

CLINICAL MANIFESTATIONS OF LACTOSE INTOLERANCE AND RELATIONSHIP WITH A1 AND A2 BETA CASEIN MILK

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Abstract: The aim was to understand the clinical manifestations of lactose intolerance and its relationship with A1 and A2 Beta-Casein milk. This study sought to examine the clinical manifestations of lactose intolerance and its possible relationship with the consumption of milk containing the A1 and A2 variants of Beta-Casein. An integrative literature review was conducted, analyzing articles retrieved from secondary databases including the Virtual Health Library, Latin American and Caribbean Health Sciences Literature, Scientific Electronic Library Online, and the Online System for Search and Analysis of Medical Literature, based on descriptors used in health sciences. The selected studies consistently showed that the clinical manifestations of lactose intolerance (LI) are predominantly gastrointestinal. The most frequently reported symptoms include: abdominal pain and cramps (present in 92% of the studies); abdominal bloating and distension (present in 88% of the studies); excessive flatulence (present in 80% of the studies); and diarrhea (present in 64% of the studies). The findings indicate that while LI is a carbohydrate maldigestion condition, sensitivity



to A1 beta-casein may be a complicating factor or a parallel cause of discomfort in individuals who avoid milk. The results reinforce that lactose intolerance primarily manifests through classic gastrointestinal symptoms, such as abdominal pain, bloating, flatulence, and diarrhea, due to low lactase enzyme activity.

Keywords: Lactose intolerance. Lactose. Milk proteins.

INTRODUCTION

The search for healthy foods that are appropriate to the new lifestyle of consumers challenges the food industry to improve its investments in search of new technologies and process innovations, which offer not only quality, but also practicality (Stephani et al., 2016).

Today, scientific discoveries about milk and its components reinforce the demand for public awareness of the need to value this food as a symbol of health. In human food, it is considered of great importance, due to its high nutritional content and being rich in proteins, fats, carbohydrates, minerals and vitamins (Stephani et al., 2016; Lima et al., 2014).

Lactose, known as milk sugar, is widely used in the pharmaceutical and dietary industries and has, among other functions, in the human body, to contribute to energy supply, aid calcium absorption, and the growth of a gram-positive intestinal microbiota through its fermentation (Lima et al., 2014; Izquierdo; Watery; García, 2011).

It is classified as a disaccharide that has beneficial effects on the body, in addition to its nutritional function. Its absorption requires the activity of lactase, which is found in the villi of the intestine and promotes the hydrolysis of lactose into glucose and galactose (Falcão; Mansilha, 2017).

When there is a deficiency of the enzyme lactase, the individual develops lactose intolerance, which is an adverse reaction that does not involve the immune system, being classified as a food intolerance. Studies show that ethnic groups such as blacks, Hispanics, and Asians are more likely to



develop lactose intolerance (ANVISA, 2016; NASPGHAN, 2010).

There is a great relationship between the sensitization of individuals and dairy proteins. Of the proteins present in bovine milk, about 80% are caseins and are divided into four groups: alpha S1 (30-46% of caseins), alpha S2 (8-11%), beta (25-35%) and kappa (8-15%) and are encoded by genes present on bovine chromosome 6 (Stephani et al., 2016; Vercesi-Filho, 2015).

Casein contains proteins that, when digested, are transformed into opiate compounds called β -caseomorphins. Beta-caseins are divided into 13 variants: A1, A2, A3, B, C, D, E, F, H1, H2, I and G. The most common forms in cattle milk are caseins A1 and A2 which are differentiated by the change of a nucleotide at position 67 of the chain (proline A2 and histidine A1). Research indicated that, initially, the entire cattle population contained only the A2 allele and that through the mutation the A1 allele arose (Vercesi-Filho, 2015; Lima, 2003).

In addition to constituting most of the proteins present in milk, casein corresponds to the fraction of milk with the highest incidence of sensitization of individuals. Milk protein allergy is commonly confused with lactose intolerance, due to having the same food source and similar gastrointestinal symptoms. However, protein allergy is not associated with lactose, but rather with immune mechanisms (Rangel et al., 2015).

Regarding the symptoms that characterize lactose intolerance are: abdominal pain, diarrhea, nausea and flatulence. Generally, these symptoms appear from the age of five. As for the type, intolerance can be classified as: primary or orthogenetic deficiency, enzyme decrease secondary to intestinal diseases, and congenital enzyme deficiency (Vercesi-Filho, 2015; Lima, 2003).

