9. Protein and amino acids. In: Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* Washington DC: The National Academies Press; 2006: 144–155.
10. Congenital sucrase-isomaltase deficiency. www.CSIDinfo.com. Published December 18, 2006. Accessed February 15, 2012.
11. Sucrose and starch in foods. www.CSIDinfo.com. Published December 18, 2006. Accessed February 15, 2012.
12. Treem WR, McAdams L, Stanford L, et al. Sacrosidase therapy for congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr* 1999;28:137–42.
13. Genetics Home Reference. Congenital sucrase isomaltase deficiency. *http://ghr.nlm.nih.gov/condition/congenital-sucrase-isomaltase-deficiency.* Published July 2008. Accessed September 16, 2011.

Transient Sucrose and Starch Intolerance

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Before 1964, when Shmerling et al demonstrated that sucrase-isomaltase (SI) is decreased in children with active celiac disease (1), Herter (1908), Heubner (1909), Howland (1921), Fanconi (1938), and Andersen (1947) already had shown that patients with celiac disease (CD) did not tolerate sucrose or starch (2–6). By means of continous perfusion of the small intestine with monosaccharides and disaccharides, Beyreiss and Hoepffner demonstrated a clinically relevant loss of lactose digestion and a less pronounced but still significant decrease in sucrose digestion associated with villous atrophy, which is present in several intestinal diseases in addition to CD such as inflammatory bowel disease, food allergy, infectious diseases, protein-energy malabsorption, and immunodeficiencies (7). The decrease can be reversed by successful treatment of the underlying disease. In the case of CD, the digestion of disaccharides is significantly improved after several weeks on a gluten-free diet. Reexposure to gliadin, however, results in renewed reduction of lactose and sucrose digestion (8). Studies have shown that sucrase activity, which is reduced in active CD, increases during remission when a gluten-free diet is prescribed. After 2 years, however, recovery of sucrase activity in the distal duodenum does not reach that of controls, although the clinical effect is observed much sooner (9,10). Villous atrophy in CD occurs by means of apoptosis induced by gliadin (11) and by interleukin-15 secreted by enterocytes inducing NKG2D on intraepithelial lymphocytes (12). The decline of disaccharidase activities occurs within 4 hours of exposure to gliadin (13). During this time, alterations can be noted in villous height-to-crypt depth ratio, enterocyte height, and intraepithelial lymphocyte count (14). In CD, secondary disaccharidase deficiency correlates with low-grade mucosal lesions (15,16). Sucrase activity also is suppressed by gliadin in the organ culture of biopsies from patients with CD (17).

In addition to the loss of enterocytes in villous atrophy, proinflammatory cytokines from the epithelium and dendritic cells and lymphocytes of the lamina propria contribute to the suppression of some disaccharidases. Interleukin-6 and interferon-γ decrease SI synthesis in Caco2 cells, in contrast to tumor necrosis factor-α, which increases its synthesis; such an effect could not be demonstrated for lactase (18). Expression and activity of SI also is decreased in the small intestine of the 2,4,6-trinitrobenzene sulfonic acid–induced colitis model (19). There is evidence that SI can be localized in the cytosol of a significant part of enterocytes under inflammatory (dysplastic) conditions (20). This is evident in cells characterized by rapid uptake of antigen into the cytosol of enterocytes (21). The labeling density of SI on the apical membrane, or rapid uptake of antigen into the cytosol of enterocytes cells, is decreased strongly. The cytoskeleton, which consists of actin and the actin-associated protein, villin, is severely altered in these cells. Gliadin but not ovalbumin binds to actin, affecting the cytoskeleton and SI biosynthetic transport to the apical membrane (22,23). SI also was found in the cytosol of Caco2 cells after disruption of the brush border assembly, induced by inhibition of villin expression using antisense RNA (24). The mechanism of the cytosolic localization of SI is still obscure.

The phenotypic heterogeneity of secondary (transient) sucrose intolerance is widespread and characterized by normal morphology of the mucosa. Besides perfusion studies, several diagnostic tools are available. A ^{13}C-breath test after a ^{13}C-sucrose load is a noninvasive approach to measure sucrose digestion (25). Genotyping allows the determination of mutations, including compound heterozygosity, which have effects on folding and function of SI as demonstrated in expression studies (26). Frozen intestinal biopsies can be assayed for in vivo enzyme activity (27), mosaic expression pattern (28,29), and subcellular localization of SI. Such diagnostic tests may help differentiate secondary from primary sucrose intolerance.

