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Lactose intolerance or milk allergy: Beliefs and differences

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Abstract
When we talk about lactose intolerance, we primarily refer to a syndrome that manifests as a variety of symptoms after eating lactose-containing foods. One of the most prevalent types of food intolerance, it results from decreased lactase activity in the small bowel brush boundary. Depending on how severe these symptoms are, a person may be lactose intolerant to varied degrees. Lactose can be fermented by the gut microbiota when it is not digested, which can cause lactose intolerance symptoms such diarrhoea, bloating, flatulence, and abdominal pain. There is significant intra- and inter-individual variation in the severity of these clinical manifestations. These digestive symptoms could be mistakenly classified as "milk allergy" symptoms because they resemble cow's milk allergy symptoms. There are significant variations in lactose intolerance.

Keywords: Intolerance, lactose, cow milk allergy, lactase, diarrhea

Introduction
Adverse food responses (AFRs) in children can manifest in a variety of ways [1]. Different ingredients in the same food can cause these systems to be activated. Food proteins cause immune-mediated reactions (such as food allergies and celiac disease), whereas the great majority of non-immune-mediated AFRs are from carbohydrate intolerances. Lactose intolerance is the most prevalent case of carbohydrate intolerance in children. Lactose makes up the majority of the dietary carbs during infancy. Lactose is a disaccharide, which is present in many dairy products, composed by galactose linked to glucose via a β-1→4 glucosidic bond. The small intestine brush boundary membrane-bound enzyme lactase hydrolyzes lactose, and the monosaccharides glucose and galactose are both actively absorbed as a result. Lactose intolerance primarily occurs due to ingestion of foods with lactose by people lacking sufficient lactase enzyme from brush border epithelium of intestines [2].

Three Lactose Intolerance Subtypes
The lactase deficit underlying each type is brought on by many factors:

1. Congenital lactase deficiency (CLD) is a very rare autosomal recessive condition that manifests at birth as a lack of or diminished enzymatic activity.
2. Primary lactose intolerance, also known as adult-type lactase deficiency, is a common autosomal recessive disorder caused by a developmentally controlled alteration in the expression of the lactase gene.
3. Several disorders, including infections, food allergies, celiac disease, small bowel bacterial overgrowth, Crohn's disease, and radiation/chemotherapy-induced enteritis can cause intestinal damage that results in secondary lactase insufficiency, a temporary condition.

Within the category of congenital diarrheal illnesses, CLD is a rare (just a few instances have been reported) and severe intestinal autosomal recessive disease brought on by the lack of lactase activity from birth (OMIM 223000) [3, 4]. It is important to distinguish between this syndrome with the developing lactose intolerance that may be seen in premature infants. Because enterocytes that express lactase in the small intestine grow later in the third trimester, these people may have lower levels of lactase. Watery diarrhoea, intestinal meteorism, and malnutrition are the main signs and symptoms of CLD, which start in the first days following birth with the start of lactation with breast milk or lactose-containing formula. When patients switch to a lactose-free diet, symptoms go away. The lack or very low levels of are the typical characteristics of CLD.

Because of a mutation in the lactase phlorizin hydrolase gene (LPH), which is located on 2q21.3, CLD is often characterised by the absence or very low levels of lactase expression [5, 6]. In Finland, where the illness is more prevalent because of the founder effect and genetic drift, the majority of CLD cases have been reported [5, 7]. The most frequent genotypes found in these patients include premature stop codons and a shortened protein as a result of frame shifts, missense mutations in the LPH coding area, or exon duplication [7–10]. Other scenarios include mutations that result in a single amino acid substitution and can prevent LPH from developing and performing as it should [7, 11]. More recently, severe instances of CLD triggered by LPH gene mutations that heterozygous or homozygous pattern of inheritance [3].

