Transient Carbohydrate Malabsorption and Intolerance in Diarrheal Diseases of Infancy

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Carbohydrate intolerance has been shown to be common during and immediately following an episode of diarrhea, particularly in infancy and childhood. When these infants and children are maintained on diets with high concentrations of a specific carbohydrate or class of carbohydrates, the symptoms will continue and often increase in severity. On removal of the carbohydrate(s) from their diet for a relatively short period, the infants recover; most infants so affected will have no return of carbohydrate intolerance even on long-term follow-up.

Transient carbohydrate intolerance, in conjunction with chronic malabsorption, was recognized in the early 1920s. In the subsequent decades, studies of carbohydrate intolerance have revealed a common mechanism, i.e., disaccharidase deficiency. However, congenital absence of disaccharidases has been shown to represent only a small percentage of the infants suffering from chronic diarrhea. It was not until the 1960s that Weijers (1) proposed the hypothesis of secondary disaccharidase deficiency as the underlying mechanism for the majority of the carbohydrate intolerance associated with persistent diarrhea. As the name implies, the disaccharidase deficiency is initiated and sustained by any process that damages the mature enterocytes. This entity has been called by various names, including temporary, secondary, or acquired carbohydrate intolerance. All refer to conditions that injure the small intestinal mucosa, resulting in carbohydrate maldigestion and malabsorption manifest by carbohydrate intolerance. This chapter will concentrate on this entity, with carbohydrate malabsorption associated with specific diarrheas mentioned only briefly.

SECONDARY CARBOHYDRATE INTOLERANCE

Carbohydrate, particularly disaccharide, intolerance occurs as a transient phenomenon in a wide variety of diarrheal diseases of infancy and childhood. The location of disaccharidases in the brush border of the mature small intestinal epithelial cells explains their relative susceptibility to the adverse effect of damage to the intestinal mucosa. The pathogenesis of this syndrome is usually a deficiency of lactase alone or, occasionally, in combination with sucrase and maltase.
correlation between the severity of disaccharidase deficiency and the degree of mucosal damage has been shown in some (Table 1) (2) but not all studies (3). Similarly, the lack of correlation between mucosal destruction and disaccharide malabsorption has also been described in some studies. In an early study of intractable diarrhea in young infants, Avery et al. (4) reported diffuse, generalized destruction of the mucosa of many infants who succumbed to the diarrhea, but only a small percentage of these infants showed an increase in reducing substances in their stools following disaccharide feeding when evaluated prior to death. This finding may be explained, in part, by the insensitivity of the method used to detect carbohydrate or by near total metabolism of the ingested carbohydrate by colonic flora.

The duration of disaccharidase deficiency in infants with severe small intestinal mucosal injury following various diarrheal syndromes has been reported to be variable. Barnes and Townley reported that infants with severe intestinal mucosal injury following acute gastroenteritis had normal histology and disaccharidase activities at 3 days, 5 days, and 7 weeks (5). Greene et al. found a return to normal disaccharidase levels by 6 to 9 weeks in infants with intractable diarrhea of infancy (6). Shwachman et al. reported that one case of protracted diarrhea of infancy showed lactase deficiency even after 34 months (7). Rossi et al. recently showed that most mucosal injury in intractable diarrhea of infancy did not resolve even after 24 weeks of appropriate therapy and improvement in nutritional status (2). The transient nature of the symptoms has been further confirmed by a return to disaccharide tolerance after recovery from diarrhea (8–10).

Another cause of carbohydrate intolerance in diarrheal diseases is a reduction in the capacity of the small intestine to absorb monosaccharides; fortunately, only a minority of infants with disaccharide intolerance have monosaccharide malabsorption. In an early series reported by Sunshine and Kretchmer, none of their infants with chronic diarrhea and intolerance to disaccharides showed any defect in glucose transport (9). Bowie et al. similarly reported that in a group of malnourished infants with diarrhea and lactose intolerance, all infants studied showed efficient uptake of glucose (11). In another report of 22 infants

