# Exploring the Relationship between Celiac Disease and Gut Microbiota

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## Abstract

Celiac Disease (CD) is a prevalent systemic condition arising from an aberrant immune reaction to gluten consumption, primarily affecting the small intestine. In individuals with a genetic predisposition, CD can be incited by external factors, such as viral infections and disruptions in the gut microbiota, known as dysbiosis. The gut microbiome plays a crucial role in regulating the immune system, and recent discoveries suggest that alterations in the gut microbiome might contribute to various chronic immune disorders, including CD, although the precise mechanisms are still under investigation.

Certain bacteria in the gut exhibit epitopes that resemble gliadin, potentially intensifying the host's immune response. Additionally, some bacteria, like Pseudomonas aeruginosa, may collaborate with gluten to initiate and exacerbate intestinal inflammation. The microbiota might also directly influence antigen formation by generating immunogenic or tolerogenic gluten peptides. Furthermore, it could impact intestinal permeability by releasing zonulin, a protein associated with gut barrier function.

Based on existing research, changes in the gut microbiome linked to CD typically involve a reduction in beneficial bacteria, including certain anti-inflammatory Bifidobacterium species. However, it's worth noting that there is still some debate in this area, as certain studies have not detected significant distinctions in the gut microbiomes of individuals with and without CD. Obtaining a more comprehensive understanding of how the gut microbiome contributes to the development of CD would be highly advantageous for improving both preventive measures and treatment strategies, particularly in cases that are complex or resistant to conventional therapies

**Keywords:** Intestinal microbiota • Gut microbiota • Celiac disease • Immune response

## Introduction

Celiac Disease (CD) is a systemic autoimmune disorder that primarily affects the small intestine and is more likely to develop in individuals with a genetic predisposition. This condition is triggered by the consumption of gluten, a protein found in various grains like wheat, barley, rye, spelt, and kamut, which is soluble in alcohol. CD is a prevalent condition, and its occurrence can vary depending on factors such as age, gender, and geographical location. Globally, the seroprevalence of CD is approximately 1.4%, while the confirmed prevalence of CD, verified through biopsy, stands at 0.7%. The highest prevalence is observed in Europe and Oceania (0.8%), while the lowest prevalence is found in South America (0.4%).

The accuracy of seroprevalence data may be compromised because serology tests are not specific to celiac disease, potentially leading to false-positive results. On the other hand, the prevalence determined through biopsy may be underestimated since not all individuals are willing to undergo an endoscopic examination. Celiac disease is 1.5 times more common in women than in men and is frequently diagnosed in children, although it can manifest at any age, including in the elderly.

The prevalence of CD is higher among individuals with a first-degree relative who has CD (10% to 15%). It's also more prevalent in individuals with other conditions such as Hashimoto's thyroiditis (5%), type 1 diabetes (3% to 16%), or other autoimmune diseases like autoimmune liver disease,

Sjogren's syndrome and IgA nephropathy. Additionally, CD is more common in individuals with Down syndrome (5%), Turner syndrome (3%),

and IgA deficiency (9%). Over the past half-century, the incidence of CD has risen, partly due to improved diagnostic tools and more thorough screening of individuals at high risk of the disease.

## Pathogenesis

The pathogenesis of Celiac Disease (CD) is a multifaceted process that involves a complex interaction between genetic and environmental factors. Genetic susceptibility and exposure to gluten are key triggers that set off an innate pro-inflammatory response in the gut, along with an inappropriate adaptive immune response due to the loss of tolerance to gluten.

A significant genetic predisposition to CD is linked to the presence of specific Human Leukocyte Antigen (HLA) risk alleles. These alleles, particularly the haplotypes DQ2 and DQ8, are expressed on the surface of antigen-presenting cells and have the capacity to bind to activated (deamidated) gluten peptides, thereby initiating an abnormal immune response. It's important to note, however, that while the presence of DQ2 and DQ8 haplotypes is necessary, it is not sufficient on its own to cause CD. Despite the relatively high prevalence of HLADQ2/HLA-DQ8 in the general population (25%-35%), only a small fraction (3%) of individuals carrying these HLA genes actually develop CD. This underscores the intricate nature of CD pathogenesis.

Exposure to gluten is a fundamental factor in the development of Celiac Disease (CD). However, certain factors like the duration of breastfeeding or the timing of gluten introduction into the diet do not appear to influence the risk of developing the disease. Gluten intolerance can be triggered by various factors, including gastrointestinal infections, medications, alpha-interferon treatment, and surgical procedures, and it can occur at any stage of a person's life.

