

AGA Institute Medical Position Statement on the Diagnosis and Management of Celiac Disease

This document presents the official recommendations of the American Gastroenterological Association (AGA) Institute on "Diagnosis and Management of Celiac Disease." It was approved by the Clinical Practice and Economics Committee on August 21, 2006, and by the AGA Institute Governing Board on September 25, 2006.

The Medical Position Statements developed under the aegis of the AGA Institute and its Clinical Practice and Economics Committee were approved by the AGA Institute Governing Board. The data used to formulate these recommendations are derived from the data available at the time of their creation and may be supplemented and updated as new information is assimilated. These recommendations are intended for adult patients, with the intent of suggesting preferred approaches to specific medical issues or problems. They are based upon the interpretation and assimilation of scientifically valid research, derived from a comprehensive review of published literature. Ideally, the intent is to provide evidence based upon prospective, randomized placebo-controlled trials; however, when this is not possible the use of experts' consensus may occur. The recommendations are intended to apply to health-care providers of all specialties. It is important to stress that these recommendations should not be construed as a standard of care. The AGA Institute stresses that the final decision regarding the care of the patient should be made by the physician with a focus on all aspects of the patient's current medical situation.

Celiac disease is a permanent intolerance to gluten, a term that is broadly used to describe the storage proteins in wheat, rye, and barley. Celiac disease is characterized by a chronic inflammatory state of the proximal small intestinal mucosa, which can impair digestion and absorption of macronutrients and micronutrients and results in increased net secretion of water and solute. Celiac disease can present with intestinal symptoms, can present with extraintestinal symptoms (including the intensely pruritic skin rash dermatitis herpetiformis), or may be detected in individuals who are asymptomatic as part of the screening of populations at increased risk for celiac disease. There is a spectrum of small intestinal mucosal injury that ranges from minimal with an increase in intraepithelial lymphocytes to total villous atrophy. However, most symptomatic patients with celiac disease have some degree of villous atrophy. The HLA class II DQ molecules DQ2 or DQ8 are necessary, although not sufficient, for the phenotypic expression of celiac disease.

Pathogenesis

Celiac disease is the result of an interplay that involves the host's genetic makeup, immunologic factors, and derivatives of gluten from wheat, rye, and barley. Gluten and other proline-rich proteins are poorly digested in the normal human small intestinal tract due to a lack of prolyl endopeptidases. This results in the generation of gluten peptides that can be as large as 10–50 amino acids in length. Gluten is also rich in the amino acid glutamine. Some of the glutamines in the peptides

generated in the small intestine can be deamidated by the enzyme tissue transglutaminase (tTG). This results in their conversion to negatively charged glutamic acid residues. Large peptides with a specific spacing of proline and glutamic acid may contain one or more sequences that are uniquely able to bind to the human HLA class II DQ2 molecules DQ2 and DQ8 on antigen-presenting cells with the ensuing activation of pathogenic populations of CD4⁺ T cells in the intestinal mucosa. The humoral immune response in celiac disease is directed both against the exogenous antigen gluten and against the autoantigen tTG. The full role of tTG remains to be fully elucidated, and it may be involved in multiple levels of the immune response. Recent advances in understanding the adaptive immune response in celiac disease herald the possibility of therapeutic targets that might provide an alternative to dietary exclusion of gluten.

Less is known about the early mechanisms and initiating steps that lead to celiac disease. How and when gluten sensitivity and development of autoimmunity first occur is unknown. It has been hypothesized that, at least in some individuals, an insult such as an enteric infection or recent surgery may result in compromised epithelial barrier function and the initiation of intestinal inflammation. Early introduction of cereals into the infant diet before 3 months may be associated with an increased risk of developing childhood celiac disease, but there is no evidence that delaying the introduction of gluten into the diet of children at high risk for celiac disease beyond the 3- to 6-month period is beneficial.

Epidemiology

The general population prevalence of celiac disease in the United States is approximately 1:100 (1%), with a reasonable range of 1:80 to 1:140 (1.25% to 0.71%). Most cases remain undiagnosed until later in life. Clinicians should have a heightened suspicion that celiac disease may be present at any age in both sexes and in a wide variety of clinical circumstances.

