

Lactose Intolerance: Diagnosis, Genetics and Clinical Factors

Sikander Ali Gurjeet Singh, Syed Shahid Hussan

Government College University, Institute of Industrial Biotechnology, Lahore, Pakistan

ABSTRACT

Lactose intolerance is a global health issue. As, it makes a person unable to digest lactose which is an essential and most important protein present in milk. This inability leads to symptoms like Flatulence, diarrhea, abdominal bloating and cramps, nausea, borborygmi, vomiting and etc. LCT gene is responsible for producing lactase enzyme to digest lactose. But unfortunately, among most adults worldwide this gene is switched off. As milk is an essential part of an individual's diet. In this review article, different types of lactase intolerance are discussed. i.e. Primary and Secondary lactose intolerance, Primary congenital lactesia. This review article also addresses the methods on how to diagnose different types of lactose intolerance like hydrogen breath test, Intestinal biopsy, Stool sugar chromatography, Genetic diagnostic. It also explains the ways to manage and treat lactose intolerance among effected individuals.

Keywords: LCT, C₁₂H₂₂O₁₁, DNA, CLD, FODMAP

I. INTRODUCTION

The name lactose is obtained from the Latin word "lac" means milk, and "ose" corresponds to its chemical nature (i.e. sugar). It is a disaccharide sugar, which consists of glucose and galactose units. It is a major sugar present in milk. Milk contains about 2-8% of lactose by weight. but the concentration of lactose can vary in milk, depending upon the specie and individual organisms. its chemical formula is C₁₂H₂₂O₁₁ (Saviano., 2014).

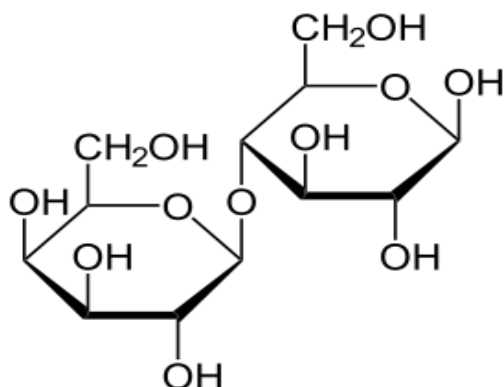


Figure 1: Structure of Lactose. Adapted from: https://en.wikipedia.org/wiki/Lactose_intolerance

“Lactose intolerance is a condition in which people have symptoms due to the decreased ability to digest lactose, a sugar found in milk products. Those affected vary in

the amount of lactose they can tolerate before symptoms develop” (Heyman & Care, 2006). Lactose intolerance, is the inability to digest milk. approximately 1/3rd of world's population is suffering from this defect, and most of them from Asian countries. naturally, infants produce lactase enzyme. which helps them too digest lactase in milk. but as most of the infants mature they lose this ability of lactase digestion in other words their lactase gene is switched off. hence, making them unable them to digest lactose. lactose intolerance since 1960's, has been used as a parameter to define the risks related to its lactose intolerance in patients effected by this deficiency (Lukito et al., 2015). Symptoms of lactose intolerance are defined or described as adversative or sensitivity to the lactose containing products. such products primarily include milk products because they are rich in lactose. the adverse effects which are reported due to lactose intolerance includes the following diseases such as flatulence, diarrhea, abdominal bloating and cramps, nausea, borborygmi, and vomiting. These manifestations appear after couple of hours of intake of lactose containing food. The sternness of these symptoms normally gets increased with the increased rate of consumption. But people with lactose intolerance can still withstand/intake a threshold or a specific level of lactose and consume it without any problem (Widjaja et al., 2015).

Types

Primary lactase deficiency corresponds to the partial or absolute absence of lactase which is developed at various stages in a person's life. this level varies depending of the racial inspectoral history of the individual. But sometimes it is referred as a major causative agent for causing lactose malabsorption and lactose intolerance. It also refers to adult-type hypolactasia, hereditary lactase deficiency and lactase non persistence. Secondary lactase deficiency results due to small bowel injury, such as acute gastroenteritis, diarrhea, cancer chemotherapy, or other causes of injury to the small intestinal mucosa, it can occur at any stage but it is more common in infants (Heyman & Care, 2006). Primary congenital lactasia, or congenital lactase deficiency (CLD), it is a condition in which the production of lactase is seized by birth, it can be severely dangerous in a society. It could be fatal to infants as new born completely rely on mother feed for their growth and development until they are able to utilize other food items for meeting their nutritional requirements. Before the formulation of modified dairy baby feed products such as lactose free and soybean-derived products , the death rates of CLD infants was significantly high. But after 20thcentury , it was observed that after such advanced formulation , the death rates were significantly dropped (Yonyang et al., 2015)

