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Lactose intolerance: a non-allergic disorder often managed by allergologists

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Summary

Lactose malabsorption is a very common condition characterized by intestinal lactase deficiency. Primary lactose malabsorption is an inherited deficit present in the majority of the world's population, while secondary hypolactasia can be the consequence of an intestinal disease. The presence of malabsorbed lactose in the colonic lumen may cause gastrointestinal symptoms. This condition is known as lactose intolerance. Lactase non-persistence is the ancestral state, whilst two single nucleotide polymorphisms in the lactase gene have been associated with lactase persistence. These are C/T 13910 and G/A 22018 substitutions. Lactase persistence, this Mendelian dominant trait, only became advantageous after the invention of agriculture, when milk from domesticated animals became available for adults to drink. Lactase persistence is then strongly correlated with the diary history of the population. Diagnosis is assessed clinically by elimination of dietary lactose or, better, by non-invasive tests including hydrogen breath test and genetic test. In patients with lactase non-persistence, treatment should be considered exclusively if intolerance symptoms are present. In the absence of guidelines, the common therapeutic approach tends to exclude milk and dairy products from the diet. However, this strategy may have serious nutritional disadvantages. Several studies have been carried out to find alternative approaches, such as exogenous beta-galactosidase, yogurt and probiotics for their bacterial lactase activity, strategies that can prolong contact time between enzyme and substrate delaying gastrointestinal transit time, and chronic lactose ingestion to enhance colonic adaptation.

Introduction

Lactose intolerance is a very common condition characterized by lactase deficiency, an enzime occurring in the brush border membrane of the intestinal mucosa that hydrolyzes lactose to its components galactose and glucose. High concentrations of this enzyme are physiologically present in neonates. Post weaning, a genetically programmed and irreversible reduction of its activity occurs in the majority of the world's population, which results in primary lactose malabsorption, the most common enzyme deficiency.

Hippocrates first described lactose intolerance around 400 years BC, but the clinical symptoms have become recognized only in the last 50 years.

Significant changes in our knowledge and approach toward lactose intolerance have occurred over the past quarter century, since the first statement on lactose intolerance was published by the American Academy of Pediatrics Committee on Nutrition. Lactose ingestion in certain

susceptible individuals can cause abdominal symptoms that are variable and can be treated with dietary restriction or enzyme replacement, depending on the amount of lactose consumed and the degree of lactase deficiency. Duodenal morphology and the activities of maltase, sucrase, and isomaltase are normal (1).

In 2003 a Finnish study by Enattah unraveled the genetic bases for lactose intolerance demonstrating the link between lactose persistence and a single nucleotide polymorphism (2).

Lactose, a disaccharide that comprises the monosaccharides glucose and galactose, is the primary carbohydrate found exclusively in mammalian milk, 7,2 g/100 ml in mature human milk, 4,7 g/100 ml in cow's milk but is negligible in the milk of some marine mammals (3). Absorption of lactose requires lactase activity in the small intestinal brush border to split the bond linking the two monosaccharides. A β-galactosidase termed "lactase-phlorizin hydrolase" (lactase) accounts for most of the lactase activity in the intestinal mucosa. Lactase is found in the small intestine and localized to the tips of the villi, a factor of clinical importance when considering the effect of diarrheal illness on the ability to tolerate milk.

Lactose intolerance can occur among infants and young children with acute diarrheal disease, although the clinical significance of this is limited except in more severely affected children. Symptoms of lactose intolerance are relatively common among older children and adolescents; however, associated intestinal injury is infrequently seen. Lactose intolerance is a distinct entity from cow milk-protein sensitivity, which involves the immune system and causes varying degrees of injury to the intestinal mucosal surface. Cow milk-protein intolerance is reported in 2% to 5% of infants within the first 1 to 3 months of life, typically resolves by 1 year of age, and is not the subject of this review (4).

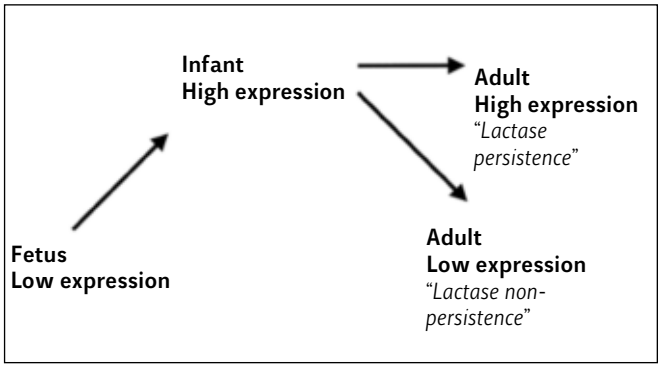
Lactose malabsorption is the physiologic problem that manifests as lactose intolerance and is attributable to an imbalance between the amount of ingested lactose and the capacity for lactase to hydrolyze the disaccharide. The presence of malabsorbed lactose in the colonic lumen does not necessarily result in gastrointestinal symptoms. Only when lactose malabsorption is associated with clinical manifestations as bloating, flatulence, abdominal pain and diarrhea, "lactose intolerance" occurs (5).

Hypolactasia or lactase deficiency exists in distinct forms: congenital, primary, secondary and developmental.

Congenital lactase deficiency is extremely rare; teleologically, infants with congenital lactase deficiency would not be expected to survive before the 20th century, when no readily accessible and nutritionally adequate lactose-free human milk substitute was available. Congenital lactase deficiency is a longlife disorder, with only around 40 cases having been reported. It is a single autosomal disorder, but very little is known about the molecular basis. Affected newborn infants present with intractable diarrhea as soon as human milk or lactose-containing formula is introduced. Small intestinal biopsies reveal normal histologic characteristics but low or completely absent lactase concentrations. Unless this is recognized and treated quickly, the condition is life-threatening because of dehydration and electrolyte losses. Treatment is simply removal and substitution of lactose from the diet with a commercial lactose-free formula.

