Celiac disease

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Purpose of review
The aim of this review was to summarize recent advances in celiac disease (CD) published between 2006 and 2012.
Recent findings
CD affects ~1% of most populations but remains largely unrecognized. During the past year, research has shown that the prevalence of CD has increased dramatically and not merely because of increased detection. Moreover, undiagnosed CD may be associated with increased mortality. Significant progress has been made in understanding how gliadin peptides can cross the intestinal border and access the immune system. New deamidated gliadin peptide antibodies have better diagnostic accuracy over other tests. The inclusion of duodenal bulb biopsy specimens may increase the rate of CD detection. Finally, refractory CD, although rare, is associated with a poor prognosis. The use of novel highly efficient exogenous prolyl endoproteases enzymes may help patients deal with occasional lapses in their diet or may protect highly sensitive individuals from inadvertent presence of gluten in food products. Nevertheless, the efficiency of this approach still needs precise assessment.
Conclusion
Mortality rates among patients with untreated CD increase two-fold every year as they age (gastrointestinal malignancies) and most can be prevented/reversed with early diagnosis and initiation of a gluten-free diet. CD is a global health problem that requires a multidisciplinary and increasingly cooperative multinational research effort.

Keywords:
celiac disease, duodenal biopsy, gliadin peptides, refractory celiac

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Introduction

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy. CD-specific antibodies comprise autoantibodies against tissue transglutaminase-2 (TG2), including endomysial antibodies (EMA), and antibodies against deamidated forms of gliadin peptides (DGP). The most obvious feature distinguishing celiac from other small intestinal enteropathies is the production of autoantibodies against tissue transglutaminase (tTG) on consumption of a gluten-containing diet. TTG is known to deamidate, and crosslink gluten-derived gliadin peptides, thereby favoring disease progression [1].

Celiac in history

CD was first described in the second century AD by Aretaeus of Cappadocia, a contemporary of the Roman physician Galen, who used the Greek word 'koeliakos', which means 'suffering of the bowels'. However, only in 1888 AD did Samuel Gee of St Bartholomew's Hospital give the classical clinical description of CD, which included irritability, chronic diarrhea, and failure to thrive, along with a cure by means of a diet [2]. No real progress in treating the disease was made until the 1930s–1950s, when W.K. Dickey, a Dutch pediatrician, showed that the health of children with CD dramatically improved when wheat, rye, and barley, which were unavailable during the Second World War, were removed from their staple diet, only to relapse at the end of the war when consumption of wheat flour started afresh in the Netherlands. In 1954, Paulley showed that in CD patients the small intestinal mucosa was abnormal, and 2 years later, Royer and Shiner used peroral biopsies to establish this pathology. Since then, biopsy techniques have evolved, with routine use of upper endoscopy and biopsy, and histopathologists play a key role in diagnosis [3].

How common is it?

CD seems to be a common disorder in North Africa. It is a frequent disorder among Egyptian children, both in the general population (0.53%) and in at-risk groups (6.4%). Data do not support the theory of a Middle East–Europe CD prevalence gradient secondary to the pattern of agriculture spreading from the so-called Fertile Crescent [4].

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Until the 1970s, the estimated global prevalence of CD in the general population was 0.03%. The presently estimated prevalence is 1%, with a statistical range of probability of 0.5–1.26% in the general population in Europe and the USA [5]. In patients at risk, the prevalence is even higher: 3–6% in type 1 diabetes mellitus patients and up to 20% in first-degree relatives of celiac patients [3].

Risk factors

Dietary factor

To date, gluten is the only known environmental factor to play a direct causal role in CD, and the only treatment for CD is a gluten-free diet (GFD). Wheat gluten proteins include gliadins and glutenins. The closely related proteins in barley and rye that activate CD are hordeins and secalins, respectively. The gliadins are subdivided into α/β, γ, and ω-gliadins, whereas the glutenins consist of low-molecular-weight and high-molecular-weight glutenins. Gluten has high concentrations of glutamine and proline residues (35 and 15% of the total amino acid content). The high proline content renders these proteins resistant to complete proteolytic digestion by gastric, pancreatic, and brush border enzymes in the human intestine, because these enzymes are deficient in prolyl endopeptidase activity, making it possible for large immunogenic gluten peptides to accumulate and reach the mucosal surface [6].

Age and sex distribution

The incidences, age at presentation, and features of CD have changed considerably over the past 20 years. In the past, CD presented most commonly either early in life, between 9 and 24 months, or during the third or fourth decade of life. In contrast to the equal sex ratio observed among CD children, two to three-fold higher number of women are diagnosed in adulthood [7]. However, patients over the age of 60 who are diagnosed as having CD are more frequently male [5].

Breastfeeding

The ESPGHAN committee at present recommends that small amounts of gluten are gradually introduced between 4 and 7 months of age during breastfeeding. Although dietary gluten exposure in children under the age of 2 seems more important with respect to CD risk when compared with exposure in older children, whether breastfeeding only delays clinical onset or whether it leads to permanent protection against CD remains to be elucidated [5].

Infections

Infections after birth have been proposed to contribute to the development of CD. Whereas the role of infection with adenovirus type 12 in this process remains controversial, the association of HCV infection and CD is well documented [5]. Frequent rotavirus infections, the most common cause of childhood gastroenteritis, represent an independent risk factor for CD in genetically susceptible individuals. Rotavirus infection changes the permeability of and the cytokine balance in the intestinal mucosa, potentially enhancing penetration of gluten peptides [8]. If this is the case, worldwide implementation of a rotavirus vaccine might diminish the occurrence of CD. The influence of infections with other common intestinal microorganisms, including *Campylobacter jejuni*, *Giardia* lamblia, and *Enterovirus*, has not yet been clarified [5].

