Catlab Informa

Newsletter No. 139

Diagnosis of malabsorption and lactose intolerance. Gaxilose test

Introduction

Lactose is the main carbohydrate present in milk and one of the main sources of energy for the newborn during the breastfeeding period. It is a disaccharide composed of glucose and galactose that must be hydrolyzed in order to be used as an energy source. In humans, the enzyme that hydrolyzes lactose is the disaccharidase called lactase or β- galactosidase.

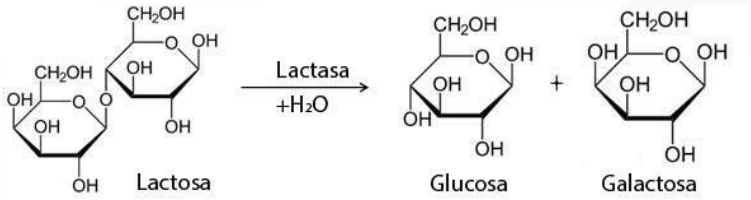


Figure 1. Hydrolysis of lactose by intestinal lactase.

This enzyme is located in the microvilli of the small intestine with higher expression in the proximal jejunum and it acts by hydrolyzing lactose into glucose and galactose, which are incorporated into the enterocyte by active transport.

Lactase is encoded by the lactase gene (LCT) located on the long arm of chromosome 2. Expression levels of this enzyme are highest during lactation and decline rapidly in most humans after weaning. This is genetically defined and known as lactase nonpersistence or hypolactasia.

Hypolactasia, malabsorption and intolerance

The term hypolactasia refers only to the lack of expression of this enzyme in the microvilli of the small intestine, while the term lactose malabsorption includes any cause of lack of digestion and absorption of lactose in the small intestine.

Lactose malabsorption can be of three types:

- Congenital: a very rare autosomal recessive disease that manifests itself from the first exposure to breast milk.
- Primary: due to a decrease in the enzymatic activity of lactase in intestinal cells. This is the most common type.
- Secondary: due to other diseases that lead to lactose malabsorption, such as celiac disease, gastroenteritis or Crohn's disease, among others.

Finally, the term lactose intolerance is used when there are symptoms in patients with lactose malabsorption, which occurs in about a third of patients. These symptoms usually appear 45 minutes after ingestion of lactose and with a maximum peak of intensity between 4 and 8 hours.

Epidemiology

About 4,000 years ago, the 13910C→T mutation in the LTC gene arose in the European population, resulting in the persistence of the lactase enzyme and thus the ability to digest lactose into adulthood. The persistence of lactase allowed these ancestors to consume milk throughout their lives, providing them with a source of calories, vitamin D, and other nutrients, leading to a rapid increase in the frequency of this mutation that spread throughout the population.

The worldwide prevalence of lactose malabsorption is 68% of the population, varying depending on the geographical area. For example, in some Asian countries the prevalence is close to 100%, while in Nordic countries the prevalence is less than 5%. In Spain, it is estimated that around 30% of the population has lactose malabsorption.

Lactose malabsorption and intolerance are clearly underdiagnosed in our setting, and are currently a clinical challenge, since they share symptoms with other pathologies such as functional dyspepsia and irritable bowel syndrome. In addition, in some cases, the symptoms may be atypical, such as general malaise, headache, fatigue, or even constipation, without a clear relationship to dairy intake.

Diagnosis

There are five tests for the diagnosis of lactose intolerance: intestinal lactase activity, oral lactose tolerance test, hydrogen and methane breath test, gaxilose test and genetic test. The differences between these tests are based on diagnostic efficacy, invasiveness, availability, cost, limitations and the ability to evaluate symptoms associated with malabsorption.

Lactase activity in intestinal biopsy

It is considered the reference method for detecting primary or secondary malabsorption. This test is based on measuring glucose concentration by fluorimetry in intestinal biopsy after adding a solution containing lactose. Although it is considered the reference method, its use in clinical practice is very low due to drawbacks such as cost, invasiveness and the fact that it can give false negative results due to the irregular expression of lactase along the small intestine.

