CSID Leadership Summit

GastroIntestinal Health Foundation

A CME Proceedings Newsletter for Gastroenterology Providers

Breaking it down
Understanding carbohydration digestion and absorption

Thinking zebras instead of horses
CSID In clinical practice

Looking for CSID
What are the options?

Managing CSID
A balancing act

A CSID Leadership Summit meeting was held with Gastro Health providers on October 6, 2023 in Hollywood, FL to discuss current evidence and understanding of CSID. A total of 24 gastroenterologists and APPs participated in the event. The key messages from these discussions are summarized in this issue.

CSID Leadership Summit at GastroHealth:
A CME Proceedings Newsletter for Gastroenterology Providers

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Target Audience
This initiative will attract an audience of health care professionals (HCPs), including gastroenterologists, nurse practitioners, physician assistants and allied health HCPs.

Program Overview
The summit will bring together three expert advisors and more than 20 gastroenterologists and advanced practice providers (APPs) to focus on functional GI and motility disorders to develop topic-specific content addressing the educational needs of health care providers managing CSID. Faculty members will collaborate with participants for a deep dive across all aspects of CSID management. The proceedings will be recorded, along with all available data and recommendations, and an educational newsletter developed.

Educational Objectives
Upon completion of this activity, participants should be able to:

- Describe the prevalence of CSID in patients with common GI disorders
- Incorporate current diagnostic strategies to differentiate CSID from other causes of persistent diarrhea seen in clinical practice, particularly among patients with suspected IBS
- Summarize benefits and limitations of current treatment strategies for CSID

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Disclosures
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Method of Participation
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Fee Information
There is no fee for this educational activity.

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MEDICAL EDUCATION RESOURCES

GastroIntestinal Health Foundation

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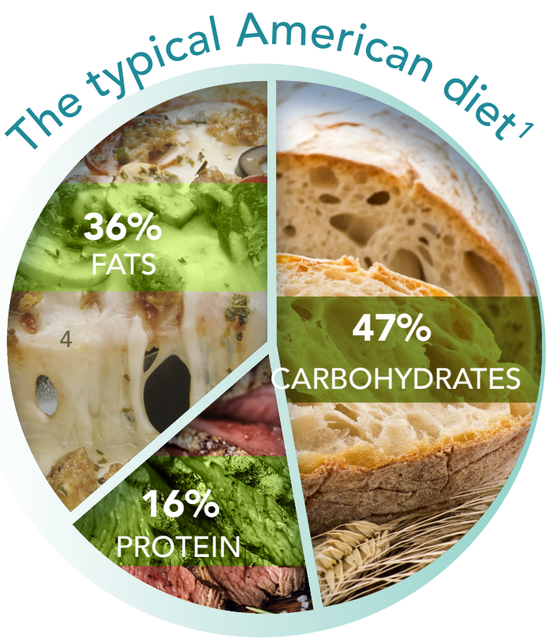
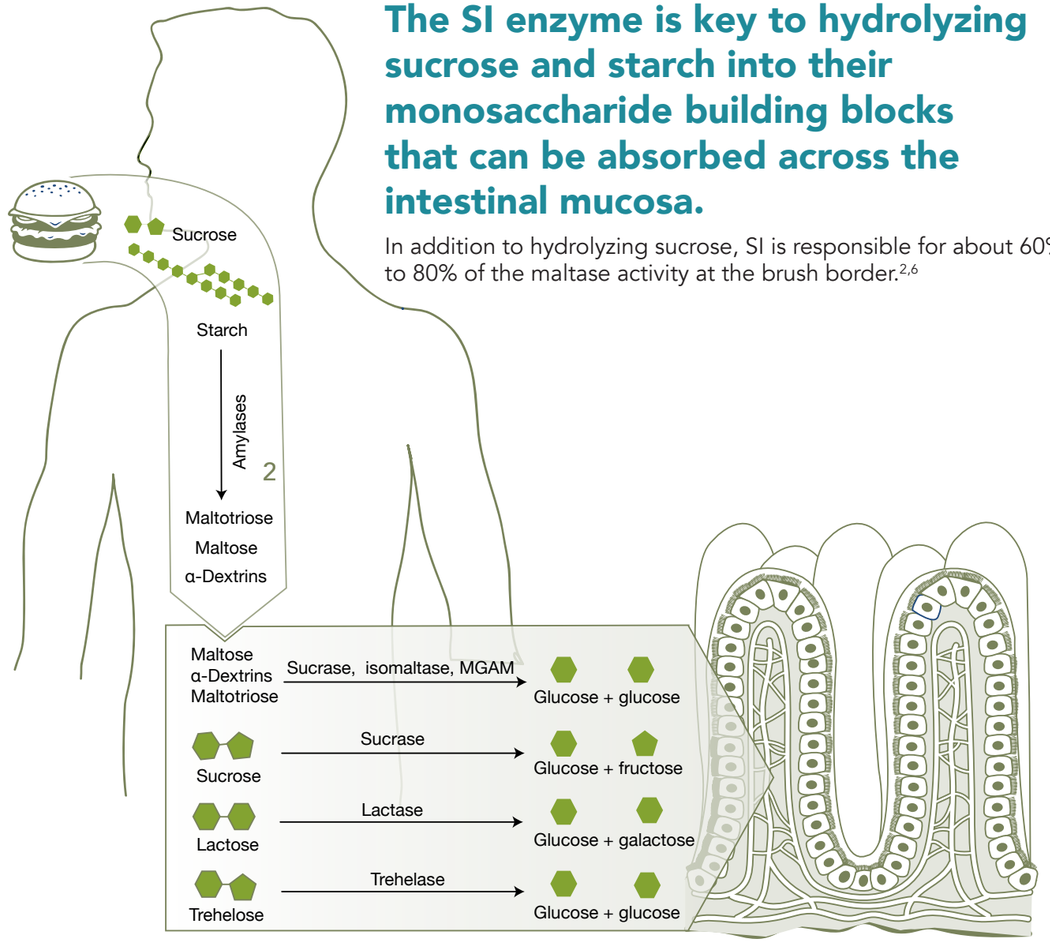
BREAKING IT DOWN

