International Journal of Biotechnology and Microbiology
www.biotechnologyjournals.com
Online ISSN: 2664-7680, Print ISSN: 2664-7672
Received: 04-10-2025, Accepted: 03-11-2025, Published: 19-11-2025
Volume 7, Issue 4, 2025, Page No. 52-61

Celiac Disease beyond gluten: Gut integrity, and the relationship between Microbiota and SCFA

Aindree, Rajnish Prakash Singh*
Department of Biotechnology, Jaypee Institute of Information Technology, Noida, Uttar Pradesh, India

Abstract
Celiac disease (CD) is a serious autoimmune condition where the body reacts badly to gluten, a protein found in wheat, barley, and rye. This reaction damages the small intestine, making it hard to absorb nutrients. The main reason some people get CD is because of certain genes especially HLA-DQ2 and HLA-DQ8. These genes increase the likelihood of the immune system attacking gluten. When gluten isn't broken down properly in the gut, small pieces of it pass through the gut lining. An enzyme called tissue transglutaminase (tTG) changes these pieces so they stick better to immune cells, which then trigger inflammation and produce harmful antibodies. Gluten itself is made up of different proteins like gliadins and glutenins. Some of these are known to cause strong immune responses in people with CD. The only current treatment is a strict, lifelong gluten-free diet, which can be hard to follow and doesn't always fully heal the gut. Researchers are now working on new ways to treat the CD. These include special enzymes that can break down gluten, medicines that block harmful steps in the immune process, and even genetically modified wheat with fewer toxic proteins. Another promising approach is restoring healthy gut bacteria, since people with CD often have an imbalance in their gut microbiota. This imbalance can lead to lower levels of helpful short-chain fatty acids (SCFAs) like butyrate, which protect the gut. Improving gut health may help reduce inflammation and improve life for people with CD.

Keywords: Enzyme therapy, immune modulation, SCFAs

Introduction

Celiac disease (CD) is an autoimmune disorder triggered by the ingestion of gluten, a protein found in wheat, barley, and rye. It primarily affects the small intestine, leading to inflammation and damage to the intestinal lining (Cazac G-D *et al.,* 2024) [1]. The primary component of gluten responsible for CD is gliadin, which is rich in proline and glutamine, making it resistant to complete digestion (Wieser H *et al.,* 2007) [2]. This partial digestion results in immunogenic peptides that trigger an immune response in genetically predisposed individuals.Gluten is a protein found in wheat, barley, and rye.It's made up of two main parts: gliadin and glutenin.When you mixgluten with water and knead it, these proteins create a sticky, stretchy network (Biesiekierski JR *et al.,* 2017) [3].This network is what makes dough elastic and helps it rise, giving bread and baked goods their chewy texture. Gliadin makes the dough stretchy, while glutenin makes it strong and firm. Together, they form a web that traps air bubbles from yeast, which makes the dough rise and gives baked goods their texture. For most people, gluten is harmless (Balakireva A *et al.,* 2016) [4].But for those with CD, eating gluten triggers their immune system to attack the small intestine.This can cause problems like bloating, diarrhea, and not getting enough nutrients.Some people also have gluten sensitivity, which causes similar symptoms without damaging the intestine.Even though it can cause problems for some people, gluten is used a lot in the food industry. It helps improve the texture and keeps baked goods moist (Biesiekierski JR *et al.,* 2017) [3]. Because more people are aware of gluten-related problems, gluten-free diets have become more popular. These diets help people with CD or gluten sensitivity manage their symptoms. However, it's important to remember that gluten is safe for most people. The word "gluten" comes from Latin, meaningglue because of its sticky nature (Biesiekierski JR *et al.,* 2017) [3] . The problems caused by gluten weren't understood until much later. In the early 1900s, a doctor found that taking wheat out of the diets of children with CD made them much healthier. This discovery helped people understand that gluten causes CD (Wieser H *et al.,* 2007) [2].

But with the understanding of gluten one should also know that celiac isn't just a gluten intolerance but also a genetic disease that involves specific genes expressed in its cis/trans form with external environmental factors making it to express and show inflammation affects, lets know about genes responsible with external environmental factors. The DQ4 and DQ8 genes, which play a significant role in the development of CD, are influenced by a combination of genetic predispositions and environmental factors. These genes code for Human Leukocyte Antigen (HLA) proteins, specifically HLA-DQ heterodimers, which are crucial in presenting gluten-derived peptides to T-cells in the immune system (Costantini S *et al.,* 2004) [5]. The expression and activation of these genes are not solely dependent on their presence but also on various external environmental factors that can trigger or exacerbate their effects. Individuals inherit these genes, primarily HLA-DQ2 and HLA-DQ8, which predispose them to CD (Cazac G-D *et al.,* 2024) [1]. These genes alter the structure of the HLA-DQ molecules, making them more likely to bind and present gluten peptides to T-cells. This genetic predisposition is a foundational element in the pathogenesis of CD.

The most important environmental factor that may affect the expression and function of the DQ4 and DQ8 genes is exposure to gluten. In people with certain genetic predispositions, gluten peptides can be detected and presented by HLA-DQ molecules, thus triggering an immune response (Costantini S *et al.,* 2004) [5]. The response is proportional to the amount and duration of glutensubsequently, the composition and variety of gut microbiota is essential in the modulation of immune

responses. Dysbiosis can lead to increased permeability of the gut barrier or increased gut inflammation, both of which may promote the presentation of gluten peptides and amplify the immune response through DQ4 and DQ8 (Koning F *et al.,* 2005) [6]. Infectionscaused by some viruses or bacteria can initiate CD in susceptible individuals. These infections can impair the gut barrier, heighten inflammation, and enhance T-cell response. Some specific viral infections are also factors behind CD such as adenovirus and rotavirus (Borbulevych OY *et al.,* 2009) [7].

Some of the earliest infant feeding measures such as breastfeeding practices and the introduction of gluten, have the potential to influence the onset of CD. For those more vulnerable, partial breastfeeding combined with late introduction of gluten can increase the risk. Stress, certain medications like antibiotics, and shifts in the permeability of the gut are some other factors that can change expression of DQ4 and DQ8 genes. These elements have the capability of modifying the immune response which further leads towards exacerbation or development of CD (Kagnoff MF *et al.,* 2007) [8].

CD4+ T-cells receive gluten derived peptides from DQ4 and DQ8 modulated HLA-DQ molecules marking the presence of T-Cells. People carrying these genes are more likely to have their HLA-DQ molecules bind to gluten peptides because the DQ molecules have stronger bonds. The activation of T-cells is caused by HLA-DQ-gluten complex associating with T-cell receptors. Many of the T-cells are turned to a specific type that attacks body tissues, releases pro-inflammatory cytokines and aggravates injury to tissues(Borbulevych OY *et al.,* 2009) [7]. Gears the immune system into action targeting DQ helps with villous atrophy, crypt hyperplasia and bring up intestinal permeability. The alteration of these augments the body's capability to absorb nutrients but manifests symptoms associated with CD and results into damage.