Primary lactase deficiency is attributable to relative or absolute absence of lactase that develops in childhood at various ages in different racial groups and is the most common cause of lactose malabsorption and lactose intolerance. Primary lactase deficiency, also referred to as *adult-type hypolactasia, lactase nonpersistence, or hereditary lactase deficiency*, is an autosomal recessive condition resulting from the physiological decline of the lactase-phlorizin idrolase (LHP) enzyme activity in intestinal cells which occurs in a significant proportion of the global population (Fig. 1). The age of onset and its prevalence differ among various populations. In USA, approximately 20% of Hispanic, Asian, and black children younger than 5 years of age have evidence of lactase deficiency and lactose malabsorption, whereas white children typically do not develop symptoms of lactose intolerance until after 4 or 5 years of age. Recent molecular studies of LPH have correlated the

Figure 1 - Representation of the level of lactase expression at different stages of development and in lactase persistent and nonpersistent adults. The levels of activity are mainly regulated at the RNA level (43)



genetic polymorphism of messenger RNA expression with persistence of lactase activity, demonstrating early loss (at 1-2 years of age) of messenger RNA expression and enzyme activity in Thai children and late (10-20 years of age) loss of activity in Finnish children (6). The clinical relevance of these observations is that children with clinical signs of lactose intolerance at an earlier age than is typical for a specific ethnic group may warrant an evaluation for an underlying cause, because primary lactase deficiency would otherwise be unusual at such a young age. Although primary lactase deficiency may present with a relatively acute onset of milk intolerance, its onset typically is subtle and progressive over many years. Most lactase-deficient individuals experience onset of symptoms in late adolescence. Although primary hypolactasia normally appears before the age of 20 years, the decline in lactase activity may on rare occasions continue after that age (7). Treatment consists of limitation of lactose containing foods or diary elimination. Because this strategy may have serious nutritional disadvantages, alternative approaches, such as exogenous beta-galactosidase are suggested.

Secondary lactase deficiency is lactase deficiency that results from small bowel injury, such as acute gastroenteritis, persistent diarrhea, small bowel bacterial overgrowth, cancer chemotherapy, or other causes of injury to the small intestinal mucosa, and can present at any age but is more common in infancy and is normally transient. Secondary lactase deficiency implies that an underlying pathophysiologic condition is responsible for the lactase deficiency and subsequent lactose malabsorption. Etiologies include acute infection (eg, rotavirus) causing small intestinal injury with loss of the lactase-containing epithelial cells from the tips of the villi. The immature epithelial cells that replace these are often lactase deficient, leading to secondary lactose deficiency and lactose malabsorption, although several reports indicate that lactose malabsorption in most children with acute gastroenteritis is not clinically important. Several recent studies and a meta-analysis found that children with rotaviral (and other infectious) diarrheal illnesses who have no or only mild dehydration can safely continue human milk or standard (lactose-containing) formula without any significant effect on outcome. However, in the at-risk infant (eg, younger than 3 months or malnourished) who develops infectious diarrhea, lactose intolerance may be a significant factor that will influence the evolution of the illness. Giardiasis, cryptosporidiosis, and other parasites that infect the proximal small intestine often lead to lactose malabsorption from direct injury to the epithelial cells by the parasite. Secondary lactase deficiency with clinical signs of lactose intolerance can be seen in celiac disease, Crohn disease, and immune-related and other enteropathies and should be considered in these children. Diagnostic evaluation should be directed toward these entities when secondary lactase deficiency is suspected and an infectious etiology is not found. Young infants with severe malnutrition develop small intestinal atrophy that also leads to secondary lactase deficiency.

Treatment of secondary lactase deficiency and lactose malabsorption attributable to an underlying condition generally does not require elimination of lactose from the diet but, rather, treatment of the underlying condition. Once the primary problem is resolved, lactose-containing products can often be consumed normally, and these excellent sources of calcium and other nutrients need not be unnecessarily excluded from the diet.

Developmental lactase deficiency is now defined as the relative lactase deficiency observed among preterm infants of less than 34 weeks' gestation. Although lactase is a non inducible enzyme, in preterm infants lactase supplemented feeding may favor the production and the expression of the enzyme.

Genetics

For many years, it was thought that lactase persistence in humans was the 'wild-type' pattern. As the lactase non-persistence phenotype is expressed in othcr mammals, this is now considered to be the ancestral type whilst lactase persistence is because of a mutation (8).

Most mammals lose the ability to digest the milk sugar lactose after weaning because of an irreversible reduction in expression of the intestinal enzyme lactase. In fact the expression of the lactase enzyme in intestinal cells dramatically declines after weaning in mammals, when lactose is no longer an essential part of their diet. In humans, this normal mammalian condition known as "lactase non-persistence" (LNP) affects most of mankind and restricts the consumption of fresh milk among adults. However, among northern Europeans and a few other ethnic populations, intestinal lactase activity persists throughout life in a substantial proportion (up to 80%-90%) of adults, a condition known as lactase persistence (LP), or lactose tolerance. The LP/LNP phenotype is genetically determined, with LP being dominant over LNP (9).

This dominant Mendelian trait is common in populations of northern and central European descent and shows in-

termediate frequencies in southern and eastern Europe (10). Africa and the Middle East show a more complex distribution, with pastoralists often having high frequencies of LP, whereas in their nonpastoralist neighbors, it is usually much less common (11).

