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Lactase Deficiency and Lactose Intolerance: Current Understanding and Future Directions

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Abstract:

Introduction and purpose: Lactose, the primary carbohydrate in milk, requires the enzyme lactase for digestion. Deficiency in lactase activity leads to lactose intolerance, causing gastrointestinal symptoms. Understanding the genetic and environmental factors influencing lactase expression and activity is crucial. Moreover, accurate diagnostic methods and effective treatments are needed to manage lactose intolerance. This review aims to explore the current knowledge on lactase deficiency, lactose intolerance, diagnostic methods, and treatment options.

State of knowledge: Lactase deficiency encompasses congenital, primary, and secondary forms, each with distinct etiologies. Although often used interchangeably, lactase deficiency and lactose intolerance differ. However, the association between lactase deficiency and lactose intolerance is complex, influenced by various factors including dietary habits, gut microbiota, and gastrointestinal motility. Diagnostic methods are limited, and treatment strategies primarily involve dietary modifications, lactase supplementation, and probiotics.

Conclusion: Lactose intolerance presents significant clinical challenges, often underrecognized and misdiagnosed. Despite diagnostic advancements further research is needed to refine diagnostic accuracy. Treatment focuses on dietary adjustments, enzyme supplementation, and probiotics. Balancing symptom relief with nutritional adequacy is essential. Future studies should explore the role of gut microbiome modulation in lactose intolerance management through clinical trials.

Keywords: lactose, lactose intolerance, lactase deficiency

1. Introduction

Lactose is the major carbohydrate and energy source in milk of almost all mammals. It is a disaccharide composed of 2 monosaccharides: glucose and galactose, linked by a β-1,4-glycosidic bond. Intestinal absorption of lactose occurs as a result of its hydrolysis by the enzyme lactase, present in the epithelium of the small intestine. Only as a result is glucose and galactose absorbed into the blood. The highest amount of lactase is found in the proximal part of the jejunum and gradually decreases distally toward the ileum [1].

Lactase is a β-D-galactosidase or, more precisely, a lactose-fluorosine hydrolase. The enzyme consists of two domains: a β-galactosidase and a glycosylceramide domain. The former is involved in the hydrolysis of lactose to glucose and galactose, while the latter degrades fluorosine and several glycolipids. The main substrate of the enzyme, however, is lactose supplied with food. The presence of lactase in the human intestinal epithelium is found as early as 8 weeks of fetal life. Its activity increases gradually during the 3rd trimester of pregnancy, reaching its highest level at birth. The ability to digest lactose is crucial for the normal development of the newborn and infant. Congenital lactase deficiency or severe lactase deficiency is a very rare, genetically determined condition that, if unrecognized soon after birth, can lead to death [2, 3].

The synthesis of the enzyme depends on the gene encoding lactase (LCT), located on the long arm of chromosome 2 (2q21-22). The expression of this gene is subject to complex regulation under the influence of various factors, such as age and ethnicity [2, 30]. In the majority of

people worldwide (about 70%), lactase activity after breastfeeding decreases to as low as 5-10% of the value from infancy, and sometimes to undetectable levels in the intestinal epithelium2. This is a physiological, genetically programmed process of silencing the gene responsible for lactase synthesis during infancy, childhood and adult life, referred to as adult-type hypolactasia. The time of onset of this type of hypolactasia varies in different populations, sometimes found as early as 2-year-old children. In contrast, in about 30% of people, high lactase activity persists both in childhood and in adulthood (normolactasia)[24]. This variation in lactase activity during adult life in populations is due to adaptive mechanisms in evolutionary processes. Thus, it can be surmised that during evolution, positive selection of individuals possessing mutations that regulate lactase activity was particularly beneficial in terms of the consumption of milk and milk products as an important component of the diet throughout the year. In northern European countries, this was particularly important due to the greater availability of calcium and phosphorus and the reduced production of vitamin D during winter periods due to less sun exposure [3, 30]. This is supported by the observation that more than 90% of the population in Scandinavian countries and the Netherlands, where the consumption of milk and its products is significant and long-lasting, have high lactase activity, in contrast to countries in Asia or most areas of Africa, where the frequency is about 10% [3, 4]. In Europe, 2 polymorphisms of the LCT gene are responsible for reduced lactase production: C/T-13910 and G/A-220186 [5]. The TT and AA variants are dominant and determine the maintenance of lactase at high levels in adults, while the CC and GG variants are responsible for the formation of adult-type hypolactasia. In CT and AG heterozygotes, lactase activity shows intermediate, varying values [4, 30].

