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Update on lactose malabsorption and intolerance: pathogenesis, diagnosis and clinical management

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SUMMARY

Lactose is the main source of calories in milk, an essential nutriedigestion, patients with visceral hypersensitivity nt in infancy and a key part of the diet in populations that maintain the ability to digest this disaccharide in adulthood. Lactase deficiency (LD) is the failure to express the enzyme that hydrolyses lactose into galactose and glucose in the small intestine. The genetic mechanism of lactase persistence in adult Caucasians is mediated by a single C⟶T nucleotide polymorphism at the LCTbo −13′910 locus on chromosome-2. Lactose malabsorption (LM) refers to any cause of failure to digest and/or absorb lactose in the small intestine. This includes primary genetic and also secondary LD due to infection or other conditions that affect the mucosal integrity of the small bowel. Lactose intolerance (LI) is defined as the onset of abdominal symptoms such as abdominal pain, bloating and diarrhoea after lactose ingestion by an individual with LM. The likelihood of LI depends on the lactose dose, lactase expression and the intestinal microbiome. Independent of lactose digestion, patients with visceral hypersensitivity associated with anxiety or the Irritable Bowel Syndrome (IBS) are at increased risk of the condition. Diagnostic investigations available to diagnose LM and LI include genetic, endoscopic and physiological tests. The association between self-reported LI, objective findings and clinical outcome of dietary intervention is variable. Treatment of LI can include low-lactose diet, lactase supplementation and, potentially, colonic adaptation by prebiotics. The clinical outcome of these treatments is modest, because lactose is just one of a number of poorly absorbed carbohydrates which can cause symptoms by similar mechanisms.

Box 1 Pathophysiology of lactose malabsorption

- Lactose malabsorption is typically caused by lactase downregulation after infancy due to lactase non-persistence which in Caucasians is mediated by the LCT −13′910:C/C genotype.
- Lactase non-persistence is the genetic wildtype and not a disease. Both lactase persistence and non-persistence are common phenotypes in healthy humans.
- The lactase genetic region is among the genetic regions strongest shaped by human evolution within the last 10 000 years, with lactase persistence providing a selective advantage of up to 4%–5% per generation.
- The LCT −13′910 is the region within the human genome with the strongest interaction with the intestinal microbiota. The LCT −13′910:C/C genotype is associated with higher Bifidobacteria levels on lactose consumption (bifidogenic effect).
- Genetic and physiological studies suggest higher bone mineral density and larger height in individuals with lactase persistence.

INTRODUCTION

Lactose metabolism continuous to fascinate anthropologists, geneticists, physiologists and clinicians.[1–3] Studying the mechanisms of lactose digestion and intolerance has provided insights not only into dietary causes of functional intestinal symptoms but also into human evolution and nutrition, culture and lifestyle (box 1). Recent evidence has demonstrated the impact of lactose digestion on the human microbiota and general health. Considering these issues has raised possible concerns of a dairy-free diet. This review will emphasise recent developments in the clinical diagnosis and management of this condition (box 2).

LACTOSE IS THE MAIN SUGAR IN MILK

Milk production by the mammary gland is a defining feature of mammals and lactose ('milk sugar'; β-galactosyl-1,4 glucose) is the main source of carbohydrate in human milk and that of other mammals, except for sea lions and walruses which produce low volume, viscous and fatty lactose-free milk.[4]

Infants are uniquely adapted to lactose-based nutrition. In a randomised controlled study, infants fed with breast milk or lactose-based formula had higher levels of glucose and other nutrients (eg, amino acids) in the blood compared with infants with lactose-free formula.[5] Lactose also seems to be the only monosaccharide or disaccharide that does not increase the risk of dental caries.[6] In adults, dairy products account for approximately 14% of energy intake in Europe and North America. In recent years, the amount of milk consumed has slightly decreased in these regions. By contrast, in China and many developing countries, milk intake contributes only 4% to energy intake; however, consumption is increasing rapidly.[3]

Cow's milk contains approximately 5 g lactose per 100 mL, equating to 12.5 g lactose in a typical serving size of 250 mL. Lactose is also present in cultured milk products such as yoghurt and cheese (the second-largest fermentation industry after alcohol).[3] Yoghurt contains ≈50% of the

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Box 2 Clinical relevance of lactose intolerance

- Lactose intolerance is defined as symptoms on lactose exposure in individuals with lactose malabsorption.
- Most individuals with lactose malabsorption tolerate a dose of at least 12 g lactose (corresponding to 250 mL of milk) without problems. Larger doses may be tolerated if consumed with food or spread over a whole day.
- Symptoms of lactose intolerance depend on the strength of the stimulus (ie, lactose dose) and the presence of visceral hypersensitivity, as observed in many patients with IBS.
- Treatment options for lactose intolerance include a low-lactose diet, oral lactase enzyme replacement, prebiotics that produce bacterial lactase in the colon and, potentially, prebiotics that adapt the colonic microbiota.
- Intolerance of low–moderate lactose doses often indicates the presence of IBS. Such individuals are sensitive to a range of poorly absorbed, fermentable foods ('FODMAPs'). Effective dietary treatment in this group requires not a low-lactose but a low-FODMAP diet.

FODMAP, fermentable oligosaccharide, disaccharide and monosaccharide and polyols.FODMAP, fermentable oligosaccharide, disaccharide and monosaccharide and polyols.

Table 1 Lactose content in dairy products and foods (representative values are provided)

Food	Lactose content (g) per 100 g	Lactose content per typical serving (g)
Milk (full)	4.7	15
Milk (skimmed)	4.8	15
Lactose-free milk	<0.1	<0.1
Goat's milk	4.5	13
Buttermilk	3.0	9.0
Butter	0.5	0.1
Yoghurt (fresh)	3.0	9.3
Yoghurt (biological)	4.0	9.5
Cream cheese	3.0	0.9
Soft cheese (eg, camembert)	0.3	0.1
Hard cheese (eg, cheddar and gruyere)	0.1	<0.1
Cream	3.6	3.2
Soft ice cream	6.4	5.7
Latte Macchiato	4.3	8.6
Lasagne	1.1	2.6
Cheeseburger	0.9	1.1
Ready sauces	3.6	4.5
Pudding/custard	3.6	4.5
Rice, nut, soy or oat beverages	0.0	0.0
Meat and alternatives contain very little lactose. Products that may include lactose are those prepared with milk or milk products such as some processed meat, sausage, breaded or battered meat or fish, commercial egg substitutes, scrambled eggs, soufflés.		
Fats and oils contain very little lactose. Products that may include lactose are those prepared with milk or milk products such as butter or margarine made with milk or whey powder and salad dressings (eg, ranch style or buttermilk).		
Prepared foods may include lactose when made with milk or milk products. These include store bought gravy or sauce mixes, vegetable or chip dips, soups, chips or snack crackers (eg, cheese flavoured), artificial whipped toppings, powdered meal replacement supplements and cream-based liqueurs.		

lactose of unprocessed milk; whereas, cheese has low lactose content, especially if long-ripened products are consumed.[3] Additionally, lactose powder is also a common additive in typical processed foods, enhancing the texture and flavour of sausages, gravy, margarines, bread, sauces, and many prepared meals (table 1).

