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REVIEW

# Dysbiosis a risk factor for celiac disease

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**Abstract** Celiac disease remains one of the most challenging pathologies of the small intestine. It involves multiple pathogenic pathways and there are no disease-changing pharmacological agents available against it yet. The term microbiota refers to the community of microorganisms that inhabit a particular region of the body. Normal gut microbiota has a vital role in maintaining the intestinal homeostasis and promoting health. Celiac disease is associated with microbiota alteration, especially with an increase in the number of Gram-negative bacteria and a decrease in the number of Gram-positive bacteria. There is a strong relationship between intestinal dysbiosis and celiac disease, and recent studies are aimed at determining whether the celiac disease is a risk factor for dysbiosis or dysbiosis is for celiac disease. Therefore, the aim of this review was to assess the latest findings regarding the gut microbiota and its impact on the celiac disease, including therapeutic aspects.

**Keywords** Celiac disease · Intestinal microbiota · Dysbiosis · Probiotics

## What is known?

- The gut microbiota contains the microorganisms that, at a certain point, colonize the intestine.
- The role of gut microbiota is to maintain the physiological homeostasis of the intestine.

## What is new?

- The human leukocyte antigen genotype influences the gut colonization, while the gut microbiota alteration contributes to the risk of developing celiac disease (CD).
- Both duodenal and colonic dysbiosis are associated with CD.
- The bacterial virulence feature is considered higher in CD patients.
- Probiotics, such as *Bdellovibrio bacteriovorus, Lactobacillus spp*, and *Bifidobacterium*, could improve the management of the CD patients.

## Introduction

Celiac disease (CD) is an immune-mediated disorder affecting the small intestine, triggered by the ingestion of gluten-containing food in people who are genetically predisposed. It is known that the prevalence of HLA-DR3 and HLA-DQ2 genes in healthy subjects increases the risk of developing CD [1]. The gut microbiota contains the microorganisms that colonize the intestine at a certain point. The entire bacterial gut population is estimated to be around 35,000 bacterial species [2]. The role of gut microbiota is to maintain the physiological homeostasis of the intestine,

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and recent data highlight the implication of the microbiota in maintaining the host's health [3]. Recent data suggest that the intestinal microbiota plays a critical role in the pathogenesis of the gastrointestinal diseases [4]. We aimed to assess the latest findings regarding the gut microbiota and its impact on the CD using the studies from the "PubMed" online database published during 2008–2016. The keywords used for the search engine were "celiac disease" and "microbiota," which yielded 152 studies out of which 49 relevant studies were included.

## The HLA genotype influences gut colonization

De Palma G et al. conducted a cohort study on newborn infants having at least one first-degree relative with CD, which concluded that the Gram-negative bacteria and the ones from the Bacteroides–Prevotella group were significantly higher in the high-risk group than in the control group [5]. This revealed that the HLA-DQ genotype interferes with the gut colonization process. Moreover, the combination between the HLA-DQ allele and the milk-feeding type in infants has an impact on the subsequent gut colonization, breastfeeding having a protective role in CD pathogenesis due to the facilitation of the gut colonization of *Clostridium leptum, Bifidobacterium longum*, and *Bifidobacterium breve* in infants with HLA-DQ genotype [6]. Furthermore, the HLA-DQ genotype favors the staphylococcal colonization of the gut [7]. The prospective study conducted by Olivares et al. on healthy children with one first-degree relative with CD revealed that those at high-risk had a lower number of *Bifidobacterium spp* and significantly higher numbers of *Corynebacterium, Gemella*, and *Clostridium sensu stricto* [8]. Therefore, it is believed that the HLA-DQ genotype may influence the first gut colonizers, contributing to dysbiosis being a risk factor.

