

Lactose intolerance and a possible permanent solution

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Lactose intolerance (LI) is a digestive disorder which is caused by lactose malabsorption, resulting in uncomfortable symptoms such as diarrhea and bloating. Currently, approximately 75 percent of the world population is lactose intolerant. In addition, Asians have the largest proportion of people with LI, resulting from genetics and cultural differences. This article aims to introduce the causes of LI, symptoms and diagnosis of LI, consequences of intolerance in different age ranges, LI in the Asian population, mistaken beliefs of LI and dairy products consumption, current short-term treatments, and potential permanent treatment. Overall, our paper would provide key information and an alternative view for the future treatment development.

Keywords: Lactose intolerance, lactose intolerance in Asians, mistaken beliefs, possible permanent solutions

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Watch a video introduction by the authors at <https://youtu.be/LFfIE1ZyNmM>

Body

1. General Information About Lactose

a. Structure

Lactose is a disaccharide also known as a milk sugar with the molecular formula $C_{12}H_{22}O_{11}$ and a molar mass of 342.30 g/mol. It consists of D-galactose and D-glucose connected by a glycosidic linkage (β -1,4-glycosidic bond)

(figure 1). The glycosidic bond is created by a reaction between monosaccharides with OH group and anomeric carbon. The beta position means a position that has either oxygen on the same side as the Carbon position 6, which resulted in a horizontal structure. Even though maltose and lactose have a similar structure, lactose has a beta-acetyl carbon #1 instead of an alpha acetyl carbon #1 (Libretexts., 2020).

Table 1. The table shows lactose content per 100g of products

Products	Lactose content (gram/100g)
Parmesan Cheese	0.06
Cotton cheese	4
Butter	0.1-1
Camembert	0.04
Soured cream	3.2
Whey powder	72.8
Ice cream	6-7
Ricotta cheese	0.3
Yogurt	3.2-4.5
Cows' milk	4.8
Sheep's milk	6.2
Camels' milk	5.2
Goats' milk	4.2
Powder milk (full fat)	35.1
Powder milk (reduced fat)	50.5
Whipping cream	4.05

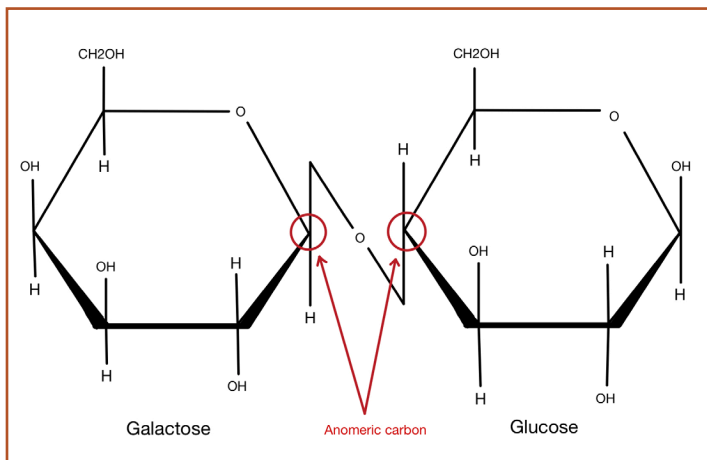


Figure 1. Structure of Lactose which shows anomeric carbon

b. Lactose Digestion

Lactase, or lactase-phlorizin hydrolase (LPH), is an enzyme produced by intestinal epithelial cells on a small intestine wall. Lactase is most concentrated in the jejunum and its concentration drops on the way down to the ileum. Lactase is used for hydrolyzing lactose into glucose and galactose through hydrolysis. As a result, glucose and galactose are small enough to be absorbed through the line of microvilli or the brush border (Adams, 2020).

Lactase is located on a single genetic locus on a mammalian chromosome. In terms of quantity, younger people have higher levels of lactase, and this amount diminishes as age increases.

c. Products that contain lactose

Lactose is found in high levels in dairy products such as, cows' milk, goats' milk, cheese, yogurt, and ice cream. In contrast, most food, including fruits, vegetables, grains, meats, and plant-based milk, are lactose-free products. Some ingredients also do not contain any lactose, such as lactate, lactitol, lactic acid, milk protein, lactic acid bacteria, baking agents. The table below shows lactose content in several products (Table 1). The amount of lactose depends on the manufacturing from various factories (Food Intolerance Network., 2013).

2. Lactose Intolerance

Most Asians and American Indians are lactose intolerant, which often affects their daily life. Unlike Asians and American Indians, about 25% of Europeans or Caucasians are lactose intolerant. Statisticians have previously reported that about 50-80% of Hispanic people and 60-80% of South Indians were also lactose intolerant in 2006-2007 (Bhatnagar & Aggarwal, 2007).

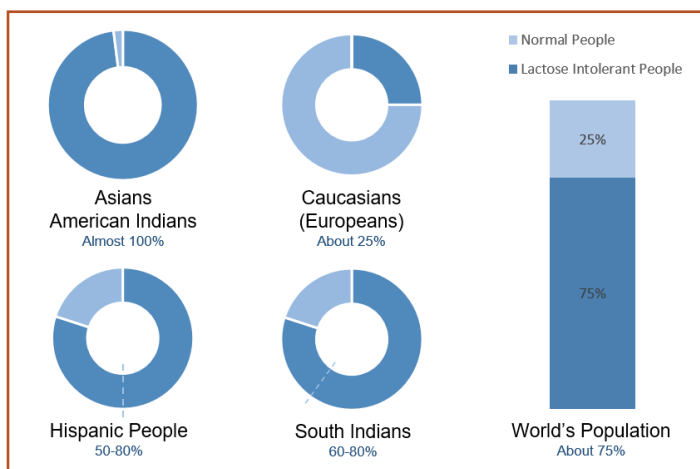


Chart 1. Prevalence of lactose intolerance of world's population in 2006-2007

a. Symptoms

Lactose Intolerance (LI) is prone to happen in lactose malabsorption (LM) individuals after ingesting lactose or lactose-containing food. Following ingestion, many individually experience symptoms such as abdominal pain, bloating or diarrhea (Misselwitz et al., 2019). Some studies emphasized that lactose intolerance may cause borborygmi, nausea (or/and vomiting), flatulence, and stomach cramps (Mayo Clinic, 2020).

The expression of symptoms after ingesting lactose in individuals with lactose malabsorption is different from lactose intolerant individuals. Many people with lactose malabsorption have no sign of symptoms if they take any dairy products in appropriate quantities, no higher than a standard serving level; for instance, bovine milk, with a typical serving size of 250 ml, has 12.5 g of lactose. Due to lactose intolerant people having less lactase, lactose is not broken down into monosaccharides, resulting in being unable to be digested and passing through the large intestine, and result in an increase in solute concentration, and osmotic pressure is higher than absorption forces of water. The osmotic pressure increases approximately 8 times the typical pressure. Diarrhea occurs when lactose load is over the amount of colonic bacteria, or the short-chain fatty acid (SCFA) is over the colonic resorption ability. Apart from the lactose fermentation to SCFA in the large bowel by colonic bacteria, it also produces gases such as hydrogen (H_2), carbon dioxide (CO_2), and methane (CH_4), which can cause abdominal pain and bloating; therefore, physicians can test the concentration of hydrogen in exhalation for diagnosis of lactose maldigestion, which is called hydrogen breath test (Misselwitz et al., 2019). Misselwitz et al. stated that lactose malabsorption with the presence of functional gastrointestinal disorder, such as IBS (irritable bowel syndrome), sometimes causes neurological symptoms such as fatigue and headache after consuming lactose, including fructose. In lactose intolerance and IBS patients have highly increased the severity of abdominal symptoms after consuming 20 g of lactose, and have high rates of psychological comorbidity and the indicator of an activated mucosal immune system. Anxiety disorders or visceral hypersensitivity and high concentration of gas production on breath tests also increase the severity of symptoms (Misselwitz et al., 2019).

However, the severity of clinical syndrome mainly depends on the classification of lactase deficiency (LD) and other factors such as the amount of lactose intake, the sort of lactose-containing food to consume in each individual, or lactose concentration passing through the colon of the large bowel (Misselwitz et al., 2019).

i. Classification of lactase deficiency

Lactase deficiency results from the brush border in the small intestine mistakenly releasing less lactase enzyme for lactose digestion; thus, lactase enzyme is incapable of digesting large amounts of lactose (Misselwitz et al., 2019). There are 4 types of lactase deficiency: primary, secondary, congenital, and developmental lactase deficiency. Knowing which type of lactase deficiency a patient has is crucial for physicians or medical personnel to know in order for a proper diagnosis and prognosis, and possible treatment management for them (Bhatnagar & Aggarwal, 2007).

1. Primary Lactase Deficiency

Primary lactase deficiency is also defined as adult-type hypolactasia, lactase nonpersistence (LNP), or hereditary lactase deficiency. Not only is lactose intolerance in late adolescence and adulthood caused by primary lactase deficiency the most common, but about 70% of individuals around the world are lactose intolerant. Primary lactase deficiency is a recessive trait in most individuals but not in Europeans and Africans (Bhatnagar & Aggarwal, 2007).

Female mammals produce milk containing valuable nutrients such as lactose for their cubs. Lactose can be digested by lactase; therefore, most mammalian cubs should have the highest lactase concentration in the brush border of the small bowel at first after birth and before weaning. Nevertheless, the lactase concentration after weaning declines up to 10%, compared to the concentration at birth, as an effect of continuously losing lactase persistent (LP) allele (Bhatnagar & Aggarwal, 2007; Waner et al., 2019).

