Nutrición Hospitalaria

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10.20960/nh.05369

04/30/2025

OR 5369

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Received: 17/06/2024
Accepted: 27/01/2025

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Funding: This research was funded by Spanish Ministry of Science and Innovation, through the funding program of the Carlos III Health Institute to promote biomedical and health research. The project code is PI19/00153 in which authors J.F.M.-T and MT are principal investigators.

Conflict of interest: The authors declare no conflict of interest.

Artificial intelligence: The authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

ABSTRACT

Background: carbohydrate intolerance presents a complex scenario where symptoms arise following the consumption of specific substrate and alleviate upon their elimination from the diet. Lactose Intolerance is one of the most prevalent types of food intolerance. Primary lactose intolerance is linked to genetic factors, Lactase Non-Persistence phenotype, while secondary lactose intolerance might be a temporary condition resulting from intestinal damage and loss of disaccharidase activity. Fructose absorption is an energy-independent process, leading to limited and variable absorption. Fructose undergoes quick absorption into the bloodstream through active transporters, specifically GLUT-5 and GLUT-2, found in the initial segment of the small intestine. The management of carbohydrate intolerance requires precise testing methods, accurate diagnostics, and customized dietary interventions. Genetic testing plays a crucial role in determining an individual's genetic profile, helping decide whether permanent restrictions on specific nutrients, such as lactose, are necessary.

Objective: this research aims to understand the origin of suspected carbohydrate intolerance, combining genetic testing with breath tests to enhance the efficacy of treatment plans, as customized dietary

interventions will be based on the patient's genetic profile and carbohydrate absorption capacity.

Material and methods: a combination of genetic testing (lactase non-persistence and celiac disease risk) and breath test for lactose and fructose were performed. Recommendations such as low lactose, low fructose or gluten-free diets; or a combination of them were provided based on each patient's testing profile results.

Results: after the nutritional intervention, a significant improvement was noted in all gastrointestinal symptoms, except for reflux and nausea, and in all of the extraintestinal symptoms.

Conclusions: designing dietary interventions based on primary and secondary causes for carbohydrate intolerance can avoid unnecessary food restrictions; improving patients' quality of life and treatment effectiveness through tailored dietary interventions.

Keywords: Food tolerance. Lactose. Intolerance. Gluten. Genetic test. Breath test.

RESUMEN

Introducción: la intolerancia a los carbohidratos presenta un escenario complejo en el que los síntomas surgen tras el consumo de un sustrato específico y se alivian al eliminarlo de la dieta. La intolerancia a la lactosa es uno de los tipos de intolerancia alimentaria más frecuentes. La intolerancia primaria a la lactosa está relacionada con factores genéticos, el fenotipo de lactasa no persistente, mientras que la intolerancia secundaria puede ser una afección temporal resultante del daño intestinal y la pérdida de la actividad disacaridasa. La absorción de fructosa es un proceso independiente de energía que conduce a una absorción limitada y variable. La fructosa se absorbe rápidamente en el torrente sanguíneo a través de transportadores activos, específicamente

GLUT-5 y GLUT-2, que se encuentran en el segmento inicial del intestino delgado. El tratamiento de la intolerancia a los carbohidratos requiere métodos de prueba precisos, diagnósticos precisos e intervenciones dietéticas personalizadas. Las pruebas genéticas desempeñan un papel crucial en la determinación del perfil genético de un individuo, ayudando a decidir si son necesarias restricciones permanentes en nutrientes específicos, como la lactosa.

Objetivo: esta investigación tiene como objetivo comprender el origen de la sospecha de intolerancia a los carbohidratos, combinando pruebas genéticas con pruebas de aliento para mejorar la eficacia de los planes terapéuticos, ya que las intervenciones dietéticas personalizadas se basarán en el perfil genético del paciente y la capacidad de absorción de carbohidratos.

Materiales y métodos: se combinaron pruebas genéticas (no persistencia de lactasa y riesgo de enfermedad celíaca) y prueba de aliento para lactosa y fructosa. Se recomendaron dietas bajas en lactosa, bajas en fructosa o sin gluten; o una combinación de las mismas en función de los resultados del perfil de pruebas de cada paciente.

Resultados: tras la intervención nutricional, se observó una mejoría significativa de todos los síntomas gastrointestinales, excepto reflujo y náuseas, y de todos los síntomas extraintestinales.

Conclusiones: el diseño de intervenciones dietéticas basadas en las causas primarias y secundarias de la intolerancia a los carbohidratos puede evitar restricciones alimentarias innecesarias; mejorar la calidad de vida de los pacientes y la eficacia del tratamiento a través de intervenciones dietéticas personalizadas.

Palabras clave: Intolerancia alimentaria. Lactosa. Fructosa. Gluten. Genética. Prueba de aliento.