## Immunological aspects in celiac disease

In the gut lumen (Fig. 1), due to the digestion process, gliadin is formed, which is considered to be toxic to the epithelial cells of CD patients. Furthermore, gliadin is transported in the lamina propria mainly by transcellular pathways [9]. From that point, tissue transglutaminase (tTG) causes the deamidation of gliadin-resulting peptides, which are taken by the antigen presenting cells (APC) more efficiently than its precursors, thus resulting in increased immunogenicity [10]. The genetic factors also play a role. For example, it has been described that the DQB1*02 homozygous genotype provokes a stronger response from the CD4+ helper T cell than the heterozygous genotype [9]. In addition to this, the tTG-gliadin complexes are presented to CD4− T

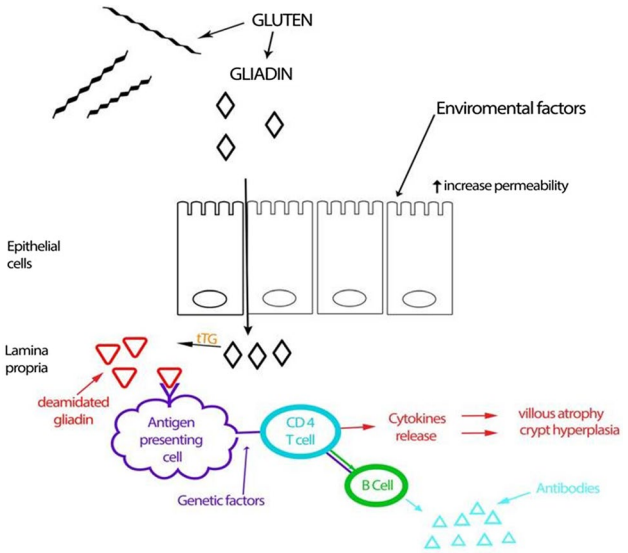


**Fig. 1** Immunological aspects in celiac disease

cells, resulting in the synthesis of antibodies against both tTG and deamidated gliadin. Moreover, the release of pro-inflammatory cytokines, such as Interferon gamma (IFNγ), IL-15, IL-18, and IL-21, has an impact on CD pathogenesis. The previous cytokines are responsible for the villous atrophy, crypt hyperplasia, and intraepithelial lymphocytes accumulation [11]. Another important factor is the increased permeability caused by environmental factors, such as: the amount of gluten and the time of gluten introduction, and the acquired infections [12].

## Dysbiosis, the possible pathogenetic role in CD

Studies suggest that microbiota alterations play a role in the pathogenesis of not only CD, but other diseases, such as: non-alcoholic fatty liver disease, hepatic encephalopathy, irritable bowel syndrome, inflammatory bowel disease, metabolic syndrome, cardiovascular disease, obesity, autoimmune disorders, such as type 1 diabetes, and rheumatoid arthritis [13–16]. One piece of evidence demonstrating the role of gut dysbiosis was concluded after the Swedish CD epidemic (2004–2007) when a study conducted by Ou G et al. revealed that rod-shaped bacteria (*Clostridium spp, Prevotella spp*, and *Actinomyces spp*) was a risk factor for developing CD, contributing to incidence increase of CD during that period [17].

Cinova et al. conducted a study on germ-free rats that were infected with various bacterial strains, which were isolated from CD and healthy subjects, in the presence of gliadin and IFN- γ known as CD triggering factors [18]. It was found that, in the presence of CD triggering factors

with *Escherichia coli* CBL2 or *Shigella* CBD8, the number of goblet cells in the small intestine was significantly lower resulting in the alteration of the intestinal barrier and tight junctions. However, gliadin and IFN-γ incubated with of *Bifidobacterium bifidum* IATA-ES2 promoted the increase in number of goblet cells. Moreover, *Bifidobacterium bifidum* augmented the production of inhibitors of metalloproteinases and chemotactic agents, enhancing the protection of the intestinal barrier. The microbiota of CD patients alters the gene expression of Toll-like Receptor 2, T Toll-like Receptor 9, and the Toll interacting protein, sustaining the pathogenic role of dysbiosis [19]. Moreover, changes in the duodenal microbiota lead to the alteration of the mucosal receptors, thus resulting in increased expression of IL-10 and IFN-γ, which are partly caused by increased TLR9 expression [20]. Furthermore, the gut microbiota components interact and influence the maturation of dendritic cells in the small intestine causing variations in its interactions with epithelial cells [21]. The dysbiosis produced by CD-associated bacteria could be a risk factor for CD, either by promoting the inflammatory response to gluten or, directly, by affecting the mucosal inflammation response [22].