There is no sign of symptoms of lactose intolerance in Caucasian children that are younger than 4-5 years. In contrast, about 20% of Asian, Hispanic, and African children who are younger than 5 years old have primary lactase deficiency and lactose malabsorption. Thai children who are 1-2 years old have lost the messenger RNA expression and lactase activity, the same phenomenon is observed in Finnish children between the ages of 10-20. As a result, the expression of primary lactase efficiency depends on the race of an individual, because it is rather unusual to happen in young aged children.

Most people with adult-type hypolactasia can maximally tolerate 12 g of lactose in 240 ml of milk (Bhatnagar & Aggarwal, 2007). Primary lactase deficiency may occur along with an onset of milk intolerance, such as hives, wheezing, vomiting, etc. There was a double-blind experiment in which adults were divided into 2 groups: one group was given 2 glasses of milk per day and another group was given 2 glasses of lactose-hydrolyzed milk per day. After the experiment, both groups had no distinction in lactose intolerant symptoms. However, many dairy products have differences in form or quantity of lactose, leading to different symptoms experienced in anyone with primary lactase deficiency. Thus, there hasn't been a permanent treatment developed (The Committee on Nutrition, 2006).

2. Secondary Lactase Deficiency

Secondary Lactase Deficiency is primarily caused by small bowel mucosal brush border injury as a result of intestinal infection. Other causes include acute gastroenteritis, persistent diarrhea, small intestine overgrowth, and chemotherapy. An Acute intestinal infection, such as rotavirus infection, causes injury in the small bowel due to loss of lactase-containing epithelial cells from villi (The Committee on Nutrition, 2006). However, apart from infections, secondary lactase deficiency also occurs after toxins or medications

(such as olmesartan) intake that affect the proximal small intestine (Szilagyi & Ishayek, 2018). Thus, secondary lactase deficiency can be called an acquired form. The expression of secondary lactase deficiency can be seen in any life stage, but it is more common in children, including infants (The Committee on Nutrition, 2006).

Children, especially in developing countries, often have diarrhea. Diarrhea in secondary lactose intolerant children is more common than primary lactose intolerant children. However, diarrhea sometimes leads them to be dehydrated and affects the child's development (Bhatnagar & Aggarwal, 2007). Although children have some or no dehydration, they can still take human milk that contains 70 g of lactose per liter, or a standard serving level of lactose-containing food that does not affect their health, including the therapy (Szilagyi and Ishayek, 2018; The committee on Nutrition, 2006). Children with secondary lactase deficiency mostly defecate acidic stools that can be examined in stool tests to verify how they are lactose intolerant. As the authors said, lactase deficiency can lead to lactose malabsorption, however, most children with secondary lactase deficiency and acute gastroenteritis do not experience lactose malabsorption (Bhatnagar & Aggarwal, 2007). Lactose malabsorption, resulting from secondary lactase deficiency, can be found in people with celiac disease, Crohn's disease, immune system disease, or other enteropathies at any age (The Committee on Nutrition, 2006).

Malnourished Infants, younger than 3 months, with secondary lactase deficiency and infectious diarrhea can get severely ill. Giardiasis and cryptosporidiosis that infect the proximal small bowel often cause epithelial cell injury leading to lactose malabsorption (The Committee on Nutrition, 2006).

It seems that diarrhea has a profound effect on infants. Nonetheless, malnutrition in children and infants in developing countries can also

contribute to lactose malabsorption and carbohydrate intolerance, but they are still able to consume lactose normally. However, the World Health Organization (WHO) has stated that children with persistent post-infectious diarrhea should avoid consumption of lactose and lactose-containing products (The Committee on Nutrition, 2006).

For the possible treatment of secondary lactase deficiency, individuals should be cured along with their enteropathies or malnutrition first, then they may be able to consume dairy products normally (The Committee on Nutrition, 2006).

3. Congenital Lactase Deficiency

Congenital means being disabled or decadent since birth. Congenital lactase deficiency (CLD) consists of an hereditary autosomal recessive gene. Besides primary lactose intolerance, CLD is one of the major types of lactose intolerance (Wanes et al., 2019). Congenital lactase deficiency is very rare among infants, only a few cases were reported. It would be normal for children with congenital lactase deficiency who were born before the 20th century to not survive due to having none of the lactose-hydrolyzed dairy products (The Committee on Nutrition, 2006). Congenital lactase deficiency is a severe disorder and affects the capacity of lactase-phlorizin hydrolase (LPH) or lactase which results in having less or none of the capacity of lactase in a normal small bowel mucosa; therefore, if not detected in the early stages, newborns will not get treated. This could be fatal or have vicious infancy development effects to the infants because of dehydration, losses of electrolyte, and metabolic acidosis (an increase in plasma acidity) (Bhatnagar & Aggarwal, 2007; The Committee on Nutrition, 2006; Wanes et al., 2019).

The main cause of congenital lactase deficiency is the mutation in the translated region of the LPH gene. The mutations occur in a pattern of inheritance of homozygote or heterozygote and could be a missense

mutation, leading to partial or complete retrenchment of the domain in the LPH gene (Wanes et al., 2019).

The onset of symptoms after breastfeeding occurs in neonates who were born in merely a few days. Besides, they consume sufficient nutrients and do not refuse food, normally having an appetite. They present with (severe) watery diarrhea or intractable diarrhea, and most do not vomit. However, the symptoms are representative of other carbohydrate malabsorption disorders such as congenital sucrase-isomaltase deficiency (The Committee on Nutrition, 2006; Wanes et al., 2019).

Consumption of lactose-free dairy products in people with congenital lactase deficiency seems like the best way to solve this disorder's problem due to the mutation in the LPH gene, genetic variation; hence, there is no permanent solution yet (The Committee on Nutrition, 2006).

4. Developmental Lactase Deficiency

Developmental lactase deficiency, or neonatal lactase deficiency, is similar to congenital lactase deficiency in that it can happen at birth, but it is not deleterious as congenital lactase deficiency. If developmental lactase deficiency is discovered in preterm infants less than 34 weeks gestation, they will lack disaccharidases, including lactase. Although preterm infants consume lactose-containing food, they are able to take them normally with no sign of short- or long-term disorder because their small intestine mucosa promptly develops after birth (Bhatnagar & Aggarwal, 2007). Nevertheless, some studies have reported that some term infants may incompletely develop their potential of lactase activity (Szilagyi & Ishayek, 2018). Typically in newborn or young infants, up to 20% of consumed lactose may pass through the large intestine, which is considered a very small quantity compared to lactose intolerant individuals with other types of lactase deficiency. In young infants, lactose metabolism by colonic bacteria

reduces the stool pH down to 5.0-5.5, which is still normal (the normal pH of stool in infants is 5.0-6.5), can protect potential pathogens (such as *Proteus* sp. *E.coli*, and *Klebsiella* sp.) from leading to infectious or other disorder, and is favorite of the beneficial microorganisms such as *Bifidobacterium* and *Lactobacillus* sp. (The Committee on Nutrition, 2006).

b. Causes

i. Genetics

Congenital lactose intolerance is an extremely rare genetic disorder, caused by both parents passing the recessive, mutated gene to their offspring. Those affected lack lactase since birth. Primary lactose intolerance, a lack of lactase production during adulthood, is a result of polymorphisms in the gene.

1. Cause from genes

The ability of the human body to digest food relies on enzymes as they help break down complex molecules into smaller and easier-to-digest molecules.

Lactase Phlorizin Hydrolase (LPH) is responsible for splitting lactose into glucose and galactose. LPH is produced and secreted by the brush border membrane, located on the epithelium enterocytes of the small intestine.

Even though lactose intolerance seems to be very commonly found, the ability to retain lactase production until adulthood is considered a dominant trait. This would imply lactose intolerance is a recessive trait. Former studies discovered that lactose restriction was caused by the expression of two alleles, LACP and LACR (Flatz, 1987). LACP was a dominant allele for lactase persistence and LACR was the recessive allele. Consequently, people with homozygous LACR allele would have lower lactase levels while those with homozygous or heterozygous LACP allele would have higher lactase levels (Arola & Tamm, 1994).

Further studies discovered another gene associated with lactase persistence: the LCT gene, which encodes instructions for the production of lactase. According to Kruse et al. (1988), the autosomal locus lies on the long arm of chromosome 2 at region 21: 2q21. With a single change of DNA sequence around the LCT gene, one could lose the ability to produce lactase after weaning.

2. Comparison between normal genes and genes with lactose intolerance

So far, individual variation in LCT expression in adults has been independently imputed to a single sequence of DNA in the regulatory region called minichromosome maintenance complex 6 (MCM6), located upstream. A single nucleotide polymorphism (SNP) of the T-allele at position 13910 in intron 13 of the MCM6, was first identified in Europeans (C/T-13910) (Enattah et al., 2002). Individuals who have both C (Cytosine) alleles will not be able to produce lactase during adulthood, a condition called lactase non persistence (LNP) and will see rapidly declined lactase production after weaning. But if there is a single SNP changing the C to a T (Thymine), one will retain the ability to produce lactase (lactase persistence: LP) and is lactose tolerant.

