Chapter 12

Celiac Disease in Adults

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Abstract

Celiac disease (CD) is a common condition affecting up to 1% of the adult population of Caucasoid origin. It arises from an inflammatory response to dietary gluten in the small intestine in genetically predisposed individuals.

Its clinical presentations are grouped into four categories: 1) Classic celiac disease, defined on the basis of diarrhea with failure to thrive or weight loss (a rare occurrence in contemporary adult presentation in); 2) “Atypical” gastrointestinal presentation, defined on the basis of a set of nonspecific and persistent gastrointestinal symptoms, often misdiagnosed as a digestive functional disorder; 3) Extraintestinal presentation, defined on the basis of signs or symptoms outside the gastrointestinal tract, such as iron deficiency anemia or short stature and 4) Silent presentation. The latter is identified through testing due to a family history of CD or a celiac disease-associated condition (i.e. type 1 diabetes mellitus).

The CD diagnosis is confirmed if at least 4 of the following 5 criteria are satisfied: typical CD symptoms, serum-positive celiac disease class-A immunoglobulin autoantibodies at high titers, presence of HLA-DQ2 and/or-DQ8, celiac enteropathy in small bowel biopsy and response to the gluten-free diet. Seronegative CD is likely to be underestimated due to the tendency to perform small intestinal biopsies only in patients with positive celiac disease serum markers. Whilst the majority of patients will respond to a gluten-free diet, a significant minority will continue to be symptomatic. In such cases, it is essential that a systematic follow-up approach be adopted.

"If the stomach be irretentive of the food and if it pass through undigested and crude and nothing ascends into the body, we call such persons coeliacs…"

Adams F. (trans.), *The Extant Works of Aretaeus the Capadocian*
London, London Sydenham Society, 1856:350

1. Introduction

The introduction of gluten-bearing cereals with the advent of agriculture, about 10,000 years ago, generated the necessary conditions for the development of a set of immune disorders due to gluten exposure, among which basically are wheat allergy and celiac disease (CD).[1] Although the first descriptions of this condition date back to the time of Aretaeus of Cappadocia, in ancient Ionian Greece (today's Turkey), it was not until the 1940-1950 decade when Dicke, a Dutch pediatrician, established a relationship between the gluten content in wheat and the symptoms of this disease.[2] Since the first consensus definitions were established in 1970[3], in which the diagnosis of the disease required the demonstration of severe villous atrophy, which retreats following the removal of gluten from the diet and reappears after allowing again the ingestion of these cereals, more than 40 years have elapsed. During the last decade, further evidence has accumulated to suggest that dietary gluten intake can cause a wide spectrum of symptoms, in some cases with no evidence of duodenal histological lesion (DHL). All this has stirred great controversy in the scientific community regarding the nomenclature to be used in each situation.[4] Three consensus conferences have been published recently, whose reading is highly recommended in order to understand the true dimensions of this problem.[1-5,6] In recent years, consumption of gluten-free foods has increased exponentially, not only among celiac patients, but in many other patients previously diagnosed with a functional gastrointestinal disorder (FGD) who finally found relief when gluten was permanently removed from their diet, either because they actually suffered from a hitherto unsuspected CD[7] or else because they suffered from non-celiac gluten sensitivity (NCGS)[8] or even due to the placebo effect involved in any diet. This chapter is primarily restricted to CD and, to that end, it will use the concepts defined by the recent guidelines established by ESPGHAN[5], as well as those established by the Oslo[6] and London[1] consensus meetings, all of them published in 2012.

2. Definitions and Nomenclature

CD forms part of a gluten-related disorder spectrum including those of a clearly immune etiology (CD, dermatitis herpetiformis and gluten-related ataxia), others of an IgE-mediated allergic etiology (wheat allergy) and others which do not depend on allergy or acquired immunity, such as NCGS (Figure 1).[1] The definitions of the different gluten-related clinical conditions[1,4,5,6] are described below.

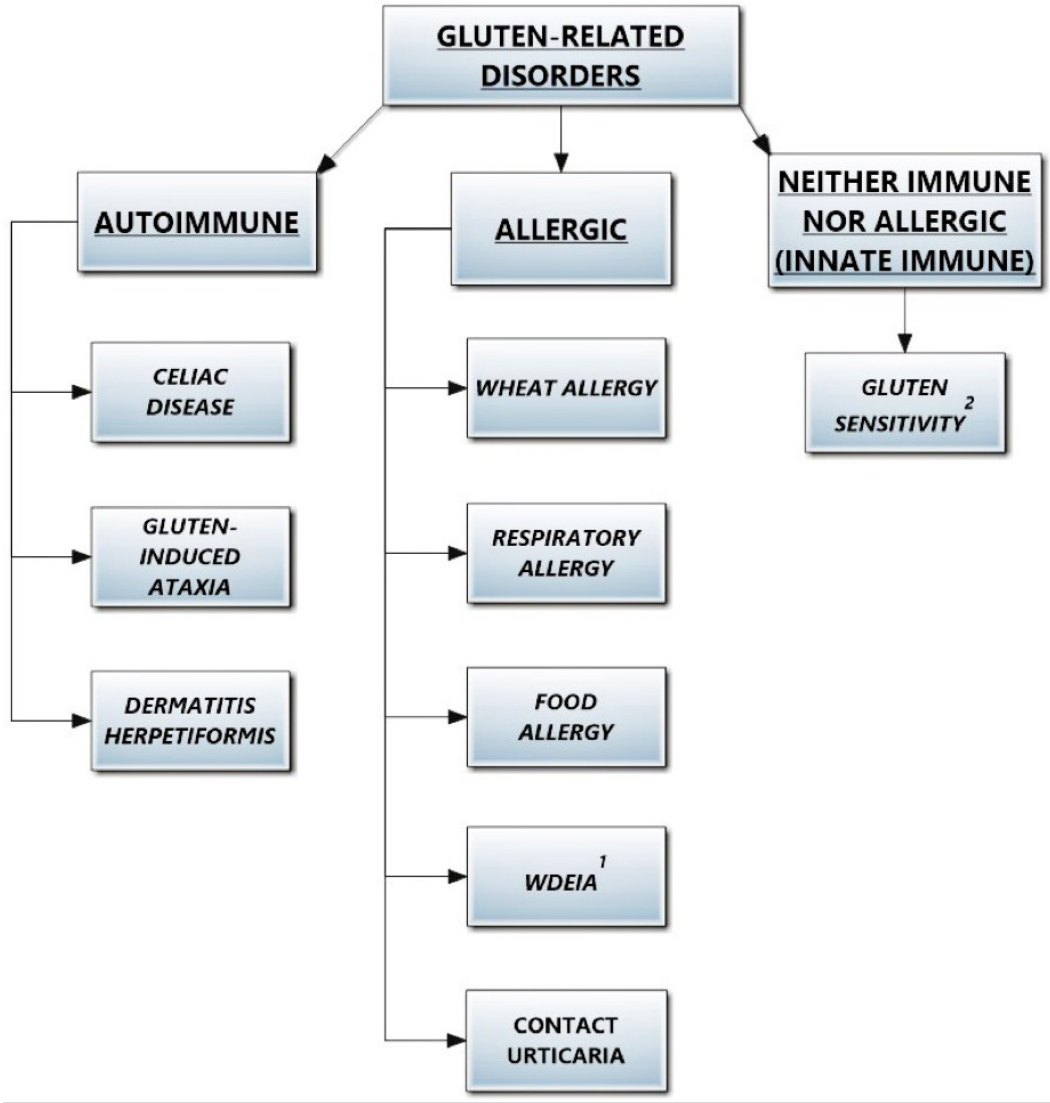

Figure 1. Classification of gluten-related disorders.

1) WDEIA: wheat-dependent exercise-induced anaphylaxis.

2) Term admitted by the London Consensus, but not by the Oslo Consensus, the latter encourages the use of the term "non-celiac gluten sensitivity".

Celiac disease. According to the ESPGHAN guide published in 2012[5], CD is defined as a systemic disease mediated by the immune system and precipitated by contact between the intestinal mucosa and gluten and other related prolamins in genetically susceptible individuals. The disorder is characterized by a variable combination of symptoms and signs depending on gluten intake, CD-specific antibodies (anti-transglutaminase-2, antiendomysial and deamidated gliadin anti-peptides), the presence of HLA DQ2 or DQ8 haplotypes and varying degrees of enteropathy.

Formerly, other equivalent terms have been used to refer to the same disease, including terms such as *sprue, celiac sprue, gluten-sensitive enteropathy, gluten intolerance, nontropical sprue* and *idiopathic steatorrhea*. None of these terms is, at this time, universally accepted, so their use cannot be recommended.[6]

Classic celiac disease. This term refers to those patients whose disease presents a clear-cut pattern of malabsorption with chronic diarrhea, steatorrhea, weight loss or delayed growth.[9] This pattern is often seen in children, in whom loss of muscular mass, loss of appetite, anemia, abdominal bloating and irritability are frequently observed; these symptoms, however, are exceptional in adults, hence the term "typical" celiac disease is not recommended at present, since both conditions (classical and typical) are not coincident. The common (typical) presentation of the disease in adults is the manifestation of nonspecific symptoms and signs that do not resemble those of a state of malabsorption with emaciation.[10,11]

Non-classic celiac disease. This definition applies to those who have symptoms and signs not associated with a state of florid malabsorption. This includes cases of patients with symptoms that mimic those of "functional" dyspepsia[8], irritable bowel syndrome (IBS) or chronic constipation and those with extraintestinal manifestations, whose presentation under monosymptomatic forms is not uncommon. This section will, therefore, include cases of thyroid dysfunction (hyper or hypo)[12], neurological symptoms[13], depression[14], fertility disorders[15,16], aphthous stomatitis[17-20], skeletal[21] or dermal[22] alterations or transaminitis.[23] Again, the term "atypical" celiac disease should be discouraged, because, at the present time, these symptoms and signs appear to be most common presentation.[6]

Asymptomatic celiac disease. This patient subgroup does not have symptoms that may suggest a diagnosis, even after being interviewed using structured questionnaire. These are often patients in whom the diagnosis has been established while conducting a screening population study or while studying bearers of comorbidities associated with a high risk of CD. It is not uncommon that, after removing gluten, the patient reveals a clear improvement of a hitherto unrecognized asthenia case. According to the Oslo Consensus, the term "silent celiac" is consistent with and equivalent to "asymptomatic" and should be abandoned.