INTRODUCTION

Carbohydrate intolerance presents a complex scenario where symptoms arise following the consumption of specific foods and alleviate upon their elimination from the diet (1,2). Malabsorption is defined as defective mucosal absorption (3). The prevalence of carbohydrate malabsorption in the general population is not well-documented (4). It can be primary or secondary, stemming from deficiencies in disaccharidases exemplified in lactose malabsorption (LM), or the intestine's inability to manage large quantities of a specific carbohydrate, as seen in fructose malabsorption (FM) (3,5).

Symptoms related to food intolerance are nonspecific, and patients often find it challenging to attribute them to a particular food (6). Lactose intolerance (LI) is one of the most prevalent types of food intolerance, worldwide its prevalence is about 33 % to 75 % (3,7). Primary lactose intolerance is linked to genetic factors, lactase non-persistence (LNP) phenotype, where intestinal lactase expression decreases in the initial two decades of life and continues to decline as individuals age (2,3,7). On the other hand, secondary lactose intolerance might be a temporary condition resulting from intestinal damage and partial or total loss of disaccharidase activity caused by: infections (giardiasis), celiac disease (CD), food allergies, small intestine bacterial overgrowth (SIBO), Crohn's disease, radiation or chemotherapy (1-4,7). The global prevalence of LM is approximately 68 %, with genetic testing indicating higher rates than breath tests (2).

Conversely, the mechanism of fructose absorption remains poorly understood, and the absence of standardized testing procedures has led to a lack of precise estimates regarding the prevalence of FM in the population (8). Normally, fructose undergoes quick absorption through facilitated passive transporters. Specifically GLUT-5, found in the initial segment of the small intestine, is responsible for fructose intake from

the intestinal lumen into the enterocyte; while GLUT2 located in the basolateral side of the enterocytes, transports most of fructose from the cytosol into the circulation (9,10). The extent of malabsorption depends not only on the availability of functional transporters, but also on the composition and quantity of sugars present in the intestinal lumen, contributing to secondary FM (4). High fructose intake, along with other nutrients like sorbitol, can hinder absorption. In contrast, co-ingestion with glucose, galactose or certain amino acids can enhance fructose absorption (3,11). On the other hand, primary FM arises from a diminished expression of the genes regulating GLUT-5 (3), or in rarer cases, from hereditary fructose intolerance (HFI), an autosomal recessive disorder caused by aldolase B deficiency, typically detected in childhood and with a prevalence of 1 in 20,000 to 1 in 60,000 (12,13). Since primary FM is often rare, when FM is detected, secondary causes including high fructose intake, intestinal damage, acute gastroenteritis, medication use, celiac disease, Crohn's disease, or prebiotic consumption (8,10,11), should also be considered. In this study, we have primarily focused on gluten-related disorders (GRD).

GRD, including CD, wheat allergy, and non-celiac gluten sensitivity (NCGS), have a worldwide prevalence of up to 5 %. CD is the most common immune condition affecting the gastrointestinal tract, affecting 1 % of the population (14-16). It triggers a systemic autoimmune response to gluten in genetically predisposed individuals (17), leading to small intestine damage and clinical manifestations of small bowel enteropathy associated with gastrointestinal and extra-intestinal symptoms (3,16-18). LM can occur in CD due to the loss of lactase enzyme on damaged villi, triggering secondary malabsorption (1). LI is frequently observed in CD cases, estimated at 10 %, rising to 50 % with malabsorption (1). Similarly, fructose intolerance has also been related with CD due to the mucosal damage associated (8).

There is an increasing prevalence of self-diagnosis and adherence to restrictive diets without a formal diagnosis, especially in patients who suffer gastrointestinal disorders (19-21). These intolerances are often treated with carbohydrate restriction (22); however, this strategy addresses symptom control, not the intolerance origin. The management of carbohydrate intolerance requires precise testing methods, accurate diagnostics, and customized dietary interventions. Standard and recommended diagnostic tools for carbohydrate intolerance include breath tests (BT) (4,5,23). However, genetic testing plays a crucial role in determining an individual's genetic profile, helping decide whether permanent restrictions on specific nutrients, such as lactose, are necessary. Additionally, genetic testing is a useful tool to consider gluten restrictions when carbohydrate intolerance may be associated with primary causes such as CD or other GRD, with the potential for carbohydrate absorption restoration (23,24). It has been reported that in patients experiencing symptoms related to the consumption of gluten-containing food, adopting a gluten-free diet (GFD) has shown to restore or improve fructose absorption (24).

Designing dietary interventions based on primary and secondary causes for carbohydrate intolerance can avoid unnecessary food restrictions, improving patients' quality of life and treatment effectiveness through tailored dietary interventions. Our research aims to understand the origin of carbohydrate intolerance, combining genetic testing with breath tests to enhance the efficacy of treatment plans, as customized dietary interventions will be based on the patient's genetic profile and carbohydrate absorption capacity.

