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**Review Article**

# Gluten is a Proinflammatory Inducer of Autoimmunity

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## Abstract

Gluten has multiple harmful effects that compromise human health, not only in gluten-dependent diseases but also in non-gluten-affected chronic inflammatory conditions. After consumption, the indigestible gluten peptides are modified by luminal microbial transglutaminase or transported through the gut epithelium to interact with the highly populated mucosal immune cells. As a disruptor of gut permeability, gluten peptides compromise tight junction integrity, allowing foreign immunogenic molecules to reach internal compartments. Gliadin peptides are distributed systemically to remote organs, where they encounter endogenous tissue transglutaminase. Following post-translational deamidation or transamidation, the peptides become immunogenic and pro-inflammatory, inducing organ dysfunction and pathology. Cross-reactivity and sequence homology between gluten/gliadin peptides and human epitopes may contribute to molecular mimicry in autoimmunity induction. A gluten-free diet can prevent these phenomena through various mechanisms. As proof of concept, gluten withdrawal alleviates disease activity in chronic inflammatory, metabolic, and autoimmune conditions, and even in neurodegeneration. We recommend combining the gluten-free and Mediterranean diets to leverage the advantages of both. Before recommending gluten withdrawal for non-gluten-dependent conditions, patients should be asked about gut symptomatology and screened for celiac-associated antibodies. The current list of gluten-induced diseases includes celiac disease, dermatitis herpetiformis, gluten ataxia, gluten allergy, and non-celiac gluten sensitivity. In view of gluten being a universal pro-inflammatory molecule, other non-celiac autoinflammatory and neurodegenerative conditions should be investigated for potential gluten avoidance.

## Introduction

Inflammation is a vital biological response that regulates interactions between humans and the environment, with nutrition playing a crucial role. Due to the surge in chronic inflammatory diseases,[1] and increasing interest in anti-inflammatory dietary therapy,[2,3] the exploration of pro-inflammatory nutrients has become a primary focus for clinical and scientific communities.[4] In fact, the understanding of immune system-driven chronic inflammation and its associated chronic diseases are still not well-developed. The contribution of dietary constituents to inflammatory, metabolic, autoimmune, cancerous, allergic, and neurodegenerative diseases remains poorly defined. The frequently consumed Western diet is considered pro-inflammatory,[5] while vegetarian, non-processed, and traditional foods are recommended as anti-inflammatory.[6,7]

**Keywords:** Pro-inflammatory nutrients; Anti-inflammatory nutrients; gluten; Gliadins; Celiac disease; Autoimmune diseases; Chronic inflammation.

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Since it is impossible to cover all pro-inflammatory nutrients, this review will focus on the role of gluten/gliadin in celiac disease (CD)-induced inflammation, and explore their potential involvement in other non-celiac chronic inflammatory conditions. Gluten is composed of two main proteins: glutenin and gliadin. Gliadins make up about 70% of the protein in gluten and are the molecules responsible for the harmful immune response that results in intestinal injury in CD. Since the gut is the entry point for gluten and a crossroads for multiple nutrients, food additives, microbes, enzymatic digestion, and absorption, various gluten-affected luminal events irradiate peripherally, inducing remote organ, gluten-related, inflammatory damage.[8,9] The luminal content impacts the enteric ecosystem. Certain dietary components, like gluten, breach tight junction integrity, resulting in increased intestinal permeability, and induce changes in the composition and diversity of the microbiome towards disease-specific dysbiosis or pathobiosis. Finally, the enhanced local enzymatic capacity for post-translational modification of proteins can turn naïve peptides to lose their tolerance and become auto-immunogenic ones. The present narrative review expands on the multiple gut-originated axes and their relationship to remote organ autoimmune diseases. Brain, joint, bone, endocrine, liver, kidney, heart, lung, and skin autoimmune diseases are connected to the deregulated events in the intestinal luminal compartment, forming the gut-systemic organ axe. Be-

ing a universal pro-inflammatory protein, affecting multiple body compartments, organs and tissue and systemically distributed, gluten peptides should be thoroughly investigated for their potential detrimental effects. If substantiated, traditional gluten dependent diseases should be ruled out and gluten-free Mediterranean diets should be recommended.

### *Gluten-induced inflammation in celiac disease*

The incidence of celiac disease is around 1–2% of the global population, representing a chronic, autoimmune, multisystem, inflammatory, and immune-mediated condition.[10] The intestine is the primary target organ; however, extra-intestinal organs are affected as well.[8,9] Currently, the only accepted and proven nutrient that induces the disease is gluten, a general name for proteins found in many grains, such as wheat, barley, rye, and partially in oats.[11] Interestingly, "gluten" stands for "glue" in Latin, named for its adhesive and viscoelastic properties. The autoantigen associated with CD is tissue transglutaminase (tTG),[12,13] and several antibodies are used for its serological diagnosis.[14–16]

Celiac disease fulfills the criteria of a gluten-induced autoimmune inflammatory condition in the following aspects[17–19]: histologically, there is epithelial and mucosal inflammatory destruction, presented by villous atrophy and intraepithelial lymphocytosis[20,21]; immunologically, the adaptive[22] and innate immune[23] systems are activated[24,25]; there is a surge in pro-inflammatory cytokines,[26] where gliadin peptides induce increased levels of IL-15, IFN-γ, IL-6, tumor necrosis factor (TNF)-α, IL-1β, CCL2, CCL3, and many more[27]; dysbiosis, a feature of many autoimmune diseases (ADs), exists in the celiac gut lumen, and gliadin can directly induce intestinal flora dysbiosis.[28–30] Upon successful gluten withdrawal, all the above-mentioned inflammatory features are significantly ameliorated[31,32]; refractory CD and celiac crisis respond to steroids or immunosuppressive therapy[33]; and finally, genetic predisposition is essential for the disease's development.[25] It can be summarized that CD is a hallmark condition where genetics, inflammation, autoimmunity, dysbiosis, and environmental gluten intersect.[25,34–38] It is well accepted that gluten-containing cereals contribute to chronic inflammatory conditions and various ADs, primarily by inducing gut dysbiosis, enhancing intestinal permeability, and initiating a pro-inflammatory immune response.[6,39–42] Interestingly, in addition to gluten, other wheat components, like lectins and enolase, might also act as proinflammatory molecules.[43–46]