Subclinical celiac disease. Today, this term is reserved for those patients with a set of symptoms or signs that are not considered sufficient to lead to clinical suspicion and which are below the threshold required to encourage clinical research to confirm or rule out the disease.[6,24]

Symptomatic celiac disease. This term refers to a CD patient who has any of the symptoms included in the wide manifestation spectrum attributable to the disease, whether it means gastrointestinal symptoms (dyspepsia, diarrhea, bloating) as well as extraintestinal symptoms (fatigue, depression or canker sores).

Latent celiac disease and potential celiac disease. At least 5 different senses or meanings have been in the literature for the term "latent"[6], the most accepted being probably that of a patient who consumes gluten, has "normal" intestinal mucosa at the time of its evaluation, but who, in an earlier or later time suffered (or will develop) a typical intestinal lesion. Regarding the term "potential", the Oslo group's recommendation is that it should be used referring to a patient with "normal" intestinal mucosa and an increased risk of developing CD after detecting positive CD serology, especially if the patient has the HLA DQ2 or DQ8 haplotypes.[25,26]

Refractory celiac disease. This term applies to those patients diagnosed with CD who maintain persistent malabsorption symptoms or signs (i.e., diarrhea with involuntary weight loss, low hemoglobin levels or hypoalbuminemia), with persistent villous atrophy despite a strict diet without gluten (GFD) for more than 12 months, after excluding other causes of villous atrophy or the presence of malignancy. This category includes those patients with severe and persistent symptoms, regardless of the GFD duration. It is obvious that not all patients who do not respond to the GFD can be labeled as refractory, since in many cases the persistence of symptoms can be explained by an unorthodox compliance of the diet or by the presence of conditions associated with CD that explain the persistence of symptoms (lactose or fructose intolerance, intestinal bacterial overgrowth, exocrine pancreatic insufficiency or microscopic colitis).

Genetic risk for celiac disease. The concept of "individual with genetic risk of CD" should be limited to relatives of CD patients who share the DQ2 and/or DQ8 HLA haplotypes, elevating the risk to 20-25% when it comes to first-degree relatives.

Dermatitis herpetiformis (DH). DH is a cutaneous expression of the enteropathy precipitated by dietary gluten (CD). It appears in 1 out of 10,000 people of Caucasoid and European descent and its incidence is of 0.98 cases per 100,000 inhabitants per year.[6,32,33] DH is rare in other continents such as Africa and Asia. The disease shares the same HLA haplotypes DQ2 (90%) and DQ8 (5%)[34] and it predominates in males (1.5 to 1.9:1). There is a clear family aggregability and the average age of onset is of about 40 years.[1] It manifests typically by the appearance of small erythematous macules which soon become intensely pruritic papules, finally bursting to form scabs. The distribution of lesions is symmetrical, affecting the elbows in 90% of cases. Other affected areas include the face, scalp, neck, shoulders, trunk, sacral region, buttocks and knees.[1] Its progression is chronic and recurrent. Although only 10% of its patients report gastrointestinal symptoms, nearly two thirds have some degree of villous atrophy in the intestinal mucosa.[6,20] The remaining cases may have normal mucosa or increased type γ/δ intraepithelial lymphocytes as an unequivocal expression of gluten sensitization. In these patients' serum the same CD autoimmunity biomarkers (anti-TG, anti-endomysium and PGD) can be identified and, in fact, they are not infrequently associated with other autoimmune diseases. Its diagnosis is based on serological evidence of these markers by immunofluorescent demonstration of granular IgA deposits in the dermal papillae. Since DH is the equivalent of CD in the skin, intestinal biopsy is not an obligatory requirement. Once diagnosed, it is essential to start a GFD; some patients require treatment with *dapsone*. In the long term, almost half of the patients who adhere well to the diet may interrupt the treatment with this neutrophil inhibitor.[35-38]

Gluten-related ataxia (GA). GA is defined as an autoimmune disease associated with the presence of antigliadin antibodies (AGA) in the serum, which can cause damage to the cerebellum resulting in a case of ataxia, all this regardless of the presence or absence of enteropathy.[1,39-43] Clinically, it is expressed as a case of pure cerebellar ataxia, or more rarely in combination with myoclonus and palatal tremor. Its onset is insidious, with a mean onset age of 53 years.[44,45] As is the case with DH, less than 10% of patients report gastrointestinal symptoms, but up to 1/3 show different degrees of enteropathy with IgA deposits in the duodenal mucosa.[45] The pathogenesis of this disorder is not clear, but in these patients anti-TG deposits have been identified around the brain vessels, these being more pronounced in the cerebellum and the spinal cord. Also, antibodies against transglutaminase-6, a transglutaminase which is mainly expressed in the brain, have been detected.[46] The current recommendation is that patients presenting progressive cerebellar ataxia should be tested for AGA, for IgG and IgA-type antibodies, anti-TG2 and anti-TG 6 (IgG and IgA) antibodies. If any of these serological tests is positive, a duodenal biopsy is recommended. If the diagnosis is made late, when there has already been a marked loss of Purkinje cells, the response to gluten withdrawal may be poor.[1]

Wheat allergy. Wheat allergy (WA) is an adverse immune reaction to wheat proteins and includes classic food allergy, the origin of gastrointestinal, skin and respiratory symptoms; it also includes wheat-dependent exercise-induced anaphylaxis (WDEIA), occupational asthma (baker's asthma) and contact urticaria (Figure 1). The pathogenesis of these disorders is mediated by IgE antibodies against various protein components from wheat grains (α-gliadin, β-gliadin, γ-gliadin, ϖ-gliadin and other high-molecular weight subunits) and its overall prevalence ranges between 1-3%.[47] Its diagnosis is based on skin prick tests and on *in vitro* IgE determination for various allergens. Often, challenge tests become necessary.[1]

Non-celiac gluten sensitivity (NCGS). A growing proportion of people have a set of gastrointestinal symptoms (some attributed to an IBS)[7] which improve or disappear entirely after removing gluten from the diet, reappearing upon ingesting again cereals that contain this ingredient. When these patients are investigated, they do not have specific antibodies to gluten and no histological lesions in the duodenal mucosa, which is why they cannot be classified as celiac patients.[5] This clinical condition was first recognized more than 30 years ago[27] and it is named by some as “gluten sensitivity”[1] or, even better, as non-celiac gluten sensitivity (NCGS)[4], a term accepted by most authorities on this subject.[7,27,28] Both diseases (CD and NCGS) share the presence of nonspecific symptoms that improve after establishing a GFD, but differ by the fact that in the latter (NCGS) no allergic or autoimmune mechanisms, alterations in intestinal permeability or morphological changes in the duodenal mucosa can be identified.[29,30] There is some evidence that this disorder may affect up to 6% of the population, being commonly associated with abdominal pain (68%), skin symptoms like rush and/or eczema (40%), headache (35%), confusion (34%), fatigue (33%), diarrhea (33%), depression (22%), anemia (20%), numb legs, hands and fingers (20%) and joint pain (11%).[1] DQ2 gene prevalence (50%) is lower than that observed in CD patients and somewhat higher than that observed in the general population.[31] It is an exclusion diagnosis, in which one of the criteria (symptomatic improvement after introducing the GFD) should be validated in a blinded fashion to avoid the placebo effect inherent to any diet.

Gluten intolerance. This term lacks specificity, which can lead to confusion and contradictions. In the light of current knowledge it may not be synonymous with CD and moreover, the symptoms often attributed to gluten may be a consequence of other components of the grain, so today this expression is inappropriate and is not subject to consensus.

Having clarified these terms (Figure 1), essential to avoid labeling a patient as CD patient when he or she may have another disorder, hereinafter we will exclusively discuss issues related to CD.

3. Epidemiology

The prevalence of CD depends on many factors including the historical moment in which studies have been conducted[48-52], the geographical area where they have been carried out[50-55], the procedures used for screening (serology, intestinal biopsy or both) and the type of population studied (asymptomatic persons, individuals with genetic risk or healthy volunteers).[48] Studies of population-based cohorts performed on healthy volunteers in the U.S., UK and other European countries allow a prevalence estimate of 0.5-1%, which leads to consider CD as the most frequent chronic intestinal disease.[51,53] When screening studies stratify different populations, CD prevalence is estimated at 1 in 22 in first-degree relatives, 1 in 56 in symptomatic patients and 1 out of every 133 people without high risk of developing the disease.[51] Despite these high prevalence rates, the identified cases are just the tip of an iceberg, beneath which is a large contingent of undiagnosed patients (>75%).[8,55,57] The prevalence of CD in the general population is increasing.[58-64] The reasons for this phenomenon cannot be attributed solely to improved screening methods and diagnosis but also to environmental and geographical factors. In Asian countries, for example, where the prevalence has traditionally been low, the number of new cases is increasing due to changes in eating patterns introduced in urban areas, where wheat flour, used in the preparation of fast food, has begun to replace other traditional cereals like rice.[1,60] In India, there is a region where a typical syndrome known as “summer diarrhea” coincides with the season where maize crops are temporarily replaced by wheat.[65] It must be borne in mind that, in most prevalence studies, the diagnosis has been carried out based on a positive result in the determination of specific antibodies. Serology, however, has low sensitivity in patients with mild histological lesions (slight enteropathy). Not indicating a duodenal biopsy in patients with nonspecific gastrointestinal symptoms and negative serology may lead to underestimate the true prevalence of CD, especially when these patients bear the HLA system DQ2 and DQ8 haplotypes.[8,66,67] Finally, 15% of new diagnoses of CD are made in people over 65 years, most of which suffer its symptoms for a period of 11±19 years.[68] A Finnish study demonstrated a prevalence of biopsy-proven CD in 2% of the population between 52 and 74 years.[69] The pattern of presentation has also changed over time, so that in adults, a debut with severe diarrhea and malabsorption today is unusual.[64,67-71]

4. Pathogeny

CD responds to a multifactorial model of interaction between genetic and environmental factors[72,73] involving adaptive (acquired) and innate immunity.[74-81]