High-Risk Populations

Relatives. First-degree relatives of patients with celiac disease are at higher risk for biopsy-confirmed celiac disease than those in the general population, with a prevalence of ~10%. However, this may be higher if lesser histologic grades of

Abbreviations used in this paper: EMA, antiendomysial antibody; GFD, gluten-free diet; IDA, iron deficiency anemia; Ig, immunoglobulin; tTG, tissue transglutaminase; tTGA, tissue transglutaminase antibodies.

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change (ie, only an increase in intraepithelial lymphocytes) are also considered to represent celiac disease. The highest prevalence of celiac disease occurs in first-degree relatives from families with more than one index case, while the prevalence in second-degree relatives is lower (2.6%–5.5%) but still exceeds that in the general population.

Patients with iron deficiency anemia. The prevalence of celiac disease in individuals with unexplained iron deficiency anemia (IDA) is increased irrespective of whether patients have gastrointestinal symptoms. Celiac disease should be considered in any adult with unexplained IDA, including menstruating women. In asymptomatic patients with IDA evaluated by serologic testing, the prevalence of presumed celiac disease ranges from ~2% to 5%, whereas in endoscopic studies the prevalence of celiac disease in those with asymptomatic IDA is ~3% to 9%. The prevalence is still higher in symptomatic patients with IDA (~10% to 15%). Small intestinal mucosal biopsy specimens should be obtained from patients with IDA presenting for upper intestinal endoscopy.

Patients with osteoporosis and bone demineralization. The prevalence of celiac disease may be increased in patients with osteoporosis (~1.5% to 3%), especially in those with premature osteoporosis or osteomalacia.

Patients with type 1 diabetes mellitus. The prevalence of celiac disease in patients with type 1 diabetes mellitus ranges from 2% to 5% in adults and from 3% to 8% in children. Clinicians caring for patients with type 1 diabetes mellitus should be aware of this association and consider testing for celiac disease if symptoms occur. Moreover, duodenal biopsies should be considered if patients with type 1 diabetes mellitus present for upper endoscopy.

Patients with liver disease. The prevalence of celiac disease ranges from 1.5% to 9.0% in patients with elevated transaminase levels of unknown cause, from 2.9% to 6.4% in patients with autoimmune hepatitis, and up to 6.0% in those with primary biliary cirrhosis. Evidence for an increased prevalence of celiac disease is not as strong for primary sclerosing cholangitis or nonalcoholic fatty liver disease. Clinicians should be aware of these associations and have a low threshold for testing for coexistent celiac disease in patients with unexplained elevated transaminase levels, autoimmune hepatitis, and primary biliary cirrhosis. Some reports suggest that tTG antibodies (tTGA) may be falsely elevated in advanced liver disease. This was more marked when earlier-generation tests for tTGA used guinea pig rather than human transglutaminase.

Patients with genetic disorders. The prevalence of celiac disease in patients with Down syndrome ranges from 3% to 12%, with an estimate of presumptive celiac disease of ~8% by serologic testing and an estimate of confirmed celiac disease of 5.5% by biopsy. This indicates that the risk of celiac disease in patients with Down syndrome is at least 5 times that of the general population. As in the general population, celiac disease in patients with Down syndrome is restricted to those with HLA-DQ2 or -DQ8, although the prevalence of HLA-DQ2 and -DQ8 is not known to be increased in patients with Down syndrome. HLA typing can be useful to help exclude the possibility of the future development of celiac disease in patients with Down syndrome.

The prevalence of celiac disease in patients with Turner's syndrome also appears to be higher than in the general population, with a range of 2%–10% and a pooled estimate from

varying studies of 6.3%. Celiac disease in patients with Turner's syndrome is also restricted to those with DQ2 or DQ8. The prevalence of celiac disease may also be increased in patients with Williams syndrome, although limited data are available.