REFERENCES

1. Shmerling DH, Auricchio S, Rubino A, et al. Secondary deficiency intestinal disaccharidase in celiac disease. Quantitative determination of the enzymatic activity and clinical diagnosis. *Helv Paediatr Acta* 1964;19:507–27.
2. Fanconi G. Der intestinale Infantilismus and ähnliche Formen der chronisch Verdauungsstörung. Ihre Behandlung mit Früchten und Gemüsen. Berlin: S. Karger; 1928.
3. Andersen DH. Celiac syndrome. VI. The relationship of celiac disease, starch intolerance and steatorrhea. *J Pediatr* 1947;30:564–82.
4. Howland J. Prolonged intolerance to carbohydrates. *Trans Am Pediatr Soc* 1921;33:11.
5. Heubner O. Über schwere Verdauungsinsuffizienz beim Kinde. *Jahrb Kinderheilkd* 1909;70:667.
6. Herter CA. *On Infantilism From Chronic Intestinal Infection, Characterized by the Overgrowth and Persistence of Flora of the Nursing Period; Study of the Clinical Course, Bacteriology, Chemistry and Therapeutics of Arrested Development in Infancy.* New York: Macmillan; 1908.
7. Beyreiss K, Hoepffner W. Digestionsraten von Laktose und Saccharose sowie Absorptionsraten von Glukose, Galaktose und Fruktose im Jejunum von Saeuglingen und Kleinkindern mit erworbener Laktosemaldigestion. *Dtsch Gesundheitsw* 1976;31:1071.
8. Beyreiss K, Teichmann B, Mueller D, et al. Einfluss von Gliadin auf die Funktion der Duenndarmschleimhaut bei Patienten mit Zoeliakie; Perfusionsstudien. *Wiss Z Karl Marx Univ Math Naturwiss* 1988;37:5.
9. Grefte JM, Bouman JG, Grond J, et al. Slow and incomplete histological and functional recovery in adult gluten sensitive enteropathy. *J Clin Pathol* 1988;41:886–91.

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10. Sjostrom H, Noren O, Krasilnikoff PA, et al. Intestinal peptidases and sucrase in coeliac disease. *Clin Chim Acta* 1981;109:53–8.
11. Giovannini C, Matarrese P, Scazzocchio B, et al. Wheat gliadin induces apoptosis of intestinal cells via an autocrine mechanism involving Fas-Fas ligand pathway. *FEBS Lett* 2003;540:117–24.
12. Malamut G, El Machhour R, Montcuquet N, et al. IL-15 triggers an antiapoptotic pathway in human intraepithelial lymphocytes that is a potential new target in celiac disease-associated inflammation and lymphomagenesis. *J Clin Invest* 2010;120:2131–43.
13. Bramble MG, Zucoloto S, Wright NA, et al. Acute gluten challenge in treated adult coeliac disease: a morphometric and enzymatic study. *Gut* 1985;26:169–74.
14. Sturgess R, Day P, Ellis HJ, et al. Wheat peptide challenge in coeliac disease. *Lancet* 1994;343:758–61.
15. Mones RL, Yankah A, Duelfer D, et al. Disaccharidase deficiency in pediatric patients with celiac disease and intact villi. *Scand J Gastroenterol* 2011;46:1429–34.
16. Nieminen U, Kahri A, Savilahti E, et al. Duodenal disaccharidase activities in the follow-up of villous atrophy in coeliac disease. *Scand J Gastroenterol* 2001;36:507–10.
17. Fluge G, Andersen KJ, Aksnes L, et al. Brush border and lysosomal marker enzyme profiles in duodenal mucosa from coeliac patients before and after organ culture. *Scand J Gastroenterol* 1982;17:465–72.
18. Ziambaras T, Rubin DC, Perlmutter DH. Regulation of sucrase-isomaltase gene expression in human intestinal epithelial cells by inflammatory cytokines. *J Biol Chem* 1996;271:1237–42.
19. Amit-Romach E, Reifen R, Uni Z. Mucosal function in rat jejunum and ileum is altered by induction of colitis. *Int J Mol Med* 2006;18:721–7.
20. Andrews CW Jr, O'Hara CJ, Goldman H, et al. Sucrase-isomaltase expression in chronic ulcerative colitis and dysplasia. *Hum Pathol* 1992;23:774–9.
21. Kersting S, Bruewer M, Schuermann G, et al. Antigen transport and cytoskeletal characteristics of a distinct enterocyte population in inflammatory bowel diseases. *Am J Pathol* 2004;165:425–37.
22. Reinke Y, Behrendt M, Schmidt S, et al. Impairment of protein trafficking by direct interaction of gliadin peptides with actin. *Exp Cell Res* 2011;317:2124–35.
23. Reinke Y, Zimmer KP, Naim HY. Toxic peptides in Frazer's fraction interact with the actin cytoskeleton and affect the targeting and function of intestinal proteins. *Exp Cell Res* 2009;315:3442–52.
24. Costa de Beauregard MA, Pringault E, Robine S, et al. Suppression of villin expression by antisense RNA impairs brush border assembly in polarized epithelial intestinal cells. *EMBO J* 1995;14:409–21.
25. Robayo-Torres CC, Opekun AR, Quezada-Calvillo R, et al. 13C-breath tests for sucrose digestion in congenital sucrase isomaltase-deficient and sacrosidase-supplemented patients. *J Pediatr Gastroenterol Nutr* 2009;48:412–8.
26. Alfalah M, Keiser M, Leeb T, et al. Compound heterozygous mutations affect protein folding and function in patients with congenital sucrase-isomaltase deficiency. *Gastroenterology* 2009;136:883–92.
27. Dahlqvist A. Method for assay of intestinal disaccharidases. *Anal Biochem* 1964;7:18.
28. Reinshagen K, Keller KM, Haase B, et al. Mosaic pattern of sucrase isomaltase deficiency in two brothers. *Pediatr Res* 2008;63:79–83.
29. Nichols BL, Carrazza F, Nichols VN, et al. Mosaic expression of brush-border enzymes in infants with chronic diarrhea and malnutrition. *J Pediatr Gastroenterol Nutr* 1992;14:371–9.

