Chapter

Celiac Disease, Management, and Follow-Up

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Abstract

Celiac disease (CD) is a systemic immune-mediated disorder characterized by a specific serological and histological profile triggered by gluten ingestion, which is given in genetically predisposed subjects. Heterogeneous clinical presentation is characteristic in CD, affecting any organ or tissue with gastrointestinal, extraintestinal, seronegative, or nonresponsive manifestations. CD diagnosis is based on several criteria, including genetic and serological tests, clinical symptoms and/or risk conditions, and duodenal biopsy. Currently, the available treatment for CD is a strict gluten-free diet (GFD) that essentially relies on the consumption of naturally gluten-free foods, such as animal-based products, fruits, vegetables, legumes, and nuts, as well as gluten-free dietary products that may not contain more than 20 mg of gluten per kg of food according to Codex Alimentarius. However, it is difficult to maintain a strict oral diet for life and at least one-third of patients with CD are exposed to gluten. Difficulties adhering to a GFD have led to new tools to monitor the correct adherence to GFD and alternative forms of treatment.

Keywords: celiac disease, gluten-free diet, gluten immunogenic peptides, dietary adherence, non-dietary therapies

1. Introduction

Celiac disease (CD) is a chronic immune-mediated enteropathy triggered by exposure to dietary gluten in genetically predisposed individuals [1]. The diagnosis rate of this pathology has increased in the last 10 years [2], so worldwide epidemiologic data are now available showing that CD is ubiquitous, with a prevalence of 1.4% [3], higher in female than male individuals [2–7].

Clinically, CD presents with a wide variety of gastrointestinal and extraintestinal symptoms that differ considerably according to the age of presentation [8] or even be an asymptomatic disease. Digestive symptoms and growth retardation are frequent in the pediatric population diagnosed within the first years of life [9]. However, in adults, symptoms can be nonspecific gastrointestinal or extraintestinal of various kinds.

Currently, the only available treatment for CD is a strict, lifelong gluten-free diet (GFD), which requires significant patient education, motivation, and follow-up [10]. Adherence to a GFD is not easy, with the ubiquitous nature of gluten,

cross-contamination of foods, inadequate food-labeling regulations, and social constraints [11]. Current methods to evaluate adherence to a GFD include the use of a dietary questionnaire and monitoring of serological findings or clinical symptoms; however, neither of these methods generates a direct nor an accurate measurement of dietary adherence [1, 11, 12]. Small bowel biopsy is the "gold standard" for CD diagnosis, but according to most clinical guidelines, its role in the follow-up of patients with CD is limited to cases involving a lack of clinical response or symptom recurrence [13–17]. Nonresponsive CD occurs frequently, particularly in those diagnosed in adulthood. Persistent or recurring symptoms should lead to a review of patients to exclude alternative diagnoses and a review of GFD to ensure there is no obvious gluten contamination and confirm adherence to GFD [1]. Possible causes include age at diagnosis, follow-up time, the existence of social differences, the intake of certain drugs (PPIs, NSAIDs), severe clinical symptoms at diagnosis, inadequate adherence to diet, or the presence of inadvertent contamination of the diet [18, 19].

In this chapter, we synthesized the latest research findings and evidence related to the management of CD and GFD, including emerging tools to monitor the correct adherence to GFD and the development of non-dietary therapies.

2. Pathogeny

Pathogeny development of CD is due to a combination of environmental (gluten and other factors), genetic (HLA system), and immunological factors (response of intestinal T lymphocytes).

2.1 Gluten

The major environmental factor responsible for the development of CD is gluten, which is a complex mixture of prolamin and glutelin storage proteins of certain cereals, such as wheat, barley, rye, oats, and their derivates. These common dietary proteins have unusual biochemical properties that include a high abundance of glutamine and proline residues, which render them resistant to degradation by gastrointestinal proteases [20], leaving large peptides. These peptides enter the lamina propria of the small intestine via transcellular or paracellular routes where, in affected individuals, an immune reaction occurs.

