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Article

Diagnosis and Treatment of Lactose Intolerance in Children and Adults: What Has Changed during the Past 50 Years?

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Abstract: Breastfeeding is essential for the life of the mammal on this planet. From the first weeks after birth, mother's milk provides the child's body with the necessary macro-and microelements, vitamins, and proteins. It contributes to the formation of immunity and supplies the necessary environment for the formation of the future gut microbiota. To preserve the energy of the body, the mechanism of breaking the trophic bond between the mother and her children has been evolutionarily developed. Genetically determined processes lead to a transition from milk feeding to other nutrition methods. Even after that, animal milk continues to be part of the human diet. We analyzed different views on the problem of Lactose Intolerance found during the last 50 years to evaluate the significance of milk in the daily human diet as well as to study the correctful microbial composition of the human intestine against lactose intolerance.

Keywords: Lactose Intolerance, Lactase Expression, Celiac Disease, Inflammatory Bowel Diseases, MCM6 13910C>T (rs4988235) LCT gene mutation

1. Introduction

The main source of carbohydrates in mother's milk is milk sugar, that is, lactose (β-galactosyl-1,4 glucose). This sugar is an easily digestible high-energy substrate for the baby's body, affecting the growth and development of the microbiota, primarily *Bifidobacteria*. To understand the "pathogenesis" of lactose intolerance, the normal physiology of carbohydrate digestion needs to be understood. In 1958, a Nobel laureate A.M. Ugolov proposed the theory of membrane (parietal) digestion. This type of digestion is carried out in the small intestine of humans or higher animals with enzymes that are attached to the enterocytes` membrane. The enzymes are hydrophilic and oriented to the small intestine cavity, i.e., to the substrate and water medium. Membranous-phase digestion is responsible for the hydrolysis of more than 80% of all chemical bonds in polymers from food. A Brush border is a combination of 3–4 thousand plasmatic outgrowths located on the apical surface of enterocytes, covered with a network of polysaccharide threads, so-called glycocalyx, 0.5 μm thick. Due to this, the membranous-phase digestion zone is sterile and contains a minimum number of bacteria that is capable of competing with the macroorganism for food substances. However, in the absence of the necessary enzymes on the intestinal border, the substrate returns to the lumen of the small intestine, where it undergoes hydrolysis by the intestinal microbiota, determining the degree of clinical manifestations.

The membranous enzyme involved in the hydrolysis of β-galactosyl-1,4-glucose is lactase (lactase-florisine hydrolase). Lactase begins to be synthesized in the antenatal period by small intestine enterocytes at week 12 of gestation, and its activity increases until week 34 and reaches its peak at birth [1]. Thus, preterm infants born before 34 weeks of gestation have significantly lower enzyme activity than full-term infants. Lactase provides the hydrolysis of lactose to galactose and glucose which enter the enterocyte and subsequently take part in energy metabolism and the formation of glycoproteins and glycolipids due to the Na^+-ATP-dependent secondary active transport [2]. Several studies on mouse models have demonstrated the importance of galactose in brain development [3−5]. Lactase is not the most active digestive enzyme in the human body, yet in a chemical assessment of enzyme activity, the estimated time spent on hydrolysis of 33 mmol of lactose is less than 15 min (±250 ml cup of milk) [6]. The gradual transition in the first months of life from a lactotrophic to a mixed diet is accompanied by a decrease in lactase expression on the surface of enterocytes and entails the abandonment of dairy feeding by the child. This process is an integral part of the subsequent maturation of the digestive tract development in the setting of definitive feeding and leads to a break of the trophic link for avoiding

the exhaustion of the mother's body. The difference between lactase deficiency and normal lactose metabolism is presented in Fig. 1.