Dietary Issues in Recurrent Abdominal Pain

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The term recurrent abdominal pain (RAP), based on the pioneering work of Apley and Naish, describes children who have chronic abdominal pain without an identifiable organic basis (1). Community-based studies worldwide show that 10% to 46% of children 4 to 16 years old meet the criteria for RAP (2–5). Based on other reports and data from our institution, RAP accounts for approximately 25% of visits to a pediatric gastroenterologist/nurse practitioner (4,6,7). The pediatric Rome III committee introduced the term *abdominal pain–related functional gastrointestinal disorders* (APFGIDs) to supersede the term RAP (8). APFGIDs include 4 phenotypic subtypes: functional abdominal pain (FAP), irritable bowel syndrome (IBS, essentially, FAP with changes in stooling pattern), functional dyspepsia, pain in the upper abdomen), and the relatively rare disorder, abdominal migraine (8). APFGIDs are associated with variable levels of symptoms and distress, ranging from episodic mild to severe abdominal pain, often disruptive to school and other activities. Evidence demonstrates that 30% to 66% of children with RAP experience pain similar to that of adults and meet the adult Rome criteria for IBS (9–12).

Although the etiology of APFGIDs is likely multifactorial, in some patients diet may play a critical role. This is an important area for study because the symptoms of APFGIDs (eg, abdominal pain, diarrhea, constipation) also can be caused by nutrient malabsorption (eg, lactose intolerance) or inadequate intake (eg, lack of dietary fiber leading to constipation). There are, however, a limited number of large, well-controlled studies of the role of diet in children and adults with APFGIDs. Because of space limitations, only FAP and IBS are discussed in this brief review.

Three pediatric studies prospectively evaluated the role of fiber in the pathogenesis of pain in APFGIDs. Christensen reported no benefit of psyllium in a randomized trial, but critical information from the report is missing (eg, *P* values, standard deviations), making interpretation of the results difficult (13). Corn fiber was suggested to be beneficial in a study by Feldman et al, but as in the Christensen article, critical information is lacking, limiting interpretation (14). In a study by Humphreys and Gevirtz, benefit was found for increasing dietary fiber (>10 g/day), but the type of fiber used was not described (15). Retrospective studies suggest a benefit of increased fiber intake in reducing the risk of abdominal pain in children (16,17). Even in adult studies of IBS, there is controversy regarding the effectiveness of psyllium fiber supplementation in patients with IBS (18,19).

Fructose may cause osmotic diarrhea and be a substrate for colonic bacterial fermentation and gas production, resulting in abdominal pain; however, given a large enough dose, even healthy individuals will malabsorb fructose and develop symptoms (20,21). That said, studies in adults suggest that poorly absorbed, fermentable oligo-, di-, and monosaccharides and polyols contribute to

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