Lactose Intolerance: A Concise Review to Skim the Surface

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Learning Objectives: On complication of this article, the reader should be able to: 1) define the distinct terms related to lactose intolerance; 2) describe the long-term health implications for dairy and lactose avoidance; and 3) recommend treatment approaches for patients with lactose malabsorption.

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Abstract

Lactose intolerance is a common but poorly understood cause of gastrointestinal symptoms. Contrary to popular belief, there is much more to its diagnosis beyond symptoms with exposure and management beyond milk- and dairy-product avoidance. In this article, we review definitions, genetic basis, pathogenesis, clinical signs, as well as diagnostic and management strategies.

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Perhaps one of the most common food sensitivities, lactose intolerance affects many individuals and has long-term health implications. Although the exact prevalence is unclear due to self-diagnosis, lack of confirmatory testing, and poor understanding of what constitutes the syndrome, it is exceedingly common. It is widespread because of the high percentage of lactase non-persistent individuals living in regions with dairy farming and due to secondary causes related to mucosal integrity.

Infants of every race and ethnicity produce lactase-phlorizin hydrolase (colloquially, lactase) to digest human milk or lactose present in standard infant

formulas.[1,2] In a majority of children, after weaning there is a programmed reduction in lactase production.[1,3] Expression of lactase can be detected during gestation, peaks at birth, and begins to decline after a few months of life.[4] Lactose cannot be absorbed into the small intestine epithelium without first being broken down by lactase. Decreased lactase enzyme in the small intestine brush border can reduce the ability to cleave lactose into the component monosaccharides, galactose, and glucose, which can be easily absorbed in the bloodstream.[5] If the enzyme has low activity, lactose is not digested in the small bowel, and enters the lumen of the colon. When undigested lactose reaches the colon, bacterial fermentation occurs, forming lactic acid, freeing hydrogen, and often producing gastrointestinal symptoms.[5] This concise review will cover terminology, epidemiology, clinical manifestations, health implications, diagnosis, and management of lactose intolerance.

DEFINITIONS

A National Institutes of Health consensus conference defined lactose intolerance as "the onset of gastrointestinal symptoms following a single-dose challenge of ingested lactose by an individual with lactose maldigestion, which are not observed when the person ingests an indistinguishable placebo."[1] Whereas maldigestion and intolerance are often thought of as synonymous, this definition highlights that they are not. Therefore, understanding the diagnostic and therapeutic approach to lactose intolerance is based on a clear understanding of the meaning of the terms. Hypolactasia refers to non-persistence or deficiency of the lactase enzyme. Maldigestion is the inefficient breakdown of lactose. Lactose is never absorbed as a disaccharide. Thus, the term malabsorption is technically inaccurate. Primary lactase deficiency, or lactase non-persistence, describes the genetically programmed reduction in the activity of lactase after weaning in childhood which is acquired and common. The congenital absence of the enzyme is autosomal recessive and rare. Secondary lactase deficiency describes the loss of brush border in the setting of other gastrointestinal issues such as a viral gastroenteritis, inflammatory bowel disease, celiac disease, surgery, or other pathology affecting the small intestine mucosa. Conversely, persistence refers to continued lactase activity. Persistence and non-persistence are attributed at least in part to genetics, which can help explain the epidemiology of lactose intolerance.

EPIDEMIOLOGY

Lactose intolerance, in theory if not in name, has been described as far back as Hippocrates.[6] Non-persistence is the "wild type" with theories that this was evolutionarily selected for as a weaning tool. The most common genetic polymorphism that causes lactase persistence is a single nucleotide substitution on chromosome 2 involving the lactase (*LCT*) gene, often seen in whites.[2,7] However, several other polymorphisms leading to persistence have been described in geographically disparate populations from Africa to Saudi Arabia to Finland.[2,8-10] Evidence suggests these mutations occurred independently from 5000 to 10,000 years ago and were associated with cattle domestication as a form of natural selection.[3,11,12] These mutations, in part, help explain the epidemiology of lactase non-persistence and lactose intolerance today. The most affected populations in North America are Asians (variable, 15% to 100% non-persistence depending on population studied, highest in Southeast Asia), Native Americans (79% non-persistence), African Americans (75% non-persistence), and Hispanics (51% non-persistence), whereas whites (21% non-persistence), specifically Scandinavians and Northern Europeans (5% to 20% non-persistence), are the least affected.[11] Internationally, the majority of the world's children are genetic non-persisters, but that does not translate in a one-to-one fashion with clinical symptoms. For example, in a study of 492 Chinese patients, all of whom were genetic non-persisters, only 28% met the clinical definition of lactose intolerance based on symptoms and testing.[13] Therefore, while