- **Adaptive Immunity:** Gluten contains immunogenic peptides which, after crossing the epithelium and undergoing transglutaminase-2 deamidation, are presented by dendritic cells to CD4 lymphocytes in the lamina propria, in the presence of HLA DQ2-DQ8 molecules. Activation of these lymphocytes promotes the release of proinflammatory cytokines that lead to tissue damage, which provide, as well, a signal to the TG2-specific B cells for the synthesis of anti-transglutaminase-2 antibodies.[74]
- **Innate immunity:** The innate immunity mechanisms that lead to the activation of intraepithelial lymphocytes (LIEs) are less well understood. In short, certain gluten peptides such as p31-43/49 (α-gliadin) can directly damage the epithelium by activating innate immunity-dependent mechanisms and the production of (IL)-15 interleukin, responsible, ultimately, for alterations in the permeability of intercellular junctions (intestinal barrier) and of enterocyte apoptosis. IL-15 induces proliferation and activation of CD8+ IELs, while promoting the production of interferon (IFN-γ) by IELs and cytolytic-protein-dependent epithelial cytotoxicity.[74]

Summing up: the tissular damage that occurs in the intestinal mucosa of CD patients is the sum of the activation mechanisms of the lamina propria T CD4+ lymphocytes (adaptive immunity-dependent) and intraepithelial CD8+ lymphocytes (innate immunity-dependent). Both mechanisms are necessary and contribute to trigger a response dominated by Th1 IFN-γ, the T bet transcription factor and other pro-inflammatory cytokines (tumor necrosis factor [TNF]-α, IL-18, IL-21), accompanied by a decrease of immunosuppressive cytokines (IL-10 and TGF-β35-37), which normally help to maintain tolerance to dietary antigens and the production of IL-15 by enterocytes. This pro-inflammatory profile eventually activates the effector mechanisms of tissue damage, such as keratinocyte growth factor (KGF) and matrix metalloproteinases (MMPs) involved in the extracellular matrix degradation and the mucosal transformation.[74-76] All these mechanisms are disabled when the patient is in remission. Note that, although the presence of DQ2 or DQ8 haplotypes is necessary for the development of the disease, there are other multiple genes involved, without which the disease may not appear in an individual.[77-87] A good proof of this is that genes linked to the HLA are present in 25-35% of the general population, while CD appears only 1% (Figure 2).

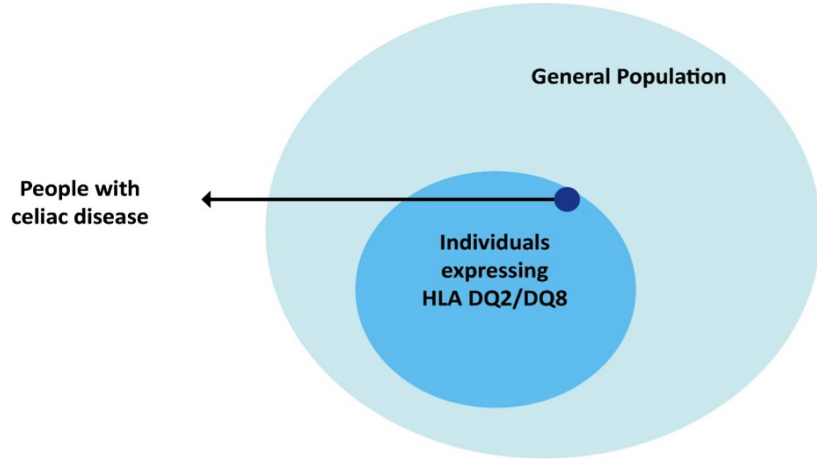

Figure 2. Prevalence of celiac disease and its relationship to the HLA DQ2 heterodimers. Celiac disease affects approximately 0.5-1% of the general population. Except in special cases, it mostly affects patients expressing the HLA DQ2 (95%) or DQ8 (5%) heterodimers. However, not all HLA DQ2/DQ8 people develop the disease. Therefore, this seems a necessary, but not sufficient, condition. The involvement of other genes is required.

5. Pathology

The changes in the small intestine of CD patients are usually confined to the mucosa while the submucosa, muscularis and serosa are preserved.[88,89] In a healthy intestine, villi constitute 65-80% of the total thickness of the mucosa, while crypts occupy the rest. The epithelium is composed of tall columnar cells with a crisp edge "brush" and a basal core. The crypts are lined by undifferentiated cells which, through a process of division, migration and maturation, replace the mature absorptive cells which are continually lost at the tips of the villi.[88] In CD, the toxic effect of gliadin peptides on enterocyte maturation results in premature loss of the same in the intestinal lumen, leading to a compensating increase of their replication in the crypts ("enteropoiesis").[90,91] This central mechanism explains most morphological changes observed in CD.

- **Changes in mucosal architecture:** In CD, there is a shortening of the villi, which seem to be wider; at the same time, there is an elongation of and hyperplasia of the crypts, which seem to be branched, with increased mitosis. In most cases, mucosal thickness is normal or only discretely reduced, because the shortening of the villi is compensated by crypt hyperplasia.[88,92] These architectural changes lead to a reduction in the anatomical absorption surface.
- **Changes in the epithelium lining:** the remaining absorptive cells lose their columnar arrangement and appear cuboidal or scaly, while the nuclei lose their basal polarity. The cytoplasm becomes more basophilic and the brush border appears markedly attenuated. Changes observable by electron microscopy include increased ribosomes and degenerative changes including cytoplasmic and mitochondrial vacuolization, plus

an increase in the number and size of lysosomes. The increase in intercellular junctions explains the increased permeability of the intestinal mucosa and the barrier's impaired function.[91] The minor activity in the endoplasmic reticulum reflects the low level of digestive enzyme synthesis (discaridases and peptidases), which supports the idea that there is not only a decrease in the number of absorptive cells, but also in their function.[88,90] An increase in the number of cells containing secretin and CCK has also been observed, which is due to an abnormality in these hormones' release mechanisms, which favors the appearance of pancreatic exocrine insufficiency. In contrast to absorptive epithelial cells, the cytological and immunohistochemical characteristics of crypt cells do not differ from their normal status. In fact, some studies suggest that, in patients with untreated CD, crypt-dependent enteropoiesis is 6 times higher than that observed in normal conditions.[91]

- **Cellularity changes:** The lamina propria cellularity is significantly increased in CD, mainly at the expense of the plasma cells that produce IgA, IgG and IgM (particularly IgA) and activated CD4 (helper/inducer) lymphocytes.[92] Other cellular components that contribute to the dense lamina propria infiltration are polymorphonuclear leukocytes (PMN), eosinophils and mastocytes.[89] Meanwhile, in the epithelium, an increased number of intraepithelial lymphocytes (IELs), which besides being real, is also the result of the proportional reduction in the anatomical absorption surface. Therefore it is fitting to express this phenomenon as a numeric value based on an absorptive area unit (100 epithelial cells).[93] In this case, these are CD8+ cells (cytotoxic/suppressors). Marsh hypothesized that morphological changes appeared described in a sequential and progressive manner.[94] Thus, starting from a normal mucosa (preinfiltrative, stage 0), the first observable morphological change would be LIE increase, followed by a lymphocytic infiltration of the lamina propria (stage I). Crypt hyperplasia (stage II) precedes villous atrophy (stage 3), a phenomenon that is observed only in the presence of a marked lymphocytosis in the lamina propria, thereby suggesting that IELs are not sufficient to induce the architectural changes described in CD. Oberhüber amended this classification by stratifying different degrees of atrophy (mild, moderate and severe). Some drawbacks of these classifications, derived from a bias introduced by interobserver variations, have been avoided largely with Corazza's simplified version (Table 1).[93]

Marsh	**Morphology**		**IELs%**
Type 0	No change in inflammatory cells or in the crypt/villi relation (preinfiltrative).		< 40
Type 1	Increase in the number of intraepithelial lymphocytes.		> 40
Type 2	Intraepitelial lymphocytosis, increase of crypt/villi relation (hyperplastic).		> 40
Type 3	Intense inflammation, villous atrophy, crypt hyperplasia (destructive).		> 40
Oberhuber			
Type 0	Normal mucosa.		< 40
Type 1	IEL increase, normal villous architecture, normal crypt height.		> 40
Type 2	Normal villous architecture, IEL increase, crypt hyperplasia.		> 40
Type 3	Destructive, with variable atrophy degrees, elongated crypts and inflammatory cells.		> 40
3a	Mild partial atrophy; widened and shortened villi with a V/C: 1.1 relation.		> 40
3b	Subtotal atrophy, atrophic villi, but separated and still recognizable.		> 40
3c	Total atrophy; rudimentary or absent villi; mucosa similar to that of the colon.		> 40
Type 4	Atrophic hypoplastic lesion, flat mucosa with normal crypt height. Barely perceptible inflammatory cellularity. Normal IEL count.		< 40
Corazza	**Morphology**	**Marsh-Oberhuber equivalence**	
Grade A	Normal architecture without atrophy.	Type 1 and type 2; type 0 discarded.	> 25
Grade B1	Atrophic with villus/crypt relation of <3:1.	Type 3a and type 3b.	> 25
Grade B2	Atrophic with no detectable villi.	Type 3c; Type 4 is not included.	> 25

IELs: Intraepithelial Lymphocytes

Table 1. Comparison between Marsh-Oberhuber/Corazza classifications.[93]

None of the described alterations is pathognomonic for CD, hence the different findings described need necessarily be harmonized by an expert clinician able to make a correct differential diagnosis. This is particularly important when the histological lesions are circumscribed to Marsh-Oberhuber types 1 and 2 (Corazza grade A) and Marsh-Oberhuber types 3a and 3b (Corazza grade B), lesions that can be shared by entities other than CD (Table 2). The distribution of lesions typical of CD has some relation to the severity of symptoms. In fact, a global intestinal alteration, from the proximal duodenum to the terminal ileum can only be seen in clinically severe forms of the disease. In the remaining cases, there is usually a lesion severity gradient; the more intense lesions are generally observed in the proximal duodenum.[88,89] The ileum and, in some cases, the jejunum, may be lesion-free, these being confined to the duodenum. In some cases, villous atrophy can only be seen in the duodenal bulb.[96]

