World Gastroenterology Organisation Global Guidelines

Celiac disease

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1 Definitions

Celiac disease (CD) is a chronic, immunologically determined form of enteropathy affecting the small intestine in genetically predisposed children and adults. It is precipitated by the ingestion of gluten-containing foods [1]. It is also referred to as celiac sprue, gluten-sensitive enteropathy, or nontropical sprue.

Gluten can be defined as the rubbery protein mass that remains when wheat dough is washed to remove starch [2]. The major protein components of gluten—gliadin and glutenin—are storage proteins in wheat. Gluten is present in wheat, rye, and barley and gives the dough the desired baking properties. It is widely used as an ingredient in food processing. Gluten exposure may create the conditions for human diseases, the best known of which is celiac disease [3].

Celiac disease is only one aspect of a range of possible manifestations of gluten reactions. Other immunologically mediated gluten-dependent disorders are wheat allergy and non–celiac disease gluten sensitivity [3].

Wheat allergy is an adverse IgE-mediated immunologic reaction to wheat proteins. Depending on the route of allergen exposure and the underlying immunologic mechanisms, wheat allergy can be classified into four categories [3]:

- Classic food allergy, affecting the skin, gastrointestinal tract, or respiratory tract; food-dependent
- Exercise-induced anaphylaxis
- Occupational asthma (baker's asthma) and rhinitis
- Contact urticaria

Non–celiac disease gluten sensitivity is a gluten-related disorder considered in cases of gluten reactions (symptoms) in which both allergic and autoimmune mechanisms have been ruled out. Patients with non–celiac disease gluten sensitivity have an apparently normal duodenal histology and a lack of celiac disease–specific autoantibodies (tissue transglutaminase and endomysial antibodies) [3].

2 Key points

Gluten and gluten-related proteins present in wheat, rye, and barley are the causative external antigens of celiac disease. CD occurs almost exclusively in patients who express the MHC class II HLA-DQ2 and HLA-DQ8 molecules. The prevalence of celiac disease in the adult population varies between roughly one in 100 and one in 300 in most parts of the world.

First-degree and (to a lesser extent) second-degree relatives have an increased risk for CD. Its clinical presentation varies widely, and the onset of the disease or symptoms may occur at any time in life. Many patients with celiac disease have few symptoms or present atypically, while a minority of patients have malabsorption (classical celiac disease). Patients with active (clinically manifest) celiac disease have an increased risk of complications, including death, in comparison with the general

population. However, this excess rate of major complications appears to return to normal after 3–5 years on a strictly gluten-free diet.

Key diagnostic findings include:

- Histopathologic changes in an intestinal biopsy, characterized by crypt hyperplasia, intraepithelial lymphocytosis, and destruction of the surface epithelial lining
- Evidence that the small-bowel enteropathy is dependent on gluten—shown by positive celiac disease–specific antibodies and/or clinical and/or histological improvement in response to a gluten-free diet

Serological tests can:

- Confirm celiac disease in patients with a demonstrated characteristic enteropathy
- Screen for individuals at risk
- Identify patients in whom biopsy may be warranted.
- Investigate patients with an increased risk of the disease

The presence of autoantibodies directed against transglutaminase-2 (TG-2) suggests that celiac disease has an autoimmune component. In adults, celiac disease is diagnosed on average more than 10 years after the first symptoms appear.

Patients with CD should not eat products containing wheat, rye, or barley. Patients usually need to follow a strictly gluten-free diet for the rest of their lives. Oats may be eaten, but they are very often contaminated by wheat, and pure oats are often not available. A small subgroup of patients with CD (fewer than 5%) may also be intolerant to pure oats.

3 Epidemiology

Introduction

Celiac disease is common throughout the world and affects around one in 100 to one in 300 of the population [4]. This prevalence is significantly higher than that recognized 20 years ago [5]. The epidemiology of CD has iceberg characteristics—there are far more undiagnosed cases (below the waterline) than diagnosed cases (above the waterline) [6] (Fig. 1).

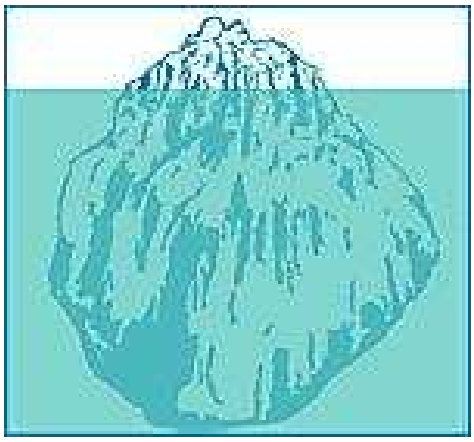
The risk of having celiac disease is much greater in first-degree relatives (up to 10%) and less so in second-degree relatives, as well in people with diabetes and other autoimmune diseases, Down's syndrome, and a number of other associated diseases [7].

A clinically severe onset may occur during pregnancy or during the puerperium in up to 17% of female patients [8]. The female-to-male ratio is 2 : 1.