Causes

Lactose intolerance is the outcome of deficiency of a key enzyme i.e., lactase responsible for the lactose metabolism. Lactose intolerance may be the consequence of being environmentally (secondary or acquired hypoalactasia) or genetically (primary hypolactasia and primary congenital a lactasia) induced. In both types, the symptoms appear due the reduced lactase enzyme units in duodenum lining. Lactose, cannot be absorbed through the wall of small intestine into the bloodstream, once it is there. Because of its disaccharide nature. Instead it goes into the colon. After it enters the colon, the bacterial colonies which are present their start metabolizing this lactose. Due to this metabolism of lactose a mixture of gases is also produced which includes carbon dioxide, Hydrogen and Methane. these gases causes an increase osmotic

pressure in stomach causing increased flow of water, which eventually leads to diarrhea. (Lember et al., 2006)

The LCT gene is responsible for the production of lactase enzyme in our body. And the DNA sequence which decides the switching ON and OFF of lactase enzyme is MCM6. it is thought that some centuries ago humans developed a mutation which keeps the LCT gene active even when an individual is mature. But this mutation is not prevalent in many. Both genes are present on long arm of chromosome number 2 in region 21. And its locus is expressed as 2q21. Sme scientists also link lactose intolerance to heritage of some specific races. As it is evident from the data that approximately 75% population of Mexican Americans, African Americans and native Americans are inherently lactose intolerant. DNA analysis of about 94 ancient skeleton squired from Europe and Russia provided enough evidence that the mutation which was caused in LCT gene is about 4,300 years old (Gastroenterology., 2012). Lactase Intolerance is also linked to the evolutionary history of humans. As some thought that in countries where fresh milk and dairy products are scarce, people have become lactose intolerant to overcome that need to intake lactose n their diet. But on the other hand people living in such geographical zones where milk and dairy products are readily available have the mutation in their LCT gene which helps them to keep metabolizing lactose even when they are adults. Although this relevance of lactose with cultural and geographical conditions cannot be accepted without a scientific proof. But it is evident that these mutations resultantly cause other independent mutations in individuals. Three different alleles are said to be developed in past few decades among African people. With persistence extending from 26% in Tanzania to 88% in Sudan among in the Beja pastoralist population (Mattar et al., 2012).

Diagnosis

For the assessment of lactose intolerance, patient is asked to increase the lactose intake more than their body can easily metabolize. So, if within 30 min or couple of hours the symptoms mentioned above become visible then the patient is diagnosed with lactose intolerance. But these clinical symptoms vary from individual to

individual. These variability's depend on the persons metabolic rate and other pathways which directly or indirectly effect the consumption of lactose rich foods. In the second step the diagnosis of primary or secondary lactase deficiency is done. physicians usually check for the presence of Crohn disease, coeliac disease or other enteropathies when secondary lactase deficiency is suspected and an infectious gastroenteritis has been ruled out. In some cases patients confuse lactose intolerance with milk allergy. But these two are completely different. And to check which one is present a very simple test could be run, by giving the patient lactose free milk. If the patients show any symptoms mentioned above then He/ She has milk allergy. But if there are no symptoms then lactose intolerance is present. allergy. But there is a possibility for an individual to have both these conditions i.e. lactose intolerance and milk allergy at a time (Olivier et al., 2012). Following are the four tests which are available to diagnose the lactose intolerance in individuals.

Hydrogen Breath Test

Hydrogen breath test is considered as one of the most accurate lactose intolerance test. In this test the patient is asked to fast for overnight. then the next day the patient is given 25 grams of lactose (in a solution with water) to swallowed. If patient's body is unable to metabolize this lactose. Enteric bacteria come into play at this step they simply metabolize lactose producing different gases i.e. Hydrogen and Methane. If the person is unable to digest lactose then by using gas chromatogram or a solid-state detector the breath of patients is tested for the presence of methane. The duration of this test is around 2.5 hours. If hydrogen level in breath is high it corresponds to the metabolic reaction underwent and confirms the lactose intolerance in patient. This test is not recommended for younger kids as it effects can cause severe kind of diarrhea (Management., 2015).