<table>
<tr><th>Primary</th><th colspan="2">Secondary</th></tr>
<tr><td rowspan="8">• Gluten-induced enteropathy
• Hypersensitivity to proteins unrelated to gluten:
- Cow milk
- Cereals
- Eggs
- Peanuts
- Soy
• Others:
- Acute gastroenteritis
- Autolimited enteritis
- Collagenous duodenitis
- Tropical sprue
- Autoimmune enteropathy
- Graft vs host disease</td><td>Autoimmune diseases</td><td>Other immune disorders</td></tr>
<tr><td>• Autoimmune thyroiditis
• Hashimoto’s thyroiditis
• Type 1 diabetes
• Graves’ disease
• Rheumatoid Arthritis
• Psoriasis
• Multiple sclerosis
• Systemic lupus erythematous
• Hemolytic anemia</td><td>• Glomerulonefritis
• IgA hypogammaglobulinemia or variable common immunodeficiency (they may coexist with celiac disease).</td></tr>
<tr><td>Chronic inflammatory disorders</td><td>Neoplastic diseases</td></tr>
<tr><td>• Inflammatory bowel disease
• Ulcerative colitis
• Crohn’s disease
• Microscopic colitis
• Collagenous colitis
• Glycogenic deposit disease</td><td>• T Cell lymphoma associated enteropathy
• CD4+ lymphoproliferative disease
• Immunoproliferative small intestinal disease (IPSID)
• Thymoma
• Refractory sprue</td></tr>
<tr><td>Drugs</td><td>Infections</td></tr>
<tr><td>• Non-steroidal anti-inflammatory drugs (NSAIDs)
• Proton pump inhibitors
• Chemotherapy
• Idiosyncrasy due to other drugs</td><td>• Giardia Lamblia
• Criptosporidium
• Viral
• Tropical sprue
• Helicobacter Pylori
• Bacterial overgrowth</td></tr>
</table>

Table 2. Lymphocytic enteropathy causes.

The introduction of a gluten-free diet (GFD) leads to a marked and significant improvement of CD lesions (Figure 3). Absorptive epithelial cells regain their columnar morphology and the polarity of their nuclei basal and their characteristic brush border. The intraepithelial lymphocyte density tends to decrease and recover villous architecture tends to recover, as does the lymphoplasmacytic infiltrate density in the lamina propria. Usually, the mucosa of the distal small intestine recovers before the more proximal segments, which are more severely affected. In some patients it can take years to observe a complete or nearly complete histologic recovery. Not infrequently, some degree of intraepithelial lymphocytosis may persist, especially when the patient is committing voluntary or unintentional transgressions.[95,97-100]

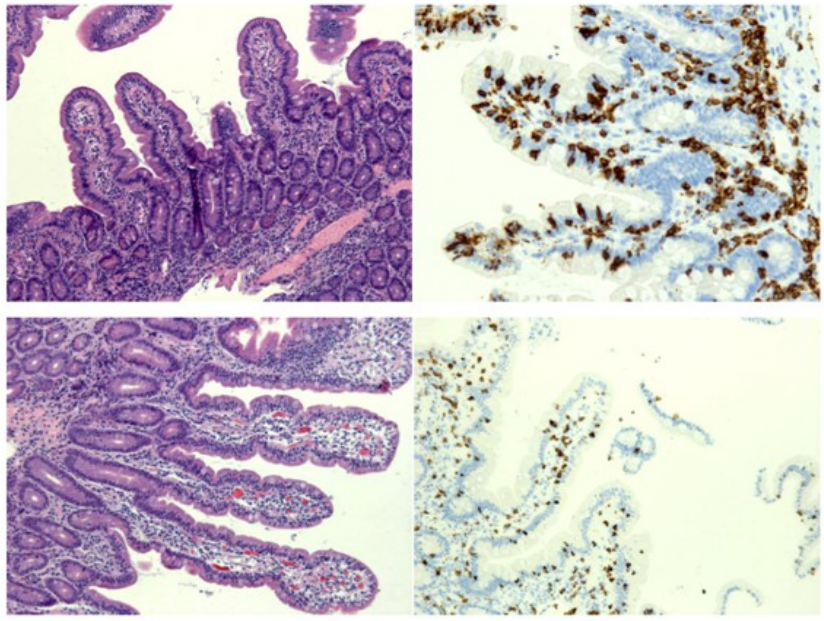

*Figure 3. Histological images of a biopsy from the duodenal 2nd portion of a 21-year-old male with symptoms of postprandial distress syndrome dyspepsia (postprandial fullness and bloating) long-term, no response to empiric treatment with prokinetics and antisecretories (PPI). Anti-TG: 2.1 U/mL/[positive DQA1*05, DQB1*02 positive].*

In the upper image (left) mild focal villous atrophy can be seen; to the right immunostaining for CD3 shows an IEL count of 31%, with a predominant localization at the tip of the villi (Marsh-Oberhuber 3a; Corazza B1). At the bottom of the images obtained 18 months later, after a GFD. To the left, the villi have recovered their height with an adequate villus/crypt relation. The right image shows immunohistochemical results, with normal IEL count (8%) (Marsh-Oberhuber 0). Courtesy of Dr. Vera, Pathological Anatomy Service, San Jorge Hospital, Huesca.

6. Clinical Presentation

The mean age of CD presentation in adults is 42-45 years (range 18-74 years), with a clear female predominance (1:3).[89] In some cases, a history of growth retardation is discovered or else other symptoms suggestive of unrecognized childhood CD. Some patients regained their growth rhythm in adolescence until it equaled that of the general population. Other patients always had a normal stature, while others show a higher body-mass index, even obesity. Factors associated with the disease onset, after a long silent period, are surgery involving accelerated gastric

emptying (gastrectomy, pyloroplasty), the postpartum period, gastrointestinal infection or period of emotional stress. In the authors' unit, up to 56% of the patients diagnosed with CD as adults had been previously diagnosed with a FGD, including refractory pyrosis, “functional” dyspepsia, irritable bowel or chronic constipation. Approximately 15-25% of the cases are diagnosed at an age equal to or greater than 65 years.

6.1. Gastrointestinal Symptoms

In adults, the classic florid presentation of the disease with malabsorption, diarrhea, steatorrhea, weight loss and flatulence is rare (<25%); “atypical” unspecific gastrointestinal symptoms are more common.[56,101-103] This is particularly applicable to patients in whom intestinal involvement is limited to the proximal small intestine.[89] Table 3 shows the set of pathophysiological changes which explain these patients’ diarrhea and their multifactorial origin. Although these are generally diurnal stools (often postprandial), it is also not uncommon for them to wake the patient at night. The stool volume may be increased due to loss of nutrients (fats, carbohydrates, proteins and electrolytes) or else rather watery stools and mixed with abundant gas, the result of bacterial fermentation of unabsorbed sugars. This fact is compounded because 2/3 of CD patients have intestinal bacterial overgrowth (SIBO) and/or lactose intolerance, which contribute to H_2, CO_2 and CH_4 production. Some patients have bouts of diarrhea alternating with periods of normalcy, or else constipation, simulating the typical IBS behavior.[101] A history of inveterate chronic constipation does not, in any way, exclude the disease. The presence of refractory pyrosis to antisecretory drugs should encourage considering CD in the differential diagnosis. A subset of these patients suffer from gaseous reflux and PPI administration may contribute to increased intra-abdominal pressure by favoring SIBO and gas production. In this context, it is not unusual for the “refractory” pyrosis in these patients to disappear completely after removing gluten from the diet. The authors have seen some cases with this peculiarity. Some patients with dyspepsia and apparent functionality criteria (absence of alarming symptoms and negative endoscopy) have, in fact, CD or NCGS, erroneously labeled as “functional” dyspepsia, as some recent studies have shown.[8,103-110] The same applies to a subset of patients with symptoms of “functional” chronic diarrhea, or IBS-D subtype.[111-116] Some of these patients cannot be categorized as celiac and correspond more closely to NCGS criteria.[1,6,115] A not uncommon clinical profile is that of patients, usually female, who complain of repeated episodes of severe epigastric pain which can simulate a “biliary colic”, without any organicity being evident in additional tests. Some experience a significant improvement in the frequency and intensity of seizures after starting a GFD. No link has been established, beyond any doubt, about the possible relationship between CD and the absence of relaxation in the sphincter of Oddi, although there is a documented relationship between idiopathic acute pancreatitis and CD.[117] Gliadinic shock prevalence, a condition characterized by uncontrollable vomiting, abdominal pain and peripheral collapse signs, 2-4 hours after gluten ingestion, is exceptional in adults.[88]

Osmotic mechanism
• Lactose malabsorption due to secondary disacaridase deficit.
Secretory mechanism
• Protein, fat and carbohydrate absorption inhibition (steatorrhea, creatorrhea). • Water and electrolyte secretion stimulus. • Exocrine pancreatic insufficiency due to duodenal mucosa secretion of secretin and CCK.[1] • Cathartic effect of unabsorbed fatty acids hydroxilated by bacteria. • Cathartic effect of bile salts hydroxilated by bacteria (only in cases with ileal involvement).
Motility alterations
• Failure in the clearing up of bacteria which leads to intestinal bacterial overgrowth.[2]
Inflammatory mechanism
• The probability of inflammatory bowel disease is 10 times higher among CD patients. • In refractory CD cases complicated with ulcerative jejunoileitis there is an exudation of blood, mucus and proteins. • Some CD patients have microscopic colitis (lymphocytic or collagenous).

[1] May even appear in cases without villous atrophy.[252,261-263]

[2] May explain persistent diarrhea and flatulence in CD patients who adhere to the GFD.

Table 3. Factors which contribute to diarrhea in CD.

6.2. Extraintestinal symptoms

The prevalence of extraintestinal manifestations in CD is very high among adult patients, especially if a specific search is performed.[13-22] In the authors' experience, more than 90% of the patients have systemic signs or symptoms, the most frequent being fatigue and lassitude, iron deficiency anemia, canker sores, dysthymia, osteoporosis and skin lesions. Not infrequently, this is one of the reasons for initial consultation, as some minor digestive symptoms may have gone unnoticed and were never serious enough to consult a physician. Sometimes, these symptoms and signs are conditioned by nutrient malabsorption and in others, the relationship with malabsorption may not be as clear (Table 4).

