

Hypolactasia: a common enzyme deficiency leading to lactose malabsorption and intolerance

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KEY WORDS

clinical picture,
epidemiology,
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treatment

ABSTRACT

Adult-type hypolactasia (lactase nonpersistence or lactase deficiency) is the most common enzyme deficiency leading to lactose intolerance and primary lactose malabsorption. Clinical presentation of the condition includes symptoms resulting from bacterial fermentation of undigested lactose in the colon, which gives rise to gas bloat, increased motility, and loose stools. Diagnosis of the disease is based on clinical symptoms, biochemical, functional, histochemical and genetic tests. Treatment includes dietary restrictions, namely, use of low-lactose milk, in which lactose has been prehydrolyzed, or non-lactose milk.

Introduction Adult-type hypolactasia (lactase nonpersistence) is the most common enzyme deficiency in the world leading to primary lactose malabsorption and intolerance.¹ Lactose intolerance is the most common reason for milk intolerance in adults. Lactase is an enzyme located at the brush border of the small intestinal mucosa that breaks lactose, a nonabsorbable disaccharide into 2 simpler sugars, glucose and galactose, which are able to absorb into the bloodstream. If the lactase activity in a human gut is low, a remarkable amount of lactose remains unabsorbed. Persons with hypolactasia may develop flatulence, borborygmi, abdominal pain, and diarrhea, if they drink milk or consume products containing lactose.^{1,2} Individuals with these symptoms often begin to avoid dairy products.

Terminology Hypolactasia or lactase nonpersistence or lactase deficiency/insufficiency are the terms to indicate that the level of brush border lactase activity is very low. The direct measurement of lactase activity is the gold standard for diagnosing this condition.

Hypolactasia can be primary or secondary. Inherited primary hypolactasia is common among adults all over the world. Congenital hypolactasia (alactasia) is an extremely rare defect.³ Secondary hypolactasia is caused by the diseases of

the small bowel mucosa (infection, celiac disease), usually the morphological structure and enzyme activities return to normal after the mucosa of the small intestine has recovered.

Lactose malabsorption is the term used to indicate that lactose is not absorbed sufficiently in the gut. Measurement of lactose absorption after the lactose load is the standard diagnostic method.

Lactose intolerance indicates that malabsorbed lactose produces characteristic symptoms (bloating, abdominal pain, diarrhea). Not all persons with lactase nonpersistence or lactose malabsorption develop symptoms of lactose intolerance. This is important to keep in mind while comparing the results of the epidemiological studies and treatment recommendations for persons who have been diagnosed with lactase nonpersistence or lactose malabsorption. Ingestion of 50 g of lactose in a clinical tolerance test cause symptoms in 80% to 100% of lactose maldigesters, and one-third to half of lactose maldigesters experience symptoms after consumption of 200 to 250 ml of milk.⁴

Clinical picture The symptoms of lactose intolerance result from bacterial fermentation of undigested lactose in the colon, giving rise to an excess gas formation, increasing motility, and loose

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stools. The mechanism of loose stools induced by unabsorbed carbohydrate is mainly due to the osmotic load of the carbohydrate, which causes secretion of fluid and electrolytes until osmotic equilibrium is reached.^{5,6} Dilatation of the intestine, caused by the osmosis, induces an acceleration of small intestinal transit, which increases with the degree of maldigestion.⁷ The accelerated transit further reduces the hydrolysis of lactose, because the contact time between lactose and the residual enzyme is decreased. Less is known about the origin of abdominal distension and cramps.⁸

The symptoms depend on the age of the subject: the older the subject, the more symptoms. The development of symptoms is associated with the quantity of lactose in diet, the residual intestinal lactase activity, the ingestion of food along with lactose, the ability of the colonic flora to ferment lactose, visceral sensitivity and the presence of functional bowel disorders, and individual sensitivity to the products of lactose fermentation. Individuals with hypolactasia can tolerate moderate quantities of milk without symptoms.⁸⁻¹¹ Although there is a hypothesis that milk fat content inhibits the development of symptoms, it has not been confirmed by later studies.¹²

Many individuals with this condition avoid consuming large quantities of milk. The symptoms manifest only after certain amount of milk/milk products is consumed. The demonstration of lactase persistence/lactose malabsorption does not necessarily indicate that an individual will be symptomatic.

Diagnosis Diagnosis of lactose intolerance is often made on a clinical basis and in response to an empirical test of lactose avoidance in the diet.¹³ However, this is considered as an unreliable method.