When a person has primary lactose intolerance, their intestinal lactase expression abruptly declines, making it difficult for them to digest dairy products later in infancy or adolescence. It is the most prevalent kind of lactose intolerance and is inherited. Approximately 70% of adults worldwide do not consistently produce enough lactase (hypolactasia). Ethnicity affects both the worldwide distribution and the age at which lactase expression starts to drop. More than 50% of people in South America, Africa, and Asia lack lactase persistence. Southern European or Mediterranean people are also susceptible to the illness. Up to 100 percent of the population in some Asian nations lacks lactase persistence. In the United States, the percentage of lactase non-persistence varies by ethnic origin, with the population of European origin having the lowest rate and Hispanics and people of African descent having the highest percentage. Primary lactose intolerant individuals are born with an abundance of lactase, which is essential for infants whose only source of sustenance is milk. Children's lactase production declines as they switch from milk to other diets. While people of European and American ancestry often do not suffer symptoms of lactose intolerance until later in childhood (5–6 years of age) or adolescence [12–14], children of African, Asian, or Hispanic heritage may begin to exhibit symptoms between the ages of 2 and 3 [12–14]. A dominant Mendelian characteristic, lactase persistence is inherited [15]. Five or more distinct single nucleotide variations in a regulatory region (a transcriptional enhancer) upstream of the lactase gene can contribute to the hereditary feature of intestinal lactase persistence.

Most cases of lactase persistence in Caucasian people are caused by one of them, 13910*T (rs4988235), whereas others, including 13907*G (rs41525747), 13915*G (rs41380347), 14009*G (rs869051967), and 14010*C (rs145946881), are found in varying numbers in the Middle East and Africa [16, 17]. The amount of lactose in the diet, intestinal transit time, lactase expression, the distribution and fermentation capacity of the gut microbiota, sensitivity to chemical and mechanical stimulation of the gut, and psychological factors are just a few of the individual factors that can affect the onset of symptoms in non-persistence lactase subjects [18–20]. The reduction of lactose intolerance symptoms is attributed to the gut microbiota's adaptation to an increasing dose of lactose and a rise in bacterial -galactosidase activity [21, 22].

Finally, almost all clinical disorders that harm the small intestine can reduce lactase expression, which results in a temporary lactase deficit. Celiac disease, minor bacterial overgrowth, and Crohn's disease are among the illnesses connected to secondary lactose intolerance. Though it may take some time, treating the underlying disease may help to reduce signs and symptoms and restore lactase levels. Lactose intolerance may also result during chemotherapy or radiation treatment for the abdomen. Lactase insufficiency can result from severe enteropathy brought on by cow's milk allergy (CMA). In these patients, gastrointestinal symptoms brought on by lactose intolerance and CMA may coexist. As a result, different processes can cause an unfavourable reaction to the same meal, such as cow's milk.

The differences between CMA and lactose intolerance

There is frequently misunderstanding between lactose intolerance and CMA among both patients and doctors, which could lead to unneeded dietary restrictions or harmful reactions. Patients and their parents frequently refer to "milk allergy," "milk intolerance," and "lactose intolerance" without being fully aware of their various definitions, the various mechanisms underlying them, or the dietary implications of the diagnosis. These disorders are managed in a very different way, and if they are improperly identified or treated, the patient could suffer grave consequences [23].

Lack of capacity to properly digest the sugar lactose causes lactose intolerance. As previously stated, CMA is one of the most prevalent types of food allergy (immune-mediated AFR), particularly in the first years of childhood, whereas lactose intolerance is a "non-immune-mediated AFR." Immunoglobulin E (IgE), non-IgE mediated, or mixed reactions may be to blame for CMA. IgE-mediated reactions often begin within 2 hours of consuming food, but non-IgE-mediated reactions appear 2–48 hours or even days later [24]. Particularly, the symptoms of non-IgE-mediated CMA are usually misdiagnosed as intolerance symptoms.

Symptoms of lactose intolerance in humans

Osmotic diarrhoea is brought on by the intestinal tract's non-digested lactose, which exerts an osmotic force that forces fluids into the gut lumen. Additionally, the intestinal flora digested lactose to produce volatile fatty acids and fumes (hydrogen, methane, and carbon dioxide). Clinical symptoms include small intestine distension, non-focal abdominal discomfort accompanied by bloating and gas, nausea, increased gut motility, and diarrhoea are all caused by these events [25]. These signs typically appear between 30 minutes and two hours after eating lactose-containing meals. Patients with functional gastrointestinal problems have long reported having food intolerances, but there aren't many randomised controlled studies in this field [26]. Up to 20% of people with carbohydrate intolerance have been reported to experience extraintestinal symptoms as headaches, dizziness, memory loss, and fatigue [27]. These systemic symptoms might be caused by toxic metabolites, which colonic bacteria make when they ferment sugar and which can change the way cells signal to one another [28]. Uncertainty exists regarding whether these unusual symptoms are caused by lactose consumption specifically or by the so-called "functional illness," which is commonly followed by a number of somatic complaints.

