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Got Lactase? A Clinician's Guide to Lactose Intolerance

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Intolerance of lactose-containing foods is a very common condition that usually arises as a result of a genetically programmed decline in the enzyme lactase. Management of lactose intolerance typically focuses on reducing symptoms by limiting dairy intake. Although complete dairy exclusion is rarely necessary, maintaining proper nutrition status – particularly as it pertains to calcium and vitamin D – can be a challenge for patients with lactose intolerance. A variety of additional tools are available to help address symptoms, but current research on their efficacy is largely inconclusive. Further work is needed to evaluate the role of lactose and dairy foods in other GI conditions, as well as on methods to avoid unnecessary dietary restriction.

INTRODUCTION: WHAT IS LACTOSE INTOLERANCE?

Lactose intolerance is a clinical syndrome in which lactose ingestion causes symptoms such as abdominal pain, bloating, flatulence, and diarrhea due to lactose malabsorption. Lactose (milk sugar) is a disaccharide found in milk and milk products. Digestion and absorption require the enzyme lactase, which is found in the brush border of the small intestine. Lactase hydrolyzes lactose into the monosaccharides glucose and galactose, which can then be absorbed and used for energy.

Lactose malabsorption is most commonly caused by reduced lactase levels. *Primary lactase deficiency* is a genetically modified condition resulting from the physiological decline of lactase activity after infancy. Other terms used to describe this condition include *lactase nonpersistence, lactase insufficiency,* and *adult type hypolactasia*. It is estimated that about 68% of the world's population is lactase nonpersistent, with wide variance levels according to region and ethnicity.[1] In the U.S., 36% of the population is lactase deficient, with highest prevalence levels found in individuals of African, Asian, Latin American, Native American, and South American descent.[1]

Not everyone with lactose malabsorption is lactose intolerant. In lactose intolerant individuals, unabsorbed lactose transits to the colon, carrying with it an increased osmotic load and serving as a ready substrate for the microbiome to ferment

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and produce short chain fatty acids and gas. This is what results in the classic symptoms of bloating, flatulence, borborygmi, abdominal pain, and diarrhea. Less often, it can present with nausea or constipation. Symptoms of lactose intolerance can range from mild to severe but generally do not occur until there is at least a 50% reduction in the lactase enzyme.[2]

There is also *secondary hypolactasia,* or *secondary lactase deficiency,* which can occur as a consequence of any condition that damages the brush border of the small intestine. Mucosal damage due to celiac disease, Crohn's disease, or ulcerative colitis may result in a transient lactase deficiency. Small intestinal bacterial overgrowth, certain medications, infectious enteritis (e.g. giardiasis), radiation enteritis, gastrointestinal surgery, and short bowel syndrome may also result in either a reduction in absorptive capacity or a downregulation of lactase expression in the small intestine. Whereas primary hypolactasia is irreversible, secondary hypolactasia can often be reversed once normal intestinal mucosa is restored.

DIAGNOSIS

Lactose malabsorption can be diagnosed using various methods (Table 1). The hydrogen breath test involves ingestion of a standard dose of lactose, usually 20-50g (roughly 400-1,000 mL cow's milk), and measuring breath hydrogen at 30-minute intervals. A diagnosis of lactose malabsorption can be made with a hydrogen level > 20 ppm within 3 hours of ingestion. This test is 78% sensitive and 98% specific for lactose malabsorption, but it is susceptible to both false positives (e.g., in the presence of small intestinal bacterial overgrowth) and false negatives (e.g. in the presence of non-hydrogen producing bacteria).

Other tests aimed at detecting lactase deficiency are available, but they are rarely performed. Biopsies of the jejunum are often regarded as the gold standard for determining lactase activity and have the advantage of determining whether a patient may have secondary lactose malabsorption. This procedure, however, is highly invasive and not particularly reflective of intestinal lactase activity as a whole. Lactase deficiency may also be assessed by way of genotyping, but the available genetic tests do not account for all the possible polymorphisms resulting in lactase nonpersistence, nor are they useful for patients with secondary lactase deficiency.

