CSID

Proceedings from a Pediatric Leadership Meeting

June 2, 2023

CSID–a rare genetic disease?
The latest data on the prevalence of CSID

The changing faces of CSID
Tips for recognizing CSID in older children and adolescents

The CSID-IBS connection
Are we missing CSID in our patients with IBS?

Finding the right balance in CSID management
Fine-tuning diet and enzyme supplementation

Looking for CSID

The when, why, and how of diagnostic strategies for CSID

A Pediatric CSID Leadership Summit meeting was held on June 2, 2023 to discuss current evidence and understanding of CSID in the pediatric population. A total of 23 pediatric and adult gastroenterologists participated in the event. The key messages from the meeting are summarized in this newsletter.

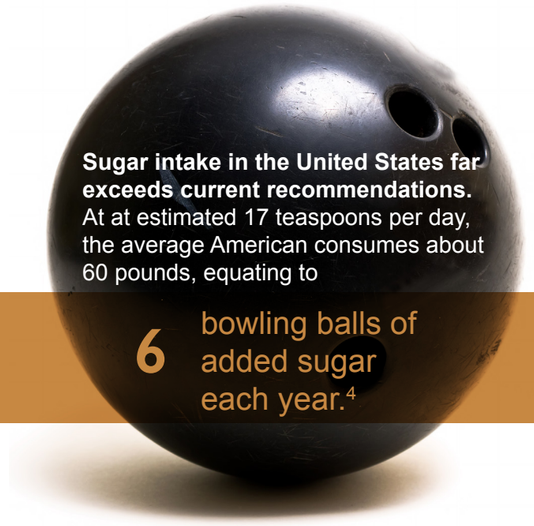
GastroIntestinal Health Foundation

REVISITING

carbohydration absorption

Nearly half of the average western diet is comprised of carbohydrates,[1] most of which are table sugars (sucrose) and starches that are composed of different α-linked sugars.[2] Sugars are intrinsic in fruit and milk products, whereas starches are found in many vegetables, legumes, and grains.[3] Added, or extrinsic sugars, are used to improve palatability or the functional properties or food or beverages. Sugar and starches are the main source of glucose for the brain, central nervous system, and red blood cells, and as such their proper digestion and absorption are essential for health.

