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REVIEW



Gluten-related disorders: Celiac disease, wheat allergy, and nonceliac gluten sensitivity

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ABSTRACT

The consumption of gluten-free products is becoming an increased alimentary habit in the general population. The scientific unfounded perception suggesting that the avoidance of gluten would improve health or that gluten could be toxic for humans are fostering medically unjustified adherences to a gluten-free diet. Currently, only patients diagnosed with celiac disease are advised to follow a strict lifelong gluten-free diet. In the same way, patients diagnosed with IgE-mediated wheat allergy must avoid exposure to wheat in any form. In that context, a third disorder, called nonceliac gluten sensitivity, characterized by distress after gluten consumption and in which neither celiac disease nor IgE-mediated allergy plays a role, has gained increased attention in the last years. Although important scientific advances have been made in the understanding of the pathologic mechanisms behind nonceliac gluten sensitivity, this disorder is still a matter of active debate in the scientific community. In the present review, the most recent advances in the immunopathology, diagnostic biomarkers and susceptibility determinants of gluten-related diseases are summarized and discussed. Furthermore, an updated overview of the new potential therapies that are currently underway for the treatment of gluten-related disorders is also provided.

KEYWORDS

Allergy; celiac disease; gluten; gluten-free; gluten sensitivity; wheat

Introduction

Gluten-containing grains were introduced in the human diet over 10,000 years ago and since then numerous wheat varieties have been selected attending to technological rather than alimentary reasons. Gluten is one of the food components more abundantly used in the food industry due to its technological and organoleptic properties (Day et al. 2006). In the context of widespread exposure to gluten, increased adverse reactions have been described in the last decades (Lebwohl, Sanders, and Green 2018). Gluten-related diseases are defined as adverse reactions to gluten that are mediated by the immune system. Celiac disease (CD) and IgE-mediated wheat allergy, are two well-known diseases associated with the exposure to gluten-containing grains. CD is an autoimmune disease that can produce relevant intestinal damage in which genetic susceptibility determinants play an important role. The prevalence of CD is around 0.5%–1% in the general population (Cabrera-Chávez et al. 2017; Mustalahti et al. 2010). On the other hand, allergy to gluten and/or other wheat proteins is a disorder mediated by IgE antibodies which recognize epitopes from specific proteins, named allergens, triggering a cascade that derives in allergic inflammation (Pietzak 2012). The prevalence of IgE-mediated wheat allergy ranges from 0.33% to 1.17% (Cabrera-Chávez et al. 2017; Ontiveros et al. 2015b; Ontiveros et al. 2018). A third disorder associated with gluten consumption is nonceliac gluten sensitivity, a recently

described condition in which distress is experienced after consumption of gluten and/or other cereal components. In nonceliac gluten sensitivity, improvement is experienced after following a gluten-free diet (GFD) or reducing gluten intake. Neither autoimmunity nor IgE-mediated allergy is implicated in this condition (Fasano et al. 2015). The prevalence of nonceliac gluten sensitivity largely varies among studies fluctuating between 0.16% and 13%. The lack of diagnostic biomarkers makes difficult such estimation (Ontiveros et al. 2015b; Cabrera-Chávez et al. 2016).

Nowadays, the only available treatment for gluten-related disorders is the adherence to a GFD. However, there is an increasing trend in the general population without gluten-related disorders to consume gluten-free products or to adhere to GFD with the unfounded reasoning that avoiding gluten can improve well-being or that gluten can be toxic for all human beings (Reilly 2016). In that regard, recent studies have shown that the prevalence rate of adherence to a GFD in general adult population can reach in some countries up to 7%. The reasons that were given to adhere to GFD were that it could help to control body weight or that GFD has the perception to be a healthy choice. In these studies, a high proportion of individuals adhered to GFD without advice from medical doctors or dietitians (Cabrera-Chávez et al. 2017; Ontiveros et al. 2018). Several studies have shown that a high percentage of the general population shows interest in reducing or avoiding

gluten from their diets (Wu et al. 2015; Cabrera-Chávez et al. 2016, 2017; Ontiveros et al. 2018). In a context in which an increased perception of gluten sensitivity is promoting self-diagnosis and new alimentary habits, nonceliac gluten sensitivity has gained increased attention and several lines of research have focused in the understanding of its etiology and pathogenesis. Together to the important advances in the understanding of CD and IgE-mediated wheat allergy achieved during the last decades, current scientific efforts are also focusing in nonceliac gluten sensitivity and in the establishment of a consensus about whether this condition can be considered a clinical independent entity or not (Sapone et al. 2012; Reese et al. 2018). A better understanding of the mechanisms behind gluten-related diseases can provide a better definition of the risk factors and susceptibility determinants that can lead to detrimental responses to gluten in certain subjects. Furthermore, an improved knowledge of the mechanisms and molecules involved in gluten-related diseases can provide new potential therapeutic targets for the treatment of gluten-related diseases. Current scientific focus also aims to give a better definition of the benefits *versus* the potential adverse effects of gluten in the health of the general population.

Gluten: origin, structure, sources

Gluten and gluten-related proteins are storage proteins from wheat (*Triticum aestivum*) and other cereals such as rye (*Secale cereale*) or barley (*Hordeum vulgare*), which are species belonging to the *Poaceae* family. In the case of rye and barley, gluten related-proteins receive the name of secalin and hordein, respectively. Gluten-related proteins can also be found in malt, triticale, spelt or kamut (Biesiekierski 2017). Gluten and gluten-related proteins have an essential function in the food industry since they provide viscosity, cohesivity, elasticity, and water absorption for the dough in bread and other baked products. They are also important in providing texture and specific organoleptic characteristics to an important variety of foods such as pasta, meat, ice cream, dressings, etc. (Biesiekierski 2017; Esteller, Pitombo, and Lannes 2005; Schalk et al. 2017b). Gluten and gluten-related proteins are constituted by gliadins and glutenins. Gliadins are prolamin proteins and are ethanol-soluble, glutenins are glutelin proteins and are soluble in weak acid solutions. Gliadins and glutenins are characterized by a high genetic polymorphism. The proportion and types of these proteins differ depending on the genetic characteristics and environmental conditions of wheat or other gluten-containing seeds (Biesiekierski 2017). Both gliadin and glutenin fractions have similar importance in the functional and rheological properties of different varieties of wheat (Barak, Mudgil, and Khatkar 2013). Gliadins and glutenins are enriched in the amino acids glutamine and proline (Nordqvist et al. 2012). Gliadins are mostly monomeric and can be classified into α/β -, γ -, $\omega 1,2$ -, and $\omega 5$ -gliadins. Usually, α/β - and γ -gliadins are in higher proportion than ω -gliadins. Glutenins are proteinic polymers bound by disulfide bonds, whose subunits are the high-molecular-weight (HMW) subunit and the low-

molecular-weight (LMW) subunit. Disulfide bonds are essential to maintain the structure of gluten proteins and they are formed after protein synthesis in order to give them their specific folded structure. Intrachain disulfide bonds are important for gliadins and intra-/interchain disulfide bonds are essential for LMW and HMW (Wieser 2007).

Gluten-related diseases

Gluten-related diseases can be classified into three different disorders: CD, IgE-mediated allergy to wheat and nonceliac gluten sensitivity.

CD is an autoimmune chronic disorder of the small intestine induced by gluten and gluten-related proteins and influenced by genetic and environmental factors. The overall prevalence of CD is estimated to be 0.5%–1% in the general population in different world areas (Mustalahti et al. 2010; Gujral, Freeman, and Thomson 2012). Major histocompatibility complexes (MHC) play a major role as genetic susceptibility determinants in CD. In the context of genetic predisposition, the consumption of gluten or gluten-related proteins can trigger immunological responses that derive in intestinal inflammation and tissue damage. Specific T cell populations, proinflammatory cytokines, autoantibodies against an intestinal enzyme, as well as impaired T regulatory cells, are involved in the intestinal damage produced in CD (Meresse, Malamut, and Cerf-Bensussan 2012) (Figure 1).

Allergy to wheat is an IgE-mediated immune response to several wheat proteins, including but not limited to gluten proteins. A T helper type 2 (Th2) cell response is involved in wheat allergy, which is key for the production of IgE antibodies by B cells. The recognition of wheat allergens by IgE antibodies induces their crosslinking which triggers activation of effector cells of allergy, that promote allergic inflammation. The prevalence of wheat allergy depends on each group of age. Clinical manifestations are diverse, with symptoms ranging from local and mild to severe systemic reactions (Inomata 2009) (Figure 2). Differences between CD and IgE-mediated wheat allergy pathogenesis can be seen in Figure 3.

Nonceliac gluten sensitivity or simply named gluten sensitivity can be defined as a distress due to the consumption of gluten and/or other cereal components. Nonceliac gluten sensitivity is not mediated by IgE or autoimmune mechanisms, therefore, neither allergy nor CD is implicated in this condition. The reactions in nonceliac gluten sensitivity do not usually lead to permanent intestinal damage and the symptoms resolve after following a GFD or a reduction in gluten intake (Rotondi Aufiero, Fasano, and Mazzarella 2018). It has been proposed that the innate branch of the immune system has an important role in nonceliac gluten sensitivity, however, the potential damage is usually low with mild symptoms compared with CD or IgE-mediated allergy. The definition of nonceliac gluten sensitivity as an independent disease entity is still a matter of debate (Reese et al. 2018) (Figure 4).

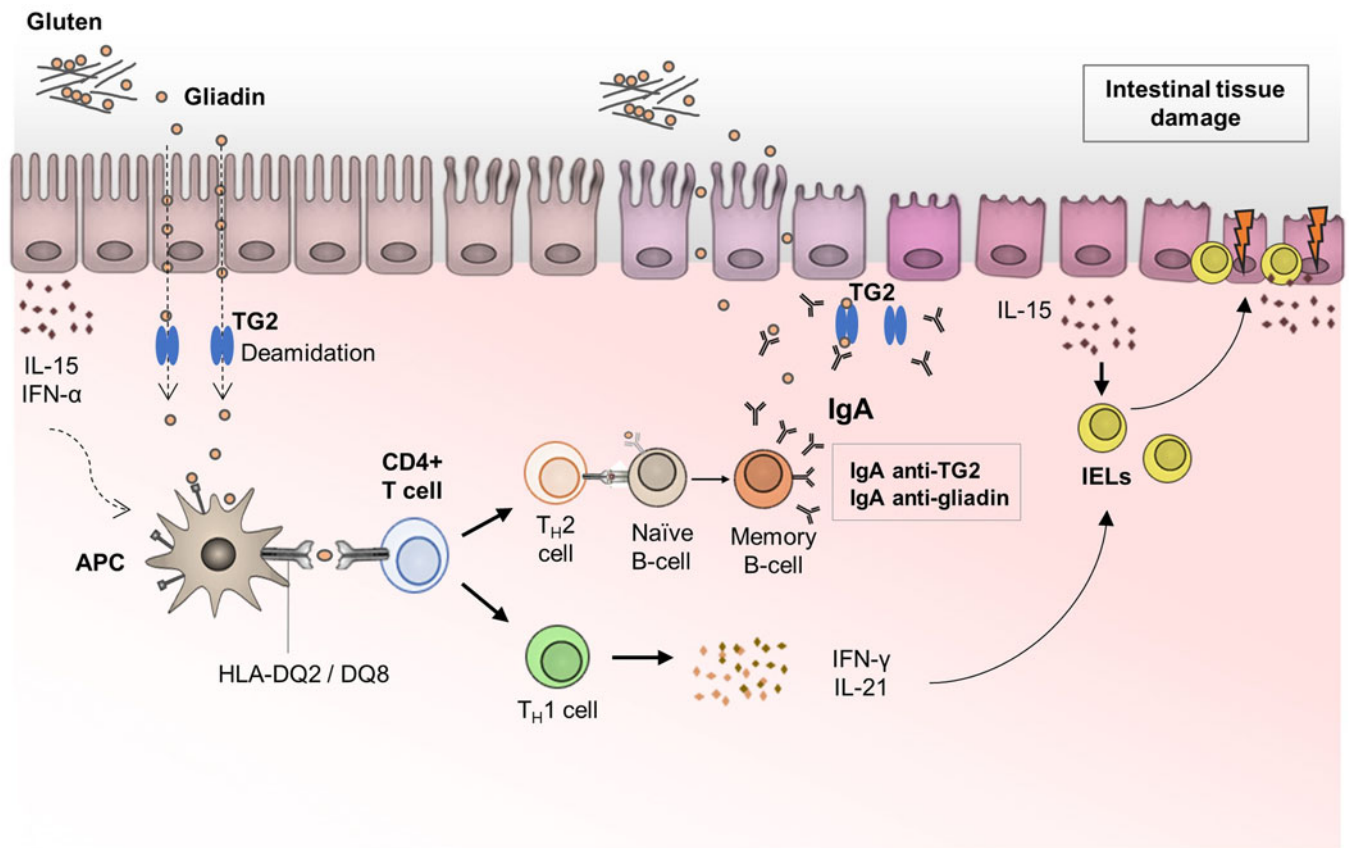


Figure 1. Celiac disease. HLA-DQ2/DQ8 in antigen presenting cells (APC) present gluten-derived peptides deamidated by TG2 to CD4+ T cells which are key in the initiation of the inflammatory response in CD. On one hand, they promote a Th1 response in which large amounts of IFN- γ and IL-21 are produced contributing to the activation of IELs, which are key in the intestinal tissue damage. Other cytokines such as IL-15 or type I IFNs are upregulated in the epithelium of the lamina propria in CD and they are key in the function and expansion of IELs. CD4+ T cells also induce a Th2 response and promote the clonal expansion of B cells and production of IgA antibodies against TG2 and gliadin.

Celiac disease

Genetic and environmental factors in celiac disease

Genetic and environmental factors have a critical role in CD. The genetic risk factors are related to the expression of the MHC class II molecules: HLA-DQ2 and HLA-DQ8. The haplotype HLA-DQ2.5 has the highest association with CD and is encoded by DQA1*0501 and DQB1*0201 alleles on the same chromosome (*cis* configuration) in the DR3-DQ2.5 haplotype. Most of the remaining CD patients express DR4-DQ8 haplotype, being DQ8 (encoded by DQA1*03 and DQB1*0302) the molecule involved in CD. There is another HLA-DQ2 molecule, DQ2.2 (encoded by DQA1*0201 and DQB1*0202 alleles) in the DR7-DQ2 haplotype, that despite its high homology to DQ2.5, presents a very low risk for CD. However, patients heterozygous for DR7-DQ2 and DR5-DQ7 have a high risk of CD, because of the expression of the DQ2.5 molecule by DQA1 and DQB1 alleles located on opposite chromosomes (*trans* configuration). Other HLA-DQ molecules can be encoded in *trans* configuration, for example, DQ2.3 and DQ8.5 which are found in DR3-DQ2/DR4-DQ8 heterozygous subjects (Fallang et al. 2009; Tollefsen et al. 2006; Ontiveros, Hardy, and Cabrera-Chávez 2015a; Sollid et al. 2012). These disease-specific MHC class II molecules are key in the initiation of detrimental immune responses in CD and they are the strongest genetic risk

factor in CD. However, they do not account for all the genetic susceptibility in CD. Additional genetic variations unconnected from HLA-DQ2 and HLA-DQ8 have also been described as genetic risk factors in CD (Gutierrez-Achury et al. 2015). That is the case of certain gene polymorphisms of IL-2/IL-21, two cytokines implicated in the pathogenesis of CD (Guo et al. 2015). Yet novel non-HLA genetic risk factors have been described in recent years (Romanos et al. 2014).