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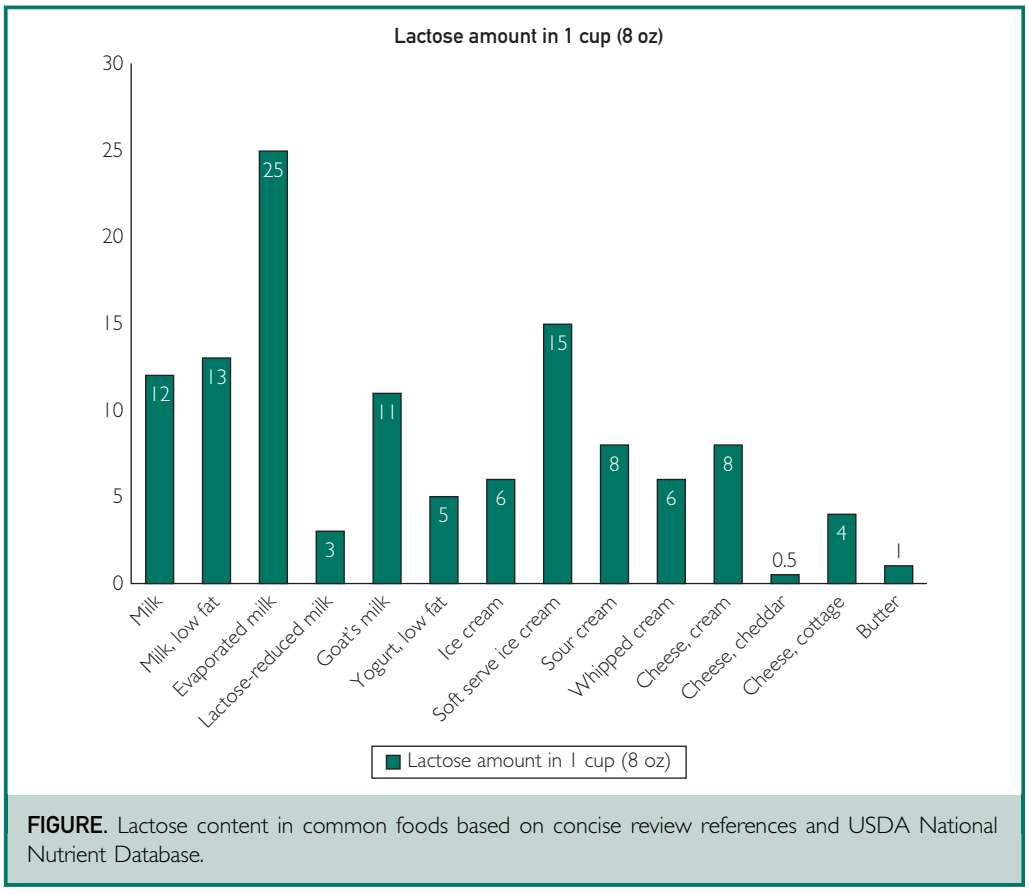

FIGURE. Lactose content in common foods based on concise review references and USDA National Nutrient Database.

genetics play a significant role, they do not tell the whole story regarding tolerance.