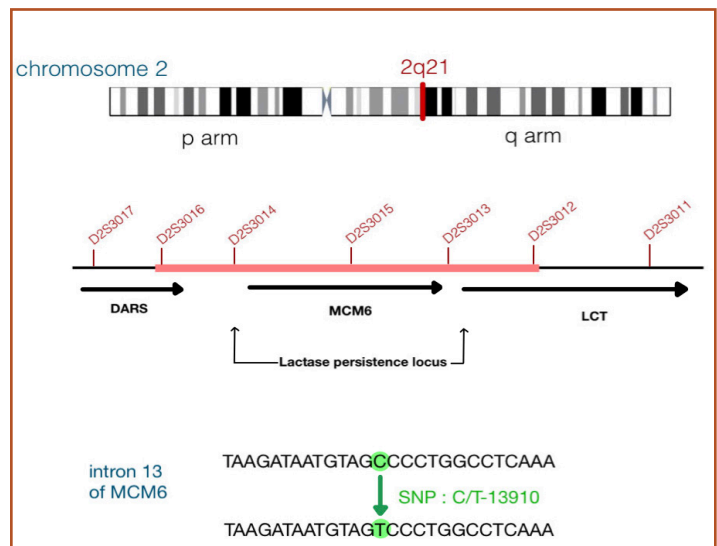


Figure 2. Single Nucleotide Polymorphism C/T-13910

There were previously no genetic reasons for SNP in Africans. However, recent studies conducted with Tanzanians, Kenyans, and Sudanese have identified three SNPs associated with LP including G/C-14010, T/G-13915, and C/G-13907 (Tishkoff et al., 2007). T/G-14009 is also one genetic variant that is widely studied and associated. Besides these widespread and highlighted five SNPs, there are eighteen new SNPs that have been found associated with LP (Anguita-Ruiz et al., 2020). Each variant seems to affect different groups of population. Studies suggest that there could be more factors that cause different LCT expressions rather than SNPs (Labrie et al., 2016).

The frequency of LP is highest in northern European and Scandinavian countries. As it gets more to the right and down the map, a decline is seen across southern European countries and the Middle East. Whereas Asians and African communities have the lowest frequencies of LP (Anguita-Ruiz et al., 2020).

ii. Nutrition

1. Breastfeeding

Mammals are animals within class Mammalia, classified by the presence of mammary glands. Lactose is present in virtually all mammalian milk except sea lions', making it widely known as "milk sugar". Lactose can only be found in milk and the only resource is the mammary glands. Human milk contains 7% or 70 g/L of lactose and that contributes about 30-40% of the energy value.

Shortly after birth and during breastfeeding age, the intestinal brush border can secrete the highest concentration of lactase. At the age of weaning or around 2-3 years old, lactase production diminishes rapidly. The rate becomes stable at a very low level starting at the age of 5. Hypolactasia, a common enzyme deficiency, affects 70% of adults. However, there is no strong evidence that breastfeeding is responsible for the high amount of LNP population

and apart from babies with congenital lactose intolerance, there is no need to halt breastfeeding.

2. Milk Consumption

Milk and other dairy products have been largely consumed by humans since the agricultural revolution. Dietary shifts since then have had big effects on our health and genetics. Milk plays an important role in western dietary and that shows some correlation between culture and consuming habits.

The concentration of lactose in cows' milk, which is the most commonly consumed milk in the world, ranges around 4.28 to 4.6% w/v in different samples (Leal Da Costa, Rossi, and Maldonado, 2013). With lactase deficiency, one is lactose intolerant and will not be able to digest lactose contained in milk. Symptoms after consuming milk such as diarrhea and irritable bowel often make lactose intolerance mismatched with milk allergy.

Studies show that many of those who hold the LNP status consumed milk although they may not be able to digest lactose well (Almon et al., 2013). Furthermore, it is proven that individuals who have primary lactose intolerance can still tolerate 12 g of lactose per day without any symptoms (Bhatnagar & Aggarwal, 2007).

iii. Malabsorption

After being broken down by the LPH enzyme, lactose divides into glucose and galactose. These two monosaccharides are absorbed by intestinal mucosa cells and carried via sodium-glucose transporter to the circulatory system. Malabsorption of glucose and galactose at the region of digestion can lead to bacteria fermentation at colonic flora, followed by undesirable symptoms. Lactose malabsorption may be the consequences of lactase non-persistence or some certain bowel conditions.

However, lactose maldigestion does not always follow lactose intolerance, therefore it may cause confusion in patients-assumed

lactose intolerance. People who believe that they have lactose intolerance without any proof of lactose maldigestion could actually be lactase persistent (Szilagyi & Ishayek, 2018; Usai-satta et al., 2012).

iv. Diseases

Diseases that injure small intestinal mucosa or small intestinal brush border cause lactose intolerance with secondary lactase deficiency. They can affect lactase non-persistence (LNP) and lactase persistence (LP) individuals and have severe symptoms according to their mucosal involvement and genetic predisposition. Lactase non-persistence individuals, who regularly consume dairy products, may not know that they are primary lactose intolerant due lack of symptoms. After getting small intestinal diseases, they can discover lactose maldigestion and realize the condition of primary lactose intolerance (Szilagyi & Ishayek, 2018).

The conditions that affect intestinal diseases include gluten sensitive enteropathy, infection of lymphoma, viral illness such as rotavirus infection in children, malnutrition, radiation exposure, upper gastrointestinal surgery, and some medications such as olmesartan, etc. (Szilagyi & Ishayek, 2018). However, the authors of this study would like to present characteristics of two diseases; gluten sensitive enteropathy and lymphoma infection, which describe some causes and symptoms of lactose intolerance due to these diseases, and others.

1. Gluten sensitive enteropathy

Gluten sensitive enteropathy commonly known as celiac disease (CD) or celiac sprue is an autoimmune inflammatory disease of the small bowel, and one of the gluten-related disorders (such as wheat allergy and non-celiac gluten sensitivity (NCGS)). Recent studies in the United States implied that one person in 250 people will be gluten sensitive enteropathy through blood tests. Susceptible individuals with celiac disease who ingest gluten or a component of wheat, barley, or rye protein, their immune system in the small intestine will respond to gluten.

(Protein actually does not stimulate the immune system of normal people.) The gluten response leads to a reduction or damage of the small intestinal mucosa and nutrient malabsorption, including lactose, which could lead to lactose intolerant effect (UAMS, 2002; Mayo clinic, 2020). The intestinal damage can also trigger other symptoms such as diarrhea and bloating, that are similar to the symptoms of lactose intolerance, anemia, weight loss, fatigue, and other severe disorders (Mayo Clinic, 2020). Gluten sensitive enteropathy normally expresses as a silent type, which has less or no symptoms which are not necessary for treatment by gastroenterologists if they do not express symptoms (UAMS, 2002). Celiac disease in younger patients, including menstruating women and persons younger than 50 years with unexplained iron deficiency should be considered, whereas other diseases, such as microscopic colitis, need to be considered in adult and older patients (Szilagyi & Ishayek, 2018; UAMS, 2002). Pregnancy women with celiac disease can affect newborns who are a few weeks gestation, and intrauterine growth restriction (Rubin & Crowe, 2020).

The normal symptoms in patients with celiac disease are diarrhea, iron deficiency, vitamin, D and calcium malabsorption. They may have steatorrhea, which is rather uncommon but can be discovered in 50% of patients with lactose intolerance. The statistics of iron deficiency anemia patients after upper endoscopy procedure found that 6-10% of patients will have celiac disease. Celiac disease can occur in patients with an unexplained metabolic bone disease or severe osteoporosis, even though there is no sign of gastrointestinal symptoms, and reduced bone density can increase the risk of fractures. Celiac disease patients sometimes could have migraines, depression, behavioral disorders, autism, and other neurologic or psychiatric conditions, but there is no proof that most of those symptoms are caused by gluten sensitive enteropathy (Rubin & Crowe, 2020). Furthermore, they can present with dermatitis herpetiformis,

which leads to itchy and blistering skin disease, in less than 10 percent of adults (UAMS, 2002). It is common to have a rash on elbows, knees, torso, scalp, and buttocks. The condition of dermatitis herpetiformis can change intestinal mucosa, similar to celiac disease, but might not lead to digestive symptoms. However, the dermatologists will treat them with a gluten-free diet (GFD) or medication to help control the rash on their skin (Mayo Clinic, 2020).

As mentioned above, it can be confusing in diagnosis for physicians, because the symptoms are similar to the symptoms of lactose or other carbohydrates intolerance and others; accordingly, the physicians must have expertise in diagnosing and managing gluten sensitive enteropathy. However, there is no treatment for patients with celiac disease, but they still can continually consume a gluten-free diet to control the symptoms and help cure their intestine (UAMS, 2002; Mayo Clinic, 2020).

2. Lymphoma (giardia) infections

Lymphoma is cancer in the lymphatic system and not much is known about its causes. Lymphoma infections lead to the mutation of lymphocytes, the leucocyte, to rapidly increase the amount of lymphocyte, resulting in lymph nodes, spleen, and liver, which is part of the lymphatic system, to swell (Mayo Clinic, 2019). It is more common in adult males. Lymphoma may be caused by the complication of celiac disease and occur in immunodeficiency syndromes (MUSC Health). Infection in lymphoma patients is at high risk, especially in neutropenic patients, caused by lymphoma in bone marrow or chemotherapy is higher at risk of infection due to the less ability of their immune system (Lymphoma Action, 2020). Intestinal lymphoma patients can have intestinal infections which may cause by bacterial infection such as *Salmonella*, protozoal infection such as *Giardia*, or infection with intestinal worms such as hookworm, tapeworm, pinworm, *Strongyloides Stercoralis*, Echinococcosis (MUSC Health). However,

early research reported that *Giardia* infection can also lead to lactose intolerance, which is classified as secondary lactase deficiency (Halliez & Buret, 2013).