Additional susceptibility determinants such as low diversity in the intestinal microbiota and differences in its composition have also been associated with CD (Wacklin et al. 2013). Furthermore, a connection between viral infections and the initiation of CD has been proposed. Data from recent studies have demonstrated that certain viruses, such as reoviruses and other enteric viruses, can break the oral tolerance and the intestinal immune homeostasis triggering Th1 immunity to gluten (Bouziat et al. 2017; Brown, Jabri, and Dermody 2018).

The main environmental risk factor for CD is the consumption of gluten and gluten-related proteins which exert a potent immunodominant function in subjects with genetic predisposition to CD. Upon consumption, gluten proteins are partially hydrolyzed in the digestive system by specific proteases such as pepsin, trypsin, and chymotrypsin. Gluten proteins are only partially hydrolyzed because they show

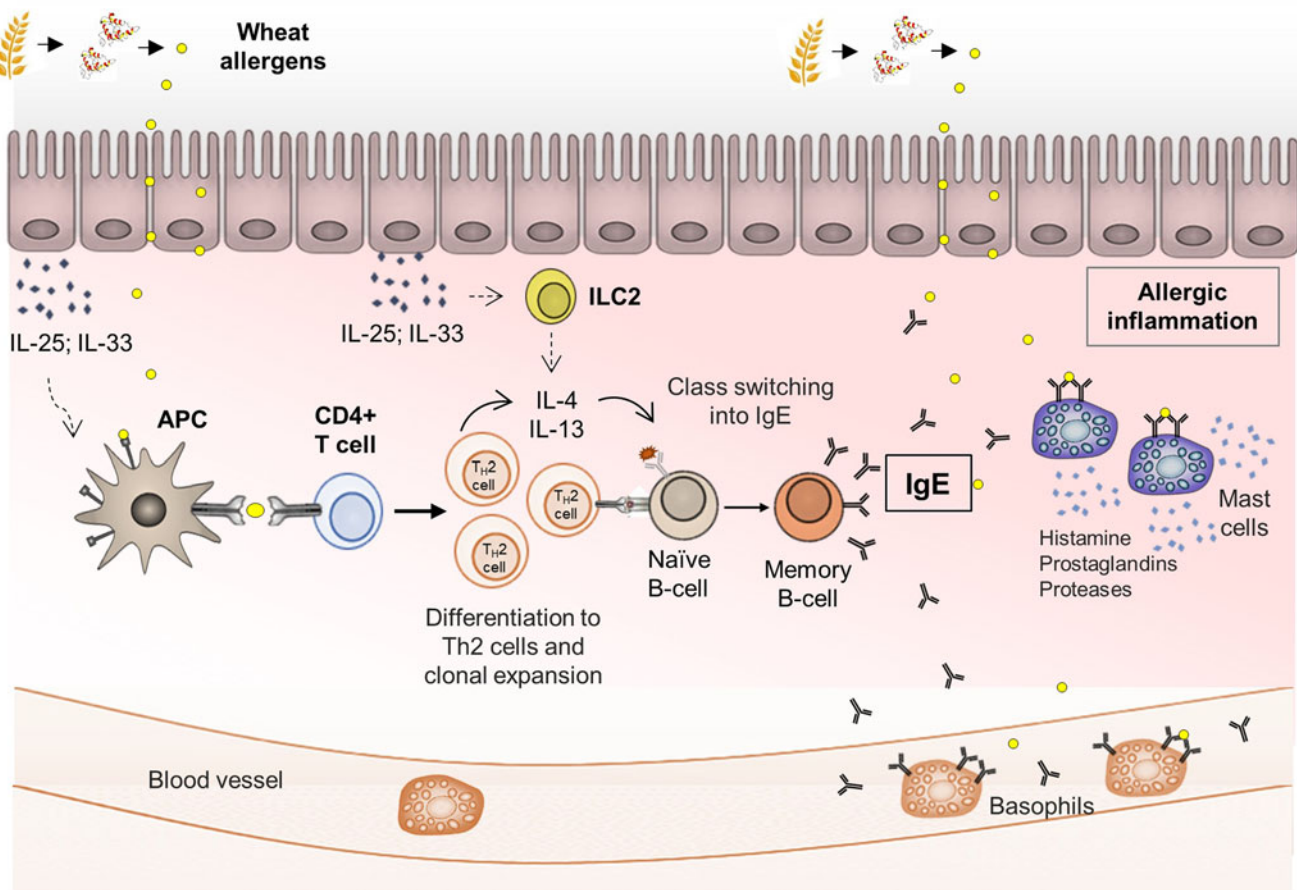


Figure 2. IgE-mediated wheat allergy. This immunological disorder can be triggered by several wheat proteins, named as allergens. Th2 cells play an essential role in the induction of IgE by B cells in the initial phase of the allergic response (sensitization phase). Other cells such as type 2 innate lymphoid cells (ILC2) also contribute to it. After a new exposure to wheat allergens, IgE antibodies bound to FcεRI on effectors cells of allergy, such as mast cells or basophils, recognize specific allergenic epitopes from wheat with consequent cell activation and release of inflammatory and vasoactive mediators. As a result, allergic inflammation is elicited.

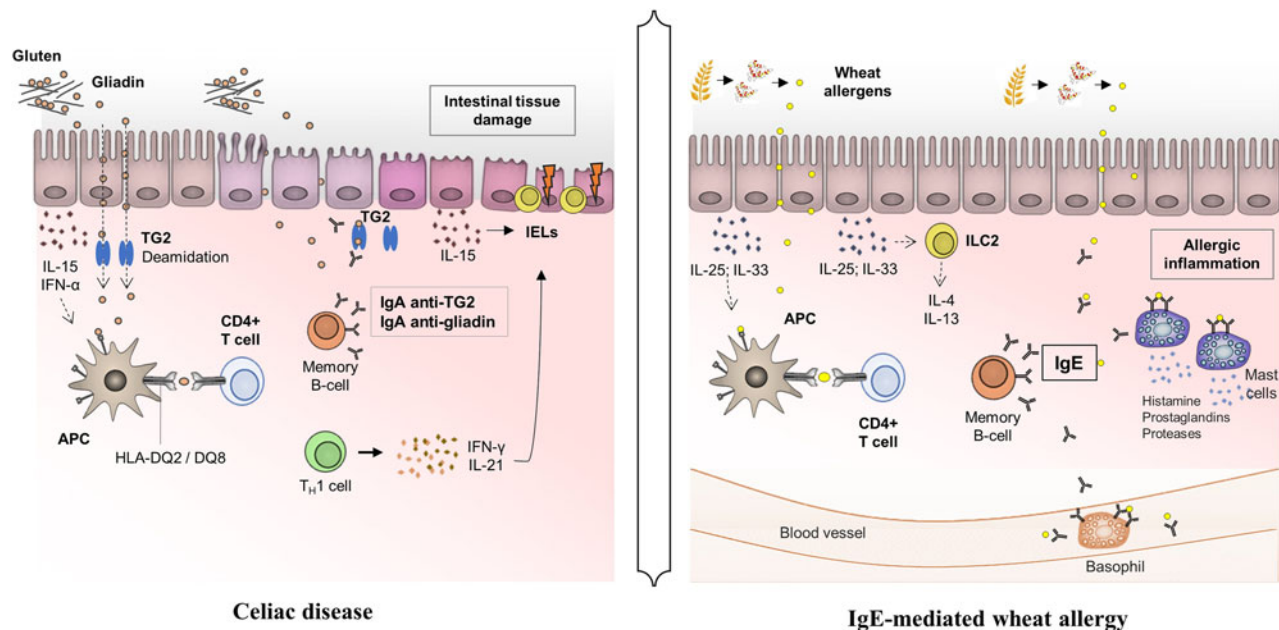


Figure 3. Differences between celiac disease (left panel) and IgE-mediated wheat allergy (right panel) pathogenesis.

protease resistance that is based on cleavage sites largely restricted to regions that are immunological silent (Tye-Din et al. 2010, Hausch et al. 2002). The resulting peptides are

transported into the lamina propria in a paracellular or transcellular way, being some of these peptides particularly resistant and immunodominant. That is the case of the 33-

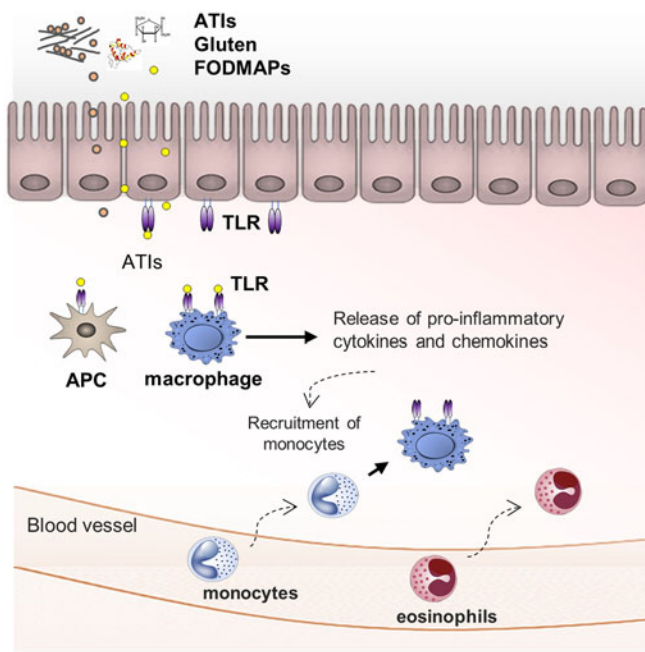


Figure 4. Possible mechanism of nonceliac gluten sensitivity. Gluten, ATIs, and FODMAPs have been proposed to have a possible role as elicitors in nonceliac gluten sensitivity. ATIs can activate dendritic cells or macrophages via TLR4 inducing the production of pro-inflammatory cytokines and chemokines. Increased infiltration of eosinophils in the intestinal mucosa has been described (Carroccio et al. 2019). The potential damage of the intestinal mucosa in nonceliac gluten sensitivity has been described to be low.

mer peptide of α -gliadin that contains three overlapping T cell epitopes, and it is present in all common wheat cultivars (Schalk et al. 2017a). Further immunogenic peptides have been described from wheat in α -, ω -, γ -gliadin, and glutenin and from other gluten-containing grains, such as from barley in hordein and from rye in secalin (Camarca et al. 2009; Camarca, Del Mastro, and Gianfrani 2012; Tye-Din et al. 2010) (Table 1). Gluten-derived peptides are rich in glutamine which is a specific substrate for transglutaminase 2 (TG2), an enzyme released during inflammation that modifies gluten-derived peptides through deamidation (Di Sabatino et al. 2012). The deamidated gluten-derived peptides have increased affinity to HLA-DQ2 or DQ8. Studies focused in the characterization of epitopes from gluten displayed by DQ haplotypes associated with CD have found that the sets of gluten peptides displayed by specific DQ variants differ in sequence and quantity, which may explain the differential risk for CD of specific DQ2/8 variants (Bergseng et al. 2015). Furthermore, the variability in the content of gluten epitopes may depend on the specific wheat variety. In that respect, it has been suggested that certain epitopes from gliadin are in higher proportion in modern wheat varieties than in ancient ones, although differences in modern varieties have also been found (van den Broeck et al. 2010; Ribeiro et al. 2016).

Immunological response in celiac disease

The presentation of deamidated gluten-derived peptides by HLA-DQ2 or HLA-DQ8 in antigen presenting cells results in a CD4⁺ T cell-mediated response. Such response initiates a cascade that derives into intestinal inflammation,

Table 1. Proteins involved in CD.

Grain species	Protein	Examples of T-cell epitopes implicated in CD
Wheat (<i>Triticum aestivum</i>)	α -gliadin	α -glia-33 mer, α -glia-17 mer
	γ -gliadin	DQ2- γ -I, DQ2- γ -II
	ω -gliadin	DQ2- ω -1
	Glutenin	Glt-17(a/b), Glt-156
Barley (<i>Hordeum vulgare</i>)	Hordein	Hor- α -2, Hor- α -9
Rye (<i>Secale cereale</i>)	Secalin	Sec- α -2, Sec- α -9

enteropathy, villi atrophy, that can produce profound damage in the intestinal tissue (Risnes et al. 2018) (Figure 1). Intestinal intraepithelial lymphocytes (IELs) have a pronounced presence in CD and they importantly contribute to the intestinal damage. IELs are composed by CD8⁺ $\alpha\beta$ T cells and $\gamma\delta$ T cells, in which CD8⁺ $\alpha\beta$ T cells have a natural killer (NK)-like function in CD producing relevant damage in intestinal epithelial cells in a TCR specific-independent manner (Abadie, Discepolo, and Jabri 2012). It has been shown that CD8⁺ $\alpha\beta$ T cells and $\gamma\delta$ T cells bear gut-homing receptors in CD patients that seem to be induced by gluten ingestion that also induces the generation of gluten-specific CD4⁺ T cells (Han et al. 2013). In that context, tissue-resident memory CD4⁺ T cells would initiate the inflammatory response triggered by gluten and they would produce large amounts of IFN- γ , IL-2, and IL-21 that contribute to the activation of IELs, key in intestinal tissue damage (Kooy-Winkelaar et al. 2017). Other cytokines increased in the inflammatory microenvironment of CD are produced by innate immune cells. That is the case of IL-15 and type-1 IFNs. IL-15 is upregulated in epithelium and lamina propria and it has a pivotal function in the expansion of IELs, induction of their NK-like function, polarization of dendritic cells, and in the impairment of local regulation by blocking of T regulatory cells (Meresse et al. 2015; Ettersperger et al. 2016). Recent studies have shown that patients with CD subjected to oral gluten challenge have a large proportion of circulating FOXP3⁺ CD39⁺ T regulatory cells, however, these cells show an impaired *in vitro* suppressive function. Such dysfunction has been proposed as a possible relevant contributor in the pathogenesis of CD (Cook et al. 2017).

Type-1 IFNs can contribute to the loss of tolerance to gluten in CD due to its effect on the activation of dendritic cells or TG2 (Di Sabatino et al. 2007). Type-1 IFN can also have an important role in the NK-like function of IELs (Kim, Mayassi, and Jabri 2015) (Figure 1). The loss of tolerance can also be promoted by the recruitment of neutrophils induced by IL-8 production that is triggered by gliadin (Lammers et al. 2015).