LACTOSE DIGESTION AND ABSORPTION

Digestion and absorption of lactose takes place in the small intestine (figure 1).[7 8] Lactose is the main substrate of lactase-phlorizin hydrolase expressed on the brush border of villi with its highest expression in the mid-jejunum. The enzyme spans the apical membrane of mature enterocytes and is made up of two identical extracellular 160 kDa polypeptide chains, as well as a short intracytoplasmic part. The alpha-glucosidase activity of this enzyme cleaves the milk sugar disaccharide into the monosaccharides glucose and galactose which are then actively transported into epithelial cells (enterocytes) by the sodium(+)/glucose (galactose) co-transporter (SGLT1). At higher concentrations, a second facilitative transporter (GLUT2) becomes involved.[9] From the enterocytes, glucose moves into the surrounding capillaries by facilitated diffusion.

LACTASE DEFICIENCY AND LACTOSE MALABSORPTION

The terms relating to lactose metabolism are often mixed-up which may cause confusion (table 2). Lactase deficiency (LD) is the failure to express lactase at the brush border of the small intestine. Lactose malabsorption (LM) refers to any cause of failure to digest and/or absorb lactose in the small intestine. Lactose intolerance (LI) is the occurrence of symptoms such as abdominal pain, bloating or diarrhoea in LM patients after ingestion of lactose.

Congenital lactase deficiency is a very rare paediatric condition that causes severe symptoms and failure to thrive in infants.[10] The most common cause of LM in adolescents and adults is primary (genetic) lactase non-persistence (LNP). The activity of lactase in the small intestine reaches a peak at the time of birth but is reduced in most populations during childhood, a process which is thought to facilitate weaning. However, in some individuals, high activity of lactase persists, enabling consumption of large amounts of lactose also in adulthood. It should be emphasised that, worldwide, most individuals have LNP with phenotypic LD and LM (figure 2). Thus, LNP, LD and LM are not diseases but normal variants of human metabolism.[11] Other

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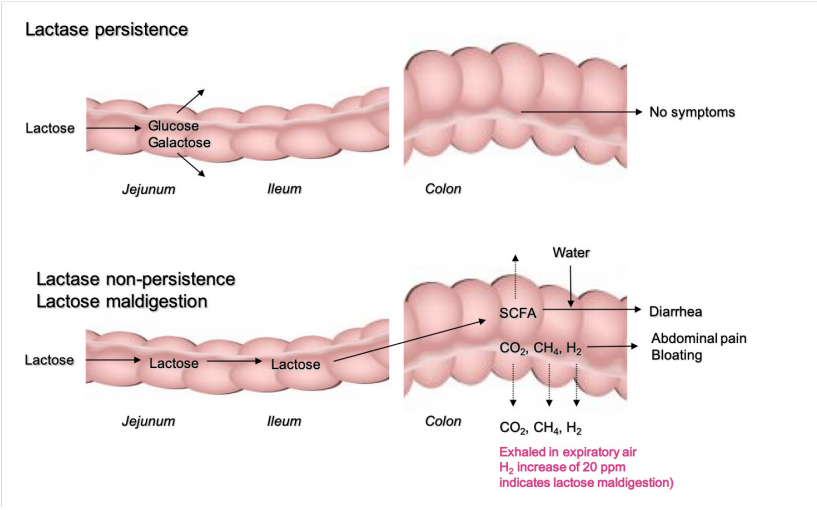


Figure 1 Physiology of lactose malabsorption. SCFA, short chain fatty acids.

causes of LM include secondary (acquired) LD, rapid small intestinal transit and small bowel bacterial overgrowth.

In case of LM (primary or secondary), undigested lactose comes into contact with the intestinal microbiota. Bacterial fermentation of lactose results in production of gasses including hydrogen (H_2), carbon dioxide (CO_2), methane (CH_4) and short chain fatty acids (SCFA) that have effects on GI function (figure 1).

LACTOSE INTOLERANCE

Lactose malabsorption (LM) is a necessary precondition for lactose intolerance (LI). However, the two must not be confused and the causes of symptoms must be considered separately. Many individuals with LM have no symptoms after ingestion of a standard serving of dairy products (table 1) whereas others develop symptoms ('intolerance') such as abdominal pain, borborygmi (rumbling tummy) and bloating after lactose intake (figure 1). The onset of these symptoms is strongly correlated to the appearance of hydrogen gas during breath tests[12] . Further, undigested lactose in the small intestine lead to osmotic trapping of water and the osmotic load in the colon is increased about eightfold by fermentation of lactose to SCFA.[13 14] Diarrhoea will result if the respective load of lactose exceeds the capacity of the colonic microbiota for fermentation or the SCFA load exceeds the colon capacity for resorption.[15]

The likelihood of developing symptoms after lactose ingestion is multifactorial (figure 3). Extrinsic factors include the amount of lactose ingested and whether dairy products are ingested with other foods that affect intestinal transit and the rate of lactose delivery to the colon. Intrinsic factors include expression of lactase at the brush border of the small intestine, history of GI disorders or abdominal surgery and the composition of the intestinal microbiome. When incubated in vitro with lactose, faecal samples from lactose-intolerant subjects mediated faster and higher production of SCFA than samples from lactose-tolerant subjects.[16 17] However, an impact of SCFA on symptoms has not been directly demonstrated in humans. Further, in the anaerobic environment of the intestinal tract, generation of reducing equivalents result in rapid hydrogen production, and in several clinical studies, the amount of gas production correlated with the presence and severity of intestinal symptoms.[18 19] Other patient factors not directly related to lactose digestion are also associated with LI. These include the presence of anxiety disorders, high levels of psychosocial stress and the presence of functional GI disorders such as IBS (figures 3 and 4).

Products of lactose fermentation may also trigger extra-intestinal symptoms. A recent review of results from >2000 patients with a clinical diagnosis of functional GI disorders, reported a high frequency of neurological symptoms such as tiredness and

Table 2 Glossary with definitions related to lactase deficiency, lactose malabsorption and lactose intolerance

Concept		Definition
Congenital lactase deficiency	CLD	Very rare genetic disorder (typically frameshift mutations) leading to lack of expression of lactase and severe symptoms immediately after birth
Lactase non-persistence	LNP	Decrease of intestinal lactase expression in the first two decades of life. Phenotype in most individuals worldwide (biological wildtype)
Lactase persistence	LP	Continued expression of intestinal lactase expression beyond infancy; dominant phenotype in Western countries.
Lactase deficiency	LD	Inability to digest large amounts of lactose due to low lactase expression in the small intestine
Lactose malabsorption	LM	Passage of lactose into the large intestine as a consequence of LD or other pathology (eg, rapid transit)
Primary lactose malabsorption		Lactose malabsorption due to lactase non-persistence (dominant phenotype worldwide).
Secondary lactose malabsorption		Lactose malabsorption due to lower lactase expression, typically in the setting of intestinal inflammation (may be reversible).
Lactose intolerance	LI	Appearance of typical intestinal symptoms such as abdominal pain, bloating, diarrhoea in individuals with LM after lactose ingestion determined by appropriate testing (ideally blinded testing).
Functional lactose intolerance		Symptoms of LI on lactose challenge in individuals without lactose malabsorption.
Self-reported lactose intolerance	SLI	History of LI symptoms without formal testing of either LM or LI.

