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Lactose intolerance: A review for facts and fictions

Shubham Arjun Lonkar
By-products Utilization Lab, Department of Dairy Technology, College of Dairy Science and Technology, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India.

Anju Boora Khatkar
Department of Food Technology, Punjab Agricultural University, Ludhiana, Punjab, India.

Narender Kumar Chandla
Department of Dairy Engineering, College of Dairy Science and Technology, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India.

Pranav Kumar Singh
Department of Dairy Technology, College of Dairy Science and Technology, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India.

Sanjeev Kumar
Dairy Technology Division, SGIDT, BASU, Patna, Bihar, India.

Mukul Sain
Dairy Engineering Division, ICAR-NDRI, Karnal, Haryana, India.

Sunil Kumar Khatkar ✉
By-products Utilization Lab, Department of Dairy Technology, College of Dairy Science and Technology, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India.

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ABSTRACT

Milk is considered a complete food due to its high nutritional status. Regular consumption of milk reduces the problems of nutrition deficiency. Milk contains sugar, mainly lactose, in significant amounts with other ingredients of milk, which also contributes to maintaining the body's energy level. But, sometimes, a problem arises due to the intake of lactose owing to a deficiency of β-galactosidase (lactase). A lack or shortage of lactase enzymes in the human body results in the body's inefficiency in degrading lactose into minor constituents. Un-degraded/ undigested lactose is consumed by the bacteria and converted into several acids and gases, which results in the rise of several types of intestinal disorders. In this article, the focus is given to lactose intolerance, its types, and its remedies.

Introduction

Milk, as a complete food, contains several components like water, fat, protein, lactose, vitamins, minerals, etc. that help to grow and provide nutrition to the body. Among these components, lactose is one of the important components which provide energy and other health benefits to the body. Lactose is the primary source of sugar which is only present in mammalian milk. Human and bovine milk contains 7.2g/100 ml and 4.7g/100 ml, respectively, of lactose, whereas the milk from marine mammals' origin contains much less lactose (Solomons, 2002). Lactose is a rich source of energy for the infant during the early growth stage. To get the nutritional value and energy from milk and lactose, a person should be able to digest the lactose after its assimilation. Lack of ability to digest lactose falls under the category of lactose intolerance, and it depends on several factors, which are discussed in detail in this article. Additionally, lactose intolerance, the inability to digest lactose, is not a new term; it has existed for many years and is well known in foreign countries. People with lactose intolerance show sensitivity to products containing lactose (especially milk and milk products). Enough scientific knowledge of lactose and the importance of lactose in milk are vital in dealing with lactose intolerance. Many physiological factors affect lactose breakdown and its absorption, like passing

Corresponding author E-mail: absuneelkhatkar@gmail.com
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through the digestive system, lactase activity, working of the visceral organs, various intestine-related disorders, and composition of the gut microflora. Considering these complex factors, there are variations in the symptoms of lactose intolerance. Simultaneously, the industry and academia are working on the causes of lactose intolerance and their remedies and exploring the dairy products' digestion regulation and their implementation in the product formulation to provide alternative products for lactose-intolerant people (Vesa *et al.,* 2000). Products derived from milk have excellent nutritional status and can be used as a functional ingredient to provide therapeutic benefits to the body. Milk is a good source of minerals (especially calcium), and vitamin D. Lack of consumption of milk causes the deficiency of these nutrients and results in several health-related issues. On the other side, most of the consumers are not that aware of lactose intolerance and the complications linked with it but being the most important part of the daily diet (milk and milk products). Thus, the facts and fiction for lactose intolerance must be explored, and consumers should also have enough scientific knowledge about lactose and its intolerance. Therefore, keeping these facts in mind, this manuscript is reviewed to enlighten the serious and important issue of lactose intolerance.