Antibiotic use can lead to intestinal dysbiosis [23]. Marild et al. conducted a study on 2,933 CD patients matched for age and sex with 28,262 controls. A positive correlation between antibiotic use, and subsequently, CD was found [odds ratio (OR) = 1.40; 95% confidence interval (CI) = 1.27–1.53]. Therefore, dysbiosis may play a role in the early pathogenesis of CD [24]. Furthermore, Galipeau et al. conducted a study on mice with the DQ8 human gene revealing that, in subjects with genetic susceptibility, dysbiosis is a risk factor for CD [25]. A more recent study conducted on germ-free C57BL/6 mice colonized with bacteria isolated from CD or healthy subjects showed that *Pseudomonas aeruginosa* produced better intestinal barrier translocating peptides, thus resulting in activating the gluten specifying T cells from CD patients. On the contrary, *Lactobacillus spp*. diminished the immunogenicity of both gluten peptides produced by humans and of *Pseudomonas aeruginosa* proteases by degrading them [26]. A study conducted in 2016 by Caminero et al. focused on how the duodenal bacteria from both healthy and CD patients influence the metabolization of gluten. The study showed that, unlike the germ-free mice, the altered Schaedler flora colonized mice indicated PQP cleavage, thus showing the existence of a correlation between specific bacterial cleavage and the variety of gliadin peptides formed during digestion. Furthermore, *Pseudomonas aeruginosa* isolated from the duodenum of a CD patient due to elastase activity produces immunogenic peptides *P. aeroginosa* responsible for the activation of gluten specific T cells in HLA-DQ 2.5 + CD patients. The degradation peptides produced by, although having a shorter chain of amino acids, resulted in the immunogenicity being higher, thus resulting in similar responses as the 33 mer parent peptide. Moreover, the reduced size of the peptides facilitates passing through the epithelial barrier, enhancing the immunogenicity. Furthermore, the role of LasB elastase secreted by *P. aeroginosa* as a gluten-degrading enzyme has been demonstrated. However, in the presence of *Lactobacillus* strains, the *P. aeroginosa* produced peptides are further proteolyzed, resulting in decreased immunogenicity, thus exposing the relationship between probiotics and pathobionts. These findings show how the pathogenic bacteria can influence the CD risk in genetically susceptible individuals. Duodenal dysbiosis influences the host–microbe interactions, including the microbe–macrophage–neuronal communication and diet–microbe–host metabolic exchanges. Therefore, the pathophysiological pathways of CD are complex and still remain unclear [27]. There is a need for more studies in vivo/vitro to clarify the spectrum of interactions between dysbiosis and CD [4, 28, 29].

## Characteristics dysbiosis in CD

Virulence features are considered higher in CD patients. For example, the prevalence of virulence genes of the *Escherichia coli*, such as P fimbriae (papC), capsule K5 (sfaD/E), and haemolysin (hlyA), was higher in CD patients than in healthy subjects [30]. Furthermore, the prevalence of methicillin-resistant (mecA) and adhesion altE virulent genes was higher in *Staphylococcus spp* isolated from CD patients than in healthy subject [31]. Other bacterial species [32, 33] isolated from CD patients are presented in Table 1.

The microbiota of CD patients is characterized by an increase in Gram-negative bacteria and a decrease in Gram-positive bacteria [34]. As shown in Table 1, many studies [35–38] have shown that there is a difference in the composition of microbiota in healthy and CD patients. However, the gut microbiota is also influenced by other factors. Nistal et al. conducted a study to compare the differences between intestinal bacterial populations in adults and children with or without CD [39]. It was shown that factors, such as age or a gluten-free diet (GFD), influence the microbiota of the CD patients. First, the GFD diet is one of the aspects that must be considered given that a diet without gluten interferes with the gut bacterial population [40]. After a GFD, the gut microbiota is partially restored. However, a decrease has been reported in the diversity of *Lactobacillus spp* and *Bifidobacterium spp* in the CD patients going under a GFD [41]. After a GFD, the number of *Escherichia coli spp* and *Staphylococcus spp* was restored to normal in CD patients [12]. Furthermore, there were no differences between the fecal pH of patients with CD and healthy

