Review Article

Gut Microbiota Dysbiosis in Celiac Disease, Exploring the Probiotic Solution

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Abstract

The gut microbiome significantly influences human health and disease, especially autoimmune disorders. During illness, the gut microbiota (GM) composition changes (dysbiosis), leading to disrupted communication between immune cells and microbiota, which can cause infections and activate autoimmune disorders. Gut bacteria are isolated from their host by a physical barrier, such as the epithelium lining the gut or the skin. Bacterial components such as lipopolysaccharides and bacterial antigens may stimulate an inflammatory response by activating and stimulating immune cells. Numerous variables influence the intestinal microbiota, including diet, age, geographical location, mode of delivery, antibiotic or probiotic consumption, and various medical conditions. Celiac disease (CD) is an immune-mediated enteropathy that exhibits gluten sensitivity and induces an immune response upon gluten consumption. Children with CD typically exhibit abdominal distension, diarrhea, and failure to thrive. Extraintestinal signs may include anemia, tiredness, arthritis, infertility, liver failure, neuropathy, schizophrenia, or autism. This review provides a potential explanation of the GMs role in CD.

Keywords: Celiac disease, dysbiosis, gut microbiota, microbiota, probiotics

Introduction

Celiac disease (CD) is characterized by a dysregulated immune condition triggered by consuming gluten and similar proteins in barley and rye in genetically predisposed individuals.[1,2] This condition is characterized by damage to the mucosal lining in the upper part of the small intestine, caused by the immune system's T-cells selectively destroying the mucosal epithelial cells.[3]

Research has demonstrated that the gut microbiome can influence alterations in the emergence of autoimmune disorders, highlighting the significant role of the host microbiome in affecting autoimmunity.[4] Healthy individuals possess a diverse reservoir of beneficial symbiotic bacteria, contributing to maintaining gut homeostasis.[5] These symbiotic microorganisms actively metabolize undigested food, assimilate essential nutrients, and synthesize valuable compounds that contribute to the maintenance of optimal gut health. Furthermore, they employ diverse mechanisms to uphold the gut mucosal barrier's structural integrity, impede the proliferation of pathogenic bacteria, as well as modulate the immune responses of the host.[6] It is believed that autoimmune diseases like CD might arise when there is a disruption to the healthy gut microbiota (GM), a condition known as gut dysbiosis.[7] Many factors such as genetics, nutrition, lifestyle, environmental pollutants, and restricting hygiene practices can lead to gut dysbiosis by disrupting the balance between beneficial bacteria and harmful bacteria, shifting toward an inflammatory condition.[8]

This narrative review explores the effect of probiotics on the GM of individuals with CD. Published papers in 2003 were identified using the keywords "gut microbiota," "microbiota," "celiac disease," "probiotics," and "dysbiosis" on Google Scholar, PubMed, and Web of Science. Additional articles were included after manually searching the references from the selected articles.

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Understanding Gut Microbiota

The microbiome of the gut is a population of organisms, including bacteria, archaea, fungi, and viruses that inhabit the digestive tract.[9,10] Along the gastrointestinal system, different parameters such as pH, oxygen levels, nutritional availability, digestion rates of flow, and release enzymes influence the diversity and quantity of bacteria. Notably, the stomach's bacterial content is only 10 CFU/g., but it progressively increases to 10^7 CFU/g in the ileum and further to 10^{12} CFU/g in the colon.[11] Aerobic bacteria predominantly inhabit the upper digestive tract, whereas anaerobic bacteria primarily reside in the lower digestive tract. The human digestive tract is home to main clusters from five phyl: Firmicutes (79.4%; including Ruminococcus, Clostridium, and Eubacteria), Bacterioidetes (16.9%; including Porphyromonas, *Prevotella*), Proteobacteria (1%), Actinobacteria (2.5%; including *Bifidobacterium*), and Verrucomicrobia (0.1%)[12,13] There are three main bacterial groups in the proximal intestine: Helicobacter, Lactobacillus, and Veillonella. While Bacilli, Streptococcaceae, and Actinomycinaeae are the most abundant in the duodenum, jejunum, and ileum, Lachnospiraceae and Bacteroidetes prevail in the colon.[14] GM controls multiple metabolic pathways in the host, such as those related to the control of energy, glucose metabolism, and lipid processing.[14] Due to its extensive metabolic functions, GM is frequently referred to as "a novel virtual metabolic organ."[15]