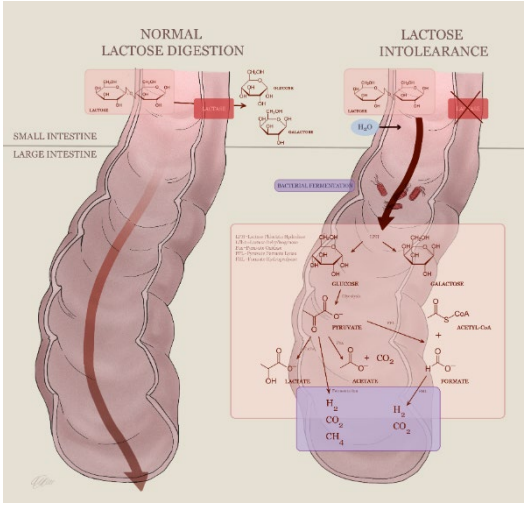

Fig. 1. Mechanism of lactose deficiency. The lactase-florisine hydrolase (membranous enzyme) is involved in the hydrolysis of β-galactosyl-1,4-glucose is lactase. Lactase is being synthesized in the antenatal period by small intestine enterocytes at week 12 of gestation. Lactase provides the hydrolysis of lactose to galactose and glucose, which, due to the Na^+-ATP-dependent secondary active transport, enter the enterocyte and subsequently take part in energy metabolism and the formation of glycoproteins and glycolipids. The gradual transition in the first months of life from a lactotrophic to a mixed diet is accompanied by a decrease in lactase expression on the surface of enterocytes and entails the abandonment of dairy feeding by the child [2].

According to up-to-date international classifications describing the activity of the lactase, the following is accepted [7].

(1) Lactase persistence (resistance) is a genetically determined high activity of lactase in adults and older children. This phenotype is characterized by the ability to digest lactose throughout life.
(2) Lactase instability manifests during weaning by a decrease in lactase expression on the brush border of less than 10 U/L, leaving a minimal ability to digest lactose.
(3) lactase insufficiency develops due to genetic causes (primary) or due to the destruction of small intestinal enterocytes as a secondary condition (secondary).
(4) Lactose maldigestion is for ineffective parietal digestion of lactose due to lactase deficiency.
(5) Malabsorption of lactose means impaired lactose absorption due to maldigestion.
(6) Lactose intolerance is a clinical presentation that occurs following lactose intake and is characterized by symptoms such as abdominal pain, flatulence, diarrhea, and sometimes cramping. These symptoms are not observed when lactose is replaced with a placebo.
(7) Lactose hypersensitivity is manifested by systemic symptoms such as headache, depression, and is increasing fatigue. It may be seen with or without lactose intolerance symptoms.

When the level of lactase enzyme activity decreases, the milk sugar is no longer broken down in the small intestine, which is characterized as "lactase deficiency" and clinically manifested as "lactose intolerance".

It is worth noting that the severity of the clinical picture is variable. Patients may be disturbed by flatulence, bloating, diarrhea, and spastic abdominal pain without clear localization. Mainly the symptoms appear within 4 h after eating lactose-containing products. According to statistical evaluation, lactose intolerance occurs in a large proportion of the world's population. The recent major systematic review included 62910 participants (over 10 years old) from 89 countries. After standardization by the country size, the global prevalence of lactose malabsorption was 68% at a confidence interval (CI) of 95%, ranging from 28% in Western, Southern, and Northern Europe to 70% in the Midwest [8].

The purpose of our review was to analyze the history of the problem and different views on Lactose Intolerance for the past 50 years. Also we wanted to emphasize the importance of breastfeeding in mammals and discuss it's role in healthy growth and development of young children. We tried to discuss all the known mechanisms of Lactose Intolerance formation and common treatment approaches, as well as to study the potential of correction of the microbial composition of the human intestine. As a result of this work, once again we confirmed that the mechanisms of membrane (parietal) digestion formed the basis of our knowledge.

We also described the importance of SCFA and essential needs in their future studies. Future studies of SCFA and their metabolism can lead us to understanding of the main lactate deficiency symptoms. We also found some data on gene polymorphisms and their correlation with lactase enzyme. And we really hope that our review will help young doctors in better understanding of the pathologycal mechanisms and treatment strategies in patients with Lactose Intolerance.

2. Literature Review

Multiple attempts were unsuccessful to find a mechanism of lactase level reduction after weaning. This is explained by the fact that the potential mechanism of regulation of lactase activity is centered around the transcription factors responsible for lactase (LCT) gene expression, rather than the processes that regulate the growth and survival of enterocytes secreting the necessary enzyme [6]. Subsequently, a series of genetic studies allowed to make a detailed description of the processes responsible for the regulation of lactase enzyme activity. This process, when being genetically determined, is regulated by the gene responsible for lactase expression (LCT). This gene is located on the long arm of the 2nd chromosome at position 21(2q21-22) [9,10]. After transcription and splicing are done, the matrix RNA contains 6274 bases and encodes a polypeptide with 1927 amino acid residues consisting of 4 domains. The catalytic activity is contained in the third domain with florizine hydrolase activity at position Glu1273 and in the fourth domain with lactase activity at position Glu1749[11].

