

Lactose Intolerance: A Comprehensive Review Of Its Pathophysiology, Diagnosis, And Management

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Abstract:

Lactose intolerance, a widespread clinical syndrome of gastrointestinal symptoms after lactose food intake, occurs in a large percentage of the world's population. Prevalence is extremely variable among ethnic groups and depends on an interesting interaction of genetics, evolution, and diet. The cause is deficiency of lactase-phlorizin hydrolase (LPH), or lactase, in the small intestine's brush border. This enzyme is critical to the hydrolysis of lactose, the major carbohydrate in milk, into its absorbed monosaccharide units, glucose and galactose. Without adequate lactase activity, unabsorbed lactose migrates to the large intestine, where it is fermented by colonic bacteria, resulting in the formation of short-chain fatty acids, hydrogen, carbon dioxide, and methane gas. This is followed by the typical symptoms of lactose intolerance such as abdominal pain, bloating, gas, and diarrhea. The most prevalent type is primary lactase non-persistence, a genetically determined condition that leads to a diminution in lactase production after infancy. The others are secondary lactase deficiency, which is acquired as a result of intestinal mucosal damage; congenital lactase deficiency, a rare autosomal recessive condition; and developmental lactase deficiency, seen in premature infants. A combination of clinical assessment and objective investigations is used for diagnosis, of which the hydrogen breath test is the most commonly practiced and sensitive test. Management approaches are dominated by dietary modification such as the elimination or reduction of lactose-containing foods, the substitution of lactose-free products, and the ingestion of fermented milk. Exogenous lactase enzyme preparations are also used and may benefit most patients. Finally, initial studies on the role of the probiotics and prebiotics in regulating the gut microbiota hold promise for new therapeutic modalities. Lactose intolerance, albeit highly prevalent, is frequently misdiagnosed or mistaken as other gastrointestinal diseases such as irritable bowel syndrome or milk allergy. Hence, a proper knowledge of its pathophysiology, precise diagnosis, and optimal management is important for clinicians to enhance patient outcomes as well as improve the quality of life. This overview seeks to summarize the existing information on lactose intolerance, including its biochemical and genetic etiology, worldwide epidemiology, diagnostic tools, and management, with areas of future research.

Keywords: Lactose Intolerance, Lactase Deficiency, Hydrogen Breath Test, Dietary Management.

1. Introduction

Milk and dairy products have been a cornerstone of nutrition in many cultures for millennia, providing essential nutrients such as calcium, vitamin D, protein, and B vitamins. The ability to digest the primary sugar in milk, lactose, is therefore of significant nutritional and physiological importance. However, for a majority of the world's adult population, the consumption of dairy leads to uncomfortable and often distressing gastrointestinal symptoms. This condition, known as lactose intolerance, is not a disease but rather a physiological state resulting from a mismatch between the amount of lactose consumed and the capacity of the body to digest it. ^(1,2)

Lactose intolerance arises from a deficiency of the enzyme lactase (lactase-phlorizin hydrolase), which is located in the apical membrane of enterocytes in the small intestine. The decline in lactase activity after the weaning period, a phenomenon termed lactase non-persistence, is the ancestral and most common phenotype in adult humans. Conversely, lactase persistence, the ability to digest lactose throughout adulthood, is a more recent

evolutionary adaptation that emerged in populations with a long history of dairy farming. This genetic trait is particularly prevalent in individuals of Northern European descent but is also found in some pastoralist populations in Africa and the Middle East. ^(1,3)

The global prevalence of lactose malabsorption (the physiological inability to digest lactose) is estimated to be around 65-70%, though the manifestation of clinical symptoms (lactose intolerance) is highly variable and depends on several factors, including the dose of lactose ingested, individual sensitivity, gut transit time, and the composition of the colonic microbiota. The symptoms are a direct consequence of the fermentation of undigested lactose by gut bacteria, leading to gas production and an osmotic load that draws fluid into the intestinal lumen. ^(1, 2)

