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Review article: lactose intolerance in clinical practice – myths and realities

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SUMMARY

Background
Approximately 70% of the world population has hypolactasia, which often remains undiagnosed and has the potential to cause some morbidity. However, not everyone has lactose intolerance, as several nutritional and genetic factors influence tolerance.

Aims
To review current clinical practice and identify published literature on the management of lactose intolerance.

Methods
PubMed was searched using the terms lactose, lactase and diet to find original research and reviews. Relevant articles and clinical experience provided the basis for this review.

Results
Lactose is found only in mammalian milk and is hydrolysed by lactase in the small intestine. The lactase gene has recently been identified. 'Wild-type' is characterized by lactase nonpersistence, often leading to lactose intolerance. Two genetic polymorphisms responsible for persistence have been identified, with their distribution concentrated in north Europeans. Symptoms of lactose intolerance include abdominal pain, bloating, flatulence and diarrhoea. Diagnosis is most commonly by the lactose hydrogen breath test. However, most people with hypolactasia, if given appropriate advice, can tolerate some lactose-containing foods without symptoms.

Conclusion
In clinical practice, some people with lactose intolerance can consume milk and dairy foods without developing symptoms, whereas others will need lactose restriction.

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INTRODUCTION

Lactose intolerance is widespread throughout the world and subjects usually avoid milk and dairy products to improve symptoms. The disaccharide lactose is a unique carbohydrate present only 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.[1] For effective utilization, lactose requires hydrolysis by the enzyme lactase and, during infancy, provides an excellent source of energy at a time of rapid growth and development. An enhanced understanding of lactase and its deficiency and why there is a special carbohydrate in milk is important for improved management of lactose intolerance.

PATHOPHYSIOLOGY

The enzyme lactase-phlorizin hydrolase, more commonly known as lactase, is a β-galactosidase responsible for the hydrolysis of lactose to the monosaccharides, glucose and galactose. These are absorbed by intestinal enterocytes into the bloodstream (Figure 1), glucose is ultimately utilized as a source of energy and galactose becomes a component of glycolipids and glycoproteins. The enzyme has two active sites, one hydrolysing lactose and the other phlorizin (an aryl α-glucoside) and a range of dietary glycolipids.[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 (see below).

Lactase is present on the apical surface of enterocytes in the small intestinal brush border with the highest expression in the mid-jejunum. It is secured by its C-terminal end with most of the molecule protruding into the gastrointestinal lumen. The enzyme is produced as a 220 kDa precursor peptide, which undergoes considerable post-transcriptional modification during transport to the cell surface as the mature 150 kDa protein. 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.[3]

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, it declines at variable rates following weaning to undetectable levels as a consequence of the normal maturational down-regulation of lactase activity.[4–6] In humans, approximately 30% of the population has continued lactase activity beyond weaning and into adulthood (lactase persistence).[7] This happens mainly in people of north European descent and relates geographically to the introduction of dairy farming

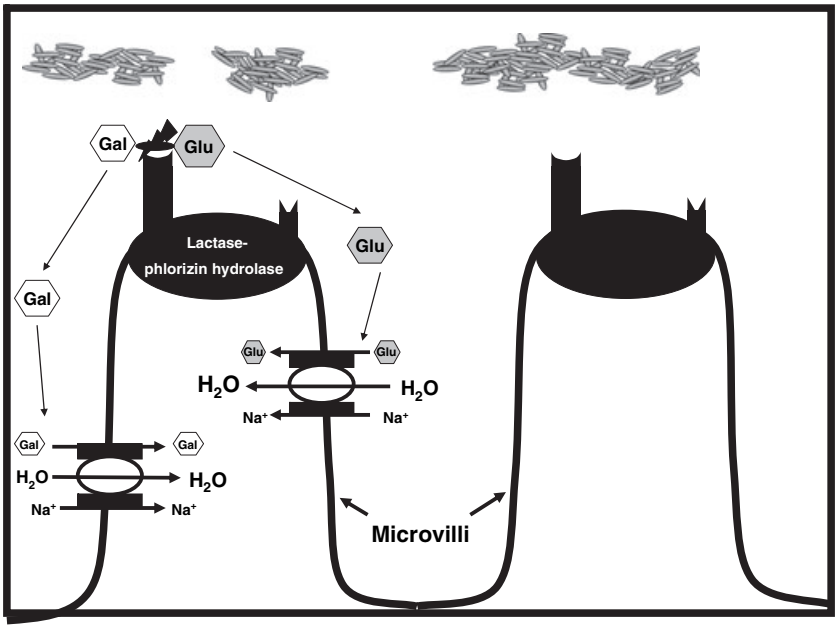

Figure 1. In lactase persistence, lactase-phlorizin hydrolase in the brush border efficiently hydrolyses lactose into galactose (Gal) and glucose (Glu) and is rapidly absorbed into the bloodstream taking luminal water with it. Hydrolysis typically occurs in the jejunum, which has low concentrations of bacteria 10^{1-4} mL^{-1}; thus, little lactose is fermented.