understanding carbohydrate digestion and absorption



Carbohydrates make up nearly half of the average Western diet.[1] Most of these are table sugars (sucrose) and plant starches that are composed of different α-linked sugars.[2]

Because sugar transporters in the intestine can only transport monosaccharides, enzymes in the brush border of the small intestine (disaccharidases) must hydrolyze disaccharide sugars into simple sugars (ie, glucose and fructose monomers) to be absorbed and metabolized.[3] This process begins with salivary and later pancreatic α-amylases that hydrolyze starches into smaller sugar residues, maltose and sucrose. These and other disaccharides are then hydrolyzed into monosaccharides by disaccharidase enzymes along the brush border of the small intestine.[4] Sucrase-isomaltase, lactase, maltase-glucoamylase (MGAM), and trehalase are the main intestinal brush border enzymes responsible for hydrolyzing lactose, sucrose, maltose, and trehelose.[5]

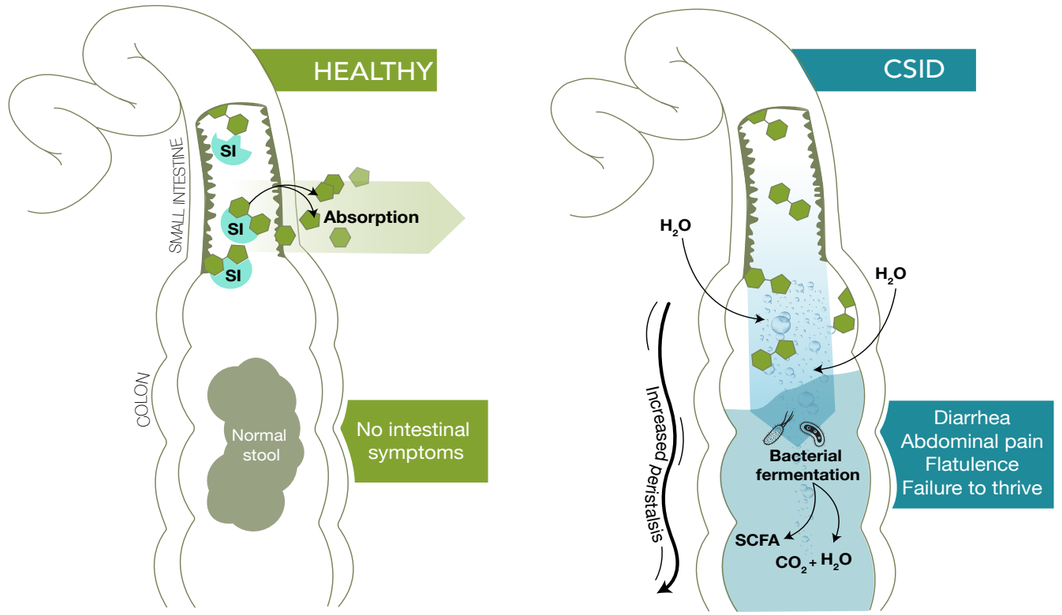


The SI enzyme is key to hydrolyzing sucrose and starch into their monosaccharide building blocks that can be absorbed across the intestinal mucosa.

In addition to hydrolyzing sucrose, SI is responsible for about 60% to 80% of the maltase activity at the brush border.[2,6]

Congenital sucrase-isomaltase deficiency (CSID) results when patients inherit 2 defective copies of the *sucrase-isomaltase* (*SI*) gene due to either recessive homozygous or compound heterozygous mutations that reduce or abolish enzymatic activity.[7] Although numerous mutations in the *SI* genes have been identified, 4 variants account for many of the clinical symptoms associated with CSID.[5]