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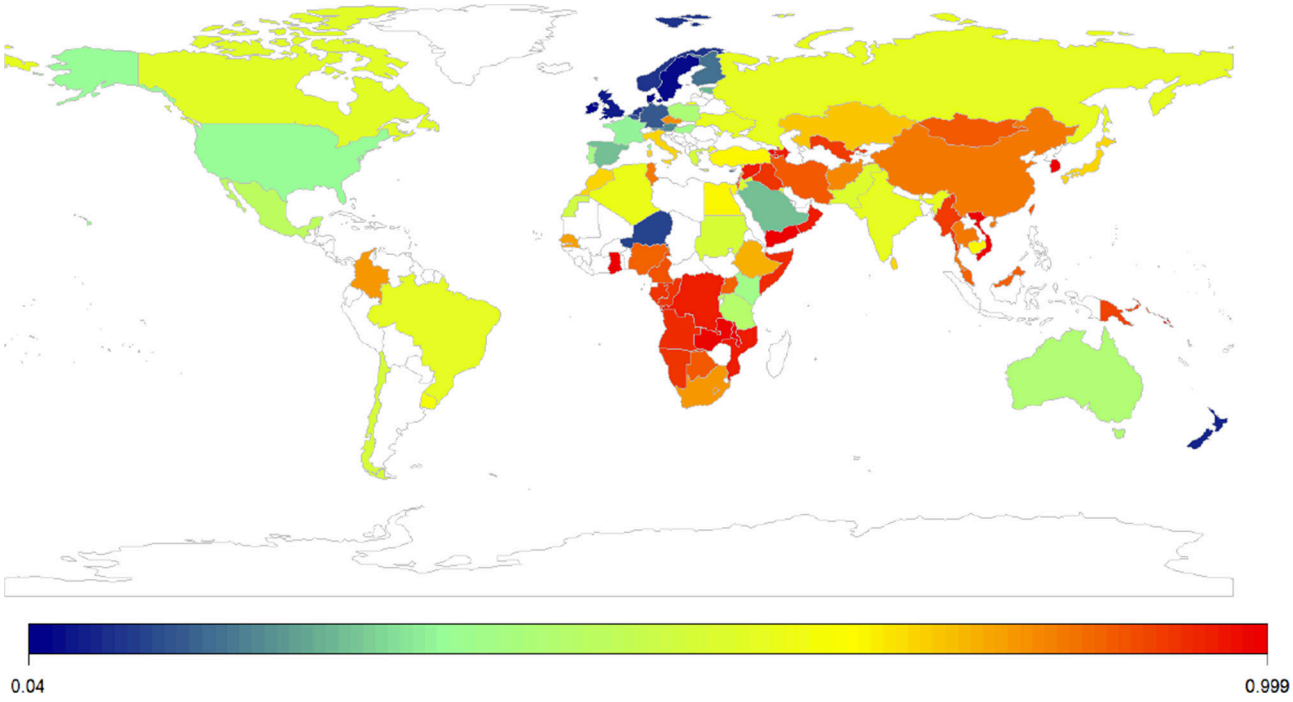


Figure 2 Worldwide prevalence of lactose malabsorption. Online supplement 1 breaks down the the evidence base in terms of the investigative modality used to acquire the epidemiological information (eg, genetic test and breath test). Online supplement 2 provides the complete reference list.

headache after lactose or fructose ingestion.[20] However, it is uncertain whether the occurrence of neurological symptoms was caused by LM, because these patients have a high prevalence of nonspecific somatic complaints[21], there was no placebo control, no statistical relationship between H_2 production and symptoms was present and no mechanistic explanation was provided.[20]

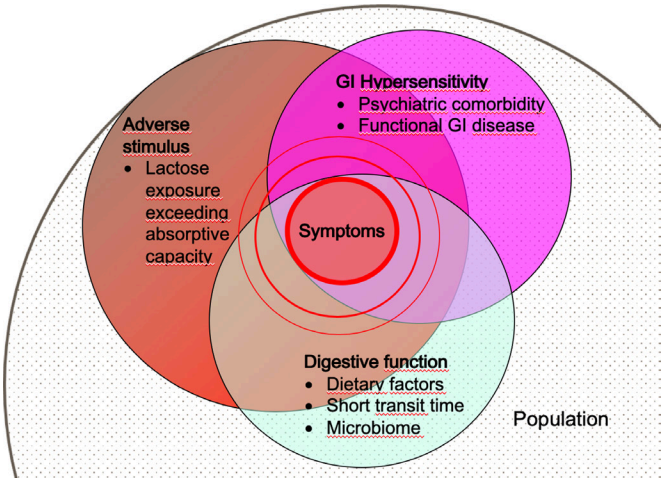


Figure 3 Schematic model of the pathogenesis of lactose intolerance symptoms. In a given population, a fraction of individuals will have digestive dysfunction resulting in lactose malabsorption. Within this population, individuals with anxiety disorders or GI disease that increase visceral sensitivity are more susceptible to the lactose challenge. In this model, the risk of developing symptoms increases with lactose dose, severity of digestive dysfunction (lactose malabsorption) and visceral sensitivity. This model of disease is not restricted to lactose but is likely to be shared by other FODMAPs, fermentable oligosaccharides, disaccharides and monosaccharides and polyols.

EPIDEMIOLOGY

A recent meta-analysis estimated the prevalence of LM worldwide at 68% with higher rates reported for genetic tests than hydrogen breath tests (HBTs).[22] LM is lowest in Nordic countries (<5% in Denmark) and highest in Korean and Han Chinese populations (approaches 100%). Large variations in LM are seen on a regional level (figure 2),[22] reflecting the underlying genetic heritage and prevalence of primary LD in these populations. Testing for LI is more complex and would require standardised hydrogen breath testing in large, carefully selected populations and, for this reason, the prevalence of LI is unknown.

GENETICS

In the Caucasian population, lactase persistence (LP) is due to a gain-of-function mutation 13.9 kb upstream of the lactase gene (LCT-13'910:C→T, "T' for tolerance') on chromosome 2. This single nucleotide polymorphism (SNP) is far upstream of the protein forming unit within the intron of an unrelated gene (figure 5A).[23] This mutation creates a new binding site for the transcription factor that promotes persistent lactase expression after infancy.[24]

Genetic LP is considered a dominant genotype, and only individuals with two LCT-13'910:C alleles should be considered to have LNP. However, heterozygotes with LCT-13'910:CT genotype may have higher H_2 levels in the HBT than LCT-13'910:TT individuals.[25] This intermediate phenotype might be relevant during nutritional challenges or intestinal diseases. By contrast, epigenetic regulation of the lactase gene appears to be critical. Methylation patterns in the region of the LCT-13'910:C/T polymorphism in small intestinal enterocytes strongly differ dependent on the genotype, from >80% modification with the LNP genotype to 20% with the LP genotype (figure 5B). It has also been shown that LCT promotor methylation is low after birth but increases in childhood in the presence of LCT-13'910:C but not LCT-13'910:T.[26] Thus, LNP is a good example of a condition

