Clinical and Experimental Gastroenterology

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REVIEW

Lactose intolerance: diagnosis, genetic, and clinical factors

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This article was published in the following Dove Press journal:
Clinical and Experimental Gastroenterology
4 July 2012
Number of times this article has been viewed

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Abstract: Most people are born with the ability to digest lactose, the major carbohydrate in milk and the main source of nutrition until weaning. Approximately 75% of the world's population loses this ability at some point, while others can digest lactose into adulthood. This review discusses the lactase-persistence alleles that have arisen in different populations around the world, diagnosis of lactose intolerance, and its symptomatology and management.

Keywords: hypolactasia, lactase persistence, lactase non-persistence, lactose, *LCT* gene, *MCM6* gene

Introduction

Lactose is a disaccharide that is abundant in mammalian milk and essential for the nourishment of newborn infants. It is hydrolyzed by the intestinal brush-border enzyme, lactase, into absorbable sugars, namely glucose and galactose. In most infants, intestinal lactase activity is maximal during the perinatal period; however, after 2–12 years of age, two distinct groups emerge, ie, a "lactase non-persistence" group with low lactase activity (hypolactasia) and a "lactase-persistence" group of individuals who retain their neonatal level of lactase activity into adulthood.[1–3]

Reduction in lactase activity causes primary maldigestion of lactose, a condition that is occasionally asymptomatic. When symptoms are present, lactose intolerance is diagnosed. It is important to distinguish between primary hypolactasia and secondary causes of maldigestion of lactose, including celiac disease, infectious enteritis, or Crohn's disease, which have distinct pathogenic and therapeutic implications. Moreover, primary hypolactasia should be distinguished from congenital lactase deficiency, a rare autosomal recessive disease with unique molecular mechanisms that affects infants from birth.[4]

Lactase-persistence alleles and polymorphisms for lactose tolerance

The *LCT* gene is 49.3 kb in length and located on the long (q) arm of chromosome 2 at position 21. It contains 17 exons and is translated into a 6 kb transcript (NCBI Reference Sequence NG_008104.1). Individuals with hypolactasia and lactase persistence have identical coding sequences, except for some silent mutations; thus, both lactases are identical.[5]

Enattah et al[6] devised a brilliant strategy using polymorphic microsatellite markers flanking *LCT*, encompassing a region of 47 kb, in a haplotype linkage analysis of

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nine Finnish families with hypolactasia. Two variants were associated with lactase persistence. A polymorph variant, *LCT*-13910C>T, in intron 13 of the *MCM6* gene that is 13,910 bp from the initiation codon of *LCT*, demonstrated a complete association, while the *LCT*-22018G>A variant in intron 9 of *MCM6* gene upstream of the *LCT* locus 22,018 bp was strongly, but not completely, associated.[1,2,6] The functional role of *MCM6* in vertebrates is unknown, but it has been implicated in "licensing" DNA replication during the cell cycle.[1] This association was confirmed in a study of DNA collected from subjects of Finnish, South Korean, Italian, German, French, or white or African North American descent.[1,6]

In subjects of European descent, the *LCT*-13910C>T variant completely associated with the lactase-persistence phenotype and presented different allelic frequencies in countries within Europe, Oceania, Asia, and the Americas, as shown in Table 1.

Both genotypes of *LCT*-13910CT and *LCT*-13910TT were associated with the lactase-persistence phenotype, indicating that the presence of one single lactase-persistence allele in the heterozygous state has a dominant effect, rendering the person a lactose digester, whereas the genotype *LCT*-13910CC, when the lactase-persistence allele *LCT*-13910T is absent, is consistent with lactose maldigestion.[2,3]

Despite the association of *LCT*-13910C>T with lactose digestion in Europeans, analysis of this variant in Africa demonstrated its restriction to populations with a high prevalence of the lactase-persistence phenotype (Table 2). This finding suggests the presence of other lactase-persistence alleles (Table 3). Thus, as shown in Figure 1, different alleles have originated in various locations around the world over the course of human history after the emergence of modern man from Africa.[17]