2.2 Immunological factors

The most accepted model for explaining CD immunopathogenesis is the two-signal model mediated by a first innate immune response (direct toxic effect of gluten on the epithelium) followed by a secondary antigen-specific adaptive response (through CD4+ T lymphocytes of the lamina propria) [20, 21]. Some peptides, such as, the 19-mer gliadin peptide, trigger an innate immune response mainly characterized by the production of IL-15 by epithelial cells. Result is the disruption of the epithelial barrier, by increasing the permeability and inducing enterocyte apoptosis [20]. These peptides enter the lamina propria of the small intestine via transcellular or paracellular routes [20] where, in affected individuals, an adaptive immune reaction occurs that is facilitated by increased intestinal permeability that allows the passage of immunogenic peptides, such as 33-mer, to the lamina propria. At the same time, some glutamine residues of these peptides are catalytically

deaminated by tissue transglutaminase (tTG). This deamination, in turn, increases the immunogenicity of peptides due to high-affinity interactions between modified residues and ligand binding sites of HLA-DQ2 and HLA-DQ8 molecules [22] expressed by dendritic cells. Gliadin peptides are then presented to gliadin-reactive CD4+ T cells. During this process, antibodies against tTG, gliadin, and actin are made through unclear mechanisms. These antibodies might contribute to extra-intestinal manifestations of CD, such as dermatitis herpetiformis and gluten ataxia. Moreover, the immune response initiates a cascade of reactions that degenerate into crypt hyperplasia and flattening of the intestinal villi.

2.3 Genetic factors

The importance of a genetic component for the development of CD is evident, based on the familial occurrence and the high concordance among identical twins [23, 24]. Almost 100% of patients with CD possess specific variants of the HLA class II genes HLA-DQA1 and HLA-DQB1 that, together, encode the two chains (α and β) of CD-associated heterodimer proteins DQ2 and DQ8 that are expressed on the surface of antigen-presenting cells [25]. More than 90% of patients with CD are DQ2 positive and most of the others are DQ8 positive [26]. HLA-DQ2 and HLA-DQ8 risk heterodimers are present in approximately 30–40% of the general population, and of these, approximately 1% develop the disease, so HLA DQ2/8 seems necessary, but not sufficient for the development of CD [27].

Several studies have been carried out to identify non-HLA susceptibility genes. Among these are a large number of CD-associated genes basically encode interleukins, interleukin receptors, and tumor necrosis factors or receptors that are involved in innate immunity and epithelial stress signals (COELIAC2, COELIAC 3, CTLA4, and COELIAC4) [28].

2.4 Other environmental factors

Other environmental factors that could contribute to the development of CD have also been studied, such as the time and manner of introduction of gluten, the type of delivery, the start and duration of breastfeeding, the microbiome or early exposure to antibiotics, among others [29, 30]. However, the studies carried out to date do not confirm the different hypotheses proposed. Recently, the link between viral infections and loss of oral gluten tolerance has been investigated, since infections caused by rotavirus, reovirus, astrovirus, enterovirus, and adenovirus are very common in childhood. This opens the door to a new field of knowledge that could allow the design of preventive strategies in the future of CD [31, 32].

3. Clinical manifestations

Clinical characteristics of CD differ considerably depending on the age of presentation, and it can also be profuse or simply present analytical abnormalities [33–36]. It can manifest clinically with a wide variety of symptoms that affect multiple organs and systems and that can be both gastrointestinal (diarrhea, vomiting, abdominal pain, bloating, bloating, constipation, gastroesophageal reflux, among others) and extra-intestinal (tiredness, dermatitis herpetiformis, anemia, osteoporosis, infertility, growth retardation, neuropathy, ataxia, delayed puberty, etc.) [8, 25]. Symptomatic

CD can be classified into classic and non-classic. Any case presenting with malabsorption is classified as a classic CD. Although the clinical presentation is changing toward an affectation of older individuals with milder symptoms. The symptomatic classical disease was previously the most common presentation, and although it remains a prominent mode of presentation, subclinical and nonclassical cases now make up roughly 30% and 40–60% of new cases, respectively [37, 38].

4. Diagnosis

The diagnosis of CD may require genetic and serological tests and a duodenal biopsy.

4.1 Genetic risk markers

The main genetic risk factor for CD is the presence of HLA-DQ2 and -DQ8 heterodimers, which are identified in 90% and 5–7% of patients with CD, respectively [7]. Since these alleles are found in 30–40% of the general population (HLA-DQ2 being the most common) [39], their absence is important due to their negative predictive value (NPV). Therefore, the HLA-DQ2/HLA-DQ8 test plays an important role in CD diagnosis and is recommended in the following situations [40]—(a) exclusion of the disease, especially in patients who have started GFD; (b) in situations of uncertain diagnosis due to negative serology, but histology suggestive of CD; (c) to differentiate siblings in whom it is intended to ensure that it is unlikely that they will develop the disease from those who will need monitoring; (d) in subjects with autoimmune diseases and other diseases in which CD should be investigated.

