Narrative review article

Probiotics and prebiotics for patients with celiac disease and non-celiac gluten sensitivity

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Abstract
Celiac disease and non-celiac gluten sensitivity are entities that have shown an increase in incidence, making them a topic of interest to provide innovative therapeutic approaches and improve intestinal and extraintestinal symptoms. This review intends to determine the effects of the use of probiotics and prebiotics in celiac disease and non-celiac gluten sensitivity. A narrative review was undertaken by searching for original and review articles no older than five years since publication through databases consulted: HINARI, PubMed and Scopus in Spanish and English. The use of probiotics and prebiotics in celiac disease has shown benefits by restoring the composition of the intestinal microbiota, especially with the use of *Lactobacilli* and *Bifidobacterium* spp.; in non-celiac gluten sensitivity, its use is limited as its pathophysiology is not exactly known, therefore, a gluten-free diet is currently considered to be the best therapeutic guideline. The use of probiotics and prebiotics could alleviate gastrointestinal symptoms and improve dysbiosis in patients with celiac disease and non-celiac gluten sensitivity. However, more studies are needed to demonstrate the benefits of its use as a therapeutic alternative.

Keywords
Celiac disease, Wheat Hypersensitivity, Probiotics, Prebiotics.

Resumen
La enfermedad celíaca y la sensibilidad al gluten no celíaca han tenido un aumento en su incidencia, esto las ha convertido en tema de interés en la búsqueda de enfoques terapéuticos innovadores que ayuden a mejorar los síntomas intestinales y extraintestinales. Esta revisión pretende determinar los efectos del uso de probióticos y prebióticos en la enfermedad celíaca y sensibilidad al gluten no celíaca. Se realizó una búsqueda en bases de datos HINARI, PubMed y Scopus en idioma español e inglés, se incluyeron artículos originales y de revisión con un máximo de cinco años desde su publicación. El uso de probióticos y prebióticos para la enfermedad celíaca ha mostrado beneficios restaurando la composición de la microbiota intestinal, en especial con el uso de *Lactobacilli* y *Bifidobacterium* spp.; en la sensibilidad al gluten no celíaca, el uso se ve limitado al no conocer con exactitud su fisiopatología; no obstante, se propone como mejor pauta terapéutica una dieta libre de gluten. El uso de probióticos y prebióticos podría aliviar los síntomas gastrointestinales y mejorar la disbiosis en pacientes con enfermedad celíaca y sensibilidad al gluten no celíaca. Sin embargo, se necesitan más estudios que evidencien los beneficios de su uso como alternativa terapéutica.

Palabras clave
Enfermedad celíaca, hipersensibilidad al trigo, probióticos, prebióticos.

Introduction

In the last two decades, there has been an increase in the incidence of diseases associated with gluten and wheat intake[1]; these diseases include celiac disease (CD), wheat allergy (WA), and non-celiac gluten sensitivity (NCGS)[2].

The prevalence of CD has increased over the last 50 years; in the general population, it is 0.5 % - 2 %[3]. Every year more than 70 % of newly diagnosed patients are older than 20 years, including patients of 70 years and older, with a male:female ratio of 1:3 to 1.5:1. In Western countries, the histological prevalence is 0.06 % and 1 % in serological screening4. There are no population-based studies of NCGS due to its recent description and the immune response it presents to different proteins from food grains. However, a prevalence of 0.6 % to 6 % has been observed in the general population, mainly in adult women from urban areas in the fourth decade of life[5].

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Probióticos y prebióticos en pacientes con enfermedad celíaca y sensibilidad al gluten no celíaca

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Human food-related conditions are a topic of general interest, with CD and NCGS being among the most common and studied for their pathology, clinical presentation, variants, genetic and environmental factors[6].

For a long time, the primary interest in this condition focused on the genetic factors involved in its presentation and development within childhood and adulthood[7], providing significant findings on the role of the human leukocyte antigen (HLA) complex, also known as the major histocompatibility complex (MHC), and immune complexes within intestinal tissue and CD[8].

The aforementioned has directed the attention of researchers towards the interaction of alterations in the intestinal microbiota, observing that in patients with persistent symptomatology, an alteration of this microbiota was evidenced in comparison with healthy patients[9].