**Table 1** Bacterial species frequently isolated from CD patients

| Authors | Year | Number of subjects | | | | Method of determination | Findings |
|---|---|---|---|---|---|---|---|
| | | CD patients | Control | Symptom Free CD patients | CD patients on GFD | | |
| Ou et al. [17] | 2009 | 45-duodenal biopsy | 18-duodenal biopsy | | | 16S rDNA sequencing<br>Scanning electron microscopy | *Clostridium, Prevotella*, and *Actinomyces spp* numbers were higher in CD patients than controls |
| Collado et al. [32] | 2009 | 30-fecal samples<br>25-duodenal biopsy | 30-fecal samples<br>8-duodenal biopsy | | 18-fecal samples<br>8-duodenal biopsy | PCR | *Bacteroides* and *Clostridium leptum* were more abundant in CD patients than in controls; *E coli* and *Staphylococcus spp*. numbers normalized after treatment |
| Sanchez et al. [30] | 2010 | 20-fecal samples | 20-fecal samples | 20-fecal samples | | PCR<br>DNA sequencing | *Staphylococcus spp* were more diversified in CD patients than in symptom free and control groups<br>*S. Epidermidis* carrying the mecA/mecA and altE gene was more frequently isolated from CD patients (active and symptom free) than in control groups |
| Schippa et al. [33] | 2010 | 20-duodenal biopsy before and after GFD | 10-duodenal biopsy | | 20-duodenal biopsy (before and after GFD) | 16 S rDNA sequencing | *Bacteroides vulgatus* and *Escherichia coli* were more frequent indentified in CD patients than in controls |
| Di Cagno et al. [34] | 2011 | | 19-duodenal biopsy and fecal samples | | 15-duodenal biopsy and fecal samples | PCR-denaturing gradient gel electrophoresis | *Bacteroides spp, Staphylococcus spp, Salmonella spp, Shighella spp*, and *Klebsiella spp* numbers were higher in CD patients than in controls<br>*Lactobacillus spp, Enterococcus spp, and Bifidobacteria spp* numbers were significantly lower in CD patients than in controls |

**Table 1** (continued)

| Authors | Year | Number of subjects | | | | Method of determination | Findings |
|---|---|---|---|---|---|---|---|
| | | CD patients | Control | Symptom Free CD patients | CD patients on GFD | | |
| Sanchez et al. [35] | 2013 | | 8-duodenal biopsy | 17-duodenal biopsy | 32-duodenal biopsy | 16 S rRNA gene sequencing | *Klebsiella oxytoca, Staphylococcus epidermidis*, and *Staphylococcus pasteuri* numbers were higher in CD patients than in controls, in spite of a GFD<br>*Streptococcus anginosus* and *Streptococcus mutans* groups were less abundant in CD patients than in control group |
| Francavilla et al. [36] | 2014 | | 13-saliva samples | | 13-saliva samples | Gas chromatography-mass spectrometry-solid-phase microextraction | *Bacteroidetes phylum* was more abundant in CD patients than in controls<br>*Actinomyces spps, Atopobium spps*, and *Corynebacterium durum* were less abundant in CD patients than in controls |
| Giron Fernandez-Crehuet et al. [37] | 2016 | 11-duodenal biopsy | 11-duodenal biopsy | | | PCR-denaturing gradient gel electrophoresis | *Lactobacillus genus* was significantly reduced in richness, diversity, and habitability in the samples isolated from CD patients |
| Argenio et al. [38] | 2016 | 20-duodenal biopsy | 15-duodenal biopsy | | 6-duodenal biopsy | 16 S ribosomal RNA DNA sequencing | *Proteobacteria phyla* numbers were higher in CD patients than in controls. *Firmicutes* and *Actinobacteria* were the most depleted phyla in CD patients<br>*Neisseria spp* were significantly more abundant in CD patients than in controls |