<table>
<thead>
<tr>
<th>Atrophy grade</th>
<th>No. of patients</th>
<th>Lactase</th>
<th>Sucrase</th>
<th>Maltase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>31</td>
<td>32.1 ± 5.83</td>
<td>52.1 ± 3.08</td>
<td>179.1 ± 8.99</td>
</tr>
<tr>
<td>I</td>
<td>4</td>
<td>27.4 ± 6.87 (85%)</td>
<td>44.3 ± 11.3 (85%)</td>
<td>128.9 ± 20.6 (72%)</td>
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<tr>
<td>II</td>
<td>16</td>
<td>20.4 ± 2.3 (64%)</td>
<td>40.6 ± 2.8 (79%)</td>
<td>125.4 ± 7.4 (70%)</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>10.3 ± 1.6 (32%)</td>
<td>20.9 ± 3.3 (40%)</td>
<td>74.6 ± 19 (42%)</td>
</tr>
<tr>
<td>IV</td>
<td>14</td>
<td>7.4 ± 1.6 (22.5%)</td>
<td>24.0 ± 2.4 (46%)</td>
<td>73.9 ± 2.9 (41%)</td>
</tr>
</tbody>
</table>

* Values are means ± SEM. Percent of normal is shown in parentheses.
with acute diarrhea, perfusion studies showed significant impairment of lactose absorption but only minimal impairment of glucose absorption (12). In a group of infants with severe diarrhea and bacterial overgrowth, Coello-Ramirez and Lifshitz showed that 60% had intolerance of disaccharides, but only 6% of the same group showed intolerance to monosaccharides (8). Further, those patients that demonstrated monosaccharide intolerance had the most severe infection. In a selected group of patients reported by the same investigators, however, all 23 patients showed mono- and disaccharide intolerance, with impaired monosaccharide uptake after an episode of gastroenteritis (10). Thus, defects in monosaccharide absorption may also occur in more severe cases of diarrhea.

In our study of the absorption of corn syrup sugars in infants recovering from an episode of acute diarrhea, those infants with normal to moderate mucosal atrophy absorbed both glucose and corn syrup sugars well. In several patients with severe mucosal injury, when their capacity to absorb glucose was impaired, they were also unable to absorb corn syrup sugars (13). These results also suggest that mucosal injury is the probable cause for acquired monosaccharide malabsorption. Overall, about 15% of the infants we studied will not tolerate a formula containing corn syrup sugar as the sole carbohydrate source; presumably all or nearly all of these have severe damage to their mucosa.

A number of mechanisms have been proposed as causes for mucosal damage. The most commonly recognized are as follows: viral and enteroinvasive bacterial strains; cytotoxins that induce alterations of enterocyte permeability in some cases and cytolyis in extreme cases; plant lectins and agglutinins that bind to carbohydrate moieties of surface membrane glycoproteins; and the detergent effect of bile acids, particularly the deconjugated varieties. The exact modes of action of these factors, individually or in combination, remain speculative and require further elucidation (for details see other chapters in this volume).

Secondary carbohydrate intolerance, however, is not always associated with proven mucosal damage as assessed by light microscopy. In a study by Phillips (14), a few children were found to have disaccharidase deficiency despite a histologically normal small intestinal mucosa. Subtle changes, however, were found when the same specimens were examined under the electron microscope, particularly in the microvillous surface area, which was found to be reduced compared to age-matched normal children.

Such reduction in surface area rather than disruption of microvillus architecture in children with secondary disaccharidase deficiency may be the result of an alteration in membrane metabolism particularly involving those biomolecules that constitute the microvillus. One example would be limitation of repair in the face of a high turnover of membrane components. On the other hand, morphometric studies by Klish et al. (15) in infants with acute acquired monosaccharide intolerance showed that in addition to a reduction of total intestinal surface areas, there was severe distortion and fragmentation of microvilli. In general, it seems that the extent of mucosal damage varies, probably depending on the severity and duration of the disease. In one extreme there is flattening
of mucosa, and in the other extreme there is no detectable structural abnormality but only a change in the membrane physiology (e.g., permeability). In either case, it will affect normal digestion and/or absorption of carbohydrates.