Prevalence and incidence

The prevalence of celiac disease—the number of cases present in a population at a given time—is globally 1%, but large variations among countries have been shown [8]. A recent multicenter study in Europe has confirmed this, with the prevalence varying from 2% in Finland to 0.3% in Germany [9]. Recent studies have demonstrated that the number of new cases of CD found in a specific period in a given population (the incidence) is increasing (in North America and Europe) [5,10].

Fig. **1** The celiac iceberg.



Experts are agreement on the iceberg image (Fig. 1): the prevalence here refers to the total size of the iceberg, while the area below the waterline represents the total number of undiagnosed cases in a given population at a particular point in time. The area above the waterline—the tip of the iceberg—represents the number of clinically diagnosed cases [8]. The ratio of diagnosed to undiagnosed cases of CD is thought to be highly variable from country to country (1 : 2 in Finland, 1 : 20 in Argentina and the United States) [7,11,12]. This suggests that most cases of celiac disease would remain undetected without active screening.

There are several reasons for the increased prevalence of celiac disease. One of these is the recognition of wide clinical variability in the disorder, ranging from patients with classical clinical presentations to patients with clinical manifestations regarded as atypical or nonclassical. In addition, patients can also present with a monosymptomatic or oligosymptomatic clinical course [4]. Finally, celiac disease frequently occurs without any symptoms at all, even when a search is made for them. The clinical characteristics can vary during a patient's lifetime. There are no substantial differences between symptomatic patients and "screening-detected" patients in any of the countries or geographic areas in which epidemiological studies have been carried out.

A key study by Fasano et al. in 2003 [7] found that the prevalence of CD was as follows:

- At risk, first-degree relatives: one in 10
- At risk, second-degree relatives: one in 39
- At risk, symptomatic patients: one in 56
- Groups not at risk: one in 100

It is now accepted that the total size of the iceberg is more or less the same in most parts of the world where the prevalence has been explored, with the exception of sub-Saharan Africa, China, and Japan [8]. However, the level of the "waterline" may differ from continent to continent. In Europe and the United States, for example, the prevalence is similar in the healthy population and in "at-risk" groups, but the iceberg appears to be more submerged in the USA—fewer cases are diagnosed there than in Europe.

Celiac disease is associated with the prevalence of HLA-DQ2, and also to a minor degree with that of DQ8. It is also associated with an extended ancestral haplotype including class I and class II HLA (A, B, DR, DQ) [13]. This is a necessary but not a sufficient condition for the development of celiac disease. Research suggests that, although they are central to the pathogenesis of celiac disease, HLA haplotypes alone confer approximately 35–40% of the genetic predisposition [14]. Recent studies exploring the genome have attempted to find non-HLA genomic regions associated with celiac disease. To date, 40 such genomic regions harboring 64 candidate genes have been identified. Globally, these regions explain only about 5% of the genetic heritability [14]. Gluten load is a key factor; there is no celiac disease without gluten.

Ethnicity

Early epidemiological studies regarded celiac disease as a disease of individuals with Caucasian ancestry, mainly located in Europe and North America [15]. However, although there is a lack of worldwide epidemiological information, further studies in other areas of the world showed a similar prevalence [12,16,17]. Some of these studies detected celiac disease among people with Amerindian or Afro-American ancestry [18,19]. Recent reports have shown that celiac disease is a common disorder in North Africa [20], the Middle East [8], India [21], and Pakistan [22]. Very recent reports from China have shown that both the celiac disease–predisposing HLA-DQ alleles and celiac disease are not rare in the provinces of Jiangsu and Zhejiang, at least [23]. In summary, the worldwide distribution of gluten-containing foods, predisposing genotypes, and factors involved in the pathogenesis of celiac disease, are likely to be responsible for the widespread and almost universal emergence of the disorder.

4 Diagnosis of celiac disease

Introduction

The considerable increase in the numbers of patients being diagnosed with celiac disease correlates with the recognition of a remarkably wide variety of clinical manifestations of the disorder [1,24–26], the development of accurate screening tests, and also a true increase in the incidence.

In the clinical setting, a wide range of symptoms are observed:

- *Classical celiac disease:* mostly gastrointestinal symptoms (diarrhea, malnutrition, weight loss, steatorrhea and edema secondary to hypoalbuminemia).

- *Nonclassic:* in this category, patients may present with gastrointestinal symptoms (abdominal pain, gastroesophageal reflux symptoms, vomiting, constipation, irritable bowel syndrome–like symptoms, distension, bloating, borborygmus, etc.); or nongastrointestinal symptoms, also known as extraintestinal manifestations (without gastrointestinal symptoms. These patients are usually monosymptomatic or oligosymptomatic.
- *Asymptomatic celiac disease (also formerly known as silent celiac disease):* the patient reports no symptoms at all, even in response to detailed questioning, despite the presence of a characteristic intestinal lesion. However, studies on the effect of a gluten-free diet on patients who were asymptomatic at the time of diagnosis show improvement in their quality of life [27] and thus support the decision to continue with dietary restriction in the long term [28].

This diversity of symptoms represents a challenge to health professionals who are not familiar with celiac disease.