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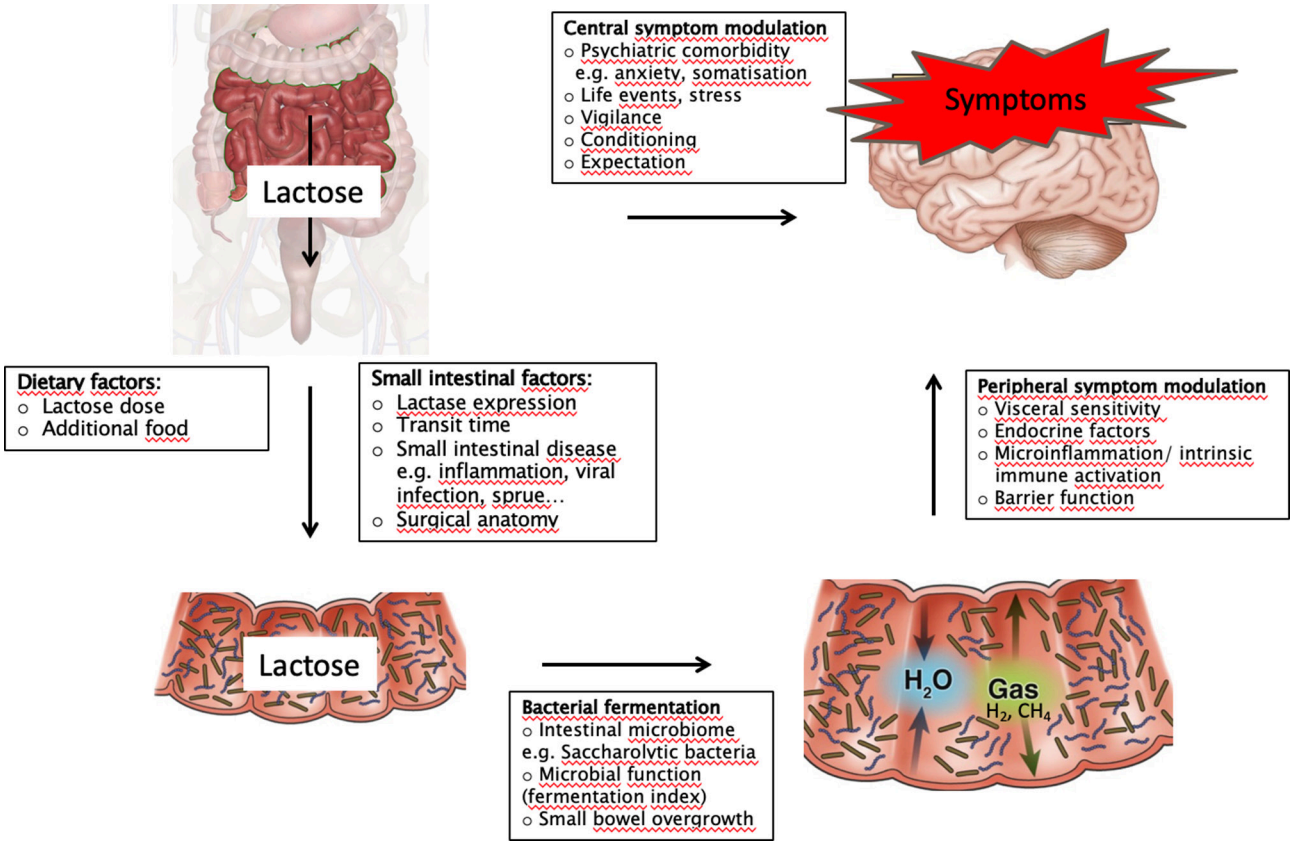


Figure 4 Mechanistic model of lactose digestion in patients with lactase persistence and lactase deficiency illustrating the relationship between lactose malabsorption, visceral sensitivity and symptoms.

in which DNA sequence variations set the stage for age-dependent methylation which later results in a clinical phenotype, a mechanism that might be applicable also to complex diseases.[27]

The LCT-13'910:T SNP associated with LP in Europe and many near Asian regions resides on the same haplotype, indicating rapid spread of a single mutation.[28] The mutation appears

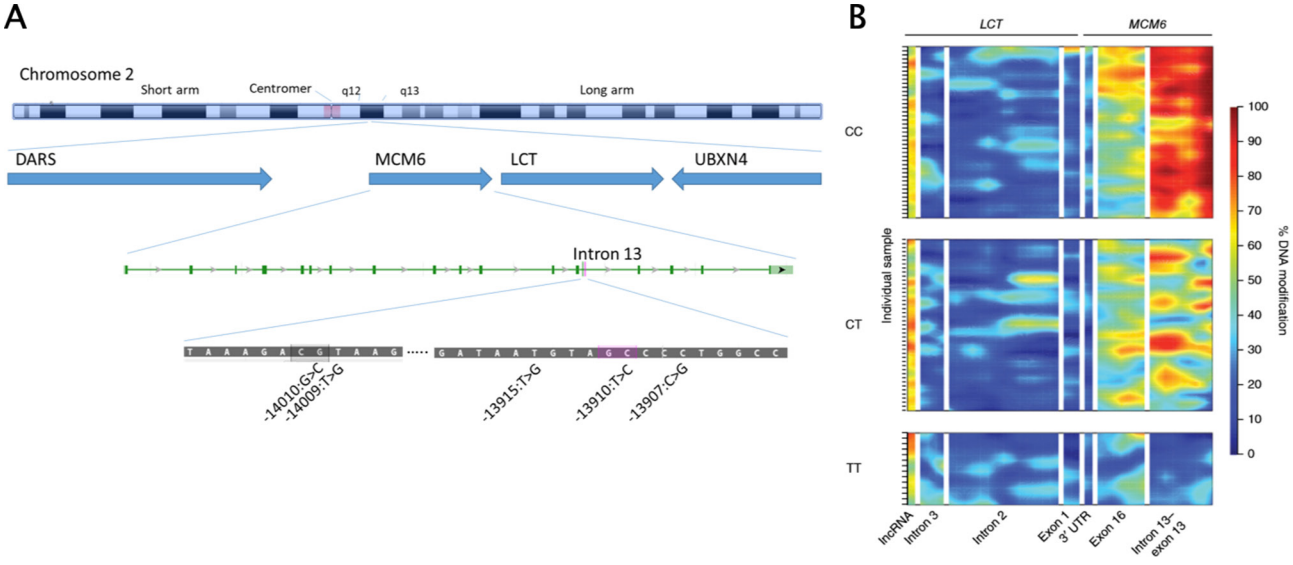


Figure 5 Genetics of lactose malabsorption. (A) Organisation of the lactase genetic locus on chromosome 2. The positions of the lactase gene (LCT) and the neighbouring genes aspartyl-tRNA synthetase (DARS), minichromosome maintenance complex component 6 (MCM6) and UBX domain-containing protein 4 (UBXN4) are indicated. Polymorphisms relevant for lactose malabsorption are located within intron 13 of the MCM6 gene, upstream of the lactase gene. (B) Differential levels of methylation of intron 13 of MCM6 and the LCT gene in individuals with genetic lactose malabsorption (LCT –13910:C/C), lactose tolerance (LCT –13910:T/T) and the clinically silent, physiologically intermediate genotype LCT –13910:C/T. Hypermethylation (red colour) results in genetic silencing of the respective gene. (*Source*: From Labrie *et al*[26]).

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Table 3 Genetic variations affecting lactase persistence and LM[1]

Mutation associated with lactase persistence	Geographic region	SNP
LCT –13'910:T*	Northern Europe	rs4988235
LCT –13'915:G	Middle East	rs41380347
LCT –13'907:G	Ethiopia and Sudan	rs41525747
LCT –14'009:G	Ethiopia and Sudan	rs820486563
LCT –14'010:C	Kenya, Tanzania and South Africa	rs145946881

*This mutation is in strong linkage disequilibrium with the LCT –22'018-A mutation. Mechanistic evidence indicates that the –13'910 mutation is responsible for lactase persistence.
LM, lactose malabsorption; SNP, single nucleotide polymorphism.
Source: Adapted from Segurel and Bon [1]

in prehistoric skeletons for the first time approximately 10 500 years ago in Anatolia with spread to Europe and Northern Africa over time in line with domestication of animals. In Africa and the Middle East, different mutations in the same genetic region are responsible for LP[1 29] (table 3), indicating convergent evolution.