Previous studies have demonstrated the crucial roles of GM in the breakdown and absorption of nutrients,[11] including the production of short-chain fatty acids, amines, phenols, and sulfurous compounds,[16] as well as the synthesis of Vitamin B and Vitamin K.,[17] The bioavailability of minerals and bile acid metabolism are directly impacted by the equilibrium of microbiota.[18] Maintenance of a balanced microbiota plays a critical role in protecting against pathogens and constitutes a fundamental aspect of the host's immune system.[19] GM profile varies among various races/ethnicities and sex/gender.[20] Antibiotic use, particularly in the early years of life, affects the unique microbiota composition of an individual,[21,22] The composition, species, and variety of bacteria found in the digestive tract are influenced by various factors. These factors encompass chronic stress, infections, and the use of pharmaceuticals such as nonsteroidal anti-inflammatory medicines. Furthermore, the makeup of the human digestive system's bacterial community is impacted by host genetics, level of physical activity, personal hygiene, and xenobiotics.[23] Nutrition has a crucial role in health, including the composition of the diet, dietary patterns, and long-term eating behaviors such as consuming snacks and junk food, eating late at night, and missing breakfast,[24,25]

Celiac Disease

CD is a prevalent autoimmune condition triggered by the consumption of gluten in people with a hereditary predisposition.[26] CD has a prevalence of 1.4% based on serological test results and 0.7% based on biopsy results, with changes depending on age, sex, and geography. CD disorder is more prevalent in children than in adults and in females than in males.[27] This disease mostly impacts the small intestine but presents a wide range of clinical symptoms, including both intestinal and extraintestinal signs.[28] Merely 1%–1.5% of the worldwide population display the CD phenotype among 30%–40% of them have the HLA DQ2/DQ8 genotype. This suggests that disease may develop as a result of other variables, such as diet and environment.[29]

Gluten is a protein that is used in large amounts by people. It consists of gliadin, a protein that is abundant in prolines and glutamines and is difficult to complete digestion by intestinal enzymes,[30,31] The key event in the development of CD is the activation of a specific immune response against gluten. This response is influenced by interaction between molecules like peptides originating from wheat being the main environment component, the HLA-DQ2/8 locus being the major genetic predisposing factor, and transglutaminase 2 (TG2) is a specific autoantigen for CD.[32] Gliadin peptides induce a natural immune response in the intestinal lining, promoting enterocytes to produce more interleukin-15 (IL-15). This leads to the stimulation of intraepithelial lymphocytes expressing the NK-G2D activating receptor, a marker for natural killer cells.[33] Upon exposure to gluten, T cells become activated and elicit different molecules that promote inflammation, including interferon-gamma, IL-21. This proinflammatory cytokine release initiates mucosal inflammation, leading to direct harm to the epithelium and ultimately resulting in atrophy of villi within the small gastrointestinal tract.[34]

Moreover, specific T cells prompt B cells to produce antibodies that target DGP and TTG2.[35,36] As a result, this adaptive T-cell response is essential for the onset of CD.[37] Apart from gluten, imbalances in the gut flora microbiota could also be a contributing environmental factor that triggers CD.[38] The intestine microbiota in healthy individuals has an impact on preserving the integrity of the intestinal barrier, enhancing nutrition metabolism and absorption, modulating immune responses, antiaging, cancer prevention, and cancer suppression.[39] Research has indicated that individuals diagnosed with CD exhibit an alteration in their GM. This is typified by a decline in the variety and diversity of beneficial commensal organisms, coupled with an increase in pathogenic microorganisms. Notably, coeliac disease is associated with gut dysbiosis, marked by the proliferation of pathobionts displaying virulent traits.[40] The Bacteroides genus is an integral component of the human GM and is generally regarded as a symbiont. However, certain species within this genus have been implicated in the disruption of the integrity of the intestinal epithelial barrier, resulting in proinflammatory effects.[41]