Patients with autoimmune thyroid disease. The prevalence of celiac disease in patients with autoimmune thyroid disease varies between 1.5% to 6.7%, with a pooled estimate from varying studies of biopsy-confirmed celiac disease of 3.0%. There is no compelling rationale for the routine screening of patients with thyroid disease for celiac disease in the absence of symptoms suggesting or compatible with celiac disease.

Patients with reproductive disorders. Celiac disease is associated with reproductive complications, including delayed menarche, fewer live births, and higher rates of miscarriage. The prevalence of celiac disease ranges between 2.1% and 4.1% in women with unexplained infertility. Intervention with a gluten-free diet (GFD) improves fertility.

Patients with other diseases. Celiac disease has also been associated with other diseases and disorders, including Addison's disease, immunoglobulin (Ig) A nephropathy, idiopathic epilepsy, occipital calcifications, and ataxia. The increased prevalence of celiac disease in several autoimmune disorders (eg, Sjögren's syndrome) appears to be based on shared HLA susceptibility genes.

Conclusion. It is the position of the American Gastroenterological Association (AGA) Institute that testing for celiac disease should be considered in symptomatic individuals who are at particularly high risk. These include those with unexplained IDA, a premature onset of osteoporosis, Down syndrome, unexplained elevations in liver transaminase levels, primary biliary cirrhosis, and autoimmune hepatitis. Situations in which testing for celiac disease should be selectively considered during the medical evaluation, especially if symptoms that could be the result of celiac disease are present, include type 1 diabetes mellitus, autoimmune thyroid disease, Sjögren's syndrome, unexplained recurrent fetal loss, unexplained delayed puberty, selective IgA deficiency, irritable bowel syndrome, Turner's syndrome, peripheral neuropathy, cerebellar ataxia, and recurrent migraine, as well as children with short stature and first- and second-degree relatives of patients with celiac disease.

Diagnosis

Diagnostic tests should be performed before the initiation of gluten restriction begins. Positive serologic test results may resolve and histologic findings may improve with the removal of gluten from the diet. The initial detection of possible celiac disease is probably best obtained by the use of a simple and accurate serologic test: the IgA tTGA.

Serologic Testing

The diagnostic approach to detecting celiac disease has undergone important changes in recent years. Serologic tests, particularly the IgA antiendomysial antibody (EMA) and the IgA tTGA, have become a relatively sensitive and specific way to initially detect celiac disease. The IgA tTGA is both sensitive and specific for celiac disease and supplants the use of gliadin antibody testing as the preferred means of serologic detection. Overall, many studies demonstrate a specificity of IgA tTGA greater than 95% and a sensitivity in the range of 90%–96%. The

EMA detected by an indirect immunofluorescence assay is more time consuming and operator dependent than the tTGA. It has a slightly lower and variable sensitivity but an excellent specificity (99.6%). IgA anti gliadin antibody by enzyme-linked immunosorbent assay predates the previously described serologic tests, but its diagnostic performance compared with IgA tTGA and IgA EMA is not attractive.

The prevalence of IgA deficiency in celiac disease is sufficiently low, such that the routine measurement of serum IgA levels along with IgA EMA or tTGA is not warranted as a first step toward diagnosis unless IgA deficiency is strongly suspected. In cases of selective IgA deficiency, either the IgG EMA and/or IgG tTGA have excellent sensitivity and specificity, although those IgG-based tests are markedly less sensitive and specific than the IgA-based tests in those with normal levels of IgA. Measurement of the serum IgA level is an appropriate next step in individuals with a negative IgA EMA or IgA tTGA in whom celiac disease is still suspected. If celiac disease is strongly suspected despite negative serologic test results, one can test for the presence of the disease-associated HLA alleles and, if present, proceed to small intestinal mucosal biopsy. Alternatively, it is reasonable to proceed directly to upper intestinal endoscopy and small bowel biopsy if the signs and symptoms that suggested celiac disease would otherwise warrant those procedures.

Conclusion. In the primary care setting, the IgA tTGA is the most efficient single serologic test for the detection of celiac disease. Evidence indicates that the additional inclusion of IgG anti gliadin antibody and IgA anti gliadin antibody is not warranted.