Understanding lactose intolerance is critical for several reasons. Firstly, its symptoms overlap significantly with other common functional gastrointestinal disorders, such as irritable bowel syndrome (IBS), leading to potential misdiagnosis and inappropriate management. Secondly, the avoidance of dairy products without proper dietary counseling can lead to deficiencies in key nutrients, most notably calcium and vitamin D, which can have long-term consequences for bone health. Finally, the growing global market for lactose-free products and dietary supplements underscores the widespread impact of this condition on public health and consumer behavior. ⁽²⁾

This review will provide a comprehensive overview of the current state of knowledge regarding lactose intolerance. We will delve into the biochemical processes of lactose digestion, explore the genetic and evolutionary underpinnings of lactase persistence and non-persistence, and examine the pathophysiology responsible for the clinical symptoms. Furthermore, we will discuss the global epidemiology, detail the various diagnostic methods available, and provide an in-depth analysis of management strategies, from dietary modifications to emerging therapies. By synthesizing information from basic science, clinical research, and population studies, this review aims to serve as a definitive resource for clinicians, researchers, and nutritionists working with individuals affected by lactose intolerance. ⁽³⁾

2. Epidemiology and Global Prevalence

The prevalence of lactose malabsorption varies dramatically across the globe, reflecting the patterns of genetic evolution described above.

Northern Europe: Prevalence is very low. In countries like Sweden, Denmark, Ireland, and the UK, over 90% of the population is lactase persistent.

Southern Europe and the Middle East: Prevalence is intermediate, ranging from 40% to 70%.

Asia: Prevalence is very high. In many East Asian countries like China, Japan, and Korea, the rate of lactose malabsorption is estimated to be between 70% and 100%.

Africa: Prevalence is highly variable. It is very high in most Bantu-speaking populations of Southern Africa (>90%), but very low in pastoralist groups like the Tutsi and Fulani (<20%), who have a history of cattle herding. ^(2, 4)

The Americas: Indigenous American populations have a very high prevalence of lactose malabsorption (>80%). In mixed populations, the prevalence reflects the ethnic admixture. For example, in the United States, prevalence is lowest in Caucasian Americans (~15%), higher in Hispanic Americans (~50%) and African Americans (~80%).

It is important to remember that these figures refer to lactose malabsorption. The prevalence of symptomatic lactose intolerance is generally lower and more difficult to quantify, as it depends on dietary habits and individual sensitivity. ^(2, 3, 4)

3. The Biochemistry of Lactose Digestion

The ability of an individual to tolerate dietary lactose is entirely dependent on the efficient enzymatic breakdown of this disaccharide in the small intestine. This section details the key molecules involved in this process: the substrate lactose, the enzyme lactase, and the products of hydrolysis, glucose and galactose. ^(5, 2)

3.1. Lactose: The Milk Sugar

Lactose is a disaccharide sugar, with the chemical formula $C_{12}H_{22}O_{11}$, found almost exclusively in the milk of mammals. It constitutes around 2-8% of milk by weight and is the primary source of carbohydrates for nursing infants, providing a significant portion of their energy needs.