A negative result for HLA-DQ2/HLA-DQ8 means a very low probability of developing the disease. Therefore, this test can be used to support the diagnosis of CD, since it has a high NPV, allowing exclusion with 99% certainty [41]. However, it has little positive predictive value (PPV) (only around 12%), so its determination has no diagnostic value in situations with elevated antibodies directed against tTG and should be reserved as second-line in patients with diagnostic doubt [42, 43].

4.2 Specific serum antibodies

Various serological tests have been developed to detect CD—antigliadin antibodies (anti-AGA), antibodies against deaminated gliadin peptides (anti-DGP), anti-endomysia antibodies (anti-EMA), and anti-transglutaminase antibodies (anti-tTG). Serological tests are important for two reasons—(1) they select patients in whom duodenal biopsy should be indicated to confirm clinical suspicion, and (2) they confirm the diagnosis in cases in which enteropathy has been observed [43].

Anti-AGA has been used for decades and is reasonably safe when the probability of suffering from CD is very high. However, it has been shown that these antibodies present variability in their diagnostic precision, due to the fact that they have low sensitivity and specificity; therefore, they should not be included in routine tests for the diagnosis of CD [41, 44].

Anti-EMA has a relatively low sensitivity (80–90%), but its specificity is close to 100%. However, they require more complex laboratory techniques and depend on the experience of the laboratory staff, remaining as a second-line test adequate to confirm clinical suspicion [1].

Anti-tTG IgA has a sensitivity and specificity of 95 and 90%, respectively [41, 45]. Anti-DGP has shown good precision, although lower than anti-tTG IgA, so an isolated positive result for IgA and/or IgG-DGP in patients at low risk for CD, predicts the disease only in 15%, being in the rest of the cases false positives. Therefore, in a first approximation, anti-tTG are the preferred antibodies for the diagnosis of CD according to the ESPGHAN diagnostic criteria [46, 47]. Anti-DGP is considered less sensitive or specific for the detection of CD compared to anti-tTG and anti-EMA. However, these last two antibodies are less sensitive in children under 2 years of age. It should also be taken into account that anti-tTG can be negative in 5–16% of patients with histologically confirmed CD [48]. Therefore, there is no serological test with perfect sensitivity and specificity [44]. In case of general IgA deficiency, which is observed in 2–3% of patients with CD, the IgG-based test (anti-DGP IgG and anti-tTG IgG) should be performed. IgG anti-tTG has diagnostic utility in patients with selective IgA deficiency (IgA < 0.07 mg/dl). Regarding anti-DGP IgG, there is no evidence of greater efficacy compared to anti-tTG IgG or anti-EMA IgG [41].

4.3 Intestinal biopsy

Duodenal biopsy of the small intestine is a key point in the diagnosis of CD. A distinctive pattern of histological abnormalities has been identified in this disease, including partial or total villous atrophy, elongated crypts, decreased villus/crypt ratio, increased crypt mitotic index, increased crypt density of intraepithelial lymphocytes (IELs), and infiltration of plasma cells in the lamina propria. An increase in IELs tends to be located at the tips of the villi and are usually CD8+ [37]. The presence of a diffuse and uniform infiltrate of these lymphocytes is the most sensitive finding, but it is not specific to CD. A count of at least 25 IELs/100 enterocytes represents a definitive increase in IELs [49, 50]. Immunohistochemical studies have shown that the increase in IELs represents an expansion of cytotoxic T cells alpha-beta and gamma-delta. Gamma-delta T cells are observed in 1–10% of the normal small intestinal mucosa but increase in patients with CD, where they may represent 15–30% of all IELs [1]. In addition, the absence of the brush border can be identified, as well as alterations in epithelial cells.

There are three grading systems to establish the severity of histological damage proposed by Marsh, Oberhuber [51], and Corazza-Villanaci [52]. Marsh system, with three types of grades, was replaced in 1999 by Oberhuber [51], which proposes a better standardization with six types [51]. In 2007, a new, simpler classification was published by Corazza-Villanacci [52]. These classifications are qualitative and subjective [1, 37]. Marsh-Oberhuber classification is used by most pathologists both for diagnosis and to ensure regression of the lesion after GFD [1]. Generally, six stages are distinguished—type 0 without lesion, type 1 (infiltrative lesion), type 2 (crypt hyperplasia), type 3 (villi atrophy: 3a: partial; 3b: subtotal; 3c: total) [51]. Furthermore, these lesions are not pathognomonic for CD, and there is a wide spectrum of diseases that can produce indistinguishable microscopic lesions.