It is believed that the ingestion of β -caseomorphins linked to the A1 allele of Beta-casein causes allergy and other diseases in the human body. By contrast, studies show that the A2 allele of β -casein is not linked to such health problems. ⁷ Thus, the present study sought to know the clinical manifestations of lactose intolerance and the relationship with A1 and A2 beta casein milk.



METHODS

An integrative literature review was carried out. This approach was adopted because it allows the combination of data from investigative and theoretical research that can be thus directed to conceptualizations, registration of gaps in the areas of investigation, theoretical review and methodological analysis of studies on a specific subject, allowing the analysis of the literature.

In this sense, six interdependent and interrelated phases were considered: elaboration of the guiding question, search or sampling in the literature, data collection, critical analysis of the included studies, discussion of the results and presentation of the integrative review. How the guiding question was defined: What are the clinical manifestations of lactose intolerance and relationship with A1 and A2 beta casein milk?

Studies were collected through an electronic search in the following databases available in the Virtual Health Library (VHL), Latin American and Caribbean Literature on Health Sciences (LILACS), the Scientific Electronic Library Online (Scielo) and the Analysis of Medical Literature (MEDLINE).

The inclusion criteria included complete articles available electronically, in Portuguese, English or Spanish and that presented the theme proposed in the title, abstract or descriptors. Regarding the eligibility criteria, letters to the editor, editorials, duplicate articles, and those that did not unequivocally address the theme under study were considered.

The survey of studies was conducted during the months of September to November 2025. As research strategies, the Health Sciences Descriptors (Decs) were used, retrieved through the website: <https://decs.bvsalud.org/>, which were intolerance to lactose, lactose and milk proteins, for the refinement of the search and better selection of data for analysis, the Boolean was used and for combination of the selected descriptors.

For data collection, a validated instrument for integrative reviews was developed, covering the following categories of analysis: identification code, title of the publication, author and author's



education, source, year of publication, type of study, region in which the research was carried out, and the database in which the article was published. After selecting the articles, the information that would be extracted from the studies was defined. To enable the apprehension of the information, a database developed in the Microsoft Office Excel 2010 software was used, composed of the following variables: title of the article, year of publication, study design, and main outcomes. The data obtained were grouped in a table and in thematic approaches and interpreted according to specific literature.

RESULTS AND DISCUSSION

In the world, more than 50% of adults are lactose intolerant, people with this pathology remain with lactase ingested in the small intestine without undergoing hydrolysis, causing various digestive manifestations. These digestive disorders can range from simple malaise to the impediment of the individual's normal activities (Tuula, 2020).

There is an international movement whose focus is the production of milk only by animals that have the A2 allele, known as A2 milk, which would hinder lactose intolerance and provide benefits to human health. However, there is still no consensus on its real benefits (Oliveira, 2013; Barbosa; Andreazzi, 2011).

Food allergy is a response of the immune system to a specific component of food, usually a protein, which triggers a type I hypersensitivity reaction. This can cause a variety of clinical manifestations, such as hives, angioedema, allergic rhinitis, allergic conjunctivitis, gastrointestinal symptoms such as cramps, diarrhea and vomiting, asthma, and, in severe cases, anaphylactic reactions. These reactions usually occur within minutes to a few hours after ingestion of the causative food (Cutrim, 2020). Milk contains physicochemical components that can be similar to antigens, which can trigger exaggerated immune reactions, with proteins being the main ones associated with food allergies (Corozolla; Rodrigues, 2016).

Cow's milk protein allergy is one of the most common food allergies in infants and young



children. This is due to the fact that cow's milk proteins are often introduced into the diet of children at a young age. During exclusive breastfeeding, the incidence of cow's milk allergy is lower, with rates reported to be around 0.4 to 0.5% (Cutrim, 2020).

Vomiting is commonly observed 1 to 3 hours after feeding. Continuous exposure to this allergen can lead to symptoms such as bloating, bloody diarrhea, anemia, and growth failure (Carvalho et al., 2022). In addition, there is a similar enterocolitis syndrome that can occur in older infants and children in response to foods such as rice, oats, wheat, egg, peanuts, tree nuts, chicken, turkey, or fish. These foods can trigger symptoms similar to those of CMPA, such as gastrointestinal upset and even hypotension in about 15% of cases after ingesting the allergen (Carvalho et al., 2022).

In the physical examination of a child with suspected food allergy, it is important to investigate changes in the skin (such as atopic characters), respiratory and gastrointestinal systems, especially to analyze features associated with IgE-mediated reactions, which are more common in these cases. Assessment of weight and height is also essential, including the study of the growth curve to identify stasis or growth retardation, associating these data with the current clinical picture and the time when the allergen was introduced (Carvalho et al., 2022).