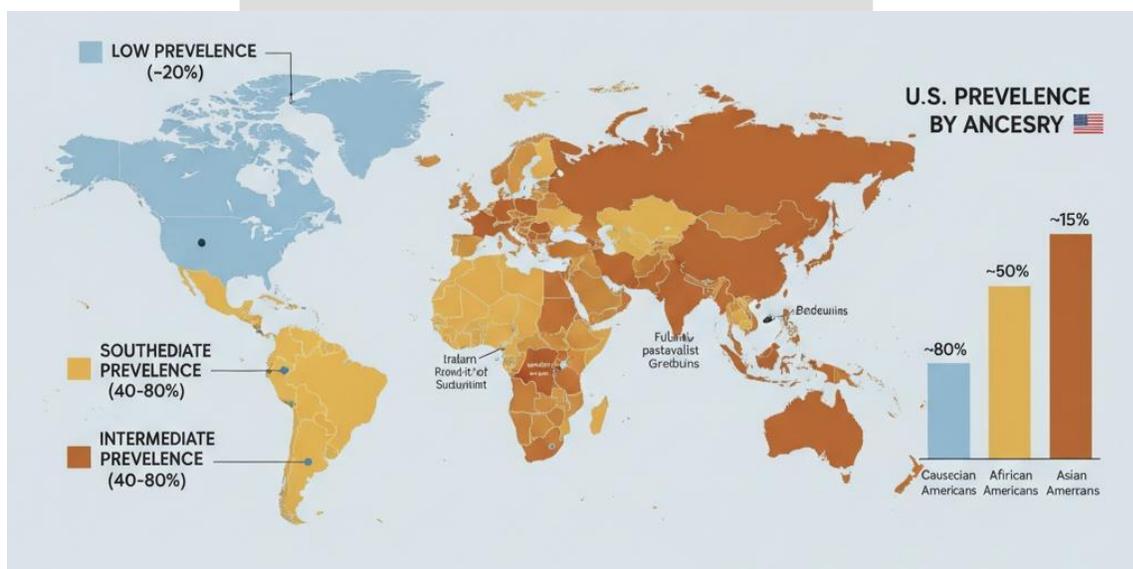
Structurally, lactose is composed of two simpler monosaccharide units: a molecule of D-galactose and a molecule of D-glucose, linked together by a β -1,4 glycosidic bond. This specific linkage is crucial, as it can only be cleaved by the lactase enzyme. Other digestive enzymes, such as sucrase or amylase, cannot hydrolyze this bond, making lactase indispensable for lactose digestion. ^(6,5)

3.2. The Lactase Enzyme (Lactase-Phlorizin Hydrolase)

The enzyme responsible for lactose digestion is Lactase-Phlorizin Hydrolase (LPH), commonly referred to simply as lactase. LPH is a transmembrane protein located in the apical brush border membrane of the enterocytes, the absorptive cells lining the small intestine. Its highest concentration is found in the mid-jejunum. ⁽⁵⁾

LPH is a large glycoprotein with two primary active sites:

1. Lactase site: This site has a high affinity for lactose and is responsible for its hydrolysis.
2. Phlorizin hydrolase site: This site is capable of hydrolyzing various other glucosides, including phlorizin and certain glycolipids. Its physiological significance is less understood than the lactase site. ^(4,5)



The synthesis of LPH is a complex process. It is initially synthesized as a large precursor protein (pro-LPH) in the endoplasmic reticulum. It then undergoes extensive glycosylation and dimerization before being transported to the Golgi apparatus, where it is cleaved into its mature, active form and inserted into the cell membrane. The activity of this enzyme is highest at birth and in early infancy, which aligns with the high lactose content of a milk-based diet. ⁽⁴⁾

3.3. Mechanism of Digestion and Absorption

The process of lactose digestion begins when ingested food reaches the small intestine.

1. **Hydrolysis:** The lactase enzyme, situated on the surface of the enterocytes, binds to lactose molecules present in the intestinal lumen. It catalyzes the hydrolysis of the β -1,4 glycosidic bond, breaking lactose down into one molecule of glucose and one molecule of galactose.
2. **Absorption:** Glucose and galactose are then immediately available for absorption. They are co-transported with sodium ions into the enterocytes via the Sodium-Dependent Glucose Transporter 1 (SGLT1).
3. **Transport:** Once inside the cell, glucose and galactose are transported out of the enterocyte, across the basolateral membrane, and into the bloodstream via the Glucose Transporter 2 (GLUT2). From the bloodstream, they are distributed throughout the body to be used for energy.