Genotyping of *LCT*-13910C>T versus *LCT*-22018G>A has shown almost full agreement. Patients with *LCT*-13910CC were also *LCT*-22018GG, while individuals with *LCT*-13910CT had the *LCT*-22018GA genotype. *LCT*-13910TT was associated with *LCT*-22018AA, except for a few cases in Finland[6] and China,[32] and in Japanese Brazilians.[33]

Functional in vitro studies of these polymorphic alleles have shown that *LCT*-13910T,[1,34,35] *LCT*-13907G, *LCT*-13915G, and *LCT*-14010C act as enhancers of the *LCT* promoter[29] unlike in ancestral constructs (*LCT*-13910C, *LCT*-13907C, *LCT*-13915T, and *LCT*-14010G). These effects are most likely mediated by the Oct-1 transcriptional factor binding site in the variant enhancer and by HNF1α binding in the *LCT* promoter. However, further evaluation is required to determine whether these actions correspond to the situation in vivo.[34–36]

Table 1 Frequencies of the European variant *LCT*-13910C>T in countries within the Americas, Asia, Europe, and Oceania

Country or population	Allele frequency (%)	Reference
US (Utah)	74.5	7
Sweden	73.7	8
New Zealand (Christchurch)	72	9
The Netherlands (Rotterdam Study)	69	10
Basques	65.9	7
Finland	58.1	11
Austria	53	12
Estonia (Väike-Maarja)	51.4	13
Poland	43.9	11
Russia (northern)	38.9	15
Portugal (northern)	37	17
Canary Islands	36.5	18
Hungary	35.9	16
Kola Sami (Murmansk)	30.5	14
Brazil (Caucasian)	24.7	21
Italy (North-east)	23.7	20
Chile (Hispanics)	22	22
India (Northern)	19.5	19
Brazil (African origin)	18.3	21
Uzbekistan (Kazakh, nomadic)	15.7	23
Italy (North-central)	13.3	20
Italy (Central)	13; 11.2	17,20
Uzbekistan (Tajiko-Uzbek)	10	23
Greece	9	20
US (African origin)	9	7
Italy (Southern)	5.5; 8	7,20
Sardinia	7.2	20
India (South)	6.6	19
Chile (Amerindians)	5.8	22
China	0	7
Japanese Brazilian	0	21

Note: In some publications, the percentage of *LCT*-13910-C>T allele frequencies were calculated based on the number of individuals with the *LCT*-13910-CT and *LCT*-13910-TT genotypes in relation to the total.

LCT gene regulation of lactase-persistence alleles occurs at the transcriptional level. *LCT* mRNA levels, which are distinguished by polymorphic markers in the coding region of *LCT*, were several times higher in individuals with *LCT*-13910T/-22018A alleles than in individuals with *LCT*-13910C/-22018G alleles.[1] After 5 years of age, an imbalance appears in the mRNA levels of *LCT*-13910C and *LCT*-13910T, with the *LCT*-13910T allele representing approximately 92% of *LCT* mRNA in children heterozygous for *LCT*-13910CT.[3]

Several transcription factors (Cdx2, GATA-4, GATA-5, GATA-6, and HNF1α) activate the *LCT* promoter in intestinal cell culture at the –100 to –20 bp binding site regions of

Table 2 Frequencies of the lactase persistence allele (*LCT*-13910C>T) reported in African countries

Country and/or population	Allele frequency (%)	Reference
Cameroon (Fulbe)	11.2, 21, 39	24,17,25
Mali (Fulbe)	37	26
South Africa (Xhosa mixed)	21.8	27
Morocco	17.3	7
Cameroon (Hausa)	13.9	24
Cameroon (agricultural)	4.3	24
São Tomé	4	17
Somalia	3.2	7
Senegal	2.6	24
Mozambique	1	17
Ethiopia (Somali camel herders)	1.9	28
Nigeria	0	24
Malawi	0	24
Sudan (north and south)	0	24
Ethiopia	0	24
Uganda	0	24

LCT which are repressed by PDX-1.[1] Mutation of the PDX-1 binding site does not prevent *LCT* promoter repression, which suggests that PDX-1 might function by binding to another DNA binding site or by inhibiting other transcriptional factors. PDX-1 overexpression resulted in strong repression of Cdx2 and HNF1α activation of the *LCT* promoter.[1] However, the exact mechanism for downregulation of *LCT* after weaning is unknown.

