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The Gut Microbiota and Probiotics in Celiac Disease

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ABSTRACT

Celiac disease (CD) is an immune-mediated enteropathy that occurs in genetically predisposed individuals associated with gluten intake. Currently, the only effective treatment for CD is life-lasting elimination of gluten from the diet, but adhering to it throughout life is burdensome. In addition, strict compliance with a gluten-free diet (GFD) does not lead to a complete restoration of intestinal microbiota. Although gluten is known to be a trigger in CD, various studies have demonstrated that the gut microbiota is involved in gluten metabolism, regulation of intestinal barrier permeability, and modulation of the immune response. Therefore, the gut microbiota has an important role in the pathogenesis, progression, and clinical manifestations of CD. This evidence supports the hypothesis that probiotics act as a strategy to modulate the intestinal microbiota into an anti-inflammatory state. Probiotics such as some bacterial species of the genera *Bifidobacterium* and *Lactobacillus* can protect the epithelial cells from gliadin-induced damage and improve symptoms and quality of life in GFD-treated patients, as an adjunctive treatment. This narrative review aims to discuss the recent scientific evidence of the relationship between the intestinal microbiota changes in CD and to understand the role of probiotics in CD treatment.

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Introduction

Celiac disease (CD) is a common lifelong autoimmune disorder initiated by dietary gluten intake in genetically predisposed individuals. The prevalence of CD is 1.4% based on serological test results and 0.7% according to biopsy results, which varies according to age, sex, and place of residence. CD is more common in children than adults and in females than in males (1). As per recent reports, the prevalence of CD is 0.8% in Europe and Oceania, 0.6% in Asia, 0.5% in Africa and North America, and 0.4% in South America (1). In a study by Mohammadibakhsh et al., the prevalence of CD in Iran was reported 3% based on serological test results and 2% based on biopsy, which is higher than the developed countries and almost the same as in other developing countries (2). CD causes inflammation in the small intestine, followed by crypt hyperplasia, villous atrophy, and an altered intestinal barrier, which subsequently impede the absorption of nutrients (3).

The clinical manifestations of CD are highly variable and CD can be divided into four categories according to the presentation as classical, non-classical, subclinical, and potential. Classical CD is characterized by gastrointestinal (GI) symptoms, including vomiting, chronic diarrhea, steatorrhea, abdominal pain, and weight loss. Although CD primarily affects the GI tract, some patients with CD present only with extra-intestinal symptoms, such as irritability, fatigue, dermatitis herpetiformis, iron deficiency anemia, depression, osteoporosis, and neurological problems. Moreover, non-classical can present as anemia in teenagers. DC They may also be asymptomatic, and CD can be detected by screening at-risk individuals. Both environmental factors (gluten) and genetic factors (HLA and non-HLA genes) are involved in CD (3).

Gluten is the general term for the proteins found in various cereals, such as gliadin, secalin, and hordein that exist in wheat, rye, and barley, respectively. These proteins are collectively known as gluten because of their structural similarities (4). Another important aspect of CD is its genetic predisposition. It is most commonly associated with human leucocyte antigen (HLA)

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DQ2 or DQ8, which is involved in the body's immune system for recognizing self and non-self-molecules (5).

The mainstay of CD treatment is complete adherence to a gluten-free diet (GFD), recommended by dieticians, to prevent micronutrient deficiencies and hidden gluten (6). Even a small amount of gluten (e.g., 50 mg per day) can be immunogenic; therefore, all foods and supplements that contain gluten or its derivatives should be excluded from the patient's diet (7). Nevertheless, many patients have difficulty in following the GFD completely. According to some previous research, adherence to treatment in patients diagnosed before the age of four years was about 80%. However, in patients diagnosed after this age, it was 40% (8). Due to the fact that lifelong adherence to GFD is a constant challenge for patients, and they have difficulty in maintaining the treatment, new treatment options have been studied.

