



## Lactose Intolerance - A Review

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### ABSTRACT

Now a day's lactose intolerance is primarily seen in the persons who are unable to digest the enzyme lactose & during infancy which provides an excellent source of energy at a time of rapid growth and development. Common symptoms such as abdominal pain, bloating, diarrhea, lactose malabsorption patients after ingestion of lactose. Lactose intolerance is present in up to 68% with higher rates around worldwide. A diagnosis of lactose intolerance can usually be made with a careful history supported by dietary manipulation, if necessary diagnosis can be confirmed by using a lactose intolerance test / hydrogen breather. The main treatment is to improve digestive symptoms rather than reducing malabsorption and reduction of lactose intake is recommended. Enzyme replacement therapy is a choice of therapy and other therapy involves probiotics. However, the evidence that unabsorbed lactose is causing infantile crying and colic contradictory. Unabsorbed lactose has bifidogenic effect and improves calcium absorption. The American academy of pediatrics suggests use of dairy foods(milk,cheese,ghee etc) as an important source of calcium for bone health and of other nutrients that enhance growth in children and adolescence.

**Keywords:** Lactose, Infants, Milk, Galactose.

### Introduction

Lactose intolerance is globally spread to those subjects who avoid milk and dairy products to improve symptoms. The disaccharide lactose is a carbohydrate present only in the mammalian milk, 7.2 g/100 ml in mature human milk, 4.7 g/100 ml in cow's milk but it is worth in the milk of some marine mammals (1).

#### Source

Lactose is the mainly produced in the milk by the mammary gland is a defining feature of mammals and lactose('milk sugar';  $\beta$ -galactosyl-1,4 glucose) and it is the main source of carbohydrate in human milk and other mammals, except for walruses and sea lions because they produce low volume, viscous and fatty lactose-free milk.

Cow's milk approximately contains 5 g lactose per 100 mL, equating to 12.5 g lactose in a typical serving size of 250 ml. Lactose is also present in cultured milk products such as yoghurt and cheese (the second-largest fermentation industry after alcohol) (2).

The main carbohydrate and energy source in the mammalian milk is lactose. Lactose is a disaccharide consisting of 2 monosaccharides, glucose and galactose, linked together via a  $\beta$ 1 $\rightarrow$ 4 bond. In most mammals, intestinal lactase activity is high at birth but starts to progressively decline after weaning, eventually curtailing the ability to digest dietary lactose(3).

## Absorption

### Mechanisms of Lactose Absorption

Lactase or lactose  $\beta$ -phlorizin hydrolase is located on the brush border of the small intestine and it belongs to the group of intestinal disaccharidases. Spatially, the presence of LPH is highest in the proximal part of the jejunum and eventually declines towards the ileum, LPH contains 2 enzymatically active sites:

1. The  $\beta$ -galactosidase site
2. Glycosylceramidase site

The  $\beta$ -galactosidase site forms the lactase which hydrolyzes lactose to glucose and galactose.

Whereas the phlorizin hydrolase activity located on the glycosylceramidase site breaks phlorizin and several dietary glycolipids (2, 5). Despite the presence of this latter activity, lactose is the most significant nutritional substrate of LPH (1).

### Lactose digestion and absorption

Digestion and absorption of lactose takes place in the small intestine .7 8 Lactose is the main

substrate of lactase-phlorizin hydrolase expressed on the brush border of villi with its highest expression in the mid-jejunum. The enzyme spans the apical membrane of mature enterocytes and is made up of two identical extracellular 160kDa polypeptide chains, as well as a short intra cytoplasmic part. The alpha-glucosidase activity of this enzyme cleaves the milk sugar disaccharide into the monosaccharide's glucose and galactose which are then actively transported into epithelial cells (enterocytes) by the sodium (+)/glucose (galactose) co-transporter (SGLT1). At higher concentrations, a second facilitative transporter (GLUT2) becomes involved.<sup>9</sup> From the enterocytes, glucose moves into the surrounding capillaries by facilitated diffusion (2).

### Metabolism

Lactose metabolism may cause confusion. At the brush border of the small intestine the lactase causes the deficiency called Lactase deficiency (LD). If there is any failure in the absorption and digestion of Lactose in the small intestine it is called as Lactose malabsorption (LM)(2).