As opposed to lactose malabsorption, lactose intolerance is much more difficult to ascertain. A

Table 1. Summary of Tests for Lactose Malabsorption[26]

	H2 Breath Test	Genetic Test	Jejunal Biopsy
Test Principle	Increase of respiratory H2 after lactose challenge	-13910C/T polymorphism	Enzymatic activity of lactase enzyme in jejunal biopsy sample
Cut-off	>20 ppm within 3 hours	C:C13910 lactase nonpersistence	<17-20 units/g
Availability	Good	Variable	Rare
False Positives	Rapid GI-transit, SIBO	Rare (<5%) in Caucasians	Probably rare
False Negatives	Non-H2 bacteria, colonic adaptation	All causes of secondary lactose malabsorption	Patchy enzyme expression
Secondary causes	Cannot be excluded	Cannot be excluded	Can be excluded (histopathology at same procedure)
Symptom assessment	Possible	Not possible	Not possible
Cost	Low	High	Highest

Table 2. Lactose Content of Dairy Products

Product	Lactose Content (g)
Milk (1 cup)	
• Whole, 2%, 1%, skim	9-14
• Buttermilk	9-12
• Evaporated	24-48
• Sweetened condensed	31-50
• Goat's milk	11-12
• Acidophilus, skim	11
• Lactaid/lactose-reduced	0-3
Yogurt, low-fat (1 cup)	
• Plain, low-fat	4-17
• Greek	8-9
• Kefir	2
Cheese (1 oz)*	
• Cheddar (sharp)	0.4-0.6
• Mozzarella (part skim, low moisture)	0.08-0.9
• American (pasteurized, processed)	0.5-4
• Cream cheese	0.04-0.5
• Cottage cheese (1/2 cup)	0.7-4
• Ricotta (1/2 cup)	0.3-6
• Nacho cheese dip (1/4 cup)	1
Butter (1 pat)	0.04-0.5
Cream (1 tbs; light, whipping)	0.07
Sour cream (1 tbs)	0.41
Ice cream (1/2 cup)	2-6
Sherbet (1/2 cup)	0.6-2
Frozen Yogurt	4.5

* Aged, hard cheeses (e.g. gouda, parmesan, swiss, romano, very sharp cheddar) have less lactose than fresh, soft cheeses (e.g. mozzarella, queso fresco).

Information obtained from the USDA Food Composition Databases.[27]

presumptive diagnosis can be made in patients with symptoms that occur within a few hours after significant lactose ingestion (>2 servings of dairy/day or >1 serving in a single dose that is not associated with a meal), which resolve after 5-7 days of lactose avoidance.[3]

It is important to note that whereas lactase deficiency and malabsorption can be objectively measured, demonstration of lactose intolerance relies on subjective self-reporting of symptoms, which are very common even in the absence of lactose ingestion and are also highly susceptible to the placebo effect. Indeed, the few double-blind trials that have been conducted reveal a poor association between self-reported lactose intolerance and the occurrence of symptoms after lactose ingestion, even in patients with known lactase deficiency.[4]

SOURCES OF LACTOSE

Lactose is in virtually all milk and milk products (Table 2). By far, the highest concentration of lactose per serving is present in milk, ice cream and some yogurts, while cheeses generally contain much lower quantities of lactose. Lactose may also be found in other foods and beverages containing milk or milk products, including boxed, canned, frozen, packaged, and prepared items. Table 3 lists common types of these foods, as well as terms on the ingredient list that indicate whether a product contains lactose.

There are also certain medications that contain lactose, including over-the-counter pain relievers, multivitamins, and anti-diarrheal agents. Usually, the amount is so small (less than 0.5g) that it will not raise hydrogen levels, much less cause GI symptoms.

MANAGEMENT: LACTOSE RESTRICTION

The most common therapeutic approach to lactose intolerance involves limiting milk and milk products in the diet. Complete lactose avoidance is rarely indicated. Most blinded studies suggest that people with lactose intolerance can consume around 12g of lactose – roughly the same amount in one cup of milk – in a single dose with no or mild symptoms. When consumed with other foods and/or spread out in small amounts over the course of the day, up to 18g of lactose can generally be tolerated.[5]

Table 3. Non-Dairy Sources of Lactose

Variable amounts of lactose may be found in:

- Bread and other baked goods, such as pancakes, biscuits, cookies, and cakes
- Processed foods, including breakfast cereals, instant potatoes, soups, margarine, salad dressings, flavored chips, and other snack foods
- Processed meats, such as bacon, sausage, hot dogs, and lunch meats; breaded or battered meat, commercial egg substitutes, and scrambled eggs
- Vegetables and fruits prepared with milk or milk products, such as creamed vegetables and fruit pudding or custard
- Milk-based meal replacement liquids and powders, smoothies, and protein powders and bars
- Nondairy liquid and powdered coffee creamers, and nondairy whipped toppings