In the immunological response of CD, TG2 not only has an essential function as an enzyme that deamidates gluten-derived peptides increasing their avidity for HLA-DQ2/DQ8 but also TG2 is the target of autoantibodies produced in CD (Di Sabatino et al. 2012). In that regard, the responses of CD4⁺ T cell to gluten-derived peptides include a Th2 cell response that induces the clonal expansion of B cells and their differentiation into plasma cells producers of IgA

antibodies against TG2 and against gliadin (Figure 1). In normal conditions, B cells specific for TG2 exist but the secretion of antibodies against TG2 is produced with the help of gliadin specific CD4 $\pm$ T cells when gliadin and TG2 are linked in the small intestinal mucosa (Sollid et al. 1997). The autoantibodies are primarily deposited in the lamina propria where they can be transferred into the intestinal lumen and circulation (Di Niro et al. 2012). IgA anti-TG2 autoantibodies are produced in CD in higher concentration than IgM or IgG anti-TG2. Importantly, although IgA anti-TG2 autoantibodies have high affinity to TG2, they do not interfere with its enzymatic activity (Di Niro et al. 2012). In fact, they seem to favor intracellular TG2 activation due to the induction of Ca²⁺ mobilization (Caputo et al. 2013). TG2 also has a cross-linking function that catalyzes the cross-link between gliadin peptides and itself. In this context, it has been demonstrated that IgA autoantibodies are also generated against the product formed by TG2 cross-linked with gliadin peptides. Therefore, the cross-linking function of TG2 together to the exposure to gliadin would facilitate the autoimmune response in CD (Lytton et al. 2013). Although the role of IgA anti-TG2 in the pathology of CD is still not fully understood, it has been observed a positive correlation between the concentration of these autoantibodies and intestinal damage (Alessio et al. 2012). Interestingly, IgA anti-TG2 autoantibodies are a hallmark of CD and they can be found in nearly all CD patients, being an important diagnostic marker of CD with high sensitivity and specificity (Verma et al. 2018).

Clinical picture of celiac disease

CD can affect individuals of any age. The pronounced intestinal inflammation in CD causes changes in the architecture of the intestinal mucosa with villi atrophy, flattening, enteropathy, that can derive in total villous degeneration. Consequently, the most common symptom in children and adults with CD is abdominal pain, followed by diarrhea, that can be chronic or intermittent. Vomits, abdominal distension or loss of weight are also common symptoms (Guandalini and Assiri 2014). Extraintestinal symptoms such as fatigue, iron deficiency, or skin symptoms in the form of dermatitis herpetiformis can also be found in pediatric and adult patients (Repo et al. 2017; Collin et al. 2017; Guandalini and Assiri 2014). Low mineral content of bones is common in newly diagnosed children with CD and in severe cases can derive in fractures and osteoporosis in adults (Zanchetta, Longobardi, and Bai 2016; Guandalini and Assiri 2014). Neurologic and psychiatric complications in both pediatric and adult CD patients have also been observed with a possible link with autoantibodies against TG2 (Jackson et al. 2012; Hadjivassiliou et al. 2019; Jericho, Sansotta, and Guandalini 2017). In children, youth but also adult subjects with CD have been found a higher prevalence to other autoimmune diseases such as diabetes mellitus type I (Craig et al. 2017; Kurppa, Laitinen, and Agardh 2018; Mahmud et al. 2005).

Diagnosis of celiac disease

For the diagnosis of CD in adults, a combination of serological tests and duodenal biopsies is necessary. Regarding serologic tests, measurement of serum IgA anti-TG2 antibodies constitutes the first-line screening test due to its high sensitivity and specificity (Hopper et al. 2008). Moreover, it has a lower cost than the measurement of IgA anti-endomysial (EMA) antibodies, however, the latter may be performed in the case of a weak positivity result of IgA anti-TG2. When the patient has IgA deficiency, measurement of IgG anti-TG2, IgG anti-EMA, and IgG anti-deamidated gliadin can be performed instead (Lebwohl, Sanders, and Green 2018). Depending on the serological results, a duodenal biopsy may be performed in order to establish the diagnosis of celiac disease. Villous atrophy, hyperplasia, and increased IELs on the duodenal biopsy together to positive serological results confirm celiac disease diagnosis. HLA genotyping is not used in routine diagnosis, except when a discrepancy between serological and histological results exists (Leonard et al. 2017). In the case of children, the European Society for Pediatric Gastroenterology, Hepatology, and Hepatology has recommended that duodenal biopsy should be avoided if symptomatic pediatric patients have levels of anti-TG2 antibodies ten times higher than the upper limit of normal, positive anti-EMA antibodies, and HLA genotype that predisposes to celiac disease (Husby et al. 2012).

Treatment of celiac disease

The adherence to a GFD is currently the only available therapy for CD. A GFD consists in a strict avoidance of gluten and gluten-related proteins which implies that wheat, rye, and barley (that contain gluten, secalin, and hordein, respectively) together to products containing them should be completely avoided (Rubio-Tapia et al. 2013). Pure oat does not contain gluten; however, oat is frequently contaminated with wheat or barley, therefore, its introduction into a GFD should be done with caution and it should be closely monitored (Pinto-Sánchez et al. 2017). It should be taken into account that, although infrequent, some CD patients can react to avenin, the gluten-related protein of pure oats, whose toxicity depends on the variety of oat (Arentz-Hansen et al. 2004; Real et al. 2012).

The proper adherence to a GFD usually involves an improvement of clinical symptoms, increase of the density of bones, balance of body weight or improvement of nutritional values (Kelly et al. 2015). An important reconstitution of the damage at the intestinal level can be reached after long-term adherence to GFD (Rubio-Tapia et al. 2010). However, GFD can be associated with digestive problems such as constipation produced by poor intake of fiber. Moreover, a strict GFD is in many cases difficult to follow due to the presence of gluten traces in determined food products (Allen et al. 2014; Sharma, Pereira, and Williams 2015). GFD also involves negative effects at a social level and poor satisfaction of patients due to its restrictive nature and the distress produced by a possible inadvertent exposure to gluten (Häuser et al. 2010; Barratt, Leeds, and Sanders 2011; Silvester et al. 2016). For all these reasons, currently,

there is an active area of research that focuses on the development of alternative treatments for CD. As the knowledge of the mechanisms involved in CD has increased in the last decades, new molecules or mechanisms have been proposed as potential therapeutic targets in CD (Lebwohl, Sanders, and Green 2018). The most promising strategies involve mechanisms able to detoxify gluten, to improve the permeability of the intestine, or to induce changes in the immune response to gluten. In this context, larazotide acetate is a peptide that modulates intestinal tight junctions preventing the translocation of gliadin peptides through the mucosal barrier. Early phase trials with larazotide acetate showed improvement of gastrointestinal symptoms in patients with CD compared with placebo (Leffler et al. 2015). The agent is currently in phase III trial. Another agent under investigation is the protease latiglutenase (previously ALV003). This protease can degrade gluten intragastrically into small peptides that lack immunogenic capacity. Latiglutenase is currently in late phase II clinical trial and although initial studies demonstrated a decrease in mucosal injury due to this agent (Lähdeaho et al. 2014), current trials have shown that its administration did not decrease gluten-related damage in the intestine compared with placebo (Murray et al. 2017). It has been proposed that a possible trial effect could be behind these observations, therefore further trials are underway. Further potential treatments of CD currently under research are specific vaccines able to modulate gluten-specific T cells (Goel et al. 2017), or monoclonal antibodies with the capacity to block pro-inflammatory cytokines such as IL-15 or IFN- γ (Castillo, Theethira, and Leffler 2015).

Wheat allergy

Immunological response in wheat allergy

Wheat allergy has in common with CD that is an adverse reaction to proteins from wheat in which the immune system is involved. However, wheat allergy is mediated by IgE and it is mainly elicited by proteins contained in wheat and not necessarily in other grains such as rye or barley, although IgE-cross reactivity is possible in certain patients (Pourpak et al. 2005). In wheat allergy, different factors such as epithelial damage facilitates the exposure to wheat proteins. The secretion of IL-25 or IL-33 by epithelial cells promotes the differentiation of dendritic cells into a phenotype that induces a Th2 cell response. Other cells such as type 2 innate lymphoid cells also contribute to the Th2 cell response (Yu, Freeland, and Nadeau 2016). Such response involves the production of cytokines such as IL-4, IL-5, and IL-13, that have an important role in the induction of IgE, by IgE class-switching in B cells. Upon a new exposure to wheat allergens, IgE antibodies bound to their high affinity receptor Fc ϵ RI on cells such as basophils and mast cells recognize specific epitopes in wheat allergens. The recognition results in IgE-crosslinking that triggers cell activation and the release of inflammatory and vasoactive mediators. As a result, allergic inflammation is elicited that could range from local manifestations to severe systemic responses (Berin and

Sampson 2013; Tordesillas, Berin, and Sampson 2017) (Figure 2).

Clinical picture of wheat allergy

Wheat allergy presents diverse clinical manifestations that have a differential incidence depending on the age group. Allergy associated with wheat ingestion has a higher prevalence in children than in adults due to the fact wheat allergy is usually outgrown during school age (Keet et al. 2009; Nilsson et al. 2015). Wheat allergy associated with ingestion can produce symptoms such as vomiting, abdominal pain, urticaria, angioedema, anaphylaxis, respiratory symptoms, and skin symptoms, among others. In adults, although the prevalence of allergy to ingested wheat is low, it is frequently linked to anaphylactic reactions associated with exercise. This condition receives the name of wheat-dependent exercise-induced anaphylaxis (WDEIA) and involves severe anaphylactic reactions to wheat when there is a practice of intense exercise after its consumption, and in some cases, when it is associated with other factors such as aspirin consumption (Christensen et al. 2019). The underlying mechanism of WDEIA could involve an increase in the intestine permeability and absorption of wheat allergens that are facilitated by the intense exercise. Higher activation of TG2 function that triggers cross-linking of wheat allergens with an increased allergenic potential could also be associated with WDEIA (Scherf et al. 2016).

Wheat can also induce IgE-mediated allergy through inhalation, being denominated baker's asthma. This condition is one of the most frequent occupational allergies in several countries and its prevalence seems to be increasing (Quirce and Diaz-Perales 2013). Inhalation of wheat flour in its raw form is the main trigger of baker's asthma. Rhinitis frequently precedes asthmatic symptoms in this occupational allergy. Conjunctivitis together to skin symptoms can also occur (Brant 2007). Patients with baker's asthma do not usually have symptoms when they consume cooked wheat or products that contain it, but they can react after ingestion of products contaminated with raw wheat flour (Armentia et al. 2009).

Wheat allergens

The allergens implicated in IgE-mediated wheat allergy are wide distributed in the different protein fractions of wheat. Protein content represents 10%–15% of the dry weight of wheat grains. That content is classified in different protein fractions according to its extraction capacity in different solvents. Salt-soluble fractions are formed by albumins and globulins and they configure the 15%–20% of the wheat total protein content. This fraction includes amylase/trypsin inhibitors or lipid transfer proteins (LTP), among others. The remaining protein fractions from wheat are not extracted by salt solutions and are formed by prolamins (gliadins) and glutelins (glutenins) (De Brier et al. 2015; Salcedo, Quirce, and Diaz-Perales 2011).

Currently, there are 28 allergens described in wheat according to Allergen Nomenclature Sub-Committee IUIS

Table 2. Wheat proteins implicated in IgE-mediated wheat allergy.

Wheat allergen	Biochemical name	Molecular weight (kDa)
Tri a 12	Profilin	14
Tri a 14	Nonspecific lipid transfer protein 1	9
Tri a 15	Monomeric alpha-amylase inhibitor 0.28	13.2
Tri a 17	Beta-amylase	56
Tri a 18	Agglutinin isolectin 1	21.2
Tri a 19	Omega-5 gliadin	65
Tri a 20	Gamma gliadin	35–38
Tri a 21	Alpha-beta-gliadin	32.6
Tri a 25	Thioredoxin	13.3
Tri a 26	High molecular weight glutenin	88
Tri a 27	Thiol reductase homolog	27
Tri a 28	Dimeric alpha-amylase inhibitor 0.19	13
Tri a 29	Tetrameric alpha-amylase inhibitor CM1/CM2	13
Tri a 30	Tetrameric alpha-amylase inhibitor CM3	16
Tri a 31	Triosephosphate-isomerase	26.8
Tri a 32	1-cys-peroxiredoxin	23.9
Tri a 33	Serpin	43.3
Tri a 34	Glyceraldehyde-3-phosphate-dehydrogenase	36.5
Tri a 35	Dehydrin	11.5
Tri a 36	Low molecular weight glutenin GluB3-23	40
Tri a 37	Alpha purothionin	12
Tri a 39	Serine protease inhibitor-like protein	9.9
Tri a 40	Chloroform/methanol-soluble 7 protein (alpha amylase inhibitor)	15.96
Tri a 41	Mitochondrial ubiquitin ligase activator of NFKB 1	6.9
Tri a 42	Hypothetical protein from cDNA	8.2
Tri a 43	Hypothetical protein from cDNA	11.6
Tri a 44	Endosperm transfer cell specific PR60 precursor	11.9
Tri a 45	Elongation factor 1 (EIF1)	9.7

Source: Allergen Nomenclature Sub-Committee IUIS.

(Table 2). Some of these allergens are associated with specific clinical manifestations of wheat allergy, while others are implicated in all of them. α -amylase/trypsin inhibitors or nonspecific LTP (Tri a 14) are heat-resistant allergens that are frequently recognized by IgE of patients that have severe reactions after wheat ingestion, WDEIA, or baker's asthma (Palacin et al. 2007, 2009, 2010). Tri a 37, a plant defense protein, is also resistant to heat and digestion and it has been linked to severe allergic reactions to wheat (Pahr et al. 2013). ω -5-gliadin also named as Tri a 19 has been implicated in WDEIA and in anaphylactic reactions to wheat in children (Morita et al. 2009; Le et al. 2016). Several other wheat food allergens have been identified and characterized, such as α -, β -, γ -gliadins, LMW glutenin subunit, HMW glutenin subunit, α -amylase inhibitor subunits, etc. (Baar et al. 2012; 2014; Hofer et al. 2018). Some of these allergens have also been associated with baker's asthma in different study populations. That is the case of several prolamins such as α -, β -, γ -, and ω -gliadins and LMW glutenin subunits. Other allergens implicated in baker's asthma are Tri a 25, a thioredoxin (Weichel et al. 2006), Tri a 39, a serine protease inhibitor-like protein (Constantin et al. 2008), or Tri a 32, a peroxiredoxin (Pahr et al. 2012) (Table 2).

IgE-cross reactivity of wheat with other cereal grains and grass pollen

The potential of wheat allergic patients to develop allergy to other cereal grains such as rye, barley, oat, rice, or corn, due to IgE-cross reactivity has been addressed in several studies. In general, the presence of IgE against other cereal grains in patients with wheat allergy is common, however, its clinical significance has been demonstrated to be low. In a study

performed in the nineties, Jones et al. showed in a cohort of patients with clinical allergy to cereal grains confirmed by the gold standard for food allergy diagnosis, double-blind placebo-controlled food challenge (DBPCFC), that 80% of the patients were clinically allergic to only one cereal grain, being the most frequent wheat (Jones et al. 1995). Further studies demonstrated a lack of clinical reactivity to corn and rice in 18 wheat allergic patients, however, 55.5% of these patients had positive open food challenge test (OFC) to barley (Pourpak et al. 2005). Based on the obtained results, the recommendation of elimination of cereal grains from the diet once established clinical allergy to one or more of them should be based in the results of food challenges under medical supervision (Jones et al. 1995).

Regarding the potential of wheat allergic patients to have IgE-cross reactivity to grass pollen, early studies found a lack of cross reactivity between them (Jones et al. 1995). Support for the latter observation comes from more recent results that showed a lack of cross-reactivity between two important wheat allergens (α -amylase/trypsin inhibitor and LTPs) and grass pollen allergens (Pastorello et al. 2007). However, a recent study provided evidence that other allergens such as profilin and carbohydrate determinants could have a higher implication in IgE-cross reactivity between grass pollen and wheat but with a low clinical relevance (Nilsson et al. 2018).

Diagnosis of wheat allergy

The diagnosis of wheat allergy in its different clinical presentations (allergy associated with wheat ingestion, WDEIA, or baker's asthma) relies on an accurate clinical history, physical examination, and the selection of the appropriate

tests. The first tests involve measurement of specific IgE to wheat extract and wheat allergens in blood serum and skin prick test (SPT). In the case of allergy to wheat due to ingestion in pediatric and adult patients, the clinical history and the results of the mentioned tests can lead to an oral food challenge, for which double-blind placebo-controlled wheat challenge remains the gold standard. Although oral food challenges are described as safe, they must be performed with caution by medical personnel, since anaphylactic reactions may occur (Sicherer and Sampson 2018). In the case of WDEIA, this condition is frequently difficult to be recognized by the physicians since it can be mistaken with other common diseases. Diagnosis of WDEIA involves an accurate clinical history, testing the presence of specific IgE against wheat, and specific wheat allergens (such as ω -5-gliadin), and placebo-controlled wheat/exercise challenge may also be needed. This challenge involves controlled wheat ingestion and exercise for 15–20 minutes using a treadmill 30 minutes after wheat intake (Scherf et al. 2016; Cianferoni 2016). On the other hand, the diagnosis of baker's asthma is based on clinical history, confirmation of specific IgE to wheat in serum and/or by SPT, and a positive response in the bronchial challenge test, which is the gold standard for the diagnosis of baker's asthma (Cianferoni 2016).

Treatment of wheat allergy

The only available therapy for IgE-mediated wheat allergy is strict avoidance of wheat. In the case of allergy associated with wheat ingestion, instructions should be provided to patients in order to follow an adequate wheat elimination diet and also to train them for the correct interpretation of labels (Quirce, Boyano-Martínez, and Díaz-Perales 2016; Cianferoni 2016). Prevention of WDEIA involves a total restriction of exercise up to 6 hours after the consumption of wheat or wheat-containing products. Avoidance of wheat consumption in any circumstance can also be recommended for WDEIA (Scherf et al. 2016). In the case of baker's asthma, a total restriction of exposure to wheat flours is advised (Cianferoni 2016).

However, the underlying problem of a wheat elimination diet is that wheat is widely used in different food products and inadvertent exposure to small traces can occur. Therefore, strict avoidance of wheat is in many cases difficult to reach. For that reason, new treatments able to mitigate the effects of inadvertent exposure to wheat are needed. Nowadays, the development of new strategies for the treatment of IgE-mediated wheat allergy, especially wheat food allergy, is actively addressed. One promising treatment is immunotherapy, which is based on the administration of increased amounts of an allergenic source in order to modulate the immune system and to reach remission of allergic symptoms (Burks et al. 2012). Three different types of immunotherapy are currently considered and analyzed as potential treatments of food allergy: oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). From those, OIT is the most studied in different food allergenic sources. OIT consists of three phases: scalation or rush phase, in which a small dose

of the allergenic food in a food vehicle is administrated and then rapidly increased; build-up phase: in which the dose is increased every 1 or 2 weeks until a maintenance dose is reached; and the maintenance phase, in which the maintenance dose is kept for years. The initial phases are performed in a hospital under expert observation and the whole treatment is periodically monitored by oral food challenges (Cianferoni 2016; Pacharn and Vichyanond 2017). OIT has been largely studied in egg, milk, or peanut (Burks et al. 2012; Skripak et al. 2008; Blumchen et al. 2010). In the case of wheat OIT, only small studies are available. Sato et al. investigated the efficacy of OIT in 18 children with wheat anaphylaxis. Wheat OIT was performed with boiled Japanese wheat noodles. The results showed that OIT for 2 years increased the threshold dose of symptoms, moreover, successful tolerance to wheat was reached in 60% of the subjects. The levels of specific IgE to wheat was reduced during the therapy. The incidence of adverse effects was lower compared to OIT performed with other allergenic foods such as raw milk (Sato et al. 2015). In line with these results, other studies have demonstrated the efficacy and safety of wheat OIT, however, such studies present some limitations such as small cohorts or lack of placebo group (Rodríguez Del Río et al. 2014; Khayatizadeh et al. 2016).

Nonceliac gluten sensitivity

Clinical picture of nonceliac gluten sensitivity

In nonceliac gluten sensitivity, gluten and other grain components trigger intestinal symptoms that appear after hours or days of their consumption. The symptoms include abdominal pain, abdominal distension, gases, diarrhea, among others. Extraintestinal symptoms can also occur and include fatigue, headache, pain in muscles and joints, eczema, etc. (Leonard et al. 2017). Although the symptoms can mirror to CD or wheat allergy, the patients with nonceliac gluten sensitivity do not have IgA anti-TG2 autoantibodies or specific IgE against wheat proteins. These patients also have normal intestinal permeability (Sapone et al. 2011), although gluten components such as gliadins can increase it at some extent by interaction with CXCR3 receptor and other mechanisms important for the release of molecules that regulate gut permeability (Lammers et al. 2008; Hollon et al. 2015). The definition of nonceliac gluten sensitivity as an independent clinical entity still generates controversy in the scientific community (Reese et al. 2018; Sapone et al. 2012), since this condition has been frequently associated with irritable bowel syndrome (IBS) and other disorders associated with gut function (Talley and Walker 2017).

Diagnostic biomarkers and diagnosis of nonceliac gluten sensitivity

Diagnostic biomarkers are currently lacking for nonceliac gluten sensitivity. Therefore, the diagnosis is based on exclusion criteria of CD and wheat allergy and on an objective improvement after the exclusion or reduction of gluten from the diet. Once the symptoms have remitted due to a gluten-

free or gluten-reduced diet, the diagnosis must be confirmed by means of double-blind, placebo-controlled, (DBPC) cross-over gluten challenge to establish that the symptoms were associated with the ingestion of gluten or gluten-related proteins (Carroccio et al. 2012; Catassi et al. 2015). DBPC gluten challenge is considered the gold standard for the diagnosis of nonceliac gluten sensitivity according to the Salerno Experts' criteria (Catassi et al. 2015). Yet, DBPC gluten challenges present certain difficulties such as the obtention of undistinguishable gluten vehicle and placebo. Currently, there is a lack of a standardized method for the preparation of vehicle and placebo in DBPC gluten challenges, therefore the development of such standardization by cereal technologists and clinical researchers should be reached in the coming years (Figueroa-Salcido, Ontiveros, and Cabrera-Chávez 2019; Francisco, Gerardo, and Noé 2018).

Recently, it has been suggested that certain markers of inflammation such as an increased in eosinophils infiltration in rectal mucosa could constitute a possible disease-specific biomarker for the diagnosis of nonceliac gluten sensitivity (Carroccio et al. 2019). Besides gluten, other components have also been associated with nonceliac gluten sensitivity. That is the case of amylase/trypsin inhibitors (also named ATIs) from wheat, rye, and barley, which are highly resistant, and they seem to contribute to the activation of the innate immune system in nonceliac gluten sensitivity (Zevallos et al. 2017). Fermentable oligo- and disaccharides, monosaccharides, and polyols (FODMAPs) may also contribute to the symptomatology (Biesiekierski et al. 2013). In fact, it has been shown that FODMAPs could be the main trigger of nonceliac gluten sensitivity in certain patients (El-Salhy et al. 2015; Reese et al. 2018). Therefore, the term nonceliac gluten sensitivity could not be the most appropriate since other components besides gluten can be important in this condition. Other terms such as nonceliac gluten/wheat sensitivity have been proposed to be more convenient.

Immunological response in nonceliac gluten sensitivity

Although the implication of the immune system in nonceliac gluten sensitivity was initially questioned (Pietzak 2012), several studies have suggested that the innate branch of the immune system could have a predominant role in this condition (Figure 4). However, a certain implication of the adaptive immune system has also been observed. In early studies, intestinal biopsies from patients with nonceliac gluten sensitivity had a greater expression of toll-like receptors (TLR) 1 and 2 than healthy subjects. Nonceliac gluten sensitivity patients, as opposed to CD patients, have only a small increase in IELs, and negative IgA anti-TG2 autoantibodies. Furthermore, nonceliac gluten sensitivity patients had lower expression of cytokines implicated in the adaptive immune response at the intestinal level than CD patients (Sapone et al. 2011). Nonceliac gluten sensitivity is only slightly higher associated with HLA-DQ2 and/or HLA-DQ8 than the general population (Sapone et al. 2011). Altogether these data seem to indicate a predominant role of the innate

immune response in this condition, which is also supported by the relative immediacy of the reactions (Sapone et al. 2011). In this context, it has been suggested that components from cereals implicated in nonceliac gluten sensitivity may activate predominantly the innate branch of the immune system. In line with this assumption, it has been demonstrated that wheat ATIs implicated in nonceliac gluten sensitivity activate dendritic cells *via* TLR4 together to macrophages and monocytes (Figure 4). ATIs are therefore potent activators of the innate immune system (Junker et al. 2012; Zevallos et al. 2017). Interestingly, modern (hexaploidy) wheat seem to have higher TLR4-activating ATIs than older wheat variants (Zevallos et al. 2017). A 33-mer peptide from gliadin has shown to activate the innate immune system *via* TLR4 and TLR2 inducing secretion of pro-inflammatory cytokines such as TNF- α and IP-10/CXCL10, which it may be key in gluten-related disorders (Herrera et al. 2018). However, the potential damage of the activation of the innate immune system in nonceliac gluten sensitivity is low and it translates into mild symptoms compared to CD or IgE-mediated allergy (Leonard et al. 2017). Interestingly, the concept of the unique role of the innate immunity in nonceliac gluten sensitivity has been recently challenged in studies that have shown increased levels of INF- γ gene expression in nonceliac gluten sensitivity patients after gluten challenge (Brottveit et al. 2013). However, an exploratory study found gluten-specific INF- γ producers T cells in peripheral blood of CD patients but not in subjects without CD that present digestive and systemic symptoms to gluten (Ontiveros et al. 2014). Furthermore, in approximately 50% of patients with nonceliac gluten sensitivity, IgG anti-gliadin can be found, although their role in nonceliac gluten sensitivity is still not fully understood (Infantino et al. 2015; Infantino et al. 2017).

Treatment of nonceliac gluten sensitivity

Patients diagnosed with nonceliac gluten sensitivity would potentially benefit from a gluten-free or gluten-reduced diet, which should be limited in the time due to the transient nature of this condition (Catassi et al. 2015; Talley and Walker 2017; Reese et al. 2018). Analysis of the tolerance status to gluten and other grain components involved in nonceliac gluten sensitivity would be recommended after a specific period of time under GFD (Roncoroni et al. 2019). A GFD is in most cases free of ATIs (Escudero-Hernández et al. 2016). Patients with nonceliac gluten sensitivity also seem to benefit from a FODMAPs-reduced diet, since it has been shown that it is associated with an improvement of gastrointestinal symptoms on these patients (Biesiekierski et al. 2013; Dieterich et al. 2019; Muir et al. 2019).

Different lines of research are investigating new ways to manage nonceliac gluten sensitivity. For instance, the toxicity of different varieties of wheat has been analyzed in several studies. Interestingly, it has been found that ancient diploid wheat such as *Triticum monococcum* ssp. *monococcum*, unlike modern tetraploid or hexaploidy wheat, have a reduced capacity to activate different immune cells implicated in gluten-related disorders (Molberg et al. 2005).

Although clinical studies have shown that these varieties cannot be consumed by CD patients, it has been suggested that they would be safe for patients with nonceliac gluten sensitivity (Zanini et al. 2015). Novel hybridized cereals such as tritordeum, the hybridization product of *Triticum durum* with barley, has also been suggested as an option for patients with nonceliac gluten sensitivity due to its low content in gliadin (Vaquero et al. 2018). Novel studies using CRISPR/Cas9 technology have produced nontransgenic wheat with a reduced amount of α -gliadins, which translates into an 85% reduction of immunoreactivity (Sánchez-León et al. 2018).

Conclusions and future directions

Gluten-free products currently constitute a profitable segment in the food industry with an estimated value of several billion dollars (Talley and Walker 2017; Wu et al. 2015). The unfounded perception in the general population that a GFD is a healthy choice is fostering medically unjustified alimentary habits of gluten avoidance. Currently, only patients diagnosed with CD should follow a strict lifelong GFD and patients with IgE-mediated wheat allergy must avoid exposure to wheat in any form. In this context, and despite several scientific advances, nonceliac gluten sensitivity has been demonstrated to be a not fully understood condition for which the scientific community has not reached a consensus for its classification as an independent clinical entity (Reese et al. 2018; Sapone et al. 2012). Although recent advances have been made in the definition of possible diagnostic biomarkers, the current diagnosis recommendation of nonceliac gluten sensitivity relies on exclusion criteria of diseases such as CD or IgE-mediated wheat allergy and an objective improvement after following a gluten-reduced or GFD. The diagnosis should be then confirmed by means of double-blind, placebo-controlled, cross-over gluten challenge, which is the gold standard for nonceliac gluten sensitivity diagnosis (Catassi et al. 2015; Figueroa-Salcido, Ontiveros, and Cabrera-Chávez 2019). It is also yet to be identified the main triggering compound that mostly contributes to nonceliac gluten sensitivity, since gluten can only explain a certain proportion of the reactions, and other grain components such as FODMAPs or ATIs have been tightly associated with this condition. Therefore, future scientific efforts would be necessary in order to establish the pathogenic mechanism and disease-specific markers associated with nonceliac gluten sensitivity. The adherence to a GFD without a well-defined diagnosis is unjustified and can carry out several drawbacks and adverse effects since it has been demonstrated that a GFD is neither healthier nor advantageous than gluten-containing diet for subjects without a medical proven diagnosis of gluten-related disorders. Therefore, the advice for an adherence to a GFD should be provided by medical doctors after careful evaluation following the current standards for gluten-related diseases diagnosis (Niland and Cash 2018; Reilly 2016; Wu et al. 2015; Reese et al. 2018).

Conflict of interests

The author declares no conflict of interest.

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References

- Abadie, V., V. Discepolo, and B. Jabri. 2012. Intraepithelial lymphocytes in celiac disease immunopathology. *Seminars in Immunopathology* 34 (4):551–66. doi: [10.1007/s00281-012-0316-x](https://doi.org/10.1007/s00281-012-0316-x).
- Alessio, M. G., E. Tonutti, I. Brusca, A. Radice, L. Licini, A. Sonzogni, A. Florena, E. Schiaffino, W. Marus, et al. 2012. Correlation between IgA tissue transglutaminase antibody ratio and histological finding in celiac disease. *Journal of Pediatric Gastroenterology and Nutrition* 55 (1):44–9. doi: [10.1097/MPG.0b013e3182470249](https://doi.org/10.1097/MPG.0b013e3182470249).
- Allen, K. J., P. J. Turner, R. Pawankar, S. Taylor, S. Sicherer, G. Lack, N. Rosario, M. Ebisawa, G. Wong, E. N. C. Mills, et al. 2014. Precautionary labelling of foods for allergen content: Are we ready for a global framework? *World Allergy Organization Journal* 7:10. doi: [10.1186/1939-4551-7-10](https://doi.org/10.1186/1939-4551-7-10).
- Arentz-Hansen, H., B. Fleckenstein, Ø. Molberg, H. Scott, F. Koning, G. Jung, P. Roepstorff, K. E. Lundin, and L. M. Sollid. 2004. The molecular basis for oat intolerance in patients with celiac disease. *PLoS Medicine* 1 (1):e1. doi: [10.1371/journal.pmed.0010001](https://doi.org/10.1371/journal.pmed.0010001).
- Armentia, A., A. Díaz-Perales, J. Castrodeza, A. Dueñas-Laita, A. Palacin, and S. Fernández. 2009. Why can patients with baker's asthma tolerate wheat flour ingestion? Is wheat pollen allergy relevant? *Allergologia et Immunopathologia* 37 (4):203–4. doi: [10.1016/j.aller.2009.05.001](https://doi.org/10.1016/j.aller.2009.05.001).
- Baar, A., S. Pahr, C. Constantin, S. Giavi, A. Manoussaki, N. G. Papadopoulos, C. Ebner, A. Mari, S. Vrtala, and R. Valenta. 2014. Specific IgE reactivity to tri a 36 in children with wheat food allergy. *Journal of Allergy and Clinical Immunology* 133 (2):585–7. doi: [10.1016/j.jaci.2013.10.044](https://doi.org/10.1016/j.jaci.2013.10.044).
- Baar, A., S. Pahr, C. Constantin, S. Scheiblhofer, J. Thalhamer, S. Giavi, N. G. Papadopoulos, C. Ebner, A. Mari, S. Vrtala, and R. Valenta. 2012. Molecular and immunological characterization of tri a 36, a low molecular weight glutenin, as a novel major wheat food allergen. *The Journal of Immunology* 189 (6):3018–25. doi: [10.4049/jimmunol.1200438](https://doi.org/10.4049/jimmunol.1200438).
- Barak, S., D. Mudgil, and B. Khatkar. 2013. Relationship of gliadin and glutenin proteins with dough rheology, flour pasting and bread making performance of wheat varieties. *LWT - Food Science and Technology* 51 (1):211–7. doi: [10.1016/j.lwt.2012.09.011](https://doi.org/10.1016/j.lwt.2012.09.011).
- Barratt, S. M., J. S. Leeds, and D. S. Sanders. 2011. Quality of life in coeliac disease is determined by perceived degree of difficulty adhering to a gluten-free diet, not the level of dietary adherence ultimately achieved. *Journal of Gastrointestinal and Liver Diseases* 20: 241–5.
- Bergsgen, E., S. Dørum, M. Arntzen, M. Nielsen, S. Nygård, S. Buus, G. A. De Souza, and L. M. Sollid. 2015. Different binding motifs of the celiac disease-associated HLA molecules dq2.5, dq2.2, and dq7.5 revealed by relative quantitative proteomics of endogenous peptide repertoires. *Immunogenetics* 67 (2):73–84. doi: [10.1007/s00251-014-0819-9](https://doi.org/10.1007/s00251-014-0819-9).
- Berin, M. C., and H. A. Sampson. 2013. Mucosal immunology of food allergy. *Current Biology* 23 (9):R389–400. doi: [10.1016/j.cub.2013.02.043](https://doi.org/10.1016/j.cub.2013.02.043).
- Biesiekierski, J. R. 2017. What is gluten? *Journal of Gastroenterology and Hepatology* 32:78–81. doi: [10.1111/jgh.13703](https://doi.org/10.1111/jgh.13703).
- Biesiekierski, J. R., S. L. Peters, E. D. Newnham, O. Rosella, J. G. Muir, and P. R. Gibson. 2013. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology* 145 (2):320–8.

- Blumchen, K., H. Ulbricht, U. Staden, K. Dobberstein, J. Beschoner, L. C. De Oliveira, W. G. Shreffler, H. A. Sampson, B. Niggemann, U. Wahn, and K. Beyer. 2010. Oral peanut immunotherapy in children with peanut anaphylaxis. *Journal of Allergy and Clinical Immunology* 126 (1):83–91. doi: [10.1016/j.jaci.2010.04.030](https://doi.org/10.1016/j.jaci.2010.04.030).
- Bouziat, R., R. Hinterleitner, J. J. Brown, J. E. Stencel-Baerenwald, M. Ikizler, T. Mayassi, M. Meisel, S. M. Kim, V. Discepolo, A. J. Pruijssers, et al. 2017. Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. *Science* 356 (6333):44–50. doi: [10.1126/science.aah5298](https://doi.org/10.1126/science.aah5298).
- Brant, A. 2007. Baker's asthma. *Current Opinion in Allergy and Clinical Immunology* 7 (2):152–5. doi: [10.1097/ACI.0b013e328042ba77](https://doi.org/10.1097/ACI.0b013e328042ba77).
- Brottveit, M., A. C. Beitnes, S. Tollefsen, J. E. Bratlie, F. L. Jahnsen, F. E. Johansen, L. M. Sollid, and K. E. Lundin. 2013. Mucosal cytokine response after short-term gluten challenge in celiac disease and non-celiac gluten sensitivity. *The American Journal of Gastroenterology* 108 (5):842–50. doi: [10.1038/ajg.2013.91](https://doi.org/10.1038/ajg.2013.91).
- Brown, J. J., B. Jabri, and T. S. Dermody. 2018. A viral trigger for celiac disease. *PLOS Pathogens* 14 (9):e1007181. doi: [10.1371/journal.ppat.1007181](https://doi.org/10.1371/journal.ppat.1007181).
- Burks, A. W., S. M. Jones, R. A. Wood, D. M. Fleischer, S. H. Sicherer, R. W. Lindblad, D. Stablein, A. K. Henning, B. P. Vickery, A. H. Liu, et al. 2012. Oral immunotherapy for treatment of egg allergy in children. *The New England Journal of Medicine* 367 (3):233–43. doi: [10.1056/NEJMoa1200435](https://doi.org/10.1056/NEJMoa1200435).
- Cabrera-Chávez, F., G. V. Dezar, A. P. Islas-Zamorano, J. G. Espinoza-Alderete, M. J. Vergara-Jiménez, D. Magaña-Ordorica, and N. Ontiveros. 2017. Prevalence of self-reported gluten sensitivity and adherence to a gluten-free diet in argentinian adult population. *Nutrients* 9 (1):81. doi: [10.3390/nu9010081](https://doi.org/10.3390/nu9010081).
- Cabrera-Chávez, F., D. M. Granda-Restrepo, J. G. Arámburo-Gálvez, A. Franco-Aguilar, D. Magaña-Ordorica, M. E. J. Vergara-Jiménez, and N. Ontiveros. 2016. Self-reported prevalence of gluten-related disorders and adherence to gluten-free diet in Colombian adult population. *Gastroenterology Research and Practice* 2016:1. doi: [10.1155/2016/4704309](https://doi.org/10.1155/2016/4704309).
- Camarca, A., R. P. Anderson, G. Mamone, O. Fierro, A. Facchiano, S. Costantini, D. Zanzi, J. Sidney, S. Auricchio, A. Sette, et al. 2009. Intestinal t cell responses to gluten peptides are largely heterogeneous: Implications for a peptide-based therapy in celiac disease. *The Journal of Immunology* 182 (7):4158–66. doi: [10.4049/jimmunol.0803181](https://doi.org/10.4049/jimmunol.0803181).
- Camarca, A., A. Del Mastro, and C. Gianfrani. 2012. Repertoire of gluten peptides active in celiac disease patients: Perspectives for translational therapeutic applications. *Endocrine, Metabolic & Immune Disorders - Drug Targets* 12:207–19. doi: [10.2174/187153012800493549](https://doi.org/10.2174/187153012800493549).
- Caputo, I., M. Lepretti, A. Secondo, S. Martucciello, G. Paoletta, D. Sblattero, M. V. Barone, and C. Esposito. 2013. Anti-tissue transglutaminase antibodies activate intracellular tissue transglutaminase by modulating cytosolic Ca^{2+} homeostasis. *Amino Acids* 44 (1):251–60. doi: [10.1007/s00726-011-1120-y](https://doi.org/10.1007/s00726-011-1120-y).
- Carroccio, A., G. Giannone, P. Mansueto, M. Soresi, F. La Blasca, F. Fayer, R. Iacobucci, R. Porcasi, T. Catalano, G. Geraci, et al. 2019. Duodenal and rectal mucosa inflammation in patients with non-celiac wheat sensitivity. *Clinical Gastroenterology and Hepatology* 17 (4):682–90. doi: [10.1016/j.cgh.2018.08.043](https://doi.org/10.1016/j.cgh.2018.08.043).
- Carroccio, A., P. Mansueto, G. Iacono, M. Soresi, A. D'alcamo, F. Cavataio, I. Brusca, A. M. Florena, G. Ambrosiano, A. Seidita, et al. 2012. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: Exploring a new clinical entity. *The American Journal of Gastroenterology* 107 (12):1898–906. doi: [10.1038/ajg.2012.236](https://doi.org/10.1038/ajg.2012.236).
- Castillo, N. E., T. G. Theethira, and D. A. Leffler. 2015. The present and the future in the diagnosis and management of celiac disease. *Gastroenterology Report* 3 (1):3–11. doi: [10.1093/gastro/gou065](https://doi.org/10.1093/gastro/gou065).
- Catassi, C., L. Elli, B. Bonaz, G. Bouma, A. Carroccio, G. Castillejo, C. Cellier, F. Cristofori, L. De Magistris, J. Dolinsek, et al. 2015. Diagnosis of non-celiac gluten sensitivity (NCGS): The Salerno experts' criteria. *Nutrients* 7 (6):4966–77. doi: [10.3390/nu7064966](https://doi.org/10.3390/nu7064966).
- Christensen, M. J., E. Eller, C. G. Mortz, K. Brockow, and C. Bindslev-Jensen. 2019. Wheat-dependent cofactor-augmented anaphylaxis: A prospective study of exercise, aspirin, and alcohol efficacy as cofactors. *The Journal of Allergy and Clinical Immunology: In Practice* 7 (1):114–21. doi: [10.1016/j.jaip.2018.06.018](https://doi.org/10.1016/j.jaip.2018.06.018).
- Cianferoni, A. 2016. Wheat allergy: Diagnosis and management. *Journal of Asthma and Allergy* 9:13–25. doi: [10.2147/JAA.S81550](https://doi.org/10.2147/JAA.S81550).
- Collin, P., T. T. Salmi, K. Hervonen, K. Kaukinen, and T. Reunala. 2017. Dermatitis herpetiformis: A cutaneous manifestation of coeliac disease. *Annals of Medicine* 49 (1):23–31. doi: [10.1080/07853890.2016.1222450](https://doi.org/10.1080/07853890.2016.1222450).
- Constantin, C., S. Quirce, M. Grote, A. Touraev, I. Swoboda, A. Stoecklinger, A. Mari, J. Thalhamer, E. Heberle-Bors, and R. Valenta. 2008. Molecular and immunological characterization of a wheat serine proteinase inhibitor as a novel allergen in baker's asthma. *The Journal of Immunology* 180 (11):7451–60. doi: [10.4049/jimmunol.180.11.7451](https://doi.org/10.4049/jimmunol.180.11.7451).
- Cook, L., C. M. L. Munier, N. Seddiki, D. Van Bockel, N. Ontiveros, M. Y. Hardy, J. K. Gillies, M. K. Levings, H. H. Reid, J. Petersen, et al. 2017. Circulating gluten-specific FOXP3. *Journal of Allergy and Clinical Immunology* 140 (6):1592–603. doi: [10.1016/j.jaci.2017.02.015](https://doi.org/10.1016/j.jaci.2017.02.015).
- Craig, M. E., N. Prinz, C. T. Boyle, F. M. Campbell, T. W. Jones, S. E. Hofer, J. H. Simmons, N. Holman, E. Tham, E. Fröhlich-Reiterer, et al. 2017. Prevalence of celiac disease in 52,721 youth with type 1 diabetes: International comparison across three continents. *Diabetes Care* 40 (8):1034–40. doi: [10.2337/dc16-2508](https://doi.org/10.2337/dc16-2508).
- Day, L., M. Augustin, I. Batey, and C. Wrigley. 2006. Wheat-gluten uses and industry needs. *Trends in Food Science & Technology* 17: 82–90. doi: [10.1016/j.tifs.2005.10.003](https://doi.org/10.1016/j.tifs.2005.10.003).
- De Brier, N., S. V. Gomand, I. Celus, C. M. Courtin, K. Brijs, and J. A. Delcour. 2015. Extractability and chromatographic characterization of wheat (*Triticum aestivum* L.) bran protein. *Journal of Food Science* 80 (5):C967–74. doi: [10.1111/1750-3841.12856](https://doi.org/10.1111/1750-3841.12856).
- Di Niro, R., L. Mesin, N. Y. Zheng, J. Stamnaes, M. Morrissey, J. H. Lee, M. Huang, R. Iversen, M. F. Du Pré, S. W. Qiao, et al. 2012. High abundance of plasma cells secreting transglutaminase 2-specific IgA autoantibodies with limited somatic hypermutation in celiac disease intestinal lesions. *Nature Medicine* 18 (3):441–5. doi: [10.1038/nm.2656](https://doi.org/10.1038/nm.2656).
- Di Sabatino, A., K. M. Pickard, J. N. Gordon, V. Salvati, G. Mazzarella, R. M. Beattie, A. Vossenkaemper, L. Rovedatti, N. A. Leakey, N. M. Croft, et al. 2007. Evidence for the role of interferon- α production by dendritic cells in the Th1 response in celiac disease. *Gastroenterology* 133 (4):1175–87. doi: [10.1053/j.gastro.2007.08.018](https://doi.org/10.1053/j.gastro.2007.08.018).
- Di Sabatino, A., A. Vanoli, P. Giuffrida, O. Luinetti, E. Solcia, and G. Corazza. 2012. The function of tissue transglutaminase in celiac disease. *Autoimmunity Reviews* 11 (10):746–53. doi: [10.1016/j.autrev.2012.01.007](https://doi.org/10.1016/j.autrev.2012.01.007).
- Dieterich, W., D. Schuppan, M. Schink, R. Schwappacher, S. Wirtz, A. Agaimy, M. F. Neurath, and Y. Zopf. 2019. Influence of low FODMAP and gluten-free diets on disease activity and intestinal microbiota in patients with non-celiac gluten sensitivity. *Clinical Nutrition* 38 (2):697–707. doi: [10.1016/j.clnu.2018.03.017](https://doi.org/10.1016/j.clnu.2018.03.017).
- El-Salhy, M., J. G. Hatlebakk, O. H. Gilja, and T. Hausken. 2015. The relation between celiac disease, nonceliac gluten sensitivity and irritable bowel syndrome. *Nutrition Journal* 14 (1):92. doi: [10.1186/s12937-015-0080-6](https://doi.org/10.1186/s12937-015-0080-6).
- Escudero-Hernández, C., A. S. Peña, and D. Bernardo. 2016. Immunogenetic pathogenesis of celiac disease and non-celiac gluten sensitivity. *Current Gastroenterology Reports* 18 (7):36. doi: [10.1007/s11894-016-0512-2](https://doi.org/10.1007/s11894-016-0512-2).
- Esteller, M., R. Pitombo, and S. Lannes. 2005. Effect of freeze-dried gluten addition on texture of hamburger buns. *Journal of Cereal Science* 41 (1):19–21. doi: [10.1016/j.jcs.2004.08.013](https://doi.org/10.1016/j.jcs.2004.08.013).
- Ettersperger, J., N. Montcuquet, G. Malamut, N. Guegan, S. Lopez-Lastra, S. Gayraud, C. Reimann, E. Vidal, N. Cagnard, P. Villarese, et al. 2016. Interleukin-15-dependent t-cell-like innate intraepithelial lymphocytes develop in the intestine and transform into lymphomas

- in celiac disease. *Immunity* 45 (3):610–25. doi: [10.1016/j.immuni.2016.07.018](https://doi.org/10.1016/j.immuni.2016.07.018).
- Fallang, L. E., E. Bergseng, K. Hotta, A. Berg-Larsen, C. Y. Kim, and L. M. Sollid. 2009. Differences in the risk of celiac disease associated with HLA-DQ2.5 or HLA-DQ2.2 are related to sustained gluten antigen presentation. *Nature Immunology* 10 (10):1096–101. doi: [10.1038/ni.1780](https://doi.org/10.1038/ni.1780).
- Fasano, A., A. Sapone, V. Zavallos, and D. Schuppan. 2015. Nonceliac gluten sensitivity. *Gastroenterology* 148 (6):1195–204. doi: [10.1053/j.gastro.2014.12.049](https://doi.org/10.1053/j.gastro.2014.12.049).
- Figueroa-Salcido, O. G., N. Ontiveros, and F. Cabrera-Chávez. 2019. Gluten vehicle and placebo for non-celiac gluten sensitivity assessment. *Medicina (Kaunas)* 55 (5):117.
- Francisco, C. C., S. O. Gerardo, and O. Noé. 2018. The indistinguishable gluten vehicle and placebo in the diagnosis of NCGS. *American Journal of Gastroenterology* 113 (10):1559–60. doi: [10.1038/s41395-018-0127-3](https://doi.org/10.1038/s41395-018-0127-3).
- Goel, G., T. King, A. J. Daveson, J. M. Andrews, J. Krishnarajah, R. Krause, G. J. E. Brown, R. Fogel, C. F. Barish, R. Epstein, et al. 2017. Epitope-specific immunotherapy targeting CD4-positive T cells in coeliac disease: Two randomised, double-blind, placebo-controlled phase 1 studies. *The Lancet Gastroenterology & Hepatology* 2:479–93. doi: [10.1016/S2468-1253\(17\)30110-3](https://doi.org/10.1016/S2468-1253(17)30110-3).
- Guandalini, S., and A. Assiri. 2014. Celiac disease: A review. *JAMA Pediatrics* 168 (3):272–8. doi: [10.1001/jamapediatrics.2013.3858](https://doi.org/10.1001/jamapediatrics.2013.3858).
- Gujral, N., H. J. Freeman, and A. B. Thomson. 2012. Celiac disease: Prevalence, diagnosis, pathogenesis and treatment. *World Journal of Gastroenterology* 18 (42):6036–59. doi: [10.3748/wjg.v18.i42.6036](https://doi.org/10.3748/wjg.v18.i42.6036).
- Guo, C. C., W. H. Huang, N. Zhang, F. Dong, L. P. Jing, Y. Liu, X. G. Ye, D. Xiao, M. L. Ou, B. H. Zhang, et al. 2015. Association between IL2/IL21 and SH2B3 polymorphisms and risk of celiac disease: A meta-analysis. *Genetics and Molecular Research* 14 (4):13221–35. doi: [10.4238/2015.October.26.19](https://doi.org/10.4238/2015.October.26.19).
- Gutierrez-Achury, J., A. Zhernakova, S. L. Pulit, G. Trynka, K. A. Hunt, J. Romanos, S. Raychaudhuri, D. A. Van Heel, C. Wijmenga, and P. I. De Bakker. 2015. Fine mapping in the MHC region accounts for 18% additional genetic risk for celiac disease. *Nature Genetics* 47 (6):577–8. doi: [10.1038/ng.3268](https://doi.org/10.1038/ng.3268).
- Hadjivassiliou, M., I. D. Croall, P. Zis, P. G. Sarrigiannis, D. S. Sanders, P. Aeschlimann, R. A. Grünewald, P. A. Armitage, D. Connolly, D. Aeschlimann, and N. Hoggard. 2019. Neurologic deficits in patients with newly diagnosed celiac disease are frequent and linked with autoimmunity to transglutaminase 6. *Clinical Gastroenterology and Hepatology*. doi: [10.1016/j.cgh.2019.03.014](https://doi.org/10.1016/j.cgh.2019.03.014).
- Han, A., E. W. Newell, J. Glanville, N. Fernandez-Becker, C. Khosla, Y. H. Chien, and M. M. Davis. 2013. Dietary gluten triggers concomitant activation of CD4+ and CD8+ $\alpha\beta$ T cells and $\gamma\delta$ T cells in celiac disease. *Proceedings of the National Academy of Sciences of the United States of America* 110 (32):13073–8. doi: [10.1073/pnas.1311861110](https://doi.org/10.1073/pnas.1311861110).
- Hausch, F., L. Shan, N. A. Santiago, G. M. Gray, and C. Khosla. 2002. Intestinal digestive resistance of immunodominant gliadin peptides. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 283 (4):G996–1003. doi: [10.1152/ajpgi.00136.2002](https://doi.org/10.1152/ajpgi.00136.2002).
- Häuser, W., K. H. Janke, B. Klump, M. Gregor, and A. Hinz. 2010. Anxiety and depression in adult patients with celiac disease on a gluten-free diet. *World Journal of Gastroenterology* 16 (22):2780–7. doi: [10.3748/wjg.v16.i22.2780](https://doi.org/10.3748/wjg.v16.i22.2780).
- Herrera, M. G., M. Pizzuto, C. Lonz, K. Rott, A. Hütten, N. Sewald, J. M. Ruysschaert, and V. I. Dodero. 2018. Large supramolecular structures of 33-mer gliadin peptide activate toll-like receptors in macrophages. *Nanomedicine* 14 (4):1417–27. doi: [10.1016/j.nano.2018.04.014](https://doi.org/10.1016/j.nano.2018.04.014).
- Hofer, G., S. Wieser, M. K. Bogdos, P. Gatteringer, R. Nakamura, M. Ebisawa, M. Mäkelä, N. Papadopoulos, R. Valenta, and W. Keller. 2018. Three-dimensional structure of the wheat β -amylase Tri a 17, a clinically relevant food allergen. *Allergy* doi: [10.1111/all.13696](https://doi.org/10.1111/all.13696).
- Hollon, J., E. L. Puppa, B. Greenwald, E. Goldberg, A. Guerrierio, and A. Fasano. 2015. Effect of gliadin on permeability of intestinal biopsy explants from celiac disease patients and patients with non-celiac gluten sensitivity. *Nutrients* 7 (3):1565–76. doi: [10.3390/nu7031565](https://doi.org/10.3390/nu7031565).
- Hopper, A. D., M. Hadjivassiliou, D. P. Hurlstone, A. J. Lobo, M. E. Mcalindon, W. Egner, G. Wild, and D. S. Sanders. 2008. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. *Clinical Gastroenterology and Hepatology* 6 (3):314–20. doi: [10.1016/j.cgh.2007.12.008](https://doi.org/10.1016/j.cgh.2007.12.008).
- Husby, S., S. Koletzko, I. R. Korponay-Szabó, M. L. Mearin, A. Phillips, R. Shamir, R. Troncone, K. Giersiepen, D. Branski, C. Catassi, et al. 2012. European society for pediatric gastroenterology, hepatology, and nutrition guidelines for the diagnosis of coeliac disease. *Journal of Pediatric Gastroenterology and Nutrition* 54 (1):136–60. doi: [10.1097/MPG.0b013e31821a23d0](https://doi.org/10.1097/MPG.0b013e31821a23d0).
- Infantino, M., M. Manfredi, F. Meacci, V. Grossi, M. Severino, M. Benucci, E. Bellio, V. Bellio, A. Nucci, F. Zolfanelli, et al. 2015. Diagnostic accuracy of anti-gliadin antibodies in non celiac gluten sensitivity (NCGS) patients: A dual statistical approach. *Clinica Chimica Acta* 451:135–41. doi: [10.1016/j.cca.2015.09.017](https://doi.org/10.1016/j.cca.2015.09.017).
- Infantino, M., F. Meacci, V. Grossi, D. Macchia, and M. Manfredi. 2017. Anti-gliadin antibodies in non-celiac gluten sensitivity. *Minerva Gastroenterologica e Dietologica* 63:1–4.
- Inomata, N. 2009. Wheat allergy. *Current Opinion in Allergy and Clinical Immunology* 9 (3):238–43. doi: [10.1097/ACI.0b013e32832aa5bc](https://doi.org/10.1097/ACI.0b013e32832aa5bc).
- Jackson, J. R., W. W. Eaton, N. G. Cascella, A. Fasano, and D. L. Kelly. 2012. Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. *Psychiatric Quarterly* 83 (1):91–102. doi: [10.1007/s11126-011-9186-y](https://doi.org/10.1007/s11126-011-9186-y).
- Jericho, H., N. Sansotta, and S. Guandalini. 2017. Extraintestinal manifestations of celiac disease: Effectiveness of the gluten-free diet. *Journal of Pediatric Gastroenterology and Nutrition* 65 (1):75–9. doi: [10.1097/MPG.0000000000001420](https://doi.org/10.1097/MPG.0000000000001420).
- Jones, S. M., C. F. Magnolfi, S. K. Cooke, and H. A. Sampson. 1995. Immunologic cross-reactivity among cereal grains and grasses in children with food hypersensitivity. *Journal of Allergy and Clinical Immunology* 96 (3):341–51. doi: [10.1016/S0091-6749\(95\)70053-6](https://doi.org/10.1016/S0091-6749(95)70053-6).
- Junker, Y., S. Zeissig, S. J. Kim, D. Barisani, H. Wieser, D. A. Leffler, V. Zavallos, T. A. Libermann, S. Dillon, T. L. Freitag, et al. 2012. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. *The Journal of Experimental Medicine* 209 (13):2395–408. doi: [10.1084/jem.20102660](https://doi.org/10.1084/jem.20102660).
- Keet, C. A., E. C. Matsui, G. Dhillon, P. Lenehan, M. Paterakis, and R. A. Wood. 2009. The natural history of wheat allergy. *Annals of Allergy, Asthma & Immunology* 102 (5):410. doi: [10.1016/S1081-1206\(10\)60513-3](https://doi.org/10.1016/S1081-1206(10)60513-3).
- Kelly, C., J. Bai, E. Liu, and D. Leffler. 2015. Celiac disease: Clinical spectrum and management. *Gastroenterology* 148 (6):1175–86. doi: [10.1053/j.gastro.2015.01.044](https://doi.org/10.1053/j.gastro.2015.01.044).
- Khayatzadeh, A., M. Gharagholou, M. Ebisawa, R. Shokouhi Shoormasti, and M. Movahedi. 2016. A safe and effective method for wheat oral immunotherapy. *Iranian Journal of Allergy, Asthma and Immunology* 15:525–35.
- Kim, S. M., T. Mayassi, and B. Jabri. 2015. Innate immunity: Actuating the gears of celiac disease pathogenesis. *Best Practice & Research Clinical Gastroenterology* 29:425–35. doi: [10.1016/j.bpg.2015.05.001](https://doi.org/10.1016/j.bpg.2015.05.001).
- Kooy-Winkelaar, Y. M., D. Bouwer, G. M. Janssen, A. Thompson, M. H. Brugman, F. Schmitz, A. H. De Ru, T. Van Gils, G. Bouma, J. J. Van Rood, et al. 2017. CD4 T-cell cytokines synergize to induce proliferation of malignant and nonmalignant innate intraepithelial lymphocytes. *Proceedings of the National Academy of Sciences* 114 (6):E980–E89. doi: [10.1073/pnas.1620036114](https://doi.org/10.1073/pnas.1620036114).
- Kurppa, K., A. Laitinen, and D. Agardh. 2018. Coeliac disease in children with type 1 diabetes. *The Lancet. Child & Adolescent Health* 2 (2):133–43. doi: [10.1016/S2352-4642\(17\)30172-4](https://doi.org/10.1016/S2352-4642(17)30172-4).
- Lähdeaho, M. L., K. Kaukinen, K. Laurila, P. Vuotikka, O. P. Koivurova, T. Kärjä-Lahdensuu, A. Marcantonio, D. C. Adelman, and M. Mäki. 2014. Glutenase ALV003 attenuates gluten-induced mucosal injury in patients with celiac disease. *Gastroenterology* 146 (7):1649–58. doi: [10.1053/j.gastro.2014.02.031](https://doi.org/10.1053/j.gastro.2014.02.031).

- Lammers, K. M., M. Chieppa, L. Liu, S. Liu, T. Omatsu, M. Janka-Junttila, V. Casolaro, H. C. Reinecker, C. A. Parent, and A. Fasano. 2015. Gliadin induces neutrophil migration via engagement of the formyl peptide receptor, FPR1. *PLoS One* 10 (9):e0138338. doi: [10.1371/journal.pone.0138338](https://doi.org/10.1371/journal.pone.0138338).
- Lammers, K. M., R. Lu, J. Brownley, B. Lu, C. Gerard, K. Thomas, P. Rallabhandi, T. Shea-Donohue, A. Tamiz, S. Alkan, et al. 2008. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor cxcr3. *Gastroenterology* 135 (1):194–204. doi: [10.1053/j.gastro.2008.03.023](https://doi.org/10.1053/j.gastro.2008.03.023).
- Le, T. A., M. Al Kindi, J. A. Tan, A. Smith, R. J. Heddl, F. E. Kette, P. Hissaria, and W. B. Smith. 2016. The clinical spectrum of omega-5 gliadin allergy. *Internal Medicine Journal* 46 (6):710–6. doi: [10.1111/imj.13091](https://doi.org/10.1111/imj.13091).
- Lebwohl, B., D. S. Sanders, and P. H. R. Green. 2018. Coeliac disease. *Lancet (London, England)* 391 (10115):70–81. doi: [10.1016/S0140-6736\(17\)31796-8](https://doi.org/10.1016/S0140-6736(17)31796-8).
- Leffler, D. A., C. P. Kelly, P. H. Green, R. N. Fedorak, A. Dimarino, W. Perrow, H. Rasmussen, C. Wang, P. Bercik, N. M. Bachir, and J. A. Murray. 2015. Larazotide acetate for persistent symptoms of celiac disease despite a gluten-free diet: A randomized controlled trial. *Gastroenterology* 148 (7):1311–9. doi: [10.1053/j.gastro.2015.02.008](https://doi.org/10.1053/j.gastro.2015.02.008).
- Leonard, M. M., A. Sapone, C. Catassi, and A. Fasano. 2017. Celiac disease and nonceliac gluten sensitivity: A review. *JAMA* 318 (7):647–56. doi: [10.1001/jama.2017.9730](https://doi.org/10.1001/jama.2017.9730).
- Lytton, S. D., E. Antiga, S. Pfeiffer, T. Matthias, A. Szaflarska-Poplawska, V. K. Ulaganathan, W. Placek, P. Fabbri, R. Hall, and M. Caproni. 2013. Neo-epitope tissue transglutaminase autoantibodies as a biomarker of the gluten sensitive skin disease—dermatitis herpetiformis. *Clinica Chimica Acta* 415:346–9. doi: [10.1016/j.cca.2012.10.051](https://doi.org/10.1016/j.cca.2012.10.051).
- Mahmud, F. H., J. A. Murray, Y. C. Kudva, A. R. Zinsmeister, R. A. Dierkhising, B. D. Lahr, P. J. Dyck, R. A. Kyle, M. El-Youssef, L. J. Burgart, et al. 2005. Celiac disease in type 1 diabetes mellitus in a North American community: Prevalence, serologic screening, and clinical features. *Mayo Clinic Proceedings* 80 (11):1429–34. doi: [10.4065/80.11.1429](https://doi.org/10.4065/80.11.1429).
- Meresse, B., N. Korneychuk, G. Malamut, and N. Cerf-Bensussan. 2015. Interleukin-15, a master piece in the immunological jigsaw of celiac disease. *Digestive Diseases* 33 (2):122–30. doi: [10.1159/000369521](https://doi.org/10.1159/000369521).
- Meresse, B., G. Malamut, and N. Cerf-Bensussan. 2012. Celiac disease: An immunological jigsaw. *Immunity* 36 (6):907–19. doi: [10.1016/j.immuni.2012.06.006](https://doi.org/10.1016/j.immuni.2012.06.006).
- Molberg, Ø., A. K. Uhlen, T. Jensen, N. S. Flaete, B. Fleckenstein, H. Arentz-Hansen, M. Raki, K. E. A. Lundin, and L. M. Sollid. 2005. Mapping of gluten T-cell epitopes in the bread wheat ancestors: Implications for celiac disease. *Gastroenterology* 128 (2):393–401. doi: [10.1053/j.gastro.2004.11.003](https://doi.org/10.1053/j.gastro.2004.11.003).
- Morita, E., H. Matsuo, Y. Chinuki, H. Takahashi, J. Dahlström, and A. Tanaka. 2009. Food-dependent exercise-induced anaphylaxis - Importance of omega-5 gliadin and HMW-glutenin as causative antigens for wheat-dependent exercise-induced anaphylaxis. *Allergy International* 58:493–8.
- Muir, J. G., J. E. Varney, M. Ajamian, and P. R. Gibson. 2019. Gluten-free and low-FODMAP sourdoughs for patients with coeliac disease and irritable bowel syndrome: A clinical perspective. *International Journal of Food Microbiology* 290:237–46. doi: [10.1016/j.ijfoodmicro.2018.10.016](https://doi.org/10.1016/j.ijfoodmicro.2018.10.016).
- Murray, J. A., C. P. Kelly, P. H. R. Green, A. Marcantonio, T. T. Wu, M. Mäki, and D. C. Adelman; CeliAction Study Group of Investigators. 2017. No difference between latiglutenase and placebo in reducing villous atrophy or improving symptoms in patients with symptomatic celiac disease. *Gastroenterology* 152 (4):787–98. doi: [10.1053/j.gastro.2016.11.004](https://doi.org/10.1053/j.gastro.2016.11.004).
- Mustalahti, K., C. Catassi, A. Reunanen, E. Fabiani, M. Heier, S. Mcmillan, L. Murray, M. H. Metzger, M. Gasparin, E. Bravi, et al. 2010. The prevalence of celiac disease in Europe: Results of a centralized, international mass screening project. *Annals of Medicine* 42 (8):587–95. doi: [10.3109/07853890.2010.505931](https://doi.org/10.3109/07853890.2010.505931).
- Niland, B., and B. D. Cash. 2018. Health benefits and adverse effects of a gluten-free diet in non-celiac disease patients. *Gastroenterology and Hepatology* 14:82–91.
- Nilsson, N., C. Nilsson, H. Ekoff, S. Wieser-Pahr, M. P. Borres, R. Valenta, G. Hedlin, and S. Sjölander. 2018. Grass-allergic children frequently show asymptomatic low-level IgE co-sensitization and cross-reactivity to wheat. *International Archives of Allergy and Immunology* 177 (2):135–44. doi: [10.1159/000489610](https://doi.org/10.1159/000489610).
- Nilsson, N., S. Sjölander, A. Baar, M. Berthold, S. Pahr, S. Vrtala, R. Valenta, E. Morita, G. Hedlin, M. P. Borres, and C. Nilsson. 2015. Wheat allergy in children evaluated with challenge and IgE antibodies to wheat components. *Pediatric Allergy and Immunology* 26 (2):119–25. doi: [10.1111/pai.12334](https://doi.org/10.1111/pai.12334).
- Nordqvist, P., D. Thedjil, S. Khosravi, M. Lawther, E. Malmström, and F. Khabbaz. 2012. Wheat gluten fractions as wood adhesives—Glutenins versus gliadins. *Journal of Applied Polymer Science* 123 (3):1530–8. doi: [10.1002/app.34312](https://doi.org/10.1002/app.34312).
- Ontiveros, N., M. Y. Hardy, and F. Cabrera-Chávez. 2015a. Assessing of celiac disease and nonceliac gluten sensitivity. *Gastroenterology Research and Practice* 2015:1. doi: [10.1155/2015/723954](https://doi.org/10.1155/2015/723954).
- Ontiveros, N., J. A. López-Gallardo, M. J. Vergara-Jiménez, and F. Cabrera-Chávez. 2015b. Self-reported prevalence of symptomatic adverse reactions to gluten and adherence to gluten-free diet in an adult Mexican population. *Nutrients* 7 (7):6000–15. doi: [10.3390/nu7075267](https://doi.org/10.3390/nu7075267).
- Ontiveros, N., C. I. Rodríguez-Belgarrigue, G. Galicia-Rodríguez, M. J. Vergara-Jiménez, E. M. Zepeda-Gómez, J. G. Arámburo-Galvez, M. H. Gracia-Valenzuela, and F. Cabrera-Chávez. 2018. Prevalence of self-reported gluten-related disorders and adherence to a gluten-free diet in Salvadoran adult population. *International Journal of Environmental Research and Public Health* 15 (4):786. doi: [10.3390/ijerph15040786](https://doi.org/10.3390/ijerph15040786).
- Ontiveros, N., J. A. Tye-Din, M. Y. Hardy, and R. P. Anderson. 2014. Ex-vivo whole blood secretion of interferon (IFN)- γ and IFN- γ -inducible protein-10 measured by enzyme-linked immunosorbent assay are as sensitive as IFL- γ enzyme-linked immunospot for the detection of gluten-reactive T cells in human leucocyte antigen (HLA)-DQ2.5($\pm$)-associated coeliac disease. *Clinical & Experimental Immunology* 175:305–15.
- Pacharn, P., and P. Vichyanond. 2017. Immunotherapy for IgE-mediated wheat allergy. *Human Vaccines & Immunotherapeutics* 13:2462–6. doi: [10.1080/21645515.2017.1356499](https://doi.org/10.1080/21645515.2017.1356499).
- Pahr, S., C. Constantin, A. Mari, S. Scheiblhofer, J. Thalhamer, C. Ebner, S. Vrtala, I. Mittermann, and R. Valenta. 2012. Molecular characterization of wheat allergens specifically recognized by patients suffering from wheat-induced respiratory allergy. *Clinical & Experimental Allergy* 42:597–609. doi: [10.1111/j.1365-2222.2012.03961.x](https://doi.org/10.1111/j.1365-2222.2012.03961.x).
- Pahr, S., C. Constantin, N. G. Papadopoulos, S. Giavi, M. Mäkelä, A. Pelkonen, C. Ebner, A. Mari, S. Scheiblhofer, J. Thalhamer, et al. 2013. A-purothionin, a new wheat allergen associated with severe allergy. *Journal of Allergy and Clinical Immunology* 132 (4):1000–3. doi: [10.1016/j.jaci.2013.05.016](https://doi.org/10.1016/j.jaci.2013.05.016).
- Palacin, A., J. Bartra, R. Muñoz, A. Diaz-Perales, A. Valero, and G. Salcedo. 2010. Anaphylaxis to wheat flour-derived foodstuffs and the lipid transfer protein syndrome: A potential role of wheat lipid transfer protein tri a 14. *International Archives of Allergy and Immunology* 152 (2):178–83. doi: [10.1159/000265539](https://doi.org/10.1159/000265539).
- Palacin, A., S. Quirce, A. Armentia, M. Fernández-Nieto, L. Pacios, T. Asensio, J. Sastre, A. Diaz-Perales, and G. Salcedo. 2007. Wheat lipid transfer protein is a major allergen associated with baker's asthma. *Journal of Allergy and Clinical Immunology* 120 (5):1132–8. doi: [10.1016/j.jaci.2007.07.008](https://doi.org/10.1016/j.jaci.2007.07.008).
- Palacin, A., J. Varela, S. Quirce, V. Del Pozo, L. Tordesillas, P. Barranco, M. Fernandez-Nieto, J. Sastre, A. Diaz-Perales, and G. Salcedo. 2009. Recombinant lipid transfer protein tri a 14: A novel heat and proteolytic resistant tool for the diagnosis of baker's