Now, with this understanding of celiac let's shift our focus on other gluten intolerance disorders sothat we can understand gluten as a protein, humangut and celiac on a broader perspective, Unlike CD, which is an autoimmune disorder, glutenintolerance does not cause damage to the small intestine. However, it can still lead to a range of uncomfortable symptoms that can significantly impact an individual's quality of life. The symptoms of gluten intolerance can vary widely among individuals and may include ,Digestive issues: Bloating, abdominal pain, gas, diarrhea, andconstipation Fatigue: Feeling tired or weak, even after adequate rest, Headaches: Frequent or persistent headaches, including migraines Skin problems: Rashes, eczema, or other skin irritations Joint pain: Aches and pains in the joints Brain fog: Difficulty concentrating, memory problems, and mental confusion Mood disturbances: Anxiety, depression, or irritability (Dochat C *et al.,* 2024) [9]. The exact cause of gluten intolerance is not yet fully understood. Unlike CD, it does not involve an autoimmune response or damage to the small intestine. However, several factors may contribute to its development. Increased intestinal permeability: Also known as "leaky gut," this condition allows substances to pass through the intestinal lining into the bloodstream, potentially triggering an immune response *(*Saviano *A et al.,* 2023) [10]. Changes in the gut microbiota: an imbalance in the gut bacteria may play a role in gluten intolerance and Genetics: a family history of gluten intolerance may increase an individual's risk (Ertaş Öztürk Y *et al.,* 2024) [11].

Gluten and its Relation to CD

Gluten isn't as simple as it sounds it does cause a lot of uncomfort or say inflammation, lets understand the inflammation caused in brief. Chronic inflammation of the small intestine, triggered by an abnormal immune response to gluten. When individuals with CD consume gluten-containing foods, the undigested gluten peptides, particularly gliadin, cross the intestinal epithelial barrier. This process is facilitated by increased intestinal permeability, partly mediated by zonulin, a protein that regulates tight junctions between intestinal cells. Once in the lamina propria, gluten peptides undergo deamidation by tissue transglutaminase (tTG), increasing their immunogenicity (Abdulkarim AS *et al.,* 2002) [12]. The deamidated peptides are then presented by antigen-presenting cells via HLA-DQ2 and HLA-DQ8 molecules to CD4+ T-helper cells, triggering an inflammatory cascade(Costantini S *et al.,* 2004) [5].The activation of CD4+ T-cells leads to the release of pro-inflammatory cytokines, including interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which contribute to tissue damage (Fig. 1). Additionally, intraepithelial lymphocytes (IELs), a type of immune cell found within the intestinal lining, become activated and produce cytotoxic molecules like granzyme B and perforin, leading to enterocyte apoptosis (cell death) (Jabri B *et al.,* 2009) [13]. This immune attack results in villous atrophy, a hallmark of CD, where the normal finger-like projections of the intestinal lining become flattened, reducing the surface area for nutrient absorption.

Another key inflammatory pathway in CD involves IL-15, a cytokine that promotes the activation of cytotoxic CD8+ T-cells. These T-cells, unlike the gluten-specific CD4+ T-cells, do not require antigen presentation by HLA molecules. Instead, they recognize stress signals from damaged enterocytes and contribute to tissue destruction by releasing additional inflammatory mediators (Petersen J *et al.,* 2014) [14]. The ongoing inflammation leads to symptoms such as diarrhea, malabsorption, weight loss, fatigue, and abdominal pain.

The only proven treatment for CD is a strict gluten-free diet (GFD), which gradually reduces inflammation and promotes intestinal healing. However, even minimal gluten exposure can reactivate immune responses. Therefore, ongoing research aims to develop pharmacological therapies, such as zonulin inhibitors (Larazotide acetate), transglutaminase inhibitors, and gluten-degrading enzymes (glutenases), to help mitigate inflammation and improve quality of life for celiac patients (Buriánek F *et al.,* 2024) [15]. A GFD is the only proven treatment for CD, requiring the complete avoidance of gluten-containing foods like wheat, barley, and rye. By eliminating gluten, the small intestine gradually heals, reducing inflammation and restoring normal nutrient absorption. However, strict adherence is difficult due to the risk of accidental gluten exposure, which can trigger immune responses even in trace amounts. Many patients continue to experience symptoms despite following a GFD, making cross-contamination a major concern. This has led researchers to explore pharmacological therapies to either prevent immune activation or reduce intestinal damage (Janatuinen E *et al.,* 2002) [16]. Additionally, probiotics are being explored for their potential to support gut health in celiac patients. Strains like *Lactobacillus casei, Bifidobacterium longum*, and *Saccharomyces boulardii* have

shown promise in reducing inflammation, breaking down gluten peptides, and modulating immune responses. While probiotics are not a standalone treatment, they may complement other therapies by promoting beneficial gut bacteria and strengthening the intestinal barrier.

Celiac Disease Progression

CD is a serious autoimmune disorder that affects the small intestine when people consume gluten, a protein found in wheat, barley, and rye. In individuals with CD, the immune system mistakenly attacks the small intestine, causing inflammation and damage to the intestinal lining (Fig.2) (Abdulkarim AS *et al.,* 2002) [12]. This can lead to a range of digestive and non-digestive symptoms, as well as long-term health complications if left untreated. CD occurs when the body's immune system responds abnormally to gluten. In people with a genetic predisposition, gluten consumption triggers an immune response that damages the villismall finger-like projections in the small intestine responsible for nutrient absorption. As a result, the body struggles to absorb essential nutrients, leading to malnutrition and other health issues(Abdulkarim AS *et al.,* 2002) [12].

CD symptoms vary from person to person and can affect different parts of the body. Some individuals experience digestive symptoms, while others have issues related to the skin, bones, or nervous system. Gluten-related disorders include CD, wheat allergy, and nonceliac gluten sensitivity (Singh A *et al.,* 2024) [17]. CD is an autoimmune enteropathy caused by damage to small intestinal mucosa when gluten is ingested in genetically susceptible individuals. Currently, the only available treatment of CD is gluten-free diet (Studerus D *et al.,* 2023) [18]. CDis usually diagnosed by serological examination. Duodenal biopsy is not necessary for the diagnosis of CD but is necessary for the treatment Disease is induced by gluten-containing food in people carrying HLA-DQ2 or DQ8 haplotype (human leukocyte antigen Class II with DQ2 and/or DQ8 molecules on antigen-presenting cells)(Abdulkarim AS *et al.,* 2002) [12]. CD is not only characterized by gastrointestinal symptoms but also by extraintestinal manifestations, some of which are a direct consequence of autoimmunity responsesfor example, dermatitis herpetiformis or gluten ataxiawhile others are an indirect consequence of anaemia, such as osteoporosis, short stature and delayed puberty (Addanki S *et al.,*2024) [19]. After the gluten enters into the digestive system, prolamin proteins are not fully hydrolyzed by proteases, which results in the emergence of gluten peptides. They are deamidated by tTG enhancing their affinity to MHC II molecules. Deamidated peptide is then recognized by DQ molecule on the surface of a dendritic cell and is presented to T cells inducing immune response. It is interesting that both DQ2 andDQ8lackcanonical aspartic acid residue at DQ 57. It results in the compensation of this negative charge by negatively charged residues either in the T cell receptor or in the deamidated peptide (Ciacchi L *et al.,* 2022) [20].