Blood test

This method is considered as a conventional old method. Its action mechanism is: the patient is asked to fast overnight. then their blood is drawn in intervals. And glucose level in blood is measured. In case of lactase malabsorption patient will show a "flat curve. while in case of lactase persistent an elevation in the graph is observed. But this method is not very efficient because

blood sampling has many disadvantages (Olivier *et al.*, 2012).

Intestinal biopsy

Intestinal Biopsy is another modern way of diagnosing the lactose deficiency. this test actually checks the level of lactase enzyme in upper part of gastrointestinal part by using gastrointestinal microscopy equipment. But obviously this test requires mRNA sequencing and other diagnostic programs as a proof (Kuokkanen *et al.*, 2006).

Stool sugar chromatography

Chromatography is one of the simplest and unreliable test. As, this test is used to check lactose level in faeces of the patient. If the faeces have considerable level of lactose then the person is supposed to be lactose tolerant and vice versa. But this is where this test goes wrong as sometimes a lactose intolerant person could have lactose in their faces. So, that is the reason this test is considered outdated (Heubi *et al.*, 2000).

Genetic diagnostic

Genetic diagnosis as we all know is the most authentic and reliable diagnostic method. As, lactase activity is associated with two polymorphic forms i.e. G/A 22018 and C/T 13910. These are located on *MCM6* gene. So, the status of these polymorphisms can be detected through DNA sequencing. The process includes the isolation of DNA from the patient's body. Once the DNA is isolated, it is conjugated or hybridized with a specific probe to study its sequential and other properties. there are different kits available for this purpose. genetic tests are considered as the best non-invasive tests with h high efficiency rate (Deng, 2015).

Biological Mechanism of Lactose Intolerance

About 2/3rd of the World's population undergoes this lactose intolerance once they mature. this genetic reprogramming causes the primary lactose intolerance. Whereas, some other medical problems can also trigger lactose deficiency is also caused by some other problems as well that includes inflammatory bowel disease, gastrointestinal infection, abdominal problems and etc. This type of lactose intolerance is called secondary lactose intolerance. Sometimes these two types are confused with congenital lactase deficiency, which is a completely different problem. This is a very rare

problem though. But whatever the kind of intolerance or deficiency it is the presence of unabsorbed lactose in gastrointestinal tract is evident (Rejane et al 2012).

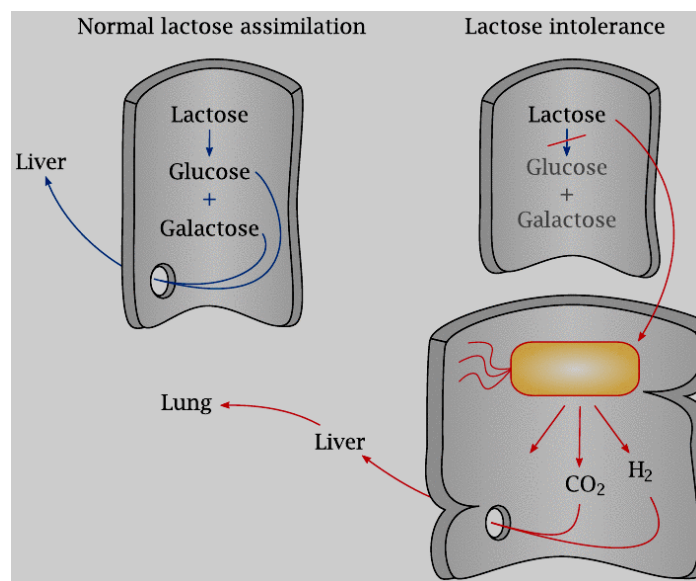


Figure 2. Lactose metabolism Adapted from: <http://watcut.uwaterloo.ca/webnotes/Metabolism/OtherSugars.html>

In the first step what happens is that, the osmotic pressure increases which elevates the water level in intestine as well. Second step includes the release of a group of gases i.e. methane, hydrogen and carbon dioxide due to the fermentation of lactose by microbes present. But this phenomenon is also present in our bodies for other monosaccharide, Di and polysaccharides which are poorly or not absorbed at all by our body. Double-blind, cross-over studies revealed that different sugars have different effects on the results and body (Murray *et al.*, 2014). Malabsorption is considered as a prerequisite for lactose intolerance or FODMAP intolerance. But two of them are not related to each other in any way and must be considered separate. The food intake limit for lactose intolerant patients depends on the amount of lactose consumed, rate of its ingestion with other foods, lactase expression, transit time for gut, bacterial growth in bowel. In addition some environmental and physiological factors are important parameters (Management., 2015).