This evidence pointed to the role that the intestinal microbiota and its modifications may play in the pathogenesis, clinical manifestations, and onset of the condition, opening up the possibility of new approaches to treatment and reduced risk of presenting this disease. Current research is looking for new nutritional options to improve the lives of patients with conditions such as CD and NCGS, suggesting innovative therapeutic approaches such as supplements capable of reducing intestinal permeability or suppressing the inflammatory response, such as probiotics and prebiotics.

A narrative bibliographic review of international scientific publications was conducted by consulting HINARI databases through Research4life, Pub-Med, and Scopus. A search was performed using keywords such as "Celiac Disease," "Non-Celiac Gluten Sensitivity," "Gluten," "Probiotics," "Prebiotics," "Microbiota," "Gluten-free diet," together with logical operators "AND" and "OR." Original and review articles related to the topic were included, prioritizing sources with publications less than five years old in Spanish and English. The quality of these articles was evaluated by analyzing their reliability, validity, and variability.

Consequently, this review aims to determine the effects of probiotics and prebiotics in patients with CD and NCGS.

Discussion

During the co-evolution of humans and microorganisms, millions of bacterial species have colonized the human organism. This vast number of microorganisms in the human body is known as the "normal flora," "microflora," or "microbiota." The microbiota consists of bacteria accompanied by fungi, viruses, protozoa, and archaea, colonizing the mouth, ears, respiratory tract, gastrointestinal tract, and skin[10]. They act as regulators of the synthesis of nutrients and metabolites, in addition to preventing the colonization of pathogenic microorganisms and maintaining the integrity of the intestinal epithelium[11].

The CD is an autoimmune enteropathy in which an inappropriate immune response occurs in individuals genetically predisposed to gluten ingestion; It has been shown to occur almost exclusively in patients who present HLA-DQ2 or HLA-DQ8 haplotypes, as well as the presence of the serological markers immunoglobulin A anti-tissue transglutaminase (ATGT) and anti-gliadin deamidated peptide antibodies; it is also characterized at the histopathological level by inflammatory changes in the intestinal mucosa[12,13]. These inflammatory changes are responsible for the intestinal and extraintestinal clinical presentation of the disease[14].

Patients with confirmed CD present an alteration of the microbiota (dysbiosis), being this intestinal microbiota the one responsible for the metabolism of gluten[15]. This is why recent studies support the hypothesis that the intestinal microbiota plays an important role in the pathogenesis, progression, and apposition of the various intestinal or extraintestinal symptoms of CD, mainly abdominal distension, abdominal pain, episodes of diarrhea or constipation, vomiting, fatigue, anemia, loss of muscle mass or weight gain/decrease[16,17].

Some studies have cataloged Firmicutes, *Bacteroides*, and Actinobacteria as the main components of the microbiota of patients with CD18. Several studies have evaluated the salivary, fecal, and duodenal microbiota of patients with CD, observing a decrease in protective species (*Lactobacilli* and *Bifidobacterium* spp, Firmicutes); and an increase in pathogenic species (*Bacteroides*, *Proteobacteria*, *Serratia*, and *E. Coli*) in comparison with healthy subjects[19,20].

On the other hand, there is an imbalance between the presence of Gram (-) and Gram (+) bacteria in patients with CD21. Bascuñán KA *et al.* demonstrated that the total Gram (-) bacteria are significantly higher in patients with active CD, while the *Lactobacilli/Bifidobacterium* ratio compared to *Bacteroides/E. Coli* was significantly lower, the latter being more abundant in patients with active CD than in control subjects[22].

In contrast, non-celiac gluten sensitivity (NCGS) is a syndrome characterized by the presence of intestinal or extra-intestinal symptoms related to the consumption of products made with gluten-containing

cereals[23,24]. At present, due to the lack of biomarkers to assess NCGS, its diagnosis involves previously ruling out CD and wheat allergy, followed by a gluten-free diet to evaluate the reduction/remission of symptoms[25]. Therefore, the following are considered criteria that can help in the diagnosis of NCGS: gluten intolerance evidenced by the presence of symptoms, negative serology for CD, and no wheat allergyo[26,27].

In NCGS, the response triggered by gluten ingestion leads to an increase in intestinal permeability, and intestinal dysbiosis, followed by a low-intensity inflammatory reaction in the intestinal mucosa and bacterial translocation that finally causes the release of cytokines and gastrointestinal peptides that favor the appearance of intestinal symptoms, the most frequent being abdominal distension, abdominal pain, diarrhea, nausea, gastroesophageal reflux, and, less frequently, extra intestinal symptoms such as headache, fibromyalgia, dermatitis, joint pain and in some cases depression[28,29].