**Table 1:**

Concept		Definition
Congenital lactase deficiency	CLD	Very rare genetic disorder leading to lack of expression of lactase and severe symptoms immediately after birth
Lactase non-persistence	LNP	Decrease of intestinal lactase expression in the first two decades of life
Lactase persistence	LP	Continued expression of intestinal lactase expression beyond infancy; dominant phenotype in western countries
Primary lactose malabsorption		Lactose malabsorption due to non-persistence
Secondary lactose malabsorption		Lactose malabsorption due to lower lactate expression, typically in the setting of intestinal inflammation
Functional lactose intolerance		Symptoms of LI on lactose challenge in individuals without lactose malabsorption
Self-reported lactose intolerance	SLI	History of LI symptoms without formal testing of either LM or LI

**Lactose intolerance:****Definition:**

Lactose intolerance is insufficiency to digest lactose (sugar), a component of milk and some other dairy products and it primarily refers to a syndrome having different symptoms upon the consumption of foods containing lactose. It is one of the most common forms of food intolerance and occurs when lactase activity is reduced.

**TYPES:**

Different factors causing the lactase deficiency are:

1. Congenital lactase deficiency (CLD): These are extremely rare autosomal recessive diseases and characterized by absent or reduced enzymatic activity from birth.
2. Primary lactose intolerance or adult-type lactase deficiency: It is a common autosomal recessive condition resulting from a developmentally regulated change of the lactase gene expression.
3. Secondary lactase deficiency: a transient condition deriving from intestinal damage secondary to several diseases such as infections, food allergy, celiac disease, small bowel bacterial overgrowth, Crohn's disease, or radiation/chemotherapy-induced enteritis.

**Epidemiology:**

A recent study has estimated that the prevalence of Lactose malabsorption worldwide at 68% with higher rates reported for genetic tests than hydrogen breath tests (HBTs). LM is lowest in Nordic countries and highest in Korean and Han Chinese populations (approaches 100%). Large variations in Lactose malabsorption are seen on a regional level reflecting the underlying genetic heritage and prevalence of primary Lactose deficiency in these populations(4).

Approximately 70% of the world population has hypolactasia, which often remains undiagnosed and has the potential to cause some morbidity

**PATHOPHYSIOLOGY AND BIOLOGICAL MECHANISM:**

After stopping suckling primary lactose deficiency is seen in about 2/3<sup>rd</sup> of the whole world's population which had shown reduction in the lactase synthesis.

Persons with the lactase constancy had shown the inflammatory bowel disease, abdominal surgery, gastrointestinal infections and other health conditions may also cause the decrease in lactase activity known to be secondary lactase deficiency.

Both the primary and secondary lactase deficiency are different from the congenital lactase deficiency which is a rare disease that occurs in infants mostly seen in individuals in Finland.

Lactose intolerance occurs in individuals due to the presence of unabsorbed lactose in the intestinal tract which may lead to the lactose deficiency.

The unabsorbed lactose at first increases the intestinal water content which increases the osmotic load and then secondly the lactose is fermented by colonic micro biome which produces the short chain fatty acids and gases like hydrogen, carbon dioxide & methane(5).

**Signs & symptoms:**

Symptoms mainly occur in the

Bowel: abdominal pain, bloating, flatulence, and diarrhea.

When the levels of lactase enzyme decreases readily, primary lactose intolerance develops which normally occurs about the age of 3 years in a few people in Africans and Asians.

Following the use of foods that contain lactose, symptoms result in about a half an hour to 2 hours.

Symptoms like bloating, cramping, flatulence will occur in about 1/3<sup>rd</sup> to 1/5<sup>th</sup> people with lactose intolerance.

The other important change with lactose Intolerance outcomes is decrease in pH of stool, peripheral to fermentation of lactose by colonic

bacteria produces lactic acid and short chain fatty acids.

Based on the severity of lactose intolerance and the consumption of lactose load, it is highlighted that different degrees of symptoms develop in individuals (6).

Extra-intestinal symptoms: headache, vertigo, memory impairment and lethargy have occurred in about 20% of individuals with carbohydrate intolerance.