Role of Lactose as Nutrient

Lactose is the primary energy source for infants, as human milk contains higher lactose than bovine milk. Lactose also acts as a prebiotic for gut microflora, providing superior health benefits to the body. Generally, the human body has lactase to break the lactose (Venema, 2012), but its deficiency results in the passage of lactose in the large intestine, which acts as an excellent substrate for fermenting microflora (lactic acid bacteria) and results in the formation of undesirable acid and gas. Due to acid and gas production, several problems arise in the body (Hill, 1983; Gibson *et al.,* 2004). Most of the microbiota from the colon can split the lactose into glucose and galactose with β-galactosidases which also produce metabolites such as short-chain fatty acids (SCFA) and other gaseous compounds like hydrogen, carbon dioxide and methane. SCFA works as a substrate and provides energy to gut microflora and colonocytes. Oligosaccharides are well-known compounds that have bifidogenic activity, thus provide excellent health benefits to the body (Vandenplas, 2015). The activity and population of Bifidobacterium in the intestine decrease with increasing human age. So, milk consumption provides milk saccharides having a bifidogenic activity to maintain the intestinal health and population of gut microbiota (Vulevic *et al.,* 2015). It is proposed that galactose is produced due to the hydrolysis of lactose. It acts as a substrate for the gangliosides, cerebrocides and mucoproteins, which have various neural and immunological roles. Due to its probable bifidogenic activity, lactose may itself be involved in promoting innate immunity. If one cannot get these benefits due to lactose intolerance, there is a need to replace it in dairy products and even in breast milk with oligosaccharides which are like those in milk and can serve as prebiotics in place of the lactose (Zivkovic *et al.,* 2011)

Lactase and Importance of Lactase Activity

Lactose-phlorizin hydrolase, mostly known as lactase, is β-galactosidase which breaks down the lactose to its subunit's glucose and galactose. This activity of lactase enzyme in adulthood is termed lactase persistence. Intestinal enterocytes absorb glucose and galactose in the bloodstream. Glucose and galactose mainly provide energy as part of glycoproteins and glycolipids (Campbell *et al.,* 2005). Lactase is primarily present in the mid jejunum of the small intestine and some parts on the apical surface and attached to the molecules of the gastrointestinal lumen through the end of C terminal (as shown in Fig. 1). Enzyme is released with 220 kDa precursor peptide. But due to post-transcriptional change, the size of the peptide obtained was about 150 kDa. Various factors play a significant role in the production of active enzymes by alteration in the protein network. The pancreatin trypsin achieves the process of cleavage of peptide bonds (Zecca *et al.,* 1998). During pregnancy, there is a progressive increase in the activity of lactase enzyme occurring from 8^{th} week to 37^{th} week of pregnancy, and at birth, lactase activity is at its peak. After a few months of life, lactose non-persistence is observed, which decreases lactase activity. Lactase activity was observed to fall at variable rates with a progressive increase in the age of mammals (Vesa *et al.,* 2000; Matthews *et al.,* 2005).

Lactase persistence which is a continuation of the lactase activity is observed in 30% of the human population after weaning and in adulthood (Savaiano and Levitt, 1987). Lactose deficiency, also known as hypolactasia is classified under three distinct forms first one is a congenital deficiency, which is associated with the inferior activity of lactase. Primary lactose deficiency is mainly observed in most of the population, which is non the persistence of lactase activity. Secondary lactase deficiency in people with lactase persistence is the progressive loss in the activity of lactase enzyme due to gastrointestinal disorders, pathologies and surgery (Leis *et al.,* 2020). For efficient lactose utilization, only 50% of the lactose activity is required (Swallow, 2003). Non-persistence of lactose does not mean the people with it are all unable to digest lactose. They can utilize lactose up to 12g if spread throughout the day.