Studies conducted in both pediatric and adult populations have indicated an elevation in Gram-negative bacteria, including Bacteroides, *Prevotella* species, and *Escherichia coli*. This

elevation has been associated with diminished levels of beneficial anti-inflammatory bacteria, such as bifidobacteria and *Lactobacilli*.[42] The gut microbiome impacts the onset and development of coeliac disorder by triggering mechanisms such as the initiation of mucosal inflammation, regulation of epithelial barrier function, and stimulation of the innate immune system.[43] Gliadin may disrupt the balance between intestinal microbiota and the human body in individuals with CD. A substantial quantity of undegraded gliadin is transported from the oral cavity and stomach to the small and large intestines, where it serves as a rich source of nourishment for diverse bacterial populations in the intestinal milieu. This process promotes the proliferation of bacteria that degrade gliadin, leading to a disruption in the equilibrium of intestinal flora.[28] Moreover, although a gluten-free diet (GFD) resulted in clinical improvements for the majority of individuals with CD, a subset of patients did not experience relief with GFD.[42] People who have CD and have been on a GFD for a long time have a different mix of microbes in their guts. There are big differences between people who have classic gastrointestinal symptoms (such as losing weight, having diarrhea, or having an enlarged abdomen) and people who have extraintestinal symptoms (such as anemia, not absorbing iron, folate, vitamin D, or calcium, or being short).[26]

Most cases of CD mostly affect the upper part of the small intestine but can also spread into the lower part known as the ileum to varying degrees. It was established that 66.6% of patients diagnosed with coeliac disease exhibited mucosal alterations that extended to the proximal small intestine.[44] Intestinal mucosal atrophy is more widespread and severe in patients with extraintestinal symptoms at diagnosis than in those with gastrointestinal symptoms alone. When this happen, the microbiota in your small intestine and colon will change significantly.[43]

The Immune System and the Host's Homeostasis in Relation to Infectious Diseases

The GM plays a crucial role in maintaining optimal immune function. Furthermore, the GM and immune system are strongly connected to various physiological functions including metabolism, behavior, the activity of the digestive tract, respiratory, and neurological systems.[45] Alteration in the gut microbial population using antibiotics or microbiota reconstitution demonstrates the significant impact of GM on immunological homeostasis.[46] A recent study documented that neonates with an enriched population of erythroid cells have a significant impact on the maintenance of an immunoregulatory environment and the prevention of mucosal inflammation subsequent to microbiota colonization.[47] Conversely, commensal bacteria and their metabolites exert influence on the homeostasis, functioning, and development of innate and acquired immunity. Consequently, the GM is implicated in the clinical manifestations, progression, and susceptibility to developing CD.[48] Gastrointestinal innate immune cells develop tolerance to commensal bacteria through the identification of harmful pathogens and the subsequent prevention of their entry from the gut cavity into the bloodstream. Once bacteria and pathogen-associated molecular patterns (PAMPs) transport through the epithelial barrier, they can trigger goblet cells to secrete mucin and stimulate a rapid restoration of the inner mucous layer.[49] In addition, PAMPs have the ability to stimulate innate immune responses by activating toll-like receptors on macrophages and neutrophils.[50]

A study discovered that germ-free rats were showing decreased phagocytic activities in their peripheral blood neutrophils due to defective superoxide anion and nitric oxide production.[51] During clinical disease, variations in the intestinal microenvironment lead to increased proliferation of opportunistic pathogens and decreased levels of commensal bacteria, resulting in GM dysbiosis and an imbalanced immune response.[52] When neutrophils are excessively involved in an inflammatory or infectious process, they can increase the generation of matrix metalloprotease, secretion of proinflammatory cytokines, and pathologic activation of immune cells, all of which can lead to collateral mucosal injury.[50] Intestinal mucosal immunity is significantly influenced by secretory immunoglobulin A (IgA) which is produced by the gut mucosa. IgA helps to eliminate pathogens and support the beneficial relationship between the host and microbes that is mediated by the microbiome. For example, Bacteroides fragilis modifies its surface to promote the binding of IgA *in vivo* which aiding in bacterial adhesion. The diversity of IgA associated with the GM is correlated with both T-cell-dependent and T-cell-independent processes.[51]

How Does Disturbed Gut Microbiota Affect the Development of Celiac Disease?