Haplotype conservation around lactase-persistence alleles indicates that these alleles emerged recently in different parts of the world and have been subject to strong positive selection in communities of high and perhaps intermittently exclusive consumers of fresh milk.[28] Nevertheless, the selective advantage provided by drinking fresh milk is not yet clear among populations reliant on agriculture with dairy farming as their main source of income, but has been discussed in detail elsewhere.[37] Gene-culture coevolution is a likely hypothesis in Africa, because high lactase-persistence allele frequencies are preferentially found in pastoral communities. In populations more likely to consume agricultural products, cheese and fermented milk, which have lower concentrations of lactose, the frequencies of lactase-persistence variants are possibly due to genetic drift.[38]

It is estimated that the *LCT*-13910T allele initially originated on the background of a more common haplotype approximately 5000–12,000 years ago and re-emerged recently (1400–3000 years ago) on another haplotype background in restricted populations west of the Urals and north of the Caucasus.[7] The *LCT*-13907G and *LCT*-13910T alleles share the

Table 3 Frequencies of other lactase persistence alleles in the *MCM6* gene

Country or population	Alleles	Frequency (%)	Reference
Saudi Arabia	*LCT*-13915T>G	48.9; 59.4	25,30
Jordan		39.1	25
Sudan (Beni Amir)		24.4	25
Ethiopia (Afar)		15	25
Sudan (Jaali)		14.2	25
Ethiopia (Amharic)		13.2	25
Ethiopia (Somali camel herders)		5.1	28
Tanzania	*LCT*-14010G>C	31.9	29
Kenya		27.6	29
Xhosa (South Africa)		12.8	27
Xhosa (mixed ancestry)		8.1	27
Angola		<7	17
Mozambique		No LP allele	17
Ethiopia (Somali camel herders)		0.5	28
Sudan (Afro-Asiatic Beja)	*LCT*-13907C>G	20.6	29
Ethiopia (Afar)		20	25
Ethiopia (Somali camel herders)		5.6	28
Northern Russia	*LCT*-13914G>A	Rare variant	31
Austria		Two individuals	12
China (Kazak)	*LCT*-22018G>A/	18	32
China (Northern)	*LCT*-13910CC	6.8	32
Japanese Brazilians		5.3	33
Tanzania (Akie)		One individual	29
Sudan (Jaali)	*LCT*-14009T>G	6.6	28
Ethiopia (Somali camel herders)		1.4	28

Abbreviation: LP, lactase persistence.