approximately 10 000 years ago.[8] Recent analysis of archaeological DNA suggests that genetic lactase persistence was rare in Northern Europeans prior to dairy farming. The so-called 'culture-historical hypothesis' proposes that the high prevalence of lactase persistence in Northern Europeans occurred as a result of a more recent selection process enabling populations to rely on mammalian milk as an important component of the diet particularly at time of poor harvest.[9–11] An opposing hypothesis 'reverse cause' proposed that dairy farming and milk consumption was adopted by those with pre-existing lactase persistence[10, 12, 13] but evidence from archaeological DNA suggests that this is less likely.[14]

Hypolactasia, or lactase deficiency, exists in three distinct forms: congenital, primary and secondary. Congenital lactase deficiency is associated with the least lactase activity. It is a lifelong disorder characterized by failure to thrive and infantile diarrhoea from the first exposure to breast milk. Congenital lactase deficiency is extremely rare, with only around 40 cases having been reported. It is a single autosomal recessive disorder, but very little is known about the molecular basis.[15] The only treatment is complete avoidance of lactose from birth. Lactase nonpersistence (primary lactase deficiency), as described above, occurs in the majority of humans. Secondary or acquired lactase deficiency refers to the loss of lactase activity in people with lactase persistence. It occurs as a result of gastrointestinal illness that damages the brush border of the small intestine, e.g. viral gastroenteritis, giardiasis or coeliac disease.[16, 17] This is usually reversible.

For effective utilization of lactose without symptoms of intolerance, only 50% of lactase activity is necessary[15] and it is present only at the level that it is required, as is the case for other intestinal disaccharides.[18]

For many years, it was thought that lactase persistence in humans was the 'wild-type' pattern.[19] As the lactase nonpersistence phenotype is expressed in other mammals, this is now considered to be the ancestral type whilst lactase persistence is because of a mutation.

GENETICS OF LACTASE EXPRESSION

The lactase gene is approximately 50 kb in size[20] and located on chromosome 2.[21, 22] 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 $C/T_{13\,910}$ 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.[15, 21, 23] Studies suggest that $C/T_{13\,910}$ 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.[24]

Individuals heterozygous for either SNP have intermediate lactase activity and are more susceptible to lactose intolerance at times of stress or gastrointestinal infection.[5] This polymorphism does not provide a complete explanation as individuals with homozygous lactase persistence (genotypes TT and AA) may occasionally develop lactose intolerance (i.e. acquired lactase deficiency.[25] Adult homozygotes with nonpersistence (CC and GG) have virtually undetectable levels of intestinal lactase as a result of down-regulation of the brush border enzyme following weaning.[26]

PREVALENCE OF LACTOSE INTOLERANCE

Hippocrates first described lactose intolerance around 400 years BC. but the clinical symptoms have become recognized only in the last 50 years.[5] Up to 70% of the world population has lactase nonpersistence,[5] but not all are intolerant to lactose as many nutritional and genetic factors influence tolerance.[8, 27]

Ethnic origin affects the frequency of lactose intolerance. In adults, white north Europeans, North Americans and Australasians have the lowest rates ranging from 5% in a British population to 17% in Finland and northern France. In South America, Africa and Asia, over 50% of the population has lactase nonpersistence and in some Asian countries this rate is almost 100%.[1, 4, 15, 23, 28–36] Interestingly, in subjects from mixed ethnicity, a lower prevalence of lactase nonpersistence is observed where a high prevalence is detected in the native ethnic group.[30]

The decline in lactase expression is usually complete during childhood but the decline has also been reported to occur later in adolescence.[33] The rate of loss of lactase activity also varies according to ethnicity but the physiological explanation for this difference in timing is currently unknown. Chinese and Japanese lose 80–90% of lactase activity within 3–4 years after weaning, Jews and Asians lose 60–70% over several years postweaning and in white