2. Lactase deficiency and lactose intolerance

There are 3 types of intestinal lactase deficiency [1, 6, 7]:

1. Congenital lactase deficiency or insufficiency - a very rare, autosomal recessive disease, genetically determined disorder, causing very severe symptoms immediately after birth and administration of lactose in food. Failure to recognize this condition early enough can even lead to the death of the newborn baby;
2. Primary lactase deficiency, which is the programmed gradual decrease in the activity of this enzyme, discussed above, from the moment breastfeeding is stopped;

3. Secondary lactase deficiency, as a consequence of organic diseases of the small intestine (such as infections, inflammatory bowel diseases) or arising from resectable surgical procedures.

The terms lactase deficiency and lactose intolerance, although sometimes used interchangeably, are not the same. Lactase deficiency refers to reduced activity of this enzyme in the epithelium of the villi of the small intestine, while lactose intolerance is a set of symptoms reported by patients after consuming this disaccharide. Symptoms usually occur when lactase activity falls below 50%, leading to insufficient digestion and absorption of lactose, and undigested lactose increases the osmotic charge in the intestines, causing diarrhea. Symptoms of intolerance can also include abdominal pain, bloating, increased gas output and, less commonly, nausea and constipation [3]. Some patients with lactose intolerance also experience systemic symptoms such as headaches, fatigue, joint pain and difficulty urinating [8]. However, it is unclear whether these symptoms are a consequence of lactose intolerance or related to other gastrointestinal disorders, such as irritable bowel syndrome (IBS), often seen in these patients [3].

Lactase deficiency does not necessarily imply lactose intolerance, as many patients with the condition tolerate a certain amount of dietary lactose, usually up to 12 g, especially if they consume it with other foods [9]. The symptoms of intolerance depend not only on the level of lactase expression in the intestines, but also on the dose of lactose consumed, other foods consumed at the same time, the influence of the intestinal microbiota, gastrointestinal motility and intestinal hypersensitivity [10].

Patients with IBS, especially those with IBS with predominant diarrheal symptoms and lactase deficiency, typically experience increased symptoms after consuming even small amounts of lactose, in contrast to those with lactase deficiency but without IBS. Lactose intolerance occurs in 27-78% of patients with IBS, depending on the source [11]. Chinese studies suggest that patients with IBS and lactose intolerance may experience activation of the intestinal immune system, reminiscent of changes seen in patients with so-called post-infectious IBS, providing new insights into the pathophysiology of food intolerance [12].

The effect of dairy products on Inflammatory Bowel Diseases (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD), is not entirely clear. There is no clear evidence that dairy products cause exacerbations of UC, although patients with CD may have secondary lactase deficiencies due to the inflammatory process in the small intestine [4]. In conclusion, not all

patients with IBD are lactose intolerant, so restricting dairy products in the diet of patients with these diseases is not always recommended [13, 14].

3. Diagnostic methods for evaluating digestive disorders and lactose intolerance

- Direct analysis of lactase activity in small intestinal mucosal samples is an established diagnostic standard; however, it is an invasive method and the inhomogeneity of the distribution of enzyme expression are its limitations;
- Genetic testing of the C/T-13910 polymorphism is used as an indicator of lactase activity in European populations, but its use in other ethnic groups is limited by differences in genetic variants [28, 30].

It is noteworthy that both intestinal biopsy and genetic tests assess only lactase activity, not taking into account possible symptoms of lactose intolerance, which may occur in only a fraction of people with deficiency of this enzyme. In addition, these tests are difficult to access and do not take into account clinical aspects [17, 18].