There is convincing genetic evidence for a strong selection pressure for LP. In a whole genome analysis of skeletons originating between 6500 and 300 BC, the LCT-13'910:T allele showed increasing prevalence over time.[30] LP provided an advantage of up to 4%–5% per generation, which is one of the largest selection pressures observed for any gene in recent human evolution and is in the same order of magnitude as resistance genes for malaria (4%–9%), skin pigmentation in Europeans (3%) and genes associated with hypoxia response in Tibetan populations at high altitude.[1]

The ability to digest lactose after infancy made milk a source of nutrition (calories, protein) and clean water accessible to adults. This is likely to have been critical in periods of famine. However, why LP increased fitness to such a high degree is unclear since many individuals with LM can consume 250 mL of milk without developing symptoms, and processing of milk to yoghurt, cheese or butter decreases the advantage of LP further.[31] Further, the 'cost' of LNP with generally mild abdominal symptoms seems modest and individuals with LNP may even benefit from milk consumption due to prebiotic activity of lactose on the colonic microbiota.[1] Increased intake of vitamin D from milk could also provide a selective advantage, especially in Northern Europe with a high risk of vitamin D deficiency due to low ultraviolet exposure.[3 32]

Taken together, impressive selection pressure took place at the lactase genetic locus after the uptake of pastoralist farming, favouring LP in many regions worldwide; however, the specific advantage of milk consumption that increased survival and whether these are present only during times of dietary or health stress or continuously remain unclear.

SECONDARY LACTOSE MALABSORPTION

Secondary LM refers to the development of LM in individuals who are potentially able to digest lactose (ie, LP individuals).[33 34] Lactase is situated at the tip of intestinal villi and thus vulnerable to intestinal injury, especially since new immature enterocytes are lactase deficient.[6] As a consequence, secondary LM can complicate GI conditions including infectious gastroenteritis, IBD, coeliac disease and systemic sclerosis (SSc).

The incidence of secondary LM, which is often transitory, caused by infectious gastroenteritis is increased and can be clinically relevant,[35] especially in infants for whom milk is the staple food. In a paediatric study (mean age 12 months) with 126 patients with rotavirus infection and 62 controls with rotavirus negative diarrhoea, LM was more frequent in the former group (60% vs 49%, p=0.002).[36] Similarly, in adult patients with chronic diarrhoea after kidney transplantation, those with norovirus colonisation had a much higher risk for LM than a control group (100% vs 12.5%).[37] A systematic review concluded that exclusion of lactose would reduce the duration of acute diarrhoea in children by up to a day and reduce 'treatment failure' (RR: 0.5, 95% CI: 0.4 to 0.7), variously described in studies as requirement for unscheduled intravenous fluid injection or persistent stool weight >30 g/kg after 3 days.[38]

Similar but more persistent results are seen in IBD. In a meta-analysis, the overall OR for LM in patients with IBD was 1.6 (95% CI: 1.0 to 2.6, p=0.048), being highest in Crohn's disease (CD) affecting the small bowel.[39] In line with this observation, a paediatric study showed reduced lactase expression in CD patients with the risk of LD correlated with villous atrophy.[39 40] High prevalence of secondary LM has also been reported in other conditions that affect the mucosal integrity or function of the small bowel. Patients with a new diagnosis of coeliac disease often have a positive lactose HBT; however, many recover the ability to digest lactose after 6–12 months on a gluten-free diet.[41]Patients with SSc also have a high prevalence of LM on breath testing, a finding that is associated with more advanced disease.[42] Secondary LD may complicate environmental enteric dysfunction (EED), a condition that affects mainly children in an environment with low resources, poor hygiene and poor nutrition. EED is characterised by intestinal atrophy and dysbiosis associated with enzyme deficiencies, malabsorption and malnutrition.[43]

LACTOSE MALABSORPTION AND THE MICROBIOTA

The human body harbours approximately 40 trillion bacteria with approximately 99% of the microbiome contained within in the human colon. Fermentation of lactose by saccharolytic ('sugar digesting') bacteria in individuals with LM can cause abdominal symptoms (figures 1 and 4). However, this process also has benefits. SCFA and other products of fermentation are required for colonic health and liberate additional calories from otherwise indigestible carbohydrates. Moreover, the intestinal microbiota adapts to facilitate intake of dairy products. As a result, although lactase expression is not upregulated by lactose ingestion, regular consumption of lactose appears to reduce breath hydrogen excretion and reduced lactose intolerant symptoms.[44] Both in vitro and in vivo studies demonstrate increases in Bifidobacteria and/or Lactobacilli that are considered to be healthy components of the microbiome.[45 46] In a large study of healthy Japanese, the abundance of Bifidobacteria correlated positively with dietary dairy intake.[47] As this population is 90%–100% LNP, this could reflect the effect of regular lactose intake on the microbiota; however, the reverse cannot be excluded .

Recent data point to interactions between human genes and the microbiota. In association studies between human genetic variations and the microbiota, to date, the association most consistently described is that between the LCT-13'910:C/T SNP and the abundance of Bifidobacterium.[48–50] Such interactions might have practical implications because SCFAs produced by microbial fermentation of lactose are involved in immune regulation,[51] glucose and lipid homeostasis,[52] colonocyte differentiation[53] with implications for homeostasis and gut-brain modulation.[54] Taken together, some experts suggest that LNP subjects may have 'more to gain than to lose' by consumption of small amounts of lactose-containing foods.[55]

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LACTOSE INTOLERANCE AND IBS

The relationship of LI and IBS has been extensively studied in a South Chinese population with near 100% LNP on genetic testing. A double-blinded, randomised, cross-over comparison of lactose tolerance at 10, 20 and 40 g lactose was performed in IBS patients with diarrhoea (IBS-D) and healthy controls.[56] There was a very strong correlation between the appearance of hydrogen gas in the breath and reports of bloating, pain and other symptoms in patients with lactose intolerance. However, the correlation between the amount of hydrogen gas in the breath and the severity of symptoms was much weaker. Consistent with preliminary findings in a European population,[57] a key observation was that the risk of symptoms and the severity of symptoms were greatly increased in IBS patients, especially at the low to moderate doses found in the normal diet. It is well known that many patients with functional GI disorders have psychological comorbidity and are hypersensitive to dietary and physical stimuli that affect the digestive tract. [21 58] Further work demonstrated that anxiety, visceral hypersensitivity (defined by rectal barostat) and high levels of gas production on breath tests all increased the severity of abdominal symptoms after ingestion of 20 g lactose.[19] Moreover, mucosal biopsies from the ileum and colon showed increased numbers of mast cells and intraepithelial lymphocytes in lactose-sensitive patients and showed that the release of inflammatory cytokines (eg, tumour necrosis factor) after lactose intake was higher in this group than controls .[59]

These observations are similar to those in post-infective IBS[58] and provide insight into the pathophysiological basis not only of food intolerance but, more generally, functional GI symptoms. IBS is a heterogenous condition; however, symptoms related to intake of food items with poorly absorbed, fermentable carbohydrates such as lactose are reported by up to 70% of patients with this diagnosis.[60–62] Patients with LI and IBS complain of similar symptoms, have high rates of psychological comorbidity and markers of an activated innate mucosal immune system. Moreover, both respond to similar dietary interventions (see below). Together, this evidence suggests a common pathological basis in which a susceptible individual with a sensitive ('irritable') bowel develops symptoms when exposed even to a modest stimulus, such as low–moderate doses of lactose (figure 3).[33]