This entire process is highly efficient in individuals with sufficient lactase activity, ensuring that virtually all ingested lactose is broken down and absorbed in the small intestine, preventing it from reaching the large intestine. ⁽⁷⁾

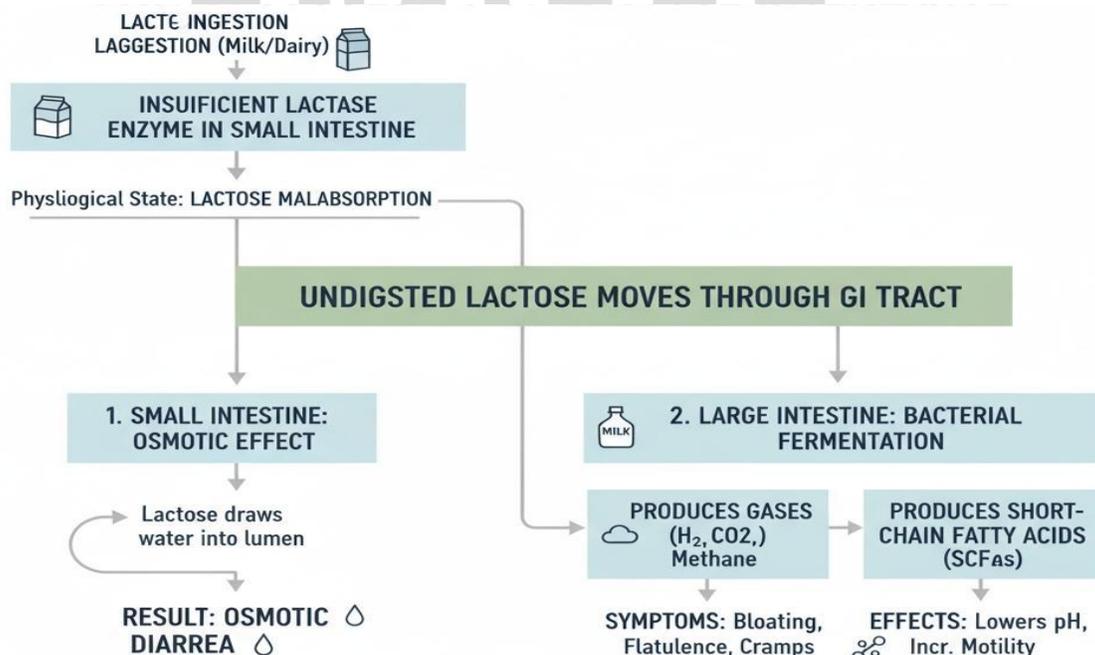
4. Pathophysiology of Lactose Intolerance

Lactose intolerance is a clinical syndrome caused by an inability to digest lactose due to insufficient lactase enzyme. This underlying deficiency is known as **lactose malabsorption**.

The symptoms of intolerance are caused by two primary mechanisms:

1. **Osmotic Effect:** In the small intestine, undigested lactose draws in excess water, leading to osmotic diarrhea.
2. **Bacterial Fermentation:** In the large intestine, gut bacteria ferment the undigested lactose, producing **gases** (causing bloating, flatulence, and pain) and **short-chain fatty acids** (which increase discomfort).

Essentially, lactose intolerance is the manifestation of these symptoms, which are a direct result of the combined osmotic and fermentation processes. ^(5,6,7)



5. Types of Lactase Deficiency

Lactase deficiency is categorized into four distinct types based on its underlying cause.

5.1. Primary Lactase Non-Persistence

This is the most common cause of lactose intolerance worldwide, affecting the majority of the global adult population. It is a genetically programmed condition where the production of the lactase enzyme begins to decline around the age of 2 to 5 years, after the typical age of weaning. The rate of decline varies, but by adulthood, lactase activity is reduced to less than 10% of the level at birth. This is not a disease but rather the normal, ancestral state for the human species. The ability to maintain high lactase levels into adulthood (lactase persistence) is the result of a more recent genetic mutation. ⁽⁸⁾

5.2. Secondary Lactase Deficiency

This form of lactase deficiency is acquired and temporary. It results from an injury to the small intestinal mucosa, which damages the brush border and reduces the surface area available for lactase production. Since lactase is located at the very tips of the intestinal villi, it is often the first enzyme to be lost following mucosal damage and the last to recover.