Gliadin, a major component of gluten, undergoes partial breakdown into peptides. These peptides have the capacity to stimulate the release of zonulin, a protein that can disrupt tight junctions in the intestinal lining, leading to increased permeability. This allows gluten to pass through the openings and enter the lamina propria through a paracellular mechanism. Once tolerance to gluten is compromised, it has been observed that gluten can also breach the intestinal barrier via the transcellular pathway. Normally, the transferrin receptor CD71 is expressed on the basolateral side of enterocytes, but in the context of CD, this regulation can be disrupted.

## Role of gut microbiota in the pathogenesis of celiac disease

There is a growing body of evidence suggesting that the gut microbiota plays a significant role in the development of Celiac Disease (CD). This can be partially explained as follows: Firstly, the prevalence of CD has seen a rapid increase over the last two decades, and this cannot be solely attributed to genetic factors. It's important to note that only a small number of genetically predisposed individuals actually develop an active form of the disease, emphasizing the role of external factors. Additionally, the mode of delivery, such as cesarean section, which has a notable impact on the

microbial composition of a newborn's intestines, has been linked to an elevated susceptibility to CD. Lastly, there is emerging evidence of a positive association between early antibiotic use and the development of CD, although the findings in this regard have been inconsistent thus far.

For example, numerous studies have delved into the analysis of both duodenal and fecal microbiota to explore potential connections between Celiac Disease (CD) and the gut microbiota. These investigations have revealed changes in the microbiota composition that are associated with CD. Notably, there is a decreased presence of beneficial bacteria in individuals with CD, particularly *Bifidobacterium* species known for their anti-inflammatory and immunomodulatory properties. Additionally, *Lactobacillus* species are considered beneficial due to their ability to influence the immune response through mechanisms such as the secretion of anti-inflammatory cytokines and modulation of the Th1 immune response.

Conversely, an overgrowth of specific bacteria has been linked to heightened intestinal permeability, a characteristic feature of Celiac Disease (CD). Notably, certain Bacteroides species have been observed in higher quantities in CD patients. This overabundance of Bacteroides may contribute to the degradation of mucins and the subsequent increase in intestinal permeability. Similarly, some studies have reported an elevated prevalence of Escherichia coli in both active CD and CD in remission when compared to healthy individuals. Furthermore, an increased abundance of specific Staphylococcus species has also been noted in this context.

Regarding the potential mechanisms through which the gut microbiota may contribute to the pathogenesis of Celiac Disease (CD), several hypotheses have been proposed. One hypothesis suggests that certain gut bacteria express epitopes that resemble gliadin, a component of gluten. These gliadin-mimicking epitopes have the capacity to activate the host's immune system, leading to the production of antibodies that target the lining of the gut, thereby causing damage.

Another hypothesis centers around lipopolysaccharides, which are molecules found in the outer membrane of Gram-negative bacteria. Lipopolysaccharides can play a significant role in both the innate and adaptive immune systems by promoting the production of interleukin-15 (IL-15). This, in turn, can trigger inflammation within the gut, contributing to the pathogenesis of CD.

Gut bacteria have the capacity to modulate both the function of the intestinal barrier and the immune response to dietary antigens by Releasing Short-Chain Fatty Acids (SCFAs). These SCFAs, which encompass compounds like acetate, propionate, and butyrate, are generated as a result of the fermentation of dietary fibers by gut bacteria. They play a pivotal role in preserving the integrity of the intestinal epithelial barrier by facilitating the formation of tight junctions, suppressing the production of pro-inflammatory cytokines, and fostering the differentiation of regulatory T-cells.

It is a widely established fact that Celiac Disease (CD) manifests in individuals with a genetic predisposition, and the presence of specific HLA-DQ haplotypes has been acknowledged as a requirement, though not in itself adequate, for the onset of the condition. It's crucial to emphasize that, as indicated by numerous prospective studies, HLA-DQ haplotypes exert an influence on the initial composition of the gut microbiota. Olivares et al., for instance, have reported on this aspect.

Several prospective cohort studies have investigated how the gut microbiota evolves in genetically predisposed infants. These studies have revealed that changes in the gut microbiota during the initial months of life, extending up to 12 months-24 months after birth, may play a role in the development of Celiac Disease (CD) in this specific group of children. A recent multicenter study, involving 31 infants participating in a large-scale prospective birth cohort study, focused on infants with a first-degree relative having CD. This study examined the impact of genetic and environmental risk factors on the longitudinal development of the gut microbiota in these individuals, all before the introduction of solid foods, including gluten.

In more specific terms, the genetic predisposition for developing Celiac Disease (CD) has been linked to certain changes in the gut microbiota composition. At 4 months-6 months of age, individuals with a genetic susceptibility to CD were found to have a reduced presence of several species of *Streptococcus* and *Coprococcus* compared to those without genetic compatibility. The study also revealed that both standard and high genetic risk for CD was associated with an increased abundance of Bacteroides and *Enterococcus* species, aligning with previous findings. Conversely, there was no observed association between genetic risk and higher levels of *Bifidobacterium* or *Proteobacteria*, which had been reported in earlier studies. Furthermore, infants with genetic compatibility exhibited a decreased abundance of *Veillonella, Parabacteroides*, and *Clostridium* perfringens in the 4 months-6 months age range.