For certain people, the ability to digest milk sugar is maintained throughout life [12]. Genetic evaluation of this feature showed several polymorphisms associated with the persistence of the lactase enzyme on the brush border of enterocytes. The first polymorphism was found in the European population: 13910C>T (rs4988235). Located upstream of the LCT gene, the 13910T dominant allele correlated with a higher level of lactase expression and lactase persistence phenotype in the Finnish population in almost 100% of cases [13]. At the same time, numerous follow-up observations have revealed different mechanisms that compensate for lactase enzyme deficiency in humans. Despite low enzyme activity, some people lack clinical symptoms and signs of lactase intolerance due to the adaptation of the intestinal microbiota to the human diet.

By the 4th century B.C. our ancestors had mastered animal husbandry and found milk as a form of subsistence production. This served as one of the most important premises for evolutionary changes in human nutritional behavior and determined the modern diet. However, in the setting of the genetically determined mechanism of "milk rejection" in childhood, the human body could not digest and assimilate dairy products without symbiotic digestion. This concept refers to the assistance of gut microorganisms in the processing and utilization of certain food macromolecules and micromolecules.

The expression of genes responsible for lactose metabolism in microorganisms was first demonstrated using *Escherichia coli* (*E. coli*) in 1961 by microbiologists François Jacob and Jacques Monod. Together with André Lvov, the scientists were awarded the Nobel Prize in 1965 for the discovery of the lactose operon (lac operon). The essence of this process is the following. When glucose, a substrate necessary for microbial growth, is not available, but a sufficient amount of lactose is present, the operon is activated to regulate the expression of the enzymes necessary for the utilization of this oligosaccharide. Thus, the lactose operon described in the example of *E. coli* determines the ability of certain bacteria, such as Staphylococcus, Streptococcus, Lactococcus, and Lactobacillus to synthesize the enzyme β-galactosidase, capable of hydrolyzing the lactose glycoside bonds to form glucose and galactose [14−16]. It is worth noting that the expression of lactase in mammals, in contrast to the expression of the β-galactosidase enzyme in bacteria, is not a substrate-dependent process. Namely, under conditions of decreased expression of endogenous lactase on the brush border of enterocytes, the introduction of large amounts of lactose does not stimulate the production of the necessary enzyme [17].

In an earlier study, Johnson et al. evaluated the maximum amount of lactose that person with lactose malabsorption could absorb. Twenty-two subjects aged 13 to 39 years old were gradually increasing the amount of lactose in their diets over time. After the study was finished, 17 patients reported a reduction in the intensity of clinical manifestations amid a gradual increase in the daily dose of lactose consumed and were eventually able to tolerate an average of 12 g of lactose per day [18]. These data indicate a possible increase in lactose tolerance due to the formation of adaptive mechanisms at the level of gut microbiota. The β-galactosidase activity of many bacteria has been considered one of such mechanisms. Indeed, the authors showed that the addition of lactose alters the ratio of microorganisms and increases the enzymatic activity concerning lactose hydrolysis. Hertzler and Savaiano demonstrated the ability of the colon to adapt to lactose utilization in their blind-controlled cross-over study involving 29 individuals with lactose intolerance. In the study, an increase in β-galactosidase activity was noted as early as 48 h from the start of the study and repeatedly thereafter with daily lactose intake [19]. Later, a larger double-blind study with 46 subjects by Briet et al. also demonstrated an increase in fecal β-galactosidase levels with oral lactose intake [20]. Thus, it has been shown that an adaptation of the intestinal microbiota occurs, namely, an increase in the number of microbial strains capable of breaking down lactose with the gradual introduction of lactose into the diet. Their study for the patients with confirmed lactase deficiency revealed the changes in the ratio of fecal microflora following oral administration of lactose,. *Lactobacilli*, *Enterococci* and *Bifidobacteria* predominated the fecal

microbiota when evaluating the observational results [21,22]. However, subsequent studies comparing the activity of the β-galactosidase enzyme in the feces of patients with and without lactase deficiency following oral lactose administration revealed no significant differences [23]. The researchers speculated that the adaptation of the organism of people with lactose deficiency does not depend solely on changes in the ratio of microbes with and without β-galactosidase activity.