LACTOSE INTOLERANCE AND QUALITY OF LIFE

Like other functional GI disorders, LI is not a trivial condition but has a negative impact on quality of life and nutrition. Anxiety increases the risk of symptoms ('intolerance') after lactose ingestion, but the fear that food will trigger bloating, pain and diarrhoea is also a cause of anxiety. Indeed, in studies, not only patients with LI but also those with self-diagnosed LI who do not have the condition describe a lower quality of life than individuals without concerns about food intolerance.[61 62] This anxiety generalises to other foods, and patients with LI often describe intolerance to a range of products, especially those known to cause bloating (eg, legumes and dried fruit).[62] As a result, individuals might adopt a restrictive diet that could impact on health in a variety of ways.[60 62 63] In severe cases, this form of behaviour is termed avoidant/restrictive food intake disorder by DSM-5, a form of eating disorder that is associated with weight loss but not with body dysmorphia.[64]

TESTING FOR LACTOSE MALABSORPTION AND INTOLERANCE

Five tests of lactose digestion are available, each of which investigates different aspects of the process and has specific advantages and disadvantages (table 4).

Genetic tests apply real-time PCR or sequencing on DNA extracted from a venous blood or buccal swab sample and are most appropriate in epidemiological studies. In Caucasians, LP is nearly uniformly mediated by the LCT-13910:C/T polymorphism, and genetic testing can detect genetic LNP. However, the genetic situation is more complex in patients with African or Asian heritage (table 3) and genetic tests are currently not advocated in these populations for clinical purposes. Importantly, secondary LM will not be detected by genetic tests.

Tests for lactase enzymatic activities on intestinal biopsies will detect primary and secondary LM. While an endoscopy with sedation is not indicated for this purpose, this test can be performed if endoscopy is indicated for other reasons. It should be noted that lactase activity is patchy and more than a single biopsy may be required for optimal test accuracy.[65]

Table 4 Brief characterisation of the diagnostic tests available for lactose malabsorption

	Hydrogen breath test	Lactose tolerance test	Duodenal lactase activity	Serum gaxilose or urine galactose test	Genetic test
Lactose challenge	Yes	Yes	No	Yes (gaxilose)	No
Assessment of symptoms and LI	Yes/possible	Yes/possible	No/not possible	No/not possible	No/not possible
Test principle	Detection of H_2 in expiratory air	Increase in plasma glucose after lactose challenge	Lactase enzymatic activity in duodenal biopsy	Detection of D-xylose in serum or Galactose in urine after cleavage of orally administered 4-galactosylxylose (gaxilose) by lactase	Detection of –13910 C/T polymorphism
Detection of secondary LM	Yes	Yes	Yes	Yes	No
Costs	Low	Lowest	High (if costs for endoscopy are included)	Intermediate	High
Limitations	False-negative tests by H_2-non-producer. False-positive tests with SIBO, rapid transit, altered bowel anatomy	Disorders of glucose metabolism, altered bowel anatomy	Patchy expression of lactase	Variable test performance in literature. False-positive tests with SIBO, rapid transit and other conditions	False negative in the presence of atypical mutations (relevant in non-Caucasian populations)
Best use	Test of choice to assess LM and symptoms (LI)	Low resource setting, LM epidemiology	If gastroscopy is performed for other reasons	To be determined	LD/LNP epidemiology

LD, lactase deficiency; LI, lactose intolerance; LM, lactose malabsorption; LNP, lactase non-persistence; SIBO, small intestinal bacterial overgrowth.

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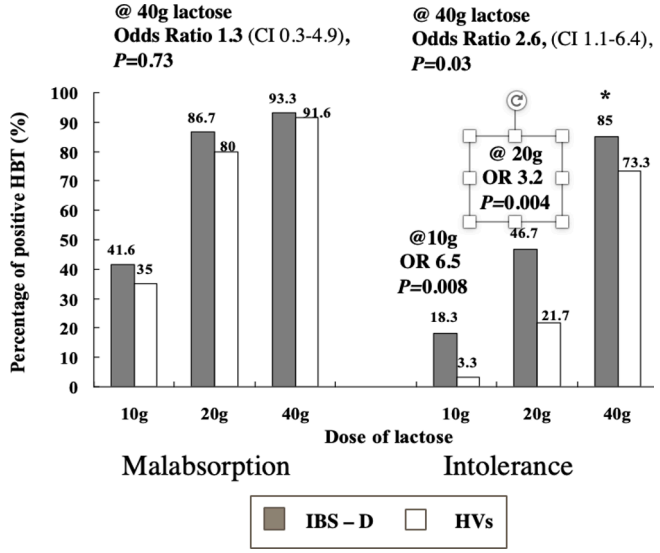
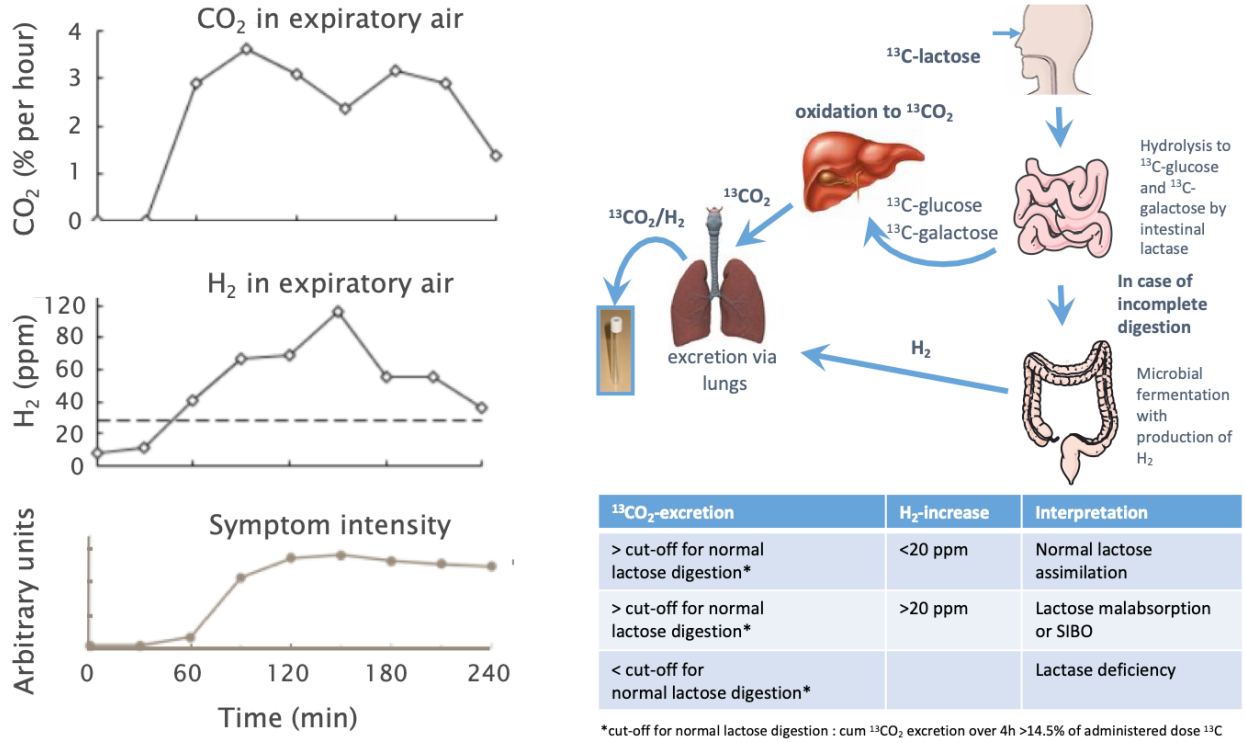