Acquired or secondary forms of sucrase-isomaltase deficiency can also occur in patients with chronic diarrhea from other causes such as include villous atrophy or alteration (eg, celiac disease, Crohn's disease); infection (eg, acute gastroenteritis, HIV enteropathy, small intestinal bacterial overgrowth); and rapid transit (eg, dumping syndrome, colitis).[3] The clinical impact of sucrase-isomaltase deficiency in these disorders may be transient, with enzymatic activity returning to normal with resolution of the underlying disorder.[3] The faculty suspect that most cases of CSID that they see in clinical practice are actually acquired rather than congenital cases.



FEEDING THE MICROBIOME

The presence of unabsorbed carbohydrates in the intestine and colon resulting from deficient discaccharidases has been likened to feeding the microbiome.

The presence of unabsorbed carbohydrates in the intestinal lumen and colon leads to an increased osmotic load, excess bacterial fermentation and increased production of short-chain fatty acids and gases.[6,8] This in turn leads to abdominal distension, cramping, pain, excessive flatulence, and osmotic diarrhea. The faculty emphasized that these symptoms are very similar to those of IBS, most notably IBS-D or mixed IBS.

The clinical presentation of CSID varies widely based on residual SI activity, dietary sucrose and starch consumption, and other physiologic factors.[2,3]

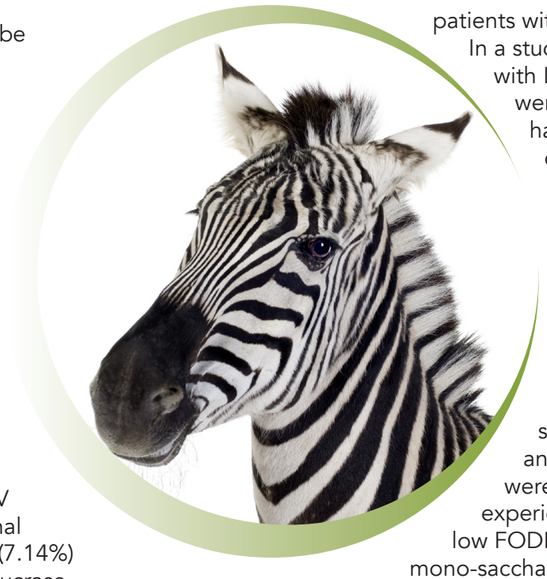
Although symptoms usually appear early in life, the clinical presentation and severity of CSID vary depending on the nature and position of the SI mutations, as well as their homozygous or heterozygous combinations.[7,9] Accordingly, sucrase activity in patients with CSID can range from completely absent to low residual activity, while isomaltase activity can range from absent to normal.[6] Maltase activity is also reduced significantly in most patients with CSID.[6,10]