### *The place of gluten in human nutrition and as a food additive*

Wheat is a major crop grown in most countries. Its annual production is 7.34 × 108 tons, cultivated on an area of 2.14 × 106 $km^2$, which sums up to the size of Greenland.[47]

Wheat consumption surpasses all other crops combined, making it the world's most favored staple food. The annual increase in gluten usage as a processed food additive over the last four to six decades is estimated at 1.8 ± 0.4%.[6] The global vital wheat gluten market, valued at $2 billion in 2019, is projected to reach $2.74 billion by 2027, representing a compound annual growth rate of 4% during the forecast period.[48]

Discovered in the Fertile Crescent nearly 14,000 years ago,[49] wheat-based foods became a staple after domestication. Wheat is a major source of protein, with gluten making up 80% of its total protein content.[6,50]

Gluten is a protein naturally found in certain prolamins, including wheat, barley, and rye. Although oats are considered gluten-free, they are often cross-contaminated with gluten.[11,51] Besides prolamins, gluten is found in numerous non-nutritional products, such as medications, toothpaste, and cosmetics. It acts as a binder, holding substances together and adding a "stretchy" quality. When omitted in baking, the resultant dough tears easily.[52]

In Western countries, wheat contributes significantly to health, providing dietary fiber, B vitamins, and mineral micronutrients, notably selenium, iron, and zinc.[53] There are two perspectives on wheat and gluten: public perception and reality.[50,53] Recently, the roles and functions of wheat and gluten have been scrutinized in unproven or pseudoscientific publications and popular media reports, giving the impression that wheat or gluten consumption has a deleterious and addictive effect on human health.[50,53] The common claim that gluten-free foods are inherently healthy is not well-supported by scientifically accepted controlled studies. Consequently, wheat/gluten withdrawal fashionistas have impacted multiple Western societies, changing their dietary habits.[50,53] While gluten itself provides no essential nutrients and its consumption can be avoided without compromising human well-being.[54] However, the only scientifically defined indication to withdraw gluten is in well-proven gluten-dependent conditions, namely, CD, dermatitis herpetiformis, gluten ataxia, and gluten/wheat allergy.[31,32,41,53,55–57] Despite the significant interest in non-celiac gluten sensitivity, much remains to be explored about its pathogenesis, and its potential nutritional triggers are still controversial.[55,58–61] A combined gluten-free and Mediterranean diet might be an attractive alternative to address the unhealthy aspects of a gluten-free diet (GFD).[53,62–64]

## The side effects of gluten

The more gluten is explored, the more side effects are disclosed. This topic has recently been reviewed by several grou ps.[6,8,9,41,42,65–67] There are various adverse effects of gluten that might impact health. These harmful effects are delivered through immunological and toxic pathways, leading to gut dysfunction or inadequacy.

### *Pro-inflammatory*

As mentioned above, gluten acts as a pro-inflammatory molecule.[8,9,25–27,34–39,68,69] The gliadin p31-43 peptide induces cellular stress, activates proliferative mechanisms of cryptic epithelial cells, drives enterocyte stress, induces a $Ca^{2+}$ surge (thus activating the CD autoantigen tTG), triggers a local pro-inflammatory storm, activates the NFκB signaling pathway, inhibits CFTR (cystic fibrosis transmembrane conductance regulator, an ion channel protein), alters vesicular trafficking, activates the inflammasome platform, and reduces autophagy.[68,70,71] Gliadin peptides are pro-oxidative, induce DNA damage, and are pro-apoptotic in in-vitro and ex-vivo studies.[72]

### *Alters the gut microbiome and increases intestinal permeability*

Gluten decreases the microbiome/dysbiome ratio composition and diversity, suppressing the beneficial metabolome toward inflammation.[28–30,73–77] Intestinal tight junction functional integrity is one of the most conserved protective mechanisms for human survival and is crucial for maintaining intestinal homeostasis. When disrupted, foreign molecules enter the epithelial barrier, come into contact with the subepithelial dense immune systems, and initiate chronic inflammation and autoimmunity. Increased intestinal permeability is a common feature of many of these conditions, including CD,[6,35–38,41,65–68,74,75] where gluten is a major disruptor of tight junction protective function.[6,78–81] Several observations strengthen the gluten-zonulin-increased permeability axis. Zonulin is a meas-

urable blood protein that reflects tight junction functionality. Increased zonulin blood level is considered a marker of an impaired intestinal barrier.[6,78–81] This active axis has been shown to operate in active and non-active CD patients and even in normal controls.[82] Larazotide acetate (AT-1001), a small peptide derived from Vibrio cholerae toxin, is one of the potential non-nutritional pharmacological strategies to treat CD patients.[56] Acting as a modulator of tight junction integrity with its anti-zonulin activity, it has been shown to be superior to placebo in improving gut symptoms in active CD patients.[83] The drug shows promise for counteracting enhanced intestinal permeability in some other chronic systemic diseases,[84–86] including severe COVID-19,[87,88] although it is not yet approved.

### *Immunogenicity*

One of the major unwanted effects of gluten is its immunological impact, closely connected to the inflammatory response. Gluten is an immunogenic protein that elicits anti-gluten/gliadin antibodies, even in non-CD patients and normal controls.[89–93] In addition, microbial transglutaminase (mTG)-treated gluten peptides in patients with CD are immunogenic.[94] When gliadin is cross-linked to tissue or mTG, transforming the naïve protein into an immunogenic one, CD patients mount substantial levels of neo-epitope tTG and mTG antibodies, respectively.[8,9,14–16,41,66,94–99] Intriguingly, in the presence of tTG and mTG-assisted gliadin docking, gluten/gliadin loses its human body tolerance, resulting in corresponding antibody secretion, representing a classical post-translation modification of proteins.[29,30,100] When tested in CD patients, the neo-epitope tTG and mTG exhibit higher immunogenic activity compared to gliadin undocked enzymes. Furthermore, the tTG neo-epitope IgA+IgG isotypes show higher optical density activity, better reflect intestinal injury, and expose higher specificity and sensitivity by targeting different autoantigens compared to the conventional tTG isotypes.[98,99] The same was found for the mTG neo-epitope.[14,16,95] However, the list of gluten's immunological adverse effects is much more extensive.[41]