Other Gluten Susceptible Disorders

The incidence of gluten-related disorders (GRDs) continues to increase and its global prevalence is estimated at approximately 5% of the population. CD, dermatitis herpetiformis (DH) (Fig.3 a) , gluten ataxia (GA), wheat allergy (WA), and non-celiac gluten sensitivity (NCGS) are the five major GRDs that present with a wide range of clinical manifestations (Roszkowska A *et al.,* 2019) [21] . The diagnosis of GRDs can be challenging because the typical and atypical clinical manifestations of the GRDs overlap. NCGS is a condition characterized by symptoms similar to CD, such as abdominal pain, diarrhea, and fatigue, after consuming gluten-containing foods However, unlike CD, NCGS does not cause intestinal damage or immune system activation. A study published in the Journal of Clinical Gastroenterology found that NCGS affects approximately 0.5% to 6.4% of the general population (Cabanillas B *et al.,* 2020) [22]. Gluten has been implicated in various neuropsychiatric disorders, including schizophrenia, bipolar disorder, and autism spectrum disorder. Research suggests that gluten may exacerbate symptoms in individuals with these conditions. A study found that a gluten-free diet improved symptoms in patients with schizophrenia (Silva-Paz RJ *et al.,* 2024) [23]. Gluten-induced neuropathy is a condition characterized by nerve damage and symptoms such as numbness, tingling, and weakness (Fig.3 b) (Catassi C *et al.,* 2015) [24]. Research suggests that gluten may trigger an immune response, leading to nerve damage.Another study we looked at found that a gluten-free diet improved symptoms in patients with gluten-induced neuropathy (Hadjivassiliou M *et al.,* 2007) [25]. Gluten has been implicated in various autoimmune disorders, including rheumatoid arthritis, lupus, and multiple sclerosis. Research suggests that gluten may trigger an immune response, leading to inflammation and tissue damage (Osman D *et al.,* 2021) [26].

Genes and other Factors Causing Inflammation

CD is an autoimmune enteropathy caused by genetic and environmental factors (Fig. 4), with an estimated worldwide prevalence of about 1%. The huge prevalence of CD in the Saharawi people (5.6%) probably indicates that events linked to wheat domestication 10,000 years ago were a 'founder effect' related to the positive selection of HLA-DQ2 haplotype(Costantini S *et al.,*2004) [5]. After gluten enters into the digestive system, glutamine and proline-rich gluten composing proteins are partially hydrolyzed by proteases presented in the gastrointestinal tract. As a result, generated gluten-derived peptides reach the lamina propria (mucosa) by transcellular or paracellular transport where they are modifiedbytissue transglutaminase (tTG) enhancing their affinity to MHC II molecules, and thereby making them toxic and immunogenic in HLA-DQ2 or DQ8 containing patients(Kagnoff MF *et al*., 2007) [8]. The repetitive presence of glutamine and proline residues determines the gluten-derived peptides as a preferred substrate for tTG. tTG-mediated modifications occur in two ways: deamidation (cleavage of the-amino group of a glutamine side chain) or more frequently transamidation (cross-linking of a glutamine residue from the gliadin peptide to a lysine residue of tTG(Ciacchi L *et al.,* 2022) [20]. Further peptides presentation by HLA-DQ2/DQ8protein subunits in the surface of dendritic cells to gluten-specific T cells induces two levels of immune response: the innate response and the adaptive (T-helper cell mediated) response with the production of interferon-and IL-15. As a result, it causes immune-mediated enteropathy, intestinal inflammation, followed by the atrophy of villi, crypt hyperplasia and increased infiltration by intraepithelial lymphocytes (Jabri B *et al.,* 2009) [13].It also produces weight loss and chronic diarrhea. Although the causative

agent is a dietary protein, the disease has marked autoimmune features, which are indicated by the presence of autoantibodies against tTG. Cross-linking between gliadin and tTG is covalent resulting in the formation of new epitopes, which trigger the primary immune response, and by which the autoantibodies against tTG are developed(Kagnoff MF *et al.,* 2007) [8].

Structure of Gluten and Immune System

Gluten is a mixture of seed storage proteins found in grains such as wheat, rye, barley and oat,
whichare closely related members of the *Triticeae* tribe. The y contain hundred groups of proteins. Rye (*Secale cereal L*., genome composition RR) and barley (*Hordeum vulgare L*.) are diploid, while wheat is represented by the most widely st udied hexaploid bread wheat (*Triticum aestivum L*., genome composition AABBDD), tetraploid pasta wheat (*Triticum d urum L*., genome composition AABB) and diploid wheat (*T riticum monococcum L*., genome composition AA). Oat (*Av ena sativa L*.) is the most closely related cereal to the Tritice ae and belongs to a separate Aveneae tribe within the same s ub-family (*Festucoideae*) (Payne PI *et al.,* 1987) [27]. Gluten proteins appear to be prolamins due to the significant amount of glutamine and proline amino acid residues present in their primary structures. Prolamins are the major endosperm storage proteins in grains (Fig. 5).
There is also a difference in the number and properties of pr olamin polypeptides. Despite these variations all prolamins are related and usually referred to as three bro ad groups: sulphur-
rich (S-rich), sulphur-poor (S-poor) and high molecular wei ght (HMW) prolamins (Fig.6) (Payne PI *et al.,* 1987) [27]. It has been shown that wheat 5-gliadin is the main allergen of gluten, inducing wheat-dependent exercise-induced anaphylaxis. some data suggest thatgliadins are IgE-binding proteins. Allergy occurs within a few hours and causes no permanent gastrointestinal or other organ damage (Shewry PR. *et al.,* 2009) [28]. The alcohol-soluble fraction, named gliadins (monomeric), and insoluble glutenins (polymeric and soluble in dilute acids and bases) have been shown to contribute to the cohesiveness and extensibility of gluten.whereas glutenins play a role in the maintenance of the elasticity and strength of the gluten (Khan K *et al.,* 2009) [29].

Therapeutic Approaches

Gluten Free Diet (GFD)

There is currently only one proven effective way of treating CD and NCGSis a gluten free diet. It means the avoidance of gluten-containing food in gluten intolerance patients' ration. There is little information in the literature on minimal disease-eliciting doses of gluten, which would be safe for CD patients. GFDcannot be regarded as a healthy diet. Gluten-free products are usually made with starches or refined flours characterized by low fiber content. It is known that the consumption of adequate amounts of dietary fiber is related to important health benefits such as prevention of colon cancer, diabetes and cardiovascular disease (Janatuinen E *et al.,* 2002) [30]. GFD appears to be an unbalanced diet inadequate in terms of both macro- and micronutrients. In order to maintain the necessary level of all the nutrients an annual screening for nutrient status of a patient is required and there is a need for additional nutrient supplementation (Mandile R *et al.,* 2024) [31]. GFD is not an optimal and healthy way to treat all the manifestations of gluten intolerance including CD, wheat allergy and NCGS. Even though a wheat free diet is optimal for wheat allergy treatment, patients can eat rye, barley and oat (Skoracka K *et al.,* 2024) [32].

Detoxification of Gluten Proteins with Enzymatic Therapy

This approach is based on the fact that gluten peptides are highly resistant to digestive pancreatic and brush border proteases. Fortunately, many organisms (e.g., bacteria, fungi, plants etc.) encode proteolytic enzymes possessing distinct features compared to endogenous proteases presented in human(Skoracka K *et al.,* 2024) [32].. It has been proposed that exogenous enzymes can be employed for additional enzyme supplement therapy to promote the complete digestion of cereal proteins, and thus destroy T-cell gluten epitopes, in particular. A number of peptidases possessing glutenase activities were isolated from germinating cereals (*Hordeum vulgare L., Triticum aestivum L.*), bacteria (*Flavobacterium meningosepticum, Sphingomonas capsulate, Myxococcus xanthus*), fungi (*Aspergillus niger, Aspergillus oryzae*), and stored-product pest yellow mealworm (*Tenebrio molitor*)(Studerus D *et al*., 2023) [18]. One of them is ALV003 enzymemodified recombinant EP-B2 enzyme from barley, and prolyl endopeptidase from bacteria *Sphingomonas capsulate*was shown to be effective *in-vitro* and *in-vivo,* non-toxic and without allergic reactions(Singh A *et al.,* 2024) [17] . Gluten-containing food can also be treated with bacterial-derived peptidases, in particular, proteases of certain *Lactobacilli* present in sourdough are able to proteolyze proline-rich gluten peptides

Modified Grains

There are several studies targeted at developing grains with reduced pathogenicity. On the basis of knowledge of peptide immunogenicity hierarchy, site-directed mutagenesis of wheat, which would not affect the baking properties, has also been proposed (Abdulkarim AS *et al.,* 2002) [12]. A subclass of-gliadins genes, encoding proteins that cause food IgE-mediated allergy, were silenced in order to decrease the level of 5-gliadins in grain(Koning F *et al.,* 2005) [6]. Transgenic wheat has reduced allergenicity without influencing the dough quality. Similar work was performed to reduce the toxicity in CD patients of all gliadin proteins through the shutdown of these genes by RNAinterference. Genes of glutenin- and-gliadins were down-regulated in these plant lines(Buriánek F *et al.,* 2024) [15]. This has led to the production of wheat lines with very low levels of toxicity for CD patients. Successful transformation of bread wheat *Triticum aestivum* Butte 86 was reported.