THE SUGAR PROBLEM IN THE UNITED STATES

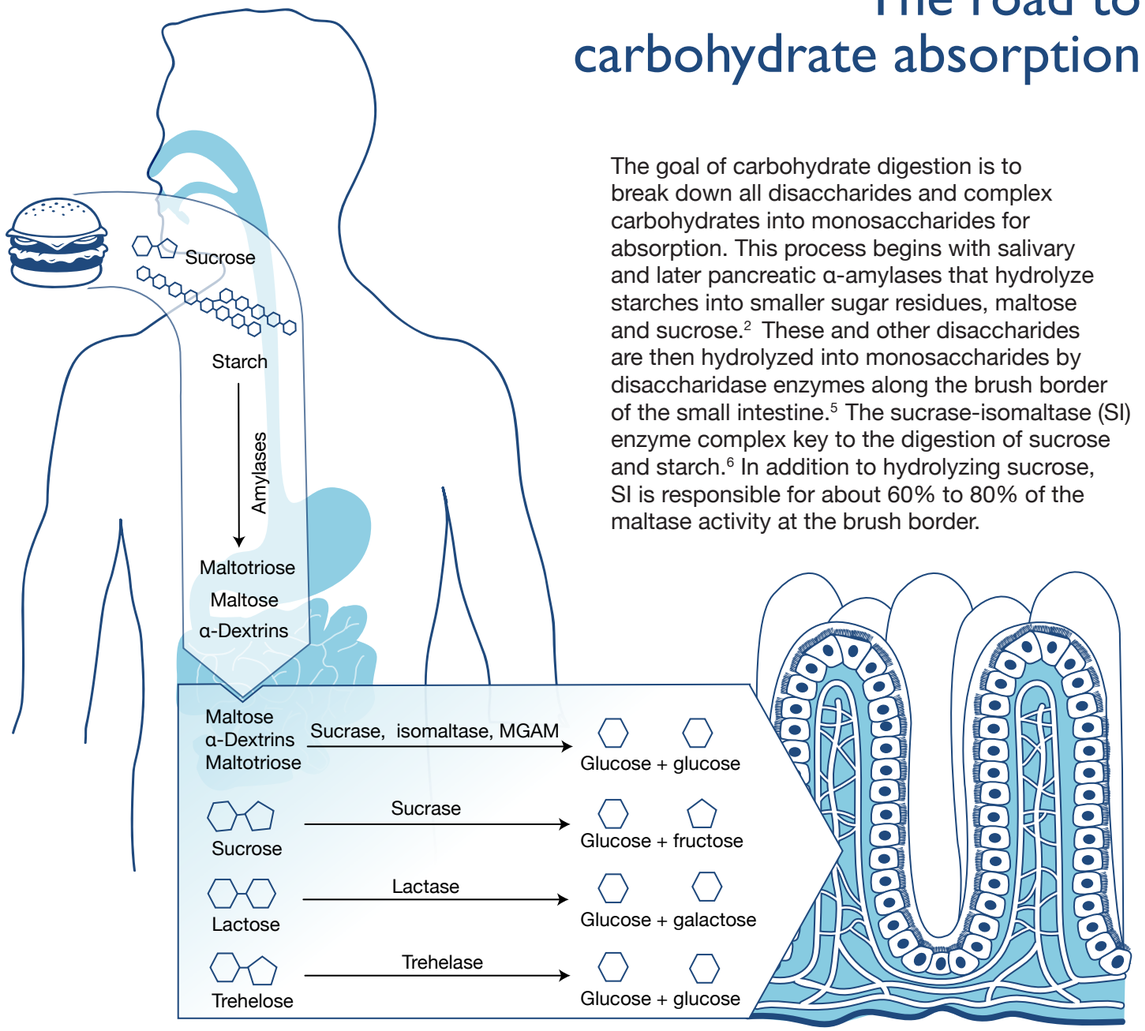


Sugar intake in the United States far exceeds current recommendations. At at estimated 17 teaspoons per day, the average American consumes about 60 pounds, equating to

6 bowling balls of added sugar each year.[4]

The road to carbohydrate absorption

The goal of carbohydrate digestion is to break down all disaccharides and complex carbohydrates into monosaccharides for absorption. This process begins with salivary and later pancreatic α-amylases that hydrolyze starches into smaller sugar residues, maltose and sucrose.[2] These and other disaccharides are then hydrolyzed into monosaccharides by disaccharidase enzymes along the brush border of the small intestine.[5] The sucrase-isomaltase (SI) enzyme complex key to the digestion of sucrose and starch.[6] In addition to hydrolyzing sucrose, SI is responsible for about 60% to 80% of the maltase activity at the brush border.



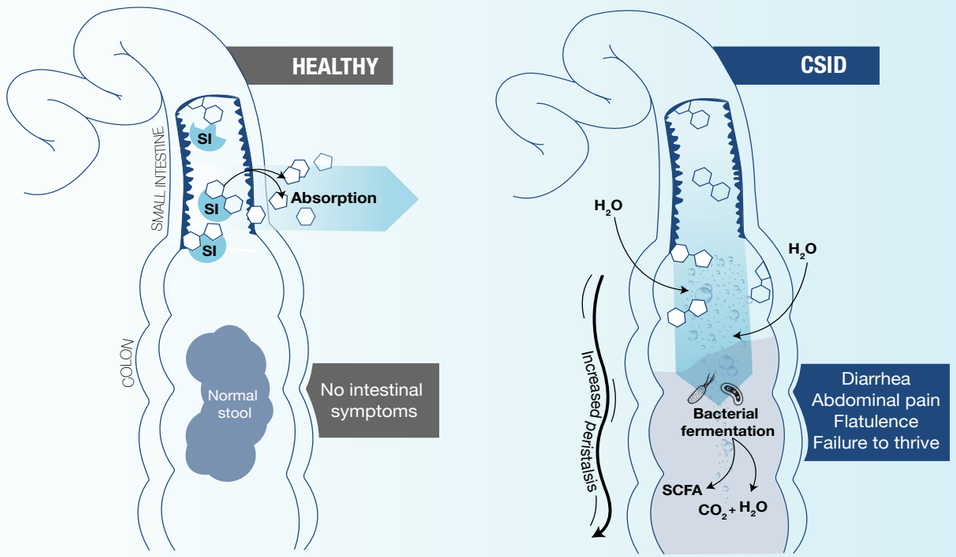
The SI enzyme is key to the digestion of sucrose and starch.