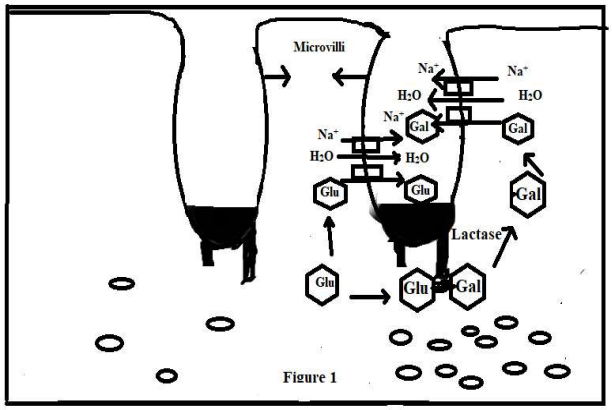

Figure 1: The mechanism of lactase activity (Reproduced from Lomer *et al.,* 2008)

Prevalence of Lactose Intolerance

The loss in lactose expression is generally completed in childhood, but some studies also revealed its decline with a progressive increase in age (Sahi *et al.,* 1994). The rate of loss of lactase activity varies concerning ethnicity. After 3-4 years of stoppage of consumption of mother milk, 80-90% decrease in the activity of lactase was observed in Chinese and Japanese, while 60-70% loss was observed in Jews and Asians over several years of stopping mother's milk. Lactase activity reached its minimal level after 18-20 years in the case of white Northern Europeans.

Congenital Deficiency

Deficient activity of lactase results in congenital deficiency and is characterized by the inability to break down lactose in the first-ever breast milk, resulting in diarrhea. It is very rare, with only 40 cases till now. It is known to be a single autosomal recessive disorder, and the exact reason at the molecular level is yet to be explored (Swallow, 2003). To overcome this type of problem, avoid the consumption of lactose altogether from birth. No treatment was available for congenital lactase deficiency before the 20th century due to the lack of availability of lactose-free human milk substitutes (Heyman, 2006).

Primary Lactase Deficiency/ Non-Persistence of Lactase

Primary lactase deficiency is a significant problem diagnosed in 70% of the world's population. Reports based on the clinical symptoms of lactase deficiency show variations according to the test subject and give confusing results during diagnosis. This means when a person showing lactose intolerance is fed with two glasses of milk or lactose hydrolyzed milk daily in a double-blind, crossover study. No statistical difference was observed in symptoms of lactose intolerance in both cases, even though the test subject said they were lactose intolerant (Suarez *et al.,* 1997). Even in the case of lactose-impatient people, some people tolerate one glass of milk and one scoop of ice cream without any symptoms, but when the same person consumes one more glass of milk or other dairy product can show symptoms.

Secondary Lactase Deficiency

In this case, various infections can cause damage to epithelial cells which contain lactase. The cells which replace these injured cells are immature and lactase deficient thus, cause secondary lactase deficiency (Sandhu *et al.,* 1997). Several studies showed that children with rotaviral diarrheal illness with the absence of or only mild dehydration do not offer any symptoms of lactose intolerance, including the status of dehydration, nutritional outcome or success of the therapy. Parasites like giardiasis and cryptosporidiosis infect the small intestine and cause damage to the epithelia cells, leading to lactose malabsorption. Diseases like celiac, Crohn's and other immune-related diseases are significant factors for secondary lactase intolerance in the case of children (Heyman, 2006).

Severe malnutrition disorders result in small intestinal atrophy, leading to secondary lactase deficiency (Nichols *et al.,* 1997). Children with

persistent post-infestation diarrhea (more than 14 days) are recommended to avoid lactose-containing milk according to the recommendations of the WHO when they fail in the dietary trial of milk or yoghurt (World Health Organization, 1996). In the case of secondary lactose deficiency, there is no need to exclude lactose from the diet; lactose consumption can be started after resolving the primary problem.

Detection of the Lactose Intolerance

In early studies, lactose digestion is detected by measuring the blood glucose level after injection of 50g of lactose, a significant rise in the blood glucose after the time interval of 30 minutes is an indication of high lactase activity (Swallow, 2003; Gugatschka *et al.,* 2005). The lactose hydrogen breath test is also one of the best-known methods for detecting the digestion of lactose. In this test, 50g gram of hydrogen is introduced into the human body orally, and the hydrogen content of the breath is measured in 3-6 hours. If it is more significant than 20 ppm above the baseline, it will indicate lactose intolerance. In case of the results of the 6 hours are taken, then the sensitivity increases from 40% to 60% (Matthews *et al.,* 2005). Real-time polymerase chain reaction (PCR) test for genotyping provides information about the specific lactase gene quickly and easily and is used to distinguish primary and secondary lactose intolerance (Gugatschka *et al.,* 2005).