The lactase gene is approximately 50 kb in size and located on chromosome 2. Wild-type is characterized by lactase nonpersistence whilst two single nucleotide polymorphisms (SNPs) in the lactase gene have been associated with lactase persistence. These are C/T_{-13910} and G/A 22 018 substitutions occurring 14 and 22 kb upstream of the 5' -end of the lactase gene in a DNA region, which functions as a cis-acting element influencing the lactase gene promoter. Studies suggest that C/T_{-13910} is the dominant polymorphism with the C allele linked to a decline in lactase mRNA expression. However, the exact mechanism of this decline after weaning is uncertain. The T allele of C/T polymorphism has been shown to associate strongly with LP in Europeans (12).

Different polimorfisms have been reported in many African milk drinking pastoralist groups where lactase persistence phenotype has been reported at high frequency (13, 14).

The identification of two new mutations are recently reported among Saudis, also known for the high prevalence of LP. The absence of the European T_{-13910} was also confirmed in this population. The European T_{-13910} and the earlier identified East African G_{-13907} LP allele share the same ancestral background and most likely the same history, probably related to the same cattle domestication event. In contrast, the compound Arab allele shows a different, highly divergent ancestral haplotype, suggesting that these two major global LP alleles have arisen independently, the latter perhaps in response to camel milk consumption. These results support the convergent evolution of the LP in diverse populations, most probably reflecting different histories of adaptation to milk culture (15).

The exact mechanisms underlying the lactase non persistence are not still completely understood. Some results show an increasing imbalance in relative mRNA expression levels of the C_{-13910} and T_{-13910} alleles in children aged >5 years. These results support previous findings on transcriptional regulation of the lactase gene and the finding that the persistent T_{-13910} allele represents a mean of 92% of expressed lactase mRNA in C/T_{-13910} heterozygous adults. The decline in lactase mRNA expression transcribed from the C_{-13910} allele in the intestinal mucosa occurs in parallel with the time period of the decline in lactase enzyme activity, indicating a causative role for the intronic region containing the C_{-13910} allele (16).

Characterization of the transcriptional regulators at the C/T_{-13910} enhancer element and the exact mechanism underlying C_{-13910} allele specific downregulation of lactase activity awaits elucidation (17).

In summary, lactase persistence is linked to a autosomic dominant transmission, being C/T_{-13910} the dominant polymorphism with the C allele linked to a decline in lactase mRNA expression. Individuals heterozygous for either SNP have intermediate lactase activity and are more susceptible to lactose intolerance at times of stress or gastrointestinal infection. This polymorphism does not provide a complete explanation as individuals with homozygous lactase persistence (genotypes TT) may occasionally develop lactose intolerance (i.e. acquired lactase deficiency). Adult homozygotes with nonpersistence (CC) have virtually undetectable levels of intestinal lactase as a result of down-regulation of the brush border enzyme following weaning.

"Culture-historical hypothesis"

During the Neolithic *ca* 10000 BP, the crucial development of domestication of wild plants and animals accompanied substantial changes in human culture, and it was during this time that the foundation was laid for our way of life today. Archaeological evidence indicates that the Neolithic culture expanded out of the Near East into the Balkans, Greece and into Northern Central Europe after 6400 BP. At that time, lactase persistence has risen to high frequency in central and northern Europeans (18).

In Northern Europe, lactase persistence is common and many people not only drink milk, but culturally it is seen as a healthy and nutritious food. How this happened is now becoming clearer.

It has been suggested (Cavalli-Sforza 1973; Hollox et al. 2001; Enattah et al. 2002; Poulter et al. 2003) that a selective advantage based on additional nutrition from dairy explains these genetically determined population differences, but formal population-genetics–based evidence of selection are only now being provided (19-21).

Although not fully understood, the biological advantages of LP probably include the continuous availability of an energy- and calcium-rich drink that enables a farming community to overcome poor harvests. Because it is unlikely that LP would have provided a selective advantage in the absence of a supply of fresh milk, and because of observed correlations between the frequency of LP and

the extent of traditional reliance on animal milk, the culture-historical hypothesis has been proposed (22).
Lactase nonpersistence is the ancestral state, and lactase persistence only became advantageous after the invention of agriculture, when milk from domesticated animals became available for adults to drink. As expected, lactase persistence is strongly correlated with the dairying history of the population. This genetic ability to digest milk has been regarded as a classic example of gene-culture coevolution, where the culture of dairying creates a strong selective advantage to those who can drink milk as adults, for only they can nutritionally benefit from the milk (23).
A recent paper confirmed this link by analysing the diversity in bovine milk protein genes and showing that the highest gene diversity (and by implication the largest historical population size) is in cows from areas of the world where dairy farming is practised and the people are lactose tolerant.
The wild ancestor of cattle, the aurochs (*Bos primigenius*), ranged widely throughout Europe. However studies of mitochondrial DNA suggest that bovine maternal lineages (at least) have a Near Eastern rather than local origin. This examination of 6000 years of missing mutational history allows a confirmation that the bulk of bovine mtDNA diversity today derives from only a few Neolithic founder chromosomes (24).
In humans, epidemiological analysis has shown that the cultural development of dairying preceded selection for lactase persistence. Since dairying is thought to have originated around 10 000 years ago, the selective pressure has been only for the past 400 generations. Despite this short time, there is suggestive evidence of recent positive selection: lactase persistence is associated with one haplotype, which is very common only in northern Europeans, and is distant from the ancestral haplotype (25). Discovery of the possible molecular basis of this polymorphism – a single nucleotide change 14 kb away from the gene, has allowed further analysis of genetic variation associated with lactase persistence/nonpersistence.
An opposing view, the "reverse cause hypothesis", has also been proposed. According to this model, human populations were already differentiated with regard to LP frequency before the development of dairying, and the presence of LP determined the adoption of milk production and consumption practices. Recent studies on DNA from alcheological human remains, make this hypothesis poorly demonstrated (26).
These data suggest that dairying practices came to Europe nearly simultaneously with cereal agriculture and domestic animals. However, the absence of the 13910*T allele in Neolithic samples indicates that the early farmers in Europe were not yet adapted to the consumption of unprocessed milk. Dairying is unlikely to have spread uniformly over Europe, and the use of milk in the Early Neolithic may have been rare. Although these data are consistent with strong selection for LP beginning with the introduction of cattle to Europe 8800 BP, it is unlikely that fresh milk consumption was widespread in Europe before frequencies of the 13910*T allele had risen appreciably during the millennia after the onset of farming (26).
Important questions remain regarding the geographic location of the earliest 13910*T allele-carrying populations, the mode and direction of spread of the allele, and the precise nature of the selective advantage(s) conferred by LP.