subjects. Nonetheless, the lower levels of *Bifidobacterium spp* in the gut microbial composition of CD patients will promote the pathological process of the disease [42]. In spite of a GFD, persistent gastrointestinal symptoms may be correlated with an unbalanced composition of duodenal microbiota [43]. Moreover, the extra-gastrointestinal symptoms such as dermatitis herpetiformis, and anemia, describe a particular microbiota composition. Wacklin P et al. conducted a study on 33 CD patients with different symptoms and 18 control subjects. The CD patients group was more abundant in *Proteobacteria phylum*, while the CD patients with dermatitis herpetiformis and controls were more abundant in *Firmicutes phylum*, suggesting the role of duodenal dysbiosis in disease manifestation [44].

Other significant factors to consider are diet changes, infant infections, and antibiotic use [45]. In infants at risk of developing CD, infections and antibiotic intake in the first 4 months of life are correlated with lymphocyte subpopulations and microbiota alteration [46].

## Microbiota as a powerful tool in therapy

Commensal bacterial species are vital to maintain gut immunological homeostasis; therefore, the identification of immunomodulatory species represents a potential tool in reversing gut dysbiosis [47].

### Mechanism of action of probiotics

The probiotics are in direct competition with the pathogens not only for nutrients and prebiotics, but also for the adhesion sites (Fig. 2). Therefore, the probiotics are inhibiting the proliferation of pathogens. Furthermore, some probiotics, such as *Saccharomyces boulardii*, are able to block toxin receptors or have even direct toxin destruction effect [48]. *Bifidobacterium* and *Lactobacillus* strains secrete short chain volatile fatty acids, hydrogen peroxide, and antibacterial peptides (lactocidin, acidophilin, and lactacin B). Therefore, the intraluminal pH is reduced and the proliferation of pathogenic bacteria is diminished [49, 50]. Enhanced barrier function is the result of promoting the expression of epithelial growth factor receptor (EGF-R) and heat-shock proteins (hsp 25, hsp 27). Moreover, it has been demonstrated that some strains of probiotics, such as *Lactobacillus GG, Bifidobacterium lactis*, and *Saccharomyces boulardii*, are responsible for humoral modulation by inducing the expression of TGFβ, IL-10, and IL-6, which will further promote the B-cell maturation in favor of IgA secretion. In addition to this, probiotics also promote the up-regulation of Ig receptors on the basolateral surface of intestinal epithelial cells, thus increasing the Ig A transcytosis in the gut lumen [50]. However, probiotics produce a series of different effects depending not only on the strain used but also on dosage, route of administration, and frequency. Therefore, strain selection into combined therapies could improve the future aspects in the treatment of bowel diseases [51].