Common causes of secondary lactase deficiency include:

Acute gastroenteritis (e.g., rotavirus infection).

Celiac disease, where gluten exposure damages the intestinal lining.

Crohn's disease, an inflammatory bowel disease.

Giardiasis, a parasitic infection.

Chemotherapy or radiation therapy affecting the gut.

Severe malnutrition. ^(7,8)

Management of the underlying condition typically allows the intestinal lining to heal, and lactase production is restored over time, usually within a few weeks or months.

5.3. Congenital Lactase Deficiency (Alactasia)

This is an extremely rare autosomal recessive genetic disorder. Infants born with congenital lactase deficiency produce little to no lactase enzyme from birth. Mutations in the LCT gene, which codes for the lactase enzyme, prevent its proper synthesis or function. Upon ingestion of breast milk or a standard lactose-containing formula, these infants develop severe diarrhea, dehydration, and fail to thrive. The condition requires a lifelong, strict lactose-free diet, and diagnosis must be made promptly after birth to prevent severe complications. ^(6, 8)

5.4. Developmental Lactase Deficiency

This is seen in premature infants, particularly those born before 34 weeks of gestation. Lactase activity begins to increase late in the third trimester of fetal development. Therefore, premature infants may have insufficient lactase levels at birth, leading to difficulties digesting lactose. This condition is usually transient, and as the infant's intestines mature, lactase activity increases to normal levels. These infants may require a lactose-free or low-lactose formula temporarily. ⁽⁷⁾

6. Genetics of Lactase Persistence and Non-Persistence

The variation in lactase activity among adults is one of the clearest examples of recent human evolution. The ability to digest lactose into adulthood, or lactase persistence, is a dominant genetic trait. ⁽⁸⁾

6.1. The Lactase Gene (LCT) and its Regulation

The gene that codes for the lactase enzyme is the LCT gene, located on chromosome 2. In all humans, this gene is fully active during infancy. In individuals with lactase non-persistence (the ancestral state), the expression of the LCT gene is significantly downregulated after weaning.

This downregulation is not caused by a mutation in the LCT gene itself, but rather by a regulatory element in a nearby gene. Research has identified that the control mechanism lies within an intron of the adjacent MCM6 (Minichromosome Maintenance Complex Component 6) gene. Specific single nucleotide polymorphisms (SNPs) within this regulatory region determine whether the LCT gene remains "switched on" or is "switched off" in adulthood. ^(7,8)

6.2. Key Genetic Polymorphisms

Several different SNPs associated with lactase persistence have been identified in different populations, suggesting that this trait evolved independently multiple times.

C/T-13910: This is the most well-studied SNP, found predominantly in populations of European descent. The 'T' allele is strongly associated with lactase persistence, while the ancestral 'C' allele is associated with non-persistence. Individuals who are homozygous (T/T) or heterozygous (C/T) for this polymorphism are typically lactase persistent.

G/A-22018: This polymorphism is found alongside C/T-13910 in Europeans and is also associated with lactase persistence.

Other variants: Several other SNPs in the same regulatory region have been discovered in various African, Middle Eastern, and South Asian populations. For example, G/C-14010 is common in some East African pastoralist groups, and T/G-13915 is found in the Arabian Peninsula. ^(7,9)

6.3. Evolutionary Hypothesis

The emergence of lactase persistence is closely linked to the history of dairy farming (dairying). The "gene-culture coevolution" hypothesis posits that in populations that domesticated cattle and consumed fresh milk, individuals with the genetic mutation for lactase persistence had a significant survival advantage. Milk provided a calorie-rich and nutrient-dense food source, free from many of the pathogens found in contaminated water. During times of famine, the ability to consume milk without becoming ill could have been a powerful selective pressure, leading to a rapid increase in the frequency of the lactase persistence allele in these populations. This explains the high prevalence of lactase persistence in Northern Europe and in pastoralist groups like the Fulani in West Africa, both of which have a long history of dairying. ⁽⁹⁾

7. Diagnosis of Lactose Intolerance

Diagnosing lactose intolerance involves confirming that the patient's symptoms are directly caused by lactose malabsorption. A multi-step approach is often used.