Giardia, also known as *Giardia intestinalis* and *Giardia duodenalis*, is a parasite that leads to *Giardia* infection, or giardiasis (Adam, 2001; Delgado, 2018). *Giardia* lives in the bowels and is passed in the stool, and sometimes can live outside the body for weeks or months. This parasite gets into the human body through contaminated food, drinks, or from contact with infected individuals which is common in childcare settings. Furthermore, it can also be transmitted by touching animal waste, including stool, especially in infected pets, or from stool exposure through sexual contact from someone who is infected or recently infected (CDC, 2021). This disease can happen all around the world, particularly in developing countries and undeveloped countries that lack proper sanitary conditions (Delgado, 2018). Giardiasis affects the absorption of nutrients such as fat, lactose, vitamin A, and B12 in the small intestines (CDC, 2021). The most common symptom of giardiasis is diarrhea. Other symptoms are bleeding, bloating, nausea and vomiting, abdominal pain such as stomach cramps, and even features of complete abdominal obstruction (MUSC Health). Giardiasis patients can defecate foul-smelling and greasy and floating stool, and be dehydrated and fatigued. The less severe symptoms of giardiasis include fever, itchy skin, hives, and swelling of the eyes and joints. Giardiasis may cause weight loss in some people. Furthermore, after people have been infected with *Giardia*, the symptoms usually show up in 1-2 weeks and last for 2-6 weeks, but they may last longer in patients with susceptible immune systems. Nevertheless, some people who do not have all these symptoms can be treated by antiparasitic medications to reduce the duration of symptoms (CDC, 2021). Also, some researchers emphasized that after successful treatment in infected patients with secondary lactose intolerance, the expression of giardiasis's

symptoms can last for several weeks (Hanevik et al., 2009).

As the authors mentioned above, gluten sensitive enteropathy and the infection of intestinal lymphoma, or even *Giardia* infection, lead to lactose intolerance and lactose malabsorption. In some individuals, these infections can also lead to other diseases and complications. If they are lactose intolerant which caused by the specimen of the diseases, they should either be cured the source of the cause first, or do not stimulate more intestinal injuries, or reduce their intestinal injuries as much as possible because some conditions cannot be completely healed such as celiac disease, then the symptoms of lactose intolerance and other diseases may also be curable.

c. Diagnosis

Lactose intolerance can be diagnosed in various ways from inquiring medical history to having minor surgery. If patients suspect that they may be lactose intolerant, it is recommended to keep a food diary and the symptoms they experience before meeting the doctor. Keeping a food diary will allow patients to notice patterns of certain foods that they may be extremely sensitive to. Doctors will then closely examine patients' symptoms and prevent the patients from eating lactose products for 2 weeks to relieve the symptoms. Then the doctor will reintroduce those products again to see whether this patient is lactose intolerant or not (NHS, 2009).

Further testing may be required to confirm the diagnosis or find out what causes the patient to be lactose intolerant. There are 4 main tests that patients can take if needed

i. Hydrogen Breath Test

This breath test analyses the hydrogen of your breath to see if your body can digest and absorb lactose products. This test is commonly used in children.

After one night free of dairy products, the doctor will ask you to blow up a balloon and measure the amount of hydrogen present in scale part per million (ppm) as a control sample. Then, you will be asked to drink 50 g

of lactose solution and blow up a balloon every 15 minutes for 2-4 hours to record the amount of hydrogen.

If the result shows that the hydrogen in your breath is above 20ppm, it means that you are lactose intolerant since your body cannot digest and absorb lactose.

To avoid inaccurate results, certain preparations must be made. You must stop taking antibiotics and bowel prep 4 weeks before the test, Pepto-Bismol 2 weeks before the test, and laxatives and motility medication 1 week prior to the test 2 days. Before the test, you must have low carbohydrate and dairy diets. Smoking and vaping are not allowed at least 24 hours before the test and eating are not allowed 8 hours before the test. On the test day, you should not drink, eat (including candies and gum), or smoke until the test is done. No sleep or exercise for at least 1 hour before the test.

ii. Lactose Intolerance Test

This blood test is done to see if the patient's body can break down lactose. When eating lactose, the lactase in his stomach normally breaks down the lactose into two sugars: glucose and galactose, resulting in a higher blood glucose level in approximately 2 hours after eating. If the glucose levels do not rise after eating lactose, there is a high possibility that the person is lactose intolerant.

The lactose intolerance test measures the increase of blood glucose level after drinking 50 g of lactose diluted in 200 mL of water or 500 mL of milk. A total of 4 blood samples will be drawn; one will be done before drinking lactose, and the others will be drawn at 30 minutes, 1 hour, and 2 hours intervals after drinking the lactose.

Results from this test vary depending on the patient's medical history, age, and gender. Generally, if the patient's glucose level is higher than 20 mg/dL after drinking the lactose, he is not lactose intolerant as your body can still absorb it. If glucose levels do not increase after drinking the lactose, the patient may be lactose intolerant or have problems with absorbing lactose.

iii. Stool examination

This test is another common test for kids and infants. There are two common ways for testing fecal/stool: acidity and reducing substances.

Patients need to collect 5 mg of stool and directly send it to the laboratory within an hour for an accurate result since lactose can be broken down by chemicals. Researchers will examine your stool by 2 factors: the amount of reducing substance and pH.

For healthy people, sugar is normally absorbed in the small intestine, but for people who have lactose intolerance, with lactase enzyme deficiency, the unabsorbed sugar will be called reducing substances (glucose, fructose, lactose, galactose, and pentose). The reducing substances are fermented by the bacteria to produce Lactic acid (measure pH), methane gas, and protons (H⁺).

Benedict's solution will be used to determine the reducing substance. First, the researcher will mix 2 volumes of water with 1 volume of stool, and transfer 15 drops of the mixture into a test tube along with a Clinitest tablet that contains anhydrous cupric sulfate, sodium hydroxide, citric acid, and sodium bicarbonate.

Lactose intolerance results in more than 0.5 g/dL.

For infants, pediatricians will recommend a stool acidity test. If stool pH is under 6.0, it's likely that they lack lactase enzymes.

iv. Genetic test

Lactose intolerance is the result of a genetic mutation believed to have emerged approximately 10,000 years ago as dairy products became more common in our diet.

Originally, most people are lactose intolerant because they have no lactase enzyme. People who have a genetic mutation called a single nucleotide polymorphism where a cytosine (C) nucleotide is replaced with a thymine (T) nucleotide, which allows them to digest milk. This test requires only about

5 ml of your blood which will be amplified by using polymerase chain reaction (PCR). The restriction enzymes then cut the amplified DNA into fragments, which will then be separated by Gel electrophoresis.

The pattern of the DNA fragments indicates whether a person is lactose intolerant (C/C) or not (C/T, T/T) (Learning Hub – Pokapū Akoranga Pūtaiao, 2009).

3. Age Prevalence

a. Infants

When infants begin to consume breast milk or formula, they show some symptoms such as watery diarrhea and stomach pain. Consequently, they will be presumed to have lactose malabsorption. There are two main classes of lactose intolerance in infants. Congenital lactase deficiency, also called alactasia, is a life-threatening autosomal recessive illness of newborn infants. However, it is a rare disease commonly found in Finland and Western Russia. This disease is inherited from one of the parents. Since the mutation of the LCT gene occurred, infants with this disorder will bear without or with an undersupply of enzymes used for digesting the sources in milk. Alactasia can be diagnosed immediately after birth, and in these decades, this sickness has not been entirely treated yet (Heine et al., 2017). Breast milk can cause dehydration and electrolyte imbalance in infected infants' intestines; hence it is not given. These infants are required to have a unique lactose-free formula and supplements that include enough intake of calcium and vitamin D. Without enough calcium and vitamin D, the risk of getting bone fractures, osteoporosis, and growth problems will be enhanced (Heyman, 2006). In the other case of lactose intolerance in infants, developmental lactase deficiency is a temporary intolerance condition in infants that occurs before their guts are fully developed. Although this type of lactose intolerance is non-permanent, the gastrointestinal tract and lining of the small intestine can be affected and damaged by the most common organisms called Rotavirus and Giardia. This illness will be recovered by itself in a few weeks or months. Also, in this occurrence, continuing breastfeeding helps boost the infants' immune system and restore their intestines (Marsha, 2012).

b. Adults

i. Normal

According to The National Institute of Health, "65 percent of the global population has reduced ability to digest lactose after infancy", as humans get older, as well as getting infected in the gastrointestinal, the level of enzyme used to digest lactose shrinks which leads to excess gas and fluid.