After lactose is broken down by the colonic microflora, hydrolysis products including glucose and galactose are formed. The intestinal microflora actively breaks down these carbohydrates, producing many metabolites, mainly short-chain fatty acids (SCFAs). However, studies show that the formation of intermediate metabolites is faster for people with lactose intolerance than in the group of patients with lactase persistence [24]. In most cases, short-chain fatty acids are excreted from the colon by several pathways. The first pathway is the absorption of SCFAs, mainly acetate, by colonocytes, followed by the entry of acetate into the bloodstream and incorporation of the substrate into energy metabolism [25]. Butyrate is actively used by the intestinal epithelium [26]. A positive correlation between butyrate concentration and the number of epithelial and mucin-secreting cells, as well as crypt depth, was demonstrated in animal models [27]. The next pathway is the use of SCFAs as a substrate for bacterial growth. Several authors in their works suggested that approximately 40% of carbon atoms formed during the fermentation of the exosolic fragment (hexosyl moiety) are used in the growth of bacteria such as *Bifidobacteria* [28]. As a rule, further metabolism of SCFAs by intestinal microflora leads to the formation of gases (H_2, CH_4, and CO_2) [25], which subsequently enter the bloodstream and then they reach the lungs where they are excreted. At the same time, there are differences in the qualitative composition of the products of enzymatic catabolism in each bacterial strain [29]..

3. Results

3.1. Differential Diagnosis

The differential diagnosis of lactose intolerance for diseases presents similar clinical symptoms including unsteady stools, abdominal pain, and flatulence. First, when making a differential diagnosis, it is necessary to understand that clinical symptoms of lactose deficiency occur exclusively after the consumption of lactose-containing foods. To verify the association of symptoms with specific foods, a food diary maintenance may be recommended for the patient. Clinical manifestations of irritable bowel syndrome (IBS) are often intensified by the consumption of dairy products. Frequently, the symptoms of the related disease may be intensified by the consumption of spicy foods, caffeine, and alcohol. In a study of 122 patients diagnosed with IBS, Parker revealed that 27% of patients had IBS daily, and the symptoms were often exacerbated by eating foods such as caffeine or alcohol. He also pointed out that 27% of the subjects had lactase deficiency according to a lactose tolerance test [30].

To differentiate between lactose intolerance, celiac disease, and gluten intolerance in addition to keeping a food diary, it is advisable to evaluate the biopsy material of small intestinal mucosa (secondary lactase deficiency may develop in the setting of small intestinal villous damage), as well as to perform immunological tests such as tissue transglutaminase antibody level and antibodies to endomysium in immunoglobulin A (IgA), and the evaluation of total IgA levels [31]. When assessing the clinical picture, the presence of symptoms of concern such as hematochezia, weight loss, abdominal pain, urge to defecate at night, and inflammatory bowel disease needs to be included in the differential diagnosis. The clinical presentation of lactose intolerance accompanies inflammatory bowel diseases, such as Crohn's disease. However, in this case, the insufficiency of lactase enzyme is secondary, due to inflammatory changes in the mucosa of the small intestine and changes in the microvilli on the apical surface of enterocytes where the enzyme is directly fixed. Secondary lactase deficiency occurs in presence of infectious diseases. Studies have demonstrated that, in addition to nematodes and protozoa, a number of bacteria, such as *Clostridium difficile* or methicillin-resistant *Staphylococcus aureus*, produce toxins during colonization and can damage enterocytes, leading to secondary lactase deficiency [11].

In addition to the deficiency of a certain enzyme to ensure efficient digestion, a condition similar in clinical presentation to food allergy is often found in the clinical practice of a physician. However, with careful collection of medical history, the evaluation of clinical manifestations of the disease, and allergy to several certain products, it is possible to differentiate this condition even at the first stage of the diagnostic search. Food allergies often manifest immediately after consuming a certain product and are accompanied by extraintestinal manifestations such as hives, eczema, allergic rhinitis, chronic ear disease, and in rare cases, anaphylactic shock [32].

3.2. Instrumental and Laboratory Diagnosis

The instrumental and laboratory diagnosis of lactase deficiency is mainly related to the evaluation of lactose metabolism [33]. As a rule, a combination of two or more methods are used to confirm enzyme deficiency.