### Lactose intolerance

#### Complications:

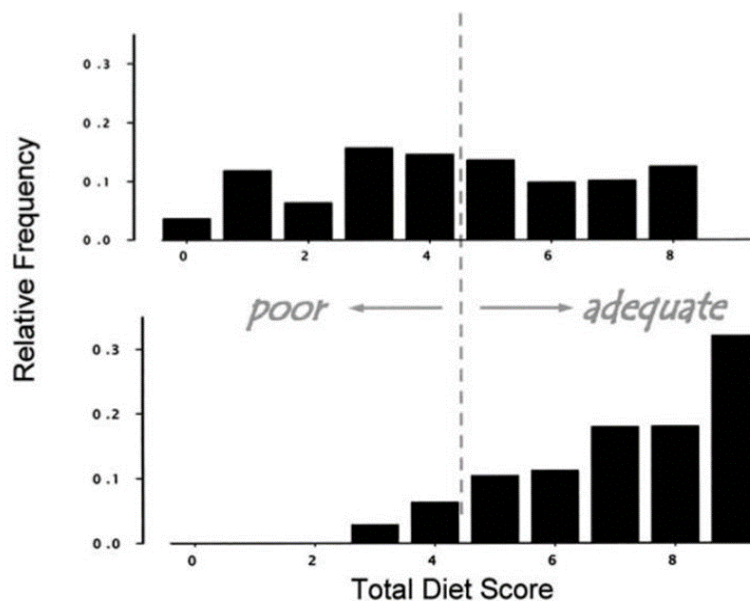
These days Avoiding dairy is not a key for any such conditions. Whatever maybe the reason people will stay away from dairy and dairy products, the result is remarkable and

unplanned health outcomes are seen. For reducing the risk for premature system failure diet quality is very important (8).

According to Robert p. FASN Jeanette N. Keith, 2011 that vitamin D plays an important role in bone mineralization and even the meta-analysis shows an increase in bone mineral density and it also Reduces the risk of Fractures for TT versus CT/CC (OR: 0.81, 95% CI: 0.7 to 0.94,  $p=0.005$ ).

### Diet quality

These days the foods are great for their nutrition value and dairy rich, with equal measures so it is very tough or even complicated to design a diet which includes everything that your body needs.



**Figure 1:** the above graph represents that the total consumption of dairy products in their daily life, the first graph shows about the diet score, for those avoiding the recommended calcium called as dairy avoiders. The bottom graph tells about those who take calcium in suggested amounts (i.e, Dairy consumers). In 272 healthy post-menopausal women[9].

### Cardiometabolic Syndromes

The benefits in consuming dairy products against cardio metabolic Syndromes are (these refers to dyslipidemia (high cholesterol or triglycerides which promote atherosclerosis or in case of triglycerides or fatty liver) and

diseases like hypertension, CAD, stroke, type2 DM, obesity remain controversial (10).

### Weight Management

These days the children/ elderly people are exposed to overweight, obesity or increased percentage of fat in the body, it is due to low supply of calcium intake.

An absolute balance of macronutrients for the weight loss of adults is disagreed so the proof is that energy-inadequate foods like which are

low in carbohydrates and rich in protein are necessary/ best for weight loss (11).

### Diagnosis

	Lactose tolerance test	H2 breath test	Genetic test
Test principle	Increase in blood sugar after lactose challenge	Increase in respiration after lactose challenge	Assessment of 13910c/t polymorphism
Availability	Excellent	good	good
False positive	Rapid GI transit	Small intestine bacterial growth	Rare in (<5%) Caucasians
Secondary cause	Cannot be eliminated	Cannot be eliminated	Cannot be eliminated
Symptom assessment	Possible	possible	Not possible
cost	lowest	low	High

Summary of tests for lactose malabsorption and lactose intolerance (12).

### Treatment

The aim in the treatment of lactose intolerance is to improve digestion rather than reducing malabsorption. The reduction of lactose intake is recommended, some patients can tolerate lactose at least 12g without experiencing symptoms and with combination of other foods up to 18 g of lactose they can tolerate.

Enzyme replacement therapy is a choice of therapy. This is combined with the dairy products and it changes the taste of the food as the digestion of lactose produces the glucose and galactose which are sweeter than the sugar.

Another therapy involves the probiotics, these alter the intestinal flora and these are beneficial in the IBS patients. The tolerance is increased by repeated providing of lactose and adaptation to the intestinal flora.

Some studies suggest that the adults or adolescents with homozygous 13910\*C genotype will consume less milk or lactose and less calcium than the others. The low intake of dietary products leads to high risk of fractures in women when compared to men. This genotype 13910\*C is a risk factor for osteoporosis (2).