Intestinal Biopsy

Positive serologic test results are supportive of the diagnosis of celiac disease. Distal duodenal biopsy specimens demonstrating characteristic histologic changes in the small intestinal mucosa, which includes a spectrum of change from total to partial villous atrophy, and crypt lengthening with an increase in lamina propria and intraepithelial lymphocytes, remain, the gold standard for establishing the diagnosis of celiac disease. An increase in intraepithelial lymphocytes without other mucosal changes may represent latent celiac disease or a part of the spectrum of gluten-sensitive enteropathy but should not be considered diagnostic of celiac disease. It is important to take multiple (ideally 6) biopsy specimens and best to obtain these from the second part of the duodenum or beyond because mucosal changes can be patchy or Brunner's glands or peptic changes may hamper histopathologic examination if biopsy specimens are obtained from the more proximal duodenum. Gluten challenge and a repeat biopsy are no longer required to establish the diagnosis of celiac disease in patients whose initial small intestinal biopsy specimen has the characteristic histologic appearance and in whom an objective response to a GFD is obtained. However, a gluten challenge with a subsequent biopsy does have a role in establishing the diagnosis in select clinical settings (eg, in those with a high suspicion for celiac disease and a negative serologic test result and who started on a GFD without biopsy confirmation of the disease). It is crucial that the dietary status of the patient at the time of biopsy be taken into account. Patients should undergo biopsy promptly after obtaining a positive serologic test result and should be instructed not to avoid gluten until after biopsy specimens are

obtained. A gluten-reduced diet may reduce the severity of the lesion and impact pathologic interpretation. How long gluten must be reintroduced before biopsy specimens are taken can vary among individuals already on a GFD. A 4-week challenge with sufficient gluten to reproduce the symptoms is adequate in most. However, some patients may have very delayed responses, and it can take up to several years for relapse to occur.

Reaching a definitive diagnosis can be difficult in those with minimal histologic findings, in those with a negative serologic test result, or if the disease is patchy or an insufficient number or poorly oriented biopsy specimens were taken. There are other disease entities that can resemble celiac disease histologically. Most of these entities are either rare in the developed world, are suggested by the clinical history, or have distinguishing histologic findings on careful review of the biopsy samples.

Endoscopy provides a ready opportunity to examine the duodenal mucosa visually and to obtain a sufficient number of biopsy specimens. However, the visual examination of the small bowel mucosa is not entirely sensitive for identifying villous atrophy, although endoscopists should be aware of the visual appearance of villous atrophy. Endoscopists should not regard the absence of visual endoscopic features of celiac disease as sufficient to rule out the diagnosis.

Use of HLA-DQ2 and -DQ8 to Exclude the Diagnosis of Celiac Disease

Approximately 40% of the general population in the United States have either the HLA class II heterodimer HLA-DQ2 or HLA-DQ8, which reflects the presence of the DQ alleles DQA1*05 and DQB1*02 (DQ2) or DQA1*03 and DQB1*0302 (DQ8). However, almost all patients with celiac disease have either DQ2 (~95% of patients with celiac disease) or DQ8 (~5% of patients with celiac disease). A very small number of patients with celiac disease have been noted to have only DQA1*05 or DQB1*02, the latter usually being associated with HLA-DR7 heterozygosity or homozygosity.

Because virtually all patients with celiac disease have the celiac disease-associated alleles mentioned previously at the DQA1 and DQB1 loci, the absence of these alleles provides a negative predictive value for the disease of close to 100% (ie, if individuals lack the relevant disease-associated alleles, celiac disease is virtually excluded). HLA testing for the relevant DQ alleles can be a useful adjunct in an exclusionary sense when the diagnosis based on other tests is not clear. When using HLA testing in the context of disease susceptibility in families, one must have the resources available to provide genetic counseling.