CLINICAL MANIFESTATIONS

Typical gastrointestinal symptoms include bloating, diarrhea, flatus, borborygmi, and cramps. Onset usually occurs 30 minutes to a few hours after eating or drinking the lactose-containing food. A number of variables determine if a patient who maldigests lactose manifests symptoms including dose (Figure), dilution, lactase expression (only clearly shown in children), gut transit, colonic flora, and sensitivity to fermentation products. These risk factors can be categorized as intake specific (easily modifiable) or patient specific (more difficult to manipulate).

Lactase expression is genetically driven, but patients have variable enzyme expression which is quantifiable and can impact the capacity for digestion and tolerance. The colonic microbiome further determines how the maldigested lactose will be fermented, with the byproducts of this breakdown having implications for symptoms. Hypersensitivity to visceral events such as product fermentation is an important consideration, as fermentable oligo-, di-, and mono-saccharides, as well as polyols are confounders when it comes to determining the etiology of symptoms. In addition, patients respond to these products inconsistently. These contributing variables will be discussed in further detail in the management section. There is a growing body of literature that some individuals could be symptomatic with abdominal pain and looser stools after dairy ingestion related to other components of milk and milk products, such as A1 beta-casein protein.[14]

Symptoms of lactose intolerance also depend on how and how much lactose is consumed. There appears to be a

TABLE. Available Tests for Lactose Maldigestion[4,6,22]

	Stool testing	Hydrogen breath test	Lactose tolerance test	Lactase activity at brush border	Genetic test
Principle	Osmotic diarrhea due to carbohydrate malabsorption	Lactose challenge induces increase of H2 in exhaled air	Lactose challenge induces increase in blood sugar	Biopsy sample collected during EGD or push enteroscopy looks at enzyme activity of lactase	13910C/T polymorphism located upstream of the lactase gene
Availability	Variable	Good	Excellent	Rare	Variable
Abnormal result value	pH<6.0, stool gap>100	>20 ppm in 3 h	<1.1 mmol/L in 3 h	<17-20 IU/g	C/C = lactase non-persistence
Assessment of symptoms	Yes	Yes	Yes	No	No
Cost	$$	$$	$	$$$$	$$$
False-positives	Laxatives, fructose, artificial sweeteners	SIBO, rapid transit	Diabetes, impaired glucose tolerance, rapid transit	Rare	Rare (<5% in whites)
False-negatives	Incorrect stool collection or storage	Colonic adaptation, non-H2 producers	Blood sugar fluctuations	Patchy or irregular enzyme expression	Non-white ethnicities (African, Arabic, Asian populations), secondary causes of lactose malabsorption

$ = significant cost from lowest ($) to highest ($$$$); C/C = lactase non-persistent genotype; EGD = esophagogastroduodenoscopy; SIBO = small intestinal bacterial overgrowth

dose-dependent effect.[15] A study on a Chinese population with proven lactase deficiency showed few symptoms at lower doses (10 g of lactose) and more symptoms at higher doses (20 g then 40 g) with an increase in a linear fashion.[16] This increase was progressive in nature and observed in both the control group and the irritable bowel syndrome group in both categories of symptoms and proportion with a positive breath test.[16] Consumption of a 50-g dose of lactose in a single setting is sufficient to induce symptoms in a majority of individuals.[15] However, dilution with other foods can decrease symptom burden. Each of these variables can be modified and are potential targets for treatment. Amazingly, not all maldigesters report symptoms with large quantities (50 g) of lactose.

IMPLICATIONS

There is concern about the long-terms health effects of lactose avoidance. Many people with true or perceived intolerance of lactose avoid milk. Dairy and milk products are excellent and common sources of calcium and vitamin D. Dairy products are also sources of potassium, magnesium, riboflavin, protein, and other nutrients. Inadequate intake of these nutrients is a risk factor for osteoporosis and thus fragility fractures.[1] Lactose avoidance may predispose to deficient bone acquisition in children, loss of bone mineral density in adults, and adverse outcomes. Young girls who avoid milk have lower bone densities, even at the early ages of 10 to 13 years.[17] Yet, increased milk or dairy intake and reduced fracture risk are not linearly correlated; in fact, numerous systematic reviews and meta-analyses have been conducted with conflicting results on the impact of dairy consumption on osteoporotic fracture risk making specific conclusions elusive.[18] Additionally, some epidemiologic studies indicate concerns about possible adverse health

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effects from milk and its processing.[18] Lactose and calcium absorption do not seem to be correlated; lactose does not decrease the efficiency of calcium transport across the intestine and into the bloodstream.