In this context, a review article reported that probiotics supplementations could have interesting therapeutic effects (9). Probiotics are live microorganisms with health benefits which exert health effects when digested, by restoring or improving the gut flora (10). The gut bacteria are important regulators of digestion in the GI tract and play an important role in the synthesis of nutrients and metabolites. In addition, the gut microbiota has an important immune function of maintaining the intestinal epithelial integrity and inhibiting the growth of different pathogens (11). On the other hand, commensal bacteria and their derivatives affect the homeostasis, and the function and development of innate and adaptive immune cells. Therefore, Gut microbiota is involved in the clinical manifestations, pathogenesis, and risk of developing CD (12).

Patients with CD have more pathogenic microorganisms, such as *Klebsiella*, *Salmonella*, and *Shigella,* in the gut microbiota than the healthy individuals, which cause inflammation and progression of CD (13). Besides, gut dysbiosis has been reported in CD patients, which allows finding new therapeutic approaches by regulating the intestinal microbiota with probiotics. An imbalance between beneficial and pathogenic microbes is called dysbiosis, which is usually caused by exposure to atypical microbes, a diet change, host genetics, and the use of antibiotics and drugs (14). Probiotics can correct the inconsonance between beneficial microorganisms and dysbiosis and improve intestinal restoration (13). Certain probiotics have been discovered that can alter or even digest gluten polypeptides and make them less toxic for CD patients. In addition, research showed that some bacterial species in the genera Lactobacillus and *Bifidobacterium* provide protective benefits for epithelial cells from the damage caused by gliadin (13). This study aimed to evaluate the use of probiotic supplementations as an adjunct or primary treatment for CD.

Material and Methods

The most recent evidence about the effects of probiotics on the gut microbiota of patients with celiac disease is discussed in this narrative review. All published papers in English from inception to October 2020 were searched with the keywords of microbiota, Gluten, celiac disease, probiotics, and gluten-free through Google Scholar search engine and PubMed and Web of Science databases. Additional articles were added after manually searching the references of the selected articles.

Gut Microbiota and Celiac Disease

There are many microorganisms in the gut of healthy individuals that contribute to the normal functioning of the gut, including immune homeostasis and metabolic regulation (14). The gut microbiota is formed in the first three years of life by intestinal maturity, which is affected by various environmental factors such as the type of delivery, birth gestational age, breastfeeding method, lactation period, cultural habits, lifestyle, and diet. After the formation of the gut microbiota, it relatively remains constant all over the person life time in a symbiotic relationship with the host. The main bacterial phyla of the gut microbiota include *Bacteroides*, *Firmicutes*, and *Actinobacteria*. Some types of HLA genotype (HLA-DQ2/8) are associated with intestinal colonization by some bacteria in CD patients; for example, in a study by Olivares et al., *Firmicutes* and *Proteobacteria* increased in infants with a high genetic risk, while *Bifidobacterium* and *Actinobacteria* decreased (15).

In genetically predisposed infants, the intestinal microbiota is more affected by the type of feeding, so that breastfeeding has a protective effect against CD. *Bifidobacterium longum*, *Clostridium leptum*, and *Bifidobacterium breve* are higher in breastfed infants. On the other hand, *E.coli*, *Bacteroides fragilis,* and *Clostridium*

coccoides-Eubacterium rectale are higher in formula-fed infants. While some studies have discussed the protective role of breastfeeding in the development of CD, other studies did not confirm these results (16).

In terms of the type of delivery, in vaginal delivery, the body of the infant is usually characterized by vaginal microbiota including *Bifidobacteria*, *Lactobacilli*, and *Prevotella* (17). While, in cesarean, the neonatal flora is mainly affected by maternal skin microbiota and environmental bacteria (18). It has been reported that cesarean deliveries could decrease the microbial diversity as well as some beneficial bacteria such as Bifidobacterium in infants, compared to vaginal deliveries. The changes in flora, as reported in a previous study, can explain the high risk of CD in cesarean-born infants (19). There are conflicting findings on the impact of antibiotics on CD, according to an observational nationwide cohort study, it has been reported that the consumption of antibiotics, especially in the first year of life, is associated with the early onset of CD and intestinal dysbiosis (20). However, in a systematic review study, Kołodziej et al. concluded that there is no association between antibiotic exposure in the early stages of life (prenatal and postnatal) and CD (21).