Curren diagnosis. In current practice, the diagnosis of celiac disease (Fig. 2) hinges on a diagnostic intestinal biopsy and the concomitant presence of a positive celiac disease–specific serology [6,29]. A second (post-treatment) biopsy is not necessary for most patients if they respond satisfactorily to the specific treatment and should be reserved for patients in whom the first biopsy and serologic test are inconclusive (e.g., seronegative enteropathy) or for patients who are receiving a strict gluten-free diet but fail to respond [30]. A gluten challenge, in which the offending agent is reintroduced while the patient is on a restrictive diet, should be reserved for patients who are receiving treatment but have a doubtful diagnosis [31,32].

Diagnostic tests

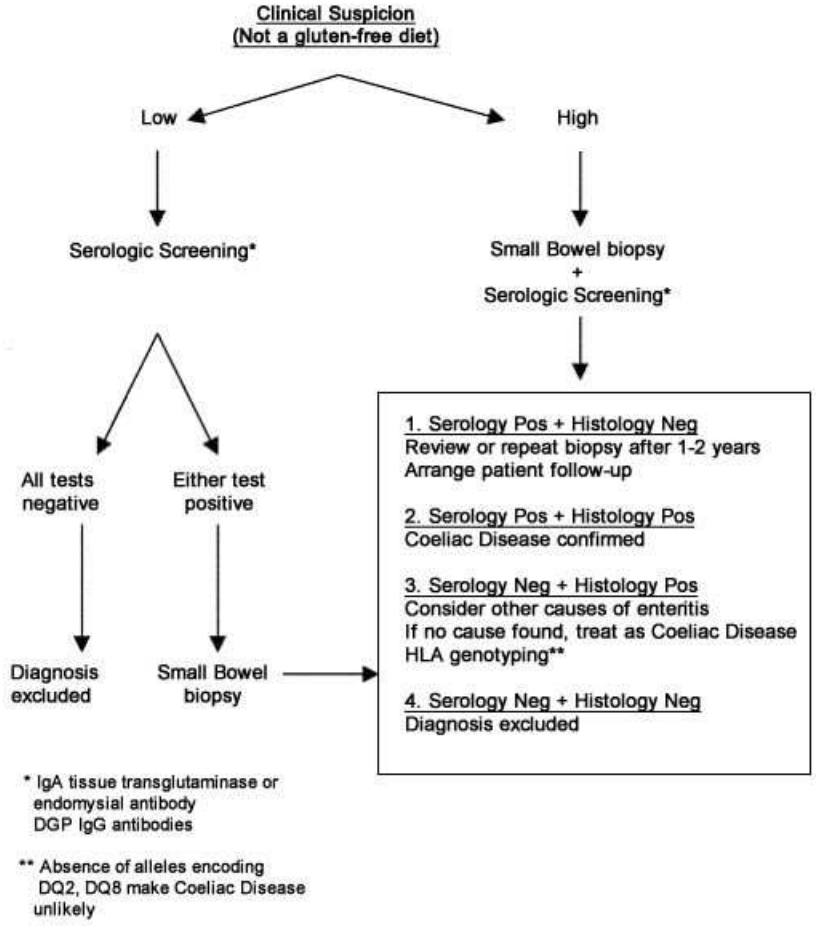
Intestinal biopsy

An intestinal biopsy together with positive serology represents the gold standard in diagnosing celiac disease. In 1992, Marsh reviewed the intensity of mucosal damage observed in treated celiac disease patients who were confronted with increased amounts of gluten. A modified Marsh classification is now widely used in diagnosing celiac disease in clinical practice [25,31].

Histological characteristics of celiac enteropathy

Histological damage is considered characteristic, but not pathognomonic, of celiac disease, as similar lesions are seen in several other disorders. Celiac disease affects the mucosa of the proximal small intestine, with damage gradually decreasing in severity towards the distal small intestine, although in severe cases the lesions can extend to more distal areas [15].

Fig. **2** Diagnosis of celiac disease.



The severity and extent of the histological damage appear to correlate with the intensity of the clinical symptoms. The proximal damage may be very mild in atypical or silent cases, with little or no abnormality histologically detectable in the intestine [15]. Abnormalities in the gastric and rectal mucosa may be observed in some cases.

The lesion in the duodenum/upper jejunum may be patchy, as a result of which it may be missed if there is insufficient mucosal sampling [25]. At least four biopsy samples must be taken—three from the second part of the duodenum distal to the papilla, and one from duodenal bulb. A negative histological diagnosis may justify a second biopsy in selected patients who have positive autoantibodies such as endomysial antibodies (EMAs).

Biopsy samples taken from the proximal duodenum above the papilla of Vater may have artifacts (e.g., stretching of villi) produced by submucosal Brunner's glands, which may be falsely interpreted as flat mucosa.

Under light microscopy, the most characteristic histological findings in patients who are taking a gluten-containing diet are [15]:

- Blunted or atrophic villi
- Crypt hyperplasia

- Mononuclear cell infiltration in the lamina propria
- Epithelial changes, including structural abnormalities in epithelial cells
- Intraepithelial lymphocyte infiltration

A series of well-designed studies by Marsh [15] made it possible to interpret the wide range of mucosal damage induced by gluten, with the celiac histological modifications being categorized as ranging from normal mucosa to completely flat villi. The modified Marsh classification [33,34] is widely used in clinical practice (Table 1).