MATERIALS AND METHODS

Patient enrollment and description

A total of sixty-three patients with gastrointestinal symptoms (GIS) attending the Gastroenterology Service of La Fe University and

Polytechnic Hospital in Valencia were recruited from November 2020 to June 2022. Forty-five were females, and eighteen were males, with ages ranging between 17 and 69 years. Exclusion criteria included the regular intake of nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, or antiparasitic medications in the previous thirty days; having undergone a colonoscopy in the previous thirty days; as well as a history of gastrointestinal surgery or diagnosed comorbidities related to the gastrointestinal system.

Ethical aspects

Written consent was obtained from all participants after they were fully informed. This study received approval from the Biomedical Research Ethics Committee of the Hospital in 2022 (Project identification code: 2019/0100), adhering to the fundamental principles of the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine, and the UNESCO Declaration.

Patient assessment

The Visual Analogue Scale (VAS) was used for GIS assessment, prompting patients to rate the intensity of GIS from 0 to 10 (zero indicating no pain, and ten indicating the maximal discomfort perceived) over the previous three months.

A combination of genetic testing for lactase non-persistence and celiac disease risk (HLA); and breath tests (BT) for lactose and fructose were performed. The results were used to classify patients into three main treatment groups with specific dietary approaches. To prevent false positives, an additional test for small intestine bacterial overgrowth (SIBO) was conducted. Patients who tested positive for SIBO were excluded from the study. Malabsorption tests indicate the intestinal capacity to metabolize specific carbohydrates (lactose and fructose), and determine the need to restrict the consumed amount of these

carbohydrates. Genetic testing is intended to provide information on the possible origin of malabsorption, thereby determining whether permanent or transient dietary restriction is required.

Dietetic recommendations

Recommendations such as low lactose (LL), low fructose (LF), gluten-free diet (GFD), or a combination of them were provided based on each patient's testing profile results. These recommendations are practical suggestions that each patient can adopt as part of their daily eating routine, according to their eating habits and tolerance threshold, aiming to facilitate adherence. A weekly diet example was also provided for the three different dietetic recommendations (Supplemental Tables S1-S3).

The low lactose dietetic recommendations (LL) suggested that the initial amount of lactose consumption should be 30-60 grams or milliliters of lactose-free cheese or milk during the first 2-4 weeks, followed by a gradual reintroduction of small quantities of dairy products (125 mL or less per day) according to each patient’s tolerance threshold and GIS improvement. Examples of dairy products with lower lactose quantity were provided, such as whole milk instead of skimmed milk and goat or sheep cheese instead of cow cheese. Recommendations to improve lactose tolerance, such as ingesting lactose along with other non-dairy foods were also offered (7,20,22,25).

The low fructose dietary recommendations (LF) aimed to help patients understand basic concepts about fructose content in foods. To support this, five lists were provided, categorizing foods by their fructose levels (3,22). Patients were recommended to initially consume only very low (1 g) and low (1-3 g) fructose content foods during the first 2-4 weeks, followed by a gradual introduction of greater quantities of fructose-containing foods according to their tolerance threshold. Patients were also advised to spread fructose intake throughout the day, avoiding eating all fructose-containing foods in one meal. The introduction of

medium fructose containing foods (3-5 g) was recommended during weeks 4-6 when GIS improved. High (5-10 g) and very high (> 10 g) fructose-containing foods were to be reintroduced gradually after GIS were diminished and according to each patient's tolerance threshold. Encouragement was given for fruits and vegetables consumption based on fructose content and personal tolerance to avoid constipation and nutrient deficiency. Ultra-processed food (UPF) consumption was discouraged.

The GFD specified total gluten restriction, avoiding wheat (including triticale and spelt), oats, barley, rye, and their derivatives (1,20). Oats and other cereals and processed foods could be consumed as long as they were certified as gluten-free (17). The initial duration was 2-4 weeks to observe GIS improvement and motivate patients with short-term goals. The initial gluten restriction could extend up to six weeks. When GIS improvement was perceived, even if mild, patients were advised to follow the gluten restriction for at least 6 months. If there was no change in GIS after 4-6 weeks, gluten was gradually reintroduced.

In addition to the specific and restrictive dietary recommendations, general guidelines for a healthy diet were included as a transverse axis of the overall dietary advice. These guidelines encompassed instructions on reading nutritional labels, avoiding UPF and sugary beverages, prioritizing home-cooked or minimally processed meals, consuming fruits and vegetables daily, staying hydrated with water, and limiting alcohol intake, among other healthful suggestions. The treatment options that can be prescribed individually or combined based on the patients' testing results and GIS tolerance threshold are summarized in figure 3.

Treatment and revaluation

To facilitate dietary prescription, treatment groups were conceived based on literature review, test results and patient's genetic profile and carbohydrate absorption capacity. Following these findings, patients

underwent assessment, diagnosis, treatment or referral and were subsequently reevaluated post-treatment. Patients repeated the breath tests at least 6 months after adhering to the dietary recommendations.

Parameters for gauging the efficacy of dietary management were established, relying on patients' self-perception of symptom progression measured through the VAS, and reassessment of breath test outcomes when recommended. Additionally, the presence or absence of symptoms served as a subjective indicator of treatment efficacy; if no improvement or worsening occurred, patients were referred to their physician to consider alternative causes of GIS and additional treatment options.