Currently, it is considered that, in patients with high levels of antibodies, the diagnosis could be based on the combination of symptoms, antibodies determination, and genetics, omitting in this case the duodenal biopsy [11, 46], unlike what was established in the previous ESPGHAN guidelines for the diagnosis of CD. However, confirmation of CD by biopsy is considered the gold standard in the diagnosis of CD in certain types of patients.

The biopsy can be used to diagnose and monitor, but CD is a burden for patients. Therefore, less invasive and objective biomarkers are required to assess the disease. In addition, in certain patients, a challenge with gluten is necessary to make a correct diagnosis of CD. Based on this, Leonard et al. [53] investigated the ability of different biomarkers to diagnose CD after provocation. These biomarkers could, complement or replace histology in the diagnosis of CD. These authors evaluated traditional diagnostic techniques, such as biopsy, antibodies, symptomatology, as well as different biomarkers to measure the response to two levels of gluten exposure, studying interleukin-2 (IL-2), the tetramer test, and the dot enzyme-linked immunosorbent assay (Enzyme-Linked ImmunoSpot Assay, ELISpot), among others. Results showed that the measurement of IL-2 in plasma might be the first and most sensitive marker for the evaluation of gluten exposure in patients with CD. This study provides a framework for the rational design and selection of biomarkers in future gluten challenge studies with the goal of incorporating them into clinical practice.

5. Treatment of celiac disease

5.1 Diet therapy: gluten-free diet

Only effective treatment available for CD consists of following a strict GFD, excluding gluten proteins from the diet from wheat, barley, rye, and oats, as well as hybrids of these cereals such as triticale and their derivatives (starch, flour, etc.) [14]. Nevertheless, such a diet is difficult to follow due to the unintended contamination of "gluten-free" products, improper labeling, social constraints, and ubiquity of gluten proteins in raw or cooked foods and pharmaceuticals. Thus, accidental gluten encounters are likely. Most patients with CD can safely tolerate approximately 10 mg of gluten cross-contamination daily. However, there is a tremendous degree of variability within this population, and some patients may have worsening histological changes with very low daily gluten exposure [1, 10].

Strict adherence to GFD leads to remission of gastrointestinal and extra-intestinal symptoms, normalization of serological tests, and recovery of the intestinal mucosa, in most cases [14]. Initiation of strict GFD generally results in a rapid improvement of clinical symptoms, while recovery of the intestinal villi requires several years of a strict GFD (around 2 years in 34% and 5 years in 66%) [44]. Therefore, it is essential that patient with CD is aware of adherence to GFD to avoid future complications.

5.1.1 Difficulties in following a gluten-free diet: transgressions

Although adherence to GFD is the cornerstone of the treatment of patients with CD, there are conditions that prevent it from being carried out and mean that a significant percentage of patients with CD do not adhere and commit voluntary or involuntary transgressions [10]. Among the conditions that can prevent the GFD monitoring, we highlight the high economic cost of gluten-free products, which are not accessible to a large number of people with CD. Another factor to highlight that can favor its involuntary intake is the ubiquity of gluten in a high percentage of manufactured products since many of the foods that are marketed contain gluten from wheat, barley, rye, or oats, including those that intervene only as a thickener or binder. In fact, several studies carried out to determine the gluten content in natural (unprocessed) gluten-free foods or in foods labeled gluten-free reveal relatively

high contamination rates, present in 9–22% of the samples analyzed [54–56]. In addition, many products contain hidden gluten, mainly due to cross-contamination with other gluten-containing foods that are processed or stored in the same place. The risk that these foods pose for patients with CD makes rigorous control of gluten content convenient [57]. Therefore, accurate detection and quantification of gluten in food are essential [10]. The Codex Alimentarius [58] has established that a food classified as "gluten-free" should not exceed 20 mg of gluten per kg of food, that is, 20 parts per million (ppm). Currently, several methods are used for the detection and quantification of gluten in foods. Enzyme-Linked ImmunoSorbent Assays (ELISAs) are the most widely used methods, as they are sensitive, rapid, and relatively easy to perform. Most commercial ELISAs use monoclonal antibodies (moAbs) such as R5 and G12 [59–64]. Other methods, such as the Polymerase Chain Reaction (PCR), developed mainly for research, are far from being able to replace ELISA, as they are not suitable for the detection of gluten in highly processed or hydrolyzed samples due to DNA degradation. Lastly, liquid chromatography/mass spectrometry methods require expensive equipment and expertise [65].