Risk elements

You or your child may be more susceptible to lactose intolerance due to the following factors:

Advancing years. Adulthood is when lactose intolerance typically manifests. When it comes to infants and young children, the condition is rare.

Ethnicity. The majority of people with lactose intolerance are of African, Asian, Hispanic, and American Indian origin.

Birth before term. Because lactase-producing cells in the

small intestine don't grow until late in the third trimester, premature infants may have lower amounts of lactase.
Ailments of the small intestine. Lactose intolerance can be brought on by bacterial overgrowth, celiac disease, and crohn's disease, among other small intestine conditions.
Certain cancer therapies. Your risk of developing lactose intolerance rises if you've received radiation therapy for stomach cancer or intestinal side effects from chemotherapy.

A diagnostic approach

When CLD is suspected in newborns with typical symptoms and a favourable response to dietary lactose removal, genetic testing for LPH gene mutations should be carried out [29]. An effective clinical history can frequently identify the connection between symptoms and lactose consumption in secondary lactase insufficiency. Anamnesis and the lactose breath test (LBT) are the mainstays of adult-type lactose intolerance diagnosis.
The LBT is a quick, non-invasive test that allows you to determine how much hydrogen is present in the exhaled air. In children, 1 g/kg of lactose is provided. Despite the fact that large lactose doses (up to 50 g) have been utilised for LBT, 25 g (equal to 500 mL of milk) is within the typical range of consumption and is the suggested dose after 8–12 hours of fasting [30]. To correct the breath sample for non-alveolar dilution of exhaled air, all breath tests should include measurement of CO2 (or O2) [31]. Because excess methane producers have a substantially lower detection rate of an early surge in H2 generation, concurrent CH4 measurement is also necessary . H2 must not exceed a cutoff level of 20 parts per million (ppm) above set level is considered positive.
Inadequate hydrogen-producing bacteria (10–15 percent of the population), high-fiber diets consumed prior to the test, small intestinal bacterial overgrowth, intestinal motility disorders, and conditions affecting the gut microbiota are some of the variables that could result in false-negative or false-positive results [32].
The lactose tolerance test is another diagnostic procedure that was once very well-liked. The patient who is thought to be lactose intolerant assumes 50 g of lactose dissolved in water for this test. At 5, 0, 15, 30, 45, and 60 minutes, capillary blood samples are collected to measure the plasma glucose levels. Lactose tolerance is indicated by a maximal increase in plasma glucose of 1.4 mmol/L or greater [33]. The lactose tolerance test is not sensitive enough, and it frequently returns false-positive results since there isn't a rise in blood glucose levels caused by a typical insulin response to a carbohydrate load. This test should not be utilised because of the high rate of false-negative and false-positive results, and the LBT has taken its place [34].
There is also a genetic test that locates single nucleotide polymorphisms linked to lactase persistence or non-persistence. It should be emphasised that the existence of the lactase non-persistent gene does not preclude the possibility of later-onset lactose intolerance.

