15.10.5 Disaccharidase deficiency 2902

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section 15 Gastroenterological disorders 2902 FURTHER READING Cellier C, et al. (2000). Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. Lancet, 356, 203–8. De Leeuw RJ, et al. (2007). Whole genome analysis and HLA geno typing of enteropathy-type intestinal T-cell lymphoma reveals two distinct lymphoma subtypes. Gastroenterology, 132, 1902–11. Isaacson PG, Du M-Q (2004). Malt lymphoma: from morphology to molecules. Nat Rev Cancer, 4, 6644–53. Isaacson PG, Du M-Q (2005). Gastrointestinal lymphoma: where morphology meets molecular biology. J Pathol, 205, 255–74. Swerdlow SH, et al. (eds) (2017). WHO classification of tumours of hae- matopoietic and lymphoid tissues. IARC, Lyon. Wotherspoon AC, et al. (1991). Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. Lancet, 338, 1175–6. Wotherspoon AC, et al. (1993). Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet, 342, 575–7. 15.10.5 Disaccharidase deficiency Timothy M. Cox ESSENTIALS Disaccharidases are abundant enzymes expressed on the microvillous membrane of the small intestine: apart from free glucose and fruc- tose, disaccharidases are required for the complete assimilation of nearly all carbohydrate present in food and drinks. The enzymes cleave disaccharides such as sucrose, maltose, and lactose, as well as dextrins derived from starch, into their component monosacchar- ides. Their activity is reduced in hereditary conditions or in general- ized intestinal diseases. Disaccharidase deficiency causes dietary intolerance of carbo- hydrate induced by the fermentation of undigested sugars in the distal small intestine and colon. Abdominal symptoms (e.g. nausea, bloating, distension, colicky pain, watery diarrhoea) are usually noticed within an hour of the ingestion of foods containing the offending sugars. By far the most common symptomatic disaccharidase deficiency is lactose intolerance. Lactase activity is high in healthy infants when milk is the principal food, but in most humans the activity declines after weaning and remains low (lactase nonpersistence), which greatly reduces the capacity to break down lactose. In contrast, those inheriting a Mendelian dominant trait that leads to sustained high intestinal lactase expression throughout life (lactase persistence) digest and tolerate large quantities (loading doses >50 g). The dis- tribution of lactase activity in adult populations is subject to great variation: nonpersistence of lactase expression predominates in nearly every population

in East Asia, whereas in those of Northern and central European origin, and in Afro-Arabian nomads who have developed or maintained pastoralist dairy cultures, intestinal lactase expression is sustained lifelong. Intestinal lactase phenotypes can be identified by assay of mu- cosal biopsy samples or appropriate sugar tolerance tests, as can other (much rarer) genetically determined disaccharidase variants. The most convenient diagnostic screen involves hydrogen breath testing after oral loading. Disaccharide intolerance is readily treated by institution of a strict exclusion diet; oral enzymatic supplementation may benefit patients with severe enzymatic deficiency. Innovative and early phase clinical trials suggest that modulation of the host intestinal microbiome with a pure short-chain galacto-oligosaccharide may be beneficial in symptom control and in favouring the outgrowth of lactose-fermenting flora. Physiology of carbohydrate digestion Luminal phase See Fig. 15.10.5.1. Free disaccharides occur in the diet or ori ginate from luminal hydrolysis of starch and glycogen by salivary and pancreatic α-amylase. Since amylase cannot hydrolyse the α- 1,6 branching linkages that contribute to the complex arborized structure of starch and glycogen, and has little action on the linear α-1,4 bonds adjacent to these points, the initial products of starch digestion are branched oligosaccharides containing at least one α- 1,6 bond. Maltase–glucoamylase is a mucosal α-glucosidase that removes glucose moieties sequentially from the nonreducing ter minus of linear oligosaccharides to generate limit α-dextrins within the lumen; these are branched, short-chain carbohydrate molecules. Mucosal phase Isomaltase (α-dextrinase) catalyses the last stages of starch diges tion at the intestinal brush border by cleaving the α-1,6 glycosidic bonds of the limit dextrins released by amylase. Isomaltase is a com ponent of the bifunctional complex sucrase–isomaltase, the sucrase moiety of which catalyses the hydrolysis of sucrose into fructose and glucose. As with the α-dextrins derived from starch, disaccharides sucrose, lactose, and trehalose are poorly absorbed: to be assimilated, these are also cleaved into their component monosaccharides by the cog nate glycosidases, sucrase, lactase, and trehalase which are also lo cated on the brush border (microvillus) membrane. Mucosal disaccharidases are optimally active at pH 6.0 and are present principally in the duodenum and jejunum; some activity persists in the ileum but is absent in the colon. Lactase is the fa miliar name for lactase–phlorizin hydrolase, a membrane-bound microvillous enzyme with β-galactosidase activity responsible for the cleavage of lactose into its component glucose and galactose moieties. Specific carriers in the microvilli for the transport of glucose and galactose, as well as fructose, mediate the uptake of monosac charides released by the mucosal disaccharidases—and absorption occurs rapidly. Active transport by the sodium-dependent glucose– galactose carrier is accompanied by the passive flux of water from the lumen. Unabsorbed disaccharides are fermented by bacteria in the colon to short-chain organic acids, hydrogen, and methane. Maldigestion of osmotically active sugars thus leads to retention