Being a recent entity, the exact role played by the intestinal microbiota in its pathophysiology is not known[30]. Transeth *et al.* mention studies of duodenal samples showing that there is often an increase in species such as Firmicutes, Actinobacillus, and Rhuminococcaceae and, in turn, a reduction in Bacteroidetes; however, this does not clarify whether the intestinal dysbiosis that occurs in these individuals is the cause or the effect of the disorders associated with gluten intake[31,32].

According to the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), probiotics are live microorganisms that when administered in adequate amounts have demonstrated beneficial effects on health, restore the composition of the intestinal microbiome, prevent dysbiosis and have demonstrated modulation of the immune system and pro-inflammatory mechanisms; although at the moment, these mechanisms have not been properly defined[33,34]. For this reason, the major risk factor in the safe application of probiotics is the lack of knowledge of their activity. They generally have a beneficial effect on the digestive system, but in some cases, they could predispose to translocation or infections[35].

The intestinal microbiota, through the production of molecules with anti-inflammatory and immunomodulatory functions, is capable of stimulating the immune system, achieving its modulation. These effects occur due to the interaction between probiotics, epithelial cells, dendritic cells, monocytes/macrophages, and lymphocytes[36,37].

Most probiotics belong to the genus *Lactobacilli*, *Bifidobacterium*, and *Bacillus* spp.38; due to their high safety and cost-effectiveness, they are good candidates as therapy for CD. A study by De Angelis *et al.*, reported enzyme formulations, *Lactobacilli* and *Bacillus*, called Consortia I: *Lactobacilli* (Lp.), plantarum (Lc.), paracasei, *Bacillus* subtilis, *Bacillus* pumilus, and Consortia II: Lp. Plantarum, Lc. paracasei, Limosi, *Lactobacilli*reuteri, *Bacillus* megatherium, B. pumilus, which, under gastrointestinal conditions, have demonstrated gluten hydrolytic activity to non-immunogenic and non-toxic peptides[39].

A study by Marasco G *et al.* demonstrated that the potential of probiotics for CD management is supported by intestinal dysbiosis, the role attributed to the degradation of toxic components by the microbiota, the maintenance of the intestinal barrier, and the innate and adaptive response of the immune system. Selected strains of *Lactobacilli* and *Bifidobacterium* can hydrolyze gliadin fragments produced by digestive proteases into smaller peptides. Probiotics mixed with gliadin fragments can significantly reduce them to being only a source of amino acids[40].

According to the International Scientific Association for Prebiotics, these are a substrate that selectively stimulates one or more groups of microbiota, mostly *Bifidobacterium* and *Lactobacilli*. Prebiotics are resistant to the digestive enzymes of the upper digestive tract, which is why they reach the intestine in favorable quantities, stimulating the growth of the microbiota. To achieve the aforementioned benefits, it is necessary to ingest supplements to acquire favorable levels[41].

There are different types of prebiotics, most of them belonging to carbohydrates, mostly oligosaccharides; however, there is evidence that prebiotics are not only carbohydrates. Among these, the following are worth mentioning:

Fructans: these consist of inulin, fructo-oligosaccharides or oligofructose. It has been shown that they can selectively stimulate *Lactobacilli*. However, recent studies demonstrate that the length of the fructan chain is an important factor in determining which bacteria can ferment therefore, other bacteria can be stimulated directly or indirectly by fructans.

Galacto-oligosaccharides: are the product of the extension of lactose; and they are divided into two groups: those with excess galactose and those manufactured from galactose, through enzymatic transglycosylation.

Starch and glucose-derived oligosaccharides: these are resistant to digestion and promote health by producing high levels of butyrate, which is why it is classified as a prebiotic[41]. Butyrate formation in the intestine occurs mainly from carbohydrate metabolism in glycolysis, but can also form from the metabolism of organic acids and amino acids[42].

The specific consequences of the role of dysbiosis in CD, the exact mechanisms of action, along the mechanisms of action of prebiotics, remain unclear. At the same time, results have been reported in which probiotics and prebiotics have demonstrated an improvement of gastrointestinal symptoms, ameliorating dysbiosis in affected patients. However, further studies are needed to confirm these results and their benefit as a therapeutic alternative[43].