Socioeconomic features

Worse socioeconomic conditions might protect against CD development. Variation in gut flora, infections, and differences in diet, which are factors involved in the maturation of immunoregulatory functions, may in turn precipitate CD development [5]. Although the 'hygiene hypothesis', which states that a reduction in childhood exposure to microbial antigens upregulates self-directed immunity and predisposes to allergy and autoimmune disease, is an attractive explanation for such an increase, CD occurs de-novo in adulthood, even at advanced age, suggesting some pervasive environmental factor(s) affecting adults and children [3].

Genetic risk factors (HLA genes)

CD is a multigenic disorder, in which the most dominant genetic risk factors are the genotypes encoding the HLA class II molecules HLA-DQ2 and HLA-DQ8. About 90% of individuals with CD carry the DQ2 heterodimer encoded either in *cis* or in *trans*, and practically all of the remaining patients express DQ8. Deamidated gliadin peptides have a high binding affinity to HLA-DQ2 and HLA-DQ8 molecules, but not to other HLA class II molecules, which explains the immunogenicity of gluten in carriers of HLA-DQ2 and HLA-DQ8. A correlation has been found between homozygosity for genes encoding the HLA-DQ2 molecule and the development of serious complications of CD, in particular refractory celiac disease (RCD) and EATL, which implies a gene–dose effect. These HLA-encoding genes are associated with ~40% of the heritable risk of developing CD [5].

Economics of celiac disease

Using a population-based study design, Long *et al.*'s [9] estimate of CD-associated costs indicate a significant economic burden of the disease, particularly for men with CD. Diagnosis and treatment of CD significantly reduces direct medical costs of care, suggesting an economic advantage to earlier detection and treatment.

New concept on celiac disease

Several classifications of CD have been used, most importantly with distinctions drawn among classical, atypical, asymptomatic, latent, and potential CD. Because atypical symptoms may be considerably more common than classic symptoms, the ESPGHAN working group decided to use the following nomenclature:

gastrointestinal symptoms and signs (e.g. chronic diarrhea) and extraintestinal symptoms and signs (e.g. anemia, neuropathy, decreased bone density, and increased risk of fractures) (Figs 1–5) [1].

Serological testing should be offered to first-degree relatives (parents, siblings, or children) with celiac disease. Serological testing should not be carried out for CD in infants before gluten has been introduced in the diet [3].

The celiac iceberg

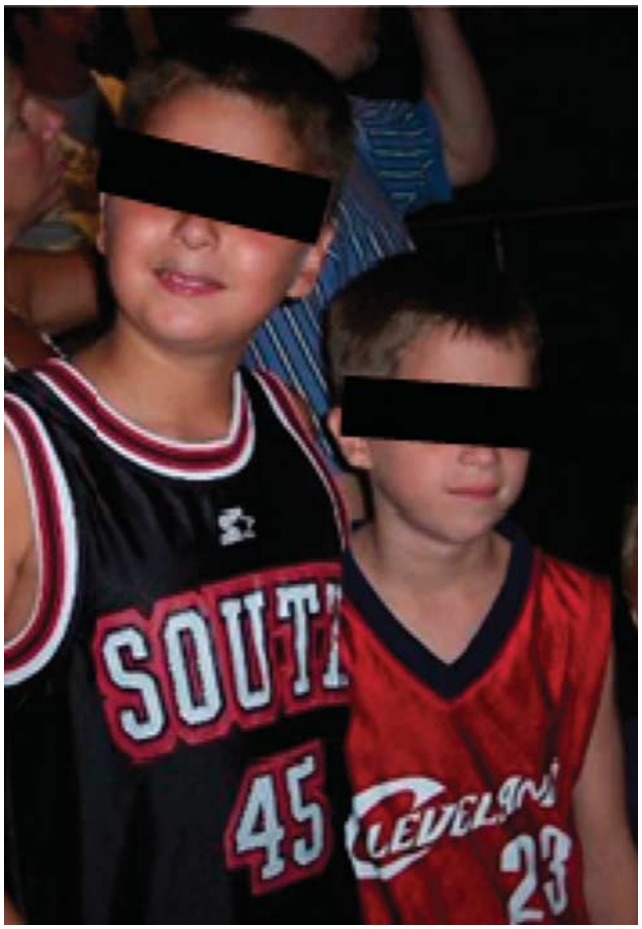
Because of the heterogeneity of CD manifestations, epidemiologists refer to the clinical and pathological spectrum of the disease as an iceberg, which includes active, silent, latent, and potential CD (Fig. 6).