In addition to residual enzyme activity, many other factors can affect the onset and symptoms of CSID, including the amount of dietary sugar and starch consumed, the rate of gastric emptying, activity of other intestinal disaccharidases, and the metabolic activity of fermenting bacteria.[2,3,6] Patient age can also influence clinical presentation, as children may be more susceptible to symptoms due to the shorter length of their small intestine and reduced reserve capacity of the colon to absorb excess luminal fluid.[2,3,6]

In contrast to the classic, severe presentation of CSID in patients with homozygous *SI* mutations,[6] a broad range of phenotypes has been observed in adults with CSID. Many of the symptoms of CSID overlap with those of IBS, particularly IBS-D.[5] Like IBS, CSID symptoms often occur postprandially, but patients with CSID may be likely to associate symptoms with sweets and other high-sucrose foods. Patients with CSID may report a lifelong history of symptoms, potentially with avoidance of carbohydrates or sweet foods, as well as family members with similar symptoms.

thinking zebras instead of horses

CSID in clinical practice

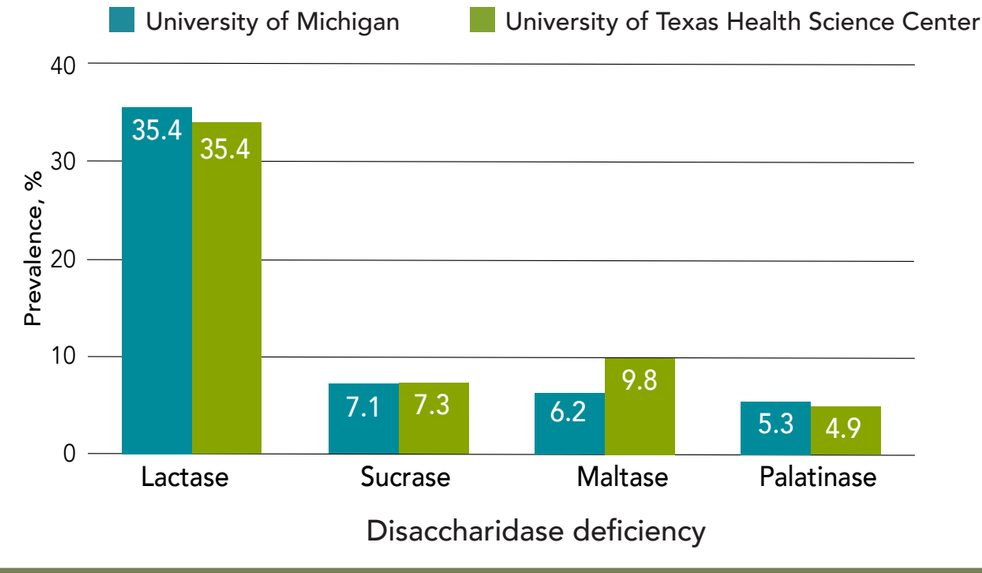


Although once believed to be a rare autosomal recessive disorder,[6] both clinical and genetic data indicate that CSID is more common than previously believed.[4,9,11–13] This is increasingly apparent in patients with unexplained functional GI symptoms, particularly with presumed IBS. Indeed, studies in adults suggest that many patients with CSID are diagnosed with IBS at some point in their lives.[5] A recent analysis of 154 adults meeting Rome IV criteria for IBS-D or functional diarrhea found that 1 in 14 (7.14%) symptomatic patients had sucrase and maltase deficiencies on disaccharidase analysis.[11] Previous studies have also reported a high prevalence of CSID in patients with chronic unexplained GI symptoms.[14,15]