Figure 6 Symptoms in individuals with lactose malabsorption depend on lactose dose and visceral hypersensitivity. A population of Chinese individuals (100% primary lactase non-persistence) including HV with no history of abdominal symptoms and individuals with IBS-D was tested three times with different lactose dosages (10, 20 and 40 g) in a blinded fashion. The likelihood of a clinically positive HBT was higher in individuals with IBS-D for the low and the intermediate lactose dose. HBT, hydrogen breath test; HV, healthy volunteers; IBS-D, diarrhoea-predominant irritable bowel syndrome. (Source: Adapted from Yang *et al*.[56])

The lactose HBT measures the excretion of hydrogen in expiratory air after an oral challenge with a standard dose of lactose. As hydrogen is not produced by mammalian enzymes, its presence indicates contact of the sugar with bacteria indicating LM, although small intestinal bacterial overgrowth cannot be excluded. In clinical practice, an intermediate lactose dosage of 20–25 g may be optimal.[56 66] Smaller amounts of lactose lack sensitivity for LM. Larger amounts used in epidemiological studies (eg, 40–50 g, figure 6) induce symptoms even in healthy individuals with LM that tolerate the amount of lactose present in normal diets (see below).[56] A baseline H_2 value <20 ppm is a requirement for a reliable test and an increase ≥20 ppm within 3 hours is diagnostic of LM.[66] Reducing observation time impairs sensitivity; however, only four measurements (0, 90, 120, 180 min) are required for valid results.[67] An H_2-non-producing microbiota can lead to false-negative HBT. In some of these individuals, methanogenic bacteria (eg, *Methanobrevibacter smithii*) convert hydrogen to methane (CH_4) in a 4:1 ratio resulting in lower H_2 excretion and a lower fraction of positive tests.[66] Simultaneous assessment of methane can partially overcome this limitation. Therefore, even though the increase in CH_4 is often low (<20 ppm) and not correlated to symptoms, combined H_2/CH_4-measurements are recommended by some authors.[66 68] A more reliable approach involves the use of ^{13}C-lactose with simultaneous breath measurements of $^{13}CO_2$ as a marker of lactose digestion and H_2 as a marker of LM (figure 7); however, this technique is not available outside specialist centers.[69]



$^{13}CO_2$-excretion	H_2-increase	Interpretation
> cut-off for normal lactose digestion*	<20 ppm	Normal lactose assimilation
> cut-off for normal lactose digestion*	>20 ppm	Lactose malabsorption or SIBO
< cut-off for normal lactose digestion*		Lactase deficiency

*cut-off for normal lactose digestion : cum $^{13}CO_2$ excretion over 4h >14.5% of administered dose ^{13}C

Figure 7 Results of a hydrogen breath test of an individual with lactose intolerance with simultaneous assessment symptoms and H_2 levels, indicating lactose fermentation by the microbiota. An H_2 increase by ≥20 ppm over baseline indicates lactose malabsorption. When ^{13}C-labelled lactose is administered, $^{13}CO_2$ levels indicate absorption and metabolisation of ^{13}C-labelled lactose by the subject. Patient reports of abdominal symptoms subsequent to increases in these markers is diagnostic of lactose intolerance.

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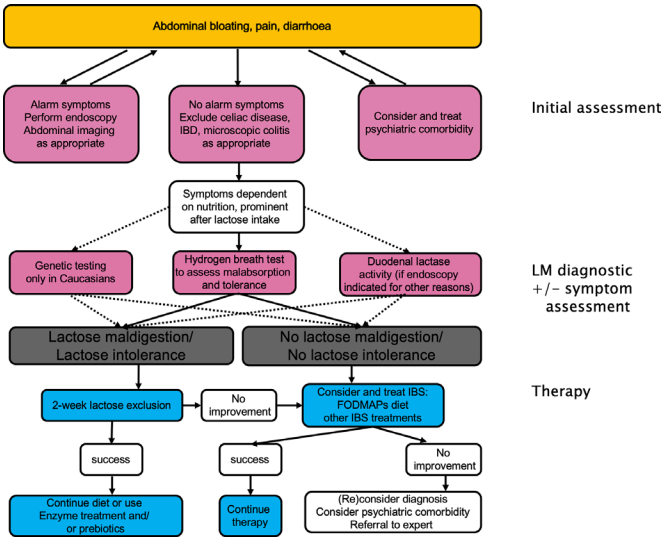


Figure 8 Management of lactose malabsorption and lactose intolerance. FODMAPs, fermentable oligosaccharides, disaccharides and monosaccharides and polyols.

The lactose tolerance test measures glucose in plasma at different times (e.g. 0, 30, 60, 120 min) after ingestion of 50 g lactose. Although the test does not require complex or expensive equipment, its invasive nature (multiple blood samples) limits its utility. Use of capillary blood measurements with portable glucose metres makes the test less invasive but does not offer the same diagnostic accuracy as measurements in venous blood.[70]

The gaxilose test involves the administration of the lactase substrate gaxilose (4-galactosylxylose) with measurement of D-xylose in urine or blood. Conceptually, gaxilose measurements are ideal for assessment of intestinal lactase since activity over the entire small intestine is measured.[71] In a manufacturer-sponsored trial, the diagnostic accuracy of gaxilose tests (0.93) was higher than HBT (0.85) or lactose tolerance tests (0.79) in comparison to duodenal biopsies.[71] However, this was not confirmed in an independent study when the genetic test (LCT-13'910:C/T) was used as reference.[72]

TESTING FOR LACTOSE INTOLERANCE

The major limitation of the genetic, enzymatic and gaxilose tests is that LM is common in healthy individuals, and a positive test does not confirm that symptoms are caused by this condition. For this reason, in our practice, HBT is the method of choice because reasonably reliable information about digestive function and patient symptoms are obtained.

The diagnosis of LI requires appropriate testing of symptoms using validated questionnaires designed for the purpose.[73] A National Institute of Health consensus conference defined LI as 'the onset of GI symptoms following a blinded, single-dose challenge of ingested lactose by an individual with LM, which are not observed when the person ingests an indistinguishable placebo',[74] thus supporting the case for blinded testing of symptoms. Although rarely performed outside clinical studies, blinded testing might be useful since in clinical practice, the correlation between self-reported symptoms of LI and objective findings on tests for lactose digestion is low.[62] Indeed, among individuals referred for HBT, about half of those with normal lactose digestion report abdominal discomfort after an unblinded lactose challenge.[69] Further, intolerance to dairy products is reported by 20% of all individuals[75] and up to 70% of IBS patients in European populations with low rates of genetic LNP.[60]

A 'blinded multiple dose challenge' would provide clarity not only regarding lactose digestion but also identify the amount of lactose that individuals could 'safely' consume (figure 6).[56] Moreover, in subjects with known LNP, these could be performed at patients' homes with a negative control, low and intermediate lactose challenge (eg, 12.5 and 25 g, corresponding to 250 and 500 mL milk, respectively).[34] This could help educate patients because, in real life, it is self-reported intolerance and not the objective results of testing that best predicts food choices.[62] However, to the best of our knowledge, blinded home-based testing has not been tested in routine clinical practice. The need for a well-accepted, practical and cost-effective investigation of food intolerance that predicts the outcome of dietary therapy is a key clinical challenge in functional GI disorders. The ability to predict the outcome of dietary therapy would be the measure for an appropriate symptom assessment.