Check the ingredients list for these lactose-containing components:

- Milk
- Milk Solids
- Malted milk
- Buttermilk
- Curds
- Cheese flavors
- Milk powder
- Sweet or sour cream
- Lactose
- Whey
- Yogurt
- Milk by-products

beneficial for some patients to completely exclude milk and milk products for 2-4 weeks (or long enough for the remission of symptoms), and then gradually reintroduce dairy products up to a threshold of individual tolerance.[6] An individual's tolerable level depends on several factors, including the amount of lactose consumed at one time, residual lactase activity, ingestion with other foods and beverages, gut transit time, and the gut microbiome.

Nutrition Considerations

While limiting dairy may reduce lactose intolerance symptoms, it comes with certain risks, particularly as it pertains to osteoporosis and bone fractures secondary to inadequate calcium and vitamin D intake. As dairy remains the primary dietary source of calcium and vitamin D for the general population, several studies have pointed to a relationship between lactose malabsorption, low intake of dairy products, and reduced bone mass.[7,8]

The recommended daily intake for calcium is based on age and sex (Table 4). Patients with lactose intolerance should be assessed for dietary calcium adequacy and instructed to increase calcium intake from other foods if necessary (Table 5). They may also need to take calcium supplements, which come in a wide range of preparations and doses (Table 6). Calcium carbonate is the most common and least expensive form of calcium supplementation. It is best absorbed with a low-iron meal, but it may not be as effective in people who take proton pump inhibitors or H2 blockers. Calcium citrate can be taken with or without a meal and may be better suited for people with achlorhydria, inflammatory bowel disease, or absorption disorders. Calcium absorption is highest in doses $\leq$ 500 mg; amounts greater than this should be taken in divided doses.

Through fortification, milk is also a major source of vitamin D, which is needed for calcium absorption. Few other foods naturally contain significant amounts of vitamin D, with the exception of fatty fish, liver, cheese, and egg yolks. Monitoring of vitamin D status and supplementation may be necessary, especially in patients with Crohn's or celiac disease, or in other patients at additional risk for deficiency.

There is a growing array of plant-based

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(non-dairy) alternatives to cow's milk, most of which are fortified to offer nutrients in amounts comparable to those found in cow's milk, including calcium (300 mg per cup) and vitamin D (120 international units per cup). These beverages can be a viable alternative for those with lactose intolerance.[9]

OTHER MANAGEMENT OPTIONS

Exogenous Enzyme Supplementation

Exogenous lactase (obtained from yeasts or fungi) can be taken before or during dairy consumption to help hydrolyze lactose. These supplements commonly come in tablet form, and a dose of 6000-9000 units/meal is typically taken (Table 7). Liquid drops, which are not widely available in the U.S. but can be ordered online, may also be added directly to milk. Results of these products vary, and research thus far has been inconclusive regarding the efficacy of supplementation, which may depend on enzyme origin, residual endogenous lactase activity, dosage, the amount of lactose consumed, stomach pH, and bile salt concentration.[10]

Low-lactose or lactose-free milk, such as Lactaid®, is milk with added lactase enzymes that have pre-hydrolyzed the lactose. In recent years, there has been an increase in reduced-lactose or lactose-free dairy foods, to include not only milk, but also yogurt and ice cream (see Table 8). These products are readily available in most large grocery stores, but they are typically more expensive than their lactose-containing counterparts. Some store brands are beginning to carry their own products at a lower price.

Yogurt and Probiotics

Plain yogurt has been shown to be as effective as pre-hydrolyzed milk in reducing hydrogen production and intolerance via lactase-containing microorganisms.[11] Sweet acidophilus milk contains the same bacteria added to cold milk but is not as effective.[12] Likewise, yogurts that contain milk or milk products added back after fermentation may still produce symptoms.

A related strategy involves probiotic supplementation with the goal of altering intestinal flora so that more lactic acid bacteria may salvage malabsorbed lactose and ferment it without excessive gas production. Some studies have shown that probiotic supplementation can lead to decreased hydrogen production and improved symptoms in lactose intolerant individuals.[13,14] The full body of evidence, however, is insufficient to recommend this approach.

