the diagnostic accuracy of the symptom-based criteria has not been validated in large patient cohorts where all structural organic diseases, or more subtle digestive disorders, had been definitively excluded.[3]

Although 50% of patients classified as having irritable bowel syndrome complain of postprandial diarrhea, symptom criteria for irritable bowel syndrome do not include the meal association.[4] In addition, there are physiological changes stimulated postprandially, such as intestinal secretion, and ileocolonic and proximal colonic transit that may contribute to symptoms including bloating, diarrhea, or urgency.[5-7]

The diagnostic work-up for these patients typically focuses on identifying medical conditions with easily detectable abnormalities such as Crohn disease, celiac disease, occult neoplasm, or microscopic colitis. Once these are excluded, physicians may diagnose irritable bowel syndrome based on symptoms. Without further testing of such recommendations, patients also may receive centrally acting medications (such as antidepressants) in an attempt to control the central perception of abnormal gastrointestinal functions. Conditions that may produce symptoms that mimic irritable bowel syndrome, such as bile acid malabsorption,

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maldigestion due to pancreatic insufficiency, food allergy, or starch/sugar maldigestion due to glucosidase insufficiency or inhibition, are not usually considered.[8,9] Consequently, patients may continue suffering, as illustrated in the case discussed below.

CASE REPORT

The patient, a 43-year-old woman, experienced episodes of diarrhea for approximately 11 years. They occurred 2-3 times weekly, approximately 2-4 hours after eating meals containing spices, corn, green beans, lima beans, oranges, cheese, salads, milk products, tomatoes, or garlic. Symptoms included cramping, which resolved after 3-5 watery, loose stools. Eating late might cause nocturnal attacks. Multiple family members, including her mother, had similar digestion problems. The patient was referred to a gastroenterologist. Colonoscopy, colon biopsies for microscopic colitis, serology for celiac disease, and small bowel follow-through were all normal. Therefore, the gastroenterologist diagnosed "irritable bowel syndrome-diarrhea" and recommended a probiotic. Because symptoms continued, her internist (author MEM) did additional tests: a Sudan stool test for fat (positive) and a fecal elastase-1 test screening for pancreatic exocrine insufficiency (normal). Subsequently, pancrelipase (PES) was prescribed before eating any "trigger meal." This treatment eliminated the symptoms. The patient has had no digestion problems since using PES "on demand" for the last 2 years.

CLINICAL SIGNIFICANCE

- A careful history of what precedes diarrhea is important.
- Postprandial diarrhea suggests a maldigestion problem: bile acid malabsorption, pancreatic insufficiency, or a glucosidase deficiency or inhibition.
- If diagnostic studies (including celiac antibodies) are negative, empirical treatment with alpha amylase, pancreatic enzymes, or bile acid binders (taken immediately before eating) is appropriate.
- Effectiveness of the above empiric treatment suggests a maldigestion condition.

DISCUSSION

The differential diagnosis of postprandial diarrhea symptoms includes a rapid colonic response to feeding,[4] food allergies or hypersensitivity, food intolerance, altered gut flora or small bowel bacterial overgrowth, fructose maldigestion,[10-13] and malabsorption. Food elimination diets or prolonged fasting may reduce symptoms to some degree.[14-17] Such patients may undergo tests to exclude malabsorption and to identify the underlying cause. When standard testing for celiac disease, Crohn disease, and microscopic colitis is negative, physicians may assume the patient is suffering a form of functional diarrhea or irritable bowel syndrome-diarrhea, and the therapeutic options offered are limited, often to the current mainstream treatments used in irritable bowel syndrome-diarrhea (**Table 2**).

However, there are 3 specific classes of disease causing postprandial diarrhea that respond to targeted therapy; in these patients, the therapeutic trial may serve as a surrogate diagnostic test when sensitive and specific tests are not available, as might occur in the primary care setting.

Table 1 Rome III Criteria for Irritable Bowel Syndrome[8]

The Rome III criteria, based only on symptoms, require that a patient experience recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months associated with 2 or more of the following:
Improvement with a bowel movement(s).
Onset of symptoms was associated with a change in the frequency of the stool(s) or
Onset of symptoms was associated with a change in the appearance of the stool(s).