*In vitro studies* have shown that gluten induces macrophages to produce proinflammatory cytokines and nitric oxide (NO).[101–103] Upregulated MHCII, co-stimulatory molecules, TRLs, cytokine, and chemokine production were observed in dendritic cells.[104,105] Higher expression of NKG2D and CD71 on NKp46(+) cells has been shown in lymphoid organs.[106] Finally, increased permeability and the production of TNFα and IL-1β were detected when gluten was applied to the Caco-2 cell line.[107]

*In vivo studies* on rats and mice have shown the following compared to controls: cytokine surge in TH1 intestinal and mesenteric lymph nodes, TH1 cytokine pattern in islet infiltrate, and increased number of intestinal pathogenic intraepithelial cells.[108–110] Studies on non-obese diabetic (NOD) mice revealed increased activated intestinal $CD4^+$ T cells, changes in TH1/TH2 intestinal cytokine ratios associated with activated dendritic and TH17 cells, increased natural killer cell cytotoxicity, and cytokine secretion of IFN-γ and IL-6.[106,111–113] NKG2D is a proinflammatory, auto-immunogenic co-stimulatory molecule; it is an activating receptor mostly expressed on cells of the cytotoxic arm of the immune system. Gluten withdrawal lowered NKG2D and its ligand expression in NOD and BALB/c mice, attesting to gluten's impact on the co-stimulatory interplay between tolerance and immune inflammation.[114]

When exposed to gliadin/gluten, BALB/c mice showed proportional changes in regulatory T-cell subsets, increased numbers of TH17 in peripheral lymph nodes, proinflammatory cytokine patterns in $FOX3^-$ and $FOXP3^+$ T cells, and robust activation of innate immune and TH17 cells.[115–117] *Ex vivo* and mice studies showed gluten-induced dendritic cells' production of IL-1β and, interestingly, enhanced neutrophil migration towards gliadin peptides.[118,119]

### *Cellular dysfunction and cytotoxicity*

At the cellular level, gliadin has been found to drive cytotoxicity, decrease cell viability and differentiation, induce LDH secretion, promote apoptosis, and decrease RNA, DNA, and glycoprotein synthesis when applied to HCT116 cells.[41] In 1976, Hudson *et al*.[120] documented growth inhibition and phenotypic changes in various human cell lines induced by gliadin exposure. Several *in vitro* studies point to the cytotoxicity of this molecule. Gliadin induced agglutination in K562 cells, decreased F-actin content in enteric 407 cell lines, suppressed cell growth and viability, induced apoptosis, and altered redox equilibrium in Caco-2 cells and cell morphology in LoVo, two- and three-dimensional cell culture while causing rearrangement of the cytoskeleton through the zonulin molecular structure. This results in the loss of tight junction functionality in IEC-6 cells.[121]

### *Disturbance of oxidative equilibrium*

Oxidative equilibrium plays an essential role in cell homeostasis, and its imbalance is involved in many chronic inflammatory diseases. Gliadin-induced oxidative stress was reported extensively on various cell lines, including Caco-2, HT29, SH-SY5Y, T84, and LoVo, and reviewed in depth.[121–123] For example, the content of glutathione was reduced (−20% vs. controls), and the activity of related enzymes was inhibited.[121] The dysfunctional antioxidant machinery can result in inflamed CD intestinal mucosa, making it more vulnerable to further oxidative stress and hindering mucosal recovery.[123]

### *Induce apoptosis*

Intestinal homeostasis relies heavily on enterocyte viability and death to maintain the high cellular turnover necessary to cope with a hostile environment. Programmed cell death is pivotal for this equilibrium but can be detrimental in pathological conditions. The apoptotic pathway is over-activated in CD patients and plays a key role in inducing gut inflammation.[73,124] Inflammatory response and enteric damage induced by gliadin p31-43 drive multiple programmed cell death pathways in the small intestine of mice.[124]

### *Gluten impacts epigenetics*

The HLA-DQ2 and HLA-DQ8 haplotypes are widely associated with CD, but some people without these genes still develop the disease. Genetic predisposition can be regulated or affected by epigenetic modifications and cannot account for all reported CD cases. Environmental epigenetics adds substantial understanding to the disease's evolution and its multi-faceted phenotypic presentations.[8,125,126] The main epigenetic pathways include histone modifications, DNA methylation, non-coding RNAs, and RNA methylation, where microRNAs might be used to characterize various classes of CD patients.[125] Gluten affects gene expression by changing methylation status.[122,127] The impact of gliadin on epigenetics has been observed in CD and non-CD MH-SY4Y and Caco-2 cell lines.[122] Wheat-derived peptide epigenetic alterations might be important during the postnatal nutritional transition from maternal breastfeeding or infant formula to complementary gluten consumption.[122,127]

### *Gluten affects cellular metabolism*

Being pro-inflammatory, cytotoxic, oxidative, apoptotic, and highly immunogenic, gluten peptides can alter fundamental cellular metabolic networks. Wheat-derived peptides induce 50% inhibi-

tion in cellular proliferation, 20% suppression of colony-forming ability, and significantly lower alkaline phosphatase activity during Caco-2 cell line differentiation.[128] Moreover, the peptic-tryptic digestion of wheat inhibited more than half of DNA and RNA synthesis, glycoprotein synthesis, and altered mitochondrial functions in Caco-2 cells.[129,130] Wheat and gluten peptides are important in nutrigenomics and nutrigenetics, revealing various interplays between diet, specific nutritional components, and gene expression.[127]

### *Gluten affects mental health*

A plethora of peripheral and central neurological manifestations affect the celiac population[65,131–135] indicating that gluten consumption can also impact psychiatric behavior and mental health. Anti-neuronal antibodies such as transglutaminase 6, GAD-65, GAD-67, cerebellar peptide, and myelin-associated glycoprotein are part of the CD-associated autoantibodies.[136] During intestinal digestion, resulting gluten fragments have strong opioid activity.[137] These morphine-like substances, called gluten exorphins, have proven opioid effects that might affect mental health.[138] Opioid receptors are scattered throughout the body, including in the gut, brain, and peripheral nervous system. Facing intestinal and blood-brain barrier disruption[139,140] caused by microbes, stress, dietary components, pollutants, alcohol, or over-the-counter drugs, gluten-originated exorphins can impact mental functions.[6,41,42,65,66,131,137] Cognitive impairment and "brain fog" might be associated with CD,[141,142] and responsiveness to gluten withdrawal has been reported.[143–145]

In a more holistic view, the association between oxidative stress, gene expression, dysbiome and its mobilome, impaired gut and brain permeability[146] and gut inflammation associated with gluten-derived peptides, is interrelated and interconnected during the autoimmune cascade evolution in CD.