Table 4. Recommended Dietary Allowances (RDAs) for Calcium in Adolescents and Adults

Age	Male	Female
14-18 years	1300 mg	1300 mg
19-50 years	1000 mg	1000 mg
51-70 years	1000 mg	1200 mg
71 + years	1200 mg	1200 mg

Table 5. Non-Dairy Sources of Dietary Calcium

Food	Serving	Mg of Ca per serving
Calcium-fortified milk alternative (e.g. soy)	1 cup	299
Sardines, canned, with bones	3 oz	325
Calcium-fortified orange juice	1 cup	261
Salmon, pink, canned	3 oz	181
Tofu, soft	½ cup	138
Ready-to-eat cereal, calcium-fortified	1 cup	100-1000
Turnip greens, fresh, boiled	½ cup	99
Broccoli, raw	½ cup	21

Colonic Adaptation

Although lactase expression cannot be up-regulated by the presence of lactose, it is thought that "tolerance" may be induced despite malabsorption by way of adaptive processes involving the gut microbiota and some colonic functions and features. Consecutive incremental doses of lactose compared to dextrose have been shown to reduce flatulence, but not abdominal pain or diarrhea.[16] Current research, however, is not convincing enough to support incremental increases of lactose ingestion to treat symptoms of intolerance, as results have been variable and often conflated with the placebo effect.[17]

Slowing Gastrointestinal Transit

Co-ingestion of other foods has been demonstrated to improve lactose tolerance, possibly by way of delaying gastric emptying, slowing down intestinal transit time, and prolonging contact time with available lactase.[15] It is thought that consuming full-fat milk versus low-fat or skim may have the same effect, but current research is inconclusive. Pharmacological agents such as loperamide can also slow GI transit, but they often come with significant side effects and/or high cost.

CONSIDERATIONS FOR PATIENTS WITH OTHER GI CONDITIONS

Observational studies point to an overlap between lactose intolerance and irritable bowel syndrome (IBS), as well as other gastrointestinal conditions that may result in secondary lactase deficiency, such as inflammatory bowel diseases, celiac disease, and small intestinal bacterial overgrowth (SIBO).[6] Relationships, however, are confounded by several factors, including:

- the transient nature of secondary hypolactasia
- the preponderance of individuals with a genetic predisposition for primary hypolactasia
- the symptom profiles of these GI conditions, which share many of the same attributes as lactose intolerance
- the overlap with fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs);
- the subjectivity of self-reporting symptoms

Patients with a concomitant GI condition, whose diets may already be limited to some degree, should have suspected lactase deficiency confirmed before starting a low-lactose or lactose-free diet

Table 6. Content of Different Calcium Supplements

Name	Amount of elemental Ca per tablet	Ca compound	Amount of Vitamin D
Caltrate 600 + D3	600 mg	Carbonate	800 units
Caltrate Gummy Bites	250 mg	Tribasic calcium phosphate	400 units
Citracal Maximum	315 mg	Citrate	125 units
Citracal Plus Magnesium & Minerals	250 mg	Citrate	125 units
Citracal + D Slow Release	600 mg	Citrate + Carbonate	500 units
Citracal Calcium Gummies	250 mg	Tricalcium phosphate	500 units
Os-Cal Calcium + D3	500 mg	Carbonate	200 units
Os-Cal Ultra	600 mg	Carbonate	500 units
Os-Cal Chewable	500 mg	Carbonate	-
Tums	200 mg	Carbonate	-
Tums Extra Strength	300 mg	Carbonate	-
Tums Ultra	400 mg	Carbonate	-
Viactiv Calcium plus D+K	500 mg	Carbonate	500 units

so as to avoid unnecessary restrictions. In patients with secondary lactose malabsorption, successful treatment of the primary disorder can lead to restoration of lactase activity. However, lactose intolerance may persist for months after healing starts.

Irritable Bowel Syndrome

Retrospective studies have shown that up to 85% of IBS patients with lactose malabsorption have improved symptoms when they restrict lactose in their diet.[18] At the same time, prospective studies show that symptom improvement is highly susceptible to the placebo effect, and that lactose restriction alone is not sufficient for effective symptom relief in functional GI diseases.[19] In IBS, lactose intolerance tends to be subsumed under a wider intolerance of FODMAPs and may not be directly related to lactase deficiency. Several randomized controlled trials indicate that IBS patients can benefit from a low-FODMAP diet that includes lactose restriction.[20] However, the specific impact of lactose and lactose restriction on symptoms is difficult to assess.