As an overarching aspect of patient management, PCR-based parasite diagnosis was considered as another potential cause of GIS. Upon identifying parasitic infections, the medical team prescribed antiparasitic treatment following guidelines from The Medical Letter on Drugs and Therapeutics, specifically Drugs for Parasitic Infections (26).

Statistical analysis

A descriptive analysis was performed using percentages and frequencies. Student’s t-test was used to determine if there was a significant difference between the reported symptoms prior and post nutritional treatment. Any *p*-value less than 0.05 was considered statistically significant. Data analysis was performed using Jamovi software (version 2.5.3), accessed via its web interface.

RESULTS

Group of treatment definition

Out of the initial 63 patients, three patients withdrew from the study due to non-compliance with dietetic recommendations, and sixteen patients diagnosed with SIBO were excluded from the study. A total of forty-four patients (female, $n = 31$; male, $n = 13$) were treated and classified into treatment groups.

Three primary treatment groups were established based on the presence or absence of LNP and LM breath test results, combined with possible combinations of HLA and FM. The initial focus was on LNP genetic predisposition, as it is the most common cause for LM and the dietary treatment is relatively simple, primarily consisting in lactose restriction. Furthermore, a positive HLA genotype may necessitate GFD recommendations, which involve a more stringent restriction as it encompasses a broader range of foods.

The patients were categorized into three main groups and subgroups. Group A consists of patients who presented positive LNP. Group B included patients who presented LM, but were lactase persistent (LP). Group C consisted of patients who tested negative for LM and LP. Subgroups were created based on the possible combinations of HLA and FM test results, please refer to table I for a better understanding of this classification.

- *Group A:* presented GIS and LNP genotype. A1 subgroup is only combined with LM and this is the first suspected cause of LI (malabsorption + symptoms). A2 subgroup additionally presents FM and A3 subgroup presents the four positive test results including HLA. A4 subgroup presents LNP, LM and HLA. A5 subgroup only presents LNP and no other genetic or BT positive results.
- *Group B:* presented LI (LM + GIS) and LP have been included in this group. B1 subgroup only presents positive LM, however, B2 subgroup additionally presents FM. B3 and B4 subgroups, in addition to LM, both present positive HLA, however, only B3 subgroup presents FM as well.
- *Group C:* presented GIS and negative LM and NPL conformed Group C. C1 subgroup patients presented negative results for the genetic testing and breath test. The C2 subgroup only presented positive FM patients, however patients in the C3 subgroup

additionally presented HLA. The C4 subgroup is represented by patients who only presented HLA.

The aim of this classification is to group patients with similar genetic and malabsorption profiles and associate positive testing results to specific dietetic restriction needs. The dietetic recommendations can be prescribed individually or combined according to the patients' needs and their response to treatment.

Treatment efficacy assessment

We have assessed groups and subgroups of patients based on their response to different dietetic approaches or the combination of them. The following detailed explanations include the primary treatment option according to each patient profile, followed by secondary treatment options based on the patients' primary response and GIS improvement. Please refer to each group's treatment efficacy assessment tables (Tables II-IV) for a better understanding of the dietetic management procedure.

Group A

In this group, testing results suggest the manifestation of LNP genotype as the potential primary cause of LI, characterized by malabsorption and GIS (Table II). Therefore, as the primary treatment option, LL were prescribed. If GIS disappear upon adherence to LL, it is advised to maintain this dietary approach permanently, considering the individual tolerance threshold and genotype. This recommendation applies to A1 to A4 subgroups. Conversely, if symptoms persist after at least six months of LL and HLA and FM tests are negative (A1), patients should be referred for further assessment.

As shown in table II, self-reported improvement (SRI) was noted by 50 % of patients in A1 subgroup following LL, while the remaining patients were referred to their physicians for additional evaluation. In cases

where FM is also present (A2), LF should be added to LL. 75 % of patients reported self-improvement, and 25% showed FM recovery post-treatment. If symptoms persist despite lactose and fructose restriction (LL+LF), exploring other potential causes of intolerance and further assessment are recommended. For patients with a positive HLA genotype (A3 and A4), the initial approach aligns with previous groups, involving carbohydrate restriction for GIS control and adjusting lactose and/or fructose content in the diet based on the presence of LM (A4) and FM (A3).

A3 subgroup, reporting no improvement after carbohydrate restriction, was prescribed a GFD, resulting in 100 % SRI and FM recovery. A4 subgroup, despite a positive HLA genotype, reported 100 % self-improvement after LL, without presenting FM and no GFD was needed. A5 subgroup, lacking LM, did not require LL. Although healthy diet recommendations were provided, no SRI was observed, leading to a referral for further assessment.

Due to the genetic predisposition, lactose malabsorption reevaluation with BT is not recommended to avoid patients' unnecessary discomfort. However, fructose reevaluation in A2 and A3 subgroups, following GIS improvement and adopting appropriate dietetic recommendations for at least six months, is advised. Breath test reevaluations served as an objective indicator of treatment efficacy, though GIS did not always correlate with a negative BT result.