Breath test for hydrogen and methane

This test detects these gasses produced by intestinal bacteria in the exhaled air after oral administration of a standard dose of lactose. Despite being the most widely used, this test has a number of limitations, such as the presence of false positives due to bacterial overgrowth or when fasting is not followed, or false negatives in the case of recent administration of antibiotics or due to adaptation of these bacteria to the ingestion of lactose. In addition, it is a difficult test to tolerate because it causes symptoms.

Oral lactose tolerance

This test is based on measuring the concentration of glucose in serum at different times (basal, 30, 60 and 120 minutes) after the administration of an oral lactose overload. It allows the

assessment of lactose malabsorption and even lactose intolerance if clinical symptoms appear after the administration of the preparation. However, it is a test with lower performance than the breath test and has limitations in patients with diabetes, bacterial overgrowth and in patients with slow gastric emptying.

Gaxilose test

It is a non-invasive diagnostic test based on the administration of a synthetic analogue of lactose formed by galactose and D-xylose (4-galactosylxylose). This disaccharide is not absorbed at the digestive level and is transformed by intestinal lactase into galactose and D-xylose. The latter is absorbed in the small intestine and around 50% is metabolized, while 48% of the administered xylose is eliminated in urine remaining unchanged. Thus, the total amount of xylose in urine is directly correlated with the enzymatic activity of intestinal lactase.

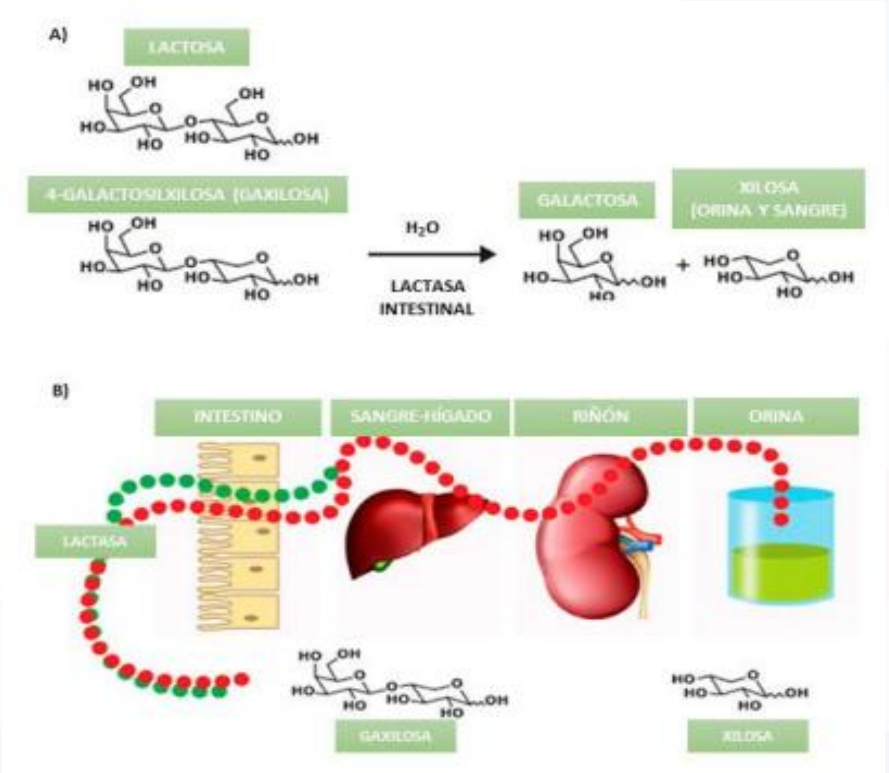


Figure 2. A) Hydrolysis of gaxilose by intestinal lactase. B) Metabolism of gaxilose. Information obtained from Venter Pharma ®.

The test is performed by administering 0.45 g of xylose dissolved in a glass of water (100-250 mL) on an empty stomach and after discarding the first urine of the morning to allow bladder emptying. Next, the urine emitted for 5 hours is collected and the xylose excreted in urine is quantified. It is performed using an automated assay where the cut-off point to determine lactose malabsorption is 19.18 mg xylose in urine over 5 hours. It is essential to know the volume of urine excreted by the patient, since the result is obtained from the concentration of xylose and the volume of urine excreted.