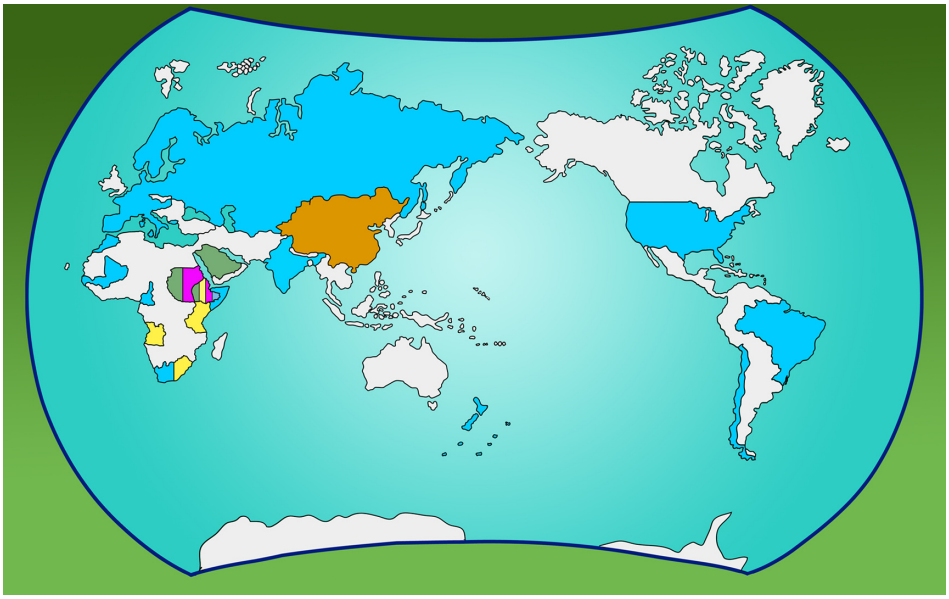

Figure 1 Tendency of lactase-persistence polymorphic variants in the world, based on the reports presented in Tables 1, 2, and 3.
Notes: In places where there was more than one variant, the most frequent variant was considered. *LCT*-13910C>T; *LCT*-22018G>A/-13910CC; *LCT*-13915T>G; *LCT*-14010G>C; *LCT*-13907C>G.

same ancestral lactase non-persistence haplotype, although they are on backgrounds of different lactase-persistence haplotypes.[25,28,35] *LCT*-13915G and *LCT*-14010C originated on different haplotype backgrounds,[25,28,29,35] but age estimates are similar for both, at approximately 4095 ± 2045 years.[35]

Diagnosis

Initially, the most accurate method available for the diagnosis of lactose maldigestion was direct biochemical assay of lactase activity from a jejunal sample. This assay is performed with a glucose oxidase reagent, which detects glucose liberated from lactose, with a cutoff value of 10 U/g protein.[1,2] Due to the invasiveness of a jejunal biopsy, this method has been replaced by endoscopic duodenal biopsy.[39,40] Mean lactase activity was about 40% lower in the duodenum compared with the jejunum,[39] but the Quick lactase test performed in samples taken from the postbulbar duodenum effectively identified patients with severe duodenal hypolactasia, with a sensitivity and specificity of 95% and 100%, respectively.[40]

Lactose tolerance tests have been developed to confirm the ability of intestinal lactase to hydrolyze and absorb lactose, and to avoid intestinal biopsies. Blood glucose levels were measured before and after an oral load of lactose at prespecified time intervals, with a maximum rise of 20 mg/dL, indicating lactose tolerance.[41] Oral ethanol administration before lactose load is used to inhibit galactose metabolism for the determination of the blood maximum rise of glucose (at least 20 mg/dl) and galactose (at least 10 mg/dl), indicating lactose tolerance. Thus, galactose concentration in combination with glucose concentration improves the correlation with jejunal lactase activity than using only glucose maximum rise after lactose load.[42] Nonetheless, of all the indirect lactose tolerance tests currently available, breath hydrogen after ingestion of 50 g of lactose was considered the most suitable test for population screening for lactase deficiency.[43] Use of the 50 g lactose dose has been criticized, because it is equivalent to 4–5 cups of milk, an amount that is far more than an individual usually ingests at one time,[44] so an oral load of 25 g, ie, the mean quantity contained in 500 mL of semiskimmed milk, may be considered a more appropriate amount, with high sensitivity and specificity.[41,44,45]

The lactose breath test is based on fermentation of undigested lactose by intestinal flora, producing hydrogen, carbon dioxide, and methane that are absorbed and eliminated via the lungs, but these gases also cause bloating, flatulence, abdominal pain, and diarrhea. Despite being widely used, the reliability of this test depends on the activity of bacterial flora. A false-negative result can occur if antibiotics have been taken within one month of being tested, if colonic pH is acidic enough to inhibit bacterial activity, or if there has been adaptation in the bacterial flora as a result of continuous lactose exposure.[41,44,45]