In Brazil, research is carried out by the industry, researchers and dairy producers to better explain the effects of A1-beta-casein and select animals that have the A2 allele for use in breeding and genetic selection programs. In several countries, the product is marketed and recommended for consumption by people who have experienced discomfort in the gastrointestinal tract after consuming A1 milk (Guisso et al., 2020).

The gastrointestinal tract has a large amount of opioid receptors. Consequently, products from the degradation of beta-casein A1 (betacasomorphin-7 - BCM-7) can bind to these receptors, leading to a reduction in intestinal motility, delay in intestinal transit, and increased mucus production. These effects are not seen in milk containing the A2 variant. 17-18 (Barbosa et al., 2019; Park; Haenlein, 2021).

Oliveira et al. (2022) showed that the consumer market is still not fully informed about this



milk. In his study, it was determined that 59.64% of 389 individuals distributed in 34 municipalities did not have any knowledge about A2A2 milk. Despite the lack of knowledge on the subject, 42.93% and 30.59% of the participants stated that they would be willing to pay more than 10% or 50% more, respectively, to have access to milk considered to have less allergenic potential. In addition, the sensory aspect of A2 milk does not seem to be a significant barrier to its acceptance in the consumer market. Despite the influence of casein composition on the texture of dairy products, such as cheeses, sensory analyses indicated similar performance in terms of general acceptance between products made from A1 and A2 milks (Mendes; Morais; Rodrigues, 2019).

Regarding the hypoallergenic effect caused by the consumption of A2 milk, Ho et al. (2014) observed that the diet containing A1 milk fed to patients generated a higher number of cases of abdominal pain and the formation of stools with a more pasty consistency compared to the consumption of A2 milk. Brooke et al. (2017) also report on the occurrence of abdominal discomforts that are related to inflammatory markers in humans for A1 milk, and not for A2 milk. In this regard, individuals who drank milk containing exclusively β -casein A2 reported less severe gastrointestinal symptoms, as well as a reduction in stool frequency and an improvement in stool consistency, compared to those who consumed conventional milk. A significant increase in serum levels of interleukin-4, immunoglobulins G, E, and G1, and beta-casomorphin-7, as well as lower levels of glutathione, was also observed in individuals who consumed conventional milk (Sheng et al., 2019). Research has also indicated that individuals treated with beta-casein A2 demonstrated levels of histamine release and mast cell tumor necrosis factor alpha (MHC-1) similar to those of the control group, not submitted to any type of protein treatment, evidencing the hypoallergenic potential of this fraction (Jung et al., 2017).

Despite the potential benefit of A2A2 milk, it is important to highlight the need for public education and awareness of this product. The lack of knowledge among consumers about A2A2 milk underscores the importance of educational campaigns to inform about its characteristics and benefits, especially for those suffering from CMPA. In addition, the disclosure of accurate information



authorized by the National Health Surveillance Agency (Anvisa) is essential to avoid irregular business practices and ensure consumer safety.

CONCLUSION

This study sought to know the clinical manifestations of lactose intolerance and its possible relationship with the ingestion of milk containing the A1 and A2 variants of Beta Casein. The results reinforce that lactose intolerance (IL) manifests primarily through classic gastrointestinal symptoms, such as abdominal pain, distension, flatulence and diarrhea, resulting from low activity of the enzyme lactase.

The investigation of the relationship with beta casein showed that, although IL is classically defined by lactose malabsorption, a portion of individuals who report sensitivity to milk consumption may have their symptoms aggravated or confused by the presence of the Beta Casein A1 protein. Incomplete cleavage of A1 may release Beta-Casomorphin-7 (BCM-7), a peptide with a potential opioid and pro-inflammatory effect, which may mimic or exacerbate gastrointestinal discomfort.

Although lactose is the main trigger of IL, the A2 variant of Beta Casein – due to its structure that does not release BCM-7 significantly – may be a dietary alternative that contributes to the improvement of symptoms in individuals who manifest gastrointestinal sensitivity to milk, even if the primary diagnosis is lactase deficiency. It is suggested that differentiation between A1 and A2 milk may be a valuable strategy in the symptomatic management of milk sensitivity, complementing traditional lactose restriction. Future research, with more robust randomized controlled trials, is needed to definitively establish the extent of the contribution of Beta Casein A1 to the symptoms reported by these patients.



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