The GM is responsible for several tasks, one of which is participating in the metabolism of gluten. *Bifidobacterium* species and *Lactobacilli* are responsible for the breakdown of gluten and related peptides, which results in a reduction in the immunogenic action of gluten and its peptides. Thus, *Lactobacilli* and *Bifidobacterium* spp. have the potential to be utilized as supplementary therapy for people with CD, as they possess proteolytic and peptidolytic activity, aiding in the degradation of gluten.[53] On the other hand, harmful microorganisms such as Pseudomonas aeruginosa can enhance the ability of gluten-derived peptides to trigger an immune response.[54] Alterations in the composition of the intestinal microbiota may lead to an increased permeability across intestinal epithelial cells by inducing disruptions in the intestinal barrier, compromising zonulin, a protein that regulates tight junctions. These zonulin-related changes have been associated with the development of CD.[55] Gliadin and microbes are two crucial elements that enhance the development and secretion of zonulin, as part of a typical physiological condition.[56] Dysbiosis disturbs tight junctions by upregulating the secretion of zonulin, leading to an increase in epithelial

permeability. Due to the increase in permeability, a greater number of partially digested gliadin peptides can pass through into the lamina propria.[57] In addition, the commensal flora has a substantial function in controlling the defense mechanism and metabolic process.[58] Serena *et al*.[59] showed that the intestinal microbiome enhances the likelihood of autoimmunity through epigenetic mechanisms. The intestinal microbiota has a role in the development of CD by influencing the immune system, gluten digestion, and intestinal permeability, as previously mentioned. The restoration of the GM is not fully achievable by GFD treatment alone, necessitating the use of additional therapeutic approaches to deal with dysbiosis in patients with CD. Probiotics can restore homeostasis and could be a valuable resource for additional therapy of CD. Probiotics can be utilized by either supplementation or the consumption of pretreated foods that have been enhanced with probiotic strains.[60]

Probiotics and Prebiotics

Probiotics, as defined by the World Health Organization, are living microbes that have positive effects on the individual when consumed in enough amounts as part of food.[61] Probiotic supplementation may serve as a preventative measure to preserve optimal intestinal microflora health. Probiotics are acknowledged as a therapeutic method for preserving health and preventing various diseases. They can help regulate the immune system and treat conditions such as atherosclerosis, arteriosclerosis, cancer, *Helicobacter pylori* infections, lactose intolerance, atopic dermatitis, diarrhea, constipation, candidiasis, and urinary tract infections.[62] Probiotics are currently extensively promoted as additional and functional food items, including cheese, ice cream, yogurt, chocolates, and nondairy food products.[47] Probiotics function in the body by manipulating the populations of microorganisms in the intestines, suppressing harmful pathogens, promoting the growth and specialization of cells that line the intestines, and strengthening the protective barrier of the intestines.[63] Probiotics primarily consist of Lactobacillus and *Bifidobacterium* species that produce lactic acid. However, it has been noted that not all probiotics are universally good in all conditions. Therefore, it is considered to be an effective method for the treatment of a condition to make a careful selection of a certain organism to get the desired clinical outcome.[47]

Prebiotics are indigestible components of food that promote the growth and activity of specific beneficial bacteria in our bodies, such as *Lactobacilli* and *Bifidobacteria*. This contributes to our health and helps maintain a stable level of energy. They alter the microbiota, restoring and/or maintaining eubiosis or normobiosis, to reduce the risk of dysbiosis and associated gastrointestinal pathologies.[64] So far, fructo-oligosaccharides, oligo-fructose, and inulin have been the most extensively researched prebiotics.[47] An arabinoxylan is a kind of hemicellulose found in the cell wall of plants, where it serves a structural function. Dietary fiber can be found in both soluble and insoluble forms, whereas fructans are exclusively found in soluble dietary fibers.[47] According to reports, prebiotics are able to relieve constipation, promote weight gain or loss, keep blood glucose and lipid levels stable, and even fight cancer.[65] Because prebiotics are substrates that are selectively fermented, they promote the growth and activity of the microorganisms of interest, which in turn produces the desired health effects in the host.[66]

A combination of probiotics and prebiotics, referred to as synbiotics, has been used for a beneficial impact. As an example, the microbiota was changed from Clostridium perfringens to *Lactobacillus* and *Bifidobacterium* when oligofructose-enriched inulin, *Lactobacillus rhamnosus*, and *Bifidobacterium lactis* were combined.[67] This seems to work better than either probiotics or prebiotics used alone, as shown in *in vitro* tests[68] but more studies must be done on humans.[69]