The prevalence of CD can be conceived as the overall size of the iceberg, which is not only influenced by the frequency of the predisposing genotypes in the population but also by the pattern of gluten consumption. The visible part of the iceberg, in quantitative terms, is expressed by the incidence of the disease. In developed countries, for each diagnosed case of CD, an average of 5–10 cases remain undiagnosed (the submerged part of

Figure 1

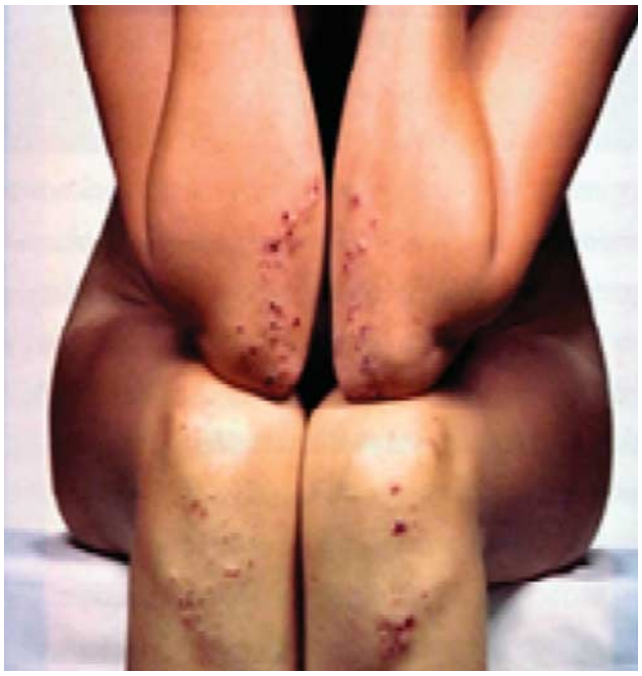
Gastrointestinal: failure to thrive.

Figure 2



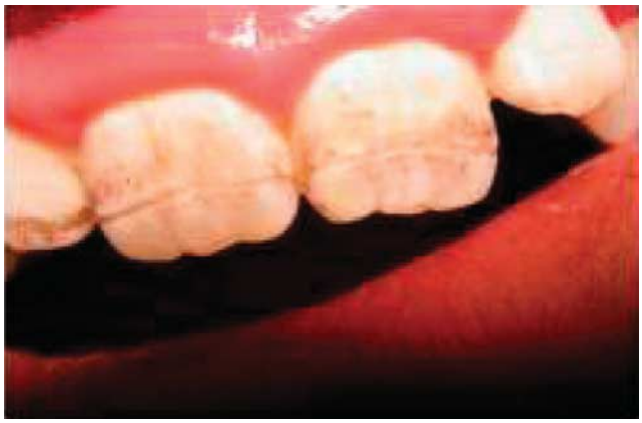
Gastrointestinal: stunting.

Figure 3



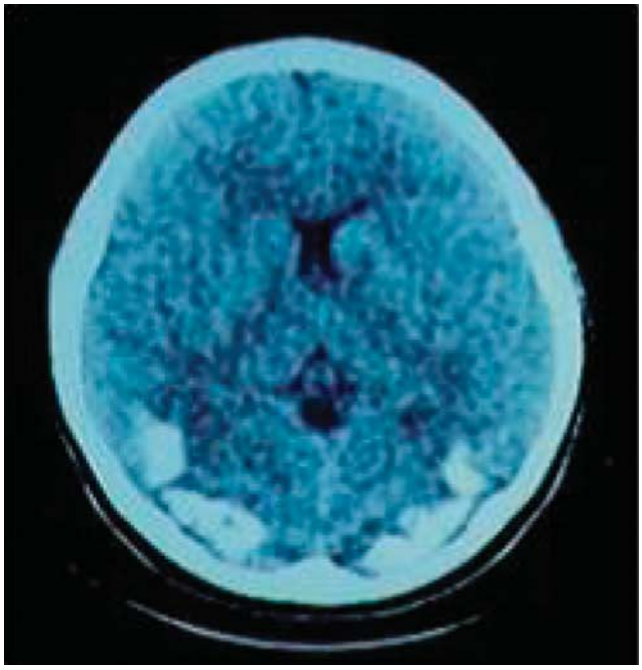
Extraintestinal symptoms and signs: dermatitis herpetiformis.

Figure 4



Extraintestinal symptoms and signs: enamel hypoplasia.

Figure 5

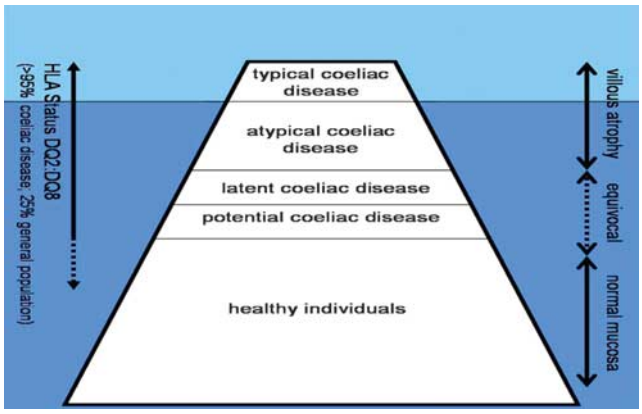


Extraintestinal symptoms and signs: gluten ataxia.

the iceberg), usually because of atypical, minimal, or even absent complaints. These undiagnosed cases remain untreated and are therefore exposed to the risk of long-term complications. The 'water line', the ratio of diagnosed to undiagnosed cases, mostly depends on the awareness of the clinical polymorphisms of CD. The best approach to the iceberg of undiagnosed CD seems to be a systematic process of case finding focused on at-risk groups. The most frequent risk factors for undiagnosed CD are: thyroid disease, positive family history for CD, persistent gastrointestinal complaints, and iron deficiency with or without anemia [10].

Silent CD is defined by the presence of positive CD-specific antibodies, HLA, and small-bowel biopsy findings

Figure 6



The epidemiological 'iceberg model' of celiac disease.

that are compatible with CD but without sufficient symptoms and signs to warrant clinical suspicion of CD.