In this century, there are many ways to diagnose lactose intolerance in an adult based on different detection; characterized by either gene mutation since birth or malabsorption caused by any lesion. However, the primary self-reported way to detect is to monitor particular symptoms such as bloating, cramps, and diarrhea after consuming dairy products. Still, breath and blood tests are more reliable when compared to self-diagnosis. The severity can be categorized into two degrees; those who can consume a limited quantity of dairy products and those who totally can not at all. In the first instance, plenty of research done by different researchers concluded that the symptoms of lactose intolerance, based on diverse generation and sex, seemed to be similar, except for patients who were considered as LND. More crucially, body weight seems to affect the amount of lactose that patients can consume without showing any symptoms. Therefore, the restricted amount of lactose, proportional to body weight, has the potential to be ingested without any signs (Lapides, 2018). On top of that, lactose-free products, low lactose products, and other alternatives may be solutions for this degree. But for the second degree, in the absence of dairy products, counseling with a doctor for extra calcium and vitamin D supplements is essential. While calcium supplements are requisite to lessening the risk of getting bone fractures and growth issues, vitamin D supplements are also prescribed for adjusting the calcium and phosphate in the blood. As evidence from conducted research states that, "since the primary source of vitamin D comes from dairy products, patients who genetically encounter lactose intolerance have a propensity in vitamin D deficiency." (Das, 2017)

Subsequently, as the patients continue lactose-free or lactose-restricted diets to avoid any further insecure symptoms, some following prolonged effects might arise. The concentration of probiotic bifidobacteria, bacteria that help protect the infractions in the gut and another intestinal inflammatory, is considerably reduced after four weeks of the restricted FODMAP diet. FODMAP is a group of carbs that will cause unpleasant digestive responses. In consideration of the quality of living, food restrictions may enhance the possibility of malnutrition. Also, limited choices in diet, gluten-free and lactose-free, can be strenuous, expensive, and pressured (Deng et al., 2015).

Meanwhile, current studies have shown that "isolated" lactose intolerance patients can ingest dairy products without any bother by lactase enzyme replacement. *Kluyveromyces lactis*, one kind of yeast used in crossover genetic studies, can break down lactose and galactose without further concomitant. Additionally, milk that contains *Lactobacillus acidophilus*, a positive type of bacteria that lives inside the intestines, can be another solution for lactose intolerance. Accordingly, adults with lactose intolerance, either since birth or develop afterward, along with advice from doctors, will have opportunities to eat dairy products (Deng et al., 2015).

ii. Pregnant woman

During pregnancy, particularly during the first couple of months, a massive amount of calcium is needed for infants' skeletal growth as they are still in the mothers' womb. In the circumstance of lacking calcium, the infants tend to pull out calcium from their mothers' bones which tend to increase the risk of getting osteoporosis in mothers. The researchers suggest that about 3-5% of the bone mass will be lost because of lessening in the production of hormones called estrogen that is used to protect our bones. As a result, the bones will regain their strength after the baby's delivery and breastfeeding. Simultaneously, pregnant women have the potential to absorb more calcium than those who do not. The Institute of Medicine states 1,000 mg of calcium is needed a day during

pregnancy and 1,300 mg for pregnant teens for both the mother and child's needs (NIH, 2018).

Calcium is significant for a developing baby to form healthy bones and teeth. Thus, lactose intolerant mothers need to find substitutes instead; lactose-free diets came into action. Examples of calcium-rich foods include vegetables like broccoli and spinach, nuts such as almonds and chickpeas, and some patients might be able to consume yogurt and fermented products because the amount of lactose in yogurt is digested by the bacteria living inside it. Therefore, some might be able to handle it without soreness (Katherine, 2020).

Doctors or dietitians may require some pregnant women to take calcium supplements in order to reach the recommended pregnancy calcium intake. Calcium carbonate and calcium citrate are two types of calcium supplements that are familiar. Michelle Collins suggested that "Calcium citrate is much more absorbable and doesn't cause constipation, so it tends to work better for pregnant women." Nevertheless, each person shall decide along with the advice of doctors. Lactase enzyme supplement is also one of the supplements that are commonly used among pregnant women, but it works a bit differently. Lactase enzyme supplement allows the body to digest lactose, and it is allowed to be brought without any prescription (Fink, 2014). Vitamin D is also necessary for absorbing calcium during the second half of pregnancy. Thus, vitamin D supplementation also is required along with other supplements. Yet, more importantly, if expectant women are taking supplements, excessive calcium needs to be in consideration because of the following consequences: kidney stones, abnormal heart rate, and constipation. Counseling with doctors, on what vitamins and quantity of them need to take, is very necessitated.

In spite of that, in some cases especially during later pregnancy, the capacity to digest lactose will be improved (Katherine, 2020). As a consequence, pregnant women need to track their symptoms carefully so as to achieve healthy bones in both mothers and infants.

4. Lactose intolerance in Asians

Lactose Intolerance affects nine out of ten people in South East Asia, which is three times more than other ethnic populations. Many factors could explain this circumstance.

During the early age, humans could digest milk properly. Most children have a specific enzyme in their intestines that allows them to digest milk produced by their mothers through breastfeeding and start to experience a drastic decrease in the amount of this enzyme, often beginning after the age of five. Asian countries are near the equator, Asians benefit from a continuous year of sunlight.

As a result, sunlight provides an essential element in vitamin D production. Vitamin D is highly vital to the absorption of calcium that humans rely on. Therefore, Asians can get a higher level of vitamin D than other races, So there is no need for Asians to develop the need for calcium intake from other alternatives such as milk and other dairy products. Another factor is that Asians have a different kind of diet than many European countries. There are various kinds of Asian diets across Asia that mainly focus on eating vegetables, fruits, nuts, seeds, legumes, and whole grains daily.

Many European countries have developed a better genetic makeup for tolerating lactose from the cultivation of dairy products through agriculture, resulting in having greater resilience to the lactose in dairy over the centuries. Moreover, the best method to prevent lactose intolerance symptoms is to avoid dairy products. The most common dairy products are yogurt, butter, and cheese (National Health Service, 2019). However, consuming dairy products is still safe when consumed in the proper amount.

Since the majority of Asian people suffer from lactose intolerance, there has been an increasing demand for lactose-free products in Asia. As a result, more and more lactose-free products are beginning to pop up in many convenience stores. Ultimately, lactose-free products have become a staple of the Asian diet.

5. Mistaken Beliefs

Milk and dairy products play an important role in our diet. They provide essential nutrients that cannot be found in dairy-free products; thus, the World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO) recommends

daily consumption of dairy-containing foods. Nevertheless, there are some beliefs related to LI and dairy products that have been mistaken; for example, people who suffer from lactose intolerance should not consume dairy products, you need to drink milk or eat dairy products to get enough calcium in your diet, simple way to diagnose yourself with lactose intolerance is based on the symptoms that show up after the consumption of milk or dairy foods. These misguided beliefs need to be dispelled to help people be aware of their decisions (Zaitlin & Gleason, 2013).

“Individuals who suffer from lactose intolerance should not consume milk or other dairy products.”

This statement is, in fact, incorrect. If a person is lactose intolerant, it isn't necessary to restrict dairy products from their diet. According to the American Academy of Pediatrics (AAP), not every lactose-intolerant patient needs to avoid all foods containing lactose. Even people with lactose intolerance may be able to eat small amounts of dairy products. It depends on how much lactose one can tolerate before having any symptoms. Therefore, the better solution is to go see a physician before cutting any dairy product out of your diet (Rosario, 2020). It also depends on what forms of lactase deficiency the patient is. If the patient has congenital lactase deficiency, there is currently no treatment available. In this case, the only thing he can do is to abstain from any dairy products as possible (Zaitlin & Gleason, 2013).

“To get enough calcium in your diet, you must drink milk or eat other dairy products.”

Calcium is one of the essential minerals that our bodies require. We cannot produce calcium by ourselves, we need to gain it from digesting the food that we eat. The recommended dietary allowance for calcium is 1,000 - 1,200 mg. Some people believe that dairy products are the only source of calcium, which is wrong. According to the National Health Service (NHS), sources of calcium include dairy foods, green leafy vegetables, bread, fish where you eat the bones, etc. (NHS, 2020). Consequently, if an individual is lactose intolerant, he can still meet his calcium needs by eating vegetable-based foods. However, people who suffer from lactose intolerance are more likely to have calcium deficiency than others. Studies have shown that teenage girls, particularly athletes, people with lactose intolerant or dairy allergy, and the older should observe their calcium levels more carefully (Mayo Clinic, 2019).

“Simple way to diagnose yourself with lactose intolerance is based on the symptoms that show up after the consumption of milk or dairy foods.”

There are many ways to diagnose lactose intolerance. The hydrogen breath test is one of them. This test is performed by blowing up a bag, then the doctor will take a breath sample to measure how much hydrogen is present. If the breath contains more than 20 ppm of hydrogen, there is a chance of this patient having lactose intolerance. Another way of testing LI is to take the blood sample. First, the suspicious patient will be given a drink of lactose solution. After that, his blood will be taken, and the doctor will find out how much blood sugar it contains. In case he is LI, his blood sugar will either slowly rise or not rise at all (NHS, 2019). There is no simple way to self-diagnose yourself with LI because the symptoms may be caused by bacterial infection, and in this case, avoidance of dairy products may not help. Moreover, it can cause a lack of proper nutrition which your body needs (Zaitlin & Gleason, 2013).

“Lactose intolerance and cows' milk allergy (CMA) are the same thing.”

There is some misunderstanding between LI and CMA. They are quite different from each other in terms of causes and treatments. Lactose intolerance is a digestive disorder which is caused by lactose malabsorption, resulting in unpleasant symptoms such as diarrhea, stomach cramps and bloating (NHS, 2019). LI is one of the most common forms of intolerance in food. It appears whenever lactase activity is diminished in the brush border of the small bowel mucosa. On the other hand, cows' milk allergy is an immune system response to the protein in milk and other products containing milk resulting in swelling of the face, headaches, vomiting, diarrhea or constipation. Another thing that distinguishes LI and CMA is that CMA is usually detected during the time you were an infant, but only rare cases of LI are diagnosed during early infancy.

