

Narrative Review: Celiac Disease: Understanding a Complex Autoimmune Disorder

Armin Alaedini, PhD, and Peter H.R. Green, MD

Celiac disease is a common autoimmune disorder that has genetic, environmental, and immunologic components. It is characterized by an immune response to ingested wheat gluten and related proteins of rye and barley that leads to inflammation, villous atrophy, and crypt hyperplasia in the intestine. The disease is closely associated with genes that code for human leukocyte antigens DQ2 and DQ8. Transglutaminase 2 appears to be an important component of the disease, both as a deamidating enzyme that can enhance the immunostimulatory effect of gluten and as a target autoantigen in the immune response. Sensitive and specific serologic tests, including those for anti-transglutaminase

antibody, are facilitating fast and noninvasive screening for celiac disease. Thus, they are contributing to a more accurate estimate of the prevalence of the disease and its association with other disorders. Celiac disease is associated with increased rates of anemia, osteoporosis, cancer, neurologic deficits, and additional autoimmune disorders. A gluten-free diet is the mainstay of safe and effective treatment of celiac disease, although its effect on some of the extraintestinal manifestations of the disease remains to be determined.

Ann Intern Med. 2005;142:289-298.

www.annals.org

For author addresses, see end of text.

Once considered a rare childhood disorder, celiac disease is now known to be a common condition that may have multiple complications. Nevertheless, the disease remains widely underrecognized. Use of new serologic markers in the diagnosis of celiac disease, in particular anti-transglutaminase antibody, has resulted in more efficient screening. Information on the pathogenic mechanism of the autoimmune response in celiac disease is emerging, although many aspects remain unclear. We discuss current concepts in the clinical presentation and diagnosis of celiac disease; the usefulness of serologic markers, including the sensitivity and specificity of available tests; the pathogenesis of the disease; and the association of celiac disease with other disorders.

Celiac disease is one of the most common immune-mediated disorders. Its presence has been documented in North and South America, Europe, north Africa, south and west Asia, and Australia (1, 2). Large studies in the United States and Europe show the prevalence of the disease to approach 1% (3–6). Celiac disease is triggered by ingestion of wheat gluten and related cereal proteins, particularly those in rye and barley. These molecules induce an inflammatory response in the small intestine, resulting in villous atrophy, crypt hyperplasia, and lymphocytic infiltration (2). Elimination of gluten and related proteins from the diet leads to clinical and histologic improvement. A strong genetic susceptibility is demonstrated by a 75% concordance rate among monozygotic twins (7). This relationship is due in part to close genetic linkage to specific class II human leukocyte antigens (HLA). Human leukocyte antigen-DQ2 is expressed in about 95% of patients with celiac disease, and HLA-DQ8 is found in most of the remainder (2). The DQ2 and DQ8 molecules confer susceptibility to celiac disease by presenting specific gluten peptides to T cells of the immune system in the intestine (8–10). Celiac disease is also strongly associated with the presence of antibodies against gluten proteins and of autoantibodies to connective tissue components, the main tar-

get of which is transglutaminase 2 (also known as *tissue transglutaminase*).

CLINICAL PRESENTATION

The clinical presentation of celiac disease varies greatly and ranges from asymptomatic to severe malnutrition. The most common manifestations of celiac disease include abdominal pain, increased frequency of bowel movements, weight loss, bone disease, anemia, and weakness. Celiac disease is sometimes divided into clinical subtypes. The terms *symptomatic* or *classic* apply to cases that meet the classic features of celiac disease, which include chronic diarrhea, abdominal distention and pain, weakness, and sometimes malabsorption. In contrast, in the now-common *atypical* form of the disease, gastrointestinal symptoms may be absent or less pronounced; instead, extraintestinal features, such as anemia, osteoporosis, short stature, infertility, and neurologic problems, are more prominent (11–41) (Table 1). Patients with *asymptomatic* or *silent* celiac disease lack classic or atypical symptoms but have villous atrophy that may be discovered during endoscopy or intestinal biopsy for other reasons, or as a result of serologic screening. Because atypical presentations are increasingly found to predominate, celiac disease is now considered to resemble a multi-system disorder rather than a mainly gastrointestinal one (42, 43).