Congenital sucrase-isomaltase deficiency (CSID) was first recognized as a deficiency of "sugar-splitting enzymes" in 1960.[7] This condition results when patients inherit 2 defective copies of the *SI* gene due to either recessive homozygous or compound heterozygous mutations that reduce or abolish enzymatic activity.[8] In addition to congenital forms of the disorder, acquired or secondary forms of sucrase-isomaltase deficiency have been observed in patients with chronic diarrhea from other causes.[9] Such causes 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).

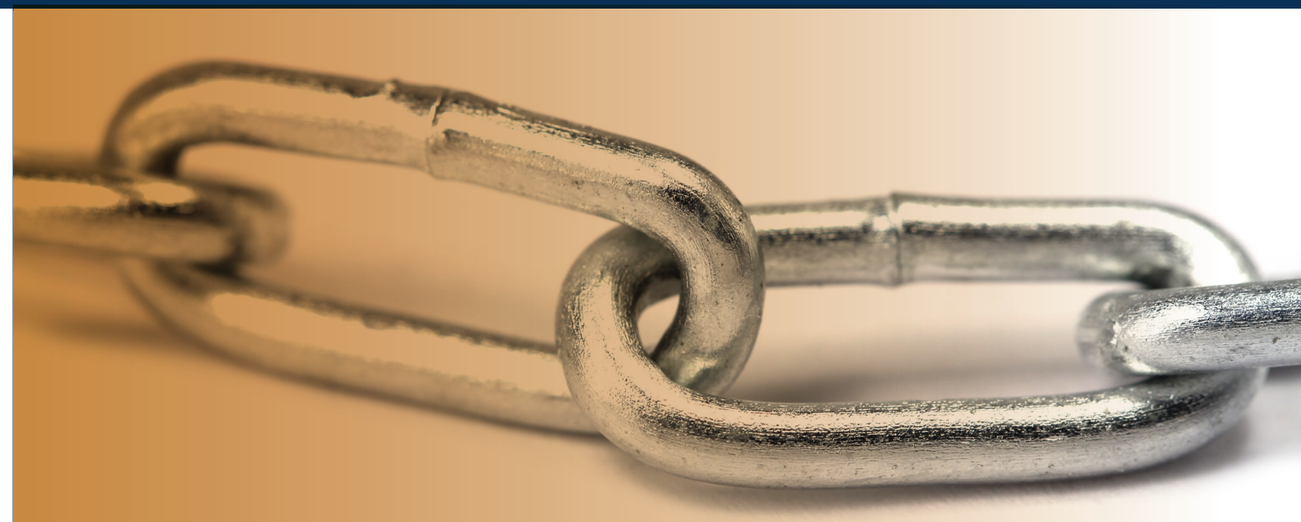
Although historically considered a rare disease, recent studies demonstrating that heterozygous carriers of *SI* variants also experience symptoms suggest that CSID may be more common than once believed.[8-13] In a 6-year retrospective study involving disaccharidase assay of 27,875 mucosal biopsy tissue samples in symptomatic children, at least one disaccharidase deficiency was present in 45% of samples, with 9.3% deficient in sucrase and maltase.[11] A subsequent systematic review of 30 observational studies in children undergoing esophagogastroduodenoscopy (EGD) found similar results, with an overall prevalence of lactase, sucrase, and maltase deficiencies noted to be 39.2%, 9.0%, and 9.1%, respectively.[14]

CSID
A RARE GENETIC DISEASE?

The pathophysiologic basis of symptoms in CSID



When the SI enzyme is deficient or absent, non-absorbed carbohydrates enter the colon causing excess bacterial fermentation and increased production of short-chain fatty acids and gases.[5,6] This in turn leads to abdominal distension, cramping, pain, excessive flatulence, and osmotic diarrhea.