Growing evidence also suggests that specific pathogenic *SI* gene variants are more common in patients with IBS than those without.[7,9] In a study involving 1031 patients with IBS, patients with IBS were nearly twice as likely to have a genetic SI mutation compared with controls (odds ratio=184).[7] In a larger study involving 2207 patients with IBS, 4.2% of patients with IBS-D were found to carry rare SI pathogenic variants, a higher frequency relative to a large matched reference population.[9] In another study, patients with IBS-D and pathogenic SI variants were 3 to 4 times less likely to experience symptom relief with a low FODMAP (fermentable, oligo-, di-, mono-saccharides, and polyols) diet than patients without such variants.[16] Additionally, a recent pilot study demonstrated better response to a starch and sucrose-reduced diet among adults carrying 2 *SI* variants than those carrying single or no variants.[17]

Although CSID goes largely unrecognized in adults, recent evidence suggests that it may be present in approximately 4% to 9% of patients with chronic diarrhea or IBS-D.

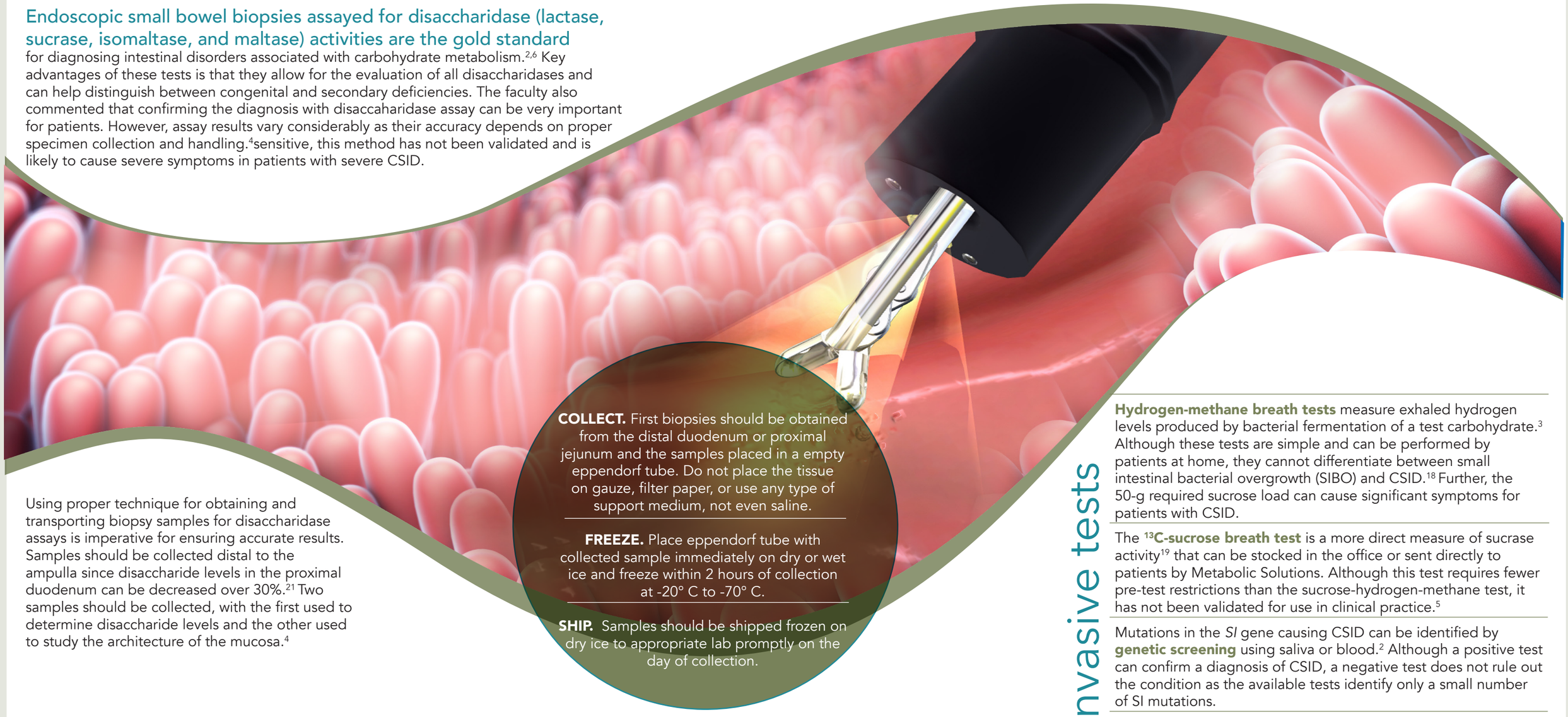
Prevalence of disaccharidase deficiency in adults with Rome IV-defined IBS-D or functional diarrhea (N=154)[11]