6. Current treatment of lactose intolerance

Lactose digestion capability in over 60% of people is diminishing. Most people with lactose intolerance can directly consume 12 g of lactose and 18 g with other foods without any LI symptoms (Misselwitz et al., 2013). During these days, there are several alternative treatments to encourage lactose digestion. The following information pertains to these methods.

a. Substitutes

Currently, an observational study reported that patients with LI are no longer recommended to avoid dairy products. Furthermore, people with LI should be supported to limit the lactose consumption amount to contain the nutrients and ascend the absorption (Szilagyi & Ishayek, 2018). Therefore, lactose-free and lactose-reduced products are compensated for these conditions.

Plant-based milk substitutes have become more ubiquitous in people with LI and also in some countries where animal milk is costly. Plant-based substitutes are produced by extraction of plant substances in water, segregation fluid and forming. These make them similar to cows' milk features. Nevertheless, some of them lack protein and calcium. Therefore, it is essential to consider product selection for a durable solution (Mäkinen et al., 2016).

Selecting smaller servings less than 4 ounces per time. The smaller amount likely causes fewer gastrointestinal issues. Consuming dairy products with other foods delays the digestive system and may reduce LI symptoms (Mayo clinic, 2020).

Most people with LI can consume low-fat milk products, for example, skimmed milk without LI symptoms. Moreover, it is plausible to ascend dairy products tolerance with careful adding in daily diet. Testing different types of dairy products and choosing the suitable ones also avoid LI circumstances (Mayo clinic, 2020).

b. Enzyme supplement

Yeasts and fungi can produce microbial exogenous lactase (β -galactosidase), which can be used in Enzyme-replacement therapy to improve variability not only in lactose digestion (reduce hydrogen production) but also symptoms. Meanwhile, the enzymes from different microorganisms have different effectiveness in reducing lactose, the comparative studies have shown lactase obtained from *K. lactis* are hydrolyzing lactose better than *A. niger* (Montalto et al., 2006).

Since there are several forms of enzyme supplementations, such as gels, liquids, capsules and tablets, that can be applied in different situations (Szilagyi & Ishayek, 2018). Adding liquid form enzymes into milk and waiting

some hours before consumption will help reduce lactose content and turn the milk into "preincubated milk" (low-lactose milk). Several studies show that solid lactase in the form of capsules and tablets are high-priced and less effective compared to pre-hydrolyzed milk. Those are commercially available and recommended to be used for solid dairy products (Montalto et al., 2006). Glucose and galactose are sweeter than sugar, causing the treated food to be more sweet (Misselwitz et al., 2013).

c. Probiotics and Yogurt

Lactic acid-producing bacteria are qualified as probiotics (Szilagyi & Ishayek, 2018). Probiotics are living microorganisms which supplement the gastrointestinal flora (Oak & Jha, 2019). They grant the health profits if administering is adequate. Probiotics have potential benefits in increasing immune response, reducing the infection and encouraging lactose digestion. As lactic acid-producing bacteria have β -galactosidase at their cell membranes, they can alleviate LI symptoms. Probiotics are commonly found in fermented milk and dairy products, such as yogurt, kefir, leben, and others and as supplements in capsule form (Mayo clinic, 2020).

Yogurt is one of the products obtained by dairy fermentation. Additionally, yogurt has two species of lactic acid bacteria, which are *Lactobacillus bulgaricus* and *Streptococcus thermophilus*. It is reckoned that fermentation dwindles lactose proportion around 25-50% (Montalto et al., 2006). These bacteria have β -galactosidase to hydrolyze lactose and reduce the pH of yogurt. Moreover, yogurt delays gastric forwarding and intestinal transit to escalate the ability of β -galactosidase and reduce the lactose absorption load. This leads to less lactose-induced osmotic forces which contribute to having less gas and abdominal pain (Szilagyi & Ishayek, 2018).

On the other hand, in non-fermented dairy products, the measuring H^2 excretion comparison of two β -galactosidase bacteria, *L. bulgaricus* and *Lactobacillus acidophilus*, found that *L. bulgaricus* is a better alternative for producing non-fermented milk products because the cell wall membrane *L. bulgaricus* structures are less strong than *L. acidophilus*, therefore they have more potentiality to release the enzyme (Montalto et al., 2006).

Lastly, probiotics are assumed as a safe solution and may be used if other methods are ineffective (Mayo clinic, 2020).

However, many clinical studies reported that the treatments can improve a small number of patients with LI symptoms. Lack of improvement can be related to bowel disorders or IBS. These patients are intolerant of numerous nutrients, not only lactose. Additionally, all of the means above only alleviate the severity of symptoms, not absolutely cure of this disorder (Misselwitz et al., 2013).

7. Possible Permanent Solution for Lactose Intolerance

Currently, there is no permanent treatment for individuals who suffer from lactose intolerance as scientists are unable to find any ways to make the body produce more lactase. Although there is a high demand for a permanent treatment, there are several reasons why it is very likely to be impossible to establish the treatment. Nevertheless, there are potential permanent treatments for lactose intolerance which are involved with genetics.

a. A Potential Permanent Treatment for Lactose Intolerance Tested on an Individual

Even though there seems to be no potential cure for lactose intolerance, a treatment developed by Matthew J. (TheChemlife, 2018). Researchers make curing lactose intolerance become promising (during et al., 1998).

The method of gene therapy is used in the experiment in order to increase intestinal lactase activity among individuals with lactase deficiency. A viral vector, taken orally, called adeno-associated virus (AAV) is experimented as it possesses three main factors, which potentially lead to the success of the research. Firstly, AAV is incapable of recombining and expressing viral genes. In the AAV vector, there are only 145-base-pair repetitions of terminals as the rest of the coding is taken away. As a result, the AAV cannot cause disease, and unlike other earlier adenoviral vectors, it results in such minimal immunological responses. Secondly, the AAV is hard, which enables it to move through the digestive tract, because it can resist extreme temperature, pH levels, and solvents. In addition, the AAV can be generally found in the secretions of the respiratory and gastrointestinal tract. Finally, AAV vectors are capable of generating

gene expression in the brain's differentiated cells in the long run.

The viral vector, adeno-associated virus, is applied to rats with lactose intolerance. A week after, this set of rats is fed with lactose-only diets, and they are compared to another set of rats that are not given the AAV. Interestingly, the result shows that rats that receive AAV have increased blood glucose levels, which means that lactase enzyme is generated, and it can be used as calories.

According to the research, lactose intolerance treatment seems possible. Therefore, a Floridian scientist, Justin Atkin, took a risk to biohack himself by using the adeno-associated virus (Grossman, 2018). One benefit of the AAV is that the DNA that is packed inside of the virus regularly merges with humans' DNA at specific locations. Therefore, it can be absorbed by the human body, and allow changes in genetics. Atkin decided to mix the virus with a low amount of microcrystalline cellulose, and packed the substance into the gel caps to create pills. After Atkin's virus intake, he waited for three days to let the virus be delivered into the DNA, and let his body produce lactase. To test the effectiveness of the pill, Atkin ate milky and cheesy pizzas. He observed himself one week, one night, two days, and two weeks after the gene therapy and his consumption of lactose; however, none of his usual sick symptoms appeared.

Atkin followed up his body changes after the experiment on himself. He found out that the lactase pills took a very long time to wear off. From his observation, it took about a year until the effectiveness of the pill started to fade, and it had been a total of eighteen months before he had to retake the lactase pills.

Although the population size of the experiment is still $n=1$, it is a groundbreaking experiment on lactose intolerance permanent solution in human species (TheChemlife, 2018). Hence in the future, lactase pills that are safer and last longer may be mass-produced, even though it would take a long time for in-depth research and trials.

b. The danger in Genetic Treatment

Referring to the experiment, the human body could only produce more lactase when genes are edited or re-organized. When genes are decoded

in a particular way, they control the body and function in the way they are coded. However, it is difficult and dangerous to proceed with the treatment that engages in gene editing or therapy.

In the modern era, the advancement of technology has contributed to the discovery of CRISPR-Cas9. It is the method of gene editing and allows scientists to edit as well as alter DNA sequences. Therefore, it is possible nowadays to cure genetic diseases including cystic fibrosis, hemophilia, and sickle cell disease. The process of CRISPR-Cas9 has several steps. Firstly, scientists must create a small piece of RNA that includes a short “guide” sequence which can bind with a targeted DNA genome. Cas9 is also attached to the RNA. Then, they were transferred to the specific target area and cut to that location. After that, the DNA sequence is replaced by the new customized DNA. In some cases, they were not replaced as the objective of the cut is just to delete a certain sequence (MedlinePlus, 2020).

Lactose intolerance is also a form of genetic disorders that humans can obtain as soon as they are born and it can develop throughout the age. Apparently, it might sound plausible to cure lactose intolerance with the method of CRISPR-Cas 9, yet there are obstacles to this. As mentioned in section 2, the location where the genes that are responsible for lactase production are located in many locations, making it difficult to determine where the genes for lactase production are. As a result, it might not be possible to cure lactose intolerance with CRISPR-Cas9.

Moreover, the method has raised ethical concerns among healthcare providers as it can detrimentally affect the health if there is a mistake while providing the treatment. One of the potential risks is that the body might function in the wrong way due to the off-target genome editing effects. In addition, scientists are still unable to find a way to undo once the method has been proceeded (Baltimore et al., 2015).