There are two types of clinical choice for the management of lactose intolerance, they include alimentary restriction and drug therapy. In primary hypolactasia the dairy products and milk is not included in the diet until the symptom remission, in case of secondary hypolactasia the diet is maintained until the regression of acquired disorders.

### Strategies for improving tolerance to dairy products:

Maintain the amount of the lactose consumed. According to how much they can tolerate, start with less than one cup of milk with food and increase the amount gradually until symptoms re appear.

- Consume the milk and other dairy products with the meal. Allow for slow gastric emptying and allowing more time for lactose enzymes to digest it in the colon.
- Choose the foods which are well tolerated:
  - Yogurts are well tolerated
  - Choose whole milk rather than low fat milk
  - Choose chocolate milk rather than any flavored milk
  - Choose the cheeses such as cheddar, Colby, parmesan which are in low lactose.
  - Choose fermented milk, yogurt milk, sweet acidophilus milk which are better tolerated.

Try lactose free products or low lactose containing products

- Use lactose hydrolyzed milk
  - Use of commercial lactose preparations (capsules, tablets, chewable tablets)
  - Add drops of liquid lactose in milk to breakdown.
  - Consume oral lactase tablets before consuming the lactose containing foods.
- Development of tolerance
    - Consume the large amount of lactose containing products.
    - Continue the exposure of lactose to colonic bacteria to enhance the efficacy and to metabolize the lactose and to produce the lower intolerance symptoms.(13)

**Table 1: Lactose content in milk, dairy products and some manufactured products:**

Food type	% by weight
Milk skimmed	4.8
Semi skimmed	4.7
Whole milk	4.6
Condensed milk	12.3
Dried skimmed	52.9
Evaporated whole	8.5
Goat	4.4
Human	7.2
Sheep	5.1
Cream	2.2
Double cream	1.7
Sour cream	2.7
Creme fraiche	2.1
Creme fraiche half fat	3
Imitation cream	2.3
Cheddar	2.1
Cheese spread	4.4
Cheese spread, reduced fat	7.3
Cottage cheese	3.1
Cream cheese	Trace
Danish blue	Trace
Stilton	0.1
Feta	1.4
Goat cheese	0.9
Parmesan	0.9
Parmesan cheese slices	5
Yogurt plain	4.7
Fruit	4
Drinking yogurt	4
Fromage frais plain	4
Puddings	3
Ice cream non dairy	4.8

Ice cream dairy	5.2
Rice pudding	3.9
Custard made with whole milk	5.2
Chocolate mousse	3.8
Cow's milk	*
Choc ice	4.7

Lactose may be present in the products where the labels mention the inclusion of lactoserum, whey, milk solids or modified milk ingredients.

Lactose is found in foods such as:

- Processed meats,
- Gravy stock powder,
- Margarines,
- Sliced breads,
- Breakfast cereals,
- potato chips,
- Processed foods,
- Medications,
- Pre-prepared meals,
- Meal replacements (powders and bars),
- Protein supplements (powders and bars) and even milk stout-style beers.

Some barbecue sauces and liquid cheeses which are used in fast-food restaurants may also contain lactose (14).

**Table 2: Food ingredients to avoid on a lactose exclusion diet:**

Milk lacto globulin
Milk solids
Buttermilk
Artificial cream
Lactose
Whey powder
Feta
Caseinate
Quark
Skimmed milk powder
Ricotta
cream
Cheese
Modified milk
margarine
Evaporated butter milk
Condensed milk powder

#### **Recommendations for management of lactose intolerance:**

- Start the day with cow's milk 30-60ml per day and increase to 250 ml. consume them with meals as the lactose is released slowly in the intestine rather than the empty stomach.
- High fat milk is recommended
- The aged cheese is included as it contains low lactose content (0.1-0.9g of lactose in 30g of hard cheese)
- The lactose reduced products are included. These are nutritionally similar to the normal dairy products.

- The lactose tablets, drops are used before consuming the dairy products or after consuming the dairy products.
- The calcium rich foods are recommended (green leafy, legumes, dried beans)
- Green leafy vegetables are rich in vitamin K which play an important role in calcium regulation and formation.
- Due to presence of fibers, phytic, oxalic acids the bioavailability of calcium is less when compared to dairy products.
- In case of non -dairy foods the serving of the calcium from one serving of dairy as follows:

Serving fortified soy beverage, serving of bony fish, serving of green leafy vegetables.