The discovery of lactase-persistence alleles prompted use of genetic tests for diagnosis of lactase non-persistence by polymerase chain reaction restriction fragment length polymorphism,[45–47] real-time polymerase chain reaction,[48–50] and Pyrosequencing® technology.[51] Compared with the lactose

hydrogen breath test, the genetic test is a simple, noninvasive, and more comfortable examination that does not provoke symptoms of lactose intolerance and is less cumbersome,[46,51] with easy transfer of a venous blood sample to the laboratory.[45,47] However, other polymorphic variants in Europeans (*LCT*-13914G>A)[50] and in African and Arab populations (*LCT*-13907C>G, *LCT*-13913T>C, and *LCT*-13915T>G, close to *LCT*-13910C>T, depicted in Table 3) affect the diagnostic accuracy of *LCT*-13910C>T typing by altering the melting profiles of the real-time polymerase chain reaction kit.[50] The reverse-hybridization strip assay based on multiplex DNA amplification and ready-to-use membrane test strips that detect *LCT* polymorphic variants (-13907C>G, -13910C>T, -13913T>C, -13914G>A, -13915T>G, and -22018G>A) represents a reliable tool for genetic diagnosis of lactase non-persistence, overcoming the interference of different melting profiles of the real-time polymerase chain reaction kit by the other polymorphic variants.[12]

The genetic test provides a more direct result, ie, a hypolactasia or lactase persistence genotype, whereas interpretation of the lactose breath test depends on the cutoff level, dose of lactose given, and duration of the test and age of the individual, among the other factors already discussed,[45–47,49,51] and is costly.[47,51] The discovery of other single nucleotide polymorphisms associated with lactase persistence (see Table 3) implies that DNA genotyping should provide information on the DNA sequence around the polymorphic site of the *MCM6* gene.[51] In addition to the reverse-hybridization strip assay,[12] Pyrosequencing technology may be a cost-effective option (€10 per test for polymerase chain reaction and Pyrosequencing reagents) for direct DNA sequencing, allowing genotyping of other single nucleotide polymorphisms.[51] The genetic test does not provide information on symptoms of lactose tolerance; however, measurement of lactase activity in intestinal biopsy does not provide it either.[47]

Contribution of lactose ingestion to symptomatology

The age of onset of primary hypolactasia varies between different ethnic groups. Hypolactasia does not cause any disturbance or discomfort unless lactose-containing food is consumed. Colonic microflora ferment undigested lactose in the intestinal lumen, which leads to production of short-chain fatty acids, hydrogen, carbon dioxide, and methane. These byproducts cause bloating, flatulence, and abdominal pain. Undigested lactose acidifies the colon and increases the osmotic load, resulting in loose stools and diarrhea.[52] Stools are usually voluminous, foamy, and aqueous. Although hypolactasia-related diarrhea can become chronic, affected individuals typically do not lose weight. However, some patients can experience constipation due to decreased intestinal motility, possibly caused by production of methane.[52]

Some authors have reported that the clinical presentation of lactose intolerance is not restricted to gut symptoms. Systemic complaints, such as headache, vertigo, memory impairment, lethargy, muscle and joint pains, allergy, cardiac arrhythmia, mouth ulcers, and sore throat, have been reported in less than 20% but up to 86% of these patients.[53,54] Putative toxic metabolites, such as acetaldehyde, acetoin, ethanol, peptide, and protein toxins, can alter cell signaling mechanisms and are possibly responsible for these systemic symptoms. They are generated by lactose fermentation in colonic bacteria.[53,55] When systemic complaints are present, it is important to assess whether they result from lactose intolerance, are coincidental, or emanate from an allergy to cow's milk protein, which is present in up to 20% of patients with symptoms of lactose intolerance.[52] Minenna et al reported a possible association between gastroesophageal reflux disease and lactose malabsorption in 30 subjects; however, further studies are required to ascertain a causal relationship, given that both lactose intolerance and reflux are very common conditions.[56]