Pathogenesis of Celiac Disease by Gut Microbiota

One of the functions of the intestinal microbiota is to participate in gluten metabolism. With this regard the immunogenic function of gluten and its peptides is decreased through degradation by *Bifidobacterium* spp. and *Lactobacilli*. Therefore, *Lactobacilli* and *Bifidobacterium* spp. can be used potentially as a complementary treatment of CD patients, as they have proteolytic and peptidolytic activity and contribute to the breakdown of gluten (22). In contrast, pathogenic microbiota like *Pseudomonas aeruginosa* can increase the immunogenicity of gluten-derived peptides (23). Alteration in the intestinal microbiota composition can increase intestinal epithelial permeability by modifying the intestinal barrier that compromises zonulin, which is a protein involved in modulation of tight junctions and its changes has been implicated in CD pathogesnesis (24). Gliadin and microbes are two important factors that increase the expression and release of zonulin, through a normal physiologic state (25). Dysbiosis also disrupts tight junctions by increasing the release of zonulin, which in turn increases epithelial permeability. As a result of this permeability augmentation, more incompletely digested gliadin peptides enter into the lamina propria (26). Furthermore, the intestinal microbiota plays an important role in regulating the immune system and metabolism (27). Serena et al. showed that the intestinal microbiota increases the risk of autoimmunity through epigenetic processes (28). As already discussed, the intestinal microbiota is involved in the pathogenesis of CD by affecting the immune system, gluten digestion, and intestinal permeability. The gut microbiota cannot completely be restored after GFD treatment, and other therapeutic methods are needed to manage dysbiosis in CD patients (29).

Probiotics may be useful in the restoration of homeostasis and can be a potential resource for adjunct treatment of CD. The use of probiotics can be in the form of supplementation or pre-treated foods enriched with probiotic strains (30).

Probiotics in Celiac Disease

According to the definition provided by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), probiotics are "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (31). The benefits of probiotics on gut health include blockage of adhesion sites, competition for nutrients with pathogen microbes, production of inhibitory substances that target pathogens, regulation of immunity, and degradation of toxin receptors. Among intestinal bacteria, *Bifidobacterium* and *Lactobacillus* are the main probiotics. In addition to strengthening the epithelial barrier, *lactobacilli* prevent the apoptosis of epithelial cells. They also secrete mucins and improve the tight-junction function. Regarding the function of *bifidobacteria*, we can mention the synthesis of exopolysaccharides, which cause the fermentation of other gut bacteria (32). As it follows in the next sections, several in vitro and in vivo preclinical studies and clinical trials have been conducted to evaluate the benefits of using probiotics in CD patients.

In Vitro and In Vivo (Animal) Studies

Animal studies proposed evidence that probiotics may affect the modulation of innate and adaptive immunity. Mouse models that

underwent gluten diet, present CD histological changes, including intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy. In fact, these changes are related to the overexpression of mediators that increases intestinal permeability including CD71, which is an IgA receptor on the gut epithelial cell thus overexpression of it increases IgA and IgA-gluten peptides in the gut epithelium and induces intestinal inflammation in CD IgA. When gluten digested with *Saccharomyces boulardi KK1* was given to mice, a decline in CD 71 expression was observed, and local cytokine production decreased as well. Therefore, it reverses the histological changes that indicates the beneficial effects of probiotics (33).