 of fluid in the gut. When digestion of disaccharides is incomplete, ingestion of carbohydrate induces pain caused by distension of the bowel with fluid and gas, accompanied by watery diarrhoea. For most carbohydrates, hydrolysis in the lumen and at the mu cosal surface is sufficiently rapid for the transport of glucose and fruc tose to occur at maximum efficiency. For lactose, however, the rate of mucosal hydrolysis, rather than glucose and galactose uptake, is often limiting. The functional reserve of lactase in the human intestine is restricted and when there is inflammation or infection of the small intestinal mucosa, assimilation of lactose is often noticeably impaired. Complete turnover of the enzyme molecules occurs several times during the lifespan of the mature enterocyte. While the biosynthesis of disaccharidases and their incorporation into the brush border membrane continues throughout the life of the epithelium, the en zymes are only active in mature epithelial cells on the upper reaches of small intestinal villi.

Brush border disaccharidases are complex glycoproteins that undergo proteolytic processing; extensive glycan modification in the Golgi apparatus occurs before insertion into the membrane. The mature enzymes are derived from large, single-chain polypeptides. The genetically determined mechanism by which lac tase expression decreases after infancy is not fully understood but influences transcription of the lactase gene. Maldigestion: the syndrome of carbohydrate intolerance See Table 15.10.5.1. Abdominal symptoms are usually noticed within 30 to 60 min of ingesting foods containing the offending sugars. There is nausea, bloating, and distension of the abdomen accom panied by borborygmi and flatulence. Colicky pain precedes watery diarrhoea, usually associated with flatus, and it may be explosive; the anal region is often sore as a result of stool acidity. Diarrhoea due to the maldigestion of carbohydrate, particularly starch intolerance, can occur several hours after ingestion of the noxious food or drink. These symptoms may be induced by only a few grams of the offending sugar. Intestinal hurry aggravates fat malabsorption and may obscure the underlying cause of the diarrhoea. Deficiency of particular disaccharidases is responsible for the dietary intoler ance of specific foods and drinks: milk-containing products in the case of lactase deficiency; table sugar and starch in asucrasia; and mushrooms (and probably shellfish) in the rare trehalase deficiency. Given the ubiquity of sucrose and lactose in commercial foods, iden tification of a cause-and-effect relationship between particular items and the intolerance syndrome may be challenging. Lactose intolerance The ability to digest lactose after weaning requires the persistence of lactase activity in the intestinal mucosa. Most patients suffering from intolerance of lactose in the diet suffer either from lactase deficiency acquired as a result of intestinal disease, especially postinfective gastroenteritis in children, or as a result of genetically determined restriction of lactase expression. Primary lactase deficiencies Congenital lactase deficiency A few infants have been reported in whom diarrhoea occurred after the first feed with breast milk and who responded completely to a lactose-free formula feed. This disorder is distinct from congenital glucose–galactose malabsorption, in which lactose exclusion alone is ineffective. Congenital lactose intolerance is associated with mu tations in the human lactase gene which lead to a severe deficiency of mucosal lactase activity and, unlike the intolerance of lactose as sociated with prematurity or secondary to diffuse intestinal disease, are present from birth, and remain lifelong. This syndrome leads to lactosuria due to the abnormal absorption of intact lactose, prin cipally in the stomach; renal tubular acidosis and aminoaciduria have been recorded in this autosomal recessive disease that leads to vomiting, dehydration, and failure to thrive. Lactase deficiency of prematurity Unlike the other mucosal glycosidases, which appear early during fetal development, intestinal lactase activity is not fully expressed until after the 28th week of gestation and transient intolerance of Fig. 15.10.5.1 Carbohydrate digestion and absorption. Table 15.10.5.1 Deficiency of disaccharidases and carbohydrate intolerance Lactose intolerance Congenital (inherited) lactase deficiency Lactase restriction (genetically determined) Lactase deficiency secondary to intestinal disease Sucrose intolerancea Congenital asucrasia (inherited) Sucrase deficiency secondary to intestinal disease Trehalose intolerance Congenital atrehalasia a Accompanied by reduced tolerance of starch.

