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Lactose intolerance and malabsorption revisited: exploring the impact and solutions

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Declaração de Integridade

Eu, Ana Isabel Sousa Borralho, que abaixo assino, estudante com o número de inscrição 43936 do Mestrado Integrado em Medicina da Faculdade de Ciências da Saúde, declaro ter desenvolvido o presente trabalho e elaborado o presente texto em total consonância com o **Código de Integridades da Universidade da Beira Interior**.

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Ana Isabel Sousa Borralho

Dedication

To my maternal grandparents.

Acknowledgments

To my mother, my sister, and my father for the support they gave me, for believing in me, and for always wanting the best for me.

To my maternal grandparents, who are no longer with us, but whose memory and teachings remain alive in me, inspiring me and giving me strength throughout this journey.

To the rest of my family for their affection and support. To my cousins, Filipe and Ismael, for the help that made all the difference.

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Abstract

Background: Lactose intolerance (LI) is a condition in which the consumption of lactose-containing products leads to gastrointestinal symptoms. Despite being a common digestive disorder worldwide, LI is often overlooked, and there are few established recommendations for its diagnosis and management. This review aims to provide a comprehensive overview of LI, focusing on its clinical features, diagnostic evaluation, and management strategies.

Summary: Review of literature published from 2013 to 2023 on PubMed. Systematic reviews, meta-analyses, randomized controlled trials, case-control studies, cohort studies, and expert reviews were prioritized for analysis. LI is a common condition that shares symptoms with several other diseases. Various diagnostic tests are available to identify LI, including the hydrogen breath test (HBT), the lactose tolerance test, the urinary galactose test, the gaxilose test, the rapid lactase test, and genetic testing. Managing LI may involve adopting a lactose-free or low-lactose diet, taking oral enzyme supplements, using probiotics and prebiotics, or consuming plant-based alternative beverages.

Key Messages: LI affects many people worldwide and can significantly impact their quality of life. The HBT is the most widely used and effective method for diagnosing LI, along with a thorough assessment of symptoms. Instead of following a completely dairy-free diet, adopting a low-lactose diet - allowing up to 12-15 grams of lactose per day - has been shown to be well tolerated and beneficial for most individuals with LI. While probiotics, prebiotics, and plant-based beverages may be helpful, their effectiveness in managing LI has not yet been proven.

Keywords

lactose intolerance; lactase; lactose; malabsorption.

Resumo

Introdução: A intolerância à lactose (IL) é uma condição em que o consumo de alimentos que contêm lactose provoca sintomatologia gastrointestinal. Apesar de ser uma patologia prevalente em todo o mundo continua a ser frequentemente esquecida e negligenciada, existindo poucas recomendações estabelecidas para o seu diagnóstico e tratamento. Esta revisão tem como objetivo fornecer uma visão abrangente da IL, com destaque para as suas características clínicas, avaliação diagnóstica e estratégias de tratamento.

Sumário: Revisão dos artigos publicados na PubMed entre 2013 e 2023. Foi priorizada a análise de revisões sistemáticas, meta-análises, ensaios clínicos randomizados, estudos de caso-controlo, estudos de coorte e revisões por *experts*. A IL é uma condição prevalente cujas manifestações clínicas são comuns e partilhadas com outras doenças. Existem vários testes de diagnóstico disponíveis, tais como o teste de hidrogénio expirado (THE), o teste de tolerância à lactose, o teste de galactose urinária, o teste da gaxilose, o teste rápido da lactase e o teste genético. O tratamento pode incluir uma dieta sem lactose, dieta com pouca lactose, suplementação enzimática oral, uso de probióticos e pré-bióticos ou consumo de alternativas derivadas de plantas.

Mensagens Principais: A IL afeta um grande número de pessoas em todo o mundo, podendo ter um impacto significativo na sua qualidade de vida. O THE é o método mais amplamente utilizado e eficaz para diagnosticar a IL. Em vez de uma dieta completamente isenta de lacticínios, a adoção de uma dieta restrita em lactose até 12-15 gramas de lactose por dia é a opção mais adequada, pois geralmente é bem tolerada e mais benéfica para a maioria das pessoas com IL. Embora os probióticos, pré-bióticos e opções dietéticas alternativas derivadas de plantas possam ser úteis, a sua eficácia no tratamento da IL ainda não foi comprovada.

Palavras-chave

Intolerância à lactose; lactase; lactose; malabsorção.

Index

List of Acronyms

LI	Lactose Intolerance
NIH	National Institutes of Health
Ig	Immunoglobulin
FODMAPs	Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols
SIBO	Small Intestine Bacterial Overgrow
IBS	Irritable Bowel Syndrome
CD	Celiac Disease
HBT	Hydrogen Breath Test
IU	International Units
GOS	Galacto-oligosaccharides

Introduction

Lactose intolerance (LI) is among the most frequent food intolerances worldwide. It results from reduced enzymatic activity of lactase in the brush border of small intestine mucosa, causing symptoms like diarrhea, abdominal pain, and bloating after lactose ingestion (1, 2).

Lactase enzyme expression increases in newborns' intestines, enabling them to digest lactose found in milk. Over time, this enzyme production naturally decreases, aiding the weaning process. Historically, with the domestication of cattle, cow's milk became a significant food source due to the development of a genetic mutation that allowed for continued lactase expression in some individuals (3). However, approximately 65-70% of the world's population still loses the lactase enzyme after infancy and is lactose intolerant. Although the clinical symptoms of lactose intolerance have been documented since as early as 460 before Christ, scientific studies on the condition have only emerged since the 1960s (4).

There are a few study groups on this topic, mainly the "National Institutes of Health (NIH) Consensus Development Conference Statement on Lactose Intolerance and Health" (5). Despite affecting about 65% of the population, LI often presents as chronic abdominal complaints, which makes it a diagnostic challenge and frequently leads to underdiagnosis (6, 7). Additionally, errors and delays in diagnosis contribute to increased healthcare costs (8). The purpose of this review is to provide an overview of LI, focusing on its diagnosis, available tests, differential diagnoses, and management strategies. This work is based on studies published in MEDLINE via PubMed. Preference was given to systematic reviews, meta-analyses, randomized controlled trials, case-control studies, cohort studies, and expert reviews published between 2013 and 2023. The baseline search query used was as follows: "Lactose Intolerance/classification"[Mesh] OR "Lactose Intolerance/diagnosis"[Mesh] OR "Lactose Intolerance/diet therapy"[Mesh] OR "Lactose Intolerance/etiology"[Mesh] OR "Lactose Intolerance/genetics"[Mesh] OR "Lactose Intolerance/physiopathology"[Mesh] OR "Lactose Intolerance/therapy"[Mesh] and the time range set from 2013 to 2023, resulting in a total of 330 results. As some topics lacked sufficient articles, additional searches were conducted using the search bar. Relevant studies published before this time interval were also included. Ultimately, 34 articles were used for this review.

Definitions

Lactose maldigestion is related to inadequate hydrolysis of lactose (9). Lactase deficiency may result in undigested lactose (lactose maldigestion) and consequently unabsorbed, known as lactose malabsorption (10).

When lactose is not entirely absorbed in the small intestine (lactose malabsorption), it can reach the colon, which might cause gastrointestinal symptoms. When these symptoms occur, it is recognized as lactose intolerance (2, 11).

Individuals with lactase deficiency can develop lactose malabsorption upon consuming lactose-containing foods, which may trigger symptoms, i.e., lactose intolerance (2). However, lactose malabsorption does not always lead to lactose intolerance. While lactose malabsorption is necessary for lactose intolerance (LI), it is not sufficient on its own to cause it (12).

Epidemiology

The prevalence of LI-confirmed cases throughout the world is about 57%, although the actual prevalence is estimated to be over 65%. Broken down by continent, it is around 100% in Africa, 70% in Asia, and 50% in America, compared to just 28% in Europe (6). Overall, two-thirds of the global population is estimated to have lactose malabsorption (13).

Pathophysiology

The expression of the lactase enzyme is highest at birth and then gradually decreases over time (9). This enzyme, also named lactase-phlorizin hydrolase, consists of two polypeptide chains, acts in the villi of the brush border of the small intestine, and is found in higher concentrations in the jejunum. It is responsible for the hydrolysis of the disaccharide lactose into glucose and galactose, which can then be absorbed (14).

LI arises when individuals with lactose malabsorption experience gastrointestinal symptoms following the intake of products containing lactose (14). In these cases, the lactose that is not absorbed reaches the colon, where certain bacteria ferment it. This fermentation produces short-chain fatty acids and gases such as hydrogen, methane, and carbon dioxide. As a result, an osmotic gradient is created, leading to water retention in the colon (14).

The presence of carbohydrates in the colon increases intestinal transit time and interacts with intestinal flora (2). Surpassing the capacity to re-absorb short-chain fatty acids results in diarrhea (14). Accumulation of gases in the colon contributes to abdominal symptoms (2).

Etiology of lactase deficiency

The etiology of lactase deficiency includes primary, secondary, congenital, and development-associated forms, with primary being the most common (1, 2, 12).

Primary lactase deficiency occurs due to lactase non-persistence, where the activity of this enzyme gradually decreases with age (1). Lactose intake by these individuals results in lactose malabsorption and possibly LI (15).

Lactase activity decreases during the first 10 years of life, except for individuals with mutations in the lactase gene enhancer region, which enables this enzyme's persistence (13). Some nucleotide polymorphisms of the lactase gene are related to the persistence of this enzyme, such as C/T-13910 and G/A-22018 (1, 15).

Secondary lactase deficiency results from any condition that causes damage to the small intestine mucosa, where lactase is present. Enteropathies, infections, or surgical procedures can cause it (1, 2). It can develop at any age and is typically a transitional condition that disappears once the underlying cause has been treated (2).

Congenital deficiency is an uncommon autosomal recessive disorder that appears in the first days of life, as soon as a newborn starts consuming milk with lactose, whether it be breast milk or formula, due to the lack of lactase activity (1, 16, 17). Symptoms resolve once patients follow a lactose-free diet (2, 16).

Developmental lactase deficiency occurs in premature infants with less than 34 weeks of gestation and occurs due to the immaturity of their small intestine. This condition improves over time as the intestine matures (2, 12).

Clinical Presentation

Symptoms of LI include gastrointestinal and extra-gastrointestinal manifestations (10). Common gastrointestinal symptoms include abdominal distension and pain, flatulence, borborygmi (the rumbling sounds made by the movement of gas in the intestines), nausea, vomiting, and diarrhea (10, 18). Additionally, about 30% of individuals may experience constipation, which occurs as a result of delayed intestinal transit due to the production of methane (18).

Extra-gastrointestinal symptoms include headache, lack of concentration, muscle and/or joint pain, asthenia, mouth ulcers, and increased urination frequency (10).

Symptom occurrence is affected by lactose dosage, the foods consumed with lactose, gastrointestinal transit time, residual enzyme levels, mucosal diseases, microbiome composition, and stress levels (14).

Most people who do not digest lactose can tolerate about 12.5 grams of lactose, which is the amount present in a 250 ml glass of milk, experiencing only minimal symptoms or none at all (19).

Differential diagnosis

It is important to differentiate between LI and cow's milk allergy. Because the gastrointestinal symptoms of cow's milk allergy are similar to those of LI, sometimes these conditions are confused. They are both triggered by the ingestion of milk; however, while LI is not immune mediated, cow's milk allergy is an immune-mediated reaction that can either be due to immunoglobulin E (IgE), non-IgE mediated, or a set of both. Particularly, the symptoms of the non-IgE mediated reaction are similar to those of LI, presenting with vomiting, diarrhea, and abdominal pain. When the allergy is mediated by IgE, it usually causes urticaria, angioedema of the lips, pruritus, colicky abdominal pain, nausea, vomiting, and diarrhea. To confirm this diagnosis, an oral food challenge can be conducted in a hospital setting. A prick test or specific IgE serology test can also be useful. The recommended treatment is a diet free of cow's milk proteins (20).

There are other carbohydrates, besides lactose, that when not totally absorbed in the small bowel can present with the same symptoms as LI. These are known as fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs), which include lactose but also fructose, sorbitol or xylitol. When consumed in high amounts, some of these FODMAPs can exceed the absorption capacity of the small intestine, leading to symptoms associated like LI (2). Following a low FODMAP diet typically results in an improvement of symptoms (21).

Small Intestine bacterial overgrow (SIBO) can also result in abdominal distension, pain, and gases. A diagnosis of SIBO can be done using a hydrogen breath test conducted after the ingestion of lactulose or glucose (2).

Irritable bowel syndrome (IBS) and celiac disease (CD) are important differential diagnoses to consider. IBS is a functional disorder that is diagnosed by excluding other potential causes and applying the Rome IV criteria. It is also important to note that CD can lead to LI, which may be the primary manifestation in individuals with undiagnosed CD (21, 22).

Diagnosis

Symptoms like abdominal pain, distension, or diarrhea are nearly always present in LI (10). Clinical history and physical examination are crucial. Additional symptoms, past surgeries, medications, other illnesses, and family history should be assessed (23).

Diffuse and chronic abdominal pain can occur in conditions such as LI, CD, IBS, or colorectal cancer (23). Diarrhea characteristics are important. Osmotic diarrhea can occur in carbohydrate malabsorption, like lactose, fructose, or sorbitol. Secretory diarrhea can be due to diabetic enteropathy. Inflammatory diarrhea can occur in inflammatory bowel diseases, some forms of SIBO, and colorectal cancer or villous adenomas. Diarrhea that occurs during the day and at night suggests an organic cause. Symptoms triggered by the consumption of milk make LI or allergies more likely (24).

Alarm symptoms or signs that necessitate immediate attention and investigation include the following: unintentional weight loss, loss of appetite (anorexia), iron deficiency anemia, gastrointestinal bleeding, persistent vomiting, and a family history of colorectal cancer or inflammatory bowel diseases (23).

A physical examination is crucial because it can reveal signs that may suggest other underlying conditions. For instance, dermatitis herpetiformis may indicate CD, while erythema nodosum can occur in inflammatory bowel disease. Additionally, acanthosis nigricans might point to a potential malignant disease. During the examination, abdominal palpation can help detect masses or organ enlargement, and a rectal examination can provide valuable information about bleeding or the presence of masses (23).

If malabsorption is suspected, several tests can be helpful, including a complete blood count, C-reactive protein, vitamin B12, folic acid, transferrin saturation, fecal calprotectin, fecal elastase, and tissue transglutaminase antibody along with IgA, IgG and IgM levels. Colonoscopy, along with ileoscopy and eventual gastroscopy (a bidirectional endoscopic study), can help identify or exclude inflammation or lesions. These procedures are essential for individuals with alarm symptoms or for those aged 45 and older who do not have a recent high-quality digestive endoscopy (24). In cases of persistent symptoms or recent worsening despite medication targeted at a suspected diagnosis, abdominal imaging, and bidirectional endoscopy should be considered if they have not been performed previously. Computer tomography or magnetic resonance enterography are particularly useful for identifying or ruling out conditions affecting the small bowel and other abdominal and pelvic issues (25).

LI diagnosis requires both lactose malabsorption evidence and associated symptoms (9). Markers of lactose malabsorption indicates lactase non-persistence (15).

Hydrogen Breath Test. In our body, hydrogen, and methane result from the anaerobic fermentation of carbohydrates by gastrointestinal microorganisms. A breath analysis indicating high concentrations after ingestion of carbohydrates suggests incomplete absorption, forming the basis for the hydrogen breath test (HBT) (2). HBT is preferred for diagnosing lactose malabsorption, given its properties: not being invasive, having a mean sensibility of 77.5%, and a mean specificity of 97.6% (6, 26). Assessing symptoms alongside this test is crucial for diagnosing LI. This test emerged in clinical practice in the 1970s and has been widely used since then (2). It is available in Portugal, typically costing more than the lactose tolerance tests but less than the genetic test. For HBT, it is recommended to fast for 8 hours beforehand. Additionally, avoid taking antibiotics for 4 weeks before the examination, and refrain from consuming poorly absorbable carbohydrates (such as lactose, fructose, and xylitol) for 1 day before the test. Patients should also avoid physical exercise and smoking leading up to the assessment. It is advisable to suspend prokinetic, laxative, and probiotic medications the day before the examination (2). To diagnose lactose malabsorption in adults, consuming 25 to 50 grams of lactose is recommended, with 25 grams being the standard for diagnosing LI. The test should last 3 to 5 hours, and measurements should be taken every 30 minutes. Taking measurements at intervals of 10 to 15 minutes may also help identify intolerance, particularly if a connection between increased hydrogen production and the onset of symptoms can be established. An increase in hydrogen levels of at least 20 parts per million compared to the baseline value indicates malabsorption or maldigestion (2). False-positive results may occur due to excessive bacterial overgrowth. False-negative results might be due to slow intestinal transit time or when hydrogen production is too low to be detected (2). Assessing symptoms after the test is crucial for determining the appropriate treatment, and it should be considered an essential part of the testing process (2). Symptoms related to LI typically appear 50 to 100 minutes after ingestion, which is when the substrate reaches the colon (27).

Lactose Tolerance Test. A lactose tolerance test depends on measuring blood glucose levels after ingesting lactose. First, baseline blood glucose levels are taken. Then, the individual consumes 50 grams of lactose, and blood sugar levels are measured again at 30, 60, and 120 minutes after ingestion (6). If plasma glucose levels increase by less than 20 mg/dl (1.11 mmol/L), this indicates malabsorption (27). This test can diagnose LI in individuals whose bacterial flora fails to produce hydrogen. However, false-negative results may occur in diabetics, and the test's reliability can be affected by gastroparesis (6, 28). Lactose tolerance test is the least expensive option (14). However, it is known for having low sensitivity, low specificity, and low accuracy (6, 15).

Urinary Galactose Test. The urinary galactose/creatinine ratio is calculated 3 hours after lactose ingestion. A ratio that does not exceed 0.10 indicates lactose malabsorption. However, the accuracy of this test in diagnosing lactose non-persistence is still uncertain, and the procedures for conducting this test may vary (15).

Gaxilose Test. The gaxilose test is based on the principle that gaxilose is broken down by intestinal lactase into galactose and xylose. Xylose is then absorbed in the intestine and metabolized. Therefore, measuring its levels allows for assessing the activity of the lactase enzyme (29). This test stands out for its ease of use and patient comfort (28). However, scientific literature shows that its performance can be variable: while some studies report positive accuracy, others do not (14).

Rapid Lactase Test. Previously, jejunal biopsies were the standard method for assessing lactase enzymatic activity (22). Nowadays, duodenal mucosal biopsies are preferred for this purpose (6). In the updated procedure, biopsies are placed on a test plate where a substrate solution is added and incubated. Then, a chromogenic solution and a signaling enzyme solution are added, resulting in a color change that indicates lactase activity: dark blue signifies normolactasia, light blue indicates hypolactasia, and a lack of reaction suggests severe hypolactasia (30). Despite these advances, this testing method is still considered somewhat inadequate due to its invasiveness and limitations, such as patients' clotting problems, high costs, and the biopsy sample size, which may affect the results (6).

Genetic Test. Genotyping single nucleotide polymorphisms is an alternative to intestinal biopsy for diagnosing lactase non-persistence. However, this genetic test can be expensive, and its implementation may vary by region due to the presence of different polymorphisms (15). Additionally, these genetic tests are unable to detect secondary forms of LI (6).

Self-reported LI is ineffective for diagnosing lactose maldigestion, as it produces variable results in systematic reviews (9, 19). Comparing different methods for diagnosing malabsorption, hydrogen tests are more reliable than the lactose tolerance test and urinary galactose/creatinine ratio (15). Clinical literature indicates that gaxilose and galactose tests yield inconsistent results across different studies (14). The lactose tolerance test currently lacks a specific protocol and cut-off value, although the most used is an increase of 20 mg/dl. This test can be an alternative to the HBT when it is not recommended, making it particularly useful in low-resource settings (14, 26). In Portugal, the available diagnostic tests include the genetic, HBT, and lactose tolerance tests.

Given all of the above, diagnosing LI requires simultaneous evaluation of lactose digestion and abdominal symptoms. The diagnosis should be based on an assessment of

medical history alongside an HBT. HBT is the most widely used among the existing tests and provides the best diagnostic value, supported by extensive scientific literature (20, 26, 27).

Management

Several approaches can be applied to patients with LI: a lactose-free diet, a low-lactose diet, oral supplementation of the lactase enzyme, and modulation of the microbiome using probiotics and/or prebiotics (31, 32).