Northern Europeans it may take up to 18–20 years for lactase activity to reach its lowest expression.[5]

DIAGNOSIS OF LACTOSE MALDIGESTION

Early studies of lactose digestion involved measuring blood glucose levels following a lactose load of 50 g, a significant increase in blood glucose after 30 min indicating high lactase activity.[15, 25] In research, serum measurements of ^{13}C-labelled lactose following an oral dose have also been used, but are not appropriate for use in clinical practice.[37]

More recently, lactase activity from jejunal biopsies has been used but is less sensitive than the lactose hydrogen breath test, which is currently considered to be the most cost-effective, non-invasive and reliable test to measure lactose maldigestion.[38] The lactose hydrogen breath test usually involves taking 50 g lactose orally (equivalent to that found in 1 L of milk) and measuring breath hydrogen levels over the following 3–6 h with >20 p.p.m. above baseline indicating lactose intolerance. The sensitivity increases from 40% to 60%, if measurements are taken for 6 h.[5]

Hydrogen non-excretion (a false-negative lactose hydrogen breath test) occurs in up to 20% of patients with lactose malabsorption.[39] This is because of a predominant population of methane-producing bacteria in the bowel that use hydrogen to reduce carbon dioxide to methane[40] or may occur as a result of prior antibiotics.[39] Often, there is interference and competition between different strains of bacteria within the gastrointestinal tract leading to significant hydrogen excretion as well as moderate methane production.[40]

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.[25]

Genotyping, using a new real-time PCR assay, is quick and easy and has high specificity for the lactase gene.[25] 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.

SYMPTOMS OF LACTOSE INTOLERANCE

Lactose maldigestion occurs when lactose is not absorbed in the small intestine. It passes through the gastrointestinal tract to the colon, where, in some subjects, it then leads to symptoms of lactose intolerance.

The typical symptoms of lactose intolerance include abdominal pain, bloating, flatus, diarrhoea, borborygmi,[5, 6, 25] and on some occasions, nausea and vomiting.[5] In a few cases, gastrointestinal motility is decreased and subjects can present with constipation possibly as a consequence of methane production. Animal models have shown a marked reduction in the major migratory complexes of the gut when infused with methane, slowing gut transit.[41]

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 (Figure 2).[42] Acidification of the colonic contents and an increased osmotic load resulting from the unabsorbed lactose in the ileum and colon lead to a greater secretion of electrolytes and fluid and a rapid transit time resulting in loose stools and diarrhoea.[43–47]

Care should be taken when subjects describe systemic symptoms as whilst these may be coincidental, they could be an indication of cow's milk protein allergy,[48] which affects as many as 20% of patients with symptoms suggestive of lactose intolerance.[5, 49] Cow's milk protein allergy is rare in adults; Truelove and Wright showed that a few ulcerative colitis patients benefited from exclusion of dairy products but this work has never been repeated.[50] Aside from bloody diarrhoea, extra-intestinal symptoms occur and may include muscle and joint pain, headaches, dizziness, lethargy, difficulty with short-term memory, mouth ulcers, allergies (eczema, pruritis, rhinitis, sinusitis and asthma) cardiac arrhythmia, sore throat, increased frequency of micturition,[5, 51–53] acne and depression.[25]

Some patients do not associate their symptoms of lactose intolerance with foods[38] and in one study, 52% of patients did not relate their symptoms with the intake of lactose.[54] In addition, substantial amounts of lactose given to patients with proven lactase nonpersistence and a history of lactose intolerance who were properly blinded, did not cause significant symptoms.[55] Furthermore, in symptomatic patients, excluding lactose does not always eliminate symptoms[56, 57] probably because there is another underlying cause, e.g. irritable bowel syndrome (IBS).