Latent CD is defined by the presence of compatible HLA but in the absence of enteropathy in a patient who has had a gluten-dependent enteropathy at some point in his or her life. The patient may or may not have symptoms and may or may not have CD-specific antibodies.

Potential CD is defined by the presence of CD-specific antibodies and compatible HLA but without histological abnormalities in duodenal biopsies. The patient may or may not have symptoms and signs and may or may not develop a gluten-dependent enteropathy later [1].

Complications of celiac disease

(1) Irritable bowel disease.
(2) RCD.
(3) Intestinal lymphoma.

Immunopathology of celiac disease

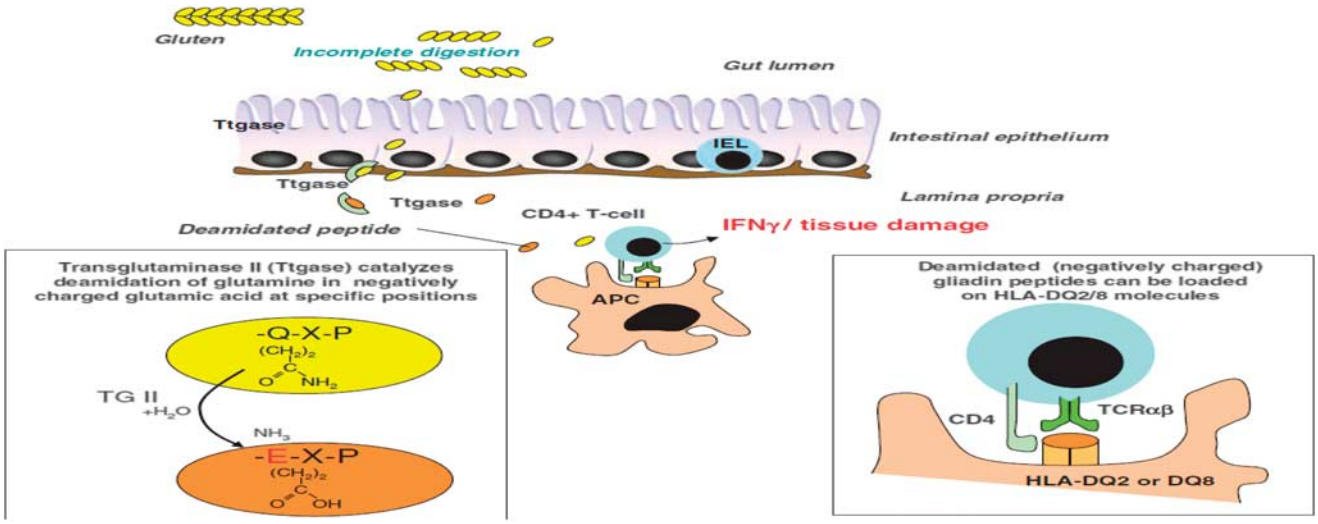
The adaptive immune response toward gluten orchestrated by HLA-DQ molecules is summarized in Fig. 7.

Who should be screened?

(1) Patients with persistent intestinal symptoms (Table 1).
(2) Patients with nonintestinal symptoms of CD (Table 1).
(3) Patients belonging to high-risk groups.

All tests should be performed in patients who consume a gluten-containing diet to avoid misdiagnosis. If gluten exposure was short or gluten had been withdrawn for a long period of time, a negative result is not reliable [1].

Figure 7



A keystone mechanism in celiac disease (CD) pathogenesis: the lamina propria adaptive CD4+ T-cell response to gluten orchestrated by HLA-DQ2/8 molecules. In active CD, gluten peptides left undigested by luminal and brush border enzymes can enter into the intestinal mucosa. Because of their primary sequence rich in Q-X-P motifs, gluten peptides are preferential substrates for tissue transglutaminase II (Ttgase). This enzyme is activated by tissue damage and can deamidate neutral glutamine residues into negatively charged glutamic acid (left box). Negative charges in gluten peptides, as well as the presence of proline residues at specific positions, facilitate their binding into the peptide pocket of HLA-DQ2 (or HLA-DQ8) expressed by antigen-presenting cells (APCs; including likely CD11c+ dendritic cells, 33 and CD123+ plasmacytoid dendritic cells 126; right box). Gluten presentation promotes the activation of a gliadin-specific TH1 CD4+ response in the intestinal lamina propria. Interferon (IFN-γ) can participate in the induction of mucosal damage [11].

Table 1 Who to test? [3]

	Offer serological testing in following conditions, signs, and symptoms	%[a]	Consider offering serological testing in following conditions, signs, and symptoms	%[a]
Gastrointestinal	Chronic or intermittent diarrhea		Microscopic colitis	
	Persistent or unexplained gastrointestinal symptoms including nausea and vomiting		Persistent or unexplained constipation	
			Persistently raised liver enzymes with unknown cause	
	Recurrent abdominal pain, cramping or distension, and sudden or unexpected weight loss		Aphthous stomatitis (mouth ulcers)	
	Irritable bowel syndrome		Dental enamel defects	
Malaise	Prolonged fatigue (tired all the time)			
	Failure to thrive or faltering growth (in children)			
Hematological	Unexplained iron deficiency anemia, or other unspecified anemia	4–15		
Immunological/autoimmune	Type 1 diabetes mellitus	8–9	Addison's disease	8
			Autoimmune thyroid disease	
			Autoimmune myocarditis	
			Autoimmune liver conditions	6
			Chronic thrombocytopenia purpura	
			Sjogren's syndrome	10
Neurological	Ataxia		Polyneuropathy	5
			Epilepsy	
			Depression or bipolar disorder	
Metabolic bone disease/ low mineral density	Vitamin D deficiency		Low-trauma fracture	
			Reduced bone mineral density	2–7
			Metabolic bone disease (such as rickets or osteomalacia)	
Gynecological			Recurrent miscarriage	
			Turner's syndrome	6
			Unexplained subfertility	
			Amenorrhea	
Dermatological	Dermatitis herpetiformis	6–7	Unexplained alopecia	3–4
Associated conditions			Sarcoidosis	5–10
			Down's syndrome	
Malignancy			Lymphoma	
			Small-bowel adenocarcinoma	

[a]Percentage of positive celiac disease in screening of these disorders [7].