## Gluten peptides are systemically distributed

Prolamins containing gluten are main nutritional staples, and processed food gluten is heavily consumed.[6,41,42,65,66,94] Consequently, gluten is widespread in the environment, in the gut lumen, and in contact with the epithelial monolayer and mucosal immune systems. CD is considered a gradually developing, mostly hypo-symptomatic or even asymptomatic chronic enteric inflammatory condition. In reality, it can abruptly erupt as an acute, symptomatic, sometimes life-threatening event involving the gut and extra-intestinal peripheral organs.[8,147] Many *in vivo*/*ex vivo* or *in vitro* models involving CD duodenal biopsies, intestinal cell lines, or incidental gluten intake have reported acute effects within 48 h of incubation or ingestion, which were recently summarized. These acute phenotypic, cellular, and laboratory events demonstrate the potential ability of gluten peptides to impact the entire human body.[8,9,147,148] A major question is whether gluten/gliadin peptides pass the protective mechanical or immunological intestinal barriers to penetrate inside the body and reach remote compartments and organs. Several observations support the systemic distribution of these peptides, and suggested mechanisms include:

### *Transepithelial passage of gluten peptides*

The discussion on how gliadin peptides pass the gut epithelial monolayer is ongoing, but it is known that both paracellular and transcellular pathways are involved.[67] There are three methods of transporting molecules through a cell: endocytosis,[67,149] endoplasmic reticulum-assisted transcytosis,[150] and secretory IgA-transferrin receptor-assisted translocation of intact gluten peptides below the epithelium.[151] Paracellularly, following gliadin digest binding to its CXCR3 receptor, increased zonulin levels compromise tight junction function by activating the EGFR-PAR2-MyD88-mediated signaling pathways, resulting in increased intestinal permeability.[152]

Most recently, Stricker S. *et al*. visualized gliadin peptide transport into CD enterocytes using intestinal biopsies and the RACE (Rapid uptake of Antigen into the Cytosol of Enterocytes) cell line.[150] The nutrition-originated peptides were transported through the endoplasmic reticulum and deposited below the enterocyte monolayer. This deposition proves that luminal gluten peptides penetrate the epithelial barrier, hence, facing the mucosal and submucosal immune networks.

In fact, gluten-dependent subepithelial deposits involving IgA-tTG are among the hallmark markers for early CD, even in seronegative patients and before histological damage occurs.[153] The cohabitation of gluten peptides with these specific IgA-tTG deposits in the subepithelial space reinforces the transepithelial transport of gluten peptides.[13,154] Additionally, the immunogenic CD supramolecule, a 33-residue peptide from alpha-2 gliadin, was directly visualized in gluten-sensitive macaques,[155] and gluten-stimulated CD-specific enteric T cells were shown to increase the transepithelial flux of gluten peptides.[156] TTG-gluten polymeric complexes are potent antigens for tTG-specific mucosal B cells, supported by diverse subepithelial gluten-specific T cells.[157] Finally, gluten peptides can be presented by subepithelial dendritic cells.[158] Thus, isolated or complexed gluten/gliadin peptides located in the lamina propria are presented by local antigen-presenting cells, activating the adaptive and innate mucosal networks and inducing CD-specific autoantibodies.

### *Gluten metabolites are found in human body fluids*

Physio-anatomical logic indicates that urinary secretion of a peptide most likely originates from the bloodstream. Recently, Upadhyay D *et al*. reported that gluten sensitivity expresses itself in a potential CD at the metabolic level before any intestinal damage.[159] Decreased levels of histidine, tyrosine, glycine, and tryptophan, and altered levels of another six metabolites were detected in the mucosa or plasma of potential CD patients compared to active CD patients and healthy controls. Intriguingly, raising the topic of gluten addiction and mental health, gluten metabolites, namely, exorphin B4 and B5, are found in normal human blood.[160,161] A hypothetical mechanism for gluten masking its own toxicity by these gluten-originated exorphins has been suggested.[138] Additionally, multiple gluten-dependent circulating miRNAs that appear before IgA-tTG positivity and are responsive to gluten withdrawal have been characterized.[162,163]

Urinary gluten metabolites have been extensively reported. Gluten dose escalation, gluten-free diet adherence assessment, urinary gluten intake-dependent miRNAs, urine peptidomics analysis, and urinary metabolic alterations have all been documented.[159,163–166]

### *Tissue transglutaminase whole body distribution and biological functions*

Before describing gluten peptide distribution in tissues and organs, it is important to remember that tTG is ubiquitous in the human body.[13] It is the autoantigen in CD,[12] its prime substrate is gluten,[94] and the enzyme induces posttranslational modification of gluten,[29] making gluten immunogenic in several gluten-dependent conditions.[13,66] Cellular-wise, the enzyme spans all intracellular organelles and compartments, including transmembrane areas, and is secreted extracellularly.[13,167] Tissue-wise, it is ubiquitously ex-

pressed in most human tissues.[13,167] Due to its enzymatic biochemical activities, tTG is involved in multiple human biological events and diseases.[13,167,168] Since gluten peptides circulate systemically, the chances of tTG encountering them are high. The missing part of the tTG-blood-gluten triangle is the localization of gluten/gliadin metabolites in remote extra-intestinal organs.