Table **1** The modified Marsh classification of gluten-induced small-intestinal damage [33,34]

Stage 0	Preinfiltrative mucosa; up to 30% of patients with dermatitis herpetiformis (DH) or gluten ataxia have small-intestinal biopsy specimens that appear normal
Stage 1	Increase in the number of intraepithelial lymphocytes (IELs) to more than 30 per 100 enterocytes
Stage 2	Crypt hyperplasia. In addition to the increased IELs, there is an increase in crypt depth without a reduction in villus height. Gluten challenge can induce these changes, which can also be seen in 20% of untreated patients with dermatitis herpetiformis and celiac disease
Stage 3	Villous atrophy: A, partial; B, subtotal; C, total. This is the classic celiac lesion. It is found in 40% of DH patients. Despite marked mucosal changes, many individuals are asymptomatic and therefore classified as having subclinical or silent cases. This lesion is characteristic of, but not diagnostic of, celiac disease and can also be seen with severe giardiasis, infantile food sensitivities, graft-versus-host disease, chronic ischemia of the small intestine, tropical sprue, immunoglobulin deficiencies, and other immune deficiencies and allograft rejection

General considerations on histological diagnosis

A small-bowel biopsy together with positive serology is the current gold standard for the diagnosis of celiac disease. Histological findings are not pathognomonic of the disorder. However, histological examination does not always allow correct diagnosis of celiac disease. A correct histological diagnosis requires a series of factors related to number of samples, sample quality, processing and reading. A recent analysis of adherence to the current guidelines showed that 66% of more than 132,000 biopsy procedures performed in the United States obtained less than the recommended number of samples. The same study showed that there was a direct relationship between the number of samples per procedure and the number of new patients diagnosed with celiac disease.

In view of the subjective aspect of histopathological analysis, it is important to have access to pathology expertise (Table 2). The literature shows evidence of suboptimal performance in biopsy histology for the diagnosis of celiac disease in clinical practice [36].

Table **2** Key factors to be considered for ensuring reliable histological diagnosis

- Number of biopsies procured
- Quality of biopsy samples

- Handling of samples
- Patchiness of mucosal damage
- Different grades of lesion
- Subjective histologic interpretation

Role of endoscopy in patients with suspected celiac disease

During the last 20 years, upper gastrointestinal endoscopy has gained importance as a procedure allowing histological sampling of the mucosa, as it is less invasive and time-consuming than peroral biopsy. The endoscopic procedure also allows incidental observation of typical duodenoscopic features that are highly predictive of the disease [37,38]. Although endoscopy may provide an indication for intestinal biopsy in patients who are being examined for other reasons than suspected celiac disease, it may not be sufficiently sensitive to detect the disorder [39]. The characteristic findings on endoscopy include [40]:

- Scalloped folds, fissures and a mosaic pattern
- Flattened folds
- Smaller size and/or disappearance of folds with maximum insufflation

If endoscopy produces findings of this type, a duodenal biopsy becomes necessary. In contrast, a clinical suspicion of celiac disease requires a small-bowel biopsy even when there is a normal duodenoscopic appearance.

Serum antibodies for suspicion and diagnosis of celiac disease

Celiac disease–specific serological tests, which have been in use for more than 20 years now, are important for two purposes: to select patients in whom biopsies are appropriate and to confirm the diagnosis in cases in which an enteropathy has been detected [36,41]. A number of serological markers have been shown repeatedly in many studies to be highly sensitive and specific for untreated celiac disease. On the basis of the target antigens, serologic tests for celiac disease can be divided into two groups [41,42]:

- *Autoantibodies:*
  — Antiendomysial (EMA) and anti-tissue transglutaminase (tTG) antibody tests
- *Antibodies targeting the offending agent (gliadin):*
  — Conventional antigliadin antibodies (AGAs) (nowadays considered obsolete for diagnostic purposes)
  — Antibodies against synthetic deamidated gliadin peptides (DGPs)

All of these antibodies are based on immunoglobulin A (IgA) or immunoglobulin G (IgG). Specifically, IgG-based tests are useful for detecting celiac disease in selected IgA-deficient patients.

IgA EMA

IgA EMA antibodies bind to endomysium, the connective tissue located around smooth muscle, producing a characteristic staining pattern that can be visualized with indirect immunofluorescence [43]. The test result is reported simply as positive or

negative, since even low titers of serum IgA endomysial antibodies are specific for celiac disease. The test is expensive, observer-dependent, and labor-intensive, requiring expert input for correct interpretation. The target antigen has been identified as tissue transglutaminase (transglutaminase 2). IgA endomysial antibody testing is moderately sensitive (around 80%) and highly specific (with close to 100% specificity) for untreated (active) celiac disease [41].

IgA tTG

The antigen against which EMAs are directed is tTG. Anti-tTG antibodies are highly sensitive and specific for the diagnosis of CD [44]. Enzyme-linked immunosorbent assay (ELISA) tests for IgA anti-tTG antibodies are now widely available and are easier to perform, less observer-dependent, and less costly than the immunofluorescence assay used to detect IgA EMA antibodies [41,42]. The diagnostic accuracy of IgA anti-tTG assays has been further improved by the use of human tTG instead of the nonhuman tTG preparations (with poorer diagnostic accuracy) used in earlier immunoassay kits. Today, tTG antibodies are used throughout the world, but there are still substantial differences between the different commercial kits available, the cut-off points suggested by the manufacturers, and standardization of laboratory techniques [42].