Prevalence

Lactase persistence varies widely in frequency among different human populations, both between and within continents. It is generally found at high frequencies in populations of European descent, in which, for example, Dutch and Swedish studies recorded frequencies of 100% and 99%, respectively. Approximately 70% of the world population has lactase nonpersistence but not all are intolerant to lactose as many nutritional and genetic factors influence tolerance. The condition of lactase nonpersistence is most prevalent in Asian and African countries with 80-100% frequency, whereas within Northern European countries the prevalence of adult-type is very low. (27) Its prevalence in Western countries varies from less than 4% in Denmark to around 50% in northern Italy. Less is known about the presence of hypolactasia in Asian populations, but when the same criteria are used as in Western countries, prevalence is generally considered to be much higher, e.g. 60% in Pakistan, 90% in Thailand and 90% in China. The prevalence was however shown to be age-related in Chinese children, being 38, 5% in 3-5 yr age group, 87% in the 7-8 and 11-13 yr old group. In north Indians the frequency of maldigesters was reported to be 48% out of 200 subjects when measured by breath test (28). In North West of Russia the lactase non persistence varies from 16% to 23% independently from ethnicity of people living in that region (29).
In Italy the prevalence of lactose intolerance varies widely,

Table 1 - Prevalence of Acquired Primary Lactase Deficiency (1, modif.)

Examples of groups among whom lactase deficiency predominates (60%-100% lactase deficient)
Near East and Mediterranean: Arabs, Ashkenazi Jews, Greek Cypriots, Southern Italians
Asia: Thais, Indonesians, Chinese, Koreans
Africa: South Nigerians, Hausa, Bantu
North and South America: black Americans, Latins, Eskimos, Canadian and American Indians, Chami Indians
Examples of groups among whom lactase persistence predominates (2%-30% lactase deficient)
Northern Europeans, Northern Italians
Africa: Hima, Tussi, Nomadic Fulani, Saudi
India: individuals from Punjab and New Delhi

from the regions. In southern Italy and in the islands, the prevalence is more than 70%.
Sardinians, who are an ancient genetic isolate with a peculiar distribution of allele at multiple loci showing a genetic pattern different from Italy, Mediterranian areas, and Europe, show the same genetic association of hypolactasia with the C/T_{-13910} variant as other North-European populations (30). Recent studies show that in Sardinia doesn't exist the T/T allele. Thus lactase persistence is sustained only by the C/T allele (31).
It has also seen that in Sardinians, adult-type hypolactasia becomes phenotypically evident in all individuals older than 9 years, suggesting that this should be considered the minimum age at which the genetic test for lactase nonpersistence should be clinically applied (32).
Despite the importance of dairy products, many individuals avoid these foods to prevent symptoms believed to result from lactose maldigestion. However, the results of a meta-analysis used to estimate the incidence of lactose intolerance symptoms by comparing the occurrence of symptoms among lactose maldigesters after consuming milk or other lactose-containing foods compared with placebo under masked conditions, indicate that lactose is not a major cause of symptoms in patients either maldigester or normal following usual intakes of diary foods, that is a cup (33).

Fall in milk consumption

There is evidence that milk consumption has fallen over the past 20–25 years in many countries. Evidence from the UK shows that the fall overall has been 33% during the past 25 years and within the UK there is a marked social class gradient, the average milk intake in households in classes IV and V being 10–20% lower than in households in classes I and II (34). In most countries more than half the dietary intake of calcium come from milk, and particular concern focuses on younger people (35). Some maldigesters who have experienced symptoms following the consumption of large amounts of milk may become psychologically sensitized to the consumption of any amount of milk. Subjects complain that even a very small amount of milk in coffee results in symptoms of intolerance. Others just state that they "do not like milk" and choose to avoid it. Such avoidance of milk is likely a major obstacle in obtaining adequate calcium in the U.S. (33) (Tab. 2).
Furthermore this fall in milk consumption is probably due to the correlation between milk and lactose consumption and different types of disease, reported in many papers. A number of hypothesis have been suggested in support of the claim that milk consume increases the risk of vascular disease, decreased bone health, diabetes and increased body weight without any significant result.
Dairy products have also been proposed as possible risk factors for some types of cancer (colon cancer, ovarian cancer, prostate cancer) in ecological and experimental studies, but their roles in the development of cancer have not been confirmed in case-control or large scale cohort studies (36-38).

Table 2 - Lactose and Calcium Content of Common Foods (1, modif.)