From: Camilleri M. Do the symptom-based, Rome criteria of irritable bowel syndrome lead to better diagnosis and treatment outcomes? The con argument. *Clin Gastroenterol Hepatol.* 2009;8(2):129.[8]

Pancreatic Exocrine Insufficiency

Recently, pancreatic exocrine insufficiency was detected in 6.1% of patients who fulfilled the Rome II criteria for irritable bowel syndrome-diarrhea by measuring the stool concentration of fecal elastase-1 (FEC).[18] Frequently, diarrhea in diabetic patients is considered as being due to an autonomic defect, but pancreatic insufficiency has been identified by the presence of a reduced FEC concentration in both Type 1 and Type 2 diabetes in 56.7% and 35%, respectively.[19] In another study, 21.1% of 546 patients with diabetes mellitus requiring insulin were found to have pancreatic exocrine insufficiency based upon a FEC <100 μg/g.[20] The sensitivity of the FEC test (55%) compared with the secretin-cerulein test (which requires duodenal intubation and aspiration of duodenal contents following hormonal stimulation) for determining pancreatic exocrine sufficiency has been questioned. Measurement of FEC may not accurately diagnose mild pancreatic exocrine insufficiency, and a therapeutic trial of PES may still be helpful.[21]

Glucosidase Inhibition and Deficiency

Carbohydrates comprise a large percentage of most diets. Carbohydrates in the diet are complex entities and must be broken down into monosaccharides before they can be absorbed. Digestion starts with oral salivary amylase, followed by gastric amylase in the stomach until the amylase (which has a pH optimum of 7[22]) becomes inactive due to the low intragastric pH as a result of

Table 2 Current Treatment Recommendations for Irritable Bowel Syndrome-Diarrhea[2]

Bulking fiber agents
Lactase supplementation
Probiotics, antibiotics
Smooth muscle relaxants
Opioids: loperamide, diphenoxylate-atropine, deodorized tincture of opium
Serotonergic agents: 5-HT_3 antagonist (eg, alosetron)
Antidepressants: tricyclic agents
Bile acid binders: cholestyramine, colesevelam

From: Lacy BE, Weiser K, De Lee R. The treatment of irritable bowel syndrome. *Therap Adv Gastroenterol*. 2009;2(4):221-238.[2]

stomach acid secretion, and continues with small intestinal brush border glucosidases.

The glucosidases are divided into α-glucosidases: maltase, isomaltase, sucrase, glucoamylase, and trehalase; and a β-glucosidase: lactase. Lactase deficiency is a well-recognized cause of diarrhea, although it has been demonstrated that the load of lactose is a significant factor in determining whether an individual who is lactase-deficient will actually develop diarrhea. Thus, when lactose intake is limited to the equivalent of 240 mL or less of milk a day, symptoms are likely to be negligible in individuals who identify themselves as severely lactose-intolerant.[23] Symptoms identical to those of lactose intolerance may occur when starch is incompletely digested due to an inhibition or deficiency of α-glucosidases.

There is considerable research being conducted on the relationship between the phytochemicals (ie, chemical compounds that occur naturally in plants, and may affect health, but are not established as essential nutrients) in food and their effect on the human body. These substances may potentially reduce the incidence of cancer, cardiovascular disease, diabetes, and osteoporosis.[24] Over 1200 different plant species have been recognized as possible hypoglycemic agents by inhibiting amylase or glucosidases.[25] Food extracts with this effect have included berries, vegetables (including beans, corn, eggplant, and pumpkin), and some colored grains.[26] In vitro studies have demonstrated glucosidase inhibition with cinnamon extract,[27] certain tropical pepper spices,[28] basil extract,[29] certain strains of maize,[30] certain Indian spices,[31] the Welsh onion,[32] the Maitake mushroom (*Grifola frondosa*),[33] and chamomile tea.[34] A consequence of glucosidase inhibition includes abdominal symptoms: bloating and postprandial diarrhea. Drugs marketed to reduce hyperglycemia and complications of diabetes: acarbose (Precose; Bayer Healthcare Pharmaceuticals Inc., West Haven, Conn), miglitol (Glyset; Pfizer, New York, NY), and voglibose are associated with gastrointestinal side effects. In the STOP-Noninsulin Dependent Diabetes Mellitus international trial from 1995 to 2001, 29.5% of patients assigned to acarbose, compared with 18.2% using placebo, discontinued the drug because of adverse gastrointestinal tract effects: flatulence, diarrhea, and abdominal pain.[35] Quercetin, which is found in high concentrations in onions and garlic, is 5 times more potent than acarbose in α-glucosidase inhibition.[36]