Diagnosis: serology, endoscopy, and histopathology

The most important diagnostic test in CD is suspicion of the disease.

Diagnostic tools

Celiac disease-specific antibody tests

Immunoglobulin A (IgA) tissue transglutaminase (tTg) and IgA EMA serological tests show high levels of sensitivity and specificity in the diagnostic process. These are very sensitive and specific for the diagnosis of CD, and the first-choice test is IgA–tTg. If this result is equivocal, then IgA EMA testing should be performed.

Tests for the detection of IgG or IgA antibodies against native gliadin peptides (conventional gliadin antibody test) should not be used for CD nor should the tests for the detection of antibodies of any type (IgG, IgA, and secretory IgA) in fecal samples be used.

Determination of serum level of immunoglobulin A (IgA) antitissue transglutaminase (anti-tTG) is the first choice in screening for CD, displaying the highest levels of sensitivity (up to 98%) and specificity (around 96%). Anti-endomysium IgA-antibodies (EMA-IgA), in contrast, have a specificity of about 100% and a sensitivity of greater than 90% [12].

For the interpretation of antibody results, total IgA levels in serum, age of the patient, pattern of gluten consumption, and intake of immunosuppressive drugs should be taken into account. If gluten exposure was short or gluten had been withdrawn for a longer period of time (several weeks to years), a negative result is not reliable. For IgA-competent individuals, the conclusions should be drawn primarily from the results of IgA class antibody tests. For individuals with low serum IgA levels (total serum IgA < 0.2 g/l), the conclusions should be drawn from the results of the IgG class CD-specific antibody tests [1].

HLA testing for HLA-DQ2 and HLA-DQ8

Typing for HLA-DQ2 and HLA-DQ8 is a useful tool to exclude CD or to make the diagnosis unlikely in the case of a negative test result for both markers.

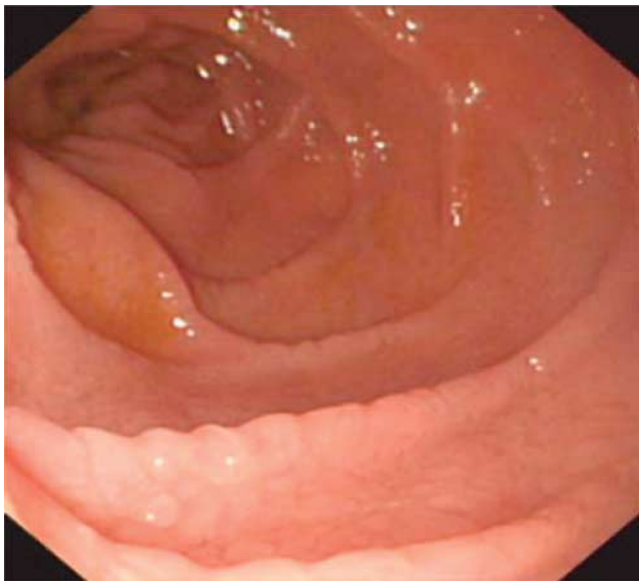
HLA testing may be offered to asymptomatic individuals with CD-associated conditions to select them for further CD-specific antibody testing [1].

Endoscopy

The histological features of small intestinal enteropathy in CD have variable severity: it may be patchy, and in a small proportion of patients with CD it appears only in the duodenal bulb. The alterations are not specific for CD. Biopsies should be taken preferably during upper endoscopy from the bulb (at least one biopsy) and from the second or third portion of the duodenum (at least four biopsies) (Fig. 8).

The pathology report should include a description of the orientation, the presence or absence of normal villi or degree of atrophy and crypt elongation, the villus : crypt ratio, the number of intraepithelial lymphocytes (IELs), and grading according to the Marsh–Oberhuber classification [3].

Figure 8



The Classical scalloping of duodenal mucosa seen in established disease at endoscopy.