There is considerable intraindividual and interindividual variability in the severity of symptoms, according to the amount of lactose ingested and the patient's ability to digest it. Factors contributing to this variability include osmolality and the fat content of lactose-containing food, gastric emptying rate, ability of colonic microflora to ferment lactose, intestinal transit time, colonic water absorption capacity, and individual perception of abdominal pain and discomfort.[52,57] Valid evidence is missing for a relationship between symptoms and amount of lactose ingested.[57] Most studies have included a small number of participants and/or subjects, with lactose maldigestion diagnosed by the breath hydrogen test but not always concomitant with lactose intolerance. In this regard, the available data[58] demonstrate that a single dose of lactose (up to 12 g, equivalent to that contained in approximately one glass of milk) administered alone produces no or minor symptoms in persons with lactose intolerance or maldigestion. Lactose doses of 15–18 g are well tolerated when offered together with other nutrients. With doses larger than 18 g, intolerance becomes progressively more frequent, and quantities over 50 g elicit symptoms in most individuals.[58]

Various reports indicate that symptoms typically considered secondary to lactose ingestion are not truly

related to maldigestion.[59,60] On self-report questionnaires, individuals commonly associate ingestion of lactose-containing products with onset of abdominal symptoms, even in the absence of objective evidence for lactose maldigestion, such as an altered lactose breath test.[61,62] Symptoms frequently attributed to lactose maldigestion can be secondary to irritable bowel syndrome,[62] which shares a similar clinical presentation, or food allergy.[63] Even a "nocebo effect", ie, occurrence of symptoms after ingestion of an inert substance when negative expectations about its content exist,[64] has been considered to be contributory to this exaggerated perception of lactose intolerance.[65] However, this concept requires more consistent evidence.[66] The misleading diagnosis of lactose intolerance and subsequent implementation of a dairy-restricted diet is not without consequences. The negative clinical impact of imposed restrictions, which mainly involve bone metabolism, is a topic that will be discussed in a following section.

Along with irritable bowel syndrome and cow's milk protein allergy, the differential diagnosis of lactose intolerance includes bacterial overgrowth, celiac disease, and inflammatory bowel disease.[57,67] When bloating and flatulence are the predominant symptoms, it is also advisable to rule out the possible contribution of other dietary sources of intestinal gas, such as beans, which contain two indigestible sugars, stachyose and raffinose.[57,68]

Management

The goal of treatment is to improve symptoms while maintaining an adequate intake of calcium, thus preventing secondary bone disease caused by a milk-restricted diet. Considerable efforts have been made to confirm whether decreased lactase enzyme activity can impair calcium absorption and prevent attainment of optimal peak bone mass. When evaluating peak bone mass and bone turnover rate in a young population with molecularly defined lactose maldigestion, Enattah et al showed that hypolactasia and lactose maldigestion do not alter calcium absorption or bone turnover rate, nor do they impair acquisition of peak bone mass. Moreover, the *LCT*-13910CC genotype does not appear to be a risk factor for stress fractures in this population.[69] Although decreased calcium absorption, evaluated by the strontium absorption test in patients with the *LCT*-13910CC genotype, was reported by Obermayer-Pietsch et al,[70] the predominant idea in the literature is that low calcium intake, rather than deficient calcium absorption, is the major factor contributing to loss of bone mass.[57,69] Several studies in patients with presumed or confirmed lactose intolerance have also reported lower calcium intake in this population.[57,71,72]

Several reports have been published that address the relationship among the *LCT*-13910C>T genotype, lactose intolerance, bone mineral density, and fracture risk. Studies in postmenopausal women[73] and elderly people[74] with the *LCT*-13910CC genotype have identified lower bone mineral density and a higher incidence of bone fractures in comparison with individuals with other lactase genotypes. However, these results have not been confirmed by other studies[75,76] or in younger subjects.[69,77]