7.1. Clinic

The diagnostic process usually begins with a thorough medical history and dietary assessment. The clinician will ask about the nature, timing, and severity of symptoms and their relationship to the consumption of dairy products. A temporary elimination diet, where all lactose-containing foods are removed for one to two weeks to see if symptoms resolve, followed by a reintroduction (challenge) to see if they return, can be a simple and effective initial step. ⁽⁷⁾

7.2. Hydrogen Breath Test (HBT)

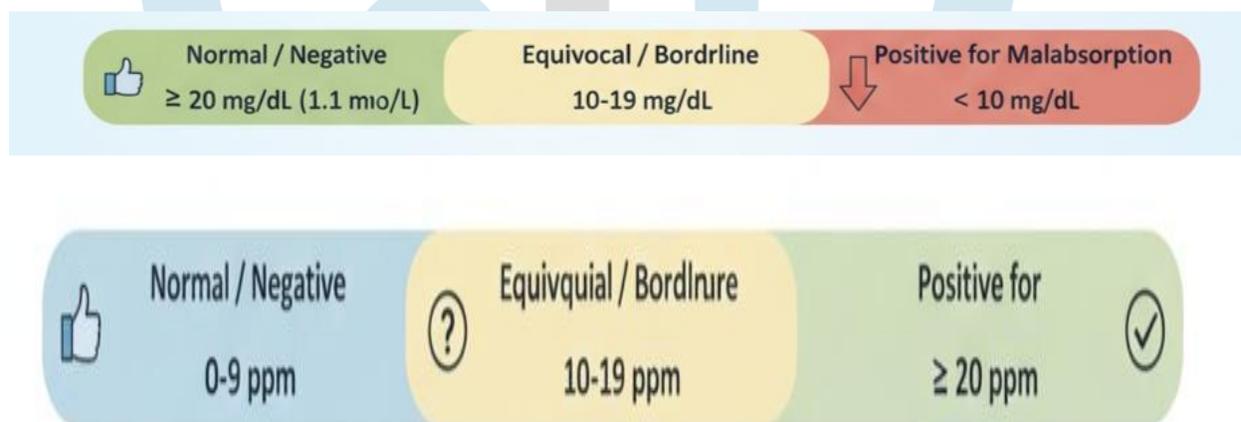
The HBT is considered the gold standard for diagnosing lactose malabsorption.

Procedure: The patient fasts overnight and then consumes a standardized oral dose of lactose (typically 25-50 grams, equivalent to the lactose in 2-4 glasses of milk). Breath samples are collected at baseline and then at regular intervals (e.g., every 15-30 minutes) over 2-3 hours.

Principle: If lactose is not absorbed, it is fermented by colonic bacteria, producing hydrogen gas (H_2). This hydrogen is absorbed into the bloodstream, transported to the lungs, and exhaled.

Interpretation: A significant rise in the hydrogen concentration in the breath (typically >20 parts per million above the baseline) after the lactose load indicates lactose malabsorption. The test is often combined with a symptom diary to correlate the positive breath test with clinical intolerance.

Limitations: False negatives can occur in patients who do not have hydrogen-producing bacteria (about 10-15% of the population) or who have recently taken antibiotics. False positives can occur due to small intestinal bacterial overgrowth (SIBO).



7.3. Lactose Tolerance Test (LTT)

This is an older, less commonly used test that measures the body's response to a lactose load by monitoring blood glucose levels.

