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Lactase enzyme deficiency and lactose intolerance

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Abstract

The digestion and absorption of lactose occur in the small intestine. Lactose is the primary substrate of lactase-phlorizin hydrolase, which is expressed on the brush boundary of intestinal villi, with peak expression occurring in the mid-jejunum. Lactase insufficiency is the most prevalent kind of disaccharidase deficiency. A lactase deficiency, whether primary or secondary, leads to clinical manifestations. The severity of the disease varies among individuals. Lactose is found in dairy, milk products, and the milk of mammals. It is sometimes termed lactose malabsorption. A lactase deficiency, whether primary or secondary, leads to clinical manifestations. The severity of the disease varies among individuals. Lactose is found in dairy, milk products, and the milk of mammals. It is sometimes termed lactose malabsorption.
Lactase insufficiency is the most prevalent kind of disaccharidase deficiency. Enzyme levels reach their peak immediately postnatally and then decline, despite ongoing lactose consumption. In the animal kingdom, nonhuman animals often lose the capacity to digest lactose into its constituent parts upon reaching maturity.
Lactose intolerance manifests as stomach distension and discomfort, diarrhea, nausea, excessive gas, and rumbling abdominal sounds (borborygmi). Numerous individuals begin to eliminate milk from their diet immediately upon receiving a diagnosis or even at the mere suspicion of lactose intolerance. This results in the use of specially formulated goods, including digestive aids, thereby increasing healthcare costs.
The reduction of lactose from dairy products, particularly yogurt, may alleviate the symptoms of lactase enzyme deficiency.

Keywords: Lactose, lactase, lactose intolerance, malabsorption

Introduction

Commonly known as milk sugar, lactose is the main sugar used in dairy goods such as yogurt and cheese. It is a major source of calories and gives dairy products a faintly sweet flavor. If you make enough enzymes, lactose is easily broken down into smaller sugars and absorbed in your intestines. If not, lactose intolerance develops, causing several gastrointestinal problems (1).

A kind of carbohydrate known as a disaccharide, lactose is composed of two types of sugars (2). This molecule is linked by a β (1→4) bond; galactose and glucose are the two simple sugars that form lactose. This bond must be hydrolyzed by lactase, a particular enzyme that breaks down lactose into its component parts, therefore enabling the absorption of galactose and glucose from the gut. Most animals have strong intestinal lactase activity at birth but gradually lose it after weaning, thereby reducing their capacity to break down dietary lactose (3).

Milk's lactose content ranges from 2% to 8%; human milk has higher lactose than cow and goat milk. Human milk is therefore somewhat sweeter and more calorie-dense than milk from most other animals. But lactose is much less sweet than sucrose, the sugar used to produce granulated white table sugar (4).

1.1 Absorption and Digested Lactose

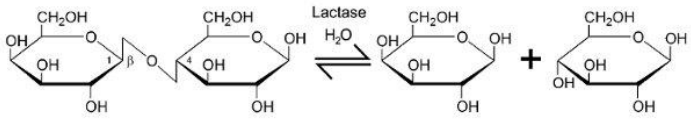
The small intestine finalizes the digestion and absorption of lactose (5). Lactose is primarily expressed on the brush edge of villi, with maximum expression occurring in the mid-jejunum, where it serves as the substrate for lactase-phlorizin hydrolase (6). The enzyme consists of two identical extracellular polypeptide chains, each weighing approximately 160 kDa, along with a minor intracellular component (7), and it is associated with the apical membrane of mature enterocytes. The alpha-glucosidase activity of this enzyme hydrolyzes milk sugar disaccharides into the monosaccharides glucose and galactose, which are then actively transported into enterocyte epithelial cells by the sodium/glucose (galactose) co-transporter. Increased concentrations necessitate the involvement of an additional facilitative transporter (8).

1.2 The lactase enzyme:

Produced by several species, lactase (EC 3.2.1.108) is an enzyme essential for the complete digestion of lactose in milk. Its constituent parts are both glucose and galactose, which it separates from the sugar lactose. Lactase is located on the brush border of the small intestine of humans and other animals. Individuals who lack functional lactase or have a lactase deficiency may develop lactose intolerance after consuming milk products (10). Often known as lactase, microbiome \u03b2-galactosidase is introduced to milk to produce "lactose-free" milk products (11), purchased as a nutritional supplement.