Group B

Positive lactose malabsorption indicates that the patients are LI (malabsorption + GIS) and all four subgroups will require lactose restriction for symptom control. However, the absence of LNP genotypes indicates that the lactose restriction may not be permanent. In this group of patients, LM is not due to a genetic predisposition that can cause lack of lactase enzyme production and other causes should be

considered, such as positive HLA or FM in the context of this study. When all the other test results are negative (B1), LL is recommended for GIS control, followed by patient referral in case there is no GIS improvement. In this research, there were no patients who represented subgroups B1 and B4. When there is also FM (B2 and B3), both lactose and fructose should be restricted. As displayed in table III, B2 subgroup, after carbohydrate restriction (LL+LF), resulted in 100 % self-reported improvement and LM and FM recovery. If GIS persist or it is not possible to reintroduce a regular diet, patients from B2 subgroup should be referred.

The B3 subgroup, reporting no improvement after carbohydrate restriction and presenting HLA genotype, was prescribed a GFD, resulting in 25 % self-reported improvement. 66.7 % exhibited FM recovery and LM remained the same. In group B, both carbohydrates should be gradually reintroduced according to the patient's tolerance threshold because there is no genetic predisposition for carbohydrate intolerance.

Since LNP genotype is not present, lactose and/or fructose malabsorption reevaluation is recommended respectively for these subgroups after GIS improvement and following the dietetic treatments for at least six months. One patient in this group and some others in different groups could not be reevaluated due to repeated antibiotic treatments and other diagnoses or personal conditions.

Group C

As there is no genetic predisposition for LNP, and LM is absent in Group C, it was not recommended to restrict lactose from the diet. It is advisable to investigate other potential causes for GIS, such as HLA presence and FM, within this study's framework.

Eight patients presented with negative results for all four tests (C1). Healthy dietetic recommendations were provided to enhance the quality

of consumed foods in this subgroup. Two patients were additionally treated for *Giardia intestinalis*, and 87.5 % self-reported GIS improvement, as exhibited in table IV. One of the patients was referred for further assessment.

In cases of FM (C2 and C3), the primary recommended dietary approach was LF. Some instances of malabsorption may result from an over-intake of fructose, hindering complete absorption and causing GIS. In the C2 subgroup, as shown in table IV, 25 % of patients self-reported GIS improvement, and a 50 % FM recovery was observed after following LF. In the C3 subgroup, a 20 % improvement occurred after fructose restriction, and 20 % registered FM recovery. For the patients who didn't show improvement in the C3 subgroup, a GFD was prescribed, leading to 50 % self-reported improvement and 50 % FM recovery. If GIS persist, a thorough evaluation of other possible causes of GIS should be conducted, and patients should be referred.

Patients in the C4 subgroup, only characterized by a positive HLA, carbohydrate restriction was unnecessary, as confirmed by the BT, which indicated unaffected absorption. GFD was prescribed, even in the absence of carbohydrate malabsorption. Notably, one patient reported GIS improvement after adopting the GFD. FM revaluation was not considered necessary, given its initial negative status, possibly indicating uncompromised absorption at the time. In patients who showed no GIS improvement after at least 6 months, gluten was gradually reintroduced.

Symptoms evolution after dietetic treatment

Prior to the nutritional treatment, the most prevalent GIS were abdominal pain and distention, both present in 75 % of the patients population, followed by flatulence (68.2 %), borborygmi (43.2 %), and burping (43.2 %), among other symptoms as shown in figure 2. At least six months after the nutritional intervention a substantial improvement

was observed in the GIS reported on the VAS scale. A significant improvement was noted in all gastrointestinal symptoms, except for reflux and nausea. Abdominal pain showed the most notable improvement (36.4 %), followed by reductions in abdominal distention (45.5 %), flatulence (31.8 %), borborygmus (20.5 %), burping (18.2 %), among others.

Regarding extraintestinal symptoms, higher pretreatment prevalence was observed in all of the symptoms: articular pain (25 %), itching (25 %), fatigue (20.5 %) headache (13.6 %) weight loss (11.4 %) (Fig. 3). Following nutritional treatment, an improvement tendency was observed for all of the extraintestinal symptoms; articular pain (11.4 %), itching (11.4 %), fatigue (15.9 %), headache (6.8 %) and weight loss (4.5 %). Itching and articular pain showed a significant improvement.

DISCUSSION

Growing evidence suggests that diet plays a significant role in functional digestive symptoms, leading to frequent dietary restrictions among patients with chronic gastrointestinal issues (19,27). Additionally, in recent years, the increasing unspecified reactions to food have led people and patients to adopt long-term dietary restrictions (2), often unsupervised (27), without fully improving their condition and jeopardizing their nutritional requirements (5,28-30). In some cases, this leads to a worse quality of life, eating disorders, and dysbiosis (2,27). Combining genetic testing with breath testing aims to improve the efficacy of treatment plans, as the dietary interventions designed will be based on the patient's genetic profile and carbohydrate absorption capacity (1,20,31,32).