Next Steps

Experiment on how lactase chemically works in the human body would allow researchers to understand the mechanism of lactase and be able to develop a

permanent solution. This can be done by testing how change in temperature affects the activity of lactase. The method includes using different test tubes with different amounts of lactose drop but the same amount of lactose product. Then, place them in a location with different temperatures. After that, when lactase has broken down lactose, glucose and galactose should appear; therefore, glucose test stripes can be used to test this. From the experiment, the concept of chemical reaction speed that was affected by the levels of the enzyme could improve the researcher’s understanding of the idea of lactose intolerance (Cooper, n.d.).

According to the potential permanent solutions, most of the solutions are related to genetics. All of the permanent solutions are associated with editing the genes in different ways. Interestingly, it is now possible for high school students to access CRISPR in a Box Educational Toolkit in a science class. In St. Georges Technical High School, the United States of America will be the first school to experience this innovation. “This toolkit will provide STEM students with a visual understanding of how the exciting CRISPR technology can unlock medical treatments to improve lives,” said Siobhan Hawthorne, Education and Community Outreach leader at ChristianaCare’s Gene Editing Institute (Schmitt, & Demarest, 2021).

Another experiment that can be done in order to strengthen the researchers’ understanding about lactose intolerance is the “Milk: How Sweet Is It?” experiment. This experiment simulates determining blood glucose levels by mixing artificial intestinal fluid samples, which are made of water or a lactase solution, with milk. Afterwards, the glucose levels produced over time will be identified. To begin the experiment, there are four steps to follow.

1. Prepare for the equipment including plastic medicine cups, permanent marker, glucose reagent test strips, glucose color chart, stirring rods, graduated cylinder, timer, paper towels, large and small beakers, funnel, a box of lactase capsules, coffee filter, mortar and pestle, and tap water.
2. Set up six medicine cups by using the rinsed graduated cylinder and label them.
 - a. Patient 1: Prepare 5 mL of intestinal fluid.
 - b. Patient 2: Prepare 5 mL of intestinal fluid.
 - c. Patient 3: Prepare 5 mL of intestinal fluid.
 - d. Patient 4: Prepare 5 mL of intestinal fluid.

- e. Negative Control: Prepare 5 mL of water.
- f. Positive Control: Prepare 5 mL of lactase solution.

Set up another six medicine cups, which are contained with 5 mL milk, which can be either skim, low fat, or whole milk, and label them.

3. Test the baseline glucose levels in each cup by using the glucose test strips. The procedures are as follows.
 - a. In the Patient 1 cup, dip the test area of the strip in and take it out as soon as possible.
 - b. Put the strip down and label 0 min.
 - c. Wait for 30 seconds.
 - d. View the glucose color chart, and match it to the color of the test area. However, it must be remembered that colors may change through time, so the data must be recorded no longer than 30 seconds after the strip is drawn out from the medicine cup.
 - e. Repeat the steps for the rest of the cups.
4. For each cup, follow these steps.
 - a. Pour 5 mL milk into the first cup and stir slowly.
 - b. Start the timer.
 - c. At 2 minutes, dip the glucose test strip, take it out, wait 30 seconds, and determine the glucose concentration by using the strip to compare to the Lactase Data Table.
 - d. Do c) again when it is 7 minutes.
 - e. Repeat the steps for other cups.

By doing this activity, lactose tolerance is observed, and researchers will be able to distinguish between samples that have and do not have lactase enzymes. Therefore, researchers will potentially have a better understanding of lactose production over the timer and its concentration in dairy products (Biointeractive, 2011)

Author Contributions

Members in our group searched for the information and related research on their own topics as follows: S.J.:

General Information About Lactose; C.U.: Symptoms; N.L. and C.U.: Causes; C.U.: Diagnosis; N.N.: Age Prevalence; S.A.: Lactose Intolerance in Asians; N.T.: Mistaken Beliefs; N.W. and S.M.: Current treatments; and T.T. and J.R.: Possible permanent solution.

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References

- Adam, R. D. (2001). Biology of *Giardia lamblia*. *Clinical Microbiology Reviews*, 14(3), 447-475. <https://doi.org/10.1128/CMR.14.3.447-475.2001>
- Adams, A. (2020, August 31). *The Facts on Lactose and Milk Sugar*. The Spruce Eats. <https://www.thespruceeats.com/what-is-lactose-1000969>
- Almon, R., Sjöström, M., & Nilsson, T. K. (2013). Lactase non-persistence as a determinant of milk avoidance and calcium intake in children and adolescents. *Journal of Nutritional Science*, 2. <https://doi.org/10.1017/jns.2013.11>
- Anguita-Ruiz, A., Aguilera, C. M., & Gil, Á. (2020). Genetics of lactose intolerance: An updated review and online interactive world maps of phenotype and genotype frequencies. *Nutrients*, 12(9), 2689. <https://doi.org/10.3390/nu12092689>
- Arola, H., & Tamm, A. (1994). Metabolism of lactose in the human body. *Scandinavian Journal of Gastroenterology*, 29(sup202), 21-25. <https://doi.org/10.3109/00365529409091741>
- Baltimore, D., Berg, P., Botchan, M., Carroll, D., Charo, R. A., Church, G., Corn. J.E., Doudna. J., Fenner. M., Greely.H, Jinek. M., Martin. G. S., Penhoet. E., Puck. J., Sternberg. S. H., Weissman. J.S., & Yamamoto, K. R. (2015). A prudent path forward for genomic engineering and germline gene modification. *Science*, 348(6230), 36-38. <https://doi.org/10.1126/science.aab1028>
- Bhatnagar, S., & Aggarwal, R. (2007). Lactose intolerance. *BMJ* 334 1331. <https://doi.org/10.1136/bmj.39252.524375.80>

- Cooper, A. (2015, May 6). *Lab Activity: Milk Makes Me Sick Investigation (Part 2 of 2)*. BetterLesson. <https://betterlesson.com/lesson/632917/lab-activity-milk-makes-me-sick-investigation-part-2-of-2>
- Daisy. (2019, December 24). *Eating habits in Asia are weird " Foodtalk "*. All day every Daisy. <https://www.alldayeverydaisy.com/foodtalk-en/weirdest-eating-habits-in-asia/?lang=en>.
- Das, S. (2017, May 18). *Lactose intolerance can cause slow bone growth: All due to vitamin D deficiency*. The Science Times. *Can Cause Slow Bone Growth: All Due to* <http://www.sciencetimes.com/articles/15426/20170518/lactose-intolerance-cause-slow-bone-growth-due-vitamin-d-deficiency.htm>.
- da Costa, S. L., Rossi, N. P., & Maldonado, R. R. (2013). Evaluation of lactose in milk and dairy products. *International Journal for Innovation Education and Research*, 1(4).
- Delgado, A. (2018, September 17). *Giardiasis: Causes, symptoms, and treatment*. Healthline. <https://www.healthline.com/health/giardiasis>.
- Deng, Y., Misselwitz, B., Dai, N., & Fox, M. (2015). Lactose intolerance in adults: Biological mechanism and dietary management. *Nutrients*, 7(9), 8020-8035.
- De Vrese, M., & Schrezenmeir, A. J. (2008). Probiotics, prebiotics, and synbiotics. *Food biotechnology*, 1-66. https://doi.org/10.1007/10_2008_097 <https://doi.org/10.3390/nu7095380>
- Di Costanzo, M., & Canani, R. B. (2018). Lactose intolerance: Common misunderstandings. *Annals of Nutrition and Metabolism*, 73(4), 30-37. <https://doi.org/10.1159/000493669>
- During, M. J., Xu, R., Young, D., Kaplitt, M. G., Sherwin, R. S., & Leone, P. (1998). Peroral gene therapy of lactose intolerance using an adeno-associated virus vector. *Nature Medicine*, 4(10), 1131-1135. <https://doi.org/10.1038/2625>
- Enattah, N. S., Sahi, T., Savilahti, E., Terwilliger, J. D., Peltonen, L., & Järvelä, I. (2002). Identification of a variant associated with adult-type hypolactasia. *Nature genetics*, 30(2), 233-237. <https://doi.org/10.1038/ng826>
- Fink, J. L. W. (2014, August 19). *Lactose intolerance during pregnancy: How can you get enough calcium when you can't have dairy? Here's how to handle being*
- lactose intolerant during pregnancy*. theBump. <https://www.thebump.com/a/lactose-intolerance-during-pregnancy>
- Flatz, G. (1987). Genetics of lactose digestion in humans. In H. Harry and H. Kurt (Eds.) *Advances in human genetics*, 1-77. Springer. <https://doi.org/10.1007/978-1-4757>
- Forsgård, R. A. (2019). Lactose digestion in humans: Intestinal lactase appears to be constitutive whereas the colonic microbiome is adaptable. *The American journal of clinical nutrition*, 110(2), 273-279. <https://doi.org/10.1093/ajcn/nqz104>
- Gantz, V. M., & Bier, E. (2015). The mutagenic chain reaction: a method for converting heterozygous to homozygous mutations. *Science*, 348(6233), 442-444. <https://doi.org/10.1126/science.aaa5945>
- Ghoshal, U. C. (2011). How to interpret hydrogen breath tests. *Journal of Neurogastroenterology and Motility*, 17(3), 312. <https://doi.org/10.5056/jnm.2011.17.3.312>
- Grossman, D. (2018, February 14). *Scientist Painstakingly Documents His Own DIY Gene Therapy*. Popular Mechanics. <https://www.popularmechanics.com/science/health/a17804128/scientist-painstakingly-documents-his-own-diy-gene-therapy/>.
- Halliez, M. C., & Buret, A. G. (2013). Extra-intestinal and long term consequences of Giardia duodenalis infections. *World Journal of Gastroenterology: WJG*, 19(47), 8974. <https://dx.doi.org/10.3748/wjg.v19.i47.8974>
- Hanevik, K., Dizdar, V., Langeland, N., & Hausken, T. (2009). Development of functional gastrointestinal disorders after Giardia lamblia infection. *BMC gastroenterology*, 9(1), 1-5. <https://doi.org/10.1186/1471-230X-9-27>
- Heine, R. G., AlRefaee, F., Bachina, P., De Leon, J. C., Geng, L., Gong, S., Madrazo, J. A., Ngamphaiboon, J., Ong, C., & Rogacion, J. M. (2017). Lactose intolerance and gastrointestinal cow's milk allergy in infants and children—common misconceptions revisited. *World Allergy Organization Journal*, 10(1), 1-8. <https://doi.org/10.1186/s40413-017-0173-0>
- Heyman, M. B. (2006). Lactose intolerance in infants, children, and adolescents. *Pediatrics*, 118(3), 1279-1286. <https://doi.org/10.1542/peds.2006-1721>
- Katherine Zeratsky, R. D. (2020, June 9). *Pregnancy and lactose intolerance: How do you get enough calcium?*