1.2.1 Mechanism

Human lactase's ideal temperature is probably 37°C (12), whereas the pH optimum is 6(14). The β-glycosidic link in D-lactose breaks down in metabolism to produce D-galactose and D-glucose, which the gut walls and circulation may then absorb. Lactase catalysis is an overall reaction as follows:



Lactose D-galactose D-glucose

D-lactose hydrolysis uses a catalytic process that preserves the substrate's anomeric structure (14). This retention results from a twofold displacement mechanism, although its specifics remain unknown. Research on E. coli lactase reveals that a glutamate nucleophile attacks the axial side of the galactosyl carbon in the β-glycosidic bond (15), thereby initiating hydrolysis. Mg-dependent acid catalysis (15) may facilitate the removal of the D-glucose leaving group. Water's equatorial nucleophilic attack releases D-galactose, freeing the enzyme. Substrate modification studies reveal that enzyme recognition and hydrolysis depend on the 3′-OH and 2′-OH groups of the galactopyranose ring (16). The 2′-group is not essential for recognition but is involved later, while the 3′-hydroxy group is crucial for initial binding. A 2-deoxy analog, with a Ki of 10 mM, acts as a competitive inhibitor, highlighting its importance. Removing some hydroxyl groups on the glucopyranose does not prevent catalysis (16).

Lactose intolerance is treated using lactase as a medicine. Being an enzyme, the acidity of the stomach might cause inhibition of its activity. Still, it's packed in an acid-proof pill so the enzyme passes through the stomach whole and stays in the small intestine. Acting on lactose molecules in the small intestine helps the body absorb the broken-down sugar, thereby preventing cramps and diarrhea typically caused by it. The enzyme passes with the following bowel movement as it is not absorbed (17).

1.2.2 Structural and biosynthesis

Preprolactase, the main translation product, has a 1927-amino-acid polypeptide structure with five domains: a 19-amino-acid cleaved signal sequence, a prosequence absent in mature lactase, the mature lactase segment, a membrane-spanning hydrophobic anchor, and a short hydrophilic carboxyl terminus. The endoplasmic reticulum cleaves the signal, and the 215-kDa pro-LPH moves to the Golgi, where it undergoes glycosylation and proteolytic processing. The pro-domain acts as an intramolecular chaperone in the ER, preventing trypsin cleavage and aiding proper folding for Golgi transport.

The intestinal epithelial cells' brush boundary membrane hosts mature human lactase, a 160 kDa monopeptide. LPH has two catalytic glutamic acid sites, with the C-terminus in the cytoplasm and the N-terminus outside. Glu-1273 is linked to phlorizin hydrolase activity, while lactase activity in humans is associated with Glu-1749.

1.2.3 Genetic control and expression

Lactase is encoded on chromosome 2 and is expressed mainly in mammalian small intestine enterocytes, with low levels also present in the colon during fetal development. Humans inherit high lactase levels, but after weaning, most individuals experience a decrease in transcription, leading to lactose intolerance. The LCT gene provides instructions for the production of lactase. Mutations in the LCT gene cause congenital lactase deficiency, impairing babies' ability to digest lactose in milk or formula.

Some population groups have lactase persistence due to a mutation believed to have occurred 5,000–10,000 years ago, coinciding with the domestication of cows (25). Nearly half the world can digest lactose without issues thanks to this mutation. Two SNPs, about 14 and 22 kb upstream

of the LPH gene's 5'-end, are linked to lactase persistence (26). These include mutations C→T at -13910 and G→A at -22018 (27), both of which are independently associated.

The lactase promoter, 150 base pairs long and located upstream of the transcription start region, contains conserved sequences indicating vital cis-regulatory elements. Transcription factors such as Cdx-2, HNF-1α, and GATA are involved (27). Studies on hypolactasia reveal that, despite polymorphisms, lactase expression in newborns is similar; mutations become more significant with development. Lower LPH levels during weaning may result from transcription down-regulation or mRNA destabilization by developmentally regulated DNA-binding proteins (28).

1.3 Lactase enzyme deficits

Lactose intolerance is a clinical condition characterized by symptoms when consuming lactose-containing foods. Normally, lactase in the small intestine breaks down lactose into glucose and galactose. Symptoms result from primary or secondary lactase deficiency, with severity varying among individuals. Lactose is present in mammalian milk, dairy, and milk products. The term lactose malabsorption is also used.