The CSID-IBS connection

reported prevalence of sucrase deficiency in adults with IBS-like symptoms

via disaccharidase assay

7.1% among 152 adults with IBS-D or functional diarrhea who underwent duodenal biopsy and disaccharidase assay at the University of Michigan or University of Texas Health Science Center at Houston[13]

35% among 31 adults with presumed IBS-D or IBS-M who underwent duodenal biopsy and disaccharidase assay at the University of Miami[t10]

via ^{13}C-sucrose breath test

26.5% among 147 adults with chronic unexplained GI symptoms[15]

Many of the symptoms of CSID overlap with those of irritable bowel syndrome (IBS), particularly diarrhea-predominant IBS (IBS-D).[6] Like patients wtih IBS, many patients with CSID also report that their symptoms are triggered by meals. With this overlap, there is speculation that CSID may be unrecognized and/or misdiagnosed as IBS-D in older children and adults.

Studies in adults suggest that many patients with CSID are diagnosed with IBS at some point in their lives.[6] 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.[13] Previous studies have also reported a high prevalence of CSID in patients with chronic unexplained GI symptoms.[10,15]

Growing evidence also suggests that specific *SI* gene variants are more common in patients with IBS than those without.[16,17] An additional finding has been that patients with IBS-D and pathogenic *SI* variants are significantly less likely to experience symptom relief with a low FODMAP diet than patients without such variants.[18]

the changing faces OF CSID

Given the genetic and clinical heterogeneity of CSID, clinicians should maintain a high index of suspicion in patients with unexplained GI symptoms, even those who do not present with classic symptoms of diarrhea and failure to thrive in infancy.

Congenital sucrase-isomaltase deficiency classically presents as severe watery diarrhea, failure to gain weight, irritability, and diaper rash in infants who have been exposed to sucrose and starch in baby juices, baby food fruits, teething, biscuits, crackers, and other starches.[19] Although these classic symptoms usually appear early in life, the clinical presentation and severity varies considerably depending on the nature and position of the mutations, as well as their homozygous or heterozygous combinations.[16,17]

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.[19] Maltase activity is also reduced significantly in most patients with CSID.[19,20] Other factors that can influence clinical presentation in CSID include the amount of sugar and starch being consumed and patient age, 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.[9,19]

The faculty noted that the phenotype of CSID in older children is changing to include those with nonspecific abdominal discomfort, gas, and bloating. Although patients may present with abdominal pain, other symptoms such as gas, bloating, diarrhea, constipation, and vomiting are also seen in this population.

Importantly, growing evidence suggests that CSID can present later in life, either in children with diagnoses of nonspecific diarrhea of childhood or in adolescents or adults often carrying diagnoses of IBS-D.[16,19,20] In either case, clinical features that are characteristic of CSID include symptoms that are lifelong, frequent (typically multiple events per day and multiple days per week), and occur postprandially. Patients may report avoiding carbohydrates or sweet foods, as well as a family history of close relatives with similar symptoms.

> The autosomal recessives are really that infant-onset disease, and the heterozygotes are looking like what we've called IBS or chronic diarrhea. So they are a much more heterogeneous group of patients. And many of these patients, almost all of them, have normal growth. That's a really big difference in this subset—their growth is normal and not all of them have diarrhea.
>
> Meeting participant

The gold standard for diagnosing intestinal disorders associated with carbohydrate metabolism is endoscopic small bowel biopsies assayed for disaccharidase (lactase, sucrase, isomaltase, and maltase) activities.[2,6,19] However, the invasiveness of the procedure is an important disadvantage in pediatric patients. The need for special handling (ie, immediate freezing) and assay variability are also limitations.[5] In contrast, disaccharidase assay allows for the evaluation of other disaccharidases as well as causes of secondary disaccharidase deficiencies.

Although genetic tests are available, they currently test for only a small number of common pathogenic variants[5] and the results do not provide reliable information regarding the clinical phenotype. The ^{13}C-sucrose breath test is a simple, noninvasive option[21] that can be obtained free of charge from Metabolic Solutions. The test kits can be stocked in the office or sent directly to patients. The key limitations are the lack of validation and uncertainty around the normal thresholds, since they were derived from biopsies of patients with classic homozygous *SI* mutations. Additionally, it can be challenging for toddlers to perform the test reliably. The sucrose-hydrogen-methane breath test is another option, but it requires more pre-test restrictions than the ^{13}C-sucrose breath test and does not differentiate CSID from small intestinal bacterial overgrowth (SIBO) or transit disorders. The sucrose challenge is a simple test that may be suitable for toddlers, although the proper sucrose load for this age group has not been determined.