A rapid method of detecting antibodies to self-tTG antigen (red blood cells) released by hemolysis and forming complexes with tTG-specific IgA class antibodies has recently been developed. The test can be conducted within a few minutes, during a single consultation [45]. The method can help with rapid decisions and its diagnostic accuracy appears to be very similar to that of the conventional tTG test [46]. However, as the rapid test can have false-positive and false-negative results, it should not replace serological and histological diagnosis.

IgA AGA and IgG AGA assays

Gliadins are the major components of the wheat storage proteins collectively termed gluten. Purified gliadin is readily available and is used as the antigen in ELISA tests to detect serum antigliadin antibodies. Serum antigliadin antibody levels are frequently raised in untreated celiac disease, and antigliadin assays have been used for some years as a diagnostic aid. Although these tests demonstrate moderate sensitivity and specificity, with the IgA tests being superior to IgG, their positive predictive value in the general population is relatively poor [41,42]. AGA tests are no longer routinely recommended for diagnosing celiac disease, because of their lower sensitivity and specificity. However, AGA tests are currently the only biomarkers that may be present in patients with non–celiac gluten sensitivity [3].

IgA and IgG DGP antibodies

An enzyme-linked immunosorbent assay (ELISA) based on the detection of a combination of synthetically developed deamidated gliadin peptides (DGPs) was introduced a few years ago, and clinical research has shown that this assay has a very high level of diagnostic accuracy in high-risk and low-risk populations—very similar

to autoantibody testing [47,48]. Studies have shown that detection of the IgG class is highly sensitive and specific for a suspicion of celiac disease in general, and also for detection of the disorder in tTG-seronegative cases and in patients with selective IgA deficiency. More recently, the two DGP tests have been combined in a single assay, including IgA and IgG tTG determinations [48]. Early studies show a high level of sensitivity but, as expected, low specificity. However, this may be improved in association with other tests.

General considerations regarding serum antibodies

The accuracy and reliability of serological tests were established in studies conducted in research settings in experimental conditions and may not reflect the level of accuracy in clinical practice [41]. Studies reporting the best performance of antibody tests were carried out with selected cases and controls and/or in populations with a high prevalence of the disease. Testing for patients in low-risk populations has shown that the sensitivity and specificity of all antibody tests are affected [48]. In low-risk populations, while the negative predictive values of different tests are very high, the positive predictive values are low. In this context, the diagnostic accuracy of serology might be improved by increasing the cut-off values to reach 100% positive predictive values, or by adding other serologic tests simultaneously or sequentially. With the last strategy, agreement of the results (with results of both tests positive or negative) would imply very high sensitivity, specificity, and positive and negative predictive values. Tissue transglutaminase antibodies appear to be of limited value in children under 2–3 years of age, and some studies have shown that DGP tests perform better and may allow better detection. It used to be the case that serological findings were usually negative in patients with mild enteropathy (Marsh grades 1, 2, or 3b) [33]. However, this was based on conventional AGAs and EMAs as the only biomarkers. With the introduction of tTG and DGP, the sensitivity for detecting patients with mild enteropathy (Marsh $\geq$ 2) has increased (Table 3).

Table **3** Sensitivity and specificity ranges for celiac disease serology tests, according to systematic reviews and studies in low-risk and high-risk populations

	Sensitivity (%)	Specificity (%)
IgA AGA *	<70–91	80–95
IgG AGA *	17–100	80–95
IgA EMA *	75–100	98–100
IgA tTG *†	75–95	91–99
IgA DGP *†	82–96	93–96
IgG DGP †	70–95	99–100
IgA + IgG DGP †	76–97	96–99
IgA and IgG DGP and tTG †	83–100	88–93

Note: There is considerable heterogeneity among the studies. Reported data were obtained from systematic reviews (*) [31,50,51] and from a population-based study including high-risk and low-risk populations (†) [48,52,53]. AGA, antigliadin antibody; DGP, deamidated gliadin peptide; EMA, endomysial antibody; IgA, immunoglobulin A; IgG, immunoglobulin G; tTG, tissue transglutaminase.

Choosing the most appropriate serologic test in different clinical scenarios

1. *To confirm gluten dependence in patients with enteropathy (diagnosis):* both IgA EMA, IgA tTG and IgG, and IgA DGP perform similarly, offering the most valuable surrogates for gluten dependence. IgG DGP appears to be very helpful in IgA-deficient patients and for some EMA-negative and tTG-negative patients.