In speaking to these data, the faculty pointed out that finding nearly identical prevalence of sucrase deficiency at 2 different clinical sites indicates that these findings are reproducible and generalizable.

Looking for CSID

Endoscopic small bowel biopsies assayed for disaccharidase (lactase, sucrase, isomaltase, and maltase) activities are the gold standard for diagnosing intestinal disorders associated with carbohydrate metabolism.[2,6] Key advantages of these tests is that they allow for the evaluation of all disaccharidases and can help distinguish between congenital and secondary deficiencies. The faculty also commented that confirming the diagnosis with disaccaharidase assay can be very important for patients. However, assay results vary considerably as their accuracy depends on proper specimen collection and handling.[4]sensitive, this method has not been validated and is likely to cause severe symptoms in patients with severe CSID.



COLLECT. First biopsies should be obtained from the distal duodenum or proximal jejunum and the samples placed in a empty eppendorf tube. Do not place the tissue on gauze, filter paper, or use any type of support medium, not even saline.

FREEZE. Place eppendorf tube with collected sample immediately on dry or wet ice and freeze within 2 hours of collection at -20° C to -70° C.

SHIP. Samples should be shipped frozen on dry ice to appropriate lab promptly on the day of collection.

Using proper technique for obtaining and transporting biopsy samples for disaccharidase assays is imperative for ensuring accurate results. Samples should be collected distal to the ampulla since disaccharide levels in the proximal duodenum can be decreased over 30%.[21] Two samples should be collected, with the first used to determine disaccharide levels and the other used to study the architecture of the mucosa.[4]

non-invasive tests

Hydrogen-methane breath tests measure exhaled hydrogen levels produced by bacterial fermentation of a test carbohydrate.[3] Although these tests are simple and can be performed by patients at home, they cannot differentiate between small intestinal bacterial overgrowth (SIBO) and CSID.[18] Further, the 50-g required sucrose load can cause significant symptoms for patients with CSID.

The **^{13}C-sucrose breath test** is a more direct measure of sucrase activity[19] that can be stocked in the office or sent directly to patients by Metabolic Solutions. Although this test requires fewer pre-test restrictions than the sucrose-hydrogen-methane test, it has not been validated for use in clinical practice.[5]

Mutations in the *SI* gene causing CSID can be identified by **genetic screening** using saliva or blood.[2] Although a positive test can confirm a diagnosis of CSID, a negative test does not rule out the condition as the available tests identify only a small number of SI mutations.

A **sucrose 4-4-4 challenge** is a simple test that consists of monitoring for the presence of symptoms (bloating, gas, diarrhea) for a 4 to 8-hour period after the patient drinks 4 ounces of water with 4 tablespoons of dissolved table sugar.[3,20] Although theoretically sensitive, this method has not been validated and is likely to cause severe symptoms in patients with severe CSID.