A number of approaches are available to diagnose lactose malabsorption. It can be diagnosed by having individuals ingest a standard 50 g dose of lactose after fasting. Undigested lactose is fermented by the colonic microflora with production of hydrogen detectable in pulmonary excretion. The lactose breath hydrogen test is nowadays considered a very simple and useful test in subjects with suspected lactose malabsorption.¹⁴ Other possibilities include the measurement of blood glucose or urinary galactose before and after lactose load.^{14,15}

Direct lactase enzyme activity measured on small intestinal tissue biopsy samples may be utilized, but it is an invasive procedure and its reliability can be low because disaccharidase activity in a small biopsy specimen does not necessarily reflect the jejunal activity as a whole. Still, this has been considered as a gold standard for other tests.¹⁶

Recent evidence suggests that a genetic test of the 13910 C/T polymorphism can be used as the first stage-screening test for adult-type hypolactasia.¹⁷ A variant of C/C 13910 determines

hypolactasia and C/T 13910 and T/T 13910 – lactase persistence. The C allele is the most prevalent allele, while the less common T allele is dominantly associated with lactase persistence.¹⁸

We have recently compared 3 different methods to diagnose lactose malabsorption: 1) lactose load with determination of blood glucose concentration; 2) lactose load with urinary galactose measurement; and 3) the duodenal lactase activity assay. Our studies have shown a higher false-negative rate when using blood glucose measurements, which causes lactose malabsorption to remain undiagnosed in many patients.¹⁵ The sensitivity and specificity in our studies was only 60% and 96%, respectively. The specificity is comparable with the use of breath hydrogen or urinary galactose measurement tests.^{19,20} Therefore, the lactose test with blood glucose measurement should not be used as a screening test when high sensitivity is important.

When assessing the effectiveness of these tests in the clinical practice setting, one must consider predictive values as well as false-positive and false-negative results. Although the sensitivity and specificity of the test can be the same, positive and negative predictive values depend on the pretest probability or disease prevalence. For example, our studies produced an increase in the positive predictive value from 82% among the general Estonian population with lower lactose malabsorption prevalence of 23%, to 95% among the Russian population in Estonia with high lactose malabsorption prevalence of 57%, to 99.5% among the Khanty population in Siberia with the prevalence of lactose malabsorption estimated at 83%.^{21,22} If the test is used in patients with an increased pretest probability of lactose malabsorption (e.g., patients reporting milk intolerance), the positive predictive value of the test is higher than in the general population.

Epidemiology While comparing the prevalence studies, one of the key aspects is the methodology. There have been studies assessing the prevalence of lactose intolerance based on lactose tolerance tests, studies using tests for lactose malabsorption, and studies assessing the actual lactase activity. The current best standard is to assess the prevalence of hypolactasia based on genetic tests. Most of the epidemiological studies performed since 1970s have used lactose load with measurement of glucose in blood, breath hydrogen, or urinary galactose.

The prevalence of adult-type hypolactasia differs between the ethnic groups. The prevalence is above 50% in South America, Africa, and Asia, reaching almost 100% in some Asian countries. In the United States, the prevalence is 15% among whites, 53% among Mexican-Americans, and 80% in the Black population. Australia and New Zealand have the prevalence of 6% and 9%, respectively. In Europe, it varies from around 2% in Scandinavia to about 70% in Sicily. In general, it can be stated that about two-thirds of the world

adult population is lactase nonpersistent.^{1,23} In Central and Eastern Europe, the prevalence of hypolactasia is 38% in Poland,²⁴ 39% in Hungary,²⁵ 32% in Lithuania,²⁶ 24% in Estonia, but in people with Russian background the prevalence is higher – 57%.²¹

The recent studies on the prevalence of adult-type hypolactasia genotypes in some European countries have confirmed the earlier studies based on indirect diagnostic methods: the frequency of the genotype of the C/C 13910 was found to be 17% in Finland,²⁷ 11% in Sweden,²⁸ 25% in Estonia,²⁹ and 27% in Austria.³⁰

A considerable variability in the prevalence of hypolactasia is explained by a cultural-historical hypothesis, which suggests that persons with persistent high lactase activity in adulthood have had an advantage in natural selection in periods of dietary stress.³¹ As a result of increased survival, high intestinal lactase activity would have become typical of such a group. Lactase persistence is, indeed, more common in the areas with long traditions of dairy farming.