2. *To select patients for duodenal biopsy:* to reduce the need for duodenal biopsies, and on the basis of the different accuracy of serologic tests, a series of serological algorithms are used to select patients for biopsy in different clinical scenarios:

- *From the general population (screening).* tTG and DGPs show similar performance and have a high sensitivity. These tests have low positive predictive values in low-risk populations. A serologic algorithm, with serial use of more specific screening assays (e.g., EMA) has therefore been widely used to improve the diagnostic accuracy in the general population. A recent study has suggested that the single assay detecting IgA and IgG subtypes of tTG and DGP is the most sensitive test. Simultaneous or serial use of two tests (e.g., IgA and IgG DGP/tTG plus either IgA tTG or IgA DGP or IgG DGP) provides the highest positive and negative predictive values. A combination of tests therefore improves case-finding.
- *Case finding in high-risk populations.* Any of the given tests can be used as a single assay, as they all show similar performance—as a single test, or in combination. A combination of tests does not improve case-finding.

The EMA test requires expert observers, and ELISA tests for detecting tTG antibodies should therefore be recommended in settings with low expertise.

Clinical aspects and key symptoms

1. In adults with classic celiac disease:

- Chronic diarrhea (formerly considered the most common symptom)
- Weight loss
- Anemia
- Abdominal distension
- Lassitude and malaise
- Edema

2. In children with classic celiac disease:

- Failure to thrive, weight loss, short stature
- Vomiting
- Diarrhea
- Recurrent abdominal pain
- Muscle wasting
- Irritable bowel
- Hypoproteinemia
- Irritability and unhappiness

3. In adults and children with non-classic celiac disease. The presentation may be monosymptomatic or oligosymptomatic, or with low intensity:

- Abdominal distension
- Abdominal pain
- Chronic fatigue
- Iron-deficiency anemia
- Chronic migraine
- Dermatitis herpetiformis
- Peripheral neuropathy
- Folic acid deficiency
- Reduced bone density
- Unexplained infertility
- Late menarche
- Unexplained abortion

Asymptomatic clinical course

Family studies have shown that almost 50% of newly diagnosed celiac disease patients have an asymptomatic clinical course. It is likely that half of the undiagnosed population has this asymptomatic clinical form. However, many patients with "asymptomatic" disease report a "new normality" after starting a gluten-free diet, and most of them remain on the diet.

CD should be considered in the following cases (estimated prevalences are given in brackets, if available) [6,54]:

- First-degree and second-degree relatives of celiac patients (10% and 5%, respectively)
- Unexplained iron-deficiency anemia (3–15%)
- Unexplained folic acid, iron, or vitamin B_{12} deficiency
- Reduced serum albumin
- Unexplained hypertransaminasemia (2–9%)
- Osteoporosis and osteomalacia of premature onset (2–4%)
- Recurrent abdominal pain or bloating
- Skin rashes
- Other autoimmune disorders: type 1 diabetes mellitus (2–15%), thyroid dysfunction (2–7%), Addison's disease, autoimmune hepatitis (3–6%)
- Ataxia and idiopathic neuropathy
- Down's and Turner's syndromes (6% each)
- Irritable bowel syndrome (3%)

Why is celiac disease difficult to diagnose?

- Alternative diagnoses (often irritable bowel syndrome)
- The condition may be oligosymptomatic or asymptomatic
- The condition may have latent periods
- The complexity of the clinical presentation (systemic disease)
- Clinicians are unaware of the condition and there are several "myths," such as:
  — CD is rare
  — CD only occurs in Caucasians

— CD occurs mostly in Europe and the United States
— CD only occurs in childhood
— CD only occurs in patients with chronic diarrhea
— CD can be cured after (a period of) treatment

Differential diagnosis

CD presents a very complex and protean clinical picture, and there are many diseases in which mucosal changes similar to those of CD are seen (Table 4).

Table **4** Conditions with mucosal changes similar to those in celiac disease

• Tropical sprue
• HIV enteropathy
• Combined immunodeficiency states
• Radiation damage
• Recent chemotherapy
• Graft-versus-host disease
• Chronic ischemia
• Giardiasis
• Crohn's disease
• Eosinophilic gastroenteritis
• Zollinger–Ellison syndrome
• Autoimmune enteropathy
• Enteropathy-associated T-cell lymphoma
• Refractory sprue
• Collagenous sprue

Why should we detect celiac disease?

For symptomatic celiac disease patients, the introduction of a gluten-free diet (GFD) can lead to significant improvement in symptoms, abnormal biochemical measures, and impaired quality of life. Long-term treatment also reduces the risk of malignant and nonmalignant complications. Concerns remain about the long-term consequences in patients with asymptomatic celiac disease and whether maintaining a lifelong GFD is necessary for all patients. Recent studies have suggested that patients who are detected during screening, most of whom can be regarded as asymptomatic, can improve their quality of life in the longer term with a GFD [55,56].