Signs of Lactose Intolerance

In the case of lactose intolerance, as discussed above, the lactose ingested orally in the body remains unabsorbed in the intestine. The undigested lactose in its complex form, while passing through the digestive system, causes various health-related problems, considered as the symptoms of lactose intolerance. Symptoms include stomachache, gas in the stomach, and intestine, bloating, diarrhea, and rumbling and gurgling noise made by the movement of the gas and the water inside the abdomen. Occasionally, nausea and omitting are also observed (Vesa *et al.,* 2000; Gugatschka *et al.,* 2005; Matthews *et al.,* 2005). Abdominal pain and bloating result from the fermentation of unabsorbed lactose, which produces byproducts like SCFA and gases like hydrogen, methane and carbon dioxide. It further increases the transit time in the gut and intracolonic pressure. Due to the acidification of the colonic content and increased osmotic load resulting from the unabsorbed lactose, greater secretion of the fluid and the electrolytes occurs, which results in rapid transit time and causes loose stools and diarrhea (Swagerty *et al.,* 2002).

Gut Microflora and Lactose Intolerance

The human digestive system consists of about 17 bacterial families with over 500 species (Suau *et al.,* 1999). Colon has the highest gut microflora concentration, about $10^{12\text{-}14}$ ml^{-1}. It is observed that the malabsorbed lactose is fermented by the lactic acid bacteria present in the ilea and colon followed by the production of SCFA and gases (Hove *et al.,* 1999). In this process, the malabsorbed lactose is broken down by the lactase enzyme present in the lactic acid bacteria (Swallow, 2003) into glucose and galactose which is then absorbed (Fig. 2) in the small intestine. The lactase enzyme shows optimum activity at the pH 6-8 as in the small intestine. In the case of the colon where the pH decreases to 4, lactose remains unfermented due to lowering the bacterial lactase activity.

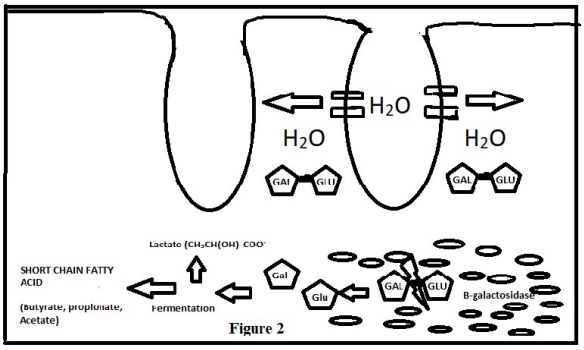

Figure 2: Mechanism of breakdown and absorption of lactose by lactase enzyme (Reproduced from Lomer *et al.,* 2008)

Dairy Foods and the Health

After weaning foods, milk and milk products are considered important, viable, convenient to feed and nutritious food materials for the children (Widodo *et al.,* 2016). Calcium is one of the major mineral constituents of milk required for bone health. During the first 50 years, the calcium requirement will be the same for males and females (Hodges *et al.,* 2019). From the previous research, it can be concluded that calcium absorption in healthy adults is independent of dietary lactose and concentration of lactase enzyme. The presence of lactose may enhance the absorption of calcium in animals (Weaver *et*

al., 2011) and infants (Abrams *et al.,* 2002) but has no stimulating effect in the case of humans (Zittermann *et al.,* 2000). Consumption of a variety of dairy products like milk, cheese, yoghurt etc., having different levels of lactose (Table 1) does not affect calcium absorption in adult women (Nickel *et al.,* 1996).