More common are indirect methods to assess lactose digestion disorders, such as:

- Lactose Tolerance Test (LTT), which assesses the hydrolytic capacity of lactase and glucose absorption into the blood after lactose ingestion.
- Hydrogen breath test (HBT), which illustrates the metabolic activity of the microbiome after lactose ingestion.

In both of these tests, the patient consumes 20-50 g of lactose orally. In the LTT, the blood glucose concentration is then measured, and the absence of an increase of more than 20 mg/dl indicates lactase deficiency. In the HBT, on the other hand, an increase of more than 20 ppm in exhaled hydrogen concentration indicates increased lactose fermentation in the small intestine [1, 17]. Studies have shown that HBT has a sensitivity of 67 to 100%, and a specificity of 90 to 100% [15]. Both of these methods have their limitations. LTT results can be affected by post-meal glucose fluctuations and other factors, such as abnormal gastric emptying. The HBT, on the other hand, can give false-positive results in the case of the syndrome of excessive intestinal bacterial proliferation (SIBO), and false-negative results due to the presence of non-hydrogen-producing bacteria in the gut [16].

4. Treatment

Treatment of lactose intolerance is mainly based on reducing or eliminating lactose from the diet until clinical symptoms resolve, which requires an appropriate dietary approach [29]. Appropriate therapeutic management includes not only limiting lactose intake or switching to a lactose-free or low-lactose diet, but also the use of oral lactase supplements and regulation of the gut microbiome with selected probiotic strains that exhibit β-galactosidase enzymatic activity [4, 29]. Lactose is mainly found in dairy products such as milk, yogurt, cream, butter and ice cream. In addition, certain foods, such as certain breads, breakfast cereals, powdered soups, pastries, candy, salad dressings, frozen French fries, sausages and some prescription or over-the-counter medications, may contain so-called hidden lactose [19]. However, exclusion of dairy from the diet should not be widespread and severe, as it can lead to serious nutritional deficiencies and bone tissue disorders such as osteoporosis [25, 26]. Most patients with lactose intolerance do not experience adverse symptoms after consuming 5 grams of lactose at a time, and lactose tolerance can increase when consumed with other nutrients. Various options are available on the food market for people with lactose intolerance, including both naturally lactose-free products and those produced using lactose hydrolysis processes [19, 27]. A study of rifaximin showed a significant reduction in symptoms of lactose intolerance in patients on a 10-day treatment with this eubiotic, which had a comparable effect to a 40-day lactose-free diet. However, these results were not confirmed in placebo-controlled studies [20]. Another promising therapeutic option for people with lactose intolerance is the use of selected probiotic strains that exhibit β-galactosidase enzyme activity. Research on them has gained popularity in recent years, confirming the beneficial effects of fermented dairy products containing lactose hydrolyzing microorganisms [4,19]. However, proper selection of probiotic species and strains is key, and conclusions about symptom reduction are often based on studies of irritable bowel syndrome, which have shown the effectiveness of probiotics such as *Lactobacillus plantarum*, *Lactobacillus acidophilus* and *Bifidobacterium lactis* in reducing abdominal pain and bloating [22, 23].

Streptococcus thermophilus and *Lactobacillus delbrueckii subsp*. *bulgaricus* have been shown to improve lactose digestion and alleviate symptoms associated with lactose intolerance. This effect has been validated through several controlled trials involving participants who consumed yogurt containing active cultures [21].

5. Conclusion

Lactose intolerance remains an underestimated and often misdiagnosed clinical problem. Although its diagnosis can be difficult, the hydrogen breath test (HBT) and genetic test, despite some limitations, are considered reliable diagnostic tools. Lactose-free diet, lactase supplementation and β-galactosidase-containing probiotics are often used in therapy. The management of lactose intolerance necessitates a balanced approach to prevent nutritional deficiencies while alleviating symptoms. Nevertheless, further high-quality clinical trials are needed to investigate and confirm the role of modulating the gut microbiome in the treatment of lactose intolerance.

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