Managing CSID a balancing act

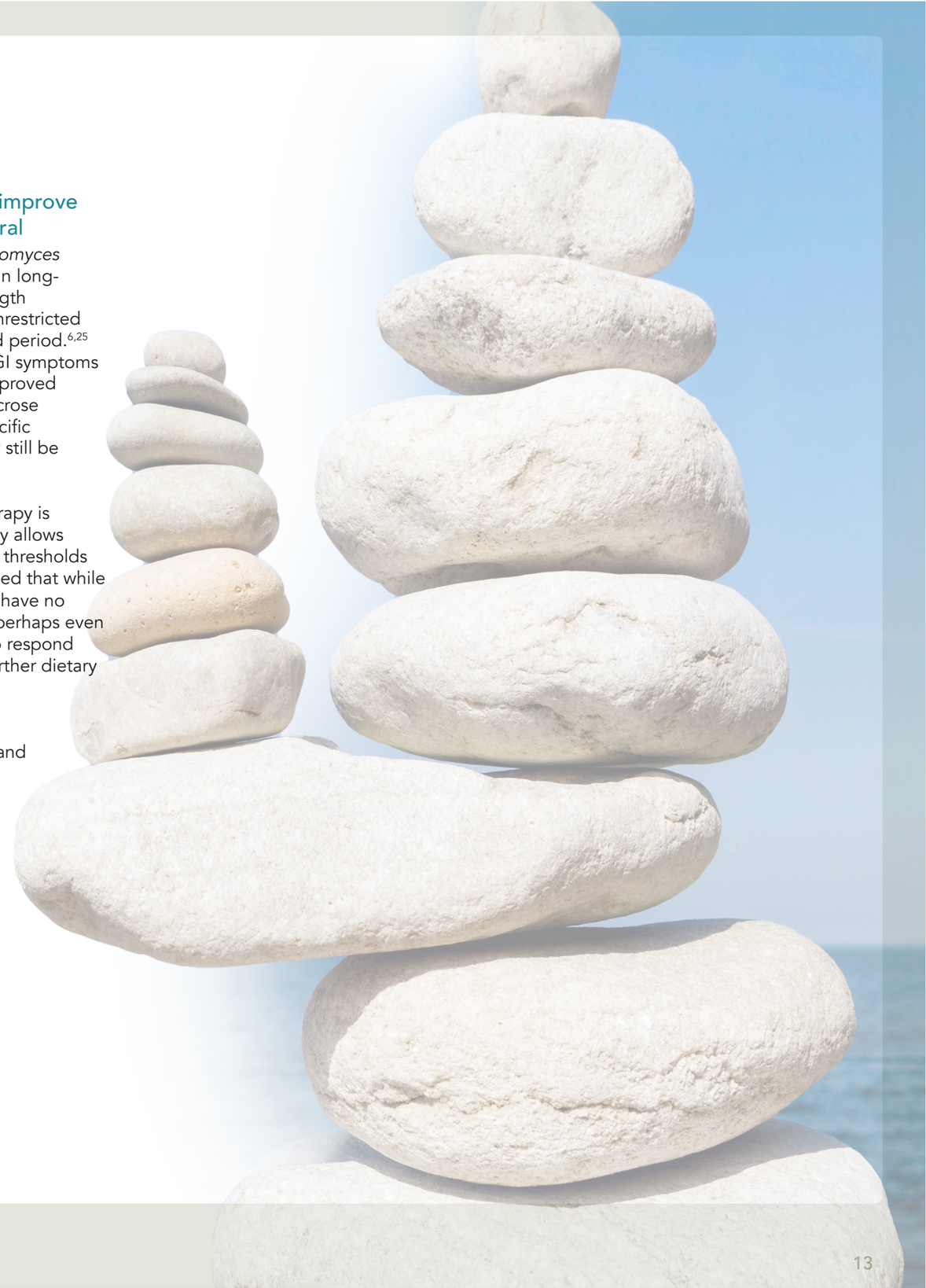
Enzyme replacement therapy and dietary restriction of starch and sucrose are the cornerstones of CSID management.[2,5] Given that all patients with CSID are sucrose intolerant, a sucrose-free diet should be started before starch intake is modified. If symptoms persist after institution of a sucrose-free diet, starch consumption can be reduced. Dietary adjustment in patients who require both sucrose and starch modification is accomplished on a trial and error basis, adjusting specific foods as needed based on symptoms. This process can be complex, involving several weeks of elimination of dietary sucrose and starch, followed by gradual reintroduction of foods int o the diet.[5] With this in mind, the faculty emphasized the importance of engaging a dietitian to help patients with this process. In addition to working with patients to determine their individual tolerance of sucrose- and starch-containing foods, dietitians can teach patients to understand food labels so they better recognize sucrose and starch in foods.[22]