The meeting participants have varied experiences and practices regarding obtaining disaccharidase biopsies. Although many obtain biopsies in select patients with unexplained symptoms, others expressed frustration with the results of these tests. In particular, the frequent finding of pandisaccharidase deficiency has led some practitioners to question the accuracy of the tests. However, there are data supporting that pandisaccharidase defiency in the absence of histologic damage is not an uncommon finding in this population.

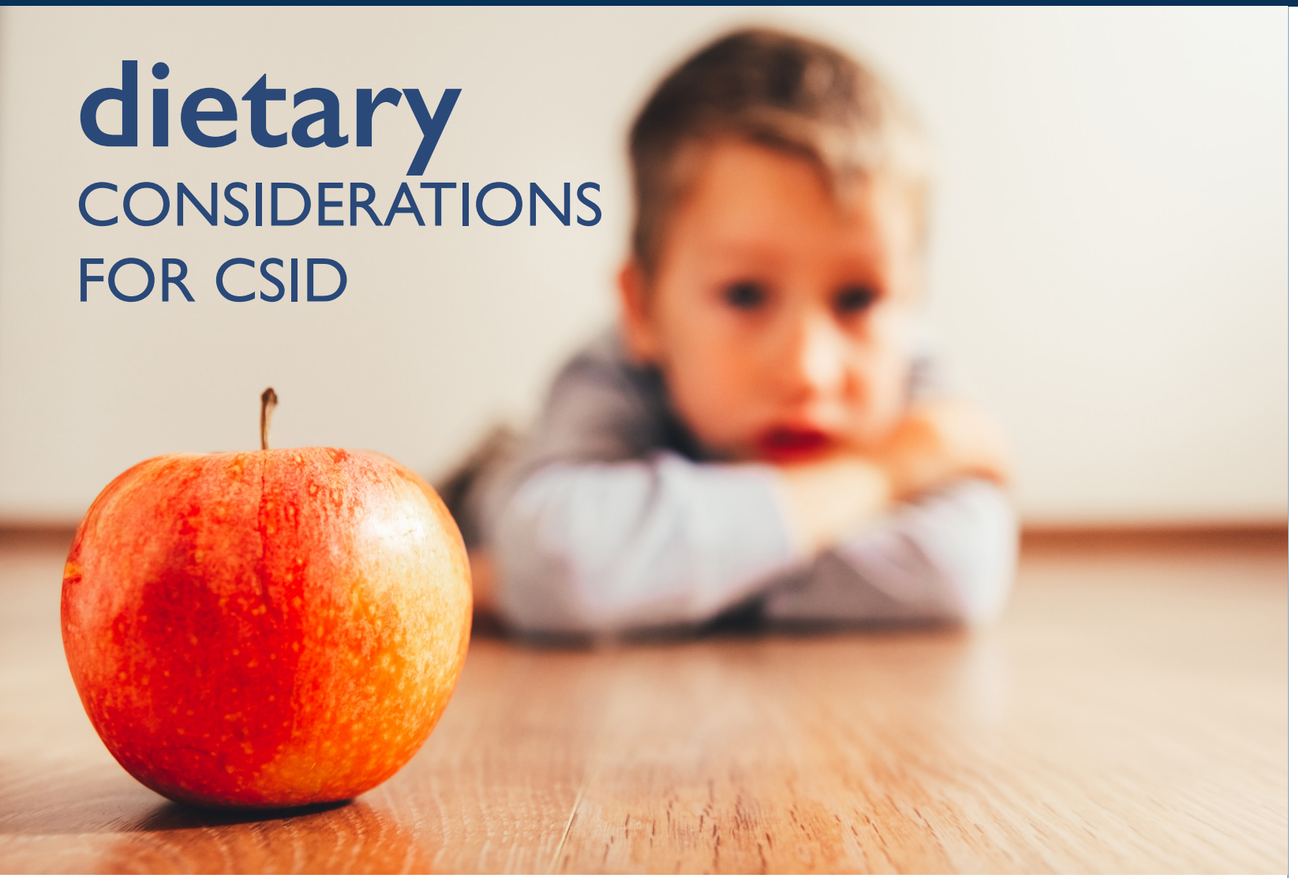
Given the problems with disaccharidase assay, there is much interest in noninvasive tests that can help diagnose CSID. Although the participants view the sucrose challenge test favorably, they emphasized that the test would require validation to be useful in clinical practice. Additionally, it is important to understand and prepare patients that the test could cause severe symptoms in those who have the disorder. The participants were also interested in the possibility of testing patients with a short (eg, 2-week) trial of sucrose restriction, as they anticipate that patients with significant CSID would respond well to such a strategy.

testing for CSID

Although the optimal testing strategy for CSID has not been defined, tailoring the use of disaccharidase assays, the ^{13}C-sucrose breath test, and/or sucrose challenge provides meaningful information in clinical practice.