All the factors described above cause nonadherence to GFD among patients with CD. Recent studies have indicated that inadvertent gluten ingestion occurs more frequently than intentional ingestion, and gluten contamination in naturally gluten-free foods is likely to be one of the most important factors in inadvertent nonadherence [66]. Other investigations based on the study of intestinal biopsies of patients with CD on GFD for more than 2 years have suggested that transgressions are relatively frequent, detecting a lack of recovery of the intestinal villi in 36–55% of the population studied [67–69]. These inadvertent or intentional violations are the main reason for uncontrolled CD in adult patients with CD [70]. Likewise, there is a small percentage of patients with CD (approximately 0.3–10%) who do not respond to GFD and have persistent symptoms of malabsorption and intestinal villi atrophy, which is known as refractory CD (RCD) [7, 71–74].

5.1.2 Gluten-free diet monitoring methods

The existence of a reliable method that makes it possible to verify whether or not patients with CD are following a GFD is undoubtedly useful not only in monitoring the patient to avoid long-term complications, but also when diagnosing RCD [16, 44]. Among the methods to monitor adherence to GFD is the determination of specific antibodies, dietary interviews, control of symptoms, biopsies, and the detection of gluten immunogenic peptides (GIP) in stool and urine (**Table 1**) [1, 41, 47, 75].

5.1.2.1 Serological tests

Anti-tTG and anti-DGP have been used frequently to assess CD follow-up [76]. Use of these serological tests has revealed that it takes several months for the specific serology of CD to return to normal values. A significant decrease in levels during the first year suggests adherence to the diet and, therefore, patients with CD whose serology tests do not improve should be reassessed regarding their exposure to gluten [16]. However, negative serological markers do not reflect strict adherence to a GFD and are a poor predictor of dietary transgressions [17, 43, 77]. Although serology shows high accuracy for the diagnosis of CD, these tests are not as useful in follow-up, since they do not correlate with histological findings or symptoms [78]. It is important to note that a negative serology in a patient with CD on GFD does not necessarily

	Strengths	Weak points
Serological tests	• High accuracy for the diagnosis of CD	• Late positives (6–24 months to normalize) • False positives and negatives, for follow-up, no correlation with biopsy and symptoms • I need a blood draw
Dietary questionnaires, symptomatology questionnaires, and dietary interviews	• Non-invasive • Low cost	• Forgetfulness, omissions • Falsified • Tedious • Non-objective
Intestinal biopsy	• Gold standard test for the diagnosis of CD	• Invasive • Expensive, consumes hospital resources • Uncomfortable for the patient
Detection of GIP in human samples	• Simple and fast method • Non-invasive • Correlation with gluten intake	
Other bookmarks (Calprotectin)	• Simple and fast method • Non-invasive	• Non-CD specific

Table 1.
A comparison of the strengths and weaknesses of the tools used to monitor GFD in patients with CD. CD, celiac disease; GFD, gluten-free diet; GIP, gluten immunogenic peptides.

guarantee the recovery of the intestinal mucosa [14, 43]. In a recent meta-analysis, PPV of persistently positive determination of anti-tTG IgA was very low and showed a sensitivity of 38% in adults. NPV of serology in adult patients with CD on GFD for one year or more was higher, with a specificity of 80%. Therefore, the usefulness of serology in the follow-up of adult patients with CD is very limited [1].

5.1.2.2 Symptomatology

Among the most widely used methods to assess the presence of gastrointestinal symptoms in patients with CD is the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire [79, 80]. This questionnaire serves to check symptoms and determine the improvement and evolution of CD. However, there are a large number of patients with CD who are asymptomatic or minimally symptomatic at the time of presentation and, in these cases, it would not be feasible to use the clinical response as an indicator of intestinal mucosal recovery and adherence to GFD [13, 70].