The most common type of disaccharidase deficiency is lactase deficiency. Although continuous lactose intake causes enzyme levels to peak shortly after birth and then decline. Generally, nonhuman animals in the animal kingdom lose their ability to digest lactose into its components as they reach adulthood. Lactase deficiency has been observed in several human groups, including those of Asian, African, and South American descent. Conversely, people from northern Europe often retain the ability to digest lactose into adulthood (31). Northwest India
Lactose intolerance causes gas, loose stools, nausea, bloating, and discomfort (32,33). Many avoid milk immediately after diagnosis or advice, increasing reliance on specialized products like digestive aids, which burdens the healthcare system.

1.3.1 Etiological Factors

Individuals with lower levels of lactase enzyme deficiency may fail to break down lactose into components fitable for absorption. Four primary factors contribute to lactase insufficiency.

- **Main Lactase Deficiency**

Lactase non-persistence, also called lactase insufficiency, is the most common cause. Enzyme activity gradually declines with age, starting in infancy and causing symptoms in adolescence and early adulthood. Lactase persistence is associated with a mutation, while non-persistence is the ancestral type, following Mendelian inheritance.

- **Secondary Lactose Deficiency**

Damage to the intestinal mucosa may lead to secondary lactase deficiency (37) caused by various viral, inflammatory, or other illnesses. Common reasons include: gastroparesis, celiac disease, Crohn's disease, ulcerative colitis, chemotherapy treatments, medications such as antibiotics, and congenital lactase deficiency. Autosomal recessive inheritance results in reduced or absent lactase enzyme activity from birth (38, 39); this condition typically manifests in infants after they begin consuming milk. It is an uncommon cause of deficiency, and its genetic basis is not entirely clear (40).

- **Developmental Lactase Deficiency**

Premature babies born between 28 and 37 weeks of gestation exhibit this (41). The undeveloped infant's bowel cannot break down lactose. As the colon matures and produces enough lactase activity, this disorder improves with age (41).

1.3.2. Epidemiology

Lactose intolerance is common, but it's rare in children under five. It's most often seen in teenagers and young adults. Overall, about 65% of people worldwide are lactose intolerant (42). Different ethnic groups have different rates of lactose intolerance, with the condition being most common among Asians, Hispanics/Latinos, and African Americans. It's least common among those of European descent (43). Higher rates in certain groups also align with a greater likelihood of lactose non-persistence (44, 45). Not everyone with lactose intolerance has symptoms. The main variant affects up to 70% of the global population (46–48). In contrast, congenital lactose intolerance is quite rare, with only around 40 reported cases worldwide (34).

In the US, lactose intolerance is more prevalent among African-Americans, American Indians, Hispanics or Latinos, and Asian-Americans compared to White Americans (49–52). North Americans, Australians, and White Northern Europeans have the lowest rates, ranging from 2% to 15% (49, 50). South Americans show rates of 50% to 80%. Among American Indians and some East Asians, the rate is nearly 100%. For Ashkenazi Jews and Africans, the rate ranges from 60% to 80%.

Generally, lactase activity decreases after infancy, with noticeable drops during adolescence, especially among Whites (53). Different ethnicities experience different levels and durations of decline. Chinese and Japanese people lose 80-90% of lactase within 3-4 years after weaning. Jewish and Asian individuals lose 60-70% over several years. In White Northern Europeans and North Americans, lactase levels may not hit their lowest until ages 18-20. People of mixed ethnicity tend to have lower rates of lactase non-persistence, while native groups show higher rates (53).

Lactose intolerance typically begins slowly, with symptoms emerging in late adolescence or adulthood (30, 31). In contrast, Native Americans, Asian-Americans, African-Americans, and Hispanics/Latinos may show signs earlier (49), unlike White Northern Europeans, Australians, and North Americans.

1.3.3. Pathophysiology

The lactase enzyme is located in the brush border of the small intestine. When lactase is deficient, lactose remains unabsorbed in the gut. This leads to osmotic diarrhea due to fluid influx into the gut lumen. Colonic bacteria ferment the unabsorbed lactose, producing gas (including hydrogen, carbon dioxide, and methane) and additional fluid in the lumen. Together, these processes lead to various abdominal symptoms.

In a community in northern Brazil, researchers have identified specific single-nucleotide polymorphisms related to lactose tolerance. The rs4982235 SNP (or -13910C>T) is associated with lactose intolerance in Indo-Europeans (55).