### *Gluten metabolites are found in human organs*

Because CD is a multifaceted condition with a plethora of extra-intestinal phenotypes, patients with the disease are at risk of developing remote organ pathologies.[8,9,30,41,42,55,65,66] The enzyme tTG can cross-link numerous protein substrates, and the resulting aggregates can be deposited in various organs.[169] Below are the main organs where tTG and gluten might orchestrate or be involved in local pathologies:

### *Gluten deposits in the cerebellum*

Gluten ataxia is an autoimmune ataxia and an integral part of gluten-dependent ADs. Brain IgA-tTG2 and tTG6 deposits have been reported in patients, primarily in the cerebellum, pons, and medulla.[170,171] Intense perivascular deposition and inflammation might allow circulating gluten peptide and IgA-tTG2/tTG6 antibody entry through a leaky blood-brain barrier, depositing in the central nervous system.[172] Indeed, when serum from gluten ataxia patients was injected into the ventricles of mice, ataxia developed within 3 h post-injection.[172,173] Moreover, cross-reactive antibodies are shared between gluten peptides and Purkinje cell epitopes, suggesting a potential molecular mimicry pathway to cerebellar autoimmunogenesis.[174] Despite these findings, the characterization of gluten-IgA-tTG2/tTG6 deposits in the patient's cerebellum requires further evaluation.

### *Gluten peptides impact chronic inflammatory brain conditions*

The gut-brain axis was recently described,[131,135,175,176] but the role of nutrients in activating these pathways is not clearly defined.[6,8,9,29,30,177] Recent papers strengthen the potential relationship between gluten consumption and neurodegenerative, neuroinflammatory, and central ADs in susceptible individuals.[65,66,134,178] It appears that gluten peptides contribute to neurodegeneration and chronic brain inflammatory diseases.[65,66,178] By specific dysbiosis, enhanced gut permeability, many cross-reactive antibodies with sequence similarity to human brain epitopes, and multiple adverse effects described above, the circulating repertoire of gluten peptides is involved in neurodegeneration.[65,66,134] The combined cross-reactivity and sequence similarity suggest molecular mimicry and allude to autoimmune mechanisms resulting in gluten-related brain conditions.

### *Gluten deposit in the thyroid*

Hashimoto's thyroiditis and CD often overlap, sharing genetic, environmental, symptomatic, immunogenic, pathological, hormonal, and even serological aspects.[179] Both entities are integral parts of polyendocrinopathy syndrome.[180] There is a continuous debate concerning whether and when to screen patients for CD serology and if there is a place for a gluten-free diet in autoimmune thyroid diseases.[179,181–183] The tTG enzyme resides in the thyroid follicles and extracellular matrix.[184,185] In CD patients, tTG antibodies bind to these thyroid regions, and their levels correlate with thyroid peroxidase antibody activity.[185] The findings suggest that CD-associated antibodies could be involved in thyroid dysfunction, thus reinforcing the gut-thyroid axis. Supporting this, Vojdani *et al*. applied affinity-purified antibodies made against wheat, alpha-gliadin peptide, and wheat germ agglutinin to various human tissue antigens, finding moderate to strong reactions with thyroid peroxidase and many other autoantigens.[44,186]

### *Gluten deposits in the skin*

Dermatitis herpetiformis is a dermatological gluten-dependent disease characterized by cutaneous anti-tTG3 IgA deposits, where tTG3c is the autoantigen of the disease.[187] Interestingly, similar aggregates can be detected in the skin of CD patients.[188] tTG3 is a member of the tTG family and can cross-link with its favorable gluten/gliadin peptides. The skin anti-tTG3 IgA deposits in dermatitis herpetiformis mirror the subepithelial IgA-tTG deposits in CD. The herpetiform dermatological eruption is only one of many gluten-dependent autoimmune manifestations of the skin.[189]

### *Gluten deposits in the pancreas*

Type 1 diabetes mellitus is highly associated with CD,[8,136,180,190] but the role of gluten in inducing insulitis remains controversial.[191] Some researchers claim that gluten-containing cereals are associated with an increased risk of pancreatic islet autoimmunity,[79,192–194] while others see no such connection.[195] Notably, gluten peptides have been shown to localize in the pancreatic islets, enhancing beta-cell hyperactivity, increasing the expression of beta-cell antigens, and resulting in pancreatic autoimmunity.[196] Additionally, the post-translational modifications of human islet antigens induced by local tTG increase the affinity to HLA-DQ, improving presentation to the adjacent pro-inflammatory T cells and initiating the autoimmune cascade.[197] Thus, gluten intake can provoke type 1 diabetes.[198]

Finally, applying a GFD to diabetes-prone animals reduced tTG activity in the pancreatic islets, reduced insulitis, and delayed or reduced diabetes incidence.[196] Recently, Hansen *et al*. substantiated these beneficial effects of gluten withdrawal in NOD mice across three generations by modulating the systemic immune system in a microbiota-independent manner, probably through epigenetic modifications.[199] Additionally, a GFD was shown to modulate inflammation in the salivary glands and pancreatic islets in NOD mice.[200]

The role of the pancreatic gluten-tTG axis in human type 1 diabetes mellitus requires further investigation.

### *Gluten deposits in the Kidney*

The CD is associated with several renal abnormalities,[201] with IgA nephropathy, also known as Berger's disease, being highly affected by gluten.[202] It is evident that interactions between tTG and gluten peptides occur in the kidneys of IgA nephropathy patients. Indeed, tTG is overexpressed in the gut of IgA nephropathy mice, and gliadin peptides participate in the disease pathology.[203] The immune mechanism of gluten-induced nephropathy involves transferrin receptors, IgA1, gliadin peptides, and soluble CD89.[202] As proof of concept, several CD patients on GFDs showed resolution of their autoimmune kidney disease.[42,204] The systemic circulation of gluten peptides excreted via urine further strengthens the concept of the enteric gluten-kidney axis, where gluten withdrawal might be beneficial.