 milk feeds is common before this age. Abdominal distress due to gaseous distension and diarrhoea requires careful attention to the diet and fluid balance in premature infants. Population genetics of lactase expression A marked decrease in intestinal lactase activity occurs after infancy in about 70% of the global population, but mucosal expression of the enzyme and the capacity to tolerate lactose in the diet varies greatly among human ethnic groups. There is strong evidence that genetic selection for the ability to digest

lactose has occurred in re sponse to nutritional exposure, and possibly other environmental factors such as the length and intensity of sunlight exposure related to the generation of active vitamin D. Where dairy-based products predominate in the diet, for example, in white-skinned people of North European origin, lactase deficiency occurs in about 2% of the population; but studies in the United States of America indicate that lactase deficiency occurs in up to 80% of Hispanic, black, and Ashkenazi Jewish people, and almost all American Indians have lactase deficiency. The age of onset and its prevalence differ among various populations. About one-fifth of Hispanic, Asian, and black children have lactase deficiency and lactose malabsorption before the age of 5 years. Retention of the capacity to digest lactose in adulthood is deter mined by a Mendelian dominant trait. Persistence of high intes tinal lactase activity is unusual in adult mammals, and in humans is believed to have been maintained by selection in populations that adopted dairy culture about 10 000 years ago. Thus, tolerance of lactose in milk and dairy products (and many processed and ready-to-eat foods; see Box 15.10.5.1), is found mainly in peoples of northern and central European descent. Lactose tolerance is also prevalent in the nomadic Tuareg and Bedouin, as well as the Peuhl of Senegal and Nigerian Fulani peoples, all of whom retain strong dairy-based pastoral traditions. In about 5% of northern European adults, compared with more than 90% of adults in most of Africa and Asia, a genetically determined decline in mucosal lactase ac tivity occurs after weaning. Decreased mucosal lactose activity is associated with reduced synthesis of the precursor protein in the epithelial cells with apparently normal processing to the mature en zyme. The physiological decline in activity occurs between 3 and 5 years of age. Low lactase activity, considered in the clinical context as lactase deficiency, is thus the predominant trait among healthy adults world wide. Extensive family studies demonstrate transmission as a simple Mendelian factor: healthy adults with low lactase activity are homo zygous for an autosomal recessive determinant of a physiological decline of lactase activity after weaning (lactase nonpersistence or restriction, also referred to as adult-type hypolactasia). Individuals in whom high lactase activity persists in adult life are either hetero zygous or homozygous for a dominant allele, the persistence allele, which prevents ‘physiological’ decline of lactase activity. Lactase persistence is thus the minor, low-frequency variant, and its high prevalence in specific populations was probably maintained by natural selection in groups that settled to invest in dairy culture from Neolithic times. Recent studies of DNA samples obtained from late Neolithic humans (c.5000 years before present) originating from the Basque region of South-West Europe, show that the frequency of determinants for lactase persistence (27%) was much lower than in modern Basque people. This suggests that evolutionary selection occurred after domestication of cattle, with the adoption of pas toral culture, and that the high frequency of lactase persistence in Europeans is only a recent phenomenon. The development of cheese manufacture, as well as yogurt and other milk fermentation prod ucts such as kvass in which the sugar content is markedly reduced, would allow individuals with diminished capacity to digest lactose to thrive. The elements which determine lactase activity in adults acts in cis with the lactase locus LCT on human chromosome 2q21; how ever, the molecular mechanism which regulates transcriptional and developmental expression of the enzyme in the intestine has yet to be definitively unravelled. The prevailing view is that genetically de termined persistence of intestinal lactase activity is accounted for by at least five independent single nucleotide variants in a regulatory region (a transcriptional enhancer) upstream of LCT. One single nucleotide variant, −13910*T (rs4988235), appears to have reached stable fixation in Europe, while others occur at variable frequencies in the Middle East and Africa. The additional sequence variants in the vicinity of the locus at position −13910 are strongly associated with determinants that lead to persistence of lactase expression in populations of sub-Saharan