Although dietary restriction should be theoretically effective, follow-up studies indicate that only a minority of patients remain consistently asymptomatic with this approach, with up to 75% of patients continuing to experience diarrhea, gas, and/or abdominal pain. Further, only half of children are typically compliant with the prescribed diet.[6,23,24]

Treatment of CSID with enzyme replacement therapy can improve symptoms while allowing patients to consume a more liberal diet.[5,6,14] Sacrosidase, which is sucrose enzyme derived from *Saccharomyces cerevisiae*, was approved by the FDA for treatment of CSID in 1998.[4] In long-term, randomized, double-blind trials, 81% of patients using full-strength sacrosidase were able to remain asymptomatic while consuming an unrestricted diet compared with 78% untreated during the baseline, diet-restricted period.[6,25] More recently, a chart review of 258 adults with chronic unexplained GI symptoms demonstrated that dietary counseling and/or enzyme replacement improved symptoms in the 60% of patients who had positive breath tests for sucrose malabsorption.[14] However, because sacrosidase does not provide specific replacement for deficient isomaltase, restricting starch in the diet may still be necessary in some patients.[20]

The faculty noted that although response to enzyme replacement therapy is usually favorable, it is not always dramatic. While sacrosidase generally allows patients to consume a more liberal diet, they will still need to find the thresholds of sucrose they can tolerate without having symptoms. They also agreed that while enzyme replacement therapy should be discontinued in patients who have no response or cannot tolerate it, a partial response is encouraging and perhaps even expected given the nature of functional GI symptoms. In patients who respond partially to enzyme supplementation, it is reasonable to implement further dietary modifications and/or evaluate for other disaccharidase deficiencies.

Although sacrosidase is the only FDA-approved treatment for CSID, nonprescription options such as Starchway, a combination of sucrase and glucoamylase, are available.[4]



How should enzyme replacement be administered?

Patients should be instructed to take sacrosidase with meals or snacks, with half the dosage taken at the beginning of each meal or snack and the remainder taken during the meal or snack.[26]

What formulations of sacrosidase are available?

Sacrosidase (Sucraid®) is available in a multidose bottle that requires refrigeration and single-use containers that are stable at room temperature for 3 days.

Are there any risks of sacrosidase therapy?

Sacrosidase is usually well tolerated, with constipation, insomnia, and headaches being the most common adverse events.[6] Patients with a known hypersensitivity to yeast or yeast products, papain, or glycerin should not take Sucraid®. Additionally, caution is warranted in patients with poorly-controlled diabetes because sacrosidase can raise blood glucose levels by hydrolyzing sucrose.

Clinical pearls for recognizing and treating CSID

When evaluating patients for CSID, listen for a history of lifelong symptoms, avoidance of high-sucrose foods, and family members with similar symptoms.

Recognize that although clinical response with sacrosidase tends to occur rapidly, it may vary based on the type and severity of symptoms.

Help patients understand that CSID management requires a combination of dietary modification and enzyme replacement therapy.

Engage the help of dietitians, when possible, to help patients determine their tolerance for various sucrose- and starch-containing foods, even those taking enzyme replacement therapy.

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