> I can safely say I've probably missed the diagnosis more than I've made it. There are many older kids who come back and have evidence of this condition, and so there's probably a whole host of kids out there with this.
>
> Meeting participant

dietary CONSIDERATIONS FOR CSID



Historically, the primary treatment option for CSID has been implementing lifelong sucrose- and starch-restricted diets adapted to the requirements of the patient.[5,6] Given that all patients with CDIS are sucrose intolerant, a sucrose-free diet should be implemented before starch intake is modified. If symptoms persist after institution of a sucrose-free diet, starch consumption may be reduced. In order to implement these restrictions, patients and their families need to be educated to understand food labels and how to recognize sucrose and starch in foods.[22] Access to a dietician who is knowledgeable about CSID is essential for optimizing management.

Although dietary restriction should theoretically be 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.[19,23,24] The faculty noted that a sucrose-free diet is likely more difficult to adhere to than either lactose- or gluten-free diets.

In light of the prevalence of disordered eating in patients with FGIDs, a primary goal is to work with patients to allow for the most liberal diet possible that will manage symptoms. With that in mind, experts advocate initiating sacrosidase without starch restriction, allowing the patient's response to enzyme supplementation guide the need for dietary restriction. A food and symptom diary can be very helpful in this regard. Even with starch restriction, most pediatric patients can tolerate 120 g of carbohydrates per day, particularly when spread out throughout the day.

In addition to disordered eating, patients should also be screened for food insecurity before implementing dietary modifications. The Hunger Vital Sign™ is a validated, 2-question tool that can identify patients at high risk for food insecurity.[25] Key nutrients of concern that have been identified in this population include potassium, calcium, magnesium, folate, and fiber.

Tips for starch restriction

Cooling rice and potatoes after cooking transforms the starches into a more tolerable form.

Sourdough bread may be better tolerated since it has a higher percentage of resistant starch than other types of bread.

Encourage patients to **chew food slowly** and thoroughly to allow for maximal exposure to salivary amylase.

Substitute zucchini and spaghetti squash for pasta and cauliflower rice.

Saltines can be used to increment and determine a patient's starch threshold, as each cracker contains ~2 g.

CSID grocery list (foods that are low in sucrose and starch)[26]

DAIRY[a]
Cow's milk
Cream cheese
Half and half
Hard cheeses (cheddar, colby, mozzarella, swiss, parmesan, provolone)
Plain cottage cheese
Plain yogurt sweetened with fructose or dextrose
Ricotta cheese
Sour cream
Whipping cream

PROTEIN[b]
Beef
Chicken
Eggs
Fish
Lamb
Pork
Tofu
Turkey

FATS
Any vegetable oils
Butter

VEGETABLES
Alfalfa sprouts
Artichoke[c]
Asparagus[c]
Bamboo shoots
Bok choy
Broccoli[a]
Brussels sprouts[c]
Cabbage[c]
Cauliflower[c]
Celery
Cucumber
Eggplant
Green beans
Greens (collards, kale, mustard, turnip, and chard)
Lettuce (arugula, endive iceberg, romaine)
Mung bean sprouts
Mushrooms
Peppers (red, green, and yellow)
Radishes
Rutabaga
Spaghetti squash
Spinach
Tomatoes
Turnips
Yellow squash
Zucchini

FRUITS
Avocado
Blackberries
Blueberries
Cherries
Coconut (fresh or dried, unsweetened)
Cranberries
Currants
Figs
Grapes
Kiwi
Lemons
Limes
Olives
Papaya
Pears
Pomegranate
Prunes
Raspberries
Rhubarb
Strawberries

NUTS & SEEDS[d]
Almonds
Almond butter
Brazil nuts
Flax seeds
Hazelnuts
Macadamia nuts
Peanuts
Peanut butter
Pecans
Pumpkin seeds
Sesame butter (tahini)
Walnuts