Dairy Products	Calcium Content, mg	Lactose Content, g
Yogurt, plain, low fat, 1 cup≈250 g	448	8.4
Milk, whole (3.25% fat), 1 cup	276	12.8
Milk, reduced fat, 1 cup	285	12.2
Ice cream, vanilla, 1/2 cup	92	4.9
Cheddar cheese, 1 oz≈30 g	204	0.07
Swiss cheese, 1 oz≈30 g	224	0.02
Cottage cheese, creamed, (small curd) 1 cup	135	1.4

Lactase persistence has also been studied as a disease risk modifier (39). However, the lactase persistence, defined by the C/T-13910 variant, didn't show significant effect on the prostate cancer risk in the Finnish or Swedish populations (40).
Probably, dietary intakes reported by patients are subject to measurement error, and associations with cancer could be due to confounders. Mendelian randomization has been recently suggested as a way to overcome confounding by exploiting the random allocation of alleles from parents to offspring (41).
A proper and correct diagnosis of food-related symptoms is particularly important for children - not only in order to find the appropriate diet but also to avoid unnecessary exclusion diets, which may lead to severe impairments in growth and development (42).

Physiopathology and clinical symptoms

The enzyme lactase-phlorizin hydrolase, more commonly known as lactase, is a β-galactosidase responsible for the hydrolysis of lactase to the monosaccharides, glucose and galactose. These are absorbed by intestinal enterocytes into the bloodstrearn, glucose is ultimately utilized as a source of energy and galactose becomes a component of glycolipids and glycoproteins. Lactase has two activities: a β-galactosidase activity hydrolyzing lactose and a β-glucosidase activity responsible for hydrolyzing phlorizin, a disaccharide found in roots and bark of plants of the family Rosaceae and some seaweeds (43). Lactase is synthesized as a pro-polypeptide of 220 kDa which undergoes considerable post-transcriptional modification during transport to cell surface as the mature 150 kDa protein. It dimerizes on the brush-border membrane to form the active enzyme. Luminal factors also contribute to final modification of the protein to produce the active enzyme by cleavage of two further amino acids by pancreatic trypsin The cleaved polypeptide has no apparent enzymatic function, but it may function as a molecular chaperone. Lactase has a C-terminal membrane-spanning domain protruding into the gastrointestinal lumen (Fig. 2).
A number of actions of the phlorizin site are useful in humans and this explains why some enzyme activity is retained following the usual decline in enzyme expression after weaning from breast milk.
By week 8 of gestation, lactase activity can be detected at the mucosal surface in the human intestine. Activity increases until week 34 and by birth, lactase expression is at its peak. However, within the first few months of life, lactase activity starts to decrease (lactase nonpersistence). In most mammals, il declines at variable rates following weaning to undetectable levels as a consequence of the normal maturational down-regulation of lactase activity. In humans, approximately 30% of the population has continued lactase activity beyond weaning and into adulthood (lactase persistence).
For effective utilization of lactose without symptoms of intolerance, only 50% of lactase activity is necessary and it is present only at the level that it is required, as is the case for other intestinal disaccharids (44).
Lactose maldigestion occurs when lactose is not absorbed in the small intestine. Il passes through the gastrointestinal tract to the colon, where, in some subjects, it then leads to symptoms of lactose intolerance.
Undigested lactose is fermented by the colonic microflora with production of hydrogen detectable in pulmonary excretion.
The typical symptoms of lactose intolerance include abdominal pain, bloating, flatus, diarrhea, borborygmi, and on some occasions, nausea and vomiting. In a few cases, gastrointestinal motility is decreased and subjects can present with constipation possibly as a consequence of methane production. Abdominal pain and bloating are typically caused by colonic fermentation of unabsorbed lactose by the bacterial microflora leading to the production of short chain fatty acids (SCFA), hydrogen, methane and carbon dioxide, thus increasing gut transit time and intracolonic pressure. Acidification of the colonic contents and an increased osmotic load resulting from the unabsorbed lactose in the ileum and colon lead

Figure 2 - Lactose digestion by brush border lactase (44)

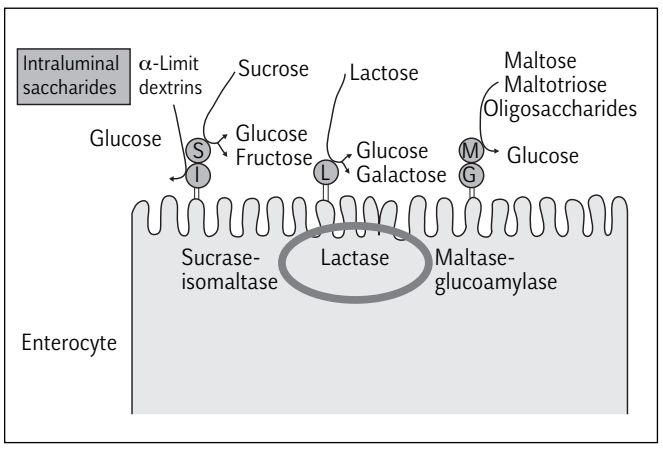


Table 3 - Hidden Sources of Lactose (1, modif.)