1.3.4. Histopathology

Microscopic analysis of the small intestine varies based on the type of lactase deficiency. In primary lactase deficiency, the mucosa appears normal. Evaluating lactase activity can gauge the severity of the deficiency. In secondary lactase insufficiency, the mucosa may exhibit abnormalities, which could be attributed to conditions such as celiac disease. If mucosal changes are localized or spotty, biopsy results might appear normal (56).

1.3.5. Physical History

Symptoms of lactose intolerance usually appear 30 minutes to two hours after consuming dairy products. Symptoms depend on factors such as lactose intake, residual lactase activity, and small bowel transit time (57, 55, 59). Less frequently, it may present as headaches, muscle pain, joint pain, mouth sores, urinary issues, or trouble concentrating (60, 61). To determine the cause of lactose intolerance and rule out secondary issues, a thorough medical, family, and dietary history is essential.

1.3.6. Medical Tests

The hydrogen breath test measures hydrogen levels after the ingestion of lactose. If the hydrogen level increases by more than 20 ppm compared to the baseline (62), it indicates lactose malabsorption. Colonic bacteria ferment unabsorbed lactose, producing lactic acid, which in turn lowers the stool pH. Eliminating lactose from the diet can help identify the underlying issue, as symptom relief suggests lactose intolerance (63). To test for milk tolerance, drink 500 mL of milk and monitor blood glucose levels. An increase of less than 9 mg/dL indicates lactose malabsorption (64). The lactose tolerance test evaluates lactose absorption after consuming a liquid containing lactose. After a fasting blood glucose measurement, a patient is given 50 grams of lactose (62). Serum glucose levels are then checked at 0, 60, and 120 minutes. In lactose intolerance, blood glucose levels that do not rise by 20 g might indicate the condition. This test has a sensitivity of 75% and a specificity of 96%. False negatives may occur in patients with diabetes or small intestinal bacterial overgrowth. Other factors, such as abnormal gastric emptying, can also affect results (65).

A small bowel biopsy is rarely done due to its invasiveness. It's usually only used to rule out secondary causes of lactose intolerance. Genotyping is an emerging test with greater sensitivity and specificity. Although it has been used in Germany and the Nordic countries, it remains relatively unavailable elsewhere (66).

1.4. Therapy and Management

1.4.1. Dietary Modification

It is recommended to take calcium supplements and consume milk products that contain added lactase. Reducing lactose intake by avoiding foods containing lactose can help alleviate symptoms. Some individuals may react to yogurt, which contains varying levels of lactose, with Greek yogurt having the lowest levels. The bacteria in yogurt cultures produce β-galactosidase, which aids in the digestion of lactose (67). Despite some challenges in terms of taste and nutritional balance, plant-based milk alternatives are becoming more available (68, 69). Probiotics, especially the DDS-1 strain of Lactobacillus acidophilus, may help relieve symptoms (70, 71). Additionally, calcium and vitamin D supplements are recommended. For those with secondary lactase insufficiency, treatment should focus on the underlying cause (73).

1.4.2. Lactase Pills

Lactase enzyme supplements break down lactose in milk and dairy products. These supplements come in the form of drops or pills.

1.5. Differential Diagnostics

Other conditions to consider in the differential diagnosis of lactose intolerance include irritable bowel syndrome, Celiac disease, Tropical sprue, Cystic fibrosis, Inflammatory bowel disease, Diverticulitis, Intestinal tumors or polyps, Overuse of laxatives, Viral intestinal infections, and Bacterial infections.

1.6. Complications

Common complications include osteopenia, Osteoporosis, Nutritional deficiency, Weight loss, Rickets, and Growth failure.

1.7. Individual Instructions

Unlike celiac disease, individuals with lactose intolerance and their families should understand that consuming lactose-containing foods usually causes only temporary symptoms without permanent harm to the gastrointestinal system. As long as they consume enough protein, calories, calcium, and vitamin D, there are no long-term effects (49).

It is not possible to prevent primary or congenital lactase deficiency. However, early diagnosis of underlying secondary causes and prompt treatment can help prevent secondary lactase insufficiency and maintain gut mucosa health. Additionally, avoiding high-lactose foods can help manage the severity of long-term symptoms.

Conclusion: Reducing lactose in dairy products, especially yogurt, may ease the symptoms of lactase enzyme deficiency. Producing low-lactose yogurt can help many people enjoy the benefits without health issues.

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