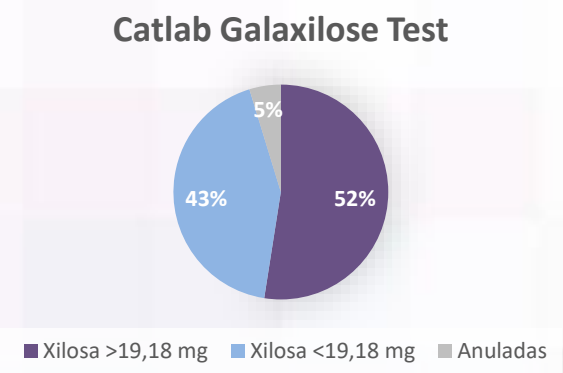
The gaxilose test has advantages such as its simplicity, the absence of discomfort for the patient during the test, as well as its quantitative nature, in addition to being a noninvasive and safe

test. This technique has sensitivity and specificity values greater than 90% and can be applied to diabetic patients without nephropathy since these patients cannot be given oral lactose overload. However, it does not allow the degree of malabsorption to be related to the presence of symptoms, so it is not useful for assessing possible lactose intolerance. In addition, it is not recommended for patients with severe kidney disease, portal hypertension, myxedema or a history of total gastrectomy and/or vagotomy. It must be kept in mind that false positives may appear if urine collection has not been correct, in dehydrated patients, with kidney failure, ascites, urinary retention, bacterial overgrowth, in the elderly and in those with slow gastric emptying.

Genetic test

The genetic test analyses two polymorphic positions (13910-C/T and 22018-G/A) in the patient's DNA located in the regulatory region of the lactase gene, which are inherited together and determine whether or not lactase persists in Caucasian adults. In Caucasian populations, it has a good relationship with the breath test for diagnosing lactose malabsorption, but it has several drawbacks, given that it is a costly test, with low availability and little use in non-Caucasian populations. It would not detect cases of hypolactasia due to other atypical polymorphisms or cases of secondary lactose malabsorption. In addition, it does not assess the patient's symptoms, since there is no exposure to lactose.

Our experience at Catlab



At Catlab we perform the gaxilose test using an automated assay. In the last 3 years (September 2021 to August 2024) we have performed a total of 6359 gaxilose tests, of which 315 samples (5%) have been cancelled due to mainly pre-analytical reasons (incorrect urine collection, lack of information on the volume of urine obtained, etc.). Regarding the rest, 2715 results were obtained below the cut-off point (19.18 mg of xylose), representing 42.8%, and 3329 results were higher than this value, representing 52.2%.

In our data we can observe that the percentage of the population with malabsorption is slightly higher than that described in the literature, however, the population we are referring to are patients with a diagnostic orientation of possible malabsorption, therefore, a biased population in which it is explained that the percentage obtained is higher than in the general population.

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Elsa Escuder Azuara
Facultativa de Bioquímica
CATLAB
Tel. 937485600 ext. 35007/ 650850749
eescuder@catlab.cat
www.catlab.cat

Dra. Catrina Colomé Mallolas
Facultativa de Bioquímica
CATLAB
Tel. 937485600 ext. 35007/ 628192841
ccolome@catlab.cat
www.catlab.cat

Amaia Fernández Uriarte
Facultativa de Bioquímica
CATLAB
Tel. 937485600 ext. 35007/ 681342975
afuriarte@catlab.cat
www.catlab.cat

Gemma Ferrer Orihuel
Facultativa de Bioquímica
CATLAB
Tel. 937485600 ext. 35007/ 628599821
gferrer@catlab.cat
www.catlab.cat

Dra. Eva Guillén Campuzano
Coordinadora Área de Bioquímica
CATLAB
Tel. 93.748.56.00 - ext. 35040 / 660676790
eguillen@catlab.cat
www.catlab.cat