Implicated organ or system	Mechanism
Hematological	
Anemia	Iron, Folate or Vitamin B12 malabsorption or pyridoxine deficiency.
Hemorrhagic diathesis	Vitamin K deficit. Thrombocytopenia due to folate deficit. There is an epidemiological association between CD and idiopathic thrombocytopenia purpura .[211-217]
Thrombocytosis	Hyposplenism.
Skeletal	
Osteopenia/osteoporosis	Calcium and vitamin D malabsorption.
Pathological fractures	Osteopenia / osteoporosis.
Muscular	
Atrophy	Malabsorption-induced malnutrition/osteoporosis.
Tetany	Calcium, vitamin D and magnesium malabsorption.
Weakness	Muscular atrophy, hypokalemia.
Dermal	
Dermatitis herpetiformis	Dermal equivalent to CD.
Edema	Hipoproteinemia.
Ecchymosis and petechia	Vitamin K malabsorption.
Follicular Hyperkeratosis	Vitamin A and B-complex malabsorption.
Psoriasiform lesions	Associated disease of immune origin.
Neurological	
Peripheral neuropathy	Vitamin B12 and thiamine deficiencies.
Ataxia	Cerebellar and posterior columnar damage.
Demyelinating lesions of the central nervous system.	Unknown mechanism.
Vertigo	Unknown mechanism.
Endocrinological	
Amenorrhea, infertility, impotence	Malnutrition, hypothalamus-hypophysis dysfunction.
Secondary hyperparatiroidism	Calcium and vitamin D absorption deficit.
Hepatological	
Aminotransferase increase	Unknown mechanism.

[1] May appear even in cases without villous atrophy.[252,261-263]

[2] May explain persistent diarrhea and flatulence in CD patients who adhere to the GFD.

Table 4. Extraintestinal CD symptoms and signs, grouped according to organs and systems.

6.3. Anemia

Anemia is a common finding among celiac patients; its origin is often associated with iron or folate malabsorption when the proximal intestine is affected.[88,118] In some cases, there is also vitamin B-12 malabsorption when there is a concomitant involvement of the ileum or when there is SIBO. There is a special difficulty involving the assessment of iron deficiency anemia, when the histological lesion is limited to lymphocytic enteropathy (>25% IELs) (Marsh 1; Corazza) associated with *H. pylori* (*Hp*) infection. The difficulty lies in that *Hp* infection is a recognized cause of iron deficiency which may disappear when the infection is eradicated.[119-121] Distinguishing both situations can be difficult in patients with negative serology and positive DQ2-DQ8, which makes a specialized assessment imperative. Figure 4 shows the case of a patient with iron deficiency anemia, lymphocytic enteropathy and Hp infection, whose histological lesion did not abate definitively until gluten was removed the diet. In severe cases, anemia can result from a hemorrhagic diathesis due to vitamin K malabsorption or gastrointestinal bleeding secondary to ulcerative jejunoileitis or lymphoma.

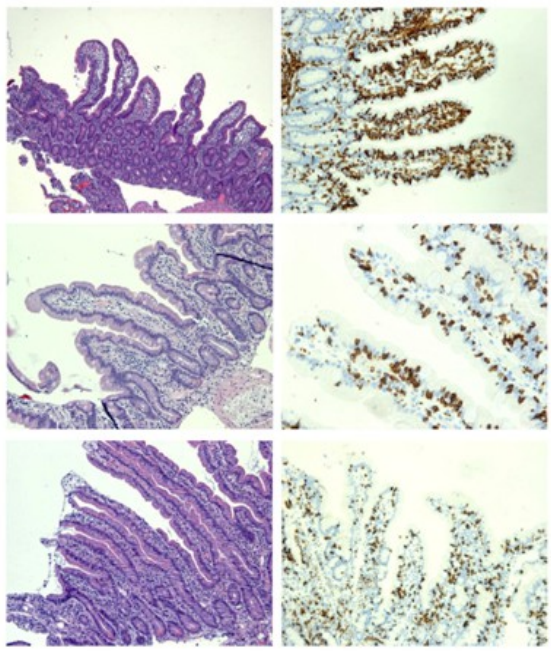

Figure 4. Images from a 45-year-old male with dyspepsia and flatulence

*Anti TG: 1.8 U/mL.[DQA1*05 positive; DQB1*02 positive] Above (left) mild focal villous atrophy can be appreciated. Immunohistochemistry (right) shows an IEL count of 35%. Below, the results of the eradication of the* Helicobacter Pylori *infection, can be seen, 4 months later. To the left, mild focal villous atrophy persists. The image on the right shows a decrease in the IEL count (19%). Further down (left) complete mucosal architecture and villous recovery can be seen, one year after withdrawing dietary gluten. To the right, the effect of the GFD on the IEL count can be appreciated, which is of 15%. Courtesy of Dr. Vera, Pathological Anatomy Service, San Jorge Hospital, Huesca.*

6.4. Osteopenia and Osteoporosis

The prevalence of osteopenia and osteoporosis among CD patients is high, both in children and in adults[88,122,123] and it is the result of a combination of factors, such as deficiencies in calcium ion transport across the intestinal mucosa, vitamin D malabsorption, secondary hyperparathyroidism which promotes bone calcium mobilization aggravating osteopenia and the effect of the inflammatory mediators. Note that osteopenia and risk of fractures also occur in patients with mild forms of enteropathy, even without villous atrophy.[124-130] There is evidence that suggests that children with a CD diagnosis who dropped the gluten-free diet and remained asymptomatic, later developed osteoporosis as adults, proof that the diet should be lifelong.[126] Figure 5 shows the case of a boy with childhood growth delay and mild gastrointestinal symptoms, who presented a vertebral fracture at age 34 ignoring that he suffered from CD. Several studies agree that the GFD allows significant bone mass recovery in children. This benefit is lesser in the adult population, but still evident.[131-135] One study showed that magnesium supplements improved bone mass in adults with CD.[136]

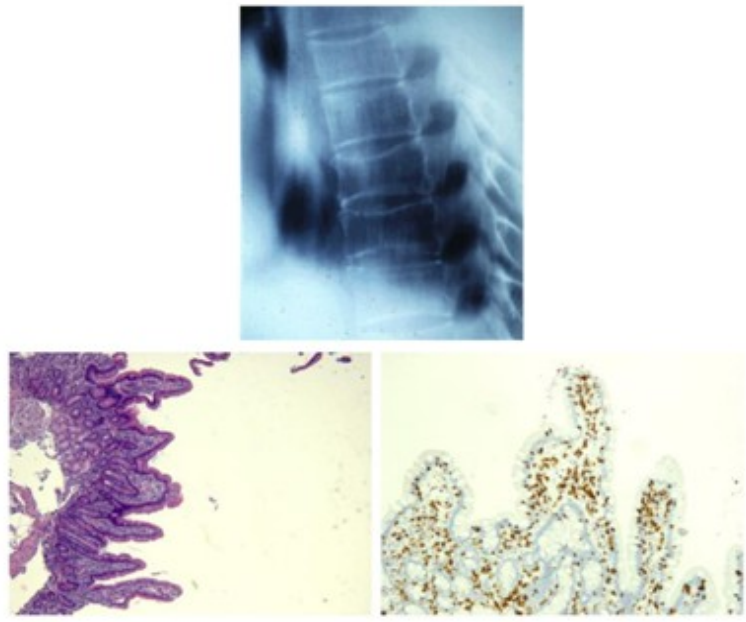

Figure 5. Histological images corresponding to a 51-year-old male with a history of unstudied childhood delay.

At 34 years of age a flattening of the 10th dorsal vertebra (backbone x-ray) occurred due to a slight fall, which led to a "young adult's idiopathic osteoporosis" diagnosis. Nine years later, a jejunal biopsy using a Crosby capsule was performed, which yielded a report of normalcy. Said biopsy was evaluated 9 years later by an expert pathologist who reported a focal mild villous atrophy and an IEL count of 24% (below right). One first-degree relative and two second-degree relatives were later diagnosed with CD; all of them were HLA-DQ2 positive. Courtesy of Dr. Vera, Pathological Anatomy Service, San Jorge Hospital, Huesca.

6.5. Neurological Symptoms

The association between CD and neurological disorders has been widely documented.[137-144] Some CD patients may develop neurological symptoms due to malabsorption of vitamin B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B12 (cobalamin) and vitamin E.[88] These deficiencies are unusual except in cases with severe and extensive intestinal involvement. Other neurological symptoms frequently observed in CD patients include headache, dizziness and peripheral neuropathy, consisting of burning, numbness and tingling in the hands and legs, symptoms that may occur in up to 50% of them before diagnosis[13] The association of cerebellar ataxia and various forms of epilepsy is well known[145-149], but it is not always related to the presence of cerebral calcifications.[149] Their prognosis is variable, ranging from mild cases to intractable forms which evolve to severe encephalopathy, including progressive myoclonic epilepsy.[149]

6.6. Psychiatric Symptoms

It has been usually described that CD patients, especially children, exhibit irritability and mood swings. The association of CD with depression in adults is unclear, as an independent variable of other clinical conditions.[14,150-152] A Swedish study involving 13,776 CD patients and 66,815 controls found a higher depression prevalence in the first group.[151] These data, however, have not been reproduced in other studies.[152] Another study has shown, in patients diagnosed with CD one year after removing dietary gluten, improvement in anxiety levels, but not in depression.[153]

6.7. Infertility and Menstrual Disorders

Women with untreated CD have a higher incidence of menstrual abnormalities, including delayed menarche, early menopause, secondary amenorrhea, unwanted abortions, infertility and intrauteral growth retardation of children.[152-159] A case-control study of women of childbearing age showed a CD prevalence of 6.7% among those who reported unwanted abortions, 5.7% among those with a history of stillbirths, 5.6% in those with infertility and 9.3% in those with intrauterine fetal growth retardation. In the same study, CD prevalence in the control group was 1.3%. These figures could be underestimated because the CD diagnosis was made on the basis of serological studies without duodenal biopsy.[159] In males, sperm abnormalities have been documented regarding morphology and motility and resistance to the effects of androgens, manifested by elevated testosterone levels and LDH which become normalized sometime after starting the GFD.[160-161]

7. Associated Clinical Conditions

A set of diseases are more prevalent among CD patients. Besides dermatitis herpetiformis, already mentioned, the following can be highlighted.