Crohn's Disease and Ulcerative Colitis

There are no viable studies to date that specifically examine lactose as a symptom mediator in inflammatory bowel diseases (IBD) such as Crohn's and ulcerative colitis. Patients are often

Table 7. Lactase Digestive Aids and Products

Product	Units of lactose per pill	Recommended Dose	Lactaid® cost per dose	Store brand cost per dose
Regular	3000	3 caplets	$0.33	$0.17
Fast Act	9000	1 caplet	$0.24	$0.12
Chewable Fast Act	9000	1 tablet	$0.24	$0.17

Table 8. Popular Dairy Food Brands that Carry Lactose-free Products

Brand	Product	Lactose Reduction
Breyers®	Ice cream chocolate or vanilla	 99%
Cabot®	Cheese cheddar, light cheddar, monterey jack, pepper jack, muenster	 Naturally lactose-free
Dairy Ease®	Milk Non-fat, 1%, 2%	 70%
Lactaid®	Milk non-fat or 1% non-fat calcium-fortified non-fat 100 chocolate Cottage cheese Ice cream Eggnog	 70% 70% 100% 100% 100% 100% 100%
Yoplait®	Yogurt low-fat vanilla	 100%
Green Valley Organics®	Butter, sour cream, cream cheese, kefir, yogurt	Not available

instructed to restrict lactose and dairy intake, but the prevalence of true lactose malabsorption is unclear, as GI manifestations of these diseases are often similar to those of lactose intolerance. Studies indicate that 40-70% of patients with Crohn's self-report that they are lactose intolerant, but in most cases, lactose malabsorption appears to be driven more by ethnicity and genetic makeup, rather than by a direct association with the disease itself.[21,22] The exceptions to this are Crohn's patients with small bowel involvement, who do appear to be at higher risk for lactose malabsorption but not necessarily lactose intolerance.[21]

Celiac Disease

If the progression of celiac disease (CD) results in damage to the intestinal brush border, patients are likely to experience secondary lactase deficiency. Most people with CD can eventually rehabilitate their brush border and regain lactase activity within 6-12 months after following a gluten-free diet, assuming they do not also have primary lactase deficiency with lactose intolerance. In some cases, the villi and microvilli damage can take up to 2 years to heal completely.[24]

Small Intestinal Bacterial Overgrowth

IBS patients with lactose intolerance are more likely to also have small intestinal bacterial overgrowth (SIBO).[25] Excessive bacterial fermentation of lactose with production of short-chain fatty acids and gas in the small bowel may particularly trigger abdominal symptoms. If during a hydrogen breath test, a patient complains of abdominal pain and has an early hydrogen peak (within 15-30 minutes of ingesting lactose), SIBO should be ruled out before attributing these symptoms to lactose intolerance.

CONCLUSION

With such a high prevalence of lactase deficiency worldwide and in the U.S., clinicians are more than likely to encounter lactose intolerance in clinical practice. There are many strategies to help patients manage their symptoms (Table 9). Complete elimination of dairy is likely not required; at least 12 mg of lactose (about 1 cup of milk) is often well-tolerated and will not induce GI symptoms. Patients with lactose intolerance may need to be monitored for adequate calcium and vitamin D status and counseled on non-dairy sources and/or supplementation of these nutrients. ■

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Table 9. Key Takeaways for Management of Lactose Intolerance

- Lactose intolerance usually does not require a completely lactose-free diet. Most individuals with lactose intolerance can still consume 12-18 g/day (equivalent to 1-1.5 cups of milk) without triggering symptoms
- Individuals with lactose intolerance may be able to increase their dairy intake if they:
  - Distribute daily lactose intake into small amounts throughout the day
  - Consume lactose with other (non-dairy) foods
  - Focus on fermented dairy, such as yogurt and cheese, which are lower in lactose and better tolerated
- Ensure adequate calcium and vitamin D intake through lactose-reduced dairy, non-dairy foods, and/or supplements
- Lactase supplementation may work for some people
- Secondary lactase deficiency may require a reduced-lactose diet until resolution of the underlying disease
- Lactose malabsorption in patients with a comorbid GI condition should be confirmed prior to restricting lactose intake

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