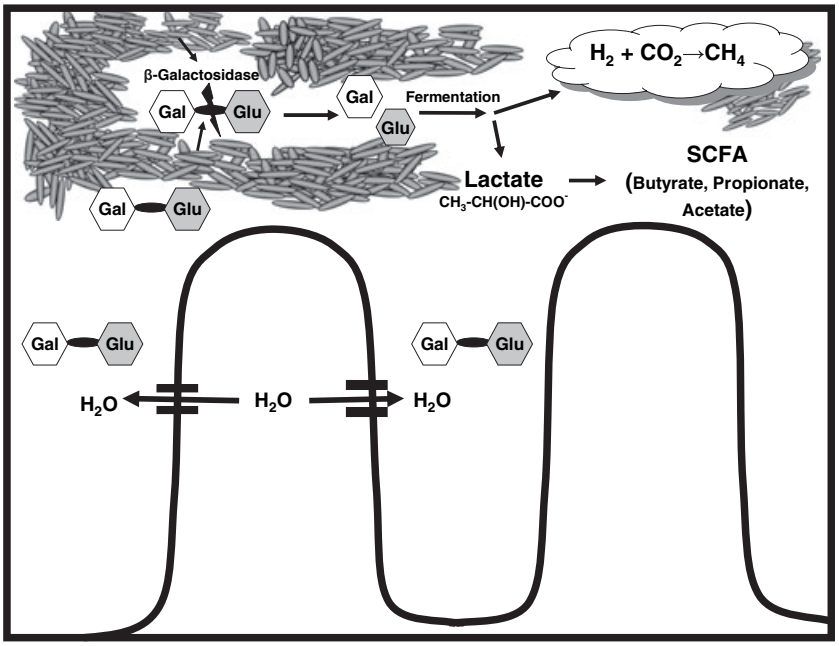

Figure 2. In lactase nonpersistence, there are several possible mechanisms for the common symptoms found in patients. First, unabsorbed lactose passing through the colon has a high osmotic load leading to increased water and electrolytes in luminal contents, speeding transit and softening stool. Secondly, unabsorbed lactose is hydrolysed to galactose (Gal) and glucose (Glu) by bacterial β-galactosidase present in lactic acid bacteria. These monosaccharides are then available for bacterial fermentation by ileal and colonic flora to short chain fatty acids with by-products of hydrogen and carbon dioxide, causing bloating in the small bowel and flatulence in the colon. Thirdly, reduction in carbon dioxide by certain bacterial strains to methane could, theoretically, lead to constipation through a reduction in small intestinal major migratory complexes.

INTESTINAL MICROFLORA, FERMENTATION AND FERMENTED FOODS

There is no evidence for adaptation of small intestinal brush border lactase activity in subjects with lactase nonpersistence after its natural decline.[4, 15, 30] The gastrointestinal tract houses at least 17 bacterial families with over 500 species having been classified[58] with the highest concentration being in the colon at levels up to 10^{12-14} mL^{-1} luminal contents.[59] It has been demonstrated that malabsorbed lactose is salvaged by the distal ileal and colonic lactic acid bacteria.[60] Lactic acid bacteria are Gram-positive, e.g. *Lactobacillus, Bifidobacterium, Staphylococcus, Enterococcus, Streptococcus, Leuconostoc* and *Pediococcus* and ferment lactose to produce lactate, hydrogen, methane, carbon dioxide and SCFAs.[61] In the process of fermentation, microbial lactase present in lactic acid bacteria[15, 62, 63] initially breaks down unabsorbed lactose by hydrolysis to its component monosaccharides, glucose and galactose, which are then absorbed or fermented as above. Lactase activity is optimal at pH 6–8, as in the small intestine. In the colon, however, where the pH drops to as low as 4,[64] bacterial lactase activity is decreased and lactose is more likely to be left unfermented. In this case, symptoms of lactose intolerance are therefore more because of the increased osmotic load. The variable ability of the colonic microflora to ferment lactose in subjects with intolerance may explain why different subjects have different levels of tolerance.[65]

Prebiotics are defined as nondigestible (by the host) food ingredients that have a beneficial effect through their selective metabolism in the intestinal tract.[66] Unhydrolysed lactose can be considered to be a prebiotic and it has been demonstrated that numbers of lactic acid bacteria increase following lactose ingestion.[67] Fermentation of milk improves tolerance to lactose because of the presence of lactic acid bacteria.[61] Thus, dairy foods in the form of cheese and fermented milk, e.g. yogurt are established components of the human diet and provide good sources of protein and calcium and often do not lead to symptoms of lactose intolerance as part of a healthy balanced diet.