7.1. Type I Diabetes Mellitus

Diabetes mellitus type 1 shares some HLA system haplotypes (HLA-DR3, HLA DQ2, and HLA-DQ8) and other genetic CD variants.[162-165] This explains the fact that 2-8% of type 1 DM patients have anti-TG2 antibodies.[166-167] One study showed that one third of type 1 DM patients who bore HLA-DQ2 had anti-TG2, while the prevalence of these antibodies in the population of type 1 diabetic without this haplotype was of 2%.[168] Although there are conflicting views[169], CD does not seem to be a contributing factor to the development of type-1 diabetes, since anti-TG2 usually appears after onset of diabetes.[170] It is not clear if instituting a GFD improves the development of type 1 DM and of its insulin requirements.

7.2. Liver Disease

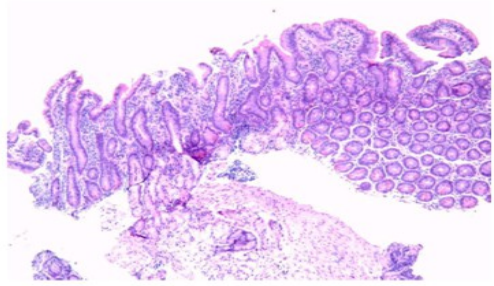

Figure 6. Histological image from a 53-year-old woman formerly diagnosed with primary biliary cirrhosis, autoimmune hypothyroidism, Sjögren's syndrome and follicular porokeratosis.

She had suffered, for several years, from dyspepsia and flatulence with no other associated gastrointestinal symptoms. The biopsy shows a marked disorganization of the mucosal villous architecture, with severe villous atrophy, crypt hyperplasia and an IEL count of 63%. A first-degree relative was later diagnosed with EC. Courtesy of Dr. Vera, Pathological Anatomy Service, San Jorge Hospital, Huesca.

Up to 25% of patients have a nonspecific transaminase elevation (<3 UNL) at the time of CD diagnosis, which returns to normal in 65-90% of the cases, after instituting a GFD.[171-175] In fact, the probability of CD among patients with chronic liver disease is 10 times higher than that observed in the population.[173-176] There is also a well-documented association with primary

biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), congenital hepatic fibrosis (CHF) and massive steatosis. Figure 6 illustrates the case of a patient with primary biliary cirrhosis who referred dyspepsia as the only gastrointestinal manifestation of the illness. The recognition both diseases in the same patient is important since both can lead to osteoporosis. One study identified the presence of CD in 4% of patients who received a liver transplant; these were patients with autoimmune hepatitis, PBC, PSC and CHF.[177-179] In some patients, the beginning of a GFD has led to a decrease of advanced liver disease.[180,182] Other authors have shown there is a decrease of steatosis associated with a metabolic syndrome.[182]

7.3. Thyroid Disease

The probability of autoimmune thyroid disease (particularly hypothyroidism) is higher among CD patients.[183,184]

7.4. Selective IgA Deficiency

The prevalence of CD among patients with this immune deficit is as high as 8%. In turn, the prevalence of selective IgA deficiency in CD patients reaches 1-2%.[185-187]

7.5. Down's Syndrome

There is a well-established association between CD and Down's syndrome, reaching, in some studies, a prevalence of up to 16%, a value 20 times higher than in the general population.[188-189] In Spain, the prevalence of intestinal biopsy-confirmed CD 286 patients was of 6.5%; most of them related both gastrointestinal symptoms as well as extraintestinal manifestations.[190]

7.6. Inflammatory Bowel Disease

The probability that a CD patient will develop or suffer from a concomitant IBD is 10 times higher than in the general population, especially for ulcerative colitis (UC).[191-193] In turn, UC is 5 times more common among the relatives of a CD patient.[194] This could be related to the fact that both share a receptor gene polymorphism for IL-23 which determines a proinflammatory state.[195-196] An association between CD, UC and PSC has been described.[199] In contrast, the prevalence of CD between IBD patients does not seem to be higher than that of the general population.

7.7. Eosinophilic Esophagitis

Several studies agree that the prevalence of eosinophilic esophagitis is higher in children or adults with CD. This should be firmly considered in celiac patients with persistent pyrosis or dysphagia.[198-200]

7.8. Pancreatitis

A study of 14,000 CD patients has shown that the prevalence of every type of pancreatitis is higher among adult CD patients (OR 3.2, 95% CI 2.5-4.3, P <.001). The risk of developing chronic pancreatitis is also higher (OR 7.3, 95% CI 4.0-13.5, P <.001). This risk was not dependent on socioeconomic status, drinking habits or the presence of gallstones.[201]

7.9. Atrophic Glossitis

Various reports agree on a higher prevalence of atrophic glossitis[17,202] and other oral symptoms among CD patients, which usually improve after starting a GFD.

7.10. Heart Disease

Other associations described for CD include autoimmune myocarditis and dilated cardiomyopathy, which also improve after starting a GFD, whether or not immunosuppressive medications are taken (most of the cases have iron deficiency).[203-205] Some studies suggest a higher incidence of ischemic cardiopathic disease.[206-208]

7.11. Idiopathic Thrombocytopenic Purpura

As with other autoimmune diseases, there are isolated reports of an association between idiopathic thrombocytopenic purpura and CD.[209-215] It is not uncommon to find a triple association with other immunoregulation disorders, including thyroiditis,[211] multiple sclerosis,[212] selective IgA deficiency,[213] ranulomatous hepatititis[216] and myositis.[215] Figure 7 shows the duodenal biopsy of one of our patients with ITP, Sjögren's syndrome and CD. There are reports that establish a relationship between Sicca's syndrome and CD.[216-218]

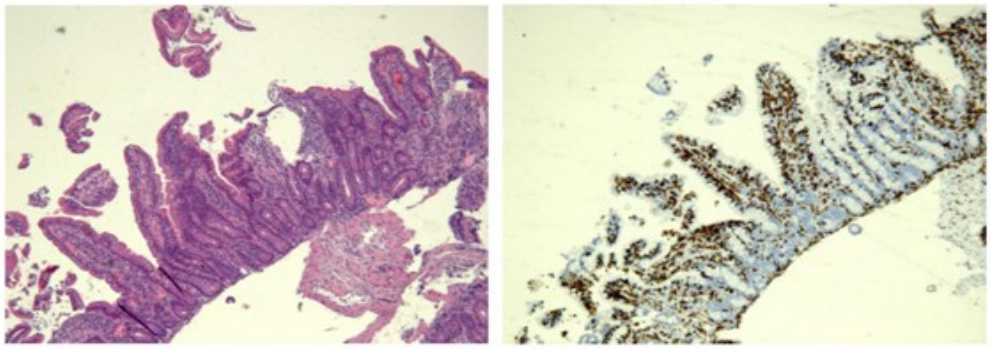

Figure 7. Images from a 45-year-old woman of low height, suffering from autoimmune thrombocytopenia, dryness of the mouth and eyes with a marked anti-Ro and anti-SSLab increase compatible with Sjögren's Syndrome.

*She only reported nonspecific gastrointestinal symptoms. Anti-TG: 2 U/mL. HLA-DQ2 positive (DQAI*05/DQB1*02). The image shows a mild focal villous atrophy (left) and an IEL count of 35% (right). Courtesy of Dr. Vera, Pathological Anatomy Service, San Jorge Hospital, Huesca.*

8. Diagnosis

8.1. Suspicion Index

The suspicion index for CD is extremely low and, in fact, at least 75% of the cases remain undiagnosed.[8-9] Data obtained from the ARETAEA registry allow establishing that the time between the onset of symptoms and diagnosis is, on average, of 10 years (unpublished observations); up to 60% of these patients have been diagnosed with one or more FGD over time and more than half have been subjected to various radiological or endoscopic studies, which are of no benefit to the clinical development of their disease.

These data are explained by several considerations:

1) The classic pattern of CD presentation, based on a florid case of malabsorption, is exceptional in adults (<20%), lesser or nonspecific gastrointestinal symptoms being the more frequent presentation;[56,101-103] a significant proportion of these patients fail to consult with a physician and those who do it are often anxiety-laden, due to the persistence and recurrence of their symptoms, leading the physician to issue a preconceived judgment of neurosis, hypochondria or somatization.[219]

2) According to the Rome Criteria, the diagnosis of a FGD is based on the presence of a set of symptoms, needing no further testing, save when there exist the so called "warning signs". The presence of pyrosis, postprandial fullness, bloating, abdominal discomfort or frequent changes in bowel habit (common symptoms in adult CD), are not sufficient to indicate a specific evaluation, unless there is anemia, vomiting, fever, rectal bleeding or weight loss.

3) Some antecedents, such as growth retardation in childhood, a history of iron deficiency, delayed menarche, early menopause, unwanted abortions, infertility, fractures due to minimal trauma, recurrent oral ulcers, psoriasiform skin lesions, are often overlooked, because the gastroenterologist's questions have focused exclusively on gastrointestinal symptoms, forgetting that CD is a disorder with a multisystemic expression.[5]

4) Experts participating in regular meetings of the Roman Committees are particularly incisive in the deliberate search for warning signs ("red flags"), aimed at the exclusion of malignancies, but are not as aware of the need to define a context favorable to the suspicion of CD (including the coexistence of other autoimmune diseases).[220,221]

5) Most IBS experts agree that an endomysial or anti-TG2 determination is useful for screening CD in IBS of the diarrheal subtype[222,223] but few consider that negative serology is quite common in patients with mild forms enteropathy (Marsh 1, 2 and 3a),[8,224-227] which excludes the patient from a fuller investigation.

6) Finally, current clinical practice guidelines do not include the need to biopsy the duodenum in patients with dyspepsia and negative endoscopy.

Besides, the application of specific immunostaining for CD3 is not standard practice, thus losing many cases of lymphocytic enteropathy that may be clinically relevant.[8,228] The Ministry of Health of Spain, promoted in 2008 development of an early diagnosis protocol as well as a decalogue of recommendations in order to increase the CD index of suspicion.[229] The Spanish Gastroenterology Association's AEGastrum recommendations project o draft recommendations of the Spanish Gastroenterological Association for clinical practice in primary care provides a number of key points for suspecting celiac disease in the field of primary health care (www.aegastro.es).

8.2. Approach to the Patient with Clinical Suspicion of CD

The diagnostic approach to a patient with suspected CD is complex, especially in adults, given the diversity of possible clinical settings.[230-231] It should be considered that, in any case, serology, genetic testing or duodenal biopsy results are pathognomonic. This means that in, certain cases, it is extremely difficult to confirm or rule out the disease. ESPGHAN published in 2012 a guide to clinical practice[5] and its readers can consult as well the Oslo[6] and London[1] Consensuses' recommendations as well as the recent criteria proposed by Catassi and Fasano[232], which emphasize the application of rigid algorithms, but do not cover the entire spectrum of situations, which makes preferable application of simple rules, which, in the hands of an experienced gastroenterologist, may be equally efficient (Table 5). Briefly we shall mention the most recommendable attitude for the two scenarios most often seen in adults. It always takes it as given that, in the face of clinical suspicion, a specific antibodies test (Anti-TG-2, antiendomysial or anti-DGP) should be the first test to be performed.

	At least 4 out of 5, or 3 out of 4 if there are no HLA genotypes
1	Typical CD symptoms.[1]
2	IgA-class specific antibodies for celiac disease at adult-level titers.[2]
3	HLA DQ2 or DQ8 genotypes.[3]
4	Celiac disease compatible enteropathy in intestinal biosy.[4]
5	Response to gluten-free diet.[5]

Note: A family history of celiac disease adds evidence to the diagnosis; in asymptomatic patients, particularly in children, it is advisable to confirm positive serology in 2 or more blood samples with a difference of at least 3 months; in selected cases a challenge test may be necessary, at least 2 years after the gluten-free diet.

[1] Examples of typical symptoms are chronic diarrhea, growth delay (children) or weight loss (adults) or iron deficiency anemia.

[2] IgA anti-TG or IgA antiendomisium in patients with no IgA or IgG anti-TG or anti-endomysium deficit, in patients with IgA deficit. The finding of IgG deaminated gliadin antipeptides adds evidence to the diagnosis.

*[3] Positive HLA-DQ2 includes subjects with half the heterodimer (positive HLA-DQB1*02).*

[4] Includes type 3 Marsh-Oberhuber lesions, Marsh Oberhuber types 1-2 associated to the presence of CD-specific antibodies or Marsh-Oberhuber types 1-3 associated with subepithelial IgA deposits.

[5] Histologic response is required of patients with negative serology or associated with IgA deficit.

Table 5. Criteria proposed by Catassi for the diagnosis of CD.

8.2.1. Symptomatic Patients with Positive Anti-TG-2

In a situation like this, if anti-TG titers are more than 10 times higher than the UNL, the intestinal biopsy could be excluded (fully accepted criterion in children), since the probability of detecting villous atrophy is quite high.[5] Before taking this decision it is prudent to investigate and confirm the presence of anti-endomysial antibodies (performing the extraction at a different time of the first time) and checking for HLA DQ2 or DQ8 heterodimers, since a positive result reinforces the diagnosis.[233] In contrast, antiTG2 antibodies titers are of <10 UNL, duodenal biopsies must be performed (2 bulb biopsies and 4 duodenal 2nd portion biopsies) to detect enteropathy. If the result is positive, a GFD should be started. If the duodenal biopsy reveals no abnormalities and the genetic test is positive, we face “potential” CD. Some authors recommend a GFD in this circumstance, to treat the symptoms and to prevent future complications.[232,234]

8.2.2. Seronegative Patients with Specific Antibodies and High Suspicion

This is a matter of crucial importance, especially in the adult population. In fact, the true prevalence of CD in this population has been underestimated, because both in population screening programs, as in symptomatic or high genetic risk people, intestinal biopsy is indicated only for positive serology.[237,238] However, there is evidence that the sensitivity of different antibodies is considerably lower in the absence of histological gravity.[225-227,237-240] Thus, once some of the causes of false negative serology have been taken into account (selective IgA deficiency, immunosuppressive treatments, low-gluten diet)[187] and having a well-founded clinical suspicion

of CD, the clinician should not hesitate to request a duodenal biopsy[230,240] since there is evidence that the GFD provides symptomatic relief and reversion of lesions even in mild enteropathy cases.[8,241,243]

8.2.3. Important Considerations for Patients with Negative Serology and Mild Enteropathy

The presence of a minor histologic injury (slight enteropathy) (Marsh-Oberhuber 1 and 2) represents a difficult to interpret "gray area". It should be noted that this type of injury is nonspecific and that the symptomatic improvement seen in some patients, after removing gluten, may reflect changes in bowel function, the placebo effect or a combination of both. These patients should be managed with caution.

Some considerations strengthen the hypothesis of a gluten-induced enteropathy:

A) According to Catassi's criteria (Table 5) the presence of mild enteropathy (Marsh 1 and 2), negative serology and IgA subendothelial deposits clearly reinforce the CD diagnosis.[234,245]

B) Other suggestive characteristics are the predominance of γ/δ lymphocyte populations in the epithelial lining and the preferential localization of IELs at the tips of the villi.[245]

C) Lymphocytic enteropathy (LE) can be caused by peptic duodenitis, Helicobacter pylori (*Hp*) infection, frequent NSAID intake, SIBO, viral infections, Crohn's disease or some other autoimmune disease (Table 2). All these causes should be seriously considered for the differential diagnosis. For example, an LE (also known as lymphocytic duodenosis) can reverse after eradicating an Hp infection or curing an iron deficiency anemia, which otherwise could have been wrongly attributed to CD.[119-121]

D) In all these cases, information on the major determinants of CD genetic susceptibility can be a valuable aid, given its high negative predictive value. Over 95% of CD patients share HLA DQ2 heterodimers either in the *cis* position (encoded by HLA-DR3-DQA1*0501-DQB1*0201) or in *trans* (encoded by HLA-DR11-DQA1*0505 DQB1*0201 DQB1 0301/DR7-DQA1 0202). Most of the remaining ones are HLA-DQ8 (encoded by DQA1*0301-DQB1*0302). Either HLA-DQ2 or HLA-DQ8 expression is necessary, but not sufficient, for development of this disease. In fact, these haplotypes are present in 30-40% of the Caucasoid population, while CD is only present in 1% of it.

On the other hand, a negative genetic test virtually excludes the possibility of CD, but cases have been reported without these haplotypes (0.4%).[244] We follow the criteria proposed by Catassi (the "4 out of 5" rule) stressing the importance of a deliberate search of compatible symptoms and signs and the need for a correct differential diagnosis in mild enteropathies.[245]

9. CD Patient Follow-up

Treatment of CD is based on a strict GFD to be maintained for life. In most situations, this will be sufficient to induce an improvement in symptoms, while normalizing serology and reverting lesions. Several studies agree that, in adults, a complete regression of mucosal lesions is the exception rather than the rule, even if the symptoms have abated.[224,246,247] Patients with more severe villous atrophy often suffer from an associated secondary lactase deficiency, making it necessary to recommend the temporary withdrawal of dairy products. Some patients with significant malnutrition states may require temporary nutritional supplements and multivitamins. Patients with osteopenia or osteoporosis require additional calcium and vitamin D supplements (it must be noted that some commercial calcium preparations contain gluten); patients with anemia, oral ferrous salts and, in some cases, folic acid and vitamin B12 depending on the type of identified deficit. Cases of refractory or oral iron-intolerant anemia can benefit from i.v. carboxymaltose iron administration. Once clinical stabilization is achieved, patients can be evaluated by their primary care physician, with the recommendation to undergo a voluntary annual check-up, monitor weight and diet compliance as well as some basic analytical parameters, including iron metabolism.

10. Procedure to be Followed for Patients with Persistent Symptoms

The persistence of symptoms in a patient diagnosed with CD forces a revaluation in which two distinct situations must be discerned:

1) Lack of initial response to GFD and

2) Refractory CD (RCD).[248]

The reader can obtain further information on the diagnosis and management of RCD, as well as on the serious complications of CD (nongranulomatous jejunoileitis and CD associated T cell lymphoma) in another section of this work (Figures 8 and 9). This last condition is defined by the persistence of malabsorption symptoms and villous atrophy despite a strict GFD, with anti-TG2 and negative AEM, which persists for >12 months.[249] This is a rare condition (8-18% of patients referred to a tertiary hospital to investigate the lack of response to diet).[250-252] The situation is different for patients who initially respond to the GFD once the hypothesis of CD has been established. The three most common causes for this situation are:

1) Incorrect initial diagnosis,

2) The patient, voluntary or inadvertently, violates the diet and

3) There is a clinical condition associated with CD which explains the persistence of symptoms.[248]

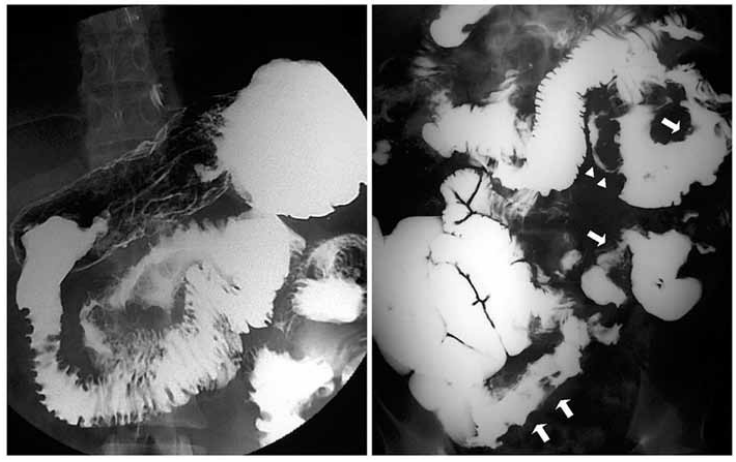

Figure 8. Lymphomas can complicate the CD patient's progress.