5.1.2.3 Intestinal biopsy

Histological lesion remains the gold standard test for the diagnosis of CD, recovery of the mucosa is the main marker of response to diet. The only method to verify this normalization of the duodenum is by performing an oral endoscopy with an intestinal biopsy, an aggressive and costly follow-up method. However, an intestinal biopsy is a method used clinically, especially in the evaluation of patients with persistent symptoms [81]. It seems advisable to perform a follow-up endoscopy in adults

1–2 years after starting GFD to ensure recovery of the mucosa [82]. In this way, it would be possible to differentiate patients who are at low risk and in whom follow-up periods can be extended, from those at high risk who may need special supervision to maintain adherence to GFD [83].

5.1.2.4 Dietary questionnaires and interviews

Adherence to GFD can be assessed through dietary interviews or questionnaires conducted by a specialist. Dietitian has an important role in providing practical advice on lifestyle and food choices [16]. Evaluation of adherence to the diet through dietary interviews has been suggested because of its low cost and because it is not invasive; however, they are difficult to standardize and are subjective.

Different questionnaires assess the frequency of food and self-reported adherence to GFD [84]. Some of the more specific questionnaires are—(a) Gluten Free Score by Biagi et al. [85], whose four items provide a score from 0 to IV and in which levels 0 and I indicate poor adherence to the diet and, (b) the Celiac Dietary Adherence Test (CDAT) developed by Leffler et al. [86], which is a brief questionnaire that allows a rapid and standardized evaluation. This last questionnaire comprises seven easy-to-apply questions with optimal psychometric characteristics that assess CD symptomatology, self-efficacy expectations, reasons for maintaining GFD, knowledge of the disease, associated risk behaviors, and the perceived degree of adherence.

Nevertheless, there is considerable controversy about the validity of dietary questionnaires in the assessment of GFD because some patients with CD do not record the actual gluten consumed intentionally in some cases. Therefore, the measurement of adherence to GFD through questionnaires appears to be subjective and imprecise and does not allow involuntary infractions to be identified [25, 84].

5.1.2.5 Detection of immunogenic gluten peptides in human samples

Recently, new noninvasive methodologies have been developed to monitor gluten exposure in patients with CD based on the detection and quantification of GIP in stool and urine samples [87–90]. These immunological methodologies (ELISA and immunochromatographic strips) based on G12 and A1 moAbs are capable of detecting GIP, which are gluten fragments resistant to gastrointestinal digestion, and mainly responsible for the immune response of patients with CD [60, 61, 91–95]. These tools make it possible to monitor adherence to GFD and detect violations cases, helping to identify the origin of clinical symptoms and avoid complications derived from gluten intake (anemia, osteoporosis, increased risk of lymphoma, etc.). These techniques have represented a revolutionary worldwide advance in the clinical practice of CD and have been introduced in the new guidelines, both European and Spanish, for monitoring the GFD of patients with CD [1, 41]. Numerous rigorous studies have evaluated the use of GIP determination in stool and/or urine to monitor adherence to GFD compared to other tools (**Table 2**). The studies included children and adults diagnosed with CD and healthy volunteers. Overall, these studies indicated that this novel technique was highly sensitive for the detection of GFD transgressions and therefore could facilitate the follow-up of patients with CD.

5.1.2.6 Other bookmarks

Other markers have been proposed for monitoring GFD, such as the permeability test [113] or fecal calprotectin [114, 115]. Determination of fecal calprotectin

	Population	Study design	References
Stool	Children	Case-control study	[87]
		Cohort study	[96]
		Prospective study	[89]
		Transversal study	[97]
		Systematic revision	[98]
		Prospective study	[99]
		Observational descriptive study	[100]
	Children and adults	Prospective study	[88]
		Transversal study	[101, 102]
	Adults	Observational prospective study	[103]
		Prospective study	[104]
		Prospective study	[105]
Urine	Children and adults	Controlled study	[106]
		Randomized controlled study	[90]
	Adults	Transversal study	[107]
		Prospective study	[108]
		Prospective study	[109]
		Prospective study	[110]
Stool and urine	Children and adults	Meta-analysis	[111]
	Adults	Prospective study	[80]
		Prospective study	[17, 77]
		Prospective study	[112]