Table 1: Lactose content of milk and milk product

Particular	Type	g/100ml
Milk	Semi skimmed milk	4.7
	Whole milk	4.6
	Condensed, whole, sweetened	12.3
	Dried skimmed milk	52.9
	Evaporated whole milk	8.5
	Human	7.2
	Ship	5.1
	Single cream	2.2
	Double cream	1.7
	Sour cream	2.7
	Imitation cream	2.3-6.8
Cheese	Brie/camembert	Trace
	Cheddar	0.1
	Cheese spread	4.4
	Cheese spread, reduced fat	7.3
	Cottage cheese	3.1
	Cottage cheese, reduced fat	3.3
	Cream cheese	-
	Danish blue	Trace
	Stilton	0.1
	Edam	Trace
	Feta	1.4
	Goat cheese	0.9
	Mozzarella	Trace
	Parmesan	0.9
	Processed cheese slice	5.0
Yoghurt	Plain	4.7
	Fruit	4.0
	Drinking yoghurt	4.0
Puddings	Milkshake average	4.0
	Ice-cream non- dairy vanilla	4.8
	Ice-cream dairy vanilla	5.2
	Rice pudding	3.9

Calcium homeostasis in Chinese adults is achieved at a low calcium intake of ≤500 mg daily (Fang *et al.,* 2016), which depends on other factors such as lactose and calcium absorption. Horowitz *et al.,* 1987 conducted a study using a calcium isotope and observed that the calcium absorption is independent of lactase enzyme efficacy in postmenopausal women. However, calcium absorption largely depends on the lactose concentration and activity of lactase in the case of the elderly. Still, there is a lack of supportive data about this statement (Hodges *et al.,* 2019). Schuette *et al.* (1991) found that calcium absorption enhanced in postmenopausal women when 12 gm of lactose was added to the non-carbohydrate milk formula. Calcium absorption in postmenopausal women largely depends upon the food source and concentration of lactose present in that food (Obermayer-Pietsch *et al.,* 2007). Cederlund *et al.* (2013) also highlighted the possible immune-protective roles of lactose. Lactose malabsorption causes the problems like loose stools or diarrhoea because of osmosis exerted by the undigested lactose. Lactase deficiency provides an excellent substrate for colonic bacteria. As a result of bacterial fermentation and gas production, problems like intestinal flatulence and swelling are raised, as well as concerns like carcinogenicity (Gibson and Macfarlane, 1995; Aimutis, 2012). Malabsorption of lactose causes the problems like osteoporosis due to impaired calcium absorption (Casellas *et al.,* 2016).

Conclusion

Lactose digestion and its assimilation is vital for the human body to get the nutritional benefits of milk. It also helps in assimilating calcium and vitamin D and its prebiotic attributes. But the lack of ability to digest lactose due to unavailability, deficiency, and rendered functioning of lactase enzyme falls under lactose intolerance and sensitivity to lactose. Lactase (lactose-phlorizin hydrolase) is a β-galactosidase that breaks down the lactose to its subunit's glucose and galactose. It presents in the mid jejunum of the small intestine and some parts on the apical surface. It is attached to the molecules of the gastrointestinal lumen through the end of C terminal. Lactase deficiency results in the passage of lactose in the large intestine, which acts as an excellent substrate for fermenting microflora (lactic acid bacteria) and results in undesirable acids and gases. The symptoms of lactose intolerance include stomachache, gas in the stomach, and intestine, bloating, diarrhea, and rumbling and gurgling noise made by the movement of the gas and the water

inside the abdomen. Occasionally, nausea and omitting are also observed. To avoid the complications linked with lactose intolerance, the sensitive person should adopt the plant of diet with lactose exclusion in daily diets and should avoid food containing milk and milk ingredients like milk from any mammalian source; milk solids; lactose; whey powder; caseinate; condensed milk; cream; SMP; evaporated milk; buttermilk; feta; quark; curd; ricotta; butter; margarine; etc. Though the caseinate does not contain lactose, all the milk ingredients must be avoided initially. Lactose deficiency, also known as hypolactasia is classified under three distinct forms (1) congenital deficiency (inferior activity of lactase); (2) primary lactose deficiency (lactase amount declines with age); (3) secondary lactase deficiency (due to gastrointestinal disorders, pathologies, and surgery). The good thing is that for efficient lactose utilization, only 50% of the lactose activity is required, and the non-persistence of lactose does not mean that the people with it are all unable to digest lactose.

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Conflict of interest

The authors declare that they have no conflict of interest.

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