African and Afro-Arabian origin. The discovery of an association between these variants and lactase persistence in close proximity (within 100 bp), located within a DNA sequence with demonstrable enhancer functions, indicates that they contribute functionally to the persistence of lactase expression: that they occur on distinct haplotype backgrounds strongly suggests that several mutations led independently to the phenotype of lactase persistence, with strong selection in the different human populations. The high frequencies at which these alleles are found in modern populations have been attributed to positive selection for lactase persistence, allowing free consumption of animal milk by adult humans without intolerance. It is compatible with a selective advantage, namely the potential for lifelong enhanced availability of critical nutrients such as vitamin D from animal sources, but other explanations are possible, including the provision of macronutrients such as dietary protein and fat. The ability of Arabian nomads to digest lactose may have advantaged their migration to Africa. The distribution of the LCT alleles ap pears also to have been affected by expansion, migration, and other Box 15.10.5.1 Foods containing lactose • Fresh, dried, skimmed, non-fat, and condensed milks • Cream • Yoghurt • Cheese • Processed meats and sausages • Sauces, stuffings, salad dressings • Custard powder • Canned and dried soups • Biscuits, cakes, cookies, pancakes, waffles, dried cereals • Confectionery • Frozen and canned fruits • Instant coffee • Lactose is also frequently used as a filler in powdered medicines and tablets

15.10.5 Disaccharidase deficiency 2905 processes in human populations which are related to human cultural preferences and practices. The −13910*T (rs4988235) variant lies approximately 14 kb up stream of the LCT gene and is tightly linked to the persistent lac tase phenotype in several populations widespread in Europe. It represents part of a haplotype extended over more than 500 kb of genomic DNA. Homozygosity for the C allele at this nucleotide position is associated with nonpersistence of lactase expression in adults. Conservation of the haplotype indicates a recent origin and its high frequency suggests that it has been subject to positive se lection through evolution. This polymorphic site might itself de termine lactase expression since it has been shown in transcription assays in vitro that the presence of the −13910 T allele enhances binding of the Oct1 transcription factor, which promotes lactase gene expression. Clinical effects of lactose intolerance Symptoms develop on exposure to excessive milk- and lactose- containing foods or medicines in late childhood or early adult life. The selective pressures that maintain this physiological reduction in mucosal lactase deficiency in childhood are unknown but the concept of ‘lactase deficiency’ in adults is difficult to justify, since lactase persistence is the least frequent state. Nonetheless, with the increasing migration of peoples and the widespread adoption of Western-style diets, physiological loss of lactase activity is a prevalent cause of abdominal distress. A significant proportion of patients with spastic colon, irritable bowel disease, or other ‘func tional’ abdominal disturbances may prove to have lactase defi ciency. Preliminary evidence based on molecular characterization of polymorphic genetic variants on human chromosome 2 associ ated with lactase expression, together with hydrogen and methane breath gas analysis and symptoms, suggests that there may be a genuine association between sensitivity to lactose and inflamma tory bowel disease. However, these putative associations require confirmation. The speculative possibility arises that lactase-deficient subjects are at risk from osteoporosis in countries at high latitudes because of a dietary deficiency of calcium or vitamin D. There is a higher frequency of lactase nonpersistence in osteoporotic women when compared with appropriate control subjects; this extends in some studies to reduced bone mineralization density with increased frac tures. It is presumed, but not proven, that reduced calcium intake is responsible. In contrast, in lactase-