Patients with (long-term untreated) CD have an elevated risk for benign and malignant complications [57–59]:

- Cancer (overall risk increment 1.35)
- Malignant lymphomas
- Small-bowel neoplasia
- Oropharyngeal tumors
- Unexplained infertility (12%)

- Osteoporosis (30–40%)
- Bone fractures (increased risk for classically symptomatic CD patients) (35% increased risk) [60,61]

Cascade for diagnosing celiac disease

Table **5** Cascade for diagnosing celiac disease

Gold standard:
intestinal biopsy and celiac disease–specific antibodies

↓

Medium resources

1. Antibody assessment as a single tool, as the only diagnostic measure when trained pathologists are not available

- Anti-tTG or EMA, or both (depending on availability and experience). IgA assays are the most commonly used test with anti-tTG more sensitive but less specific than IgA EMA
- IgG and/or IgA DGP antibodies: These have a similar performance to IgA anti-tTG, and both DGPs are very useful for children under 3 years (in whom anti-tTG has poorer performance) and in IgA-deficient patients (use the IgG DGP test)

2. Intestinal biopsy: in settings in which pathology is available, perhaps remotely, but clinical laboratories cannot reach standards

- Pitfalls in histological diagnosis are common and should be considered when biopsies are assessed by nonexpert pathologists. Findings are characteristic, but not specific. The strategy can be combined with the demonstration of clinical and/or histological improvement after introduction of a gluten-free diet

↓

Low resources

- A simple anti-tTG IgA test may be considered in low-resource settings
- Anti-tTG IgA can be assessed in the physician's office by using the self antibody–based rapid test, carried out on a fingertip blood sample. The test is simple, takes only a few minutes and has shown high sensitivity and specificity
- Endoscopic identification of duodenal markers indicative of mucosal atrophy is not diagnostic of celiac disease, but strongly increases the suspicion of the disorder

Note: A diagnosis only based on "clinical assessment" and improvement after a gluten-free diet should be strongly discouraged. This has been a source of misdiagnosis and can only be helpful in a minority of patients from the overall population (those with overt celiac disease) and in areas with extremely limited resources. It could cause confusion making a nonspecific diagnosis of celiac disease in patients with non–celiac disease gluten sensitivity. The gluten-free diet can produce a nonspecific effect due to non–gluten-dependent dietary modifications or because of a "placebo effect" that may be falsely attributable to a celiac disease diagnosis.

5 Management of celiac disease

Introduction

The only treatment for celiac disease is a strictly gluten-free diet for life [15,25,31,54]. No foods or medications containing gluten from wheat, rye, and barley or their derivatives can be taken, as even small quantities of gluten may be harmful.

Oats are not toxic in over 95% of patients with celiac disease, but there is a small subgroup (< 5%) in whom oats are not safe [62–66]. In addition, there is reluctance in some countries to advise liberal use of oats, because of difficulties in guaranteeing that commercially available oats are free of contamination with other grains. Rice and corn (maize) can be part of a gluten-free diet.

Complete removal of gluten from the diet of celiac disease patients will result in symptomatic, serologic, and histological remission in most patients [15,55]. Growth and development in children returns to normal with adherence to the gluten-free diet, and many disease complications in adults are avoided [63,64].

Approximately 70% of patients report an improvement in symptoms within 2 weeks after starting the gluten-free diet [56]. With strict dietary control, antibody levels may decrease very soon after the diet has been instituted. In contrast, complete histological resolution is not always achieved, or may take years [65].

Although most patients have a rapid clinical response to a gluten-free diet, the rate of response varies. Patients who are extremely ill may require hospital admission, repletion of fluids and electrolytes, intravenous nutrition and, occasionally, steroids.

Patients with severe cases who require hospitalization are described as having a *celiac crisis* [1]. Patients should be encouraged to eat natural high-iron and high-folate foods, especially if a deficiency in these minerals is documented. Patients should consult a dietitian who is knowledgeable about gluten-free diets. Not all dietitians are familiar with the complexity of a gluten-free diet, and local or national support groups may provide most of the information required.

Recommendations after diagnosis

The following is a summary of recommendations for follow-up after diagnosis and tools for monitoring adherence to a gluten-free diet [36,51,67], during the first year after diagnosis (with follow-up appointments every 3–6 months):

- Clinical visits: check symptoms and laboratory tests. Celiac disease serology tests (best predictors: quantitative determination of DGP IgA and tTG IgA)
- Visit to an expert nutritionist: assessment of nutritional status and adherence to a gluten-free diet based on an interview, a food diary, and the frequency of consumption (coinciding with the clinical visit)

Gluten-free diet [68–74]

Table **6** Grains, starches, and flours not permitted in a gluten-free diet

- Barley
- Bran
- Bulgur
- Couscous
- Durum flour
- Einkorn*
- Emmer*
- Farro*
- Gluten, gluten flour
- Graham flour
- Kamut*
- Malt, malt extract, malt flavoring, malt syrup
- Oats, oat bran, oat syrup#
- Rye
- Semolina (durum wheat)*
- Spelt
- Triticale
- Wheat germ, wheat starch, wheat bran
- Any item with wheat in its name

Pure oats are available in some countries, and these are allowed in certain quantities. Although many studies have indicated that a moderate amount of oats can safety be eaten by patients with celiac disease, there are concerns regarding contamination of oats with wheat and barley during processing.

Table **7** Gluten-free grains, flours, and starches allowed in a gluten-free diet

- Amaranth
- Arrowroot
- Bean flours
- Buckwheat
- Corn
- Garbanzo beans
- Seeds
- Millet
- Montina flour (Indian rice grass)
- Nut flour and nut meals
- Oats (uncontaminated)
- Potato flour, potato starch
- Quinoa

- Rice, all forms (brown, white, sweet, wild, jasmine, basmati, glutinous rice, polished rice, rice bran)
- Sorghum flour
- Soy flour
- Tapioca
- Teff flour

Note: although these gluten-free grains, flours, and starches are allowed in a gluten-free diet, there are concerns over cross-contamination with wheat and barley. Starches and flours should therefore be analyzed for gluten content before free use in diets for celiac disease patients.