PATHOGENESIS OF SECONDARY CARBOHYDRATE INTOLERANCE

Since carbohydrate intolerance is primarily a result of carbohydrate mal-digestion and/or malabsorption, a knowledge of carbohydrate digestion and absorption is important in understanding the pathophysiology. In a normal individual, a number of carbohydrases including pancreatic amylases, various small intestinal α-glucosidases and β-galactosidases are present in adequate amounts for complete or near-complete hydrolysis of dietary carbohydrates to their constituent monosaccharides. The major products of carbohydrate digestion are glucose, fructose, and galactose. Galactose and glucose are actively transported into the enterocyte by a common carrier. Fructose, however, is transported by facilitated diffusion across the plasma membrane of the enterocytes.

The locations of the small intestinal carbohydrases and monosaccharide carriers on the brush border and their distribution along the villus–crypt axis have important bearings on the pathogenesis of secondary carbohydrate intolerance. Biochemical studies have shown that the brush border carbohydrases, sucrase–isomaltase, glucoamylase, and lactase, are attached to the outer surface of the intestinal brush border membranes (16,17). A major part of the enzyme molecule including the active sites could be removed by mild treatment with papain and low concentrations of mild detergents without affecting the composition and structure of the lipid bilayer (18). In contrast, the glucose–galactose carrier molecule is believed to be an integral part of the membrane structure.

The location of carbohydrases in relation to the carrier molecules in the lipid bilayer of the brush border membrane is depicted schematically in Fig. 1. The peripheral location of the carbohydrases versus the deep-seated carriers may offer a partial explanation for the more common occurrence of secondary disaccharide intolerance. However, this same spatial relationship would not explain the difference in susceptibility of different disaccharidases to mucosal damage. If, indeed, all disaccharidases are peripherally located, it is difficult to visualize, at least mechanistically, why lactase is the first to diminish in mucosal injury but the last to return during the recovery phase. Perhaps there are more subtle structural and spatial arrangements that make lactose the most sensitive of the disaccharidases to be affected in case of mucosal damage.

The characteristic distribution of disaccharidases and carriers along the villus–crypt axis offers a different mechanism for the development of secondary disaccharide and monosaccharide intolerance. Disaccharidases and monosaccharide carriers are primarily found in the apical brush border membrane of mature epithelial cells but are nearly absent in the crypt cells. Maximal hydrolase and
carrier activities develop during the upward migration of the enterocyte through the middle and upper villous regions. Any factor that accelerates the migration rate will leave insufficient time for the maturation of these enterocytes and will in turn affect the overall digestive and absorptive capacity of the small intestine. Indeed, in a piglet model with transmissible gastroenteritis, Hamilton and associates have shown that the cells isolated from the villi become more crypt-like in enzyme profile following infection. This suggests a replacement of villous cells with immature enterocytes that lack both transport and hydrolase molecules (19).

Recent recognition of the role of the colon in carbohydrate absorption (20) has made investigators aware of yet another mechanism for acquired carbohydrate malabsorption in diarrhea. Normally, colonic salvage occurs with great efficiency when the small intestinal flow rate is moderate and the flow rate in the colon is slow. Any damage to the colon, such as bacterial overgrowth or inflammation (21), will lead to a decrease in colonic salvage. In the case of diarrhea, a significant decrease in intestinal transient time occurs (22). This decreases the absorption in both the small intestine and colon. In addition, the abnormal load of unabsorbed carbohydrate and increased volume that exits from the ileum may exceed the absorptive capacity of the colon; hence, malabsorption and further diarrhea will result.
TYPES OF DIARRHEA ASSOCIATED WITH SMALL INTESTINAL MUCOSAL INJURY

There are numerous types of diarrhea, most with unknown or ill-defined etiology. Only those that are more common or those that have been studied in reasonable detail are mentioned here.