Table 1. Main findings on the efficacy of probiotics in patients with celiac disease

Authors	Year	Age	Probiotics	Period of Administration	Population	Findings in Probiotics Group
Smecuol et al.	2013	Adults	1.2×10^{10} colony-forming units of *Bifidobacterium infa*ntis Natren life start (NLS)	Daily for 3 weeks	22 active CD; 12 participants received *B. Infantis*, 10 placebo	• Improvement in indigestion, constipation, and gastroesophageal reflux • No differences in intestinal permeability • No improvement in abdominal pain and diarrhea • No significant changes in cytokines and chemokines production • Decreased serum antibody concentration • Increased serum macrophage Inflammatory protein-1β
Olivares et al.	2014	Children	1×10^{9} colony-forming units of *Bifidobacterium longum* CECT 7347	Daily for 3 months	33 active CD (17 *B. longum* with GFD vs. 16 placebo with GFD)	• Greater height percentile • Decreased number of *Bacteroides fragilis* in stool • Decreased secretory of IgA content in stool • Decreased TNF-α concentration • Decreased peripheral $CD3^{+}$ T lymphocytes • No difference in gastrointestinal Symptoms
Pisarello et al.	2014	Children	*Lactobacillus paracasei, Lactobacillus rhamnosus*	11 months	15 CD on a GFD vs. 15 healthy controls	• The number of *Lactobacillus* in CD children on a GFD group was lower than in the healthy individuals group. • Although treatment with probiotics modifies the composition of the gut microbiota, it cannot replace GFD.
Klemenak et al.	2015	Children	2×10^{9} colony-forming units of *Bifidobacterium breve* strains BR03 and B632	Daily for 3 months	49 CD on GFD (24 probiotic and 25 placebo) vs. 18 healthy controls	• Decreased TNF-α levels (Increased in 3-month follow-up)
Harnett et al.	2016	Adults	4.5×10^{11} colony-forming units of probiotic VSL#3	Twice daily for 3 months	45 CD on GFD with symptoms (23 probiotic and 22 placebo)	• No difference in symptoms severity • No difference in the fecal microbiota counts

Authors	Year	Age	Probiotics	Period of Administration	Population	Findings in Probiotics Group
Quagliarello et al.	2016	Children	2×10^9 colony-forming units of *Bifidbacterium breve* strains B632 and BR03	Daily for 3 months	40 active CD (two groups of 20 each, with one receiving the probiotic and the other placebo) vs. 16 healthy controls	• Increased *Actinobacteria* • Re-establishment of the physiological *Firmicutes/Bacteroidetes* ratio
Pinto-Sánchez et al.	2017	Adults	*Bifidobacterium infantis* Natren Life Start super strain (NLS-SS)	6 weeks	24 active CD, no treatment; 12 active CD treatment with *B. Infantis* 5 CD with 1 year GFD	• Decreased macrophage counts • Decreased α-defensin-5 • Decreased Paneth cell counts
Martinello et al.	2017	Adults	100 g of probiotic-containing yogurt	Daily for 30 days	14 CD vs. 17 healthy controls	• Although consumption of probiotic yogurt increased the number of *bifidobacteria* in CD patients, it did not reach the concentration of healthy controls.
Francavilla et al.	2019	Adults	Mixture of five strains: 4×10^{10} colony-forming units of Lactobacillus *casei* LMG 101/37 P-17504, *Lactobacillus plantarum* CECT4528, *Bifidobacterium animalis* subsp. *Lactis* Bi1 LMG P-17502, *Bifidobacterium breve* Bbr8 LMG P-17501, *Bifidobacterium breve* Bl10 LMG P-17500	Daily for 6 weeks	109 CD on GFD with IBS symptoms (54 in the probiotic, and 55 in the placebo group)	• Improvement in IBS-type symptoms • Increased lactic acid bacteria, *Bifidobacterium* and *Staphylococcus*
Primec et al.	2019	Children	2×10^9 colony-forming units of *Bifidobacterium breve* strains BR03 and B632	Daily for 3 months	40 CD (two groups of 20 each, with one receiving the probiotic and the other placebo) vs. 16 healthy controls	• Negative relationship between *Firmicutes* and pro-inflammatory TNF-α.
Håkansson Å et al.	2019	Children	1×10^{10} colony-forming units of *Lactobacillus plantarum* HEAL9 and *Lactobacillus paracasei* 8700:2	Daily for 6 months	78 CD (40 probiotic and 38 placebo)	• Decreased level of IgA anti transglutaminase • Modulation in the peripheral immune response
Uusitalo et al.	2019	Children	Various, mainly *Lactobacillus reuteri* and *Lactobacillus rhamnosus*	Median period of 8.7 years	6520 genetically susceptible children.	• Consumption of probiotics was not associated with a different risk of developing CDA or CD
Smecuol et al.	2019	Adults	1.2×10^{10} colony-forming units of *Bifidobacterium infantis* NLS-SS	Daily for 3 weeks	12 active CD on a GFD	• Significant improvement of specific CD symptoms • No side effects were detected in either intervention