- Consumption of yogurt, fermented products

#### **Other treatment which encompass a more food tolerance symptoms:**

The symptoms of intolerance are merged with the several causes like milk intolerance due to fats, actual milk protein allergy, and A1 casein. In children the cow's milk allergy is common when compared to adults. In other cases, the celiac and Crohn's disease are seen in younger children and microscopic colitis is seen in elderly. When the LI symptoms still present (stomach pain, bloating, and abdominal pain) pharmaceutical treatments or the probiotics are recommended. The FODMAP diet is the recommended diet in LI patients. The other diet like GFD (gluten free diet) is preferred in case of celiac disease (10).

In case of hypo-lactesia, the treatment is based on the presence of intolerance symptoms. The common approach is to avoid milk and milk products.

Non-pharmacological options:

- Consumption of pre hydrolyzed milk
- Consume fermented products
- Ingest milk with other foods
- Distribute milk into little meals

- Increase the colonic adaptation

Pharmacological options:

- Enzyme supplements
- Lactase suppléments
- Probiotics
- Antibiotics

#### **Drug therapy:**

Enzyme supplementation with the lactose is an approach. This is a nonhuman source to hydrolyze the lactose.

1. **Exogen lactose**- obtained from *aspergillus oryzae* or from *kluveromyces lactis*. This break -down the lactose into glucose and galactose and allows better absorption.
2. **Exogenous beta-galactosidase**-it is taken along with meal; it is efficacious and also causes no side effects.
3. **Probiotics**-these are the live microorganisms used in the treatment of lactose intolerance. Some of these have beta-galactosidase that may aid in digestion of lactose ingested. These can be taken along with food products such as milk, yogurt, as supplements.
4. **Gut decontaminating agents**
5. **Antimicrobial agents(rifaximin) (16).**

#### **Strategies influencing the gastrointestinal transit:**

A study conducted in comparison to full fat milk and skimmed milk, aqueous lactose solution. The Leister et al showed the full fat milk increases the lactose tolerance compared to the others. The fat present in the full fat milk improves the absorption of the carbohydrate and slows the gastric emptying and increases the transit time by prolonging the contact time between the enzyme and the substrate.

#### **Pharmacological approach that modify the gastric time and intestinal transit:**

A comparative study of propantheline and metoclopramide on lactose digestion. The propantheline shows a prolonged gastric



emptying time and also improves the tolerance and reduces the symptoms and H<sub>2</sub> breathe concentration than the metoclopramide. Loperamide shows an effect on the oral-celiac activity and it improves the symptoms and H<sub>2</sub> exertion. Due to more side effects and high cost it is not used (17).

### **Exogenous oral enzymes:**

The lactase is added to the meals for the digestion of lactose which are prepared from the fungi or yeast. These enzymes are available in the form of gels, liquids, capsules, tablets.

Some studies show that the three capsules of the lactose preparations contain 3000-6000 IU beta-galactosidase for milk containing 20-50 g of lactose and in case of milk with 20 g of lactose the breath hydrogen, symptoms were significantly reduced.

### **Adaptations and prebiotics for treatment of lactose intolerance:**

During the mid-20 century, the adaptation to intolerance was reported with the milk powder in some countries. The symptoms disappeared during initial use of milk powder. This method was demonstrated by Hertzler and Saviano in which the 16 mal digesters were completely converted into the lactose digesters after 16 days of lactose consumption.

### **Probiotics as a Future Option in the Management of Lactose Intolerance:**

The probiotics with the beta-galactosidase activity are used as adjuvant therapy for the treatment of lactose intolerance. According to the WHO the probiotics are the living microorganisms which are administered in high amounts. The yogurt containing the lactose containing bacteria could hydrolyze the lactose and they alleviate the clinical symptoms of lactose intolerance. In patients with IBS 4-week therapy with *Lactobacillus plantarum* was effective and effective against bloating and abdominal pain, *Lactobacillus acidophilus* was associated with reduction of sores, discomfort, and abdominal pain. (12).

### **Conclusion**

As predicted that the world's adult population have hypolactasia after childhood the three phenotypes such as lactose non persistence, lactose persistence and heterozygotes are under genetic control with lactose persistence being the mutation i.e., seemingly the result of generations of continued milk consumptions as an historic example of positive selection. Educational efforts are being directed at encouraging people with lactose non persistence to consume large quantity of vitamin D and calcium such as high fat milk, old aged cheese, yogurt and lactose hydrolyzed products.

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