persistent subjects, increased milk consumption may contribute to hyperlipidaemia and coronary heart disease. Moreover, by analogy with the role of galactitol in galactokinase deficiency, a disorder of galactose metabolism asso ciated with cataract (‘galactose diabetes’), sustained consumption of large amounts of milk and lactose-containing foods has been im plicated in the development of premature cataract. There have been several European reports that adults with idiopathic and diabetic senile and presenile cataracts have a higher frequency of lactase per sistence than population controls without cataract and at least one other study has shown that high intake of milk correlated with cor tical cataracts. Similar surveys in populations with a higher general prevalence of lactose persistence showed no correlation; but a high risk of cataract formation has been reported in subjects with high lactose intake and low activities of galactokinase. Diagnosis of lactose malabsorption Intolerance of dietary carbohydrate caused by the maldigestion of lactose may be suspected from the dietary history of a patient typ ically complaining of abdominal pain, flatulence, and diarrhoea. Symptoms are often related to changes in social circumstances and are frequently reported by Asian and some African immigrants to Western countries; they may also become manifest when lactose- rich foods are administered inappropriately to children and adults by Western agencies in famine relief programmes. In this respect, the promotion by large multinational corporations of commercial infant feeds heavily based on milk products has attracted adverse international criticism. The relative lack of functional reserve of mu cosal lactase activity also explains the frequency with which lactose malabsorption becomes manifest after partial gastrectomy and re lated procedures that accelerate delivery of dietary carbohydrate to the jejunum. The stool has an acidic pH (<6) and the osmolality of stool water is generally greater than 350 mosmol/kg because of the presence of lactate and other organic anions; in infants and children with complete lactase deficiency, reducing substances may be abundant in the stool water. Breath-hydrogen analysis is a useful confirma tory test. Hydrogen excretion, determined by rebreathing 2 h after the ingestion of 50 g of lactose, identifies patients with lactase defi ciency diagnosed by enzymatic assay of jejunal mucosa obtained by biopsy. This latter procedure is difficult to standardize and is now rarely justified outside the research setting. A recent meta-analysis comparing the diagnostic accuracy of lactose breath-hydrogen or lactose tolerance tests for predicting the North European lactase −13910 C/T polymorphism confirms a high diagnostic sensitivity and specificity of both tests individually in relation to expected lac tase genotypes in well-defined populations. Other investigations, such as the lactose barium-meal examination and determination of blood glucose profile after oral challenge with lactose, are cum bersome and, because they give false-positive results, are now ob solete. Several initiatives are under way to promote the diagnosis of lactose persistence/nonpersistence by molecular analysis of the lactase–phlorizin hydrolase gene, with particular emphasis on the polymorphic variants at position −13910. However, without a com plete molecular understanding of the mechanisms by which lactase activity is controlled and the occurrence of different lactase haplo types in different populations, genetic diagnosis may not be infal lible in all ethnic groups and the hydrogen breath test offers more a facile and confident means of diagnosis. Secondary lactase deficiency Lactase activity may be depressed by mucosal disease of the small in testine and often occurs transiently after infective gastroenteritis. It is particularly frequent in infants suffering from gastroenteritis due to enterocytopathic viruses, and continuing symptoms provoked by milk feeds can persist for days or some weeks. Dehydration may de velop rapidly in infants and is accompanied by prominent bloating; disaccharidu ria is found and acid, sour-smelling stools may be ob vious. Malabsorbed carbohydrate may be suspected in the field or outpatient clinic by screening for reducing sugars and estimating the acidity of the stool using pH indicator paper, since excess volatile fatty acids

will be generated by colonic bacteria. However, since in fants normally consume larger amounts of lactose, which favours