Corrections of Gluten Pathogenicity Pathways

TTG is very important in CD pathogenesis. For this reason, it has become a target for suppression by the design of potent and selective inhibitors. Inhibition of tTG2 by cystamine*in -vitro* and *in-situ* was confirmed by means of abolished reactivity of gliadin-specific T-cell response(Balakireva A *et al.,* 2016) [4]. Zonulin, one of the TJ regulatory proteins involved in the proper functioning of intestinal epithelial permeability, controls the passage through the mucosal barrier, Zonulin regulates the

permeability of tight junctions in the intestinal lining, and in celiac patients, gluten triggers excessive zonulin release, leading to a leaky gut and increased immune response (Nikoloudaki O *et al.,* 2024) [33].

The inhibition of zonulin overexpression can prevent it trespassing the gut barrier. The effective synthetic peptide inhibitor was developed and named as AT1001 or Larazotide acetate, Larazotide acetate, a zonulin inhibitor, works by strengthening these junctions and preventing gluten peptides from passing through, thereby reducing inflammation (Fig.7) (Mandile R *et al.,* 2024) [31]. Clinical trials suggest that Larazotide acetate may help celiac patients experiencing symptoms despite a GFD**.**Another strategy involves transglutaminase (tTG) inhibitors. tTG modifies gluten peptides, making them more immunogenic and worsening immune activation in CD (Wu X *et al.,* 2021) [34]. Blocking tTG activity may reduce gluten-induced inflammation and intestinal damage**,** though these inhibitors are still in preclinical development. Peptides themselves are undoubtedly major CD participants. Glutenase enzymes offer another promising therapy by breaking down gluten proteins before they reach the small intestine, reducing the likelihood of immune activation. Enzymes like AN-PEP and EP-B2 have demonstrated effectiveness in digesting gluten into harmless fragments, potentially helping celiac patients manage accidental gluten ingestion when taken as an oral supplement(Costantini S *et al.,* 2004) [5].Peptide analogues of gliadin epitopes can be engineered with antagonistic effects of native peptides. Nexvax2® (Immusan T, Inc., Cambridge, MA, USA) is the peptide-based therapeutic vaccine based on desensitization therapy principles (Ciacchi L *et al.,* 2022) [20].

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is a promising new approach being explored for treating CD and other gluten-related disorders. In people with CD, the balance of gut bacteria is often disturbed, which can worsen symptoms like bloating, diarrhea, and inflammation even when following a strict gluten-free diet (Arcila-Galvis JE *et al.,* 2022) [35]. FMT involves transferring stool from a healthy donor who has a balanced gut microbiome into the patient's digestive tract. This is done through methods like colonoscopy, endoscopy, or oral capsules (Fig. 8) (Wulczynski M *et al.,* 2025) [36]. The goal is to restore healthy gut bacteria, which may help reduce inflammation, improve gut health, and possibly increase tolerance to small amounts of gluten. Recent case studies have shown that FMT may help patients with severe or treatment-resistant CD recover gut function and reduce symptoms (Rossi R *et al.,* 2023) [37]. The beneficial effects likely come from rebalancing the microbiota, calming the immune system, and healing the gut lining. While these early results are encouraging, more clinical research is needed to confirm how effective and safe FMT is for CD (Kelley K *et al.,* 2024) [38]. Still, it opens up an exciting direction for people who don't fully respond to traditional treatments. The beneficial effects likely come from rebalancing the microbiota, calming the immune system, and healing the gut lining(Addanki S *et al.,*2024) [19]. While these early results are encouraging, more clinical research is needed to confirm how effective and safe FMT is for CD. Still, it opens up an exciting direction for people who don't fully respond to traditional treatments.

Gut Microbiota Alterations

CD is an autoimmune disorder triggered by the ingestion of gluten, a protein found in wheat, barley, and ryein genetically predisposed individuals. The disease is characterized by an immune-mediated inflammatory response that leads to damage in the small intestine's mucosa, impairing nutrient absorption and causing various gastrointestinal and extra-intestinal symptoms (Saviano A *et al.,* 2023) [10]. Recent research has highlighted the significant role of gut microbiota in the pathogenesis and management of CD, revealing that individuals with CD exhibit distinct alterations in their gut microbial composition compared to healthy individuals (Helms S *et al.,* 2005) [39]. One of the most consistent findings across studies is the reduced abundance of beneficial bacterial genera such as *Bifidobacterium* and *Lactobacillus* in individuals with CD. These bacteria are known for their roles in maintaining gut health, including the fermentation of dietary fibers into short-chain fatty acids (SCFAs), which serve as energy sources for colonocytes and have anti-inflammatory properties (Kelley K *et al.,* 2024) [38]. The diminished presence of these beneficial microbes can compromise the gut's protective functions and contribute to the inflammatory processes observed in CD (Rossi R *et al.,* 2023) [37].

In addition to the reduction in beneficial bacteria, there is an observed increase in potentially pathogenic bacteria in the gut microbiota of CD patients. Specifically, higher levels of *Bacteroides*, *Staphylococcus*, *Salmonella*, *Shigella*, and *Klebsiella* have been reported. These bacteria can produce pro-inflammatory molecules, exacerbating intestinal inflammation and potentially contributing to the clinical manifestations of CD*(*Addanki *S et al.,*2024) [19]. The overall diversity of the gut microbiota is also affected in CD. A decrease in microbial diversity is commonly observed, which is significant because a diverse microbiota is generally associated with a healthy and resilient gut environment. Reduced diversity can lead to an imbalance in microbial functions, impairing the gut's ability to process nutrients effectively and protect against pathogens (Szeltner Z *et al.,* 2008) [40].

The standard treatment for CD is a GFD, which aims to alleviate symptoms and promote intestinal healing by eliminating dietary gluten. However, adherence to a GFD presents several challenges, including the risk of cross-contamination, potential nutritional deficiencies, and unintended alterations in the gut microbiota(Catassi C *et al.,* 2015) [24]. Studies have shown that even after two years on a strict GFD, the gut microbial composition of individuals with CD may not fully normalize, indicating an incomplete restoration of a healthy microbiota. The persistence of dysbiosis despite adherence to a GFD suggests that dietary modifications alone may not be sufficient to fully restore gut health in CD patients (Tjellström B *et al.,*2007) [41]. This has led researchers to explore adjunctive therapies, such as probiotic supplementation, to modulate the gut microbiota favorably. Probiotics, which are live microorganisms that confer health benefits to the host when administered in adequate amounts, have shown promise in improving the gut microbial balance in CD. Clinical trials have demonstrated that probiotic supplementation can increase the levels of beneficial bacteria like *Bifidobacterium* and *Lactobacillus*, enhance SCFA production, and reduce markers of intestinal inflammation(Balakireva A *et al.*, 2016) [4]. In children with CD, gut microbiota alterations

have been linked to nutrient absorption issues. A study focusing on pediatric CD patients found associations between specific microbial profiles and nutrient deficiencies, highlighting the importance of maintaining a balanced gut microbiota for optimal nutritional status. These findings underscore the potential of microbiota-targeted interventions to support better health outcomes in children with CD(Nikoloudaki O *et al.,* 2024) [33].