Probiotics May Serve as a Potential Treatment for Celiac Disease

Probiotics are considered an ideal therapy for CD because they can regulate the gut flora and immune response.[70] Probiotics have the potential to change the composition and functions of the microbiota in people with CD. This could lead to a delay in the beginning of illness or even prevent it. This therapy can affect the defense mechanism, break down receptors for toxic substances, compete for dietary components, block attachment sites, and produce chemicals that inhibit pathogens.[29] Additional research has indicated that certain strains of probiotics, such as Lactobacillus and *Bifidobacterium*, are depleted in individuals with CD, emphasizing the potential of probiotics in maintaining a healthy intestinal microbiota.[3] Based on current research, it is suggested that probiotic supplements could affect the development of CD through three mechanisms: breaking down gluten proteins, preserving the intestinal barrier to prevent harmful polypeptides from reaching the deeper layers of the intestine, and restoring a balanced microbial environment in the gut.[71] In contrast, prior research using VSL#3 in CD demonstrated that several bacterial species such as *Bifidobacterium infantis*, *Bifidobacterium thermophilus*, *Lactobacillus acidophilus*, *Lactobacillus casei, Lactobacillus delbrueckii* spp., and *Bulgaricus* – were capable of reducing the toxicity of wheat flour throughout long-term fermentation. This effect was attributed to the complete hydrolysis of gliadin by these microorganisms.[72]

Smecuol *et al*.[60] examined the impact of administering *B. infantis* natren life start strain to CD patients who were following a diet that included gluten. He noticed that there was an increase in intestinal permeability. The lack of change in intestinal permeability after probiotic therapy could be due to either an insufficient dose or a short duration of administration. However, it did improve gastrointestinal symptoms, such as better digestion and reduced constipation. In addition, a study conducted on newly diagnosed children with CD examined the

impact of a GFD supplemented with *Bifidobacterium longum* CECT 7347 over a period of 3 months. The intervention effectively reduced the levels of CD3 T-cells, the Bacteroides fragilis group, and IgA in stools, contributing to an overall improvement in symptoms among patients with CD.[73] A study conducted in Argentina confirmed the impact of probiotics on symptoms of CD by observing notable changes in the quantity of Lactobacillus strains in symptom-free children with CD, five distinct strains of *Lactobacilli* were identified in the feces of healthy children, among them, *Lactobacillus rhamnosus* and *Lactobacillus paracasei* were identified as optimistic probiotic strains due to their notable resistance to the situations of the gastrointestinal system.[74]

Furthermore, Klemenak *et al*.[75] demonstrated the beneficial impact of B. breve strain treatment to reduce the production of cytokines li TNF-α in children with CD on a GFD. In addition, it was discovered that *Bifidobacterium longum* CECT 7347 treatment led to a reduction in peripheral CD3+ T lymphocytes and a minor decrease in TNF.

In 2019, a study conducted by Håkansson *et al*.[76] found that the daily consumption of *Lactobacillus plantarum HEAL9* and *Lactobacillus paracasei* 8700:2 for 6 months resulted in alterations in the immune system of 78 children with CD, the variation in the majority of lymphocyte subsets identified in the placebo group closely resembled that seen in individuals with active CD, suggesting the development of disease that was not shown in the probiotic group. Two trials were done to examine the efficacy of probiotics in preventing the development of CD. The initial study conducted by Savilahti *et al*. examined data from a trial on primary allergy prevention including 1223 infants who were given probiotics until 6 months of age, compared to a control group who received a placebo. The study found no significant difference in the likelihood of acquiring CD throughout the 13-year follow-up period.[77]

Subsequently, Uusitalo *et al*.[78] carried out a multicenter trial, monitoring more than 6,000 genetically susceptible young people for 8.7 years. The investigation revealed that the treatment of probiotics did not alter the likelihood of getting CD. Specifically, another study found that α-defensin and Paneth cell counts in duodenal biopsy samples were reduced when *B. infantis* natren life start super strain was given to subjects with CD at GFD in response to gluten.[79]

Currently, there is not enough data to support the use of probiotics in improving the histopathologic or clinical symptoms of CD.

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There are no conflicts of interest.

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