Other foods for a basic gluten-free diet

- Milk, cream, buttermilk, plain yogurt
- All fresh meats
- Eggs
- Legumes: lentils, chickpeas (garbanzo beans), peas, beans, nuts, seeds

Fruits: fresh, frozen, and canned fruits no added and plain juices

- Vegetables: fresh, frozen, and canned vegetables no added and plain juices
- Liquid vegetable oils

Miscellaneous

- Sweets: honey. corn syrup, sugar (brown and white)
- Snack foods: plain popcorn, nuts, and soy nuts
- Condiments: plain pickles, olives, nature herbs, pure black pepper, vinegars (apple or cider, distilled white, grape or wine, spirit)

Note: The majority of industrially produced foods contain non-allowable ingredients—attention to labeling is important, and available lists should be checked for allowable foodstuffs. It is very important to access a support group.

A gluten-free diet is low in fiber. Patients should be advised to eat a high-fiber diet supplemented with whole-grain rice, maize, potatoes, and ample vegetables. Any dietary deficiencies such as iron, folic acid, calcium and (very rarely) vitamin B_{12} should be corrected.

Monitoring [67–74]

Lifelong strict adherence to the gluten-free diet is the best way of reducing risk and protecting against nonmalignant and malignant complications, whilst improving the patient's quality of life. Compliance is difficult. It helps if patients and relatives are well informed, if expert advice is available, and if progress and outcomes are monitored. Patients should be advised of the importance of strict adherence to the diet. Despite the importance of these aspects, there are no clear guidelines for assessing the outcome or for exploring adherence to the gluten-free diet.

The wide clinical variety of celiac disease also makes it difficult to assess clinical activity using single measurements. It is possible that a multidisciplinary approach might produce more meaningful outcome information.

There is no consensus regarding the frequency of monitoring or the best measurements for assessing compliance and outcome. Helping patients adhere to the program is especially important in the first year. During this period, consultation with a professional team should take place every 3–6 months. After the first year and once the patient is stable, visits for consultation can be reduced to one per year.

Serological screening of first-degree and second-degree relatives should be considered.

Laboratory assessment

Specific serologic tests should be less frequent, depending on the degree of compliance and the length of time spent on a gluten-free diet. Recent studies suggest that periodical testing for IgA DGP and/or IgA tTG is the preferred method for monitoring compliance. Although these tests do not identify minor dietary indiscretions, a continued reduction in serum concentrations helps to assess compliance with the diet.

Nutritionist consultation

An expert dietitian should be consulted in order to:

- Assess the patient's current nutritional status
- Identify macronutrient and/or micronutrient intake and detect deficiencies and/or excesses.
  It is important that patients with celiac disease should consume adequate daily amounts of calories, thiamin, riboflavin, niacin, foliate, iron, calcium, and fiber.
- Analyze eating habits and potential factors affecting access to the diet
- Provide information and initiate the gluten-free diet
- Provide dietary education
- Monitor and evaluate dietary compliance and reinforce alimentary counseling

Patients who are unable to adhere to the diet may require support with psychological counseling.

Persistence of symptoms

Persistence of symptoms is almost always caused by continued ingestion of gluten. A common difficulty with the gluten-free diet is *cross-contamination* and the presence of unsuspected gluten in processed foods and/or medicines (although the latter is rare). Gluten may be a hidden ingredient, so it is prudent for patients to routinely check the ingredient list before purchasing any product; *available lists should be checked for allowable foodstuffs.* Serology can detect major and continued lapses in dietary adherence. Reasons for the persistence of symptoms include:

- Inadvertent gluten ingestion (this is the most common reason)

- Wrong diagnosis
- Lactose or fructose intolerance
- Other food intolerances
- Pancreatic insufficiency
- Microscopic colitis
- Bacterial overgrowth
- Collagenous colitis or collagenous sprue
- Irritable bowel syndrome
- Ulcerative jejunitis
- Enteropathy-associated T-cell lymphoma
- Refractory celiac disease

The last three can be regarded as complications of long-lasting celiac disease.

Refractory celiac disease

A diagnosis of refractory celiac disease is made when symptoms persist and when there is villous atrophy and failure to respond to a gluten-free diet [66]. This may occur at presentation (primary), or after an initial response to a gluten-free diet (secondary) [75]. Refractory celiac disease must be considered particularly in celiac disease patients who are diagnosed over the age of 50.

There are two subtypes of refractory celiac disease:

- *Type I,* with normal intraepithelial lymphocytes
- *Type II,* with clonal expansion of intraepithelial lymphocytes and an aberrant phenotype lacking CD3, CD8, and T-cell receptors

Type II disease is considered to be a form of low-grade intraepithelial lymphoma, revealed by severe malabsorption that is not responsive to a gluten-free diet. This is the most severe form and it is associated with a high mortality rate [76].

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