THERAPEUTIC OPTIONS

Therapy of lactose intolerance aims to improve patient symptoms and to avoid risk for undernutrition or malnutrition in the long term (figure 8). A diet low in lactose is typically recommended and this is supported by common sense and clinical evidence .[56] However, in contrast to the management of sprue or food allergies, a strict lactose-free diet is not required since patients with LI often tolerate up to 250 mL milk (12 g lactose) without symptoms and more when consumed with food.[31]

Improved lactose tolerance by manipulating the colonic microbiota could also be achieved by ingestion of prebiotics.[44] A randomised placebo-controlled study in 85 LI patients reported that regular ingestion of short-chain galacto-oligosaccharides (GOS, RP-G28) tended to reduce H_2 production and improve abdominal pain during lactose HBT. After 1 month, 30% of GOS-treated patients versus 6% of placebo-treated patients considered themselves lactose tolerant.[76] Microbiological workup revealed a transient increase in lactose fermenting *Bifidobacterium* spp. on GOS treatment and a negative correlation between *Bifidobacterium* levels and abdominal pain, and re-introduction of milk prompted a further shift in bacterial composition, including an increase in the genus *Roseburia*.[77]

Lactose-free dairy products in which lactase is added to milk are widely available and considered safe, although allergic reactions have been reported.[78] Lactase treatment of milk products also reduces crystallisation of lactose, increasing sweetness and fermentation for production of yoghurt.[79] However, residual side proteolytic activity of lactase can degenerate casein and impair taste, especially after long storage.[80]

Lactase supplementation by tablets improves both lactose digestion (reduced H_2 production) and symptoms[81 82] although the effects are modest (eg, 18% with overall reduction of symptoms[82]). An alternative approach is to ingest probiotics such as *Lactobacillus* spp., *Bifidobacterium longum* or *Bifidobacterium animalis* that produce lactase in the gut. A recent systematic review of this treatment option confirmed an overall positive effect; however, the effect size was not consistently better than lactase supplementation and study quality was poor.[83]

In many clinical studies, only a minority of patients with LI on HBT report satisfactory improvement in symptoms after treatment to reduce intake of dairy products or supplement lactase. Moreover, it remains unclear, to what extent the therapy itself and conditioning of patient expectations contribute to outcome.

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Lack of improvement can also be due to the presence of functional bowel disorders, which are present in many patients referred for investigation. These patients are sensitive to various nutrients, mechanical and chemical stimuli and, therefore, rarely respond to restriction of dairy products alone.[84]

IBS patients develop symptoms after ingestion of a range of poorly absorbed, fermentable carbohydrates (fermentable oligosaccharides , disaccharides and monosaccharides and polyols (FODMAPs)) that includes but is not restricted to lactose even in LM patients.[85] A low-FODMAP diet improves abdominal symptoms in 50%–80% of IBS patients.[86 87] This dietary therapy requires commitment from the patient and is best delivered by professional dietician. Identification of factors predicting dietary outcome would improve compliance and cost-effectiveness of this intervention; however, in a large clinical study neither clinical presentation nor HBT results (high dose lactose 50 g or fructose 35 g) predicted response to the low-FODMAP diet.[87] The response to an intermediate dose of a representative, non-absorbable FODMAP (eg, lactulose 20 g) that rarely c symptoms in health, but often induces bloating, abdominal pain and diarrhea in FGID patients may improve the ability of HBT to identify individuals that respond to this dietary intervention. Alternatively, bioassays to identify saccharolytic bacteria and/or fermentation capacity in faecal samples might be developed that predict outcome of lactose (or FODMAP) restriction in patients.[88]

LONG-TERM COMPLICATIONS OF LACTOSE INTOLERANCE

Considering the objective effects of genetic LD on intestinal microbiota and recent human evolution (see above), LM and LI are likely to have a relevant impact on nutrition. Dairy products are valuable sources of protein, calcium and vitamin D.[89] However, these nutrients can also be acquired from other food sources.

The relationship between lactose tolerance and height has been demonstrated, although some of this effect could be explained by population stratification.[90] Daily milk consumption of 245 mL is associated with increased body height (0.39 cm, 95% CI: 0.29 to 0.48).[90] Similarly, milk intake and LP have been linked with higher body mass index (BMI) in some studies.[91]

Effects of nutrition on health are difficult to address in interventional studies due to need for long-term follow-up, costs and limited compliance in patients. However, since LM in Caucasians is a monogenic condition (LCT −13'910C genotype), this question can be addressed by applying a Mendelian randomisation approach that limits confounding by social, environmental or behavioural factors. A recent study using this methodology confirmed higher milk consumption in individuals with genetic LP and this was associated with vitamin D levels which were 2.3-fold (OR: 1.6–3.4) lower in individuals with LCT-13'910:CC and 1.5-fold lower in LCT-13'910:CT compared with LCT-13'910:TT.[92] Vitamin D is important for bone mineralisation and a separate meta-analysis showed a higher bone mineral density and a lower risk of fractures for TT versus CT/CC (OR: 0.81, 95% CI: 0.7 to 0.94, p=0.005).[93] However, this finding was not confirmed in a European study that applied a similar study design.[91]

Results regarding other effects of milk consumption such as cardiovascular health and cancer are controversial.[94] In a large Swedish study, individuals with high consumption of non-fermented milk and other dairy products had a higher all-cause mortality (HR: 1.32, 95% CI: 1.18 to 1.48); however, these results were not robust in the subgroup for which a Mendelian randomisation study could be performed.[95] Some of these findings might be explained by an effect of LP on BMI (see above). In any case, these conflicting results are not surprising considering the complexity of the diet with regards to availability of lactose-free milk, intake of calcium, vitamin D, saturated fats, cholesterol, proteins and calories. Moreover, other genetic markers for lipid metabolism and polymorphisms of the vitamin D receptor might also impact on health.[94] Additional studies with new approaches accounting for multiple nutrients and multiple genetic markers are needed to clarify the relationship of milk consumption, LM and long-term outcomes.

OUTLOOK

Primary genetic LP and non-persistence are common in healthy humans; however, ingestion of milk by individuals with LD leads to LM and, in susceptible patients, to symptoms of lactose intolerance. Diagnosis is based on detection either of the genetic mutation, loss of lactase activity in the enteric mucosa or evidence of malabsorption by breath tests. However, the association between self-reported LI, objective findings of tests and clinical outcome of dietary intervention is variable. Recent studies have provided important new insight into the complex relationship between LD, LM and symptom generation. This work has shed light on the important issue of food intolerance as a cause of symptoms in IBS and other functional GI disorders.

The development of a well-accepted, practical and cost-effective investigation of food intolerance that predicts the outcome of dietary therapy is one of the biggest clinical challenges in the field of functional GI disorders. Understanding the biological mechanism for food intolerance will help clinicians make a definitive diagnosis and guide rational dietary and medical management. Ongoing studies will provide high-quality evidence to document the clinical outcome, cost-effectiveness and long-term effects of these strategies.

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