See also:

Print

Glossary 290

Web-Only

Conversion of figures and tables into slides

Glossary

Adaptive immune response: Immune response mediated by B and T cells after exposure to a specific antigen. Involves memory, self/nonself recognition, and specificity.

Antigen: Molecule that can bind specific antibodies or lymphocytes of the immune system. An antigen is *immunogenic* if it can generate an immune response. An *autoantigen* is a self-antigen.

Endomysial tissue: Loose connective tissue around smooth-muscle fibers.

Epitope: Discrete site on an antigen, such as a particular amino acid sequence of a protein, that is recognized by an antibody or immune-cell receptor.

Epitope spreading: Diversification and spread of the immune response to autoantigens.

Glutens: Main storage proteins of wheat, which comprise many different species with similar amino acid sequence and biochemical properties. Glutens are divided into *gliadins* (the subject of most of the research on the immune response) and *glutenins*; both are implicated in celiac disease. The term "gluten" is often used generically to also describe similar proteins of rye and barley that are considered toxic in celiac disease.

Human leukocyte antigens: Cell-membrane proteins involved in presentation of specific epitopes (such as immunogenic gluten peptides) to T cells of the immune system, promoting T-cell activation.

Intermolecular help: Mechanism by which T cells specific for an antigen, such as gluten, help B cells produce antibodies against a self antigen, such as transglutaminase, provided that complexes are formed between the 2 antigens.

Innate immune response: Nonspecific immune response to antigens, including anatomic and physiologic barriers, endocytic and phagocytic activity, and inflammatory secretions.

helpful to also measure total IgA. If IgA deficiency is found, measurement of IgG class anti-transglutaminase 2 (or antiendomysial) and anti gliadin antibodies is recommended.

If results of testing for IgA anti-transglutaminase 2 or antiendomysial antibodies is positive, if IgA deficiency is found and results of testing for IgG antibody (anti-transglutaminase 2, antiendomysial, or anti gliadin antibodies) is positive, or if results of serologic testing are negative but clinical suspicion is high, intestinal biopsy should be performed (Figure 1). Because the disease may be patchy, as seen on chromoendoscopy and magnification endoscopy (46, 47), an adequate number of tissue samples (4 to 6 pieces) must be obtained (48, 49). Such sampling will further ensure that some sections will be oriented correctly to determine the degree of villous atrophy needed to make the diagnosis, whereas other pieces allow assessment of intraepithelial lymphocytosis, epithelial disarray, and degree of inflammation. Biopsy samples obtained with standard-size forceps from the descending duodenum at the level of the ampulla of Vater are sufficient for diagnosis (50). Interest is increasing in video capsule endoscopy for assessment of small-intestinal diseases, although use of this technique in patients with celiac disease has not been studied.

Characteristic histologic features of celiac disease include varying degrees of villous atrophy, with hyperplasia of the crypts and increased intraepithelial lymphocyte