Infection

_Virus Mediated_

In 1973, human rotavirus was first recognized as a major cause of acute gastroenteritis in young infants (23). The diarrhea is usually of short duration, lasting 3 to 7 days. In spite of the short duration, studies have shown the presence of structural abnormalities in the duodenal mucosa in many of the affected children. In two separate reports, many of the affected infants had abnormally low mucosal disaccharidase levels (5,24). Carbohydrate absorption tests performed on these patients were inconsistent between reports. Analysis of stools from affected infants revealed no significant increase in carbohydrate concentration in both the Toronto (25) and Australia series (24). In contrast, in a British study, the absorption of D-xylose, as assessed by the 1-hr serum xylose test following an intraduodenal infusion of the sugar, was found to be significantly below the normal level in patients who had rotavirus in their small intestinal aspirate and stool (26). It was further shown that xylose absorption increased in these same individuals following recovery. There is therefore a close association between xylose malabsorption and presence of intraluminal rotavirus. In view of the documented abnormal disaccharidase concentration and mucosal abnormalities, it is likely that carbohydrate malabsorption may occur transiently in the acute phases of this diarrheal disease.

_Bacteria Mediated_

Infectious gastroenteritis, as the classical example of bacterial involvement in diarrhea of infancy, has received considerable attention. The intricate relationship among bacterial colonization, malnutrition, and diarrhea has begun to emerge. The question of cause and effect among bacterial overgrowth, diarrhea, and carbohydrate intolerance has been raised (8). In a study involving 50 infants with severe acute diarrhea, all had bacterial overgrowth in their small intestine and were shown to have carbohydrate intolerance. There seemed to be a direct relationship between bacterial counts in the duodenal aspirates and the degrees of carbohydrate intolerance. In addition, when the patients recovered from the diarrhea, the bacterial counts in their duodenal aspirates decreased, accompanied by a return of carbohydrate tolerance. Very similar results were reported by Tomkins in patients with acute tropical sprue, in whom the concentrations of aerobic bacteria in the proximal jejunal lumen were found to be closely associated
with jejunal functional abnormalities (27). Although the relationship between bacterial overgrowth and carbohydrate intolerance is demonstrable, it is not clear whether the initial event is the presence of unabsorbed carbohydrate in the small bowel, promoting bacterial colonization, or the colonization of the small bowel by bacteria, as the cause of malabsorption of carbohydrates. In either case, damage to the small intestinal mucosa seems to occur prior to carbohydrate malabsorption.

One result would be decreases in disaccharidase activities. Indirect evidence from animal studies suggests that microorganisms do play a role in modifying mucosal disaccharidase concentrations. Thus, germ-free rats have higher disaccharidase activities than rats maintained in a conventional environment (28,29), and infection of germ-free rats with cecal content from control rats led to a reduction of disaccharidase activities (28). Presumably, a similar type of microbial influence may be operating in the human small intestine, particularly in the case of bacterial overgrowth in infants and children.

Parasite Mediated

Diarrhea caused by parasitic infestation of the small intestine has been studied to a limited extent in humans, and most of these studies describe giardiasis in childhood. Chronic diarrhea and malabsorption are the predominant features in children infested with *Giardia lamblia*. Although malabsorption of glucose, lactose, and xylose is prevalent (30), most giardiasis patients exhibit normal morphology or mild to moderate mucosal atrophy (31,32). Further, in two patients in whom mucosal disaccharidases were measured (32), both showed normal lactase, sucrase, and maltase activities on small intestinal biopsy. Both patients had chronic diarrhea with proven giardiasis. Thus, malabsorption of carbohydrate, at least in these two cases, is not the result of generalized losses of mucosal enzymes; focal lesions cannot be ruled out by this method. It has been suggested by the investigators that the diarrhea results from increased secretory activity by the crypts and increased cellular turnover. This results in a mucoid layer covering the entire mucosal surface, which acts as a barrier against the diffusion of nutrients. Irrespective of the mechanism, some sort of cellular damage associated with carbohydrate malabsorption in giardiasis seems to occur.