The pathophysiological mechanism leading to NCGS is currently unknown; therefore, the therapeutic targets for this condition are more difficult to identify. Although the gluten-free diet reduces symptoms after its implementation, some patients with NCGS continue to report symptoms despite the strict diet. In a study by Cárdenas-Torres *et al.*, it has been reported that a diet low in fermentable oligo-dimonosaccharides can reduce symptoms in patients with NCGS, but its implementation should be considered with caution due to its association with low absorption of antioxidants and micronutrients[28].

By contrast, oligo-dimonosaccharides, known to have a prebiotic effect on the microbiota, stimulate the growth of *Lactobacilli* and *Bifidobacterium*. Therefore, prebiotic and vitamin supplements are recommended for patients following a diet low in oligo-dimonosaccharides. Few clinical studies have been performed in patients with NCGS investigating the effect of probiotics and prebiotics to reduce the toxic effects of the external precursors, or to improve symptomatology. Hence, there is a need to investigate the pathophysiology, aiming to find more effective interventions apart from the gluten-free diet[44-46].

Gluten-free diet and use of probiotics

Traditionally, when the diagnosis of CD and NCGS is confirmed, the main line of treatment requires the total elimination of foods containing gluten or food that was exposed to gluten during their preparation. On the other hand, another current of thought on the management of patients with CD and NCGS considers that it is impossible to eliminate gluten from the diet of patients due to the patient's already ingrained adherence to their eating habits and cross-contamination in the industrial production of food[46]; therefore, quantitative restriction of the consumption of gluten-containing products is proposed, suggesting the establishment of a limit of up to 10 mg daily as the maximum dose without histological changes that have been observed in the intestinal mucosa of genetically susceptible patients[47].

On the other hand, some studies have shown that, after maintaining a gluten-free diet, children can reverse up to 95 % of the inflammatory alterations of the intestinal mucosa and up to 66 % in adults[48]. In addition, other studies have shown improvement in extraintestinal symptomatology, such as changes in bone mineralization and malabsorption syndrome, after adaptations in the diet of patients. Even so, although the degree of reversibility observed seems to be mainly related to age and early diagnosis of the disease, it should be taken into account that prolonged intake, delayed diagnosis, and the time of initiation of a gluten-free diet are determining factors in the irreversible damage to the intestinal mucosa[49].

One of the main challenges of the gluten-free diet line of treatment is the acquisition of foods that meet the duly certified requirements and provide the assurance that they were not affected by any cross-contamination during processing[50]. Concerning this problem, Silvester J *et al.* stated in their study that the high costs of these products contribute to the difficulty for patients to adhere to a diet strictly free of this protein.

Furthermore, given the proposal for consumption based on quantitative restriction, it is difficult to make a precise quantitative assessment of the gluten contained in the food consumed during the day by a patient and the variability in terms of the cytotoxic dose in each person[51,52]. Because of the various limitations of the traditional form of treatment, there is a need for alternatives, mainly pharmacological, that are accessible, effective, and efficient.

A study by Francavilla R *et al.* showed that the combined use of several strains of bacteria of the *Lactobacilli* and *Bifidobacterium* genus in 104 patients during several weeks significantly improved intestinal symptoms compared to placebo53. In a study conducted by Ali B *et al.*, a similar conclusion was reached, regarding the consumption of oral probiotics on gastrointestinal symptoms54. Despite the above, there are no studies comparing the endoscopic and histopathological improvement

of inflammatory processes in the intestinal mucosa with the gluten-free diet and the consumption of probiotics.

The gluten-free diet is traditionally the treatment of choice for the management of CD and NCGS, as it has proven to reverse the inflammatory process. Intestinal and extraintestinal symptoms represent a real challenge for patient adherence, in addition to increased consumption costs and difficulty in acquiring food products duly certified as gluten-free.

Conclusions

The use of probiotics and prebiotics evidenced a significant improvement in intestinal symptoms through the regeneration of the intestinal mucosa, modulation of the immune response and appropriate degradation of gliadin glycoprotein, due to the close relationship between the microbiota and the pathogenesis of CD and NCGS. The use of probiotics and prebiotics to treat CD and NCGS, the *Lactobacillus* and *Bifidobacterium* genera are the ones that show major implication in the improvement of the clinical symptomatology of these conditions, even though there is still little evidence of the effects on the control of the inflammatory processes of the intestinal mucosa and consequently the effects they could have on the histological integrity of the intestine.

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