Studies also indicate that those with lactose intolerance have poorer quality of life scores compared with controls.[13] It has been noted that patients with self-reported lactose intolerance scored lower in the physical but not emotional score of the short form questionnaire examining quality of life.[13] These subjects also restricted their intake of other food items (specifically legumes and fruit), which puts them at risk for additional nutrient deficiencies.[13] In a survey of patients with irritable bowel syndrome examining food intolerances, patients with multiple intolerances noted quality of life reductions in terms of energy, sleep, social functioning, food, and physical status.[19] The health impact of lactose avoidance appears to be both physical and psychological; as such, determining the etiology for a patient's gastrointestinal symptoms is vital as it may have significant downstream effects.

DIAGNOSIS

Self-reported intolerance to milk is neither sensitive (30% to 71%) nor specific (25% to 87%).[20] In double-blind trials, the correlation between intolerance and maldigestion is poor — the diagnosis requires both.[13,21] One is objective and the other is subject to bias and patient interpretation of symptoms. There are multiple modalities to test for lactose maldigestion. The merits and shortcomings are shown in the Table.[22] One method is quantifying lactase activity at the intestinal brush border from duodenal biopsy specimens (conducted more in pediatric populations).[23] Lactose digestion can be examined in the blood and expired air. The lactose tolerance test requires an oral challenge followed by measuring blood glucose. A lower level indicates maldigestion as lactose fails to be split into glucose and galactose; thus, glucose is not detected at a high level in peripheral blood samples. The hydrogen breath test also measures a breakdown product that is produced by bacterial fermentation of undigested lactose that has presumably reached the colon. Following an overnight fast, a person drinks an amount of lactose as a syrup (historically, this was equivalent to about 32 ounces of milk, a rather large amount creating somewhat of an artificial test environment). The individual then provides breath samples by exhaling into a bag. The breath is analyzed to quantify the amount of hydrogen. This level increases in those who are lactose maldigesters. In one study of Chinese patients with self-reported lactose intolerance, the positive predictive value of gastrointestinal symptoms during the breath test was 60% and the negative predictive value was 44%.[13] Additionally, genotype determination is available for the 13910 position where T leads to persistence of lactase and C nonpersistence.[7] This test is best applied to Europeans and their descendants who are most likely to have this polymorphism. Stool testing reveals an osmotic diarrhea with a pH less than 6 related to carbohydrate malabsorption. Unabsorbed carbohydrates increase osmolality of intestinal lumen pulling in fluid resulting in diarrhea. Lower pH reflects hydrogen and short-chain fatty acid release as the carbohydrates are fermented in the colon. For adults, the hydrogen breath test is the most commonly used and we would advocate for its use in clinical practice — it is one of the more available, less expensive tests, applicable to multiple ethnicities, is noninvasive, and allows for symptom correlation. In summary, the diagnosis can be detected through maldigestion in breath or blood, lack of enzyme activity at the level of the enteric mucosa, or presence of the genetic mutation. Lactose maldigestion is fundamental, but not sufficient to diagnose lactose intolerance. Symptom correlation is key.

MANAGEMENT

Traditional management relied heavily upon avoidance of dairy products. There are numerous strategies that can be applied to reduce maldigestion, and to reduce gastrointestinal symptoms. We support reduction as

opposed to exclusion. In blinded studies, patients can tolerate 12 g or approximately 1 cup of milk without experiencing symptoms, despite their lactose intolerance status.[15,21] Larger amounts (up to 18 g) were also well tolerated if ingested with meals and distributed throughout the day and can be considered the maximum tolerable dose.[15,24] When milk is consumed as a part of a meal, gastric emptying is slowed by the solid content of the meal, which reduces the lactose load entering the intestines. There are no studies or trials addressing the impact of lactose exclusion in the diet on patient symptoms.