Emerging research is also investigating the relationship between gut microbiota and obesity in the context of CD. While CD is traditionally associated with malabsorption and weight loss, there is a growing recognition of obesity prevalence among CD patients(Dochat C *et al.,* 2024) [9]. Alterations in the gut microbiota may influence energy metabolism and fat storage, suggesting a complex interplay between CD, gut microbiota, and body weight regulation. Understanding these interactions could lead to more personalized dietary and therapeutic strategies for managing CD in individuals with varying body mass indices(Buriánek F *et al.,* 2024) [15].

In summary, CD significantly impacts the composition and diversity of the gut microbiota, characterized by a reduction in beneficial bacteria, an increase in potentially pathogenic microbes, and decreased microbial diversity. While a gluten-free diet remains the cornerstone of CD management, it may not fully restore a healthy gut microbiota. Adjunctive therapies, such as probiotic supplementation, show potential in modulating the gut microbiota and improving clinical outcomes. Ongoing research into the gut microbiota's role in nutrient absorption and weight regulation in CD patients may further inform comprehensive management strategies, aiming to restore gut health and enhance the quality of life for individuals with CD.

SCFA Levels

SCFAs primarily acetate, propionate, and butyrate, are vital metabolites produced by the fermentation of dietary fibers by gut microbiota. These compounds play crucial roles in maintaining intestinal health, modulating immune responses, and serving as energy sources for colonocytes. In individuals with CD, an autoimmune disorder triggered by gluten ingestion, alterations in gut microbiota composition have been observed, leading to changes in SCFA production and concentrations. A study investigating free fatty acid profiles in various intestinal disorders identified a significant association between butyric acid levels and CD (Arcila-Galvis JE *et al.,* 2022) [35]. This research found that individuals with CD had altered concentrations of butyric acid compared to healthy controls, suggesting a disruption in the metabolic activities of butyrate-producing bacteria. Butyrate is essential for maintaining intestinal barrier integrity and regulating inflammation; thus, its altered levels may contribute to the pathogenesis of CD(Arcila-Galvis JE *et al.,* 2022) [35].

The gut microbiota of first-degree relatives of children with CD also exhibits distinctive characteristics. These individuals, despite not having CD themselves, showed differences in their gut microbial composition compared to unrelated healthy controls, indicating a potential genetic or environmental influence on gut microbiota that could predispose them to CD (Saviano A *et al.*, 2023) [10]. Such alterations may affect SCFA production, although specific SCFA levels were not detailed in this study. Dietary interventions have been explored to modulate SCFA production in CD patients. A study examined the effects of fiber supplementation on mucosal healing in CD patients (Rossi R *et al.,* 2023) [37]. The findings suggested that increased dietary fiber intake could enhance SCFA production, particularly butyrate, promoting mucosal healing and potentially alleviating CD symptoms. This approach underscores the therapeutic potential of dietary modifications in managing SCFA levels and improving intestinal health in CD patients(Addanki S *et al.,*2024) [19].

Therefore, CD is associated with alterations in gut microbiota that impact the production and concentration of short-chain fatty acids, particularly butyrate. These changes may contribute to intestinal inflammation and barrier dysfunction observed in CD patients. Dietary interventions, such as fiber supplementation, show promise in restoring SCFA levels and promoting mucosal healing, offering potential therapeutic strategies for managing CD.

Figure legends

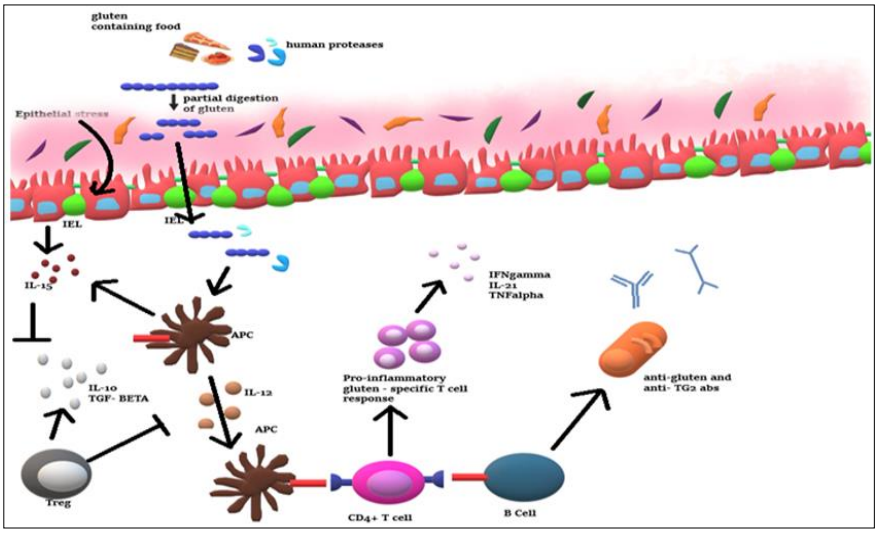

Fig 1: Immunopathogenesis of Celiac Disease Triggered by Gluten Exposure Upon ingestion, gluten is partially digested and crosses the stressed intestinal epithelium, leading to IL-15 production and activation of intraepithelial lymphocytes (IELs). Antigen-presenting cells (APCs) stimulate pro-inflammatory $CD4^+$ T cells, promoting cytokine release (IFN-γ, IL-21, TNF-α) and B cell activation, which results in anti-gluten and anti-TG2 antibody production. Regulatory T cells (Tregs) are suppressed, amplifying the inflammatory response.

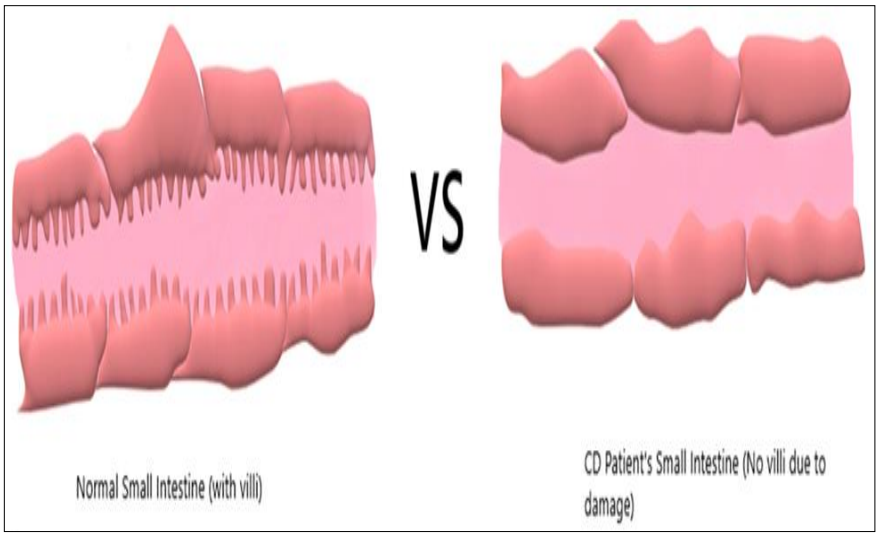

Fig 2: Comparison of Small Intestinal Morphology in Healthy Individuals vs. Celiac Disease Patients. The left panel shows a healthy small intestine with intact villi essential for nutrient absorption. The right panel illustrates the flattened and damaged mucosa in a celiac disease (CD) patient, where villous atrophy impairs absorption due to immune-mediated injury.

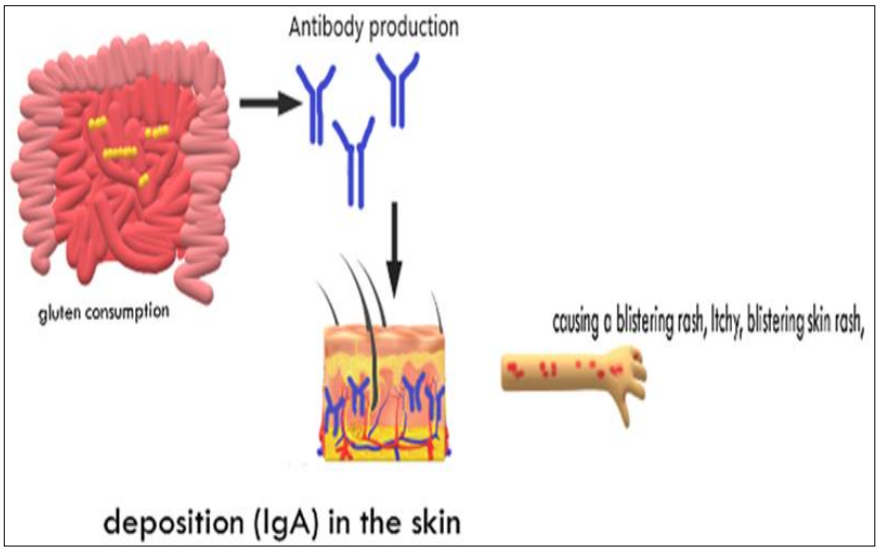

Fig 3: A) Pictorial Depiction of Dermatitis Herpetiformis (DH). Gluten consumption triggers the production of IgA antibodies, which deposit in the skin and lead to an intensely itchy, blistering rash—characteristic of dermatitis herpetiformis, a common skin manifestation of celiac disease.

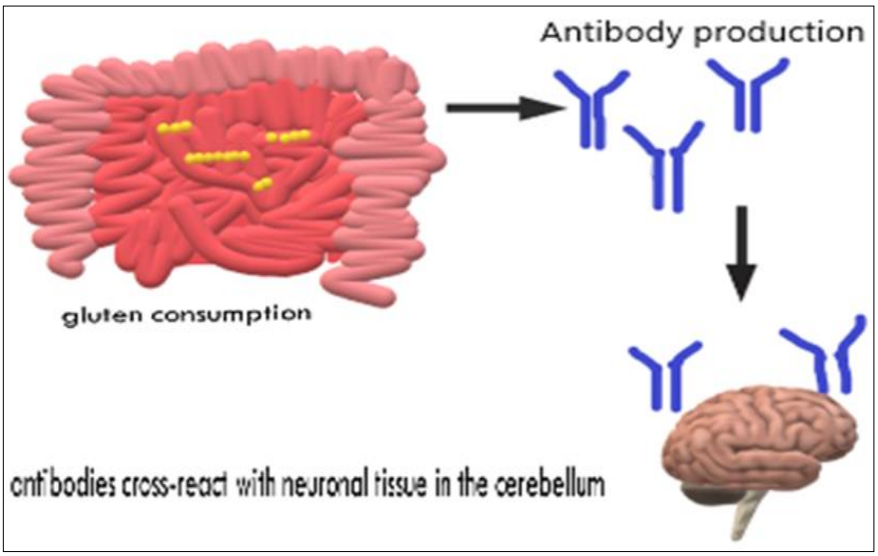

Fig 3: B) Pictorial Depiction of Gluten Ataxia (GA) In gluten ataxia, gluten ingestion stimulates antibody production, and these antibodies cross-react with neuronal tissue in the cerebellum, potentially leading to impaired coordination and balance due to autoimmune damage. Since the normal and atypical clinical signs of GRDs overlap, diagnosing them can be difficult.

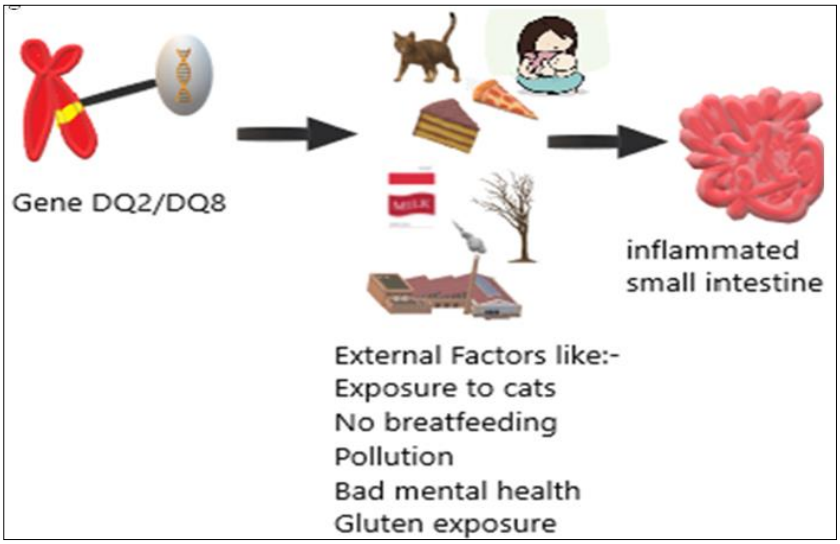

Fig 4: Pictorial Depiction of How Genetic and Environmental Factors Contribute to Celiac Disease (CD) Individuals with HLA-DQ2 or DQ8 genetic predisposition are more susceptible to developing CD when exposed to external factors such as gluten intake, pollution, lack of breastfeeding, pet exposure, poor mental health, and other environmental triggers, ultimately leading to inflammation of the small intestine.

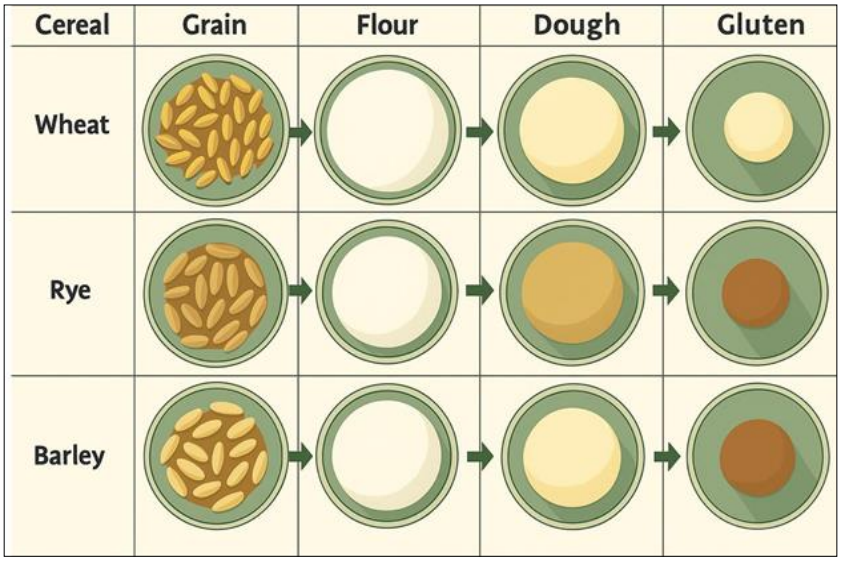

Fig 5: Gluten in cereal grainsdemonstrates how gluten is derived from wheat, rye, and barley through stages of grain to dough, emphasizing their gluten content visually.

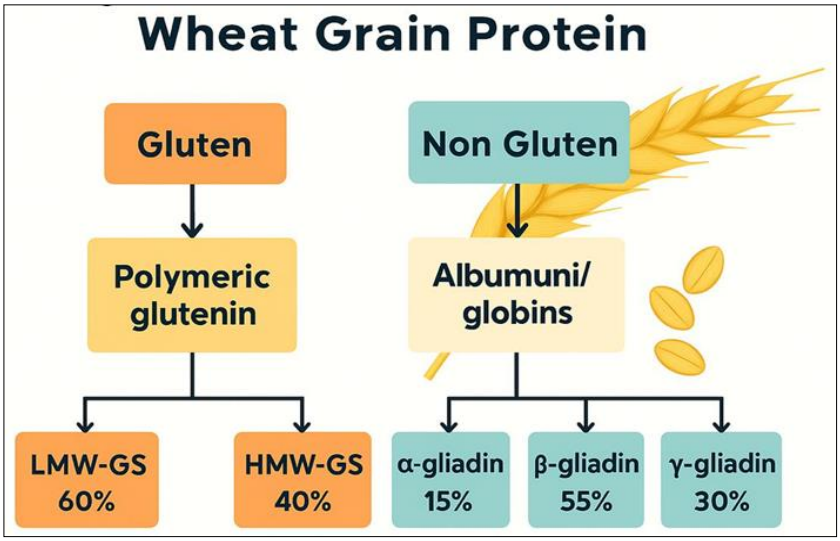

Fig 6: Schematic representation of wheat grain protein composition highlighting gluten and non-gluten fractions. Gluten comprises polymeric glutenin (with low and high-molecular-weightsubunits) and monomeric gliadins (α-, β-, and γ-gliadins), while non-gluten proteins include albumins and globulins.

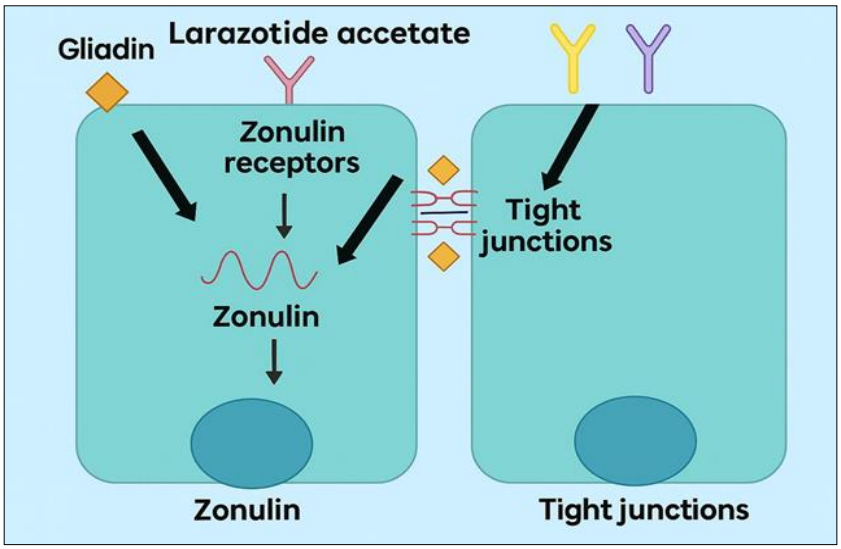

Fig 7: Illustration of the zonulin pathway, where gliadin triggers zonulin release leading to the opening of intestinal tight junctions. Larazotide acetate blocks zonulin receptors, helping to maintain tight junction integrity and reduce intestinal permeability.

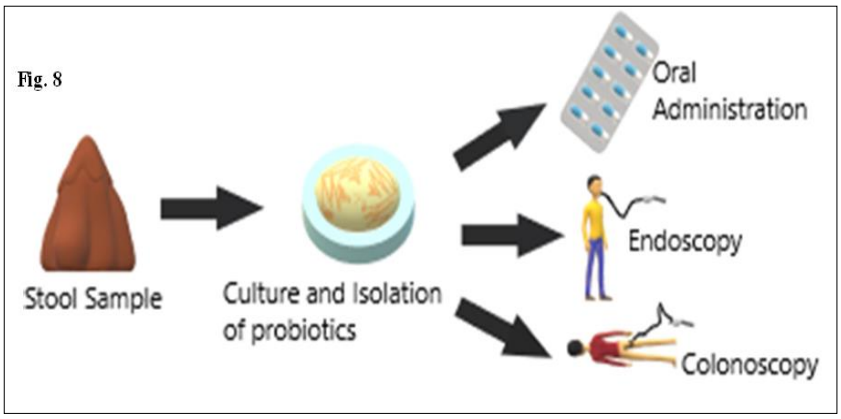

Fig 8: Overview of the fecal microbiota transplantation (FMT) process involving collection of stool samples, culture and isolation of probiotics, followed by administration via oral capsules, endoscopy, or colonoscopy for therapeutic purposes.

Conclusion

CD is a long-term autoimmune condition that is provoked by gluten, which is a protein found in wheat, barley, and rye. It predominantly affects individuals with a genetic predisposition, particularly those carrying the HLA-DQ2 or HLA-DQ8 alleles. Gliadin, a component of gluten, is resistant to digestion and becomes more immunogenic after being modified by tissue transglutaminase (tTG), resulting in damage to the intestines. At present, the only successful treatment is a lifelong gluten-free diet, but adhering to this regimen can be challenging and may not always lead to complete healing of the gut. Research is underway into alternative treatments, such as oral enzymes that degrade gluten, medications that impede gluten absorption or immune responses, and wheat that has been genetically altered. An imbalance in gut microbiota (dysbiosis), particularly a decrease in short-chain fatty acids such as butyrate, also contributes to CD. The use of probiotics, prebiotics, and dietary changes may assist in restoring microbial equilibrium. CD is characterized by a complex interaction among genetics, immunity, and environmental factors. Although diet remains essential, new treatment options might provide more effective solutions.

Acknowledgments

The authors acknowledge department of biotechnology, JIIT Noida for providing the necessary infrastructure. First author Aindree thankful to Department of Biotechnology, Council of Science and Technology, Uttar Pradesh (UP-CST) for providing the fellowship.

Declaration

Ethics approval and consent to participate Not applicable.
Competing interests, the authors declare no competing interests.

References

1. Cazac G-D, Mihai B-M, Ștefănescu G, Gîlcă-Blanariu G-E, Mihai C, Grigorescu E-D, *et al*. Celiac Disease Gluten-Free Diet and Metabolic Dysfunction-Associated Steatotic Liver Disease. Nutrients,2024:16:2008.
2. Wieser H. Chemistry of Gluten Proteins. Food Microbiology,2007:24:115–119.
3. Biesiekierski JR. What Is Gluten. Journal of Gastroenterology Hepatology,2017:32:78–81.
4. Balakireva A, Zamyatnin A. Properties of Gluten Intolerance Gluten Structure Evolution Pathogenicity and Detoxification Capabilities. Nutrients,2016:8:644.
5. Costantini S, Rossi M, Colonna G, Facchiano A. Modelling of HLA-DQ2 and Its Interaction with Gluten Peptides to Explain Molecular Recognition in Celiac Disease. Journal of Molecular Graphics and Modeling,2005:23:419–431.