### *Gluten deposits in the liver*

The gut-liver axis operates in CD, with several liver conditions associated with hepatic disease, ranging from isolated transaminasemia to autoimmune hepatitis.[8,9,30,41,42,205,206] Recently, a causal relationship was demonstrated for hepatic IgA-tTG deposits in CD patients, showing 100% sensitivity and 85% positive predictive value, establishing the association between gluten consumption,

liver IgA-tTG aggregates, and liver pathology in CD.[207] Not surprisingly, the resolution of liver injury and disappearance of these colocalized deposits were demonstrated with GFD in patients.[207]

### *Gluten deposits in the heart*

IgG and IgA immune deposition can be detected in the pericardium of individuals with gluten-dependent dermatitis herpetiformis suffering from recurrent pericarditis.[208] However, the gut-heart axis presents multiple clinical phenotypes in CD, including atrial fibrillation, dilated cardiomyopathy, pericarditis, myocarditis, angina pectoris, myocardial infarction, and even death from anoxic heart disease.[209–211] Some of these manifestations arise from hypercoagulability in CD, which is caused by multifactorial mechanisms involving nutritional deficiencies and autoantibodies.[212–214] Alpha-enolase, a glycolytic enzyme expressed in most tissues that plays a role in many cell functions, has been identified as an autoantigen in Hashimoto's encephalopathy. Recently, alpha-enolase has been suggested to play a role in the cardiac manifestations of CD.[46] Regarding cardiac involvement, CD IgA-tTG antibodies have shown strong fluorescence when applied to heart structures.[215,216]

### *Gluten and neurodegenerative diseases*

The well-established gut-brain axis has been thoroughly reported and reviewed.[131,176,217] However, the topic of gluten involvement in neurodegenerative conditions has recently generated scientific and clinical interest.[8,65,66,134,217,218] The current hypothesis is that indigestible luminal immunogenic gluten peptides are transported transcellularly and enter paracellularly. After crossing the blood-brain barrier, gluten peptides, cross-linked gluten complexes, gluten-induced antibodies, or gut-originated gluten-restricted CD4 T cells initiate and maintain proinflammatory cytokines, driving neurodegenerative diseases.[65,66,131,134,217,218] Most recently, cross-reactive antibodies between gluten and human brain epitopes have been described.[44,45,219–222] Specifically, cross-reactive antibodies between tTG, mTG, and amyloid-beta 1-42 have been identified,[223] potentially contributing to intraneuronal deposition of A-beta-P-42 in Alzheimer's disease Similarly, cross-reactivity between tTG, mTG, wheat proteins, and alpha-synuclein has been reported,[220] reinforcing the role of gluten-tTG-mTG interactions in both Alzheimer's and Parkinson's diseases.

Both human endogenous and microbial exogenous transglutaminases are heavily involved in CD evolution. The tTG is the autoantigen in CD,[12,13] while mTG, a heavily consumed processed food additive, is described as a potential driver in CD[66,94,134,224–229] and systemic autoimmunity. Gluten is a prime substrate for both enzymes.[66,94] Gliadin-cross-linked complexes formed by these enzymes elicit high antibody levels in untreated CD children,[13–16,66,96,98,99] and the corresponding serological markers are very reliable for diagnosing gluten-sensitive enteropathy.[14–16,97,99] Finally, sequence similarity between gluten and brain epitopes was recently detected for Parkinson's disease and other neurodegenerative conditions.[65,220] Both mechanisms—cross-reactivity and sequence similarity between gluten peptides—contribute to molecular mimicry, which may result in neurodegenerative, neuroinflammatory, and neuropsychiatric conditions.

## A GFD might be beneficial in many non-celiac autoimmune diseases

If gluten is a proinflammatory and auto-immunogenic nutrient and is the offending toxic inflammatory molecule in gluten-dependent ADs, a major question arises considering its beneficial curative effects when withdrawn: Might a GFD be helpful for patients affected by non-celiac ADs? This topic was recently reviewed and summarized.[41,42,55,230] In a recent systematic review summarizing 83 publications, we found that 911/1,408 AD-affected patients showed improvement on a GFD. Abstaining from gluten intake was found to be efficient in 80% of the publications and clinically beneficial to 65% of the patients.[42] The following ADs were screened: rheumatoid arthritis, antiphospholipid syndrome, dermatomyositis, undifferentiated connective tissue disease, Raynaud's phenomenon, spondylarthritis, psoriasis, vitiligo, pemphigus, erythema elevatum diutinum, inflammatory bowel disease, Crohn's disease, ulcerative colitis, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune pancreatitis, autoimmune enteropathy, thyroiditis, Graves' disease, Hashimoto's disease, type 1 diabetes, Addison's disease, autoimmune hypopituitarism, multiple sclerosis, myasthenia gravis, autoimmune myocarditis, autoimmune pericarditis, IgA nephropathy, uveitis, idiopathic thrombocytopenic purpura, and idiopathic dilated cardiomyopathy.[42] We concluded that a GFD might be beneficial for some patients affected by ADs. We suggested screening autoimmune patients for CD-associated antibodies, and only those who test positive should consider gluten withdrawal.[42] Overall, there is insufficient evidence to support a GFD for all AD patients, and official guidelines for patient selection have not yet been issued.[42,55,230,231] The topic is still controversial, and some studies oppose gluten withdrawal in non-celiac ADs.[232–234]

Logically, a GFD might counteract the harmful effects of gluten consumption. Before detailing the potential pathways and mechanisms by which gluten withdrawal might alleviate the clinical phenotype, evolution, and behavior of ADs, the following is a summary of gluten's side effects.

A challenging puzzle is the pathophysiological pathways and mechanisms by which gluten peptides induce inflammatory pathologies in various organs. Clarifying these mechanisms will improve our understanding of the beneficial effects of a GFD. The following summary (Table 1) is based on past and recent publicati ons.[6,8,9,14–16,25–30,34–39,41,42,55,65-68,70–82,89–119,121–130,134,224-230,235] It should be stressed that most studies were done *ex vivo* or on animal models. Substantiation of all of them *in vivo*, on humans, is highly encouraged.