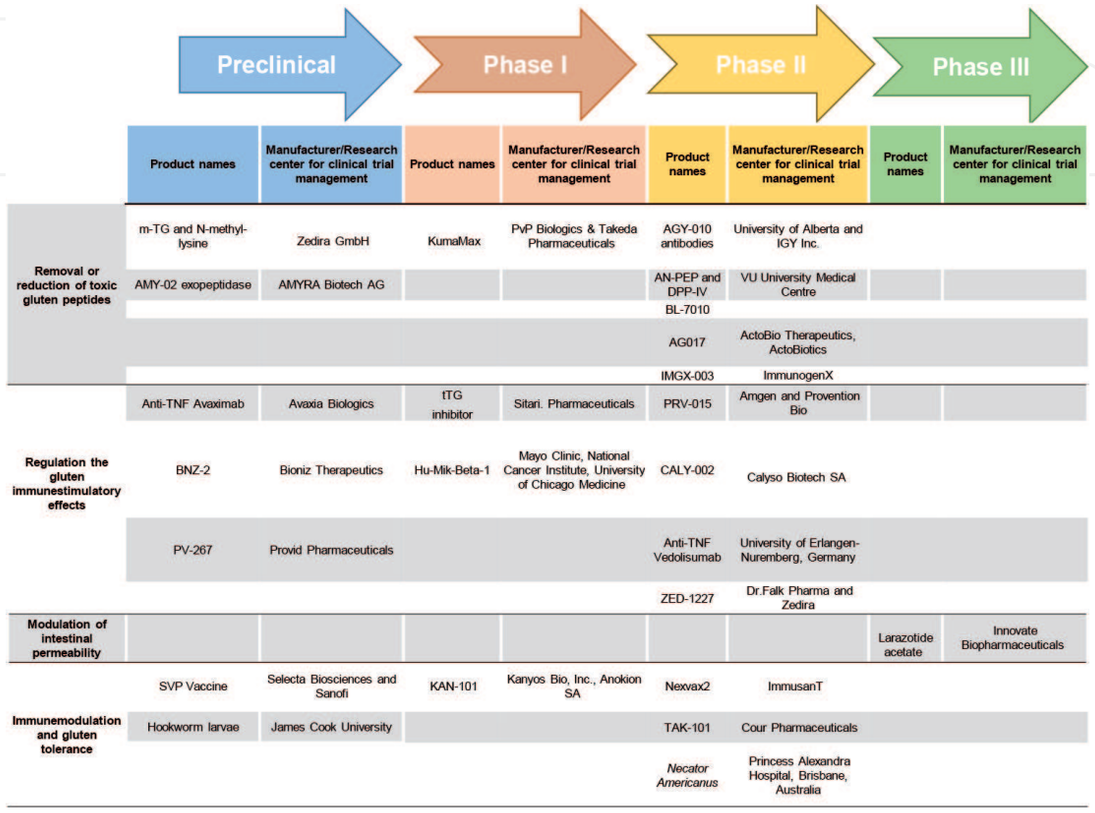
Table 2.
Studies based on GIP determination in stool and/or urine for monitoring of gluten-free diet. GIP, gluten immunogenic peptides.

concentration has established itself in recent years as a new useful marker of gastrointestinal pathologies. Several studies show that there is an association between calprotectin levels and the degree of inflammation, so it can be used to monitor response to treatment and predict the risk of recurrence. In addition, results obtained by Oribe et al. [116] have shown that patients with positive anti-tTG IgA antibodies, that is, those in contact with gluten, showed significantly higher values of fecal calprotectin than patients undergoing GFD and non-celiac patients. These methods, by demonstrating the presence of intestinal inflammatory processes, are generally not specific for CD and, therefore, if their values are modified, it could also be due to other causes such as infectious diseases, inflammatory bowel disease (IBD), or allergic processes.

5.2 Non-dietary therapies

Since strict follow-up of GFD presents many difficulties for patients with CD, additional treatments are needed for this disease. In recent years, CD research has focused on the search for non-dietary therapies to control GFD [17, 77]. Emerging

therapeutic options for CD can be broadly classified into one of the following strategies—(1) removal of toxic gluten peptides before reaching the intestinal tract, (2) regulation of the immunostimulatory effects of toxic gluten peptides, (3) modulation of intestinal permeability, (4) immune modulation and induction of gluten tolerance, and (5) restoration of imbalance in the intestinal microbiota (**Figure 1**).