6. Koning F. Celiac Disease Caught Between a Rock and a Hard Place. Gastroenterology,2005:129:1294–1301.
7. Borbulevych OY, Piepenbrink KH, Gloor BE, Scott DR, *et al*. T Cell Receptor Cross-Reactivity Directed by Antigen-Dependent Tuning of Peptide-MHC Molecular Flexibility. Immunity,2009:31:885–896.
8. Kagnoff MF. Celiac Disease Pathogenesis of a Model Immunogenetic Disease. Journal of Clinical Investigation,2007:117:41–49.
9. Dochat C, Afari N, Satherley R-M, Coburn S, McBeth JF. Celiac Disease Symptom Profiles and Their Relationship to Gluten-Free Diet Adherence Mental Health and Quality of Life. BMC Gastroenterology,2024:24:9.
10. Saviano A, Petruzziello C, Brigida M, Loprete MRM, Savioli G, Migneco A, *et al*. Gut Microbiota Alteration and Its Modulation with Probiotics in Celiac Disease. Biomedicines,2023:11:2638.
11. Ertaş Öztürk Y, Karabudak E, Eğritaş Gürkan Ö, Dalgıç B. Gut Microbiota Alterations and Associations with Nutrients in Children with Celiac Disease. Food Science and Nutrition, 2024, 4337.
12. Abdulkarim AS, Murray JA. Celiac Disease. Current Treatment Options in Gastroenterology,2002:5:27–34.
13. Jabri B, Sollid LM. Tissue-Mediated Control of Immunopathology in Coeliac Disease. Nature Reviews Immunology,2009:9:858–870.
14. Petersen J, Montserrat V, Mujico JR, Loh KL, *et al*. T-Cell Receptor Recognition of HLA-DQ2–Gliadin Complexes Associated with Celiac Disease. Nature Structural and Molecular Biology,2014:21:480–488.
15. Buriánek F, Gege C, Marinković P. New Developments in Celiac Disease Treatments. Drug Discovery Today,2024:29:104113.
16. Janatuinen E, Kemppainen TA, Julkunen R, Kosma V-M, *et al*. No Harm from Five Year Ingestion of Oats in Coeliac Disease. Gut,2002:50:332–335.
17. Singh A, Silvester J, Turner J, Absah I, Sparks BA, Walsh CM, *et al*. Celiac Disease in North America What Is the Current Practice of Pediatric Gastroenterology Providers. JPGN Reports, 2024, 12087.
18. Studerus D, Schümann M. What Is Established in the Management of Celiac Disease. Innere Medizin Heidelberg, 2023.
19. Addanki S, Mashukova A, Levy AS. Exploring the Link between Celiac Disease and Obesity A Potential Role of Gut Microbiome. Intestinal Research, 2024.
20. Ciacchi L, Farenc C, Dahal-Koirala S, Petersen J, *et al*. Structural Basis of T Cell Receptor Specificity and Cross-Reactivity of Two HLA-DQ2.5-Restricted Gluten Epitopes in Celiac Disease. Journal of Biological Chemistry,2022:298:101619.
21. Roszkowska A, Pawlicka M, Mroczek A, Bałabuszek K, *et al*. Non-Celiac Gluten Sensitivity A Review. Medicina Buenos Aires,2019:55:222.
22. Cabanillas B. Gluten-Related Disorders Celiac Disease Wheat Allergy and Nonceliac Gluten Sensitivity. Critical Reviews in Food Science and Nutrition,2020:60:2606–2621.
23. Silva-Paz RJ, Silva-Lizárraga RR, Jamanca-Gonzales NC, Eccoña-Sota A. Evaluation of the Physicochemical and Sensory Characteristics of Gluten-Free Cookies. Frontiers Nutrition,2024:10:1304117.
24. Catassi C. Gluten Sensitivity. Annals of Nutrition and Metabolism, 2015.
25. Hadjivassiliou M, Chattopadhyay AK, Grünewald RA, Jarratt JA, *et al*. Myopathy Associated with Gluten Sensitivity. Muscle & Nerve,2007:35:443–450.
26. Osman D, Umar S, Muhammad H, Nikfekr E, Rostami K, Ishaq S. Neurological Manifestation of Coeliac Disease with Particular Emphasis on Gluten Ataxia and Immunological Injury A Review Article. Gastroenterology and Hepatology from Bed to Bench,2021:14:313–322.
27. Payne PI. Genetics of Wheat Storage Proteins and the Effect of Allelic Variation on Bread-Making Quality. Annual Review of Plant Biology,1987:38:141–153.
28. Shewry PR. Wheat. Journal of Experimental Botany, 2009.
29. Khan K, Shewry PR. Wheat Chemistry and Technology, 2009.
30. Janatuinen E, Kemppainen TA, Julkunen R, Kosma V-M, *et al*. No Harm from Five Year Ingestion of Oats in Coeliac Disease. Gut an International Journal of Gastroenterology & Hepatology,2002:50:332–335.
31. Mandile R, Lerro F, Carpinelli M, D'Antonio L, Greco L, Troncone R, *et al*. Potential Celiac Disease in Children Health Status on a Long-Term Gluten-Containing Diet. Nutrients,2024:16:1708.
32. Skoracka K, Hryhorowicz S, Tovoli F, Raiteri A, Rychter AM, Słomski R, *et al*. From an Understanding of Etiopathogenesis to Novel Therapies What Is New in the Treatment of Celiac Disease. Frontiers in Pharmacology,2024:15:1378172.
33. Nikoloudaki O, Celano G, Polo A, Cappello C, Granehäll L, Costantini A, *et al*. Novel Probiotic Preparation with *in Vivo* Gluten-Degrading Activity and Potential Modulatory Effects on the Gut Microbiota. Microbiology Spectrum,2024:12:03524-23.
34. Wu X, Lin Q, Liu K, Wu J, Shan Z. Gastrointestinal Microbiome and Gluten in Celiac Disease. Annals of Medicine,2021:53:1797–1805.
35. Arcila-Galvis JE, Loria-Kohen V, Ramírez de Molina A, Carrillo de Santa Pau E, Marcos-Zambrano LJ. A Comprehensive Map of Microbial Biomarkers along the Gastrointestinal Tract for Celiac Disease Patients. Frontiers in Microbiology,2022:13:956119.
36. Wulczynski M, Constante M, Blom J, Rueda G, Rossi L, El-Chaar N, *et al*. A57 Suboptimal Fibre Consumption and Altered Fibre Metabolism in Celiac Disease Throughout the Gastrointestinal Tract. Journal of the Canadian Association of Gastroenterology, 2025, gwae059.057.
37. Rossi R, Dispinzieri G, Elvevi A, Massironi S. Interaction between Gut Microbiota and Celiac Disease from Pathogenesis to Treatment. Cells,2023:12:823.
38. Kelley K, Dogru D, Huang Q, Yang Y, Palm NW, Ludvigsson J, *et al*. Children Who Develop Celiac Disease Exhibit Distinct Metabolic Pathways Among Their Gut Microbiota Years Before Diagnosis. bioRxiv Biology Research Archive, 2024.
39. Helms S. Celiac Disease and Gluten-Associated Diseases. Alternative Medicine Review,2005:10:172–192.
40. Szeltner Z, Polgár L. Structure Function and Biological Relevance of Prolyl Oligopeptidase. Current Protein and Peptide Science,2008:9(1):96–107.
41. Tjellström B, Stenhammar L, Högberg L, Fälth-Magnusson K, *et al*. Gut Microflora Associated Characteristics in First-Degree Relatives of Children with Celiac Disease. Scandinavian Journal of Gastroenterology,2007:42:1204–1208.