DIAGNOSIS AND MANAGEMENT

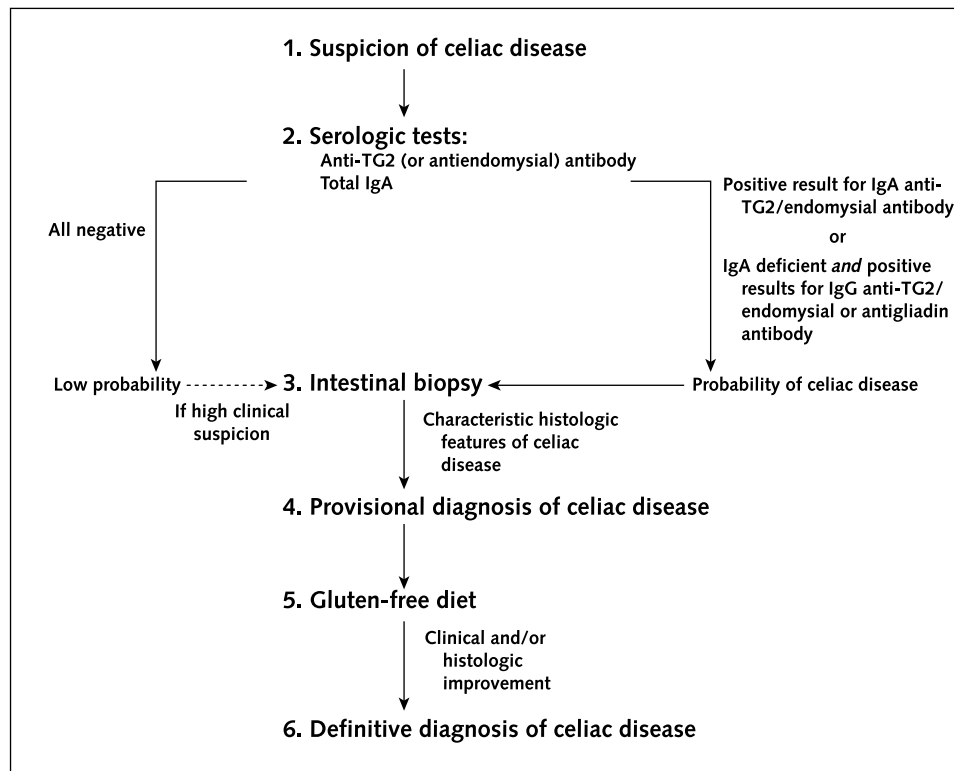
Current diagnostic criteria for celiac disease in clinical practice are based on revised guidelines proposed by the European Society for Paediatric Gastroenterology and Nutrition, which have been extrapolated to adults (44). According to these guidelines, celiac disease is present if histologic changes are found on intestinal biopsy while the patient consumes a gluten-containing diet and unequivocal clinical improvement occurs while he or she consumes a gluten-free diet.

Figure 1 shows a possible algorithm for diagnosing celiac disease that is based on the European Society for Paediatric Gastroenterology and Nutrition criteria (44) and on recommendations from the National Institutes of Health Consensus Development Conference on Celiac Disease (45). Patients usually undergo tests for serologic markers once celiac disease is suspected, either because characteristic symptoms are present or because they are in an at-risk group, such as having disorders associated with celiac disease (Table 1) or being a first-degree relative of a person with the disease. Measurement of anti-transglutaminase 2 (or antiendomysial) antibodies of the IgA isotype is more sensitive and specific for celiac disease than is the IgG isotype and is recommended for initial screening. However, IgA deficiency occurs in 1.7% to 2.6% of patients with celiac disease, which is a 10- to 16-fold increase over that in the general population (35). It is therefore

Table 1. Disorders Associated with Celiac Disease

Disorder	Reference
Endocrine	
Type 1 diabetes	11–13
Autoimmune thyroid disorders	14
Addison disease	15
Reproductive disorders	16, 17
Alopecia areata	18
Neurologic	
Cerebellar ataxia	19–21
Neuropathy	22–24
Epilepsy	25
Migraine	26
Cardiac	
Idiopathic dilated cardiomyopathy	27
Autoimmune myocarditis	28
Hepatic	
Primary biliary cirrhosis	29
Autoimmune hepatitis	30, 31
Autoimmune cholangitis	32
Other	
Anemia	33
Osteoporosis	34
Selective IgA deficiency	35
Sjögren syndrome	36
Juvenile chronic arthritis	37
Turner syndrome	38
Down syndrome	39
Dental enamel defects	40, 41

Figure 1. Proposed algorithm for evaluation of patients in whom celiac disease is suspected.



Confirmation of characteristic mucosal abnormalities by intestinal biopsy and clear clinical or histologic improvement after institution of a gluten-free diet are required for a positive diagