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Lactose Intolerance—Old and New Knowledge on Pathophysiological Mechanisms, Diagnosis, and Treatment

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Abstract

Lactose intolerance is a pathology frequently encountered today. It occurs when the activity of lactase in the intestine is reduced or absent, with consequent failure to digest lactose. The global prevalence of this clinical condition is estimated of about 57% with instrumental methods, while the real prevalence exceeds 65%. The absence of lactase determines both the excessive osmotic load in the small intestine and the fermentation of lactose by the bacterial flora with consequent production of short-chain fatty acids and gas. This latter process is responsible for the onset of symptoms associated with lactose intolerance (abdominal pain, bloating, flatulence, etc.) which arise after the intake of lactose. Several studies have shown an increased risk of developing various pathologies for lactose-intolerant subjects (some types of cancer, osteoporosis, etc.). Therefore, it is essential to diagnose and properly treat this pathology. Various options exist for diagnosing lactose intolerance: Hydrogen Breath Test, genetic test, Quick Lactose Intolerant Test, Lactose Tolerance Test, Gaxilose Test. Like diagnostic methods, there are several options for treating intolerance. In addition to a food restriction, the use of exogenous enzymes and/or probiotic and the selection of milk containing specific types of beta-caseins less correlated to the appearance of gastrointestinal symptoms are very useful. The aim of this review is to illustrate the main and most modern diagnostic and therapeutic choices for lactose intolerance currently available.

Keywords Lactose intolerance · Hydrogen Breath Test · Lactase · Probiotics · Hypolactasia

Introduction

Lactose malabsorption or hypolactasia is a common condition caused by a low lactase activity, with consequent reduction of lactose absorption. Lactose intolerance occurs when the malabsorption causes symptoms [1].

The severity of the symptoms is subjective and depends on the amount of ingested lactose, on the concentration of lactase present in the intestinal mucosa, on the intestinal flora, on the gastrointestinal motility, and on the individual sensitivity in the perception of symptoms [2].

Epidemiology

Lactose intolerance diagnosed with instrumental methods has a global prevalence of about 57%. Instead, it is estimated that the real prevalence exceeds 65%. This condition has a prevalence of about 50% in South America, Africa, and Asia. In the USA, the prevalence is 15% among whites, 53% among Mexican-Americans, and 80% in the Black population. In Europe, the prevalence is about 28%, with variable percentages between the North and South of the continent. Indeed, it varies from 2% in Scandinavia to about 70% in Sicily [3].

Lactose Biochemistry and Metabolism

Lactose is a disaccharide composed of D-galactose bound to D-glucose. It is present in dairy products. The concentration of

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lactose in a mother's milk is 7.2 mg/100 ml whereas in a cow's milk it reaches only 4.7 mg/100 ml [4].

Lactose is synthesized in the mammary gland from glucose and galactose by the action of lactose synthetase. It is an enzyme which has two subunits: one with galactosyltransferase activity and other with regulatory actions, which catalyze the union of galactose and glucose to form the disaccharide [5].

For its use in the human body, lactose must be hydrolyzed by lactase enzyme, that is, present on intestinal mucosal surface. From week 8 of gestation, lactase activity can be detected at the mucosal surface in the human bowel. This activity increases until week 34 and lactase reaches its maximum peak at birth. The ability to digest lactose during the period of breastfeeding is essential to the health of the infant. This importance has been demonstrated by the fact that one of its congenital deficiency is fatal if not recognized very early after birth. Lactose hydrolyzing hesitates with the formation of the two monosaccharides, glucose and galactose, which are absorbed by active transport mediated by Sodium-Glucose Linked Transporter 1 (SGLUT-1). The latter is a membrane protein that co-transports glucose or galactose and two ions sodium (Na^+) from the intestinal lumen to enterocyte cytosol. Subsequently, the monosaccharides pass from the cytosol to the blood by Glucose Transporter 2 (GLUT-2), present on the enterocyte membrane [5, 6].

A deficiency of lactase leads to a reduction in the absorption of lactose present in the intestinal tract and this can cause the appearance of the symptoms (Fig. 1). First, the excessive osmotic load increases the intestinal water content. Second, lactose is readily fermented by the colonic microbiome leading to production of short-chain fatty acids and gas (mainly hydrogen - H_2 -, carbon dioxide - CO_2 -, and methane - CH_4 -) [7].

The amount of ingested lactose that causes the appearance of symptoms is variable from one individual to another and it is dependent on several factors: the dose consumed, residual lactase expression, ingestion of lactose with other dietary components, gut-transit time, small bowel bacterial overgrowth, and also composition of the enteric microbiome [8].

Genetic of Lactase

Lactase is encoded by a gene, LCT, of about 50 kb and localized on chromosome 2 (*locus 2q21*). Gene has 17 exons and it encodes an mRNA from which is obtained a pre-protein that is processed to a smaller protein, which has one active site. Lactase expression is restricted to the enterocytes of the small intestine. In particular, it is expressed at the highest levels in the mid-jejunum. Two possible polymorphisms of this gene were sequenced. The first is C/T-13910, located at 14 kb. It is based on the presence of one cytosine (C) or one thymine (T) in position 13910. The variant C/C is related to the non persistence of lactase; instead, the variants C/T or T/T are expression of lactase persistence. The second polymorphism is G/A-22108, located at 22 kb. It is based on the presence of one guanine (G) or one adenine (A) in position 22108. The variant G/G is related to the non persistence of lactase, while the variants G/A or A/A are expression of lactase persistence [9].

However, in other countries of the world, more polymorphisms have been identified, for example, in Africa and in Middle East have been found: C/G-13915, G/C-14010, and T/G-14009 [10].

In addition to gene mutations, other mechanisms may be responsible for lactose intolerance. In fact, epigenetic modifications in DNA and histone proteins can contribute to lactase non persistence [11].

Clinical Conditions

Typical symptoms of lactose intolerance are abdominal pain, bloating, flatulence, diarrhea, borborygmi, and in some cases, constipation, nausea, and vomiting. They usually begin around 1 h after the intake of lactose, but they may appear earlier or later [12].

In subjects with lactose intolerance, gas is produced because lactose is not digested and absorbed in the small bowel, and it is fermented by intestinal flora. Some studies have shown that there are minimal or no differences between gas production in lactose malabsorbers and in lactose intolerance. Therefore, it is the sensitivity to bowel distension to determine the appearance of symptoms, in this case swelling and abdominal pain. In addition, other factors that influence the bloating are abnormal colonic flora, small bacterial overgrowth, and impaired absorption of substrates [13].

Moreover, other extra-intestinal symptoms have been described in patients with lactose intolerance, for example, memory deterioration, cephalalgy muscoskeletal pain, depression, anxiety, ulcers in the oral mucosa, and heart rhythm disorders. The cause could be the toxic effects of chemical substances such as acetone, acetaldehyde, ethanol, and peptides which are formed in the course of maldigestion and malabsorption of lactose [5, 14].

Diagnostic Process

Various options exist for diagnosing lactose intolerance.

Hydrogen Breath Test

The formal test which is commonly used in patients suspected of having lactose intolerance is the H_2 Breath Test (HBT). It has become widely available and it is often used for diagnosis

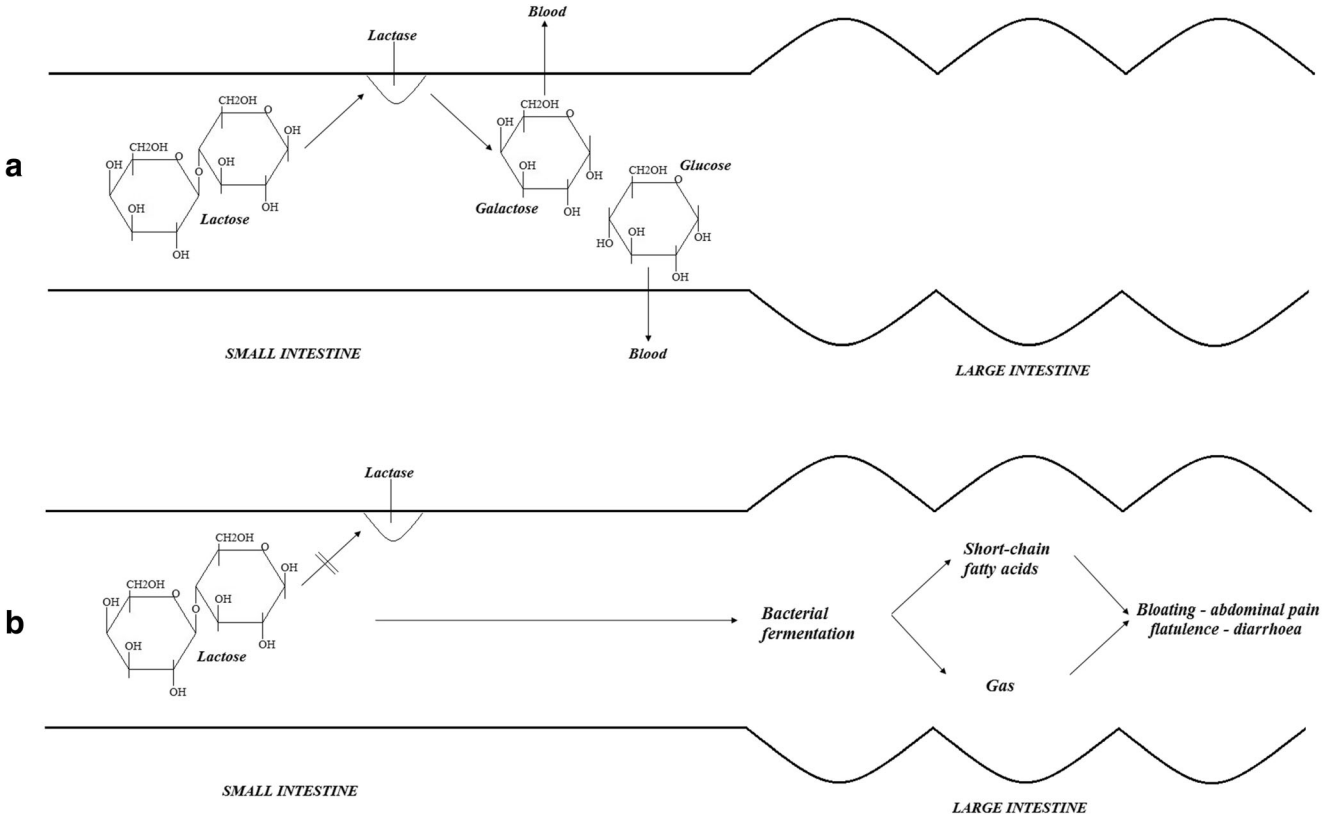

Fig. 1 **a** Normal digestion of lactose in the presence of the lactase. **b** Lactose intolerance due to lactase deficiency and subsequent onset of symptoms

of lactose intolerance. The test is based on the principle that undigested lactose undergoes fermentation by the microbial flora, with subsequent gas production, including hydrogen. It involves ingestion of 25 to 50 g of lactose and the measurement of hydrogen every 15 min for 3–6 h. An increase in breath hydrogen concentration greater than 20 ppm (parts per million) over baseline, after lactose ingestion, suggests hypolactasia [15].

A disadvantage of the test is its long duration (from 3 to 6 h) and the high number of measurements to be performed during this time (every 15 min for a total of 12–24 measurements). Recently, Yang et al. have proposed a protocol (Four-Sample Lactose Hydrogen Breath Test, 4SLHBT) that provides only 4 measurements (at 0 min, 90 min, 120 min, and 180 min). They found a high concordance between the classic test and 4SLHBT. All this translates into better patient compliance, the possibility of reducing waiting lists in public hospital centers since in this way more people can perform the breath test in the same session, and a reduction in health care costs with a minor consumption of medical resources. Therefore, this protocol could be proposed as a standard for performing the breath test [16].

HBT is positive in 90% of patients with lactose malabsorption and false negatives can also be detected. A first explanation is given by the presence of bacteria that do not produce hydrogen but methane (CH_4). Therefore, Houben et al. conducted a study which showed that the measurement of CH_4, in addition to that of hydrogen, involves an increase in the diagnostic accuracy of the breath test. In this way, it is possible to diagnose lactose intolerance even in those subjects with a bacterial flora that does not produce hydrogen [17]. Also according to Rojo et al., this method could be applied to identify intolerant subjects with normal H_2 excretion, even if in their study a greater number of intolerant was not detected using the measurement of CH_4 [18].

Other factors that can cause false-negative values are slow orocoecal transit, exercise, and all those conditions that affect the normal bacterial flora, such as recent use of oral antibiotics, abuse of laxatives, or invasive procedures that require preparatory bowel cleansing with enemas. Even the use of probiotics should be avoided before the test is performed, since these drugs cause an alteration of the intestinal bacterial flora [19].

Instead, factors that can determine false-positives are previous use of aspirin or proton pump inhibitors, and smoking (since the combustion of tobacco causes an increase in gases, including hydrogen). Also some foods (for example, beans, corn, white wheat, potatoes, oats) can cause an increase in the production of hydrogen and, therefore, a greater excretion of this gas with breath. In these cases, the increase in hydrogen may not be related to a lactose intolerance [20, 21].

Regarding the costs of HBT, these depend mainly on the type of preparation used, the execution time, and the cost of the disposable materials that are chosen. In Italy, the cost of the analyzer varies between €10,000 and €18,000, since two types of machines are available: those that use a solid-state sensor and those that use an electrochemical sensor. The first are expensive and not able to detect alterations of concentration of a single gas, even if some of these machines have been modified so as to be able to detect the alterations of one or two gases. Those which use an electrochemical sensor represent the gold standard today. In Italy, the cost of HBT is around €30.29 in public hospitals [22, 23].

Genetic Test

In response to the hypotheses put forward over time regarding the genetic predisposition to lactose intolerance, polymorphisms of the gene that codes for lactase predisposing to this intolerance have been identified [24]. Considering this knowledge, a method that can be used for the diagnosis of lactose intolerance is the genetic test, which consists in the isolation of DNA through a blood sample and the subsequent analysis of polymorphisms LCT-13910C>T and LCT-22018G>A. However, this test has some limitations. In fact, the presence of a predisposing polymorphism (C/C or G/G) does not allow us to predict if and when intolerance will develop. Moreover, in the presence of a symptomatology suggestive of lactose intolerance, a negative result of the genetic test does not allow to identify a possible secondary intolerance, while it is important to distinguish a primary hypolactasia from a secondary one, in order to undertake an appropriate therapeutic pathway. Instead, the genetic test could be performed after HBT in order to predict whether there is a primary or secondary intolerance [25].

Then, as proposed by Tomczonek-Moruś et al., genetic testing would be preferable in subjects who cannot perform HBT. In fact, they found a significant correlation between a positive HBT and the presence of the aforementioned polymorphisms [26].

Quick Lactose Intolerant Test

Quick Lactose Intolerant Test consists in execution of mucosal biopsies at the post-bulbar duodenum level and their subsequent incubation with lactose on test plate. This incubation aims to verify the presence or absence of lactase activity. If lactase activity is present, a dark blue–colored reaction occurs; if there is a slight hypolactasia, there will be a light blue; if no staining develops, this result will be indicative of severe hypolactasia [27].

Ojetti et al. showed that this test could be used when the common HBT proves to be negative despite the symptoms instead of the genetic test. In fact, they have found an agreement between the Quick Test and the HBT of 81% [28].

Also Tsadok Perets et al. found a high agreement between HBT and the Quick Test regarding intolerant subjects with positive HBT results. In these patients, in fact, a null or reduced lactase activity was detected in intestinal biopsies. However, in the case of subjects who tested negative for HBT, the agreement between the two tests was much lower. In fact, many patients with HBT negative results had a bioptic picture of hypolactasia. Therefore, from the conclusions of this study, it can be deduced that the execution of the Quick Test is useful only in the case of a negative result of HBT, since the Quick Test is an invasive test that can be avoided in the case of a positive HBT [29].

Moreover, this exam can also exclude secondary form of lactose intolerance as celiac disease, but although it has a high sensitivity, the Quick Test has limitations. Among these limitations is the size of biopsies which, if larger or shorter than 2 mm, may give false-negative or false-positive hypolactasia, respectively, due to patchy expression of lactase. Another limit is the invasiveness and high cost of the endoscopic method. Moreover, since it is a bioptic examination, it is conditioned by the coagulation and the patient's clinical conditions. Furthermore, the execution of the incubation of the samples must be carried out quickly and this requires the presence of a laboratory technician in the endoscopy room. This test could be used in the case of patients for whom there are other indications for an endoscopic examination [8, 30].

Lactose Tolerance Test

Lactose Tolerance Test (LTT) involves the administration of 50 g of lactose and the glycaemia dosage before lactose intake and after 30 min, 60 min, and 120 min based on plasma-glucose dosage after lactose ingestion. The digestion of lactose determines the elevation of blood glucose: the absence of such increase indicates failure absorption of lactose. This test is rarely performed due to low sensitivity and specificity. In fact, false-positive and false-negative test results occur in 20% of normal subjects because of the influence of variable gastric emptying and glucose metabolism [15, 31].

According to Goshal et al., Lactose Tolerance Test could be used in association with HBT or even alone in centers where it is not available. In fact, they have demonstrated a validity of this test comparable to the breath test. One of the advantages of the LTT is the possibility of diagnosing lactose intolerance even in subjects who are negative for HBT due to a bacterial flora that does not produce hydrogen. However, an important limitation is represented by diabetes mellitus. In fact, in diabetic patients, there may be an increase in blood glucose levels after ingesting lactose, even in the presence of intolerance [32].

Gaxilose Test

This is a new non-invasive test that consists of administration of Gaxilose (4-O-β-D-galactopyranosyl-D-xylose), a synthetic disaccharide provided with a structure similar to lactose. Like the latter, Gaxilose is also metabolized by lactase in the intestine. From this process, they derive a molecule of galactose and one of xylose, which will then be absorbed by enterocytes. Subsequently, xylose will be measurable in the blood and urine, through which its excretion is carried out. By measuring the amount of xylose in the blood and urine, it will be possible to quantify lactase activity [33].

This is not currently marketed and the execution costs are not known. With phase IV of a randomized controlled trial, Monsalve-Hernando et al. compared the results obtained from the Gaxilose Test and from HBT, demonstrating a non-inferiority of the Gaxilose Test compared to HBT. Therefore, they propose the Gaxilose Test as a valid diagnostic choice, since they were not detected moderate-severe, but only mild adverse effects. Contraindications to the examination are currently unknown, but could be inferred from the exclusion criteria considered in the study, among these: pregnancy or lactation, diabetes mellitus, portal hypertension, alteration of glomerular filtration, recent use of some drugs (antibiotics, aspirin, or indomethacin). In practice, contraindications that normally exist for most diagnostic tests performed today. Moreover, compared to the other tests used today for the diagnosis of lactose intolerance, the Gaxilose Test is easy to use, it does not cause discomfort to the patients, and it is a quantitative test [34, 35].

Domínguez Jiménez et al. compared the results obtained from the Gaxilose Test and from the shortened Lactose Tolerance Test (sLTT) and their conclusions are that the Gaxilose Test has a diagnostic accuracy similar to sLTT and it has the advantage of being non-invasive and well tolerated. Furthermore, they performed the genetic test on some patients in the study and highlighted a high concordance between the results of the two tests. In particular, this concordance (expressed with p value) was greater if the cut-off of the amount of xylose in urine considered pathological was shifted from 37.87 mg ($p < 0.01$) to 35.50 mg ($p < 0.001$) [36].

Thus, the Gaxilose Test could be considered the new gold standard for the diagnosis of lactose intolerance, but further studies are needed to reach this conclusion.

Treatment

Typically, management of primary lactose intolerance consists of two possible clinical choice: alimentary restriction and drug therapy. The usual behavior for this condition is the avoidance of milk and dairy products from the diet. However, as previously mentioned, dairy foods provide calcium, protein, magnesium, and other minerals and substances that are essential for preventing various diseases and ensuring different physiological functions, such as bone remodelling. The avoidance of all dairy products in patients with lactose intolerance is no longer recommended. Most people with lactose intolerance can tolerate up to 12–15 g of lactose per day. Strategies can be implemented to increase tolerance of lactose in these patients [12, 37].

People with lactose intolerance should be encouraged to restrict rather than avoid lactose. So they can maintain dairy products in the diet without losing the benefits associated with these foods. An available strategy for the management of patient with this intolerance contemplates:

1- Temporary lactose-free diet to obtain remission of symptoms
2- Gradual introduction of cow milk (from 30 to 250 ml/day) which should be consumed together with other foods to slow release of lactose in the small intestine
3- Consumption of aged cheese, which contains a low share of lactose
4- Consumption of lactose-reduced milk products, which are nutritionally identical to milk products
5- Consumption of fermented products like yogurt, that are also a source of probiotics and prebiotics, and both exert beneficial effects on gastrointestinal microflora [12, 38, 39]

Enzyme supplementation therapy with lactase from nonhuman sources to hydrolyze lactose is another important approach. The intake of exogenous lactase is expected whenever foods containing lactose are ingested. This enzymatic compound is obtained from yeast (*Kluyveromyces lactis*) or fungi (*Aspergillus oryzae*, *Aspergillus niger*) and it is able to break down lactose into glucose and galactose to allow a better absorption. Administration of exogenous lactase as pills has been used to treat lactose intolerance in children, adolescents, and adults with extremely good results in terms of improving the clinical picture [40, 41]. However, not all clinical studies that have been performed to evaluate the efficacy of exogenous lactase have led to satisfactory results.

Montalto et al. found a reduction in H_2 excretion in intolerant patients who had taken exogenous lactase obtained from *K. lactis*. They also achieved an improvement in the clinical picture of these patients, showing that exogenous lactase represents a valid therapeutic approach in lactose intolerance [42].

Ojetti et al. conducted a randomized clinical trial to compare the effects of exogenous lactase (tilactase) and those of a probiotic containing *Lactobacillus reuteri*. The patients in their study, who were diagnosed with lactose intolerance by HBT, were divided into 3 groups: one group administered the tilactase, the second group administered the probiotic with

L. reuteri, and the third group administered the placebo. After treatment, patients were re-placed on HBT. What emerged from this clinical study is that both the probiotic and the tilactase caused a reduction in the amount of hydrogen excreted. However, this reduction was clearly more marked in the case of the tilactase. Symptoms that had been taken into account at the beginning of the study (bloating, abdominal pain, flatulence, diarrhea) also improved in both groups (tilactase group and *L. reuteri* group), but the improvement was greater for patients of tilactase group. Therefore, according to Ojetti et al., the use of exogenous lactase is useful for the treatment of lactose intolerance, also to avoid the risk of osteoporosis connected to the lack of milk and dairy products intake. On the other hand, even the administration of this probiotic can be advantageous, since its effects continue to be expressed even after having suspended its intake [43].

Also Ibba et al. conducted a study aimed at assessing whether the intake of exogenous lactase by lactose-intolerant subjects determined or not a change in the hydrogen excretion rate with HBT. The enzymatic compound used in this study was Beta-Galactosidase (15,000 Units) obtained from the fermentation of *Aspergillus oryzae*. The results of their study showed some variability. In fact, a reduction in hydrogen excretion after taking Beta-Galactosidase was recorded in 40% of patients, while in the remaining 60% of them, the amount of hydrogen excreted did not change. However, an improvement in symptoms was observed in a much higher percentage of patients and it was highlighted a non-direct correlation between the excreted hydrogen value and the severity of symptoms reported by the patient. The reason why exogenous lactase determines different effects in subjects suffering from the same type of intolerance is still not completely clear [44].

Although the results of these studies are in contrast with each other, it can be said that the administration of exogenous lactase represents, in most cases, a valid therapeutic option. Exogenous lactase does not generally determine serious adverse effects and its use is safe and effective almost always. In fact, in most of the patients, an improvement of the symptoms and therefore of the quality of the life has been found. However, other studies are needed to assess the real efficacy and the exact benefits of using exogenous lactase.

Recently clinical trials have been conducted regarding other possible approaches aimed at improving the symptomatology of lactose intolerance and better absorption of the nutrients contained in dairy products.

Various substances are contained in cow's milk, including β-casein. Two types of this protein have been identified: type A1 and type A2, which may be present in the milk individually or in combination. Type A2 is considered the original variant. In fact, the gene encoding A1 is the result of a point mutation of the gene encoding A2, with proline substitution with histidine at position 67. At intestinal level, β-casein undergoes proteolysis and among the peptides formed by this process, there is β-casomorphin-7 (BCM-7). Higher amounts of BCM-7 are obtained from A1 type degradation than from A2 [45]. BCM-7 is a ligand of μ-opioid receptors. These receptors are located in various tissues, including the gastrointestinal tract. An effect of the overproduction of BCM-7 is represented by a slowing of the intestinal transit demonstrated by a greater consistency of the stools. This observation was made by Ho et al. who detected an increased fecal consistency in subjects who had ingested milk containing A1 β-casein compared to those who had ingested milk with A2 β-casein. Furthermore, a higher intensity of abdominal pain was detected in the group of patients who had ingested type A1 [46].

Jianqin et al. conducted a comparative study between these two types of β-casein. In particular, they created two groups of 45 patients. After 14 days of washout, during which the consumption of milk or dairy products was not allowed, one group was given milk with only A2 β-casein, while the other group was given milk with the combination of A1 and A2, for 14 days. At the end of this period, all patients in the study underwent a new 14-day washout period. Later, milk containing both A1 and A2 was given to the group that had ingested milk with only A2 β-casein. Conversely, the group that had previously taken milk with the combination of β-casein was given the one containing only A2. The study found that the consumption of milk containing A1 and A2 β-casein caused a worsening of gastrointestinal symptoms, an increase in intestinal transit time, an increase in serum inflammation markers, a slowing of cognitive abilities, and an increase in elimination fecal short-chain fatty acids. All these events did not occur, however, during the administration of milk containing only A2 β-casein. Thus,, the exacerbation of symptoms was related to the presence of type A1 [47]. The same conclusions were drawn from He et al. who conducted a study similar to the one previously illustrated. They also detected the appearance or worsening of gastrointestinal symptoms after ingesting milk containing both A1 and A2 β-casein, while the milk containing only the type A2 had not determined the same effects. Therefore, more than lactose, A1 β-casein causes the symptoms [48].

A possible further therapeutic approach, therefore, could be the selection of milk containing only the type A2.

Mummah et al. conducted a study aimed at determining the possible efficacy of raw milk. In fact, some studies had shown that the consumption of raw milk was associated with the reduction of atopic diseases, irritable bowel syndrome, and with the same lactose intolerance. This was a double-blind cross-over trial that involved 16 subjects who had been diagnosed with lactose intolerance via the HBT. Each participant was given 3 types of milk, each for 8 days, alternating the intake of each type of milk with a washout period. The 3 types of milk were raw milk, pasteurized milk, and non-flavored soy milk. The outcomes were evaluated by execution of HBT and the use of visual analog symptom scales at the beginning and

at the end of each 8-day therapy. From this study, it was found that, in reality, the intake of raw milk led to a worsening of symptoms and no significant reduction in hydrogen excretion at HBT. Therefore, according to Mummah et al., the consumption of raw milk instead of the pasteurized one cannot be considered an adequate therapeutic choice for subjects with lactose intolerance [49].

Another possible therapeutic approach is represented by probiotics. Probiotics are live microorganisms which upon ingestion in sufficient concentrations can exert health benefits to the host. Hundreds of different bacteria species are the natural and predominant constituents of intestinal microbiota. Among the greatest benefits attributed to probiotics, there are improvement of gastrointestinal microflora, reinforcement of immune system, reduction of serum cholesterol, treatment of irritable bowel-associated diarrhea, and improvement of lactose metabolism [50, 51]. The species most frequently used for the production of probiotics are *Lactobacillus* spp. (*L. acidophilus*, *L. rhamnosus*, *L. casei*, etc.), *Bifidobacterium* spp., and *Saccharomyces boulardii*. Among the various functions of the bacteria present in the intestine, there is the maintenance of constant and low levels of short-chain fatty acids, which are implicated in the genesis of symptoms, such as abdominal pain and diarrhea. The main advantage of probiotics is the absence of absolute contraindications [52, 53].

Pakdaman et al. conducted a clinical trial aimed at evaluating the efficacy of DDS-1 strain of lactobacillus (manufactured by Nebraska Cultures, Inc.) in patients with lactose intolerance. Their study found that the use of these probiotics, compared to placebo, was safe and reduced diarrhea, abdominal cramps, and vomit [54].

Gingold-Belfer et al. conducted a study in which a mixture of probiotics, Bio-25 (SupHerb, Israel), consisting of lactase-producing bacteria (*L. acidophilus*, *L. rhamnosus*, *L. casei*, etc.), was evaluated. The result was a significant improvement in the gastrointestinal symptoms associated with lactose intolerance. There was no reduction in hydrogen excretion to HBT in the same patients who experienced improvement in symptoms. According to Gingold-Belfer et al., this probiotic formula can be considered a valid therapeutic option, mainly referring to the clinical characteristics [55].

In the clinical trial of Vitellio et al., the effects of a combination of *B. longum*, *L. rhamnosus*, and vitamin B_6 on the symptoms of lactose intolerant were analyzed. The enrolled patients were divided into two groups. One group was given the preparation, while the other group received the placebo. After 30 days, the patients stopped taking one or the other product and, after a 15-day washout period, a cross-over was performed followed by 30 days of treatment. The study showed that even the association of the probiotic with vitamin B_6 determines the improvement of the clinical picture of lactose intolerant. This is mainly the result of the positive modulation of the composition and metabolism of the intestinal bacterial flora by the action of the probiotic but also by the action of the vitamin B_6. Therefore, although other studies will be needed to confirm this evidence, it is possible to consider the association probiotic/vitamin B_6 a valid therapeutic option for lactose intolerance [56].

The bacteria contained in probiotics can also be found in foods, for example, in yogurt. In previous years, various studies have shown how the consumption of these foods, in addition to probiotics, can influence the composition and metabolism of the intestinal bacterial flora. He et al. found an increase in fecal β-galactosidase activity in lactose-intolerant subjects after 2 weeks of consumption of yogurt and probiotics. The yogurt used by these authors was a derivative of fermented milk containing both traditional yogurt strains (*Lactobacillus bulgaricus* and *Streptococcus thermophilus*) and a specific probiotic strain (*Bifidobacterium animalis*). Instead, probiotics contained *Bifidobacterium longum*. The association of yogurt and probiotics has led to an improvement in symptoms related to lactose intolerance in the patients of this study. Therefore, even the dietary approach represented by yogurt is a valid therapeutic option aimed at improving the clinical picture [57].

Also de Vrese et al. conducted a study aimed at evaluating the association between yogurt and probiotics. In this case, the yogurt contained *S. thermophilus* and *L. delbrückii* ssp. *bulgaricus*, while probiotics were based on *Aspergillus oryzae*. In this case, greater efficacy emerged in the association of yogurt and probiotics rather than in the administration of yogurt alone or only probiotics. In fact, an increase in the ability to digest lactose was observed, demonstrated by the reduction of the hydrogen excretion peak at HBT. Furthermore, an improvement in abdominal pain and flatulence has also occurred [58]. Therefore, this preparation can also be considered a valid therapeutic approach.

In addition to probiotics, prebiotics have also been considered, which are non-digestible oligosaccharides fructans and galactans [59]. Furthermore, they facilitate the development of specific bacterial strains of the intestinal flora that are beneficial to the health of the organism [60]. However, products containing less than 48% of weight/volume of prebiotics are currently marketed [61]. According to Gibson et al., the use of probiotics could lead to an improvement in health and a reduction in the risk of developing various diseases. However, it is important to include prebiotics with a healthy lifestyle and a healthy diet [62].

Savaiano et al. conducted a clinical trial to evaluate the efficacy of RP-G28 (a product containing over 95% galacto-oligosaccharide) in reducing gastrointestinal symptoms in lactose-intolerant individuals. Patients in the study were randomized into two groups, one group was given RP-G28 while the other group was given a placebo for 35 days. At the end of this period, patients were encouraged to ingest products containing lactose for 30 days. Furthermore, all patients underwent HBT and a questionnaire on the evaluation of symptom severity (Patient Global Assessment), before

Table 1 Summary table of clinical trials with preparation used, number of subjects, age, inclusion and exclusion criteria, and effect of preparation (*LI*, lactose intolerance; *HBT*, hydrogen breath test; *IBD*, inflammatory bowel diseases; *GI*, gastrointestinal; *IBS*, irritable bowel syndrome; *BMI*, body mass index; *ppm*, parts per million; *n/a*, data is not provided)

Authors	Preparation used	Subjects [number]	Age [years]	Inclusion criteria	Exclusion criteria	Effect of preparation
Gingold-Belfer et al. 2019 [55]	BIO-25	8	> 18	Symptoms of LI after ingestion of milk; HBT positive	IBD; pancreatic exocrine insufficiency; chronic diseases; diagnosis of cancer; use of probiotics and antibiotics in the last 3 weeks	Reduction of intolerance symptoms (in particular bloating and flatulence); no modification of the amount of excreted hydrogen
Vitellio et al. 2019 [56]	Formulation of *Bifidobacterium longum* BB536, *Lactobacillus rhamnosus* HN001, and vitamin B6	23	20–67	Symptoms of LI after ingestion of milk; HBT positive	Organic GI diseases (as IBD); pregnancy; abdominal surgery in the previous 6 months; infective diseases; drug or alcohol abuse; metabolic disease; mental illness; chronic or neoplastic disease; severe heart failure	Improvement of some GI symptoms and metabolism of intestinal microbiota
He M et al. 2017 [48]	Milk containing only A2 β-casein vs milk containing A1 and A2 β-casein	600	20–50	Self-reported LI and digestive discomfort after consuming traditional milk	Eating disorder; metabolic and/or GI chronic disease; acute infection/gastroenteritis at time of enrollment; allergy to cow's milk products; immunodeficiency	Milk with A2 β-casein attenuates symptoms; milk with A1/A2 β-casein reduces lactase activity and it worsens symptoms
Jianqin S et al. 2016 [47]	Milk containing only A2 β-casein vs milk containing A1 and A2 β-casein	45	26–68	Self-reported intolerance to traditional milk; mild or moderate digestive discomfort after milk consumption	IBS; constipation; IBD	Milk with A1/A2 β-casein increases GI inflammation, worsens symptoms, delays intestinal transit time, deteriorates cognitive processes; milk with only A2 does not worsen the symptoms
Pakdaman M et al. 2016 [54]	DDS-1 strain of *Lactobacillus acidophilus*	126	30–75	Healthy volunteers; BMI between 18 and 35 kg/m2; Lactose Challenge Test 6-hour Symptom Score > 10	Congenital lactose deficiency; GI diseases (as IBD); recent nausea, vomiting, or diarrhea; pregnancy; breastfeeding; history of cancer in the last 5 years or surgery in the last 6 months	DDS-1 strain of *L. acidophilus* reduces symptoms of LI (in particular diarrhea, cramping, and vomit)
Ibba et al. 2014 [44]	Beta-Galactosidase obtained from *Aspergillus oryzae*	96	18–65	Symptoms of LI after ingestion of milk; HBT positive	Diagnosis of cancer; IBD; previous GI surgery; allergy to milk's protein; chronic diseases; use of antibiotics, laxatives, prokinetics in the last 30 days	Reduction of hydrogen excreted in 40% of cases; symptom improvement in most patients (although there was no correlation between excreted hydrogen levels and symptoms)
Mummah S et al. 2014 [49]	Raw milk	16	> 18	Patients with peak hydrogen concentrations greater than 25 ppm with simultaneous symptoms of LI	Self-reported symptoms of excessive severity; recent use of antibiotics; GI diseases	Worsening of symptoms; no significant reduction in hydrogen excretion
De Vrese et al. 2014 [58]	Combination of acid lactase from *Aspergillus oryzae* and yogurt bacteria	24	> 18	Self-assessed lactose maldigestion; willingness to participate in all test days	Participation in a clinical trial with drug or medical device in the last 30 days; surgery in the last 3 months; metabolic and/or GI diseases; alcohol or drug abuse	Reduction of hydrogen excretion peak at HBT; improvement of abdominal pain and flatulence

Table 1 (continued)

Authors	Preparation used	Subjects [number]	Age [years]	Inclusion criteria	Exclusion criteria	Effect of preparation
Savaiano DA et al. 2013 [63]	Galacto-oligosaccharide (RP-G28)	85	18–64	Self-reported history of LI of at least 1 month; HBT positive	Diabetes mellitus; disorders of GI motility; IBS; IBD; celiac disease; history of GI surgery	Reduction of hydrogen excretion at HBT; improvement of abdominal pain, flatulence, cramping, and bloating
Ojetti V et al. 2010 [43]	Supplementation with *Lactobacillus reuteri* or tilactase	60	18–65	Symptoms of LI after ingestion of lactose; HBT positive	Diagnosis of small intestinal bacterial overgrowth; allergy to milk proteins	Reduction of hydrogen excretion at HBT (more with tilactase than *L. reuteri*); improvement of abdominal pain, flatulence, bloating, and diarrhea (more with tilactase than *L. reuteri*)
He T et al. 2008 [57]	Capsules of *Bifidobacterium longum* and a yogurt with a specific probiotic strain (*Bifidobacterium animalis* DN173010)	11	23–54	Healthy subjects; Lactose Challenge Test 6-hour Symptom Score > 10	Use of antibiotics or laxatives during the last 3 months	Changes in the metabolism of intestinal bacterial flora; improvement of symptoms
Montalto et al. 2005 [42]	Exogenous beta-galactosidase	30	18–65	Symptoms of LI after ingestion of lactose; HBT positive	n/a	Reduction of hydrogen excretion at HBT; improvement of symptoms

starting the study, after 35 days of taking RP-G28 or placebo and after 30 days of consumption of lactose-containing products. The study found a high efficacy of the RP-G28 in symptom reduction, demonstrated by the results obtained with HBT and the questionnaire in the patients of the group who took the product. These patients had better clinical outcomes than patients who received placebo. Therefore, this high efficacy, together with the safety of the use of this product, makes RP-G28 a valid option for lactose-intolerant patients who can consume products containing lactose without developing gastrointestinal symptoms [63]. Table 1 schematically shows the studies cited in this section.

Conclusions

On the basis of above, it is possible to state that, among the diagnostic methods available today, HBT represents the most valid choice both in terms of diagnostic accuracy and inexpensiveness. However, it would be useful to associate methane with hydrogen measurement too, so as to increase the sensitivity and specificity of the test. In fact, in this way, it is possible to identify lactose intolerance also in subjects with a bacterial flora which does not produce H_2 but CH_4 [17, 18].

From the results obtained in the various clinical trials mentioned above, in reference to therapeutic option, it is not possible to define a standardized therapy. This is determined by the fact that the effects obtained by the administration of a certain compound are not always homogeneous, as, for example, in the case of exogenous lactase [40–44]. Instead, we should define a treatment tailored to the patient, evaluating which therapeutic options are most effective for the person in question. In general terms, it is possible to state that probiotics represent a valid strategy that has proved effective, many times, in improving the symptoms of lactose intolerance [50–56].

Availability of Data and Material Not applicable.
Code Availability Not applicable.

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Declarations

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