Procedure: The patient fasts and consumes a 50-gram dose of lactose. Blood samples are taken at baseline and at 60 and 120 minutes to measure blood glucose.

Principle: If lactose is properly digested into glucose and galactose, the absorbed glucose will cause a rise in blood glucose levels.

Interpretation: A failure of blood glucose to rise by a certain amount (typically <20 mg/dL or 1.1 mmol/L) above baseline suggests lactose malabsorption.

Limitations: This test is less sensitive and specific than the HBT and can be affected by other factors like diabetes and gastroparesis. It is also more invasive due to the need for multiple blood draws.

7.4. Stool Acidity Test

This test is sometimes used for infants and young children, for whom breath tests are difficult to administer. Undigested lactose fermented in the colon produces lactic acid and other SCFAs, which lower the pH of the stool. A stool pH of less than 5.5 is suggestive of lactose malabsorption.

7.5. Genetic Testing

Genetic tests can identify the SNPs (e.g., C/T-13910) associated with lactase non-persistence. A blood or saliva sample is used to analyze the patient's DNA. A C/C genotype at the -13910 position is a strong predictor of primary lactase non-persistence. However, this test has limitations:

- * It only diagnoses primary (genetic) lactase deficiency and cannot detect secondary forms.
- * It diagnoses the genetic potential for malabsorption, not the presence of clinical intolerance or its severity.

7.6. Differential Diagnosis

The symptoms of lactose intolerance are non-specific and overlap with many other gastrointestinal disorders. It is essential to differentiate it from conditions such as:

Irritable Bowel Syndrome (IBS): There is a significant overlap in symptoms. Many patients with IBS also have lactose intolerance, and managing the latter can improve overall symptoms.

Milk Allergy: This is an immune-mediated response to milk proteins (casein or whey), not the sugar. It involves IgE antibodies and can cause symptoms like hives, wheezing, and anaphylaxis, in addition to gastrointestinal distress.

Celiac Disease: An autoimmune disorder triggered by gluten. It can cause secondary lactase deficiency due to villous atrophy.

Small Intestinal Bacterial Overgrowth (SIBO): Can cause symptoms of gas and bloating and can lead to a false positive on the HBT.



8. Clinical Management and Treatment Strategies

There is no cure for primary lactase deficiency, so management focuses on controlling symptoms through dietary and lifestyle adjustments.

8.1. Dietary Management

The cornerstone of managing lactose intolerance is modifying the diet to reduce the amount of lactose consumed to a level that does not cause symptoms.

Lactose Reduction, Not Necessarily Elimination: Most individuals with lactose intolerance can tolerate a certain amount of lactose without symptoms (typically up to 12 grams in a single dose, equivalent to one cup of milk), especially when consumed with other foods. A complete elimination is often unnecessary and can lead to nutritional deficiencies.

Identifying Lactose Content in Foods: Patients should be educated on the lactose content of common dairy products.

- High Lactose: Milk, ice cream, soft cheeses (e.g., ricotta, cottage cheese).
- Medium Lactose: Yogurt (see below), some processed cheeses.
- Low to No Lactose: Hard, aged cheeses (e.g., cheddar, parmesan, swiss) where much of the lactose is removed or fermented during processing. Butter also has very low lactose content.

Hidden Sources of Lactose: Lactose is frequently used as an additive in processed foods and medications. Patients should learn to read labels for ingredients like milk, milk solids, whey, and curds.

Lactose-Free Products: A wide variety of lactose-free milk and dairy products are now available. In these products, the lactase enzyme is added during manufacturing to pre-digest the lactose.