Treatment

Treatment of celiac disease requires a strict, lifelong adherence to a GFD. This is also the case for patients with dermatitis herpetiformis. Clinicians need to ensure that patients have adequate education, motivation, and support to achieve this diet. Consultation with an experienced dietician, referral to a support group, and clinical follow-ups for compliance are recommended. Treatment of nutritional deficiency states (eg, iron, folate, vitamin B₁₂) is essential, and a determination of bone mineral density to assess for osteoporosis is recommended.

Promoting Adherence to a GFD

Changes in dietary habits are difficult to maintain, and there are many barriers to continued compliance with a GFD. Improved knowledge of celiac disease, the GFD, gluten-containing food products, and outcomes of untreated celiac disease would likely improve compliance. Membership in a local celiac society provides patients with celiac disease with improved knowledge regarding their disease, the intricacies of the GFD, and also emotional and social support opportunities.

Follow-up is necessary to confirm the diagnosis by an objective response to a GFD and to detect and manage noncompliance. Patients with celiac disease should be evaluated at regular intervals by a health care team including a physician and a dietician. These visits can be used to assess, by history, a patient's compliance with a GFD and to reinforce the importance of such compliance. Beyond this, there are no clear guidelines as to the optimal means to monitor adherence to a GFD. In general, monitoring adherence to a GFD with serologies (ie, tTGA or EMA) is sensitive for major but not for minor transient dietary indiscretions. In children, histologic improvement on a GFD appears to occur quickly, while in adults the small intestinal mucosa heals more slowly and less completely. Monitoring adherence by clinic visits and serologic testing appears to be a reasonable approach in children. In adults, this approach is also reasonable with the understanding that a negative serologic test result does not necessarily mean improvement beyond severe subtotal or total villous atrophy.

Expected Benefits of a GFD

Compliance with a GFD is likely protective against the development of non-Hodgkin's lymphoma in celiac disease and dermatitis herpetiformis. There is compelling evidence that treatment of symptomatic celiac disease results in substantial improvement in nutritional parameters. The treatment of celiac disease with a GFD can result in improvements in bone mineral density, with the greatest improvements appearing in the first years of the GFD. Treatment with a GFD for at least 12 months can result in increased body weight, body mass index, fat mass, bone mass, triceps skin fold thickness, and nutritional and biochemical status including iron absorption. Patients adhering to a strict GFD usually consume fewer calories than noncompliers but show a trend toward greater improvements in measurements of body composition. The benefits of a GFD on short-term outcomes in diabetic patients with celiac disease are

inconclusive. They suggest that nutritional parameters can improve but no convincing change in diabetic control has been demonstrated, although insulin requirements often increase.

Nonresponsive Celiac Disease

Patients with known celiac disease can continue to have or can redevelop symptoms despite being on a GFD. These symptoms may be due to incompletely healed celiac disease, an associated condition, a complication, or a second unrelated diagnosis. Persistent or intermittent symptoms due to known or inadvertent ingestion of gluten are commonly reported. If gluten ingestion is not suggested by direct review of the dietary history or positive serologic test result, then a careful search should be undertaken for other entities such as microscopic colitis, pancreatic exocrine insufficiency, bacterial overgrowth, and disaccharidase deficiency. Intestinal lymphoma, small bowel strictures, or true refractory sprue should be considered in the absence of these and in persistently febrile or very ill patients.

Refractory sprue is a rare entity with a high morbidity and mortality and is defined as continued or recurrent malabsorption and diarrhea associated with persisting moderate or severe villous atrophy despite adherence to a strict GFD. The evaluation of these patients should include a careful evaluation for coexistent T-cell lymphomas. The optimal therapy for celiac sprue is not known but frequently includes immunosuppression.

In summary, serologic testing for tTG and EMA antibodies can detect and histologic examination of endoscopically directed duodenal biopsy specimens can confirm the diagnosis of celiac disease.

Minimizing the delay in diagnosis appears to have a variety of health benefits for patients with celiac disease. Educating patients and parents, utilizing a multidisciplinary approach to patient management, and follow-up would also be expected to improve compliance and patient outcomes. A strict lifelong GFD is still the mainstay therapy, although alternative therapies are contemplated.

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