Histological analysis of duodenal biopsies

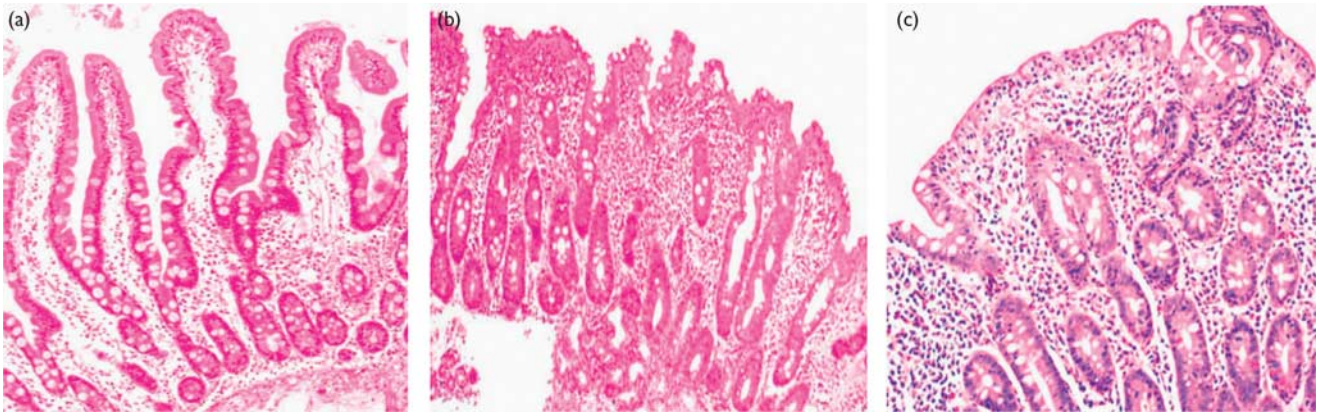
Despite advances in endoscopic in-vivo diagnosis, histological examination of the small intestine remains the diagnostic gold standard for CD.

Appropriate assessment of the biopsy requires correct orientation of three to four villi. In the absence of villi, the orientation can be assessed by the parallel crypts that reach from the muscularis mucosa to the luminal surface. Atrophy (villous blunting) is a prime feature in established celiac disease; yet, the normal villous : crypt ratio is very variable and ranges from 3 : 1 to 5 : 1, but even ratios of 2 : 1, 1.82 : 1, and 1 : 1 are cited as normal. Atrophy is preceded by crypt hyperplasia, as enterocytes have a rapid turnover, and mitoses occur frequently in the crypts toward the surface. Hyperplasia is the initial change in gluten challenge, brought about by IELs [3].

Intraepithelial lymphocytes

Simply counting the number of IELs per 20 enterocytes at the tips of five villi is a time-efficient method to assess IELs and is both sensitive and specific. Counting IELs per 50 enterocytes in two villi and summing these is also time-efficient and reliable. The distribution of IELs has been stated to be important, but although, in architecturally normal villi, increased IELs at the villus tip are seen in gluten-sensitive enteropathy, an even distribution along the entire length of the villi is even more common in celiac disease. This concluded that the decrescendo sign observed with increased IELs in the basal part of the villus, with a loss of IELs along the upper part of the villus and tip, is a pointer to something other than celiac disease. The normal reference range for IEL counts were placed originally as fewer than 40 per 100 enterocytes;

Figure 9



(a) Normal duodenal mucosa with a villous crypt ratio of 2 : 1 (Corazza Grade A, Marsh Type 0, Oberhuber Type 0) and negative serology. (b) Duodenal mucosa with partial villous atrophy, villous crypt ratio of 1 : 1, and an intraepithelial lymphocyte (IELs) count of 30 per 100 enterocytes (Corazza Grade B1). Brunner's glands are present. Serological levels of tissue transglutaminase (tTg) > 100 EliA U/ml and strongly positive for endomysial antibodies (EMA). (c) Duodenal mucosa with total villous atrophy with an IEL count of 60 per 100 enterocytes, crypt hyperplasia, eosinophil infiltrate, and numerous occurrences of mitoses in established celiac histopathological analysis (Corazza Grade B2, Marsh Type 3, Oberhuber Type 3c). Tissue transglutaminase (tTg) levels > 100 EliA U/ml and strongly positive for endomysial antibodies (EMA) [3].

IELs are mainly cytotoxic CD4 + CD8) T-cell receptor (TCR) + γδ + T cells present in a majority in CD and usually absent in other conditions. These markers are available only in fresh material and therefore cannot be recommended for routine histological analysis. IELs are cytotoxic T cells responsible for the mucosal damage observed in celiac mucosa [3](Fig. 9).

Differential diagnosis: lymphocytic duodenosis and other enteropathies

Although these features are the histological markers of CD, there is concern that other pathologies may present in the same manner – infections, including bacterial infections such as *Helicobacter pylori*, which may show villous damage with a marked active inflammatory infiltrate, and bacterial overgrowth syndrome. Other microbial agents may be obvious, for example, Whipple's [*Tropheryma whipplei* may be evident in macrophages on periodic acid Schiff (PAS) staining] opportunistic infections during immunosuppression and, rarely, *Giardia* lamblia. Other mimics of celiac histology include protein deficiency (kwashiorkor) and tropical sprue.

Lymphocytic duodenosis is defined by normal villous architecture with increased IELs (> 20–25 per 100 enterocytes). In addition, enteropathies that mimic celiac pathology, with villous atrophy and increased IELs, are also observed. However, both lymphocytic duodenosis and enteropathies will have negative serology [1,3] (Fig. 10 and Table 2).

The aims of the scoring system are as follows:

(1) To positively diagnose CD at the initial assessment and be able to accept a diagnosis made in the past using biopsy.
(2) To simplify the diagnosis of CD in patients with obvious findings.
(3) To protect against overdiagnosis when only nonspecific findings are present.

The scoring takes into account four items: symptoms, antibodies, HLA, and biopsy findings, each contributing once. To make the diagnosis, a sum of four points is required. The sum of these points may be collected from findings registered at different time points during follow-up if they can be assumed to be gluten dependent. For example, an infant having villous atrophy before the introduction of gluten and a normal biopsy at the age of 6 although consuming a gluten-containing diet will receive 0 for biopsy [1].