- Mayo Clinic. <http://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/expert-answers/pregnancy-and-lactose-intolerance/faq-20119824>.
- Kruse, T. A., Bolund, L., Grzeschik, K. H., Ropers, H. H., Sjöström, H., Noren, O., Mantei, N., & Semenza, G. (1988). The human lactase-phlorizin hydrolase gene is located on chromosome 2. *FEBS Letters*, *240*(1-2), 123-126. [https://doi.org/10.1016/0014-5793\(88\)80352-1](https://doi.org/10.1016/0014-5793(88)80352-1)
- Labrie, V., Buske, O. J., Oh, E., Jeremian, R., Ptak, C., Gasiūnas, G., Maleckas, A., Petereit, R., Žvirbliene, A., Adamonis, K., Kriukienė, E., Koncevičius, K., Gordevičius, J., Nair, A., Zhang, A., Ebrahimi, S., Oh, G., Šikšnys, V., Kupčinskas, L., ... Arturas Petronis . (2016). Lactase nonpersistence is directed by DNA-variation-dependent epigenetic aging. *Nature structural & molecular biology*, *23*(6), 566-573. <https://doi.org/10.1038/nsmb.3227>
- Lapides, R. A., & Savaiano, D. A. (2018). Gender, age, race and lactose intolerance: is there evidence to support a differential symptom response? A scoping review. *Nutrients*, *10*(12), 1956. <https://doi.org/10.3390/nu10121956>
- Mäkinen, O. E., Wanhalinna, V., Zannini, E., & Arendt, E. K. (2016). Foods for special dietary needs: Non-dairy plant-based milk substitutes and fermented dairy-type products. *Critical reviews in food science and nutrition*, *56*(3), 339-349. <https://doi.org/10.1080/10408398.2012.761950>
- MedlinePlus. (2020, August 18). *Lactose intolerance*. U.S. National Library of Medicine. <https://medlineplus.gov/genetics/condition/lactose-intolerance/>.
- MedlinePlus. (2020a, August 18). *What are genome editing and CRISPR-Cas9?*. U.S. National Library of Medicine. <https://medlineplus.gov/genetics/condition/lactose-intolerance/>.
- Misselwitz, B., Pohl, D., Frühauf, H., Fried, M., Vavricka, S. R., & Fox, M. (2013). Lactose malabsorption and intolerance: pathogenesis, diagnosis and treatment. *United European gastroenterology journal*, *1*(3), 151-159. <https://doi.org/10.1177%2F2050640613484463>
- Montalto, M., Curigliano, V., Santoro, L., Vastola, M., Cammarota, G., Manna, R., Gasbarrini, A., & Gasbarrini, G. (2006). Management and treatment of lactose malabsorption. *World Journal of gastroenterology: WJG*, *12*(2), 187. <https://dx.doi.org/10.3748/wjg.v12.i2.187>
- Muehlhoff, E., Bennett, A., & McMahon, D. (2013). *MILK and dairy products in human nutrition*. Food and Agriculture Organization of the United Nations. <http://www.fao.org/3/i3396e/i3396e.pdf>
- Murray, D. (2021, January 5). *How much calcium do you need during pregnancy?* Verywell family. <https://www.verywellfamily.com/calcium-needs-during-pregnancy-4580491>
- MUSC Health. (n.d). *Intestinal Lymphoma*. Medical University of South Carolina. <https://muschealth.org/medical-services/ddc/patients/digestive-diseases/small-intestine/intestinal-lymphoma>
- Nelsen, D. A. (2002, December 15). *Gluten-Sensitive Enteropathy (Celiac Disease): More Common than You Think*. American Family Physician. <https://www.aafp.org/afp/2002/1215/p2259.html>.
- Network, W. by F. I. (n.d.). *Food Intolerance Network*. Tables of lactose content. <https://www.food-intolerance-network.com/food-intolerances/lactose-intolerance/tables-of-lactose-content.html>.
- Oak, S. J., & Jha, R. (2019). The effects of probiotics in lactose intolerance: A systematic review. *Critical reviews in food science and nutrition*, *59*(11), 1675-1683. <https://doi.org/10.1080/10408398.2018.1425977>
- Orenstein, B. W., Gordon, S., By, Vogt, C., Miller, B., Etier, A., ... Migala, J. (n.d.). *Can You Become Lactose Intolerant Later in Life?: Everyday Health*. EverydayHealth.com. <http://www.everydayhealth.com/news/can-you-develop-lactose-intolerance-later-life/>.
- Rosario, J. F. del (Ed.). (2015, January). *Lactose Intolerance (for Kids) - Nemours KidsHealth*. KidsHealth. <https://kidshealth.org/en/kids/lactose.html>.
- Rubin, J. E., & Crowe, S. E. (2020, January 7). *Celiac Disease*. Annals of internal medicine. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7707153/>.
- Schmitt, B., & Demarest, K. (2021, April 1). St. Georges Technical High School is first high school in the U.S. to use the Gene editing institute's CRISPR in a box educational toolkit. St Georges Press release. https://news.christianacare.org/wp-content/uploads/2021/04/CC-StGeorges_press_release.html

- Szilagyi, A., & Ishayek, N. (2018). Lactose intolerance, dairy avoidance, and treatment options. *Nutrients*, *10*(12), 1994. <https://doi.org/10.3390/nu10121994>
- TheChemlife. (2018, February 12). *Developing a permanent treatment for lactose intolerance using gene therapy* [Video]. YouTube. <https://www.youtube.com/watch?v=J3FcbFqSoQY>.
- TheChemlife. (2020, May 13). *Am I still lactose tolerant? - Lactose gene therapy update* [video]. YouTube. <https://www.youtube.com/watch?v=aoczYXJeMY4>.
- Tishkoff, S. A., Reed, F. A., Ranciaro, A., Voight, B. F., Babbitt, C. C., Silverman, J. S., Powell, k., Mortensen, H. M., Hirbo, J. B., Osman, M., Ibrahim, M., Omar, S. A., Lema, G., Nyambo, T.B., Ghorri, J., Suzannah, B., Pritchard, K.J., Wray, G.A., & Deloukas, P. (2007). Convergent adaptation of human lactase persistence in Africa and Europe. *Nature genetics*, *39*(1), 31-40. <https://doi.org/10.1038/ng1946>
- Turco, R., Salvatore, S., Miele, E., Romano, C., Marseglia, G. L., & Staiano, A. (2018). Does a low FODMAPs diet reduce symptoms of functional abdominal pain disorders? A systematic review in adult and paediatric population, on behalf of Italian Society of Pediatrics. *Italian Journal of Pediatrics*, *44*(1), 1-14. <https://doi.org/10.1186/s13052-018-0495-8>
- Usai-Satta, P., Scarpa, M., Oppia, F., & Cabras, F. (2012). Lactose malabsorption and intolerance: What should be the best clinical management?. *World journal of gastrointestinal pharmacology and therapeutics*, *3*(3), 29. <https://dx.doi.org/10.4292/wjgpt.v3.i3.29>
- Vidyasagar, A. (2018). What is CRISPR. *Live Science Contributor April, 21*, 2018.
- Wanes, D., Husein, D. M., & Naim, H. Y. (2019). Congenital lactase deficiency: mutations, functional and biochemical implications, and future perspectives. *Nutrients*, *11*(2), 461.
- World Health Organization. (n.d.). *Healthy diet*. World Health Organization. <https://www.who.int/news-room/fact-sheets/detail/healthy-diet>.
- Yoo, R., Magazine, A., Lo, F., & Contributors. (2019, January 23). *Why Most East Asians Are Lactose Intolerant*. Character Media. <https://charactermedia.com/why-most-east-asians-are-lactose-intolerant/>.
- Zaitlin, P., Dwyer, J., & Gleason, G. R. (2013). Mistaken beliefs and the facts about milk and dairy foods. *Nutrition Today*, *48*(3), 135-143. doi: 10.1097/NT.0b013e3182941c62