section 15 Gastroenterological disorders 2906 growth of colonic lactobacilli, their stool is normally more acidic (pH 5.0–5.5) compared with samples from older children and adolescents. The symptoms of carbohydrate intolerance due to secondary deficiency of lactase usually resolve rapidly when dairy products are excluded. Decreased lactase activity also accompanies exten sive and long-standing mucosal disease so that a milk intolerance syndrome due to maldigestion may complicate coeliac disease, intestinal giardiasis, and Crohn's disease. If secondary lactose in tolerance is suspected, then the cause should be sought, including examination of the stool particularly for parasites such as Giardia lamblia and Cryptosporidium spp., and, if possible, enteroviral in fections including rotavirus. Blood tests for coeliac disease (total IgA concentration and antitissue transglutaminase antibodies) or immunodeficiency (leucocyte counts, lymphocyte subsets, and im munoglobulin concentrations as well as serology for HIV) may re veal the underlying cause. Where the diarrhoeal illness is persistent, mucosal biopsy of the small intestine may be needed to identify the cause of acquired lactose intolerance and the presence of underlying mucosal disorders such as coeliac disease. Biopsy also offers greater confidence in the detection of microbial or parasitic invasion; in this context, electron microscopy may provide a definitive diagnosis, for example, rotavirus or enteric protozoal infections in patients with common variable immunodeficiency and other immunodeficiency syndromes. In secondary deficiencies of disaccharidases, because of the crit ical relationship between lactase activity and the rate at which this sugar is digested, intolerance of lactose predominates. However, the use of high-calorie preparations containing large quan tities of disaccharide and short-chain carbohydrates other than lactose (especially maltose, sucrose, and dextrins) to supplement the nutrition of patients with intestinal disease, may exacerbate their symptoms and induce a florid carbohydrate intolerance syndrome. Sucrase–isomaltase (α-dextrinase) deficiency This recessively inherited enzyme deficiency of the mucosal brush border appears to be rare in all populations except the Inuit of Greenland, in whom the frequency of homozygotes is up to 10%. Cetacean mammals also lack sucrase–isomaltase. One recent small- scale study suggests that sucrase-isomaltase deficiency may not only masquerade as irritable bowel syndrome, but be a prevalent cause—the enzyme was considered to be deficient in 11 of 31 adult patients with bloating, abdominal pain and diarrhoea. Of note, pain was not a feature of this group of patients nonetheless considered to have irritable bowel syndrome. Several defects of the human gene on chromosome 3q appear to be responsible; in some, there is ab errant glycosylation and the enzyme is inefficiently transported to the brush border as a result of abnormal folding and other cellular polarization defects. Intolerance of sucrose is responsible for most of the symptoms, which develop as table sugar and sugar-containing foods are intro duced during weaning. Intolerance of starch is less prominent be cause the osmotic contribution of the larger α-dextrin molecules that remain unsplit in the gut lumen is less. However, ingestion of large, starchy meals may induce cramping discomfort, flatulence, and diarrhoea. While taking a normal diet, patients with deficiency of sucrase–isomaltase have persistent diarrhoea with the passage of acid and frothy stools containing increased concentrations of lactate and other short-chain acids. The diagnosis may be suspected on the basis of the history of diarrhoea at weaning and on the character of the stools. In several well-documented cases, inherited deficiency of sucrase–isomaltase presents after childhood, and may first come to light in later adult life. No convincing explanation for this phenomenon has been ad vanced. Differentiation from coeliac disease, cow's milk allergy, infective or postinfective gastroenteritis, pancreatic failure, and other