Unfortunately, some other management strategies lack sufficient evidence after randomized controlled trial data was pooled; however, there are additional studies showing promise and these strategies can be considered on a case-by-case basis.[15] Prehydrolyzed or lactose-reduced milk did not consistently reduce overall gastrointestinal symptom scores, abdominal discomfort, or diarrhea.[15] In less than half of these studies a control group was used that consumed more than 12 g of lactose per day, so it is difficult to interpret the clinical significance of these results.[15] It is not surprising that there was no significant difference given that we know doses of 12 g or less are well tolerated. Oral lactase replacement is another option with a number of preparations that can be purchased over the counter. Only two studies with a total of 31 patients examined this treatment strategy with mixed results in terms of effectiveness versus placebo.[15] Probiotics were not an effective means of reducing gastrointestinal symptoms.[15] Incremental escalation of doses of lactose was not efficacious.[15] It seemed to improve flatulence, but not abdominal pain nor diarrhea.[24]

Bacterial adaptation or tolerance induced by intestinal flora changes is another proposed strategy that uses prebiotics or regular consumption of lactose-containing products. With changes to relative amounts of colonic microbiota, there is an increase in beta-galactosidase activity which enhances digestion and reduces fermentation products.[25] A novel galacto-oligosaccharide, RP-G28, a lactose derivative, was investigated and half of study subjects showed complete resolution of abdominal pain at the trial end and 30 days after treatment completion.[25] Subjects also reported improved lactose tolerance post-treatment with the reintroduction of dairy.[25] When their stool was examined, a relative increase was found in lactose-fermenting bacteria such as *Faecalibacterium*, *Bifidobacterium*, and *Lactobacillus*.[26] After re-introduction of dairy, investigators noted a definitive shift in the fecal microbiome to include more *Roseburia* species, proving that alterations in diet translate to the gut microbiome.[26] To date, only one trial explores the ability of rifaximin to improve symptoms of lactose intolerance.[27] This study enrolled only 40 people who had symptoms consistent with lactose intolerance that were not mandatory for participation, and the results did not directly compare the treatment group with the placebo group — as such, its results are of unclear significance.[27] Overall, most studies are relatively small and endpoints are poorly defined as subjective assessments of symptom improvement.

Complete exclusion of lactose is unnecessary. Moderation is a more sensible treatment approach, which likely has a secondary effect of adapting the microbiome to improve tolerance even further. If symptoms show a trend towards improvement on a lactose-free diet, patients can limit ingestion to 1 serving per day and gradually increase until symptoms occur, thus defining their own maximum tolerable dose of lactose (Figure).

CONCLUSION

Many etiologies can lead to lactose maldigestion, but not every individual manifests lactose intolerance. Lactose maldigestion is extremely common and considered to be the wild type in most populations that are not historically pastoral or subsisting on dairy farming where evolutionary selection for lactase persistence occurred. Patient symptoms are a poor diagnostic tool and highly subjective. The differential diagnosis should include irritable bowel syndrome, celiac

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disease, inflammatory bowel disease, and other causes of non-descript gastrointestinal symptoms. There are numerous strategies for diagnosis, but a placebo-controlled, blinded challenge is considered the most robust; however, the hydrogen breath test is the most practical. There are many treatment options with varying degrees of success, but overall small amounts of lactose are digested without appreciable symptoms for most individuals. When it comes to lactose intolerance, misconceptions abound and public health implications exist. It is our hope that this article — although it only skims the surface of this complicated subject — gives readers a better understanding of the background and a taste of the diagnosis and management of lactose intolerance.

Potential Competing Interests: Dr Savaiano is the Virginia Meredith Professor of Nutrition Science at Purdue University. He also is a consultant for Dannon North America and Ritter Pharmaceuticals. He receives research funding from the a2 milk company. The other authors report no competing interests.

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