Bread and other baked goods
Processed breakfast cereals
Mixes for pancakes, biscuits, and cookies
Instant potatoes, soups, and breakfast drinks
Margarine
Nonkosher lunchmeats
Salad dressings
Candies and other snacks
Sausages for rice and pasta
Drugs

to a greater secretion of electrolytes and fluid and a rapid transit time resulting in loose stools and diarrhea (45).
Allergy to cow's milk protein and to other foods may coexist in patients with lactose intolerance. Probably, the intestinal defect in lactose maldigesters can affect the intestinal permeability allowing food allergens to pass through the intestinal cells (46).
In anecdotal cases, aside from gastrointestinal symptoms, systemic extra-intestinal symptoms that may include muscle and joint pain, headaches, eczema, pruritis, rhinitis, sinusitis, asthma, cardiac arrhythmia are also described as systemic syndrome caused by hidden lactose in foods and drugs (46). In these patients all hidden sources of lactose must be avoided over long periods of time (Tab. 3).
Recent papers report that ingestion of 400 mg of lactose does not cause significant difference in breath H_2 excretion and in severity of all gastrointestinal symptoms compared to placebo. Thus, in patients with lactose malabsorption and intolerance, lactase deficiency should not be considered a limiting factor to the use of drugs containing 400 mg of lactose or less (47).
All the anomalous reactions secondary to food ingestion are defined as 'adverse reactions to food'. In 1995 the European Academy of Allergology and Clinical Immunology suggested a classification on the basis of the responsible pathogenetic mechanism; according to this classification, non-toxic reactions can be divided into 'food allergies' when they recognize immunological mechanisms, and 'food intolerances' when there are no immunological implications (48).
In presence of systemic symptoms affecting the skin, the respiratory tract or showing the characteristics of anaphylaxis, allergy to cow milk proteins must be suspected and investigated (49). Allergy to cow milk protein is rare in adults, but quite frequent (3 to 8%) in children and may be life-threatening. Adrenaline is the first line treatment of anaphylactic episodes (50).

Role of colonic microflora

The variable ability of the colonic microflora to ferment lactose in subjects with intolerance may explain why different subjects have different levels of tolerance (51).
Lactase is a non inducible enzyme but it was also reported that continuous lactose consumption decreases hydrogen excretion and the severity of gastrointestinal symptoms. Decreased hydrogen excretion is not necessarily the consequence of increased lactose digestion but can depend on adaptative phenomena. This "adaptation" is associated with changes in gut microflora as well as in some colonic functions and features. The increased microbial β-galactosidase activity is one of the hypothesized mechanisms (52).
The colonic microbiota, which ferments lactose, is an important factor in the colonic processing of lactose. Thus, in addition to the lactose digestion capacity in the small intestine, the colonic processing of maldigested lactose may play a role in lactose intolerance (53).
Whether colonic fermentation of lactose would influence the occurrence of lactose intolerance, either aggravates or alleviates it, depends on the balance between the ability of the colonic microbiota to ferment lactose and the ability of the colon to remove the fermentation metabolites. A low lactose-fermenting capacity of the colonic microbiota, which leads to inefficient removal of the maldigested lactose (and/or its intermediate fermentation metabolites), or a low absorption capacity of the colon, which leads to inefficient removal of the fermentation metabolites, may contribute to the occurrence of symptoms. When lactose is converted to SCFA by fermentation, the osmotic load is increased by ~8-fold, which makes the efficiency of the colon to absorb these fermentation metabolites an important determinant for the outcome of the osmotic load caused by malabsorbed lactose.
If the colon can absorb SCFA at a sufficient rate, a higher lactose-fermenting capacity of the colonic microbiota may help to alleviate lactose intolerance
Studies are warranted to further investigate the mechanisms by which those fermentative processes after hydrolysis of lactose and the intermediate and end metabolites of those processes influence the development of symptoms. The involvment of the colon may provide the basis for designing new targeted strategies for dietary and clinical management of lactose intolerance (54).

Differential diagnosis

Subjects with gastrointestinal complaints are one of the major groups of patients seeking medical advice and are a diagnostic challenge to clinicians. These subjects have symptoms such as recurrent abdominal pains, regurgitation, chronic nonspecific diarrhea, nonulcer dyspepsia, dyschezia, and functional constipation. The elucidation of the etiologic factors underlying these symptoms has remained a controversial issue (55). Definite organic pathology may be identified to explain the symptoms. Some cases, however, remain undiagnosed.
The role of food in vague gastrointestinal complaints has been a subject of dispute (56). Many patients with IBS feel that food, especially that rich in carbohydrates and fat, triggers their symptoms. Patients often blame milk and dairy products and are sent to the allergist to investigate the presence of food allergy or intolerance. Thus, abdominal pain is becoming a challenge for the allergist.
In differential diagnosis, the following etiologic factors must be considered:
- Lactose intolerance.
- Intolerance to other sugars i.e. fructose (57).
- Celiac disease.
- Parasites (58).
- Primary gastrointestinal disturbances (Helicobacter pylori, IBS, colonic diverticulosis, tumors) to be studied, if needed, by GI specialist.
- Small Intestine bacterial overgrowth (SIBO) (59).

As previously stated, IgE mediated food allergy shows different symptoms, very rarely affecting exclusively the gastrointestinal tract.
Charles Darwin's history could be paradigmatic of a patient attending now an allergist or a GI specialist.
After returning from the Beagle in 1836, Charles Darwin suffered for over 40 years from long bouts o vomiting, gut pain, headaches, severe tiredness, skin problems, and depression. Twenty doctors failed to treat him. Many books and papers have explained Darwin's mystery illness as organic or psychosomatic, including arsenic poisoning, Chagas' disease, multiple allergy, hypochondria, or bereavement syndrome. None stand up to full scrutiny. His medical history shows he had an organic problem, exacerbated by depression. A paper shows that all Darwin' s symptoms match systemic lactose intolerance (a quite rare disturbance in Great Britain). Vomiting and gut problems showed up two to three hours after a meal, the time it takes for lactose to reach the large intestine. His family history shows a major inherited component, as with genetically predisposed hypolactasia. Darwin only got better when, by chance, he stopped taking milk and cream. Darwin's illness highlights something else he missed-the importance of lactose in mammalian and human evolution. (60) Other authors re-examining many of the abundant publications on the illness that afflicted Charles Darwin during most of his life, including some of the 416 health-related letters in his correspondence, as well as his autobiographical writings, concluded that he suffered from Crohn's disease, located mainly in his upper small intestine (61).
Unfortunately, Darwin could not undergo a lactose H_2 Breath test!
Beecause of its large diffusion, lactose intolerance must be considered in presence of GI symtoms and investigated with diagnostic tools which are now very reliable and quite easy to perform.