Management

The children and adult who are diagnosed with this deficiency must take measures. To not to burden their metabolic system with lactose. Because it is evident that in most cases decreasing the consumption of lactose helps in relieving the symptoms to some extent. However, patients suffering from primary lactose intolerance must take some amount of lactose. As, their bodies can digest some of it. But the good thing about the symptoms manifested by this disease causes less damage to gastrointestinal tract as compared to other gastrointestinal disease or problem. Those problems include: inflammation, mucosal damage, celiac and disease and other allergies. There is no evidence of calcium deficiency caused by lactose intolerance. But the inability of our metabolic system to ingest lactose, effects the calcium absorbing ability of body cells as well. So, if the use of lactose rich food is stopped then it will also cause calcium deficiency as well (Heyman & Care, 2006). Lactose-free and lactose-reduced milks (can be obtained with WIC (Special Supplemental Nutrition Program for Women, Infants, and Children) vouchers. Although milk and less lactose containing foods can be used as a substitute. These substitute milks are expensive, but they help the cause. Cow milk is free of lactose, but milk of some mammals like goat does have lactose. So, while providing the patient with complete Other mammalian milks, including goat milk, are not free of lactose. So, patients with partial milk intolerance can intake such milk types to maintain the level of nutrients present in dairy products to keep the balance. But the amount of it should be consulted with doctor before starting such intake to avoid any bad results. Some children can drink a couple of milk glasses per day without the manifestation of any symptoms. people who are lactose-intolerant are seen to be tolerant to flavored milks, yogurts and dairy products which are enhanced (Labayen *et al.*, 2001).

The reason behind this tolerance is that the bacterial strains in these modified products partially digest the lactose into glucose and galactose before consuming the product. In addition, the semi-solid state of yogurt makes the process of emptying of gastric cavity slower, which helps in minimizing the symptoms of lactose intolerance. Furthermore, the ingestion of other solid food items is also known to slow down the process of gastric emptying. Hence, giving more time for lactose

digestion. Cheeses which are old/aged are said to have decreased level of lactose, so they are also good for lactose intolerance. Oral capsules are also available in market which helps an intolerant person to digest lactose well or at least they allow the patient to consume some quantity of lactose containing food. National Medical Association of America has recommended that the consumption of lactose containing foods should be regulated even among lactose tolerant people. Because their consumption leads to different diseases such as hypertension and diabetes. Children on the other hand, show better digestion of Milk and dairy products (Bernstein *et al.*, 1994).

Lactose-Free Formulas

Among the developed countries, the consumption of lactose containing food is continued. It is done so that, the patient's body keep on digesting the amount of lactose it can. This formula is not used only on underdeveloped children, who might cause further complications. The infants who are breastfed should be fed with human milk. The use of lactase in formulas for preterm infants has been noted above. Although lactose-free cow milk–protein-based formulas are readily available and popular, no studies have documented that these formulas have any clinical impact on infant outcome measures including colic, growth, or development (Heubi *et al.*, 2000).

Lactose, Calcium Absorption, and Bone Mineral Content

Research has shown that intake of lactose enhances the calcium absorption in blood. But as we are talking about keeping the lactose intolerant away from the lactose rich foods. This can cause calcium deficiency and eventually leads to poor mineralization of bones. Hence, lactose-intolerance sometimes might also cause pediatric problems in patients. So, the effects caused by lactose-intolerance on a person's long term bone health are pretty much obvious. Calcium level is also affected by the intake of Vitamin D, Its level, Salt intake, Protein intake and other genetic and physiological factors (Saviano., 2014). All these factors needs to be studied in long term run to be aware of the bones health. The recent research made on this topic suggests that genetic mapping or testing could be a powerful tool while studying such kind of medical conditions. As, using this technique enables the early detection of a problem which in turn provides a platform for early intervention and timely treatment of disease (Heyman & Care, 2006).