Consistent with other studies, specific carbohydrate-restricted dietary treatments for lactose and/or fructose, according to breath test results, yielded positive outcomes (1,29,33). Our results denote a significant improvement in most gastrointestinal symptoms, consistent with similar

studies, after adopting carbohydrate-restricted diets (5,28,34). In our study, 58 % of patients in Group A showed improvement with LL and 25 % of patients exhibited FM reversal within at least 6 months. Additionally, one patient from the B2 subgroup presented the same results. In agreement with other authors, exclusion diets were prescribed for the briefest duration necessary to alleviate symptoms, followed by a gradual reintroduction of foods to determine individual tolerance thresholds (22,35). This approach enhances dietary diversity, ensures nutritional sufficiency, and mitigates disturbances to the gastrointestinal microbiota (22).

For patients presenting carbohydrate malabsorption and/or GIS with genetic markers indicating celiac disease risk, we recommend considering GFD trials as a secondary alternative treatment option. This recommendation applies particularly to those who continue to experience symptoms despite carbohydrate restriction and the treatment of other possible primary causes of malabsorption, such as parasitosis and SIBO (1,2). GFD was prescribed to twenty patients aiming to alleviate symptoms. It has been suggested that HLA-DQ2/8-positive patients tend to exhibit a better response to GFD compared to those who do not carry this haplotype (36-38), which aligns with the findings observed in the patients of the present study. Nine out of twenty (45 %) HLA-DQ2/8-positive patients, corresponding to subgroups A4, B4, C3, and C4, underwent a GFD and self-reported improvement. Among these patients, eight out of nine who were reevaluated for FM showed remission.

Reducing dietary restrictions, in this case solely to gluten and in most cases enabling the restoration of fructose absorption, significantly enhances patients' well-being and quality of life, thereby promoting treatment adherence (1,30). There were no patients previously diagnosed with CD in the present study; however, it is important to consider that nowadays it is more common for CD to manifest with

nonspecific digestive symptoms or through extraintestinal manifestations (14,39). Also, some authors mention that the classic presentation of malnutrition and chronic diarrhea of CD is becoming increasingly rare, especially in adults (14). Additionally, despite some patients not being diagnosed with celiac disease or other GRD, our results, in agreement with other authors, exhibit that positive HLA-DQ2/8 patients may still benefit from maintaining a gluten-free diet (36-38).

Another strategy in our study was to implement short initial periods of dietary restrictions, including both carbohydrate and gluten restriction. This approach helped improve treatment adherence and motivated patients to continue, especially for those who experienced symptom improvement in their gastrointestinal issues (GIS). This was particularly beneficial for the GFD, which can be perceived as more challenging due to the strict gluten avoidance required (5,17,22,29). Some authors explain that patients who present milder symptoms when consuming gluten may not see immediate advantages from adopting GFD, leading to lower adherence rates as they perceive gluten consumption as less detrimental (16). Our recommendation was to adopt the GFD initially for 2-6 weeks, and if GIS improved, to continue with the recommendations for at least six months. According to some authors, clinical progression after initiation of a GFD is rapid, and SGI, such as abdominal pain and bloating, improve within a few days and resolve completely within six months in more than 50 % of patients (40). Other authors suggest that clinical remission of CD may be observed within the first month and histological recovery typically starting from 2 years in most patients (14). For those patients who didn’t improve despite adopting carbohydrate-restricted diets or GFD, other causes should be assessed.

In conclusion, designing dietary interventions based on primary and secondary causes for carbohydrate intolerance can avoid unnecessary food restrictions; improving patients' quality of life and treatment effectiveness through tailored dietary interventions. The proposed

dietary treatment is tailored based on conducted tests, prioritizing patients' quality of life and aiming to minimize the impact of dietary recommendations on individuals' lifestyles and eating habits to enhance adherence and achieve better long-term outcomes.

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Table I. Treatment groups and subgroups

		LNP	**LM**	**HLA**	**FM**	***n***	**%**
Group A *n* = 13	A1	(+)	(+)	(-)	(-)	*4*	*9.1 %*
	A2	(+)	(+)	(-)	(+)	*4*	*9.1 %*
	A3	(+)	(+)	(+)	(+)	2	4.5 %
	A4	(+)	(+)	(+)	(-)	2	4.5 %
	A5	(+)	(-)	(-)	(-)	1	2.3 %
Group B *n* = 5	B1	(-)	(+)	(-)	(-)	0	0.0 %
	B2	(-)	(+)	(-)	(+)	1	2.3 %
	B3	(-)	(+)	(+)	(+)	*4*	*9.1 %*
	B4	(-)	(+)	(+)	(-)	0	0.0 %
Group C *n* = 26	C1	(-)	(-)	(-)	(-)	8	18.2 %
	C2	(-)	(-)	(-)	(+)	4	9.1 %
	C3	(-)	(-)	(+)	(+)	*10*	*22.7 %*
	C4	(-)	(-)	(+)	(-)	4	9.1 %

LNP: lactase non-persistence; LM: lactose malabsorption; HLA: celiac disease risk; FM: fructose malabsorption.