Diagnosis

The gold standard for genetic disaccharide deficiencies is an in vitro assay of enzymic activity in biopsy samples, with obligatory endoscopic sampling, a necessarily invasive procedure. The lactose tolerance test is analogous to a glucose tolerance test, with an oral loading of lactose in a fasting subject, followed by sampling of blood over a 2-hour period. A doubling of blood glucose over this time indicates that the subject is lactose tolerant.
Commonly, a diagnosis of lactose intolerance has been a diagnosis by exclusion, based on an empiric trail of dietary avoidance. This behavior can result in unecessary diets, worsening of QoL, reduced calcium intake, and increased risk of osteopenia, osteoporosis, and long bone fractures in people using milk intake as most important source of calcium. For these reasons, the diagnosis of lactose intolerance has to be performed accurately (62).
Lactose hydrogen breath test (BTH), is currently considered to be the most cost-effective, non-invasive and reliable test to measure lactose maldigestion.
Recently,genetic test has gained attention, genotyping the -13910 C>T variant.

Hydrogen Breath test

The hydrogen breath test is the least invasive and most helpful test to diagnose lactose malabsorption. The test has been shown to be more reliable than history, because some patients think they are lactose intolerant when they prove

not to be, and others prove to be lactose intolerant (lactose malabsorbers) when they think they are not. The test is performed by administration of a standardized amount of lactose (2 g/kg, up to a maximum of 25 g, equivalent to the amount of lactose in 2 8-oz glasses of milk in children,) after fasting overnight and then measuring the amount of hydrogen in expired air over a 2- to 3-hour period. A positive test requires an elevated breath hydrogen concentration higher than 20 ppm over basal values; these concentrations are indicative of a bacterial colonization of the small intestine, where bacteria can metabolize non-absorbable sugars thus producing increased H2 amounts, which are eliminated through respiration (63).
Factors that may produce false-negative or false-positive results include conditions affecting the intestinal flora (eg, recent use of antimicrobial agents), lack of hydrogen-producing bacteria (10%-15% of the population), ingestion of high-fiber diets before the test, small intestinal bacterial overgrowth, or intestinal motility (64).
In some subjects, there is a positive lactose hydrogen breath result without the subjects having had any prior symptoms of lactose intolerance. This indicates that these subjects have lactose malabsorption, but no symptoms presumably because of personal dietary restriction.
The diagnosis of lactose maldigestion is usually based upon the positivity of HBT after an oral load of lactose. The most commonly used load of lactose in adults is 20-25 g, corresponding to an intake of 400-500 mL of milk, which is rarely ingested in a single dose. Indeed, 400-500 mL of milk exceeds in most instances, the total daily intake of milk and diary products. Thus, the traditional test with 25 g lactose likely overestimates the prevalence of lactose intolerance. This may lead to unnecessary restrictions in the intake of foods that represent the main source of dietary calcium. A recent study confirmed, in a large series of patients, previous observations showing that high loads of lactose (50 g, corresponding to 1 L of milk) induce abdominal pain and diarrhea in most lactose malabsorbers. Conversely, small amounts of the sugar were usually well tolerated. Thus, a moderate intake of lactose during a standard HBT may prove harmless in the large majority of patients diagnosed as lactose intolerant or lactose maldigester (65).

Genetic test

Genotyping is quick and easy and has high specificity for the lactase gene. It may help to differentiate patients with primary hypolactasia from those with lactose intolerance caused by secondary hypolactasia. However, this test is not yet routinely available in clinical practice (66).
Genotyping may be performed either on blood or in saliva, is quick and easy and has high specificity for the lactase gene. A recent modality is suitable for clinical genotyping of patients not only of European, but also of African or Middle Eastern descent, who may harbor any combination of the three LCT mutations, LCT -13907C>G, LCT -13910C>T, LCT -13915T>G (67).
An appropriate use of genetic testing would be to exclude adult-onset hypolactasia as a cause of non-specific intolerance symptoms which may derive from a multiplicity of causes. Detection of the -13910 C/C genotype would not constitute proof that a patient's symptoms resulted from hypolactasia, but detection of the C/T or T/T genotypes would essentially rule out primary lactase deficiency as a cause of patient symptomatology (68).
The identification of a simple genetic test for adult hypolactasia is a significant advance on previous methods of diagnosis. These existant methods are both time- and labour intensive, and require specialist facilities. The lactose hydrogen breath test (LHBT) is carried out in a clinical setting, and lacks formal standardization (69).
In summary, the recent identification of DNA polymorphisms associated with lactase nonpersistence or persistence permits analysis of the genetic predisposition for lactose maldigestion by standard molecular biological techniques (70).