- asthma. *Clinical & Experimental Allergy* 39:1267–76. doi: [10.1111/j.1365-2222.2009.03280.x](https://doi.org/10.1111/j.1365-2222.2009.03280.x).
- Pastorello, E. A., L. Farioli, A. Conti, V. Pravettoni, S. Bonomi, S. Iametti, D. Fortunato, J. Scibilia, C. Bindslev-Jensen, B. Ballmer-Weber, et al. 2007. Wheat IgE-mediated food allergy in European patients: Alpha-amylase inhibitors, lipid transfer proteins and low-molecular-weight glutenins. Allergenic molecules recognized by double-blind, placebo-controlled food challenge. *International Archives of Allergy and Immunology* 144 (1):10–22. doi: [10.1159/000102609](https://doi.org/10.1159/000102609).
- Pietzak, M. 2012. Celiac disease, wheat allergy, and gluten sensitivity: When gluten free is not a fad. *Journal of Parenteral and Enteral Nutrition* 36 (1_suppl):68S–75S. doi: [10.1177/0148607111426276](https://doi.org/10.1177/0148607111426276).
- Pinto-Sánchez, M. I., N. Causada-Calo, P. Bercik, A. C. Ford, J. A. Murray, D. Armstrong, C. Semrad, S. S. Kupfer, A. Alaedini, P. Moayyedi, et al. 2017. Safety of adding oats to a gluten-free diet for patients with celiac disease: Systematic review and Meta-analysis of clinical and observational studies. *Gastroenterology* 153 (2):395–409. doi: [10.1053/j.gastro.2017.04.009](https://doi.org/10.1053/j.gastro.2017.04.009).
- Pourpak, Z., M. Mesdaghi, M. Mansouri, A. Kazemnejad, S. B. Toosi, and A. Farhoudi. 2005. Which cereal is a suitable substitute for wheat in children with wheat allergy? *Pediatric Allergy and Immunology* 16 (3):262–6. doi: [10.1111/j.1399-3038.2005.00263.x](https://doi.org/10.1111/j.1399-3038.2005.00263.x).
- Quirce, S., T. Boyano-Martínez, and A. Díaz-Perales. 2016. Clinical presentation, allergens, and management of wheat allergy. *Expert Review of Clinical Immunology* 12 (5):563–72. doi: [10.1586/1744666X.2016.1145548](https://doi.org/10.1586/1744666X.2016.1145548).
- Quirce, S., and A. Díaz-Perales. 2013. Diagnosis and management of grain-induced asthma. *Allergy, Asthma & Immunology Research* 5: 348–56. doi: [10.4168/aa.2013.5.6.348](https://doi.org/10.4168/aa.2013.5.6.348).
- Real, A., I. Comino, L. De Lorenzo, F. Merchán, J. Gil-Humanes, M. J. Giménez, M. López-Casado, M. I. Torres, Á. Cebolla, C. Sousa, et al. 2012. Molecular and immunological characterization of gluten proteins isolated from oat cultivars that differ in toxicity for celiac disease. *PLoS One* 7 (12):e48365. doi: [10.1371/journal.pone.0048365](https://doi.org/10.1371/journal.pone.0048365).
- Reese, I., C. Schäfer, J. Kleine-Tebbe, B. Ahrens, O. Bachmann, B. Ballmer-Weber, K. Beyer, S. C. Bischoff, K. Blümchen, S. Dölle, et al. 2018. Non-celiac gluten/wheat sensitivity (NCGS) – A currently undefined disorder without validated diagnostic criteria and of unknown prevalence: Position statement of the task force on food allergy of the German Society of Allergology and Clinical Immunology (DGAKI). *Allergo Journal International* 27:147–51. doi: [10.1007/s40629-018-0070-2](https://doi.org/10.1007/s40629-018-0070-2).
- Reilly, N. R. 2016. The gluten-free diet: Recognizing fact, fiction, and fad. *The Journal of Pediatrics* 175:206–10. doi: [10.1016/j.jpeds.2016.04.014](https://doi.org/10.1016/j.jpeds.2016.04.014).
- Repo, M., K. Lindfors, M. Mäki, H. Huhtala, K. Laurila, M. L. Lähdeaho, P. Saavalainen, K. Kaukinen, and K. Kurppa. 2017. Anemia and iron deficiency in children with potential celiac disease. *Journal of Pediatric Gastroenterology and Nutrition* 64 (1):56–62. doi: [10.1097/MPG.0000000000001234](https://doi.org/10.1097/MPG.0000000000001234).
- Ribeiro, M., M. Rodríguez-Quijano, F. Nunes, J. Carrillo, G. Branlard, and G. Igrejas. 2016. New insights into wheat toxicity: Breeding did not seem to contribute to a prevalence of potential celiac disease's immunostimulatory epitopes. *Food Chemistry* 213:8–18. doi: [10.1016/j.foodchem.2016.06.043](https://doi.org/10.1016/j.foodchem.2016.06.043).
- Risnes, L. F., A. Christophersen, S. Dahal-Koirala, R. S. Neumann, G. K. Sandve, V. K. Sarna, K. E. Lundin, S. W. Qiao, and L. M. Sollid. 2018. Disease-driving CD4+ T cell clonotypes persist for decades in celiac disease. *The Journal of Clinical Investigation* 128 (6): 2642–50. doi: [10.1172/JCI98819](https://doi.org/10.1172/JCI98819).
- Rodríguez Del Río, P., A. Díaz-Perales, S. Sanchez-García, C. Escudero, P. Do Santos, M. Catarino, and M. D. Ibañez. 2014. Oral immunotherapy in children with IgE-mediated wheat allergy: Outcome and molecular changes. *Journal of Investigational Allergology and Clinical Immunology* 24:240–8.
- Romanos, J., A. Rosén, V. Kumar, G. Trynka, L. Franke, A. Szperl, J. Gutierrez-Achury, C. C. Van Diemen, R. Kanninga, S. A. Jankipersadsing, et al. 2014. Improving coeliac disease risk prediction by testing non-HLA variants additional to HLA variants. *Gut* 63 (3):415–22. doi: [10.1136/gutjnl-2012-304110](https://doi.org/10.1136/gutjnl-2012-304110).
- Roncoroni, L., K. A. Bascuñán, M. Vecchi, L. Doneda, M. T. Bardella, V. Lombardo, A. Scricciolo, F. Branchi, and L. Elli. 2019. Exposure to different amounts of dietary gluten in patients with non-celiac gluten sensitivity (NCGS): An exploratory study. *Nutrients* 11 (1): 136. doi: [10.3390/nu11010136](https://doi.org/10.3390/nu11010136).
- Rotondi Auffero, V., A. Fasano, and G. Mazzarella. 2018. Non-celiac gluten sensitivity: How its gut immune activation and potential dietary management differ from celiac disease. *Molecular Nutrition & Food Research* 62:e1700854. doi: [10.1002/mnfr.201700854](https://doi.org/10.1002/mnfr.201700854).
- Rubio-Tapia, A., I. D. Hill, C. P. Kelly, A. H. Calderwood, and J. A. Murray; American College of Gastroenterology. 2013. ACG clinical guidelines: Diagnosis and management of celiac disease. *The American Journal of Gastroenterology* 108 (5):656–76. doi: [10.1038/ajg.2013.79](https://doi.org/10.1038/ajg.2013.79).
- Rubio-Tapia, A., M. W. Rahim, J. A. See, B. D. Lahr, T. T. Wu, and J. A. Murray. 2010. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. *The American Journal of Gastroenterology* 105 (6):1412–20. doi: [10.1038/ajg.2010.10](https://doi.org/10.1038/ajg.2010.10).
- Salcedo, G., S. Quirce, and A. Diaz-Perales. 2011. Wheat allergens associated with baker's asthma. *Journal of Investigational Allergology and Clinical Immunology* 21:81–92.
- Sánchez-León, S., J. Gil-Humanes, C. V. Ozuna, M. J. Giménez, C. Sousa, D. F. Voytas, and F. Barro. 2018. Low-gluten, nontransgenic wheat engineered with CRISPR/Cas9. *Plant Biotechnology Journal* 16 (4):902–10. doi: [10.1111/pbi.12837](https://doi.org/10.1111/pbi.12837).
- Sapone, A., J. C. Bai, C. Ciacci, J. Dolinsek, P. H. Green, M. Hadjivassiliou, K. Kaukinen, K. Rostami, D. S. Sanders, M. Schumann, et al. 2012. Spectrum of gluten-related disorders: Consensus on new nomenclature and classification. *BMC Medicine* 10 (1):13. doi: [10.1186/1741-7015-10-13](https://doi.org/10.1186/1741-7015-10-13).
- Sapone, A., K. M. Lammers, V. Casolaro, M. Cammarota, M. T. Giuliano, M. De Rosa, R. Stefanile, G. Mazzarella, C. Tolone, M. I. Russo, et al. 2011. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: Celiac disease and gluten sensitivity. *BMC Medicine* 9 (1):23. doi: [10.1186/1741-7015-9-23](https://doi.org/10.1186/1741-7015-9-23).
- Sato, S., T. Utsunomiya, T. Imai, N. Yanagida, T. Asaumi, K. Ogura, Y. Koike, N. Hayashi, Y. Okada, A. Shukuya, and M. Ebisawa. 2015. Wheat oral immunotherapy for wheat-induced anaphylaxis. *Journal of Allergy and Clinical Immunology* 136 (4):1131–3. doi: [10.1016/j.jaci.2015.07.019](https://doi.org/10.1016/j.jaci.2015.07.019).
- Schalk, K., C. Lang, H. Wieser, P. Koehler, and K. A. Scherf. 2017a. Quantitation of the immunodominant 33-mer peptide from α -gliadin in wheat flours by liquid chromatography tandem mass spectrometry. *Scientific Reports* 7 (1):45092. doi: [10.1038/srep45092](https://doi.org/10.1038/srep45092).
- Schalk, K., B. Lexhaller, P. Koehler, and K. A. Scherf. 2017b. Isolation and characterization of gluten protein types from wheat, rye, barley and oats for use as reference materials. *PLoS One* 12 (2):e0172819. doi: [10.1371/journal.pone.0172819](https://doi.org/10.1371/journal.pone.0172819).
- Scherf, K. A., K. Brockow, T. Biedermann, P. Koehler, and H. Wieser. 2016. Wheat-dependent exercise-induced anaphylaxis. *Clinical & Experimental Allergy* 46:10–20. doi: [10.1111/cea.12640](https://doi.org/10.1111/cea.12640).
- Sharma, G. M., M. Pereira, and K. M. Williams. 2015. Gluten detection in foods available in the United States – A market survey. *Food Chemistry* 169:120–6. doi: [10.1016/j.foodchem.2014.07.134](https://doi.org/10.1016/j.foodchem.2014.07.134).
- Sicherer, S. H., and H. A. Sampson. 2018. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *Journal of Allergy and Clinical Immunology* 141 (1): 41–58. doi: [10.1016/j.jaci.2017.11.003](https://doi.org/10.1016/j.jaci.2017.11.003).
- Silvester, J. A., D. Weiten, L. A. Graff, J. R. Walker, and D. R. Duerksen. 2016. Living gluten-free: Adherence, knowledge, lifestyle adaptations and feelings towards a gluten-free diet. *Journal of Human Nutrition and Dietetics* 29 (3):374–82. doi: [10.1111/jhn.12316](https://doi.org/10.1111/jhn.12316).
- Skripak, J. M., S. D. Nash, H. Rowley, N. H. Brereton, S. Oh, R. G. Hamilton, E. C. Matsui, A. W. Burks, and R. A. Wood. 2008. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *Journal of Allergy and Clinical Immunology* 122 (6):1154–60. doi: [10.1016/j.jaci.2008.09.030](https://doi.org/10.1016/j.jaci.2008.09.030).

- Sollid, L. M., O. Molberg, S. Mcadam, and K. E. Lundin. 1997. Autoantibodies in coeliac disease: Tissue transglutaminase – Guilt by association? *Gut* 41 (6):851–2. doi: [10.1136/gut.41.6.851](https://doi.org/10.1136/gut.41.6.851).
- Sollid, L. M., S. W. Qiao, R. P. Anderson, C. Gianfrani, and F. Koning. 2012. Nomenclature and listing of celiac disease relevant gluten T-cell epitopes restricted by HLA-DQ molecules. *Immunogenetics* 64 (6):455–560. doi: [10.1007/s00251-012-0599-z](https://doi.org/10.1007/s00251-012-0599-z).
- Talley, N. J., and M. M. Walker. 2017. Celiac disease and nonceliac gluten or wheat sensitivity: The risks and benefits of diagnosis. *JAMA Internal Medicine* 177 (5):615–6. doi: [10.1001/jamainternmed.2017.0695](https://doi.org/10.1001/jamainternmed.2017.0695).
- Tollefsen, S., H. Arentz-Hansen, B. Fleckenstein, O. Molberg, M. Ráki, W. W. Kwok, G. Jung, K. E. Lundin, and L. M. Sollid. 2006. HLA-DQ2 and -DQ8 signatures of gluten T cell epitopes in celiac disease. *The Journal of Clinical Investigation* 116 (8):2226–36. doi: [10.1172/JCI27620](https://doi.org/10.1172/JCI27620).
- Tordesillas, L., M. C. Berin, and H. A. Sampson. 2017. Immunology of food allergy. *Immunity* 47 (1):32–50. doi: [10.1016/j.immuni.2017.07.004](https://doi.org/10.1016/j.immuni.2017.07.004).
- Tye-Din, J. A., J. A. Stewart, J. A. Dromey, T. Beissbarth, D. A. Van Heel, A. Tatham, K. Henderson, S. I. Mannering, C. Gianfrani, D. P. Jewell, et al. 2010. Comprehensive, quantitative mapping of T cell epitopes in gluten in celiac disease. *Science Translational Medicine* 2 (41):41ra51. doi: [10.1126/scitranslmed.3001012](https://doi.org/10.1126/scitranslmed.3001012).
- Van Den Broeck, H. C., H. C. De Jong, E. M. Salentijn, L. Dekking, D. Bosch, R. J. Hamer, L. J. Gilissen, I. M. Van Der Meer, and M. J. Smulders. 2010. Presence of celiac disease epitopes in modern and old hexaploid wheat varieties: Wheat breeding may have contributed to increased prevalence of celiac disease. *Theoretical and Applied Genetics* 121 (8):1527–39. doi: [10.1007/s00122-010-1408-4](https://doi.org/10.1007/s00122-010-1408-4).
- Vaquero, L., I. Comino, S. Vivas, L. Rodríguez-Martín, M. J. Giménez, J. Pastor, C. Sousa, and F. Barro. 2018. Tritordeum: A novel cereal for food processing with good acceptability and significant reduction in gluten immunogenic peptides in comparison with wheat. *Journal of the Science of Food and Agriculture* 98 (6):2201–09. doi: [10.1002/jsfa.8705](https://doi.org/10.1002/jsfa.8705).
- Verma, A. K., S. Gatti, E. Lionetti, T. Galeazzi, C. Monachesi, E. Franceschini, L. Balanzoni, N. Scattolo, M. Cinquetti, and C. Catassi. 2018. Comparison of diagnostic performance of the IgA anti-tTG test vs IgA anti-native gliadin antibodies test in detection of celiac disease in the general population. *Clinical Gastroenterology and Hepatology* 16 (12):1997–98. doi: [10.1016/j.cgh.2018.03.028](https://doi.org/10.1016/j.cgh.2018.03.028).
- Wacklin, P., K. Kaukinen, E. Tuovinen, P. Collin, K. Lindfors, J. Partanen, M. Mäki, and J. Mättö. 2013. The duodenal microbiota composition of adult celiac disease patients is associated with the clinical manifestation of the disease. *Inflammatory Bowel Diseases* 19 (5):934–41. doi: [10.1097/MIB.0b013e31828029a9](https://doi.org/10.1097/MIB.0b013e31828029a9).
- Weichel, M., A. G. Glaser, B. K. Ballmer-Weber, P. Schmid-Grendelmeier, and R. Cramer. 2006. Wheat and maize thioredoxins: A novel cross-reactive cereal allergen family related to baker's asthma. *Journal of Allergy and Clinical Immunology* 117 (3):676–81. doi: [10.1016/j.jaci.2005.11.040](https://doi.org/10.1016/j.jaci.2005.11.040).
- Wieser, H. 2007. Chemistry of gluten proteins. *Food Microbiology* 24 (2):115–9. doi: [10.1016/j.fm.2006.07.004](https://doi.org/10.1016/j.fm.2006.07.004).
- Wu, J. H., B. Neal, H. Trevena, M. Crino, W. Stuart-Smith, K. Faulkner-Hogg, J. C. Yu Louie, and E. Dunford. 2015. Are gluten-free foods healthier than non-gluten-free foods? An evaluation of supermarket products in Australia. *British Journal of Nutrition* 114 (3):448–54. doi: [10.1017/S0007114515002056](https://doi.org/10.1017/S0007114515002056).
- Yu, W., D. M. H. Freeland, and K. C. Nadeau. 2016. Food allergy: Immune mechanisms, diagnosis and immunotherapy. *Nature Reviews Immunology* 16 (12):751–65. doi: [10.1038/nri.2016.111](https://doi.org/10.1038/nri.2016.111).
- Zanchetta, M. B., V. Longobardi, and J. C. Bai. 2016. Bone and celiac disease. *Current Osteoporosis Reports* 14 (2):43–8. doi: [10.1007/s11914-016-0304-5](https://doi.org/10.1007/s11914-016-0304-5).
- Zanini, B., V. Villanacci, L. De Leo, and A. Lanzini. 2015. Triticum monococcum in patients with celiac disease: A phase II open study on safety of prolonged daily administration. *European Journal of Nutrition* 54 (6):1027–9. doi: [10.1007/s00394-015-0892-3](https://doi.org/10.1007/s00394-015-0892-3).
- Zevallos, V. F., V. Raker, S. Tenzer, C. Jimenez-Calvente, M. Ashfaq-Khan, N. Rüssel, G. Pickert, H. Schild, K. Steinbrink, and D. Schuppan. 2017. Nutritional wheat amylase-trypsin inhibitors promote intestinal inflammation via activation of myeloid cells. *Gastroenterology* 152 (5):1100–13. doi: [10.1053/j.gastro.2016.12.006](https://doi.org/10.1053/j.gastro.2016.12.006).