disaccharide intolerance syndromes (particularly lactose in tolerance, caused by inflammatory bowel disease) is important, and biopsy of the jejunal mucosa for enzymatic assay and histological examination should be considered. In inherited sucrase–isomaltase deficiency, these activities are selectively reduced to less than 10% of control values in histologically normal mucosa. Hydrogen breath tests after ingestion of sucrose and isomaltose may prove to be useful in diagnosis; hydrogen excretion decreases when patients receiving sacrosidase (as opposed to placebo) during oral challenge with su crose, demonstrating the operational effectiveness of enzyme sup plementation for this disorder. Trehalase deficiency A few patients have been reported with mushroom intolerance due to the absence of mucosal trehalase. Trehalase is a brush border α-glycosidase that cleaves the unusual 1α–1α bond of trehalase into its component glucose moieties. Trehalose is found in the haemolymph of arthropods and in fungi, so that intolerance of crustacean shell fish as well as mushrooms in the diet might be expected. Given that intolerance of edible fungi is not uncommon, trehalase deficiency may prove to be more frequent than previously supposed but a study of 400 patients in the United Kingdom by enzymatic assay of intes tinal mucosal biopsies indicated that the deficiency was very rare in this population. Trehalase deficiency has also been reported to occur in at least 8% of Greenland Inuit (and in cetacean mammals from the same environment) but the functional significance of this is unknown. Management Dietary exclusion Dietary exclusion of the offending sugar is the best method of preventing symptoms in individuals with primary or acquired dis accharidase deficiency. Symptoms recur as soon as excessive lactose or sucrose is reintroduced and advice from a professional dietitian may be needed to avoid indiscretions. This is especially important in the case of young infants and children with marked deficiency of particular disaccharidases, where special food supplements may be required (see ‘Disaccharidase replacement’). In hypolactasia, complete elimination is not usually required, as lactase deficiency is rarely absolute; nevertheless, if symptoms persist there are many potential sources of lactose that warrant careful exploration (see Box 15.10.5.1). Milk preparations that are substantially free of lac tose or lactose-reduced milks (and lactose-free whole milk for in fants) are widely available in many developed countries. Many individuals who are intolerant of milk can tolerate milk chocolate

 or plain yogurt, because the bacteria in the yogurt partially break down the lactose into glucose and galactose before consumption; moreover, the fat content present in a semisolid state delays gastric emptying and gastrointestinal transit, providing more time for en dogenous lactase activity to digest the ingested lactose load. Aged cheeses also have a lower content of lactose than other cheeses and are often better tolerated. In general, defining the individual’s prac tical tolerance limits for milk with a meal, and the use of reduced lactose-content foods including hard cheeses, yogurt, and lactose- hydrolysed milk products is a recommended approach to dietary management. Disaccharidase replacement Lactase-replacement, or milk or dairy products that have been pretreated with lactase, are available; these may allow a lactose-intolerant person to ingest milk products without inducing symp toms of intolerance. Long-term avoidance of milk products to control intestinal symptoms may have consequences for optimal bone mineralization in children, since it has been shown that those who avoid milk ingest smaller amounts of calcium than are needed for normal bone mineralization. For this reason, and because the vitamin D content in milk substitutes may vary considerably, labels should be examined to check the content of particular brands and to ensure that sufficient vitamin D is being supplied, especially to young growing children. Appropriate vitamin supplements are clearly indicated according to daily recommended doses according to age and sex. Addition of β-galactosidases