Assessment of enzyme activity in fragments of a small intestinal mucosa biopsy is the most accurate method to confirm the enzyme persistence on enterocytes and ensure the minimal possibility of false-positive results. At the same time, the combination of the endoscopic and histological examination allows to simultaneously exclude the causes of secondary lactase deficiency such as celiac disease and inflammatory bowel diseases. However, as this method is invasive, routine diagnosis is difficult and complicated due to irregular lactase expression throughout the small intestine [13]. The accuracy of the genetic method for determining lactase persistence is limited by the multitude of genetic polymorphisms in different populations. Also, this test is not effective for patients with secondary lactase deficiency, as it does not reflect the enzyme activity directly on the apical surface of enterocytes.

Subsequent methods evaluate the ability to digest lactose. Under conditions of lactase persistence, lactose is hydrolyzed to glucose and galactose. Galactose is also converted to glucose after it enters the bloodstream and passes through the liver. The lactose tolerance test examines blood glucose levels 30 min after an oral administration of 20−50 g of lactose. If lactose is not subjected to enzymatic hydrolysis or is not fermented completely, the blood glucose level does not exceed 1.1 mmol/l. In this case, it is possible to confirm the diagnosis of lactose maldigestion. However, in cases of impaired glucose metabolism in the body and impaired glucose tolerance, this test gives false positive or false negative results. Enattah et al. also emphasized the variability of test results, indicating that the specificity of the test ranges from 77 to 96% and the sensitivity from 76 to 94% [34].

The most commonly used method for assessing lactase deficiency is the hydrogen breath test with lactose. The study is based on the evaluation of products of metabolism of non-fermentable lactose by the microflora of the large intestine. In the process of digestion and utilization of metabolites in the intestine, an excessive quantity of gases (H_2, CH_4) may be formed, which are subsequently absorbed by colonocytes, enter the bloodstream, and are removed from the human body through the lungs. The breath test primarily evaluates elevated hydrogen levels, but another metabolic product, methane, is detected in the test.

The studies generally used 50 g of pure lactose for the experiment. However, a recent study has shown that symptoms of lactose intolerance disappear more quickly with 25 g of milk sugar. After the patient ingests lactose, hydrogen (and/or methane) in the exhaled air is being quantified. Results are recorded every 10–15 min for 2–4 h. An increase in hydrogen levels above 20 ppm, combined with the manifestation of symptoms (abdominal bloating and diarrhea) is a reliable sign of lactose malabsorption and lactose intolerance. The non-invasiveness and ease of use allow the hydrogen breath test to be used routinely for lactase deficiency tests. To avoid false-negative or false-positive results, this method is combined with serum glucose assessment in addition to assessing the manifestation of symptoms after lactose intake.

The social significance of lactose intolerance lies in the psychologically negative environment created by the development of a vivid clinical picture when even small amounts of ingested lactose. In particular, lactose intolerance has a psychological impact on school-age children whose bodies are just beginning to adapt to the reduced expression of lactase in the small intestine. In addition, the literature provides data on the amount of lactose in various foods. Along with dairy products, bakery, and confectionery products, lactose is included in many drugs and dietary supplements. The development of clinical symptoms against the background of lactose intake leads patients to refuse to eat lactose-containing foods or medicines and replace them with plant-based alternatives such as almond milk and coconut milk/oil. Recent studies have assessed the importance of dairy products in the daily diet. One of them showed no clear correlation between milk consumption and the development of related diseases, such as obesity, diabetes, cancer, and cardiovascular disease [35]. At the same time, the consumption of fermented dairy products has a beneficial probiotic effect..

4. Conclusions

This study was carried out by investigating research results over the past 50 years to describe the clinical presentation of lactose intolerance. New research methods have increased an understanding of mechanisms not only at the cellular level but also at the genetic level. Data were obtained on gene polymorphisms correlated with lactase enzyme persisting on the enterocyte microvilli. Lactate deficiency remains a problem for most people of different ages around the world. This motivates researchers to find the solution. The mechanisms described for membrane (parietal) digestion help understand the role of microbiota in the hydrolysis of many food-borne substances. Several clinical observations have shown the importance of SCFA from carbohydrate fission by intestinal micro-organisms. The different ratios of microorganisms and consequently the products of their metabolism (SCFA) are a pathological link to symptoms caused by lactate deficiency such as pain, abdominal swelling, and diarrhea. Pre- and probiotics for correction of microbial and metabolic composition dealing with lactose intolerance will be on the same basis as products of enriched lactase. However, the establishment of an appropriate research framework for finding evidence is required for additional clinical studies that assess the different genotypes in a population that are deeply connected with the human microbiome.

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