Management of nutritional issues and lactose intolerance

Eliminating the offending food from the diet is the cornerstone of treatment for AFRs. Small amounts of protein can trigger symptoms in AFRs brought on by CMA, hence the therapy of these conditions is focused on strict dietary avoidance of allergenic peptides generated from cow's milk. Contrarily, a decrease in lactose intake rather than complete exclusion is advised in cases of lactose intolerance because the evidence suggests that adolescents and adults can typically consume up to 12 g of lactose (equivalent to 1 cup of milk, or 240 ml) in a single dose with no or few symptoms [35]. Therefore, the sole nutritional therapy for these patients is a low-lactose diet [2, 35]. The amount of lactose that children with lactose intolerance can tolerate is not known scientifically. To provide evidence-based dietary recommendations that are appropriate for each person, it is vital to ascertain the levels of lactose that can be tolerated. In order to induce symptom remission in primary lactose intolerance, lactose-containing dairy products are often avoided for 2-4 weeks. Following that, it should be advised to gradually reintroduce dairy products low in lactose up to a dose that doesn't exceed an individual's tolerance.
A restricted diet is only required temporarily in secondary hypolactasia [35]. The use of lactose in treating malnourished children has been restricted due to worries about lactose intolerance and osmotic diarrhea. Low-lactose formulas are routinely used in children with chronic diarrhea, even in those who are well-nourished. In order to accomplish the good benefits of lactose, it is important to create a balance where the amount of lactose in diet does not cause osmotic diarrhea. To more precisely define the safe and suitable lactose dietary levels for children who are moderately and severely malnourished, clinical trials are required [36]. An entirely lactose-free diet is necessary for life when the rare variant of CLD is present.
Another therapy strategy for lactose intolerant patients who still want to consume dairy products is enzyme replacement. With the administration of 1,500 U/day of -galactosidase, preliminary data demonstrated an improvement in gastrointestinal symptoms and a decrease in H2 levels at breath test. However, further information is required [37] to determine the effectiveness of this exogenous microbial enzyme. Other data revealed that Kluyveromyces lactis, Aspergillus oryzae, or Kluyveromyces lactis were sources of exogenous lactase that was effective [38, 39]. Probiotics are another tactic that may alter the composition of the gut microbiota. Consuming a probiotic combination of Lactobacillus casei Shirota and Bifidobacterium breve for four weeks reduced H2 production and alleviated symptoms in lactose-intolerant patients. They also appeared to last for at least 3 months after probiotic use was stopped [40].These effects appeared to be strain-specific because in a related trial, milk containing L. acidophilus had no impact [41]. A 36-day treatment with the highly purified (> 95 percent) short-chain galactooligosaccharide (GOS), dubbed "RP-G28" (escalating doses from 1.5 to 15 g/day) plus subsequent dairy consumption significantly improved clinical outcomes for lactose digestion and tolerance, according to a randomised, double-blind, placebo-controlled trial done in adult lactose-intolerant patients. These clinical outcomes were significantly altered in the gut microbiota, with a rise in the lactose-fermenting bacteria Bifidobacterium, Faecalibacterium, Lactobacillus, and Roseburia [42].
It is crucial to keep in mind that lactose intolerance might be a symptom of a larger sensitivity to fermentable oligo-, di-, monosaccharides, and polyols that are variably absorbed (FODMAPs). This is common among IBS patients, and to alleviate gastrointestinal symptoms in this population, in addition to lactose restriction, a low-FODMAP diet is also necessary [17].
Diets that are "free" are popular. Lactose-free items are widely available in supermarkets, and more and more cafes,

ice cream parlours, bakeries, and restaurants are offering specific menus without lactose. The USA has the lowest milk consumption among nations with a high frequency of lactase non-persistence [14]. In fact, the National Health and Nutrition Examination Survey (NHANES) found that between 2003 and 2010, only in the USA, 5% of newborns consumed lactose-reduced formula, and this trend is growing [43]. Although there is little to no evidence that lactose-reduced formulas are advantageous, this is a typical justification for the use of lactose-free newborn formulae [44]. According to preliminary research, lactose-free formula feeding causes children to have an altered plasma metabolic profile [46] and harms an infant's ability to develop a healthy gut flora [45]. Only after a precise diagnosis of lactose tolerance has been made should a lactose-free diet be advised. Other health outcomes could be impacted by a diet that completely excludes dairy. It is crucial to emphasise that if dairy products are removed from a diet, alternative food sources of calcium or calcium supplements must be given. The current recommendations for calcium intake are 700 mg/day for children aged 4–9 years, and 1,300 mg/day over 10 years, according to the EFSA guidelines [47]. Educational and commercial efforts to improve calcium and vitamin D intake are now focusing on stimulating the consumption of tolerable amounts of milk, use of lowered lactose-containing foods including hard cheeses, yogurt, and lactose-hydrolyzed products.

Conclusion

Today's definition of lactose intolerance is more nuanced than it was in the past. The persistent idea that lactose maldigestion is similar to lactose intolerance clouds laypeople's and possibly even the scientific community's conceptions of the appropriate role of lactose-specific care. When coupled with other foods, the results of lactose challenge tests and the subsequent symptoms do not adequately represent daily lactose consumption. Other food intolerances and the presence of functional gastrointestinal diseases may alter the complexity of lactose intolerance symptoms.

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