	Preclinical		Phase I		Phase II		Phase III	
	Product names	Manufacturer/Research center for clinical trial management	Product names	Manufacturer/Research center for clinical trial management	Product names	Manufacturer/Research center for clinical trial management	Product names	Manufacturer/Research center for clinical trial management
Removal or reduction of toxic gluten peptides	m-TG and N-methyl-lysine	Zedira GmbH	KumaMax	PvP Biologics & Takeda Pharmaceuticals	AGY-010 antibodies	University of Alberta and IGY Inc.		
	AMY-02 exopeptidase	AMYRA Biotech AG			AN-PEP and DPP-IV	VU University Medical Centre		
					BL-7010			
					AG017	ActoBio Therapeutics, ActoBiotics		
					IMGX-003	ImmunogenX		
Regulation the gluten immunestimulatory effects	Anti-TNF Avaximab	Avaxia Biologics	tTG inhibitor	Sitari. Pharmaceuticals	PRV-015	Amgen and Provention Bio		
	BNZ-2	Bioniz Therapeutics	Hu-Mik-Beta-1	Mayo Clinic, National Cancer Institute, University of Chicago Medicine	CALY-002	Calyso Biotech SA		
	PV-267	Provid Pharmaceuticals			Anti-TNF Vedolisumab	University of Erlangen-Nuremberg, Germany		
					ZED-1227	Dr.Falk Pharma and Zedira		
Modulation of intestinal permeability							Larazotide acetate	Innovate Biopharmaceuticals
Immunemodulation and gluten tolerance	SVP Vaccine	Selecta Biosciences and Sanofi	KAN-101	Kanyos Bio, Inc., Anokion SA	Nexvax2	ImmusanT		
	Hookworm larvae	James Cook University			TAK-101	Cour Pharmaceuticals		
					Necator Americanus	Princess Alexandra Hospital, Brisbane, Australia		

Figure 1.
Clinical and preclinical trials in the development of new non-dietary therapies in CD. CD: celiac disease; PEP: prolyl endopeptidases; TNF: tumor necrosis factor; and tTG: tissue transglutaminase [128].

To date, only larazotide acetate is in phase III studies. Larazotide is an oral peptide that modulates tight junctions and prevents the passage of gluten peptides to the lamina propria by closing the intercellular junctions of enterocytes. Therefore, it could help prevent the development of the immune cascade in patients with CD, showing a reduction in symptoms as well as a reduction in anti-tTG antibody levels. In addition, some very promising therapies are PRV-015 immunotherapy, the use of oral glutenases, as well as vaccine therapies (phase II). There are many other exciting drugs that are in the early stages of research, such as tTG inhibitors, HLA blockers, and probiotics [20, 117–128]. Similarly, some therapies are being evaluated in preclinical trials and are postulated as promising treatments for the pathogenesis of CD (**Figure 1**). Thus, we are faced with many promising and emerging options for the treatment of CD.

6. Conclusions

Research on CD is changing rapidly due to a steady increase in knowledge that addresses its pathophysiology, diagnosis, follow-up, and therapeutic options.

Diagnosis of CD is based on several criteria, including positive serology, a spectrum of duodenal damage, clinical symptoms and/or risk conditions, and response to a GFD in susceptible individuals. In the absence of some of these criteria, the diagnosis of CD becomes challenging. In this regard, studies based on gluten reintroduction combined with IL-2 measurements could provide a new clinical alternative to diagnose and monitor patients who already have a GFD.

Several patients have difficulty controlling their diet they regularly consume sufficient gluten to trigger symptoms. Despite the availability of diverse traditional GFD adherence markers, such as diet tests or serology, none of them is an accurate diet evaluation method. Thus, use of GIP detection in stool and/or urine has been developed as a direct and specific test for GFD monitoring. Furthermore, non-dietary therapies have shown encouraging preliminary results in phase II and III clinical trials, such as larazotide acetate, PRV-015, IMGX-003, vaccine, and drug therapy. However, a GFD is the mainstay of CD therapy for the immediate future. For all these reasons, a health-oriented lifestyle should be promoted for better management and control of CD, responding to the growing demand of society and the empowerment of patients with CD.

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Conflict of interest

The authors declare no conflict of interest.

Appendices and Nomenclature

Anti-AGA	antigliadin antibodies
Anti-DGP	antibodies deaminated gliadin peptides
Anti-EMA	anti-endomysia antibodies
Anti-tTG	anti-transglutaminase antibodies
CD	celiac disease
CDAT	celiac dietary adherence test
ELISA	enzyme-linked immunosorbent assays
GFD	gluten-free diet
GIP	gluten immunogenic peptides
IBD	inflammatory bowel disease
IELs	intraepithelial lymphocytes
IL-2	interleukin-2
NPV	negative predictive value
PPV	positive predictive value
PCR	polymerase chain reaction
RCD	refractory celiac disease
tTG	tissue transglutaminase

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