- Dairy Alternatives: Plant-based milks such as soy, almond, oat, and rice milk are naturally lactose-free alternatives.
- Yogurt and Fermented Products: Many individuals with lactose intolerance can tolerate yogurt better than milk. This is because the live bacterial cultures (probiotics) in yogurt (e.g., *Lactobacillus bulgaricus* and *Streptococcus thermophilus*) produce their own lactase, which aids in the digestion of lactose in the intestine. ⁽¹⁰⁾

8.2. Enzyme Replacement Therapy

Exogenous lactase enzyme supplements are available over-the-counter in tablet or liquid drop form. These supplements contain lactase derived from fungi (*Aspergillus oryzae*) or yeast (*Kluyveromyces lactis*).

- Usage: They should be taken just before or with the consumption of lactose-containing food. The drops can be added to liquid dairy products like milk to pre-digest the lactose before consumption.
- Efficacy: The effectiveness of these supplements can vary significantly among individuals and products. They can be very helpful for some in reducing symptoms when consuming dairy but may not be sufficient for others. ⁽¹⁰⁾

8.3. Probiotics and Prebiotics

There is growing interest in modulating the gut microbiota to improve lactose tolerance.

- Probiotics: These are live microorganisms that, when administered in adequate amounts, confer a health benefit. Certain probiotic strains, particularly from the *Bifidobacterium* and *Lactobacillus* genera, possess β -galactosidase activity and may help digest lactose in the colon, thereby reducing symptoms. Regular consumption of probiotic-rich foods or supplements may alter the colonic environment to better handle lactose loads.
- Prebiotics: These are substrates (like certain fibers) that are selectively utilized by host microorganisms, conferring a health benefit. Prebiotics can promote the growth of beneficial, lactose-fermenting bacteria in the gut. ⁽¹¹⁾

While promising, more research is needed to determine the most effective strains, dosages, and long-term benefits of probiotics and prebiotics for lactose intolerance.

8.4. Nutritional Considerations

A major concern for individuals who avoid dairy is the potential for inadequate intake of calcium and vitamin D, which are critical for bone health.

- Calcium: If dairy is eliminated, patients must be counseled on alternative sources of calcium, such as fortified plant-based milks, fortified orange juice, leafy green vegetables (e.g., kale, broccoli), canned fish with bones (sardines, salmon), and tofu.

- Vitamin D: Vitamin D is essential for calcium absorption. Sources include fatty fish, fortified foods, and sunlight exposure.
- Supplementation: Calcium and vitamin D supplements may be necessary for individuals who cannot meet their needs through diet alone.⁽⁹⁾

9. Future Directions and Research

Research into lactose intolerance continues to evolve. Key areas of future investigation include:

- Microbiome-Based Therapies: Developing more targeted probiotic and synbiotic therapies to enhance the lactose-digesting capacity of the colonic microbiota.
- Personalized Nutrition: Using genetic testing and microbiome analysis to provide more personalized dietary recommendations for managing lactose intolerance.
- Improved Diagnostics: Developing more accurate and less invasive diagnostic tools.
- Public Health: Improving food labeling and public awareness to help individuals with lactose intolerance make informed dietary choices and prevent nutritional deficiencies.⁽¹¹⁾

10. Conclusion

Lactose intolerance is a highly prevalent condition resulting from the physiological downregulation of the lactase enzyme after infancy. While its symptoms can significantly impact an individual's quality of life, it is an entirely manageable condition. The pathophysiology is well understood, arising from the osmotic effects and bacterial fermentation of undigested lactose in the large intestine. Accurate diagnosis, primarily through the hydrogen breath test, is crucial to differentiate it from other gastrointestinal disorders and to prevent unnecessary dietary restrictions. The management of lactose intolerance is centered on a personalized dietary approach, titrating lactose intake to an individual's tolerance threshold rather than complete elimination. The availability of lactose-free products, enzyme supplements, and the potential of microbiome-modulating therapies offer effective strategies for symptom control. A key aspect of long-term management is ensuring adequate calcium and vitamin D intake to protect bone health. With proper education and guidance from healthcare professionals, individuals with lactose intolerance can successfully manage their symptoms and maintain a balanced, nutrient-rich diet.

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