Investigation of diarrhea caused by other parasites, especially the effects on carbohydrate digestion and absorption, are rare. In rats with nematode infestation, diarrhea develops in severe cases. More importantly, evidence of mucosal injury with an accompanying decrease in brush border maltase and reduced uptake of glucose has been documented (33). It is not known whether the mucosal injury and dysfunction in carbohydrate digestion and absorption are the result of parasitic invasion of the intestinal mucosa or are secondary to the diarrhea. It is likely that in most cases of parasitic infestation, mucosal changes are caused by inflammation of the small bowel, as has been demonstrated in the case of
rats infected with *Trichinella spiralis* (34). Since parasitic infestation is more common in the developing countries, studies of carbohydrate tolerance in the affected individuals, particularly infants, are essential to further our knowledge in this area.

**Hypersensitivity to Food Proteins**

*Celiac Disease (Gluten-Sensitive Enteropathy)*

Malabsorption is a well-known feature of celiac disease. A defect in the absorption of xylose in adult celiac patients was observed when the sugar was given either orally (35) or by intestinal perfusion (36). In most cases, the patients showed both diarrhea and mucosal injury (36). In a large group of infants and young children with celiac disease, almost all with mucosal injury had an abnormal 1-hr blood xylose test (37). Similar observations have been reported recently in a study comparing patients with celiac disease, acute infectious diarrhea, and intractable diarrhea of infancy (38). Good correlation was found between the impairment of xylose absorption and the severity of mucosal injury. More important, a reduction in disaccharidase activities was demonstrated in patients with gluten-sensitive enteropathy (39,40).

*Milk and Soy Protein Sensitivity*

A number of infants under 1 year of age with protracted diarrhea have been found to be intolerant of milk-based and/or soy-based formulas. Iyngkaran studied one such group of infants and found that feeding cow's milk provokes diarrhea with increased reducing sugar concentrations in the stool of most infants so affected (41). In addition, following provocation, many of the same infants showed mucosal injury associated with a marked decrease in maltase, lactase, and sucrase activities (41). Acquired carbohydrate intolerance in such patients seems to be inducible by either cow's milk or soy milk. In a separate study by Powell (42), a positive response consisting of diarrhea and transient carbohydrate malabsorption was seen, such that a majority of the affected infants have abnormal lactose tolerance tests and increases in their stool carbohydrate concentrations. The pathophysiology of the carbohydrate malabsorption in these patients presumably is mucosal injury (43). In an infant with a history of intolerance to eggs reported by Iyngkaran (44), an egg protein challenge resulted in profuse diarrhea shortly thereafter. Small bowel biopsy 48 hr after challenge showed marked atrophy of villus architecture, reduction of disaccharidase concentrations, and depressed xylose absorption responses. Carbohydrate malabsorption in all of these cases is, therefore, secondary to mucosal injury. Whether mucosal injury was a result of the diarrhea itself, an immunologic reaction, or both is not known. Similarly, the incidence and prevalence of this disorder are unknown.
Diarrhea is almost always a part of the syndrome of protein–energy malnutrition (PEM) in infants and young children. Associated with the diarrhea, these children also exhibit intestinal malabsorption of carbohydrates (45). Severe malabsorption of glucose, xylose, and other nutrients has been found in malnourished children (46). Bowie et al. showed a decrease in lactose tolerance with concomitant decreases in disaccharidase activities in mucosal biopsies of the affected children (11). James (47) also noted poor glucose absorption, lack of lactose hydrolysis, and defective sucrose hydrolysis in children with moderate or severe PEM. Viteri and Schneider found a marked decrease in $d$-xylose and glucose absorption associated with kwashiorkor (48). All of these data suggest that malnutrition, particularly PEM, leads to a derangement of the intestinal mucosal morphology and function and thus an impairment of their hydrolytic and transport mechanisms for di- and monosaccharide malabsorption, respectively.

Morphometric studies of the mucosa in children with PEM confirm the biochemical and physiological findings. Reported changes include a reduction in mucosal thickness, cellular infiltration (49), flattening of the mucosa, loss of villi, elongation of crypts, and loss of refringence of the brush border area (50) in severe cases of kwashiorkor. A recent study by Romer et al. (3) compared the degree of malnutrition and reduction of disaccharidases and severity of mucosal atrophy. Their results showed a good correlation between the degree of malnutrition and reduction in disaccharidase activities. But in spite of a marked disaccharidase deficiency in severely malnourished children, the mucosal morphology showed only a moderate degree of atrophy (grade I to grade II according to the classification of Schenek and Klipstein). This implies that biochemical parameters are more sensitive than morphometric parameters in determining the degree of mucosal alteration in PEM.