Table II. Group A treatment efficacy assessment

Subgroup	**LNP**	**LM**	**HLA**	**FM**	***n***	**T1**	**SRI (%)**	**T2**	**SRI (%)**	**FMR (%)**
A1	(+)	(+)	(-)	(-)	4	LL	50 %	-	-	-
A2	(+)	(+)	(-)	(+)	4	LL + LF	75 %	-	-	25 %
A3	(+)	(+)	(+)	(+)	2	LL + LF	0 %	GFD + LL + LF	100 %	100 %
A4	(+)	(+)	(+)	(-)	2	LL	100 %	GFD + LL	-	-
A5	(+)	(-)	(-)	(-)	1	H	0 %	-	-	-

LNP: lactase non-persistence; LM: lactose malabsorption; HLA: celiac disease risk; FM: fructose malabsorption; T1: first treatment option; T2: second treatment option; SRI: self-reported improvement; FM Recover: fructose malabsorption reevaluation with breath test; LL: low lactose dietary recommendations; LF: low fructose dietary recommendations; Healthy: healthy diet recommendations; GFD: gluten-free diet; H: healthy dietary recommendations.

Table III. Group B treatment efficacy assessment

Subgroup	**LNP**	**LM**	**HLA**	**FM**	***n***	**T1**	**SRI (%)**	**T2**	**SRI (%)**	**FMR (%)**	**LMR (%)**
B1	(-)	(+)	(-)	(-)	0	LL	-	-	-	-	-
B2	(-)	(+)	(-)	(+)	1	LL + LF	100 %	-	-	100 %	100 %
B3	(-)	(+)	(+)	(+)	4	LL + LF	0 %	GFD + LL + LF	25 %	66.7 %*	0 %
B4	(-)	(+)	(+)	(-)	0	LL	-	GFD + LL	-	-	-

*One patient from subgroup B3 could not be reevaluated. LNP: lactase non-persistence; LM: lactose malabsorption; HLA: celiac disease risk; FM: fructose malabsorption; T1: first treatment option; T2: second treatment option; SRI: self-reported improvement; FMR: fructose malabsorption reevaluation with breath test. LM Recovery: lactose malabsorption reevaluation with breath test; LL: low lactose dietary recommendations; LF: low fructose dietary recommendations; Healthy: healthy diet recommendations; GFD: gluten-free diet.

Table IV. Group C treatment efficacy assessment

Subgroup	**LNP**	**LM**	**HLA**	**FM**	***n***	**T1**	**SRI (%)**	**FMR (%)**	**T2**	**SRI (%)**	**FMR (%)**
C1	(-)	(-)	(-)	(-)	8	H	87.5 %*	-	-	-	-
C2	(-)	(-)	(-)	(+)	4	LF	25 %	50 %	-	-	-
C3	(-)	(-)	(+)	(+)	10	LF	20 %*	20 %*	GFD	50 %	50 %
C4	(-)	(-)	(+)	(-)	4	GFD	25 %	-	-	-	-

*Patients additionally treated for parasites. LNP: lactase non-persistence; LM: lactose malabsorption; HLA: celiac disease risk; FM: fructose malabsorption; H: healthy dietary recommendations; LF: low fructose dietary recommendations; GFD: gluten-free diet; Healthy: healthy diet recommendations; T1: first treatment option; T2: second treatment option; SRI: self-reported improvement; FMR: fructose malabsorption reevaluation with breath test.

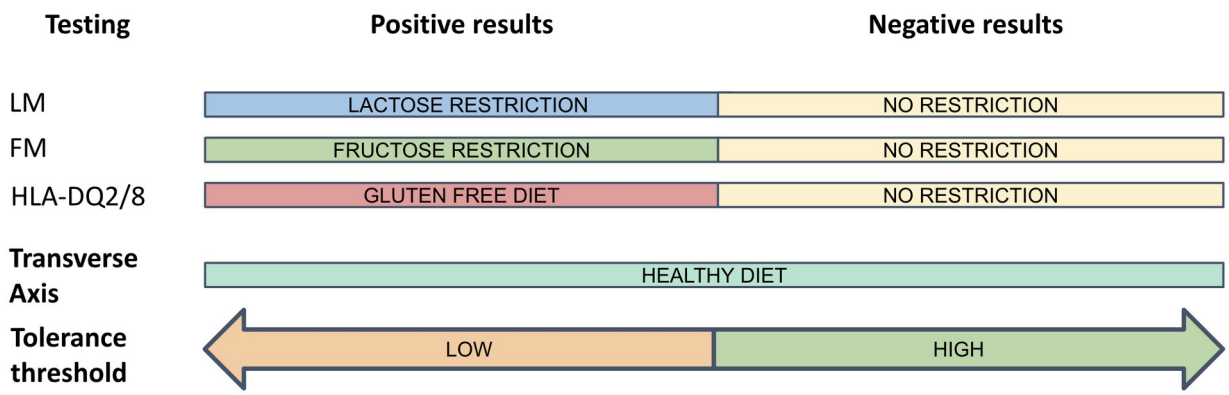

Figure 1. Treatment options based on testing results and tolerance threshold.