Examples of Lactose levels in Foods

In this era of modern industrialization the proper standardization for labeling is just s dream. As, the labels on food packaging are just a bunch of misinformation. Because the level of lactose vary in a cow's milk depending upon its geographical location, food type and quality and its manufacturing process. As an example the following table shows the variability in lactose level found in various foods (Mattar *et al.* 2012).

Table 1. Lactose content in dairy products

Dairy product	Serving size	Lactose contents	Percentage
Milk, regular	250ml/g	12g	4.80%
Milk, reduced fat	250ml/g	13g	5.20%
Yogurt, plan, regular	200g	9g	4.50%
Yogurt, plan, low fat	200g	12g	6.00%
Cheddar cheese	30g	0.02g	0.07%
Cottage cheese	30g	0.01g	0.33%
Butter	5g	0.03g	0.6%

Adopted from: (Mcbean et al., 1998)

Lactose in nondairy products

Lactose (also present when labels state lacto serum) is an commercial additive, which is added in various types of foods for the purpose of flavor, texture and to increase the adhesive quality of food. In processed meat bread slices, margarines it is also found. Barbecue sauces and few cheeses also contain lactose. Lactose is also widely used in production of sold pills in medical industries. The coating of pills is commonly contains lactose. But the label of such medicines almost never mentions the presence of lactose of milk content, which again is a violation of ethical rules. Even the pharmacists who are selling such medicines are unaware of this fact (Crispers, 2000).

Lactose intolerance and irritable Bowel syndrome

Irritable bowel syndrome approximately affects about 9–12% of the population and is common patients who have any of these symptoms bloating, abdomen pain, constipation and diarrhea. Diet also play a great part in this and worsen the symptoms, specially the intake of caffeine, eating patterns, amount of fibers taken, microbial flora present in gut, fluid intake and food intolerance as well. Lactose is not the causative factor in causing IBS but yes, its presence adds to the visceral sensitivity intolerance. The symptoms caused by IBS and Lactose intolerance and IBS symptoms are pretty very similar. Some time when these symptoms are studied in context of milk intake they does not show lactose intolerance. In two individual studies, lactose maldigestion affects about 24–27% of patients who are suffering from IBS. Change of diet only helped to improve symptoms in 52% of the patients. Interestingly, IBS patients sometimes also describe lactose intolerance symptoms even when they are not intolerant to lactose. But in many cases it is been observed that patients with lactose intolerance, even when they intake lactose free milk shows the symptoms of lactose intolerance. This shows that the patient might have undiagnosed IBS as well (Lomer *et al.*, 2008).

II. CONCLUSIONS

In the world primary lactase deficiency is considered as most common “genetic disease” .But in reality the loss of lactase gene is considered as normal or “wild-type”

and lactase persistence the abnormal “mutant” state. In secondary lactase deficiency, due to infection or any other causes the lactose digestion ability is lost. Whatever the cause, lactose malabsorption causes symptoms by several mechanisms: unabsorbed lactose leads to osmotic diarrhea; products of its bacterial digestion lead to secretory diarrhea and gas can distend the colon. Diagnosis of lactose malabsorption is based on detection either of the genetic mutation, loss of lactase activity in the enteric mucosa or evidence of malabsorption in the blood or breath. The majority of healthy individuals with lactase deficiency tolerate up to 20 g lactose without difficulty. Instead, diagnosis of lactose intolerance requires concurrent assessment of lactose digestion and abdominal symptoms. Recent studies have provided important new insight into the complex relationship between lactase deficiency, lactose malabsorption and symptom generation. This work has shed light on the wider issue of food intolerance as a cause of symptoms in irritable bowel syndrome and related conditions. Understanding the biological mechanism for food intolerance to lactose and FODMAP will help clinicians make a definitive diagnosis and guide rational dietary and medical management.