Treatment with a gluten-free diet [13]

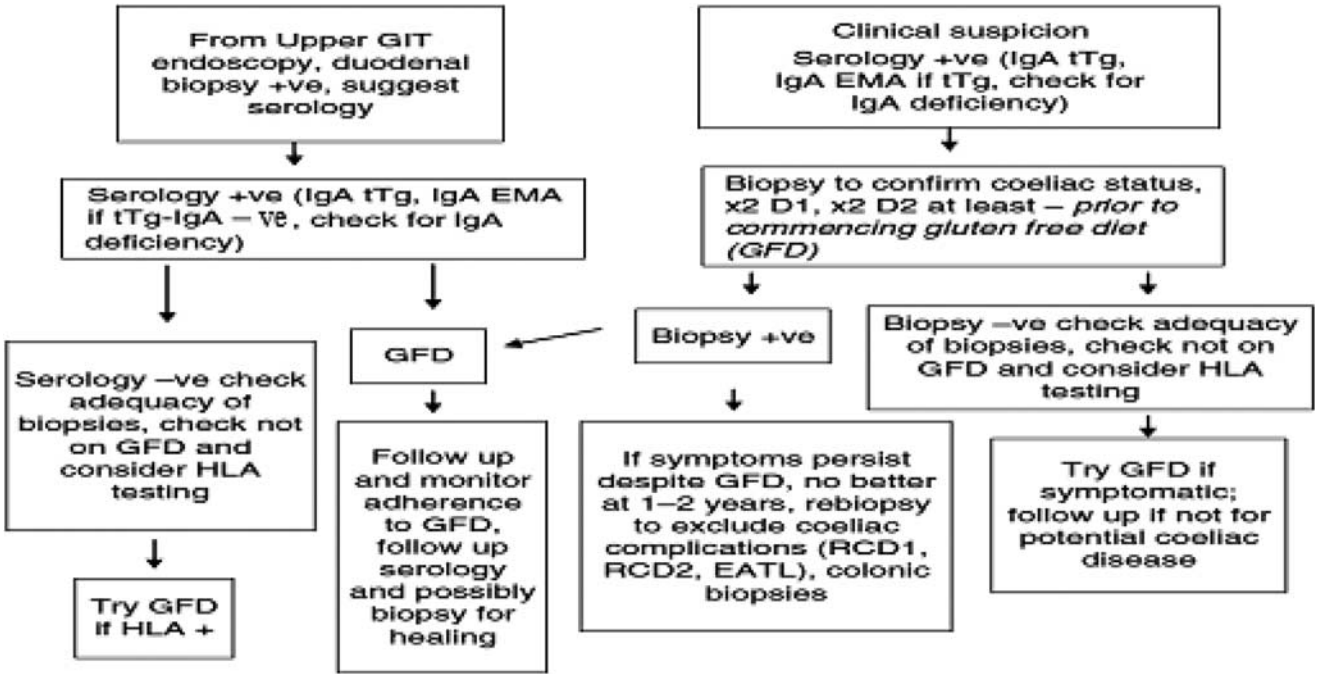
The treatment of choice in CD is a lifelong GFD. Although expected, complete recovery of intestinal mucosa is rare among adults with CD, despite adherence to GFD, a good clinical response, and disappearance of CD-specific serology. The quality of life is more severely affected in patients with classical CD compared with those with atypical/silent CD. Treatment with GFD improved the quality of life in symptomatic patients but not in silent patients.

Principle #1 – Remove obvious sources of gluten: For example, bread, cakes, cereal, cookies, pasta/noodles, pastries/pies, and rolls.

Principle #2 – Prevent gluten cross-contamination: Avoid eating out, food contaminated with gluten or mislabeled foods, and minimize contact of gluten-containing with gluten-free foods.

Principle #3 – Choose only gluten-free food items from restaurant menus: Cross-contamination can easily occur in most restaurants, for example oil used to fry gluten-containing items later used to fry gluten-free items.

Figure 10



Graphic representation of the diagnostic algorithm for patients with CD [3].
CD, celiac disease; GFD, gluten-free diet.

Table 2 A simple scoring system for the diagnosis of celiac disease [1]

	Points
Symptoms	
Malabsorption syndrome	2
Other CD-relevant symptom or having T1DM or being a first-degree family member	1
Asymptomatic	0
Serum antibodies[a]	
EMA positivity and/or high positivity (>10 ULN) for anti-TG2	2
Low positivity for anti-TG2 antibodies or isolated anti-DGP positivity	1
Serological assessment not performed	0
Serological assessment performed but negative for all celiac-specific antibodies[a]	–1
HLA	
Full HLA-DQ2 (in *cis or trans*) or HLA-DQ8 heterodimers present	1
No HLA performed or half DQ2 (only HLA-DQB1*0202) present	0
HLA neither DQ2 nor DQ8 was present	–1
Histology	
Marsh 3b or 3c (subtotal villous atrophy, flat lesion)	2
Marsh 2 or 3a (moderately decreased villous height/crypt depth ratio) or marsh 0–1 plus intestinal TG2 antibodies	1
Marsh 0–1 or no biopsy performed	0

CD, celiac disease.
[a]IgG deficiency to IgG class EMA, TG2, and DGP antibodies.