[a]Full-fat dairy products may be used if more calories are indicated. Avoid processed cheeses or cheese products that contain sucrose or starch fillers. If lactose intolerant, avoid dairy foods. Substitute lactose-free milk, unsweetened almond milk, or soy milk for cow's milk.
[b]Avoid processed meats such as bacon, sausage, luncheon meat, paté, and liverwurst that are cured with sucrose or have starch fillers.
[c]These vegetables may cause gas in all individuals and should be monitored closely.
[d]Nuts and seeds can be difficult to digest in general. Most nuts and seeds contain varying amounts of sucrose and starch. When starting the diet, it is best to avoid nuts and seeds the first two weeks. It is important to keep the portion size small (in general a serving is <1 ounce for nuts).

enzyme supplementation and diet for CSID

FINDING THE RIGHT BALANCE

The optimal combination of enzyme supplementation and dietary management should be tailored to individual patients.

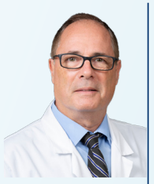
Treatment of CSID has improved considerably with the availability of enzyme replacement therapy (sacrosidase), which allows liberalization of the previously sucrose-restrictive diet.[15,19] In long-term, randomized, double-blind trials, 81% of patients using sacrosidase were able to remain asymptomatic while consuming an unrestricted diet compared with 78% untreated during the baseline, diet-restricted period.[19,27] 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.[15]

When introducing sacrosidase to patients, the faculty noted that they avoid describing CSID in isolation, but rather as a piece of a puzzle. Recognizing that disaccharidase deficiencies do not always lead to clinical intolerance, CSID is discussed with patients in the context of other abnormalities that may be contributing to symptoms, such as visceral hypersensitivity or microbiome dysbiosis. The faculty typically allow a 2-week trial window to assess patient response to sacrosidase, after which they transition to other therapies in patients who do not improve. Because sacrosidase hydrolyzes sucrose only, dietary starch restriction may also be needed to manage symptoms of CSID. Although sacrosidase allows patients to follow a more liberal diet, the optimal combination of enzyme supplementation and dietary management needs to be tailored to individual patients. One participant noted that many of her adolescent patients eat low-sucrose snacks but eat regular food for meals when they know they can dose enzyme. The recent availability of the individual sacrosidase containers[28] has made treatment in school-aged children or in other situations (eg, travel, eating in restaurants) much easier.

Recognizing the cost access challenges associated with sacrosidase, several participants mentioned their experience with other enzymes, including invertase and a combination of invertase and glucoamylase. However, the faculty noted their preference for commercially available sacrosidase whenever possible due to concerns over quality control issues with unregulated products.

Meeting faculty

Tanaz Danialifar, MD
Children's Hospital
Los Angeles, California



Miguel Saps, MD
University of Miami
Miller School of Medicine
Miami, Florida

Carlo Di Lorenzo, MD
Nationwide Children's
Columbus, Ohio

Kate Scarlata, MPH, RDN, LDN
For A Digestive Peace of Mind, LLC
Medway, Massachusetts