***CD: celiac disease; GFD: gluten-free diet; TNF: tumor necrosis factor; IgA: immunoglobulin A; CDA: celiac disease autoimmunity; IBS?

In a study by Medina et al., *Bifidobacterium bifidum* ES2 and *Bifidobacterium longum* ES1 suppressed the production of pro-inflammatory cytokines and increased the production of IL-10 (34). In another study, a mixture of gliadin-

digested fragments and *bifidobacteria* reduced the production of pro-inflammatory cytokines, such as IL-1beta, NFkB, and TNF-alpha (35). Some other studies have shown that certain probiotic strains can prevent the leakage of tight junction during inflammation and reduce gliadin-induced epithelial permeability (36, 37).

In a study carried out by Lindfors et al. to evaluate the effect of probiotics, including *Bifidobacterium lactis* and *Lactobacillus fermentum,* on human colon Caco-2 cells, they showed that *Bifidobacterium lactis* can restrain the toxic effects of gliadin on intestinal cell culture and reduce intestinal permeability, depending on the dose (38). The co-administration of gliadin with *Lactobacillus rhamnosus GG* rehabilitated barrier functions, zonulin release, and transepithelial resistance (39). In another study that examined a probiotic mixture (three different strains of *bifidobacteria* and two of *lactobacilli*) to hydrolyze gluten peptides, probiotic strains could reverse the production of gliadin-induced IL-6 and inhibited occludin and zonulin, being effective for CD patients (40). Olivares et al. in an in vivo study demonstrated that oral administration of *Bifidobacterium longum* CECT 7347 strain in gliadin-fed mice reduced inflammation. Their results confirm the beneficial effects of probiotics on CD, with a protective role in the intestinal mucosa (41). McCarville et al. indicated that *Bifidobacterium longum* NCC2705 produces a serine proteinase inhibitor which modulates gliadin-related immunopathology and prevents gliadin-induced inflammation in DQ8 mice (42). All these in vitro and in vivo studies reported the benefits of probiotics on the intestinal barrier, immune system, and digestion of gliadin peptides.

Human Studies

Even though several in vitro and in vivo animal studies have been conducted on the use of probiotics in CD, human trials data are still scant. As already discussed, intestinal dysbiosis is involved in the pathogenesis of CD. Thus, controlling the composition of intestinal microbiota through probiotics may lead to the regeneration of the intestinal microbiota to reduce the patient's symptoms and improve health. In this regard, various studies on probiotic supplements have used *Bifidobacterium* and *Lactobacillus* strains, as shown in Table 1. Studies demonstrated that *bifidobacteria* have the potential to improve symptoms in patients with CD on GFD and has an important role in reducing the harmful effects of gluten exposure (30, 43-55).

Conclusion

Studies have shown an association between altered intestinal microbiota and the development of CD, which may increase inflammation and intestinal permeability, and thus damage the mucosa. Although the root of this association has not yet been determined, it has been shown that *Lactobacillus* and *Bifidobacterium* levels are reduced in CD patients. Therefore, these bacteria can be used as probiotics in the treatment of CD. In the reviewed studies, it is discussed that probiotics can decrease mucosal inflammation and ameliorate the patient's symptoms by reducing the cytokines involved in the pathogenesis of CD. However, further studies with larger sample sizes can help to design guidelines for the management of CD and to increase knowledge about the importance and pathophysiology of probiotics administration in CD. Moreover, more randomized controlled trials are needed in order to prove these concepts in human studies.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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