## Potential mechanisms and pathways of GFD effectiveness in ADs

When gluten does not enter the body, all the positive and negative effects are eliminated or avoided. Several mechanisms can prevent the inflammatory or autoimmune phenomena triggered by gut-originated gluten peptides:

1. Gluten withdrawal will eliminate or attenuate the harmful inflammatory, immunogenic, oxidative, stressogenic, dysbiotic, metabolic, and cellular consequences described in Table 1.
2. Short-chain fatty acids (SCFA) are the main microbial fermentation products in the human gut. These molecules are essential for intestinal homeostasis and the proper functioning of many protective systems in our body.[76,236] Untreated CD patients have disturbed microbiome diversity and composition, and their stool SCFA levels are reduced.[76] After one year of abstaining from gluten, their microbiome and stool SCFA content normalized.[76,237]
3. Tryptophan and its metabolites regulate immune functions, are essential for enteric homeostasis, and are pivotal for serotonin-dependent human behavior. Depressed and anxious CD patients have lower free tryptophan concentrations. Applying a GFD

**Table 1. Harmful effects and pathogenic mechanisms of gluten peptide-induced inflammation and cellular damage**

| Detrimental effects and mechanisms of gluten peptide-induced pathology | References |
|---|---|
| Pro-inflammatory | 8,9,25–27,34–39,42,68,235 |
| Drive: cytotoxicity, apoptosis, LDH; Suppress: cell viability, differentiation, RNA, DNA and glycoprotein synthesis | 41,121,128–130 |
| Cellular stress induction | 42,68,70,71 |
| Induce zonulin production | 78,79,121 |
| Pro-oxidative | 42,72,121–123 |
| Epigenetics impact | 8,122,125–127 |
| Pro-apoptotic | 73,124 |
| Impact nutrigenomics, nutrigenetics, gene expression | 127 |
| Induce dysbiosis | 28–30,73–77 |
| Increase macrophage's proinflammatory cytokine | 101–103 |
| Increase intestinal permeability | 6,78–82,121 |
| Enhance NO production | 102 |
| Immunogenic and induced antibodies | 89–93 |
| Upregulate MHCII, co-stimulatory molecules, TRLs, cytokine and chemokine production | 104,105 |
| Cross-linked to mTG immunogenicity | 8,9,14–16,29,30,41,66,94,96–100 |
| Stimulate TH1 cytokine profile | 108–110 |
| Enhance NO production | 102 |
| Increase intraepithelial lymphocyte and intestinal damage | 110 |
| Upregulate MHCII, co-stimulatory molecules, TLRs, cytokine and chemokine production | 104,105 |
| Activated intestinal $CD4^+$ T cells, dendritic and TH17 cells, natural killer cell cytotoxicity | 106,111–113 |
| Increase expression of NKG2D and CD71 | 106,114 |
| overproduction of IL-17 | 112,115–117 |
| Induce TNFα and IL-1β | 107 |
| Increase IL-1β, activate NLRP3 inflammasome | 118 |
| Enhance neutrophil migration | 119 |

LDH- lactate dehydrogenase, MHC-major histocompatibility complex, NO-nitrous oxide, TLR- toll like receptor.

alleviates depression and anxiety.[238,239] However, a recent Iranian study did not confirm this observation.[240] Notably, mood alterations, depression, phobia, and anxiety are prevalent in many ADs,[241,242] and this mechanism should be studied in non-gluten-dependent ADs.

4. IgA-deficient patients are prone to ADs[243] and mainly to CD.[244] Mucosal IgA is a major immune protective mechanism, and its local production is encouraged by a high-fiber diet, local SCFA content, and a healthy microbiome. Increased production of IgA, a major mucosal and luminal immune barrier, is induced by a high-fiber diet, SCFAs, and the microbiome.[245] A GFD sustains a physiological microbiome, increases luminal SCFA, and combined with a high-fiber diet, could enhance enteric IgA levels.
5. GFD improves macrobiotic composition and diversity compared to untreated CD patients. The resulting higher production of SCFA, acetate, and butyrate lowers the luminal and stool pH,[76,246] improving colonic ecology by acting as anti-inflammatory and anti-cancer compounds.[76,247,248]
6. Avoiding gluten and adopting the Mediterranean diet benefit CD patients' health.[62,63,249] The recently adopted combination of the GFD-MedD pyramid avoids the harmful effects of gluten while adding the numerous benefits of the Mediterranean diet.[62,250,251] MedD represents a mental and physical health-protective menu that can easily be rendered gluten-free.[62,63,249–251] The combined diet offers higher antioxidants, anti-inflammatory nutrients, and sufficient fiber content for the CD population.[64]
7. Gluten/gliadin, being primary substrates for tTG,[94] are cross-linked or deamidated by post-translational modification, losing their tolerance and becoming immune- and auto-immunogenic.[29,30,100] In the absence of gluten, no such reactions occur, and the body avoids gluten-dependent inflammation and tissue/organ pathologies.[8,9,41,42,55,65,66]
8. Cross-reactive antibodies between gluten/wheat and human tissue epitopes might induce ADs or organ pathology by molecular mimicry.[44,45,220–223] When no gluten peptides circulate, no cross-reactive antibodies are produced, preventing molecular mimicry.[41,42,55,65,66]
9. Sequence similarity between gluten and human tissue antigens has been reported recently.[65,219,220] The shared homology and cross-reactivity between gluten peptides and human epitopes