Table 3 Gluten-free diet [14]

Gluten-free grains and grain products[a]	Serving size
Breads	
Breads, English muffins and bagels made from rice, potato, bean, soy, corn, sorghum, teff, or other flours	1 slice or piece
Frozen, gluten-free waffles	
Gluten-free pizza crust made from a mix or frozen readymade	
Homemade breads, biscuits, pancakes, waffles, muffins, or quick breads made from gluten-free flours/corn tortillas	
Cereals	
Cooked cereal made from corn (hominy, grits), rice, pure buckwheat, amaranth, or quinoa	1/2 to 1 cup
Gluten-free puffed rice/gluten-free cornflakes/rice flakes, amaranth flakes, or other dry cereals	
Snacks	
Crackers or crisp breads made from rice or corn	1 oz (check label)
Popcorn/rice cakes/pretzels made from gluten-free flours/corn chips	
Other	
Brown, wild, or white rice	1/2 to 1 cup
Pasta made from rice, corn, amaranth, quinoa, or pure buckwheat	
Kasha made with pure buckwheat	
Corn/quinoa/flax/millet	

[a]Products vary by manufacturer, so be sure that they are gluten free.

Principal #4 – Eat a well-balanced diet rich in vitamins and minerals (Table 3).

Follow-up and challenge procedures

The patients should be followed up regularly for symptomatic improvement and normalization of CD-specific antibody tests. The time until the antibody titers fall below the cutoff for normal depends on the initial level, but in general this should be achieved within 12 months after starting GFD. In patients fulfilling the diagnostic criteria for CD, it is unnecessary to perform small-bowel biopsies after starting a GFD.

If there is no clinical response to a GFD in symptomatic patients, after a careful dietary assessment to exclude

lack of adherence to a GFD, further investigations are required. This gluten challenge is not considered necessary, except in situations in which there is doubt about the initial diagnosis.

A gluten challenge should be preceded by HLA typing and assessment of mucosal histology and always should be performed under medical supervision, preferably by a gastroenterologist. A gluten challenge should be discouraged before the child is 5 years old and during the pubertal growth spurt, unless the child is HLA-DQ2 negative and HLA-DQ8 negative or has been placed on a GFD without proper testing. A gluten challenge is not considered necessary, except in situations in which there is doubt about the initial diagnosis.

The daily gluten intake during a gluten challenge should contain the normal amount of gluten intake. IgA anti-TG2 antibody (IgG in low levels of serum IgA) levels should be measured during the challenge period. A patient should be considered to have relapsed (and hence the diagnosis of CD confirmed) if he or she develops CD-specific antibodies and a clinical and/or histological relapse is observed. In the absence of positive antibodies or symptoms, the challenge should be considered completed after 2 years. However, additional biopsies on a normal diet are recommended because a delayed relapse may occur later in life [1].

Refractory celiac disease

Approximately 1–2% of patients will develop RCD, which is defined as a symptomatic malabsorption and villous atrophy that persists despite scrupulous adherence to a GFD. Assessment of adherence to diet is the first step, as more than 50% of patients will have poor compliance as adults; reassessment of the original diagnosis should then be made and exclusion of other (treatable) causes of an enteropathy sought by reassessment of the biopsy. Rebiopsy to assess RCD or other disease may then be necessary.

Two types of RCD are described: type 1, in which the IELs are normal and type 2, in which IELs show an aberrant phenotype, expressing intracellular CD3 and no surface T-cell markers. Patients with RCD have an increased risk of complications, including ulcerative jejunitis and enteropathy-associated T-cell lymphoma (EATL), particularly those with RCD2. Identification of an abnormal IEL clone has important prognostic value, as this conveys a high risk of progression to high-grade T-cell lymphoma, and 50% of patients may suffer a fatal outcome within 3–10 years owing to high-grade lymphomas, intractable diarrhea, or severe infection. Low albumin levels, advancing age, and the presence of a clone are significant predictors of a poor outcome [3]. The treatment for RCD involves first making sure that all gluten is eliminated from the diet. If there is still no improvement, medications are used. Corticosteroids, such as prednisone, have been used successfully in treating some patients with RCD. Immunosuppressive drugs, such as azathioprine and cyclosporine, have also been used. Many patients with RCD are malnourished and have weakened immune systems, and corticosteroids and immunosuppressive agents can further increase their risk of serious infections. Other new treatments include biologics and stem cell transplants, but these may also have very serious side effects [15].

Immune modulation

An important outcome of these studies is to provide rationales to improve diagnostic tools and elaborate new preventive or therapeutic strategies. On the basis of previous epidemiological studies, a preventive strategy in infants with at-risk HLA is presently being tested, which comprises the introduction of small amounts of gluten in 4-month-old babies 'protected' by breastfeeding with the hope of preserving/promoting tolerance to gluten. The triggering role of repeated rotavirus infections, if confirmed, may become an additional justification for vaccination. The identification and/or generation of 'nontoxic', good bread-making wheat breeds is an attractive proposal in the fight against CD.

As a GFD is a real burden for many patients, several alternatives to a lifelong diet are considered, including the use of immunomodulatory vaccines of Ttgase inhibitors, HLA-DQ blockers, or exogenous endoprolyl peptidases. Taken with the food, these enzymes may help patients deal with occasional lapses in their diet or may protect highly sensitive individuals from inadvertent presence of gluten in food products. Nevertheless, the efficiency of this approach still needs precise assessment [11].

Conclusion

Mortality rates in patients with untreated CD increase twofold every year as they age (gastrointestinal malignancies) and most can be prevented/reversed with early diagnosis and initiation of a gluten-free diet. CD is a global health problem that requires a multidisciplinary and increasingly cooperative multinational research effort.

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Conflicts of interest

There are no conflicts of interest.

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