As with the other factors discussed, malnutrition itself may be the primary causative agent for diarrhea and carbohydrate malabsorption, but suboptimal management of the diarrhea can also lead to malnutrition, thereby compounding the problem, i.e., perpetuating the so-called vicious cycle.

Miscellaneous Mechanisms

A highly lethal form of familial protracted diarrhea of yet unknown etiology has been reported by Harries's group in Great Britain (51). The diarrhea begins early in infancy, with some even starting on the first day of life. Of the cases studied, many showed marked decrease in glucose absorption, and one case also showed reduction in fructose uptake. Some affected patients also showed villous atrophy and low disaccharidase activities. A few patients have recovered spontaneously and survived. It is unknown whether the defect in monosaccharide uptake is the cause or the result of the diarrhea.
OVERVIEW

In diarrheal diseases of infancy, irrespective of the etiology, there seems to be an impaired absorption of carbohydrates. The underlying mechanisms(s) has not been clearly defined. Reported evidence has strongly identified mucosal injury as the final common pathway of the biochemical and functional derangements. Subnormal levels of disaccharidases result, leading to a reduction in the capacity to digest disaccharides. In severe cases, a decrease in absorptive surface, and hence a reduction in the number of carrier molecules, would limit the uptake of monosaccharides (Fig. 2). Mucosal damage may be an event caused by (a) viral or bacterial infection or parasitic infestation, (b) food protein hypersensitivity (celiac disease and milk protein allergy), or (c) malnutrition. Mucosal injury can also be a secondary event, i.e., a result of prolonged severe diarrhea.

Since carbohydrate intolerance occurs during the acute stages of diarrhea, and diarrhea itself has adverse effects on mucosal integrity, dietary carbohydrates may have a deleterious effect by aggravating diarrheal symptoms and prolonging or exaggerating mucosal injury. This then contributes to a vicious cycle of mucosal injury and carbohydrate malabsorption (Fig. 3). Temporary restriction of dietary carbohydrates, especially in the di- and oligosaccharides, in the active phase of the disease will, in most incidences, disrupt the cycle. In a majority of these patients, the mucosal injury and the associated dysfunction, including carbohydrate intolerance, then become a transient phenomenon. Improvement of diarrhea, accompanied by a recovery of intestinal disaccharidase activity and absorptive surface area, is usually achieved with a return of tolerance to carbohydrates. Thus, in children and infants with persistent diarrhea or severe acute diarrhea, in anticipation of a possible mono- and disaccharide intolerance, it is imperative that the amount of mono- and disaccharide, particularly lactose, in their diets be strictly regulated to minimize further damage to their small bowel mucosa. This is especially critical in case of acquired monosaccharide intolerance. Fortunately, this entity occurs in only a small percentage of diarrheal infants, usually in association with more severe symptoms and/or recurrence of diarrhea. In these cases, the patients not only will not tolerate glucose but also will not tolerate glucose polymers such as polycose (52) or corn syrup sugars (13). Enteral feeding of carbohydrate in these patients should be avoided. In both cases, an alternative source or route of calories should be employed to insure an adequate energy intake to promote recovery.

One last, but not least, point relates to the observed changes in intestinal permeability to sugars in villous atrophy associated with celiac diseases (53,54). Menzies and others showed that celiac patients absorbed more lactulose (up to 300–400%) (53) and cellubiose (30–40 times) (54) but less rhamnose, mannitol, and xylose than did normal individuals. This alteration in permeability is further exaggerated by an increase in intraluminal osmolarity (55). The significance of
villous atrophy in the selective increase of intestinal permeability, especially towards sugars that are not normally absorbed as intact molecules, is not certain at present. Presumably, it may increase the chances of absorption of molecules
(including various sugars) that may not be compatible with the patient, thus providing further pathogenic stimulus. As such, it provides another reason for restricting enteral feeding of carbohydrates in severe villous atrophy.

REFERENCES