Recently, Tolonen et al showed that young men with the *LCT*-13910TT genotype had the highest bone trabecular density at the distal radius and tibia, but other bone traits or low-energy fractures were not associated with the *LCT*-13910C>T genotype.[78] In addition to height and bone parameters, Koek et al assessed the correlation between vitamin D receptor polymorphisms and *LCT*-13910C>T genotypes in the elderly. This study found that the *LCT*-13910CC genotype was associated with lower dietary calcium intake and lower serum calcium levels, but not with bone mineral density and fracture risk. No interaction was detected between *LCT*-13910C>T genotypes and vitamin D receptor polymorphisms.[10]

The available data suggest that deficient calcium intake plays a major role in lactose intolerance that may be related to bone disease. Therefore, an objective diagnosis through either the hydrogen breath test or molecular detection of hypolactasia is key to the appropriate clinical management of patients with symptoms suggestive of lactose intolerance. This approach avoids inappropriate calcium-restricted diets and adverse consequences for bone health.

The initial recommendation for management of lactose intolerance is to aim for remission of symptoms by temporarily avoiding milk and dairy products. As mentioned earlier, most individuals with lactose malabsorption can tolerate up to 12 g of lactose without significant symptoms. After the initially restricted diet, lactose should be gradually reintroduced until the patient's threshold for symptoms is reached.[79] At this point, several behavioral measures can be adopted to overcome possible symptoms, including having fermented and matured milk products in the diet, consuming lactose together with other foods, and distributing lactose intake over the day. Although lactose tablets have been cited as a potential trigger of symptoms of lactose intolerance, such a small amount of lactose cannot be blamed for provoking symptoms, even when differences in individual symptom thresholds are considered.[80]

If the measures suggested here do not suffice in reducing symptoms, pharmacological strategies can be implemented.

The main pharmacological measures in use include lactase supplements, lactose-hydrolyzed or lactose-reduced milk, probiotics, colonic adaptation, and rifaximin. Ingestion of probiotics containing lactase may have the potential to aid lactose digestion in intolerant patients, but studies that have investigated this have published conflicting results. Therefore, the role of probiotics in lactose intolerance management is currently uncertain.[79] Yoghurt containing live cultures providing endogenous beta galactosidase are an alternative source of calories and calcium, and are well tolerated by many lactose-intolerant patients. However, yoghurt containing milk or its derivatives added after fermentation can cause symptoms.[79] Overall, the available evidence-based data are insufficient to ascertain the efficacy of these interventions, as discussed at a recent National Institutes of Health conference.[58]

Attention must be paid to daily ingestion of calcium and vitamin D, with supplementation as required. For adolescents and young adults, the dietary calcium recommendation is generally 1200–1500 mg. In adults, the amount varies according to gender and menopausal status. Calcium should be supplemented if there is not enough in the diet, and vitamin D should also be monitored and supplemented if necessary.[79] Well designed, randomized, placebo-controlled trials are still required before strong clinical recommendations can be made for the management of patients who are intolerant of lactose-hydrolyzed milk and yoghurt.

Conclusion

Random mutations have occurred in regions upstream of the *LCT* gene that have an enhancer effect on the *LCT* promoter, which enables carriers with the lactase-persistence phenotype to exist in populations all over the world. No "gold standard" test is available for the diagnosis of lactose intolerance. The lactose breath test, although considered the best method, may be influenced by confounding factors. Genetic testing has been a new tool for the diagnosis of hypolactasia/lactase persistence, but may not detect all the single nucleotide polymorphisms associated with this disorder. Symptoms of lactose intolerance might have been exaggerated, such that up to 12 g of lactose is possibly well tolerated by lactase non-persistence individuals, which negates the need for restrictions on lactose-hydrolyzed milk, as well as fermented and matured milk products, preventing any subsequent effects on bone mass density.

Acknowledgment

The authors thank Marcos Antonio Retzer for his contribution to Figure 1.

Disclosure

The authors have no conflict of interests to declare in this work.

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