Probiotics, defined as live micro-organisms that when given in adequate quantities will have a health benefit on the host,[68] have been known to be in the diet since the early 20th century but it is only recently that interest has grown in their health benefits. In subjects with lactose intolerance, probiotics reduce bloating symptoms possibly as a consequence of microbial lactase being present within lactic acid bacteria in the probiotics thus improving lactose digestion.[28, 69–74] There is, however, a huge variability in the amount of lactase activity in different probiotics (fermented milks 0.19–0.24 μmol/g and yogurt 0.86 μmol/g)[75] but this does not mean that the fermented product is less well tolerated in lactose intolerance.[69, 71, 76]

LACTOSE INTOLERANCE AND IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome affects 9–12% of the population and patients present with at least one of the following symptoms: abdominal pain, bloating, constipation and/or diarrhoea.[14, 77] Diet may influence these symptoms, in particular meal patterns, caffeine, the amount and type of nonstarch polysaccharides (dietary fibre), fluid intake, gut flora and food intolerance.[78] Lactose intolerance does not lead to IBS[28, 79] but patients often have increased visceral sensitivity to the luminal effects of lactose compared to healthy subjects.[80] Lactose intolerance and IBS symptoms are often very similar and when related to milk intake, they do not necessarily indicate lactose intolerance.[79, 81] In two studies, lactose maldigestion affected 24–27% of patients with IBS.[82, 83] Alpers reported that 45% of IBS patients have lactose intolerance but only 30% related their symptoms to milk and dairy products while dietary exclusion only improved symptoms in 52% of patients.[84] Interestingly, some IBS patients without lactose maldigestion describe symptoms of lactose intolerance. Furthermore, studies have shown that lactose-free milk causes the same symptoms as lactose in subjects who have been diagnosed with lactose intolerance; this may indicate that the underlying condition is IBS.[81, 85] Specific questions related to lactose-induced symptoms may improve the management of such patients.[79]

LACTOSE IN FOOD AND PHARMACEUTICALS

Lactose occurs naturally in the diet only as mammalian milk and dairy products, e.g. cow, goat, sheep (also known as ewe) and human. Levels vary considerably from only a trace in butter to 52.9 g/100 g in skimmed milk powder, although when diluted with water this equates to <5 g/100 mL (Table 1).[86] Lactose

Table 1. Lactose content of milk, dairy products and some manufactured products[86]

Food	Type	Per cent by weight
Milk	Skimmed*	4.8
	Semi-skimmed*	4.7
	Whole*	4.6
	Condensed, whole, sweetened*	12.3
	Dried skimmed*	52.9
	Evaporated, whole*	8.5
	Goat	4.4
	Human	7.2
	Sheep	5.1
Cream	Single	2.2
	Double	1.7
	Sour	2.7
	Crème fraiche	2.1
	Crème fraiche half fat	3.0
	Imitation cream, e.g. Elmlea, Tip Top, Dream Topping	2.3–6.8
Cheese	Brie/camembert	Trace
	Cheddar	0.1
	Cheese spread	4.4
	Cheese spread, reduced fat	7.3
	Cottage cheese	3.1
	Cottage cheese, reduced fat	3.3
	Cream cheese	Trace
	Danish blue	Trace
	Stilton	0.1
	Edam/gouda	Trace
	Feta	1.4
	Goats cheese	0.9
	Mozzarella	Trace
	Parmesan	0.9
	Processed cheese slices	5.0
Yogurt	Plain	4.7
	Fruit	4.0
	Drinking yogurt	4.0
	Fromage frais plain	4.0
	Fromage frais fruit	3.0
	Tzatziki	0.3
Puddings	Milkshake average	4.5
	Ice cream nondairy vanilla	4.8
	Ice cream dairy vanilla	5.2
	Choc ice	4.7
	Rice pudding	3.9
	Custard made with whole milk	5.2
	Chocolate mousse	3.8

* Cow's milk.

Table 2. Food ingredients to avoid on a lactose exclusion diet

Milk	Lactoglobulin
Milk solids	Buttermilk
Lactose	Artificial cream
Whey powder	Feta
Caseinate*	Quark
Condensed milk	Curd
Skimmed milk powder	Ricotta
Cream	Cheese
Modified milk	Margarine
Evaporated milk	Butter

* Caseinate is a milk protein and does not contain lactose but during the initial stages of a lactose exclusion diet, often all milk and dairy ingredients are avoided.