Dietary strategies play an important role in patients with LI (31). These patients often reduce or eliminate dairy consumption until their symptoms improve (1). However, since dairy products provide essential nutrients such as calcium, proteins, and vitamins B and D, its reduction or absence leads to concerns about nutritional deficiencies and related issues, such as problems with bone mineralization (1, 21). A dairy-free diet is no longer recommended. Many individuals with LI can tolerate up to 12-15 grams of lactose per day (6, 19). One effective treatment option is to consume lactose-free dairy products (1). There are also various alternatives to replace dairy with lactose, including dairy products that have had lactose hydrolyzed or plant-based options made from rice, soybeans, oats, nuts, or almonds. Nonetheless, further studies are needed to assess whether plant-based beverages are safe and nutritionally adequate alternatives (31).

Another option is to use enzyme replacement with exogenous lactase. This enzyme should be taken 5 to 30 minutes before consuming foods containing lactose. Some studies have shown that 6,000 International Units (IU) can significantly reduce hydrogen production, depending on the amount of lactose consumed. Lactase is available in various forms, including capsules and chewable tablets, and it can also be mixed with milk. The enzyme can be derived from yeast or fungi (33). Overall, evidence supporting its efficacy is still limited (10). Furthermore, using lactase may not completely eliminate symptoms associated with LI (21).

Patients with LI should gradually incorporate cow's milk into their diets. This regular and long-term lactose consumption can increase the amount tolerated over time (5, 19). It is initially recommended to start with a daily intake of 30 and 60 milliliters, which can be progressively increased to 250 milliliters per day. Consuming other foods alongside milk can help improve its tolerance (19).

Supplementation with prebiotics and probiotics can improve lactose digestion by modifying the intestinal microbiota (34). Prebiotics are non-digestible functional foods, such as galacto-oligosaccharides (GOS), that help increase the population of lactose-fermenting bacteria. However, the effectiveness of prebiotics can vary among different strains (1, 6, 32). Probiotics are live microorganisms that enhance the hydrolytic capacity of the intestinal bacteria, regulate mucosal permeability, and maintain low levels of short-chain fatty acids (6). The NIH consensus on LI indicates that existing studies on probiotics had several limitations, which prevent the formulation of definitive

recommendations for their use (5). A systematic review has concluded that probiotics, including *Lactobacillus acidophilus, L. reuteri, L. rhamnosus, L. bulgaricus, Streptococcus thermophilus,* and *Bifidobacterium longum*, have resulted in a reduction of symptoms associated with LI. However, there is still insufficient evidence to determine whether these effects persist after discontinuing probiotics (1). Finally, when managing LI, optimizing treatment for any underlying health issues is crucial to avoid unnecessary dietary restrictions. Patients with LI can typically consume small amounts of dairy products and low-lactose-containing foods. Therefore, an appropriate nutritional plan should be tailored to meet the individual of each patient (5).

Conclusion

LI is commonly underdiagnosed, with an estimated prevalence exceeding 65% (6). It occurs when individuals with lactose malabsorption experience symptoms after consuming lactose (14). The most common type of LI is primary lactase deficiency, which results from a non-persistent lactase enzyme (1). Symptoms of LI, such as abdominal pain, bloating, and diarrhea, can overlap with those of many other conditions. Therefore, obtaining a comprehensive clinical history and conducting a physical examination is essential for accurate differential diagnosis (10, 23).

Diagnosing lactose intolerance (LI) can be challenging due to the variety of tests available, each differing in availability, accuracy, invasiveness, and cost. Some tests also yield inconsistent results. Currently, there are no clear recommendations for the best diagnostic method. However, the hydrogen breath test (HBT) is favored for its high sensitivity, specificity, and non-invasive nature, often used alongside symptom assessment (2, 6, 10).

Management of LI typically involves dietary adjustments (1). A non-dairy diet is no longer universally recommended, as many patients with LI can tolerate up to 12-15 grams of lactose per day. Gradually introducing small amounts of dairy can be beneficial. Treatment options may include using lactose-free or low-lactose dairy products. Some studies suggest that supplements with the exogenous enzyme, probiotics, and prebiotics can help reduce symptoms; however, more research is needed to confirm their long-term effects (1, 6). While plant-based alternatives are increasingly available and used, their nutritional adequacy remains uncertain (31). Evidence suggests that patients with LI benefit from a tailored nutritional plan, so assessment by a nutritionist is advisable.

In the future, it would be helpful to increase awareness of this condition. Moreover, creating guidelines for diagnosing and managing the treatment of these patients can help prevent unnecessary restrictions, address their nutritional needs, and ultimately improve their quality of life.

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