Treatment

Treatment depends on the underlying type of deficiency. In primary lactase deficiency the development of symptoms depends on how much lactose needs to be ingested before the available lactase is saturated. Thus, most people with primary lactase deficiency can ingest up to 240 ml of milk (12 g of lactose) without developing symptoms. The recent American trend of larger portion sizes exacerbates individuals consuming amounts of lactose that can be tolerated. Lactose in large servings of frozen yogurts, shakes, and milk may exceed that which can be tolerated by maldigesters. Physicians and other health care workers need to work with patients to urge consumption of single servings of dairy products throughout the day, preferably with meals and reiterate that the serving size for milk is 1 cup for children and adults (33).
It may help to divide daily milk intake into several small portions and to take it with other foods. Yogurt, curds,

and cheeses are better tolerated, because lactose is partially hydrolysed by bacteria during their preparation and gastric emptying is slower as these products have a thicker consistency (71). In patients with lactase nonpersistence, treatment is considered exclusively in the presence of intolerance symptoms. In the absence of guidelines, the common therapeutic approach tends to exclude milk and dairy products from the diet. However, this strategy may have serious nutritional disadvantages, chiefly for reduced intake of substances such as calcium, phosphorus and vitamins, and may be associated with decreased bone mineral density. To overcome these limits, several studies have been carried out to find alternative approaches, such as lactase enzyme preparations (exogenous β-galactosidase), (72) yogurt and probiotics for their bacterial lactase activity, strategies that can prolong contact time between enzyme and substrate delaying gastrointestinal transit time, and chronic lactose.

There are currently no national or international guidelines on how to manage lactose intolerance.

Montalto and coll. suggest a flow chart for the therapeutic management of lactose malabsorption (Fig. 3) The authors underlie that not all subjects with lactase deficit have to be treated, but just symptomatic ones, since there are no known adverse of lactose maldigestion other than acute gastrointestinal symptoms (73).

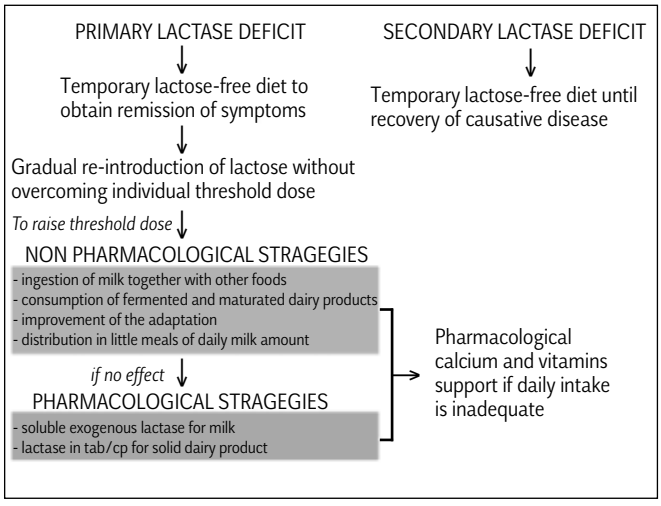
Exogenous β-galactosidase. Enzyme-replacement therapy with microbial exogenous lactase (obtained from yeasts or fungi) represents a possible strategy for primary lactase deficiency. Enzymes can be added in a liquid form to milk before its consumption or administered in a solid form (capsules or tablets) together with milk and dairy products. Several studies were conducted adding the soluble enzyme to milk some hours before its consumption, thus obtaining a "pre-incubated milk". This strategy is effective in reducing both H2 breath excretion and subjective manifestations of discomfort after milk ingestion. However, these trials were carried out on relatively small series populations. They were not placebo-controlled, and results were not comparable since there was a lack of homogeneity in patient subsets. Furthermore, pre-incubated milk was not considered practical because of the necessity to add the enzyme some hours before its consumption. The low-lactose milk is a pre-incubated milk in which the lactose is already pre-hydrolyzed; this product is commercially available but not distributed everywhere (i.e. restaurant, cafeterias, etc). To obviate these problems, several studies have been carried out to show the effectiveness of replacement therapy even when lactase is administered at mealtime. Solid lactase preparations, in capsules and tablets, are commercially available alternatives for enzyme-replacement therapy. Several studies have investigated and confirmed their efficacy. However, comparative studies have shown that these preparations are more expensive and significantly less effective than liquid form, probably due to the enzyme gastric inactivation. Their use can be suggested for solid dairy products (73).

Therapy compliance with β-galactosidase is assured by good palatability though there are some reported taste alterations. The safety of lactase preparations has recently been confirmed (74). In conclusion, the addition of exogenous lactase, especially at mealtime, seems to be effective, practical and with no side effects.

Fermented milk products can improve lactose digestion and symptoms of intolerance in lactose maldigesters. The use of fermented milk is based on the presence of endogenous lactase activity of yogurt microorganisms. Not all studies confirm the efficacy of oral probiotics in adults with lactose intolerance (75). Some evidence suggests that specific strains, concentrations, and preparations are effective

To effectively release β-galactosidase, bacteria need an intact cell wall as mechanical protection of the enzyme during gastric passage and against the action of bile. It was demonstrated that gastric acid degrades bacterial lactase activity in 20-60 min. However, the association of L. acidophilus BG2F04 with omeprazole does not result in reduced hydrogen production and gastrointestinal symptoms are not improved after lactose ingestion with respect to lactobacilli without it. These results could have been due to

Figure 3 - Proposal of therapeutic management in lactose intolerance patients with lactase deficit



the selected lactic bacteria. Further investigations are necessary to clarify the probiotics role in lactose intolerance therapy, also considering their well-known beneficial effects on intestinal functions, gas metabolism and motility.
The bacterial β-galactosidase activity of yogurt is considered to be the main factor responsible for improving lactose digestion; its greater osmolality and energy density can also play a role. Yogurt delays gastric emptying and intestinal transit causing slower delivery of lactose to the intestine, thus optimizing the action of residual β-galactosidase in the small bowel and decreasing the osmotic load of lactose (76).

In conclusion, the correct management of patients with lactose intolerance requires the following measures:
- An accurate history.
- A correct diagnosis.
- A proper personalized diet based on the individual amount of tolerated lactose.
- A correct use of drug therapies, including exogenous β-galactosidase, if needed.

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