Barium radiography of a CD patient affected by a lymphoma. Courtesy of Dr. Domínguez, San Jorge Hospital. Reproduced by permission of Jarpyo Publishing*, from the 2nd edition of the book* Problemas Comunes en la Práctica Clínica *("Common Problems in Daily Clinical Practice") (Montoro, M. and García Pagan, JC (eds) (Copyright 2012).*

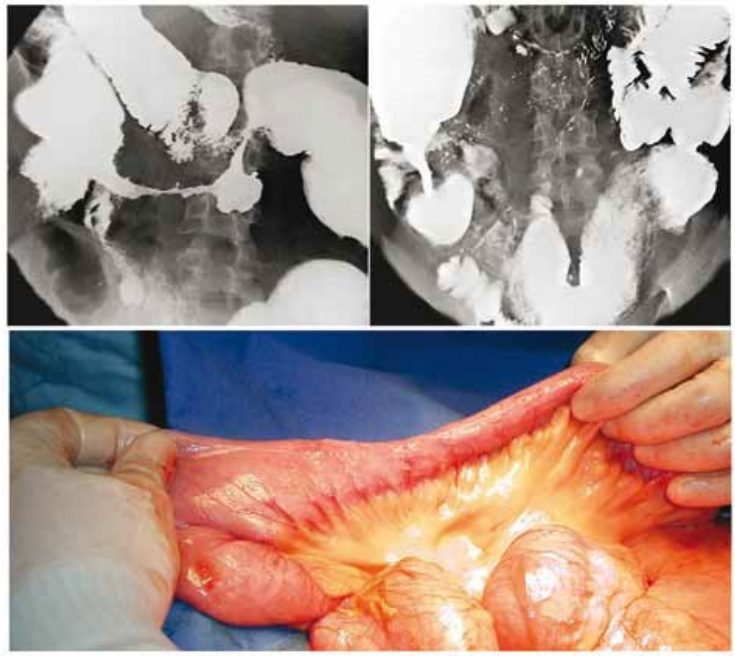

Figure 9. Ulcerative jejunoileitis in a patient with celiac disease and schizophrenia.

The radiological images show areas with stenosis and dilation in the small intestine. There is observable stenosis in the small intestine during laparotomy. Courtesy of Drs. Domínguez and Ligorred, San Jorge de la Huesca Hospital. Reproduced by permission of Jarpyo Publishing*, from the 2nd edition of the book* Problemas Comunes en la Práctica Clínica *("Common Problems in Daily Clinical Practice") (Montoro, M. and García Pagan, JC (eds) (Copyright 2012).*

10.1. Incorrect Initial Diagnosis

This can affect patients with mild enteropathy and negative serology as well as patients with villous atrophy (with or without positive serology). Some of these patients have experienced a transient improvement in their symptoms after starting the GFD, which reappear later. In both situations, an experienced pathologist should review the biopsies, including an assessment of villi orientation, atrophy degree, crypt elongation, villus/crypt ratio and degree of intraepithelial lymphocytosis. In some cases, it is advisable to repeat the biopsy to assess the presence of subendothelial IgA deposits and obtain a flow cytometry intraepithelial lymphangiogram to search for presence of an immunophenotype characteristic to CD (clear γ/δ lymphocyte predominance). In 55 patients referred to a tertiary center, the biopsy reviewed by an expert pathologist helped to finally dismiss a CD diagnosis in 6 cases.[250] The involvement of other etiologic agents in mild enteropathy forms (Table 2) has already been mentioned. Ultimately, it must be remembered that Catassi's criteria require the demonstration of a regression (or marked improvement) of histological lesions regarding seronegative enteropathies, a key issue in the validation of the diagnosis. Under special circumstances, a challenge test may be required.[5] Finally, the clinician and the pathologist ought not to forget there is a list of clinical conditions that may present villous atrophy, including allergies to different gluten proteins (chicken, cow's milk, egg, fish and soy), SIBO, hypogammaglobulinemia, giardiasis and autoimmune enteropathy, among others (Table 6).[70,248]

- Tropical sprue
- Parasitosis (*Giardia Lamblia*)
- Common variable immunodeficiency
- Lymphoma
- Whipple's disease
- Mastocytosis
- Abetalipoproteinemia.
- Vasculitis
- Amyloidosis
- Crohn's disease
- Eosinophilic gastroenteritis
- Autoimmune enteropathy
- Dietary protein intolerance (cow milk, egg, etc.)
- Infectious gastroenteritis
- Graft vs patient disease
- Small intestine chronic ischemia
- IgA deficit

Table 6. Diseases which manifest villous atrophy.

10.2. Noncompliant Patients

The first step in evaluating a patient who initially responded the GFD is to assess the degree of compliance with the diet, even if the patient assures that he or she does comply properly with it.[250] Certainly, complete lack of compliance with the GFD is unusual (<5% in most studies with a range of 0-32%),[253] but estimates of a really effective adherence to the GFD have a range of 42-91%.[253-255] The usual dietary gluten content oscillates around 13 g per day for a healthy person. Many people with CD can tolerate small amounts of gluten, but there is evidence that as little as 10 mg per day are capable of inducing mucosal abnormalities (international regulatory legislation provides that a gluten-free food must contain an amount of <20-100 parts per million (ppm)) and some patients are extremely sensitive.[248,256] Therefore, some patients, especially those with a strong drive to comply with the diet can benefit from advice provided by a nutritionist or a patients' association, making their symptoms disappear completely, particularly if they are very sensitive.[248] It is important to note that the persistence of some histological injury degree after starting the GFD in asymptomatic individuals is not an unusual occurrence and should not necessarily be considered as an indicator of dietary transgression. At this point it should be remembered that lesion reversion begins in the more distal portions of the intestine while the duodenum anatomical region is the last to experience a definitive cure.[257]

10.3. Associated Clinical Conditions which Explain the Persistence of Symptoms

Some CD patients who comply well with the diet show persistent symptoms, even in the presence of a significant improvement in their histological injuries.[258,259] Such cases may present a set of associated conditions that explain the persistence of diarrhea, either by an alteration in the small intestine's pathophysiology related to CD itself, or the existence of a concomitant disease, whose prevalence is higher among the CD patient population.[250,260] Lactose intolerance should be considered among the first,[255] fructose deficiency (an often underdiagnosed entity),[248] SIBO is probably related to microinflamatory changes which compromise the intestinal of bacterial clearing mechanisms[261-266] and pancreatic exocrine insufficiency due to a defect in the perception of the signal which activates pancreatic enzymes secretion after the release of endogenous secretin by the duodenal mucosa.[250,259-261] One or more of these pathophysiological abnormalities may contribute to persistent diarrhea after a successfully launched GFD. An H2 breath test, a culture of duodenal aspirate or, failing that, a Glucose-H2 as well as fecal elastase determination can be of valuable help in this context and allow taking specific measures aimed at controlling these mechanisms (lactose or fructose suppression, rifaximin or pancreatic enzymes). Note: pancreatic exocrine insufficiency may be present even in patients without severe villous atrophy, as has been shown in some studies where patients agreed to conduct a duodenal biopsy before prescribing pancreatic ferments.[250,259-261] The other category of patients comprises those suffering from a clinical condition whose prevalence is higher than that of the general population. Such is the case of microscopic colitis,[267] anal sphincter dysfunction,[259] intestinal inflammatory disease[191-193] or IBS itself[230,248] an entity whose prevalence in the general population[267-268] reaches 8-12%. Some patients labeled as IBS may improve after introducing the gluten-free regimen[7] others, however, may relate having constipation and swelling fostered by eating less fiber.[248] The frequent association between CD and microscopic colitis (50 times higher

than expected in the general population)[267] requires a colonoscopy with biopsies performed in cases of watery refractory diarrhea.[269]

11. Emerging Therapies

Voluntary or inadvertent dietary transgressions pose a significant handicap for CD patients. Hence, in recent years different lines of research have been developed whose primary objective is to promote effective alternatives for prevention and symptom control. Briefly, these emerging therapies include dietary modifications, aimed at developing wheat grains without harmful gluten epitopes by transgenic technology[270-271] or the addition of proteolytic enzymes (prolylendopeptidase) designed to degrade proline-rich peptides which may be finally hydrolyzed by intestinal endopeptidases.[272-276] Gluten-capturing polymers have also been tested as well as permeability modulating agents, including inhibitors for zonulin (a human protein that acts on intercellular junctions causing disruption epithelial barrier and whose expression is increased by exposure to gliadin in celiac patients).[277-278] AT-1001 (Lazarotide acetate) is an octapeptide derived from a protein secreted by *Vibrio Cholerae* that binds to zonulin, acting as a competitive antagonist and inducing inhibition of epithelial cell reordering. Its use in a double blind case-control study showed a decrease in the permeability of gamma interferon levels and gastrointestinal symptoms without significant adverse effects.[278] Other advanced therapies include targeting agents which block antigen presentation by means of tissular transglutaminase inhibitors[279-283] or agents which block the intervention of the DQ2 or DQ8 HLA system haplotypes in antigen presentation.[284-285] Advanced therapies for disease control would include different monoclonal antibodies for inflammation modulation.[286-291] It is well known that T cell activation induces IFN-γ and TNF-α secretion, these are the inflammatory response and proteolytic cascade mediators responsible for tissular damage. Good results have been reported with *infliximab* in grave refractory CD cases.[288] Other IFN-γ antibodies (*fontolizumab*) could be tested in the future.[287] This advanced therapy spectrum is completed by agents that block the overexpression of IL-15, which is responsible for epithelial cell apoptosis induced by cytotoxic lymphocytes[289-290] and by substances that selectively inhibit lymphocyte adhesion including *natalizumab*[291] as well as other molecules directed against α4-integrin and α4β7-integrin and agents that block the chemokine ligand interaction,[25] secreted by intestinal epithelium cells and CCR9, located on the lymphocyte surface. Table 7 summarizes the aforementioned emerging therapies.

Treatment	Overview
Dietary modifications	
Enzyme therapies	Prolil-endopeptidases which collaborate to degrade gluten through proteolysis, diminishing its immunogenicity.
Wheat alteration	Development of wheat grains with low or null immunogenic peptide content and high nutritional quality.
Permeability modulation	
Zonulin inhibitors	Competitive zonulin agonist which inhibits the intestinal permeability increase it produces.
Antigen Presentation Blockage	
TG2 Inhibition	Deamination process blockage, avoiding effective gluten antigen presentation.
HLA Inhibition	Blockage of the HLA DQ2 and/or DQ8 gluten peptide linkage places.
Inflammation Modulation	
Anti-Interferon-γ and anti TNF-α antibodies	Blockage of aberrant inflammatory response provoked by these cytokines.
Anti IL-15 antibodies	Stops cytotoxic T-lymphocyte proliferation.
Lymphocyte adhesion inhibition	Selective inhibition of lymphocyte adhesion in order to impede their migration to inflamed tissues.
Others	
Vaccine	Desensitation by means of repeated gluten solution injections.
Parasites	Use of intestinal parasites as immune system modulators.

Table 7. Emerging therapies for celiac disease.

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