obtained from yeast or other micro organisms added to dairy products before consumption may alter the taste and prove unacceptable, but in the United States of America, β-galactosidase obtained from yeast (LactAid) has been shown to reduce symptoms as well as breath-hydrogen excretion in subjects with maldigestion of lactose. In the United Kingdom, a concen trated liquid lactase preparation (Colief, 50 000 units/g) is licensed for use in infants and children with symptomatic lactose intolerance. β-galactosidase derived from Aspergillus oryzae (Lactrase), taken in tablet form immediately before challenge with lactose, is effective in children with late-onset intolerance of lactose. Its cost, compared with dietary exclusion, may not be justified. More recently there has been a resurgence of the avid 19th-century interest in the use of so- called prebiotic agents for a wide diversity of abdominal and other complaints; there have been claims of benefit in rotavirus infection and in the control of symptomatic lactose intolerance. At present, it is too early to decide whether these highly commercialized agents have any useful role in lactose intolerance but, despite their high cost, on balance some preparations may have a modest benefit in symptomatic control. In infants and young children with proven lactose intolerance, Farley's Soya formula, Galactomin Formula 17, Isomil, SMA FF, Enfamil Lactofree, and other preparations provide protein and suitable carbohydrate in a powdered form so that adequate nutri tion can be maintained. For older children and severely ill adults with disaccharide intolerance, other preparations may be required (see 'Asucrasia and starch intolerance'). In the future, microbial β-galactosidases might be justified for food supplementation pro grammes in countries where lactose intolerance and nutritional de privation in the adult population are widespread. Therapeutic modulation of the intestinal microbiome A promising and innovative approach to the management of lactose intolerance and maldigestion is also being explored in the United States of America (see Azcarate-Peril et al., in 'Further reading'). The concept is based on an extensive preclinical programme carried out at Chapel Hill in which host factors such the intestinal microbiome have been explored experimentally in patients with lactose intoler ance and other conditions. The investigators have examined factors other than the constitutive nonpersistence of lactase and shown that the metabolism of residual lactose in the colon can be favourably altered by using oligosaccharides to modulate the bacterial popu lation so that lactose-fermenting species are induced and appar ently favoured. Based on previous preclinical studies, a randomized double-blind trial showed that oral administration of a short-chain galactosaccharide ('RP-G28') improved lactose digestion and toler ance in patients with hypolactasia. Accompanying these outcomes, analysis of bacterial diversity by 16S rRNA sequencing showed a change in the microbiome indicating a bifidogenic response with increased abundance of lactose-fermenting Bifidobacterium spp., Faecalibacterium spp., and lactobacilli. Moreover, introduction of dietary lactose over a 30-day period induced lactose-fermenting roseburia. These findings confirm that the galacto-oligosaccharide induced marked alterations in the faecal microbiome in lactose- intolerant individuals with increased relative abundance of lactose- metabolizing bacteria, and that this adaptive response by the endogenous microflora correlated with clinical outcomes of im proved lactose tolerance. If confirmed, these promising findings would immediately suggest alternative and apparently facile means for treating symptomatic lactase deficiency which may indeed synergise with probiotic therapies. Asucrasia and starch intolerance Complete absence of sucrase–isomaltase activity in most patients with sucrose intolerance, together with the ubiquity of sucrose in modern diets, complicates symptom management. Modest re duction of amylopectin-rich foods usually suffices to improve symptoms of starch intolerance, but complete avoidance of sucrose- containing foods can be difficult especially in infants and young chil dren. Powdered and liquid preparations such as Caloreen, Maxijul LE, Polycal liquid and powder, amongst others, may

be needed for sucrase–isomaltase deficiency. Glucose (or fructose) can be used as a sweetener. It has been reported that ingestion of dried brewer's yeast (containing invertase or sucrase but little lactase activity) after food is effective in patients with sucrase–isomaltase deficiency. However, dried yeast is rather unpalatable and not readily accepted by children. A high-potency liquid preparation of invertase used in the industrial manufacture of fructose from unrefined sugar cane juice, yeast-derived sacrosidase (Sucraid), is an oral preparation containing 8500 international units/mL of β,d-fructofuranoside fructohydrolase derived from baker's yeast. It is approved by the Food and Drug Administration in the United States of America for patients with sucrase–isomaltase deficiency. In a double-blind ran domized controlled trial in patients with sucrase–isomaltase defi ciency, given orally the agent was found to be safe, acceptable, and effective for the symptomatic treatment of the disease in patients al ready receiving a low-starch diet. Although it is generally efficacious,

section 15 Gastroenterological disorders 2908 patients with allergies to yeast products, glycerine (glycerol), or pa pain may be intolerant and develop anaphylactic or other allergic reactions to sacrosidase. It is thus advised that the first dose be ad ministered in an environment that will allow severe allergic reac tions to be safely treated and where specific measures to resuscitate patients suffering acute anaphylaxis are available. The usual dosage is 1 to 2 ml of sacrosidase liquid given with each meal or snack; the enzyme preparation should be mixed with 60 to 120 ml of water, milk, or infant formula (and to avoid denaturation, no hotter than room temperature). Fruit juices are not recommended for delivery, because they usually contain abundant sucrose and fructose which attenuate the therapeutic effect. Since the agent enhances sugar ab sorption in the small intestine, patients with diabetes may encounter difficulties in postprandial blood glucose control when treatment is initiated. Half the dose of sacrosidase is best taken when food is first eaten, with the remainder ingested during consumption of the meal. Although it is licensed only for congenital sucrase–isomaltase deficiency, the use of sacrosidase in postinfective and other sec ondary disaccharidase deficiencies has not been formally examined; together with appropriate dietary restriction, sacrosidase and ad junctive supplementation with β-galactosidases may benefit patients with established disease of the small intestinal mucosa and remains to be explored.
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