is widely used in the food and pharmaceutical industry as an ingredient in processed foods or as a bulking agent or filler in pharmaceuticals and this fact needs to be taken into consideration when reducing lactose intake. It is only half as sweet as glucose and has about a sixth of the sweetness of sucrose making it very palatable. It is not easily fermented by yeast and consequently does not lead to the unwanted production of carbon dioxide and alcohol when used as an ingredient in food products. In recent years, there has been a dramatic increase in the manufacture of lactose and, in the United States alone, production has increased from 50 million kg/annum in 1979 to 300 million kg/annum in 2004.[5]

In foods, lactose may be used as a browning agent, e.g. in bread, or to add texture and bind water, e.g. in processed meats such as sausages and burgers.[6] It may also be added to processed chicken and can be used in the production of soft drinks and lager beers. Some foods can contain as much lactose as milk itself, e.g. slimming products.[87]

LACTOSE INTAKE, RESTRICTION, RE-INTRODUCTION AND NUTRITIONAL ADEQUACY

There are currently no UK national guidelines on how to manage lactose intolerance. Individuals with lactase nonpersistence do not inevitably acquire lactose intolerance, especially if they consume lactose-containing foods in modest amounts at any one time, e.g. milk added to breakfast cereal, tea or coffee.[88] However, if lactose intolerance exists or diagnostic investigations

Table 3. Common myths and practical tips

Adults with lactose nonpersistence cannot tolerate any milk or dairy products
People with lactase nonpersistence are not all lactose-intolerant. They may tolerate up to 12 g lactose if taken spread throughout the day, e.g. with breakfast cereal and in tea or coffee
Lactase nonpersistence is rare
Until recently it was believed that lactase persistence was the dominant trait, however, up to 70% of the world population is lactase nonpersistent
Goats' milk is lactose-free
Goats' milk contains 4% lactose. Soya milk and rice milk are lactose-free. Recommend calcium-supplemented products
A negative lactose breath test means that the patient can tolerate all dairy products
A lactose breath test does not always confirm lactose intolerance and hydrogen non-excretion occurs in up to 20% of patients

are inconclusive, a detailed diet and symptom history should be taken and, if appropriate, lactose can be excluded from the diet (Table 2) until symptoms resolve, usually at least 4 weeks. Dietetic advice should be sought to ensure nutritional adequacy of the diet. Lactose intolerance should be confirmed with a lactose challenge and the development of symptoms.[38]

Subjects should be encouraged to re-introduce lactose to tolerance to ensure the diet is not being restricted unnecessarily.[79] These foods provide an excellent source of bioavailable calcium and avoidance leads to a lower calcium intake,[89] which is associated with reduced bone mineral density and an increased risk of developing osteoporosis.[90, 91] Calcium supplementation may be required and the recommendation of calcium fortified foods should be considered. The current recommendations for calcium intake in the UK are 700 mg/day for men and women over 19 years and 1250 mg/day during breastfeeding.[92] Interestingly, despite lactose intolerance, calcium from milk and dairy products is still well absorbed.[93, 94]

After a period of lactose exclusion and cessation of symptoms, up to 240 mL milk (12 g lactose) is often well tolerated if spread throughout the day.[55] Furthermore, re-introduction of lactose can help decrease symptoms of lactose intolerance[95] suggesting that there may be adaptation in the colonic microflora whereby the lactose is behaving as a prebiotic as mentioned above.[8, 27] This is useful in a society where the addition of lactose in food products is increasing.

There is some evidence that lactase added to products to render them low in lactose or the use of supplemental lactase can help tolerance but this is not always the case.[96, 97] There has even been a suspected case report of an allergy to supplemental lactase although this was because of an allergy to the fungus *Aspergillus* that was used to manufacture lactase.[98]

Food temperature,[99] the presence of cereals and other solids,[100] energy content and nutritional composition of a meal[28, 88, 101, 102] can alter gastric emptying and change proximal intestinal transit time by several hours. A longer exposure time of lactose in the small intestine allows increased hydrolysis by lactase and helps to reduce symptoms of lactose intolerance in some subjects.[103]

CONCLUSIONS

Milk and dairy products are often assumed to be the cause of gastrointestinal symptoms and inappropriate avoidance can lead to nutritional inadequacy, particularly for calcium intake. Many subjects with lactose intolerance can consume milk and dairy products without getting symptoms and fermented milk products may be helpful in improving tolerance. Other individuals do benefit significantly from lactose restriction but care needs to be taken to ensure that calcium intake is sufficient. A greater understanding of the complexity of lactose intolerance, lactase deficiency and symptom generation would help clinicians treat patients more effectively (see Table 3).

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