There have been reports suggesting that cesarean section may be linked to a heightened risk of developing Celiac Disease (CD). However, it's important to note that the findings in this regard have been inconsistent in different studies. Notably, infants delivered via cesarean section exhibited an elevated presence of *Enterococcus faecalis* and a reduced presence of Bacteroides and Parabacteroides compared to infants born through vaginal delivery. This observation could be significant, as Parabacteroides appear to have a mitigating effect on the severity of intestinal inflammation.

The impact of feeding practices on the risk of developing Celiac Disease (CD) remains unclear. Some reports suggest that feeding infants with formula milk may be a risk factor for CD development, partly because it can influence the composition of the gut microbiota. However, contrasting findings from other studies indicate that breastfeeding, conversely, does not appear to be a protective factor against CD.

Furthermore, acute gastrointestinal infections have the potential to disrupt the normal balance of the gut microbiota. Consequently, some studies propose that an elevated occurrence of gastrointestinal infections, particularly those caused by rotaviruses and enteroviruses, in the first 6-18 months after birth may be linked to an increased risk of Celiac Disease (CD). This association could be mediated by the heightened gut permeability resulting from such infections.

In more specific terms, there exists diverse data regarding the potential connection with rotaviruses. According to research by Stene et al., recurrent rotavirus infections were indicative of a higher risk for CD autoimmunity. However, this finding was not corroborated in a subsequent study that observed only a 1.5% increase in CD prevalence over the last two decades, despite the introduction of a rotavirus vaccine during the study period.

## Implications for clinical practice and therapy

The role of the microbiome in influencing the development of CD is evident, as it affects the immune response, maintains the integrity of the intestinal barrier, permits the entry of gluten-related proteins, and breaks down gluten immunogenic peptides. However, there remains no agreement on the precise alterations in microbial composition observed in this particular context.

Numerous studies have identified distinct bacterial populations in individuals with CD in comparison to those without the condition. However, it remains uncertain whether gut dysbiosis is a causative factor or a consequence of CD. One appealing approach in CD management involves targeting the gut microbiota to foster the growth of beneficial bacteria and restore normal gut functions. In line with this concept, emerging therapies designed to modulate the gut microbiome are being developed as complementary strategies for CD treatment. For instance, probiotics, prebiotics, post biotics, and Fecal Microbiota Transplantation (FMT), when used in conjunction with a gluten-free diet, have the potential to influence the gut microbiome. In the future, probiotics might even serve as supplementary treatments to enhance the effectiveness of the gluten-free diet and alleviate symptoms. It is conceivable that the restoration of beneficial commensal species, such as those that produce Short-Chain Fatty Acids (SCFA) under anaerobic conditions, could have a positive impact on the integrity of the intestinal barrier and the host's immune system.

Recent findings indicate that several strains of lactobacilli possess the capability to break down immunogenic gluten peptides. Furthermore, there has been a report of a probiotic mixture containing both lactobacilli and *Bifidobacterium* strains, which has demonstrated the ability to hydrolyze gluten peptides following the digestion of gliadin. Additionally, this probiotic mixture was shown to modify the pro-inflammatory state and counteract the gliadin-induced changes to the gut's epithelial structure.

Fecal Microbiota Transplantation (FMT) is a procedure in which the gut microbiota from a healthy donor is transferred into the recipient's digestive tract with the goal of restoring a balanced and healthy gut microbial community, known as eubiosis. This transfer of fecal matter from a healthy

donor can be accomplished through various methods, such as a nasogastric tube, colonoscopy, or capsule delivery.

## Conclusion

The involvement of the gut microbiota in the development of CD is intricate. It constitutes a multifaceted community of microorganisms capable of interacting with the host's immune system and influencing the reaction to gluten. Studies have indicated that alterations in the structure and operation of the gut microbiome might play a role in the initiation and advancement of CD. Numerous hypotheses have been put forward to elucidate how the gut microbiome might play a part in the development of CD. These hypotheses encompass various mechanisms, such as the expression of epitopes that resemble gluten, the initiation of the immune system through lipopolysaccharides, heightened inflammation due to specific bacteria, and the activation of the innate immune system by viral infections.

Furthermore, the gut microbiome holds the capacity to shape the maturation and activation of the immune system, encompassing the immune reaction to gluten in CD. Additionally, the generation of short-chain fatty acids (SCFAs) by gut bacteria can contribute to the regulation of the intestinal barrier's function and the immune response to dietary antigens. In summary, the gut microbiome is a multifaceted and ever-changing community that holds a pivotal role in the onset of CD.

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