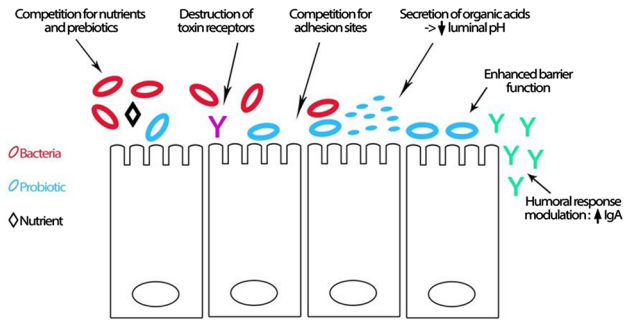


**Fig. 2** Mechanism of action of probiotics

### The need for probiotic supplements for CD patients

Iebba et al. conducted a study on 92 pediatric subjects, healthy, or suffering from CD or inflammatory bowel disease or cystic fibrosis, which disclosed that *Bdellovibrio bacteriovorus* was heavily decreased in patients suffering from CD or inflammatory bowel disease, thus sustaining the role of *B. Bacteriovorus* as a potential probiotic to restore the gut immunological homeostasis [52]. Latest findings revealed that *Lactobacillus spp* and *Bifidobacterium spp* are considered to have a favorable impact on gliadin-damaged epithelial cells [53]. Furthermore, Olivares et al. conducted a double-blind, randomized, placebo-controlled trial on 33 newly diagnosticated pediatric CD patients to assess the beneficial effects of *Bifidobacterium longum CECT 7347*. It was shown that *Bifidobacterium longum* CECT 7347 reduced the intestinal inflammatory response supported by the decrease of sIgA in fecal samples [54]. Therefore, *Bifidobacterium longum* CECT 7347 could improve the intestinal bacterial balance in CD patients. Moreover, *Lactobacillus rhamnosus* and *Lactobacillus paracasei* strains isolated from the feces of healthy children could be designed as probiotic supplements to promote the health of CD patients [55]. Another double-blinded, placebo-controlled trial on 46 CD children under GFD divided into two groups and 18 subjects in the control group, conducted by Klemenak M et al. evaluated the anti-inflammatory cytokine interleukin 10 (IL-10) and pro-inflammatory cytokine tumor necrosis factor alpha (TNF-α) serum production after receiving the probiotic strains *Bifidobacterium breve* BR03 and B632. It has been showed that, after receiving the probiotic strains for 3 months, the serum levels of TNF-α and IL-10 were decreased. *Pseudomonas aeruginosa* could also represent a potential tool

in the therapy of CD [56]. Wei G et al. conducted a study aiming to isolate potential bacteria with gluten-degrading activity, demonstrating the therapeutic role of pseudolysin (lasB) produced by active *Pseudomonas aeruginosa* strains [57].

### Parasite infections and its effects on immunomodulatory responses

Another direction in the management of CD is represented by parasite infections and its effects on immunomodulatory responses [58]. Croese J et al. conducted a study on 12 CD patients inoculated with *Necator americanus* larvae undergoing a gluten-diet [59]. It was revealed that helminths promote tolerance to gluten among CD patients. Furthermore, hookworms are responsible for the enrichment in bacterial species, aspect that could explain the regulation of gluten-induced inflammation made by hookworms [60].

## Gluten-free diet and lifestyle in celiac disease patients

The commensal microbiota is a result of the influence of lifestyle variations, such as developments in food refining process and the presence of various infectious factors. The additives and chemical substances used in food processing have modified the gut microbiota, in favor of more aggressive bacterial strains [61]. Furthermore, a diet high on proteins and saturated fats will reduce the Bacteroidetes:Firmicutes ratio. High fat diets alter the gut microbial composition by decreasing the number of both Gram-positive and Gram-negative bacteria. Studies have shown that non-dietary lifestyle factors, such as smoking, obesity, and sedentariness, influence the gut microbiota. Moreover, stress by influencing the gut-brain axis alters the microbial population of the gut [62]. The therapeutic management of CD implies a strict adherence to GFD. However, studies have shown that in spite of a GFD, fecal, and duodenal dysbiosis is present in both treated and untreated CD patients. The link between oral, intestinal microbiota, and CD has not yet been established; therefore, further studies are needed to improve the content of gluten-free food for a better therapeutic approach towards celiac disease [63].

## Conclusions

Dysbiosis and the HLA genotype have a certain role in the pathogenesis of CD. However, the mechanisms are intricate. On one hand, the HLA genotype influences the gut colonization, while the gut microbiota alteration contributes to the risk of developing CD. Moreover, both duodenal and colonic dysbiosis are associated with CD. The most frequent Gram-negative bacterial species isolated from CD patients were: *Bacteroides spp, Salmonella spp, Shighella spp, Klebsiella spp, Neisseria spp*, and *Prevotella spp*. Although CD is associated with a decrease in the number of Gram-positive bacteria, pathogenic Gram-positive species, such as *Clostridium spp, Staphylococcus spp, and Actinomyces spp*, could be isolated from CD patients. Furthermore, bacterial virulence features are considered higher in CD patients. Efforts, to date, on the effect of microbiota in the therapy of CD studies have shown that the use of probiotics for instance, *Bdellovibrio bacteriovorus, Lactobacillus spp* and *Bifidobacterium* could improve the management of the patients.

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**Compliance with ethical standards**

**Conflict of interest** None.

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