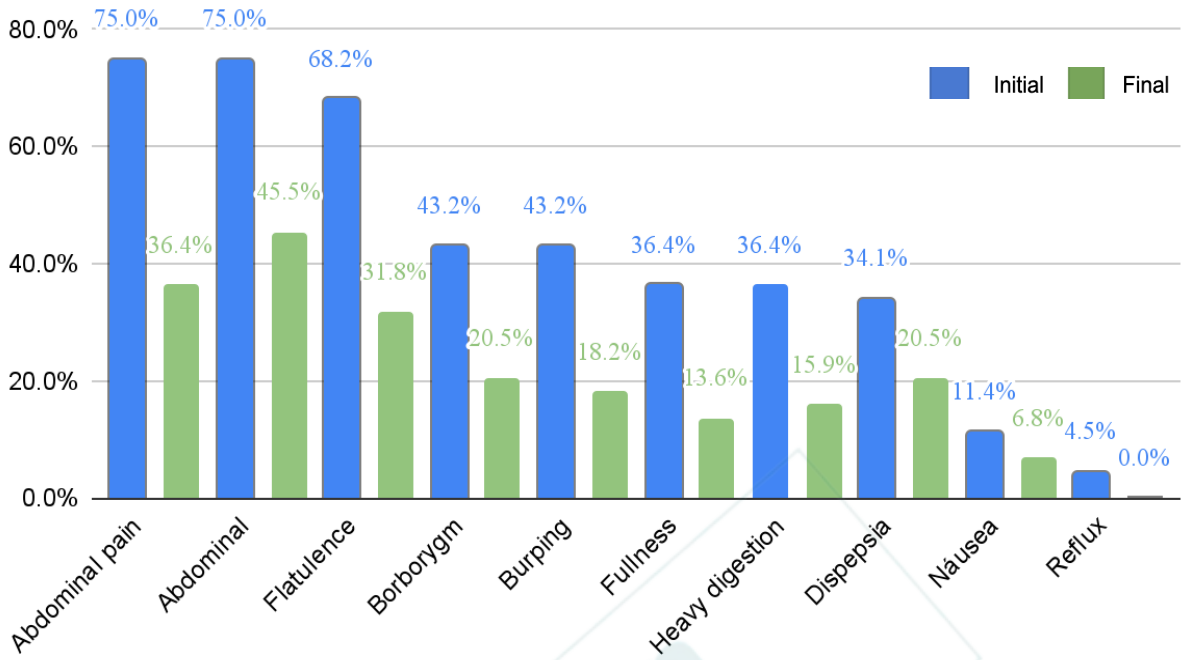

Figure 2. Gastrointestinal symptoms prevalence throughout dietary-nutritional management.

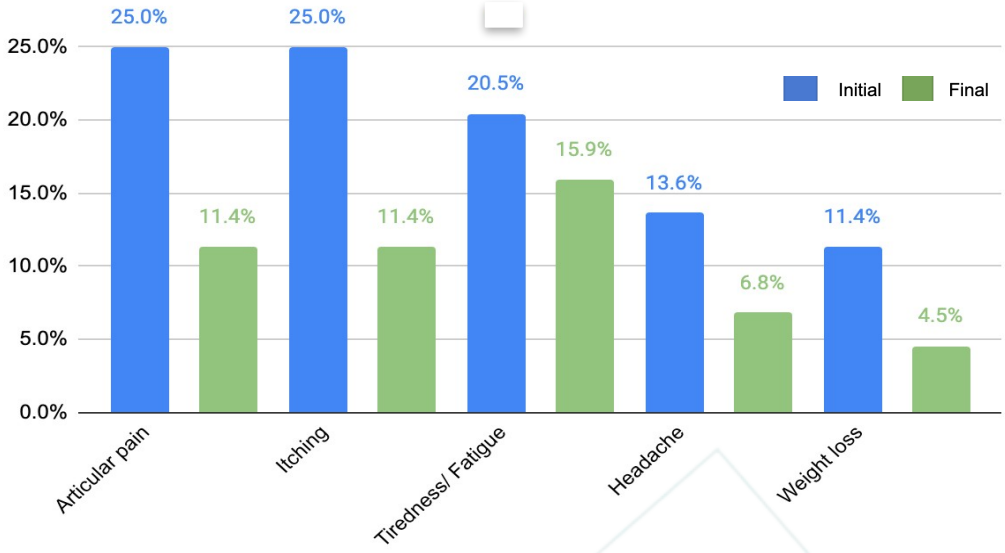

Figure 3. Extraintestinal symptoms prevalence throughout dietary-nutritional management.