Daksesh Patel, MD
St. Francis Hospital
Chicago, Illinois

References

1. Seidelmann SB, Claggett B, Cheng S et al. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. *Lancet Public Health.* 2018; 3: e419-e428.
2. Gericke B, Amiri M, Naim HY. The multiple roles of sucrase-isomaltase in the intestinal physiology. *Mol Cell Pediatr.* 2016;3: 2.
3. Slavin J, Calrson J. Carbohydrates. *Adv Nutr.* 2014;5(6):760-761.
4. American Heart Association. How much sugar is too much? Accessed September 14, 2023. https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/sugar/how-much-sugar-is-too-much#:~:text=American%20adults%20consume%20an%20average,%2Dpound%20bowling%20balls%2C%20folks!
5. Viswanathan L, Rao SSC. Intestinal disaccharidase deficiency in adults: evaluation and treatment. *Curr Gastroenterol Rep*. 2023;25:124-139.
6. Lenhart A, Chey WD, Eswaran S. Sucrase-isomaltase deficiency: hiding in plain sight? *Curr Treat Options Gastro.* 2021;19:500-508.
7. Weijers HA, va de Kmer JH, Mossel DA, WK D. Diarrhoea caused by deficiency of sugar-splitting enzymes. *Lancet.* 1960; 2: 296-297.
8. Henström M, Diekmann L, Bonfiglio F et al. Functional variants in the sucrase-isomaltase gene associate with increased risk of irritable bowel syndrome. *Gut.* 2018;67:263-270.
9. Cohen SA. The clinical consequences of sucrase-isomaltase deficiency. *Mol Cell Pediatr.* 2016;3:5.
10. Kim SB, Calmet FH, Garrido J, Garcia-Buitrago MT, Moshiree B. Sucrase-isomaltase deficiency as a potential masquerader in irritable bowel syndrome. *Dig Dis Sci.* 2020;65:534-540.
11. Nichols BL, Adams B, Roach CM, Ma CX, Baker SS. Frequency of sucrase deficiency in mucosal biopsies. *J Pediatr Gastroenterol Nutr.* 2012; 55 Suppl 2: S28-30.
12. Chumpitazi BP, Lewis J, Cooper D et al. Hypomorphic *SI* genetic variants are associated with childhood chronic loose stools. *PLoS One.* 2020; 15: e0231891.
13. Chey SW CWD, Cash BD, Eswaran SL. Prevalence of disaccharidase deficiencies in adults with irritable bowel syndrome and functional diarrhea: interim analysis from a multicenter, prospective US trial. *Am J Gastroenterol.* 2022;117:e378-e379.
14. Daileda T, Baek P, Sutter ME, Thakkar K. Disaccharidase activity in children undergoing esophagogastroduodenoscopy: A systematic review. *World J Gastrointest Pharmacol Ther.* 2016; 7: 283-293.
15. Frissora CL, Rao SSC. Sucrose intolerance in adults with common functional gastrointestinal symptoms. Baylor University Medical Center Proceedings. 2022;35:790-793.
16. Garcia-Extebarria K, Zheng T, Bonfiglio F et al. Increased prevalence of rare sucrase-isomaltase pathogenic variants in irritable bowel syndrome patients. *Clin Gastroenterol Hepatol.* 2018;16:1673-1676.
17. Henström M, Diekmann L, Bonfiglio F et al. Functional variants in the sucrase-isomaltase gene associate with increased risk of irritable bowel syndrome. *Gut.* 2018;67:263-270.
18. Zheng T, Eswaran S, Photenhauer AL, Merchant JL, Chey WD, D'Amato M. Reduced efficacy of low FODMAPs diet in patients with IBS-D carrying *sucrase-isomaltase* (*SI*) hypomorphic variants. *Gut.* 2020;69:397-398.
19. Treem WR. Clinical aspects and treatment of congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr*. 2012;55 Suppl 2:S7-13.
20. Smith H, Romero B, Flood E, Boney A. The patient journey to diagnosis and treatment of congenital sucrase-isomaltase deficiency. *Qual Life Res*. 2021;30:2329-2338.
21. Robayo-Torres CC, Opekun AR, Quezada-Calvillo R et al. ^{13}C-breath tests for sucrose digestion in congenital sucrase isomaltase-deficient and sacrosidase-supplemented patients. *J Pediatr Gastroenterol Nutr*. 2009; 48: 412-418.
22. McMeans AR. Congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr*. 2012;55:S37-S39.
23. Kilby A, Burgess EA, Wigglesworth S, Walker-Smith JA. Sucrase-isomaltase deficiency. A follow-up report. *Arch Dis Child.* 1978;53:677-679.
24. Antonowicz I, Lloyd-Still JD, Khaw KT, Shwachman H. Congenital sucrase-isomaltase deficiency. Observations over a period of 6 years. *Pediatrics.* 1972;49:847-853.
25. Hager ER, Quigg AM, Black MM, et al. Development and validity of a 2-item screen to identify families at risk for food insecurity. *Pediatrics.* 2010;126(1):e26-e32.
26. CSID cares. Accessed September 15, 2 023. https://www.csidcares.org/treatment/diet/
27. Treem WR, McAdams L, Stanford L, Kastoff G, Justinich C, Hyams J. Sacrosidase therapy for congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr.* 1999;28:137-142.
28. Sucraid (sacrosidase)[prescribing information]. QOL Medical, LLC; Vero Beach, FL; 2022.