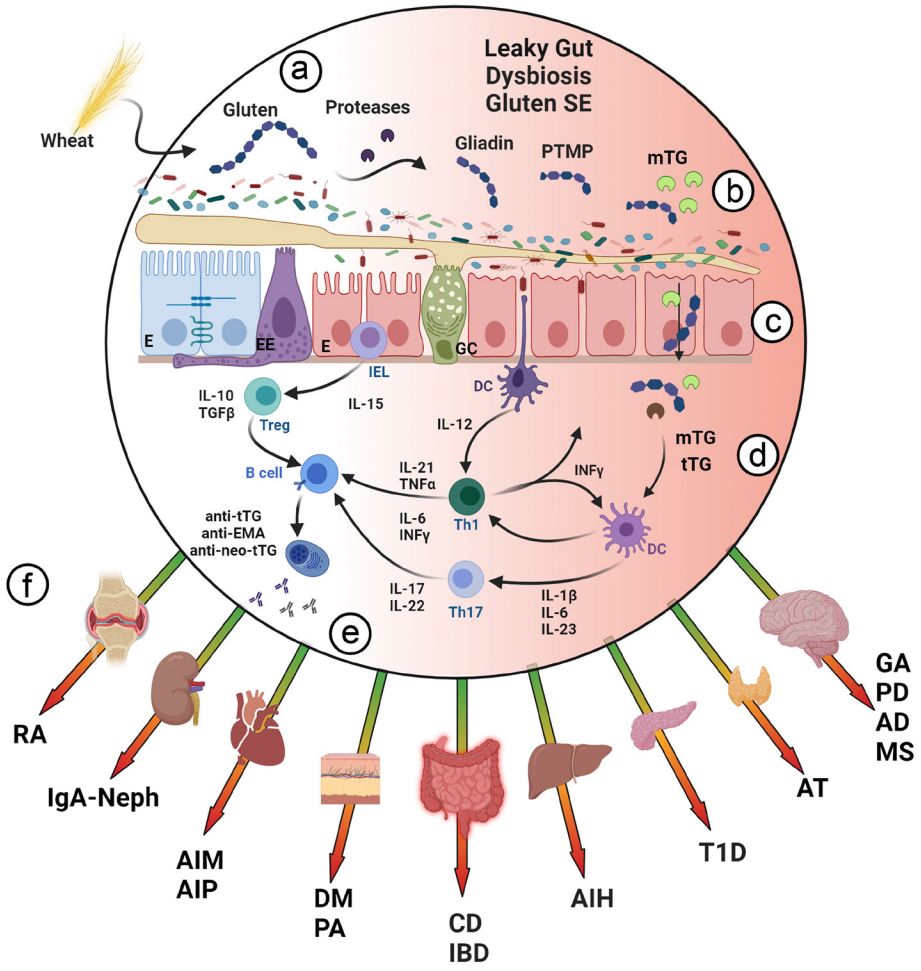


**Fig. 1. Pathogenic mechanisms by which gluten/gliadin peptides induce inflammation in remote organs, and the extended potential harmful effects in non-celiac ADs.** (a) Gluten is ingested and digested, reaching the gut lumen as gliadin peptides; (b) Gliadins are a prime substrate for deamidation and cross-linking by luminal transglutaminases. These post-translationally modified proteins (PTMP) increase their immunogenicity. Luminal digestive enzymes cannot further break down these protein complexes, leading to an inflammatory cascade that results in mucus disruption, dysbiosis, intestinal epithelial damage, and leaky gut; (c) Gliadin peptides and transglutaminases can potentially infiltrate through open junctions or trans-enterocytically into the lamina propria, exposing the highly immunoreactive sub-epithelium to foreign antigens or complexes; (d) In the lamina propria, dendritic cells (DCs) encounter gliadin-transglutaminase cross-linked complexes and migrate to lymph nodes as antigen-presenting cells to activate T cells. Secretion of IFNγ, IL-17, and IL-22 by Th1 and Th17 cells activates B cells, which secrete anti-tTG, anti-neo-tTG, and anti-endomysial autoantibodies (EMA); (e) Mucosal immune cells, immunogenic modified peptides, proinflammatory cytokines, autoantibodies, and small particles that escape the immune system enter the blood vessels. They can eventually reach remote organs and trigger an autoimmune response; (f) Some examples of inflammatory conditions that can be affected by the presence of gliadin peptides and transglutaminases or cross-linked complexes in peripheral organs. AD, Alzheimer's Disease; AIH, Autoimmune Hepatitis; AIM, Autoimmune Myocarditis; AIP, Autoimmune Pericarditis; AT, Autoimmune Thyroiditis; CD, Celiac disease; DM, Dermatomyositis; GA, Gluten Ataxia; IBD, Inflammatory Bowel Diseases; IEL, intraepithelial lymphocytes.; IgA-Neph, IgA nephropathy (Berger's disease); MS, Multiple Sclerosis; mTG, microbial transglutaminase; PA, Psoriatic Arthritis; PD, Parkinson's Disease; RA, Rheumatoid Arthritis; T1D, Type 1 Diabetes; tTG, tissue transglutaminase.

reinforce the molecular mimicry pathway toward inflammation and end-organ dysfunction. A GFD prevents these phenomena by curtailing shared sequences and cross-reactivity. Intriguingly, cross-reactivity and sequence similarity have recently been reported between various human antigens and a family member of tTG, namely, microbial transglutaminase.[252]

10. Leaky gut is reported in many, *in vivo* and *ex vivo*, metabolic, inflammatory, and ADs.[235,253–255] Gluten is a major disruptor of enteric tight junction functional integrity.[41,42,65,66,235,254,255] Gluten avoidance might protect the body from this abnormality. However, the enigma of "Gluten: yes, no, maybe" is far from being resolved.[256]

The pathogenic mechanisms by which gluten√gliadin peptides induce inflammation in remote organs, and the extended potential harmful effects in non-celiac ADs are described in Figure 1

## Conclusion

Gluten has many side effects that compromise human health, not only in gluten-dependent conditions but also in non-gluten-related chronic diseases. After entering the gut lumen, undigestible gluten peptides are modified by luminal mTG or transported through the enteric epithelium to meet mucosal immune cells or distributed systemically to remote organs where they encounter tTG. The

modified peptides become immunogenic and pro-inflammatory, inducing organ dysfunction and pathology. A GFD can prevent these phenomena by multiple mechanisms: suppressing gluten-associated detrimental effects, improving the microbiome/dysbiome ratio, avoiding post-translational modification of gluten peptides, preventing cross-reactivity and sequence similarity between gluten and human epitopes, and reducing gut leakage.

As proof of concept, gluten withdrawal alleviates disease activity in multiple chronic inflammatory, metabolic, autoimmune conditions, and even neurodegeneration. However, caution is needed. GFD consumers should be aware of the disadvantages of a gluten-restricted diet. It is advised to combine a GFD with the Mediterranean diet to harness the advantages of both. Before recommending a GFD for non-gluten-dependent conditions, patients should be assessed for gut symptomatology and screened for celiac-associated antibodies. Notably, this topic is still under discussion and is not included in the guidelines of professional decision-making societies.

It is hoped that this narrative review will encourage the scientific, nutritional, and medical communities to further explore the mechanisms by which gluten peptides induce inflammation and end-organ damage. Understanding these pathways will clarify gluten's role in the induction of human chronic inflammatory diseases.

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## Conflict of interest

AV is the CEO of Immunosciences Lab., Inc. The authors have no other conflict of interests to declare.

## Author contributions

Screening the literature (AL, CB), designing and writing the manuscript (AL), editing and revising the manuscript, designing the figure with BioRender.com permission (CB), writing part of the manuscript, revising the manuscript, and summarizing the cross-reactivity results (AV). The three authors agreed to the published version of the manuscript.

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