III. REFERENCES

- [1]. Bernstein, C. N., M. Ament, L. Artinian, .Ridgeway and F. Shanahan, 1994. Milk tolerance in adults with ulcerative colitis. *Amer. J. Gastroenterol.*, 89(6).
- [2]. Crispers, C. (n.d.). Alphabetical List of Product Names Alphabetical List of Product Names , (905), 2-12.
- [3]. Deng, Y., B. Misselwitz, N. Dai and M. Fox. 2015. Lactose intolerance in adults: biological mechanism and dietary management. *Nutrients*, 7(9): 8020-8035. *Gastroenterology*, E. (2012). Lactose intolerance: diagnosis , genetic , and clinical factors, 113-121.
- [4]. Heubi J, Karasov R, Reisinger K, . Randomized multicenter trial documenting the efficacy and safety of a lactose-free and a lactose-containing formula for term infants. *J Am Diet Assoc.* 2000;100:212-217

- [5]. Heyman, M. B., & Care, P. (2006). Lactose Intolerance in Infants, Children, and Adolescents, 118(3). <http://doi.org/10.1542/peds.2006-1721>
- [6]. Kuokkanen M, Myllyniemi M, Vauhkonen M, Helske T, Kaariainen I, Karesvuori S, Linnala A, Harkönen M, Jarvela I, Sipponen P (2006). "A biopsy-based quick test in the diagnosis of duodenal hypolactasia in upper gastrointestinal endoscopy". *Endoscopy*. 38 (7): 708-12. doi:10.1055/s-2006-925354. PMID 16761211
- [7]. Lember, M., Torniainen, S., Kull, M., Kallikorm, R., Saadla, P., Rajasalu, T., & Komu, H. (2006). Lactase non-persistence and milk consumption in Estonia, 12(45), 7329-7331.
- [8]. Lomer, M. C. E., Parkes, G. C., & Sanderson, J. D. (2008). Review article: lactose intolerance in clinical practice - myths and realities, (October 2007), 93-103. <http://doi.org/10.1111/j.1365-2036.2007.03557.x>
- [9]. Lukito, W., Dvm, S. G. M., Surono, I. S., & Wahlqvist, M. L. (2015). From "lactose intolerance" to "lactose nutrition," 24(December), 1-8. <http://doi.org/10.6133/apjcn.2015.24.s1.01>
- [10]. Management, D. (2015). Lactose Intolerance in Adults: Biological Mechanism and Dietary Management, 8020-8035. <http://doi.org/10.3390/nu7095380>
- [11]. Murray, K.; Wilkinson-Smith, V.; Hoad, C.; Costigan, C.; Cox, E.; Lam, C.; Marciani, L.;
- [12]. Gowland, P.; Spiller, R.C. Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI. *Am. J. Gastroenterol.* 2014, 109, 110-119.
- [13]. Olivier CE, Lorena SL, Pavan CR, dos Santos RA, dos Santos Lima RP, Pinto DG, da Silva MD, de Lima Zollner R (2012). "Is it just lactose intolerance?". *Allergy and Asthma Proceedings*. 33 (5): 432-6. doi:10.2500/aap.2012.33.3584
- [14]. McBean, L, Miller, G.D. Allaying fears and fallacies about lactose intolerance. *JADA*, June 1998, 671 - 676.
- [15]. Rejane, M., D.F. de campus, Mazo and F. J. carrilbo. 2012. Lactose intolerance: diagnosis, genetic and clinical factor CEG., 2012:5 113-121
- [16]. Yangyong., D., B. Misselwitz, N.dai and M.fox. 2015. Lactose intolerance in adult: biological mechanism and dietary management. *Nutrients*, 7:8020-8035
- [17]. Widjaja. L. N., S.G. Malik, I.S. Sorono and M.L. Wahlgrist. 2015. Lactose intolerance to lactose nutritou. *Asia pac J Clin Nutr.*, 24:51-58.
- [18]. Saviano, D.A. 2014. Lactose digestion from yogurt: mechanism and relevance. *Am. J. Clin. Nutr.*, 99:1251S-5S.
- [19]. Mattar, R., D.F. De Campos Mazo and F.J. Carrilho. 2012. Lactose intolerance: diagnosis, genetic, and clinical factors. *Clin. Exp. Gastroenterol.*, 5:113-21.
- [20]. Labayen, I., L. Forga, A. Gonzalez, I. Lenoir-Wijnkoop, R. Nutr and J.A. Martínez. 2001. Relationship between lactose digestion, gastrointestinal transit time and symptoms in lactose malabsorbers after dairy consumption. *Aliment. Pharmacol. Ther.*, 15:543-9.