Regulation of lactase activity Lactase is produced by expression of the lactase-phlorizin hydrolase gene in the cells lining the small intestine. Normally, lactase activity declines after the weaning. Infants of every racial and ethnic group produce lactase and successfully digest lactose provided by human milk or by infant formulas. However, sometime after weaning, in the majority of children, there is a genetically programmed decrease in lactase (lactase nonpersisters).¹³

However, a mutation has occurred in human history that maintains lactase activity high throughout life.¹ Specifically, a single nucleotide polymorphism C/T (rs4988234) residing 13910 bp upstream from the initiation codon of the lactase gene (LCT) has been shown to be associated with lactase persistence trait in Asian, European, and Northern African populations.^{32,33} More recent functional studies have shown that the C/T 13910 variant is associated with the regulation of the LCT gene at a transcriptional level.^{17,34}

Lactase is a noninducible enzyme,³⁵ but it was also reported that continuous lactose consumption decreases hydrogen excretion and the severity of gastrointestinal symptoms.³⁶ Decreased hydrogen excretion can depend on adaptive phenomena, which is associated with changes in gut microflora as well as in some colonic functions and features. The increased microbial β -galactosidase activity is one of the hypothesized mechanisms.

Possible impact on health Hypolactasia is an important, genetically determined condition that can have impact on several aspects of health and thus influence the natural selection in human development/history. Today, hypolactasia is important for the differential diagnosis of nonspecific abdominal complaints – it is easy to diagnose and manage. Whether hypolactasia has influenced the selection of diets remains to be explained in

further studies. However, it has been observed that adults with hypolactasia drink less fresh milk which may affect growth, energy, and calcium supply. It has been demonstrated that there are differences in height and weight of young adults depending on their milk-drinking habits.³⁷ There are some studies indicating the relationship between low milk consumption and increased risk of osteoporosis.^{38,39} At the same time, there are some epidemiologic studies demonstrating associations between high milk consumption and risk for cardiac diseases.^{40,41}

The health outcomes of milk exclusion diets depend on whether other sources of nutrients, such as calcium and vitamin D, occur in the diet in sufficient amounts to replace dairy products as a source of these nutrients, and to what extent other components of milk are beneficial.⁴² Calcium is necessary for normal growth and bone development as well as subsequent maintenance of bone density. Calcium is necessary for normal bone accretion and optimal peak bone mass, which is a likely determinant of risk for osteoporosis and fragility fractures later in adult life. Dairy exclusion diets usually decrease gastrointestinal symptoms in symptomatic individuals who have lactose malabsorption or intolerance. The degree of relief is likely related to the lactase activity and the amount of lactose ingested. People who remain symptomatic on a dairy exclusion diet may have other causes for their gastrointestinal symptoms, such as irritable bowel syndrome, celiac disease, inflammatory bowel disease, or small bowel bacterial overgrowth.⁴²

Treatment recommendations Current management often relies on reducing lactose consumption by diminishing milk and milk-containing products in diet. Another option is to use low-lactose milk, in which lactose has been prehydrolyzed, or non-lactose milk. Alternatively, lactase nonpersisters may tolerate moderate amounts of dairy products ingested with other foods.

Even in persons with lactose intolerance, small amounts of milk, yogurt, hard cheeses, and reduced-lactose foods may be effective management approaches. Individuals with lactose malabsorption probably can ingest 12 g of lactose (the equivalent of 1 cup of milk) without significant symptoms, particularly if ingested with other foods. Lactase-treated products may be tolerated better than nontreated products, but further research is needed.⁴²

Conclusions Lactose intolerance is a common and important clinical syndrome. The majority of people with lactose malabsorption do not have clinical lactose intolerance. There are several diagnostic tests easily available. Many individuals with real or perceived lactose intolerance avoid dairy and ingest inadequate amounts of calcium and vitamin D, which may predispose them to decreased bone accrual, osteoporosis, and other adverse health outcomes. In most cases,

individuals do not need to eliminate dairy consumption completely.

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Hipolaktazja – częsty defekt enzymatyczny prowadzący do upośledzenia wchłaniania i nietolerancji laktozy

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SŁOWA KLUCZOWE

epidemiologia,
hipolaktazja, leczenie,
obraz kliniczny

STRESZCZENIE

Hipolaktazja typu dorosłych (niedobór lub brak laktazy) jest najczęstszym niedoborem enzymatycznym prowadzącym do nietolerancji laktozy (cukru mlekowego) i pierwotnego zaburzenia jego wchłaniania. Obraz kliniczny choroby obejmuje objawy wynikające z bakteryjnej fermentacji niestrawionej laktozy w jelicie grubym, co prowadzi do zwiększonego wytwarzania gazów jelitowych, zwiększonej motoryki jelita i luźnych stolców. Rozpoznanie opiera się na objawach klinicznych, badaniach biochemicznych, testach czynnościowych, badaniach histochemicznych i genetycznych. Leczenie polega na wprowadzeniu ograniczeń w diecie, tj. stosowaniu mleka pozbawionego laktozy (wstępnie zhydrolizowanej) lub o małej jej zawartości.

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