Because the following food triggers identified by patients: spicy foods, onions, garlic, corn, and peppers, inhibit glucosidases in vitro, it is conceivable that the resultant postprandial diarrhea is due to inhibition of either amylase or an α-glucosidase.

Congenital Glucosidase Deficiencies. Glucosidase deficiency is recognized predominantly in children with congenital sucrase-isomaltase deficiency, a rare autosomal recessive genetic condition with which children cannot digest starch.[37] The prevalence of congenital sucrase isomaltase deficiency is estimated to be only 1 in 5000 patients of European descent, compared with 1 in 20 among those from Alaska, Canada, and Greenland. However, 2%-9% of European Americans have a partial deficiency in the enzyme activity due to heterozygosity for the gene mutation.[38] Other glucosidase deficiencies have been identified. A glucosamylase deficiency was identified in 3% of children with chronic diarrhea.[39] In 2002, Karnsakul et al reported that approximately 21% of children with recurrent abdominal pain syndrome (the equivalent of irritable bowel syndrome in adults), have an α-glucosidase deficiency that is not congenital sucrase isomaltase deficiency, and these children are unable to fully digest normal starches.[40]

Studies have identified adults with varied digestive problems, including intermittent postprandial diarrhea, to be deficient in one or more glucosidases.[41-43] Small bowel biopsies in adult patients with diarrhea have significantly lower levels of lactase, maltase, and sucrase when compared with those of patients with functional dyspepsia.[44] Steatorrhea has been reported with glucosidase deficiency,[45] consistent with the classical studies showing that steatorrhea may occur when diarrhea is induced by an osmotic laxative in healthy volunteers.[46] A recent study showed significant improvement in symptoms and quality of life in patients with diarrhea-predominant irritable bowel syndrome when prescribed a very low carbohydrate diet for 4 weeks.[47] It is unclear whether those patients had a subclinical form of glucosidase malabsorption.

Bile Acid Malabsorption

Bile acid malabsorption is significantly under-recognized and may account for approximately 30% of diarrhea previously diagnosed as irritable bowel syndrome-diarrhea or chronic functional diarrhea.[48] Unfortunately, confirmatory testing requires stool collection and the measurement of whole body retention of ^{75}Se-homocholic acid taurine, a gamma-emitting conjugated bile salt homologue, which is not available in the US. Although an intermediate in bile acid biosynthesis, 7α-OH-4-cholesten-3-one leaks from the hepatocyte into plasma in direct proportion to the rate of bile acid synthesis; measurement of this key intermediate is available in only a few academic centers at the current time.

Even when the ^{75}SeHCAT testing is available, only a small fraction of patients get tested.[49] It has recently been recognized that bile acid malabsorption may result from an overproduction of bile acids due to a defect in the feedback regulation of hepatocyte bile acid synthesis from the ileal hormone, fibroblast growth factor 19.[50] This reduced feedback regulation results in increased bile acid synthesis in the hepatocytes, increased passage of bile acids into the colon, and diarrhea because of the secretory effects of dihydroxy bile acids.

Even if there is no absolute increase in bile acids, their presence may cause diarrhea by affecting starch digestion. New research has identified that bile salts can bind to starch, which may inhibit starch digestion by pancreatic enzymes.[51]

Alternative Treatment Options for Postprandial Diarrhea

Because the 3 conditions discussed above are difficult to prove, empirical treatment with an over-the-counter alpha amylase supplement, PES, or a bile acid sequestrant is a reasonable option, especially when specific testing is not available, and when exclusion of "trigger" dietary factors cannot be identified or their exclusion does not solve the clinical problem.

How Effective is PES for Postprandial Diarrhea? PES is effective in reducing the diarrhea of patients with irritable bowel syndrome among patients with proven reduced fecal elastase as a marker of pancreatic insufficiency.[18] In addition, PES improved digestion in normal subjects consuming a fatty meal.[52] PES also reduced bile acid malabsorption in patients with cystic fibrosis[53,54] and chronic pancreatitis,[55] and improved fat malabsorption due to cystic fibrosis,[56] human immunodeficiency virus,[57] and the mild steatorrhea associated with the irritable bowel syndrome.[58] A large double-blind study comparing PES to placebo among patients with otherwise unexplained postprandial symptoms who have normal pancreatic exocrine function has not been conducted to date.

In a small double-blind, placebo-controlled, crossover pilot study involving 49 patients with irritable bowel syndrome-diarrhea, there was a reduction in postprandial symptoms among the irritable bowel syndrome-diarrhea patients who were willing to consume their "trigger meals." The primary end point was the number of patients who chose PES as the effective drug. In an intention-to-treat analysis, 30/49 (61%) patients chose PES ($P = .078$) as the effective drug. Analysis of patients who identified PES as the effective drug demonstrated a reduction ($P \leq .001$) of the following symptoms: bloating, cramping, borborygmi, urgency to defecate, and number and consistency of stools compared with the period when they received placebo.[59]

In a large internal medicine practice, PES has been used as first-line therapy for patients with postprandial diarrhea for the last 10 years. In a recent retrospective review of all patients with irritable bowel syndrome treated by one physician (author MEM), 104/144 patients received PES: median age 60 years (range: 17-95 years); 70% were female. Duration of symptoms ranged from 1 to 50 years; frequency of postprandial diarrhea ranged from daily to once monthly. Eighteen (17%) either never tried the medication or were lost to follow-up. Of the 86 patients with follow-up information, 71 (82.5%) reported that PES improved or eliminated their symptoms, while 15 (17.4%) reported no improvement. Approximately 15% reported mild constipation that was managed by a reduction in the frequency or amount of PES; 1 individual had an exacerbation of asthma; and 3 had worsening abdominal pain. After a median 3.7 years, 43 (50%) patients still take PES as needed upon "demand." Special testing was conducted with equal frequency in the responders and nonresponders: colonoscopies in 55 of 71 (77.5%) positive responders and 11 of 15 (73%) nonresponders; testing for celiac disease in 39 of 71 (54.9%) responders and 9 of 15 (60%) nonresponders. All of these tests were normal. Some patients are now using an over-the-counter enzyme supplement containing α-amylase with equal success at a considerable cost savings.

Why are Pancreatic Enzymes Effective? The mechanism for this apparent efficacy of PES in postprandial diarrhea is unknown unless there is pancreatic insufficiency as proven by a low fecal elastase-1 value. However, amylase, a component of PES, has been shown to augment glucosidases,[60] and any fat malabsorption that results from rapid transit or osmotic diarrhea (up to 14 grams of fat can be expected to be malabsorbed per day[46,61]) is potentially ameliorated by the lipase in PES. PES has not been shown to substantially affect gastrointestinal motility unless pancreatic insufficiency is present.[62,63] Direct measurements of pancreatic enzyme secretion in response to a meal have not been made.

How Effective is Bile Acid Sequestrant Therapy? An extensive review of 18 studies on the incidence of bile acid malabsorption in patients with irritable bowel syndrome-diarrhea based upon ^{75}SeHCAT retention testing was published in 2009. Therapy with a bile acid binder resulted in 96% improvement in the 10% of patients with severe bile acid malabsorption (SeHCAT $<5\%$), 80% improvement in the 32% with moderate (^{75}SeHCAT $<10\%$), and 70% improvement in the 26% with mild malabsorption (^{75}SeHCAT $<15\%$).[64] Habba[65] reported a 68% improvement in diarrhea with bile acid sequestrant therapy among patients labeled as having irritable bowel syndrome-diarrhea. The bile acid sequestrant, colesevelam, reduces the accelerated ascending colon transit in patients with irritable bowel syndrome-diarrhea;[66] the transit rate in the ascending colon is a determinant of stool consistency.

Some foods do not cause the diarrhea syndrome and may actually ameliorate these symptoms. Sun-dried raisins have been shown to lower total fecal bile acid concentration by a reduction in lithocholic and deoxycholic acid.[67] In addition, an extract of wine from the Jacquez grapes has been shown to inhibit the castor oil-induced diarrhea in mice.[68]

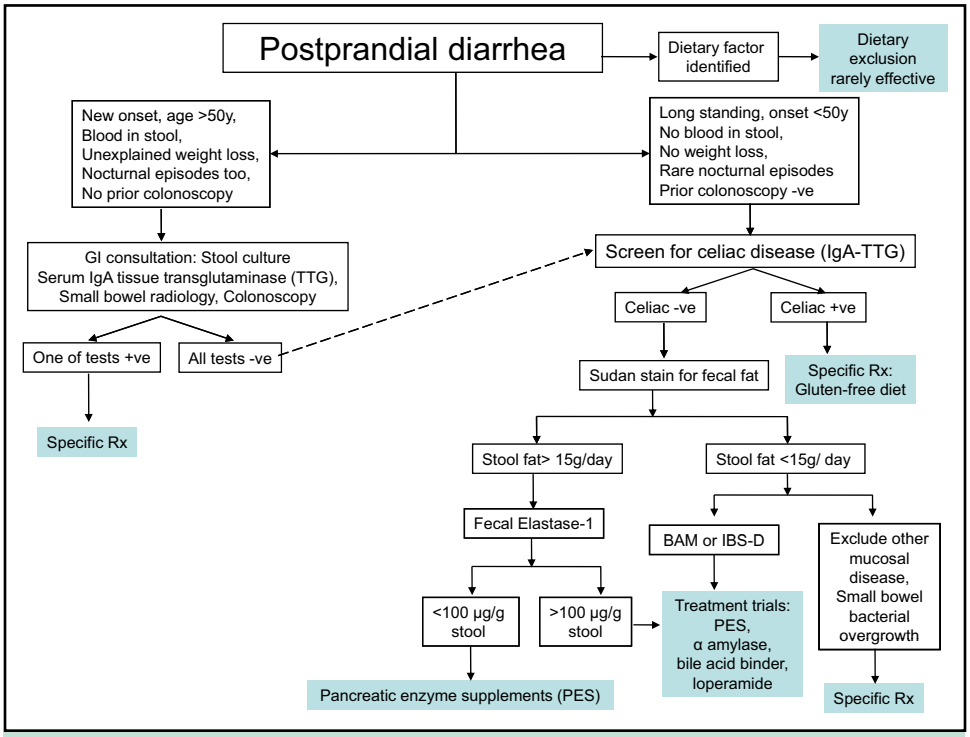

Figure Management and treatment algorithm for postprandial diarrhea. BAM = bile acid malabsorption; GI = gastrointestinal; IBS-D = irritable bowel syndrome-diarrhea; IgA = immunoglobulin A.

CONCLUSION AND RECOMMENDATIONS

Using only symptom-based criteria to establish the diagnosis of irritable bowel syndrome-diarrhea and failing to ask about the relationship of symptoms to eating currently limit physicians. We recommend that primary care physicians focus on the history: when a patient clearly identifies that their episodes of diarrhea occur after eating, a maldigestion condition also should be considered after exclusion of celiac and Crohn disease (**Figure**). Stool specimens could be analyzed for fecal elastase-1 and fat, not only because these may identify maldigestive process with moderate sensitivity, but because a negative test is useful to exclude the need for further consideration of maldigestive disorders.

Effective treatment with PES or bile acid binders may serve as a surrogate diagnostic test for maldigestion due to bile acid malabsorption, pancreatic or glucosidase insufficiency or inhibition. Current diagnostic testing for any of these conditions is not readily available.

If neither enzyme supplementation nor bile acid sequestrants help, then treatment for small bowel overgrowth is reasonable, followed by testing for rare endocrine tumors, (which account for <1% of cases for chronic diarrhea) such as carcinoid, medullary thyroid cancer, systemic mastocytosis, gastrinomas, VIPomas, glucagonomas, and somatostinomas.[69]

More research is required to better understand this postprandial diarrhea syndrome. However, there is enough known to conclude that to include these maldigestive conditions reviewed as simply irritable bowel syndrome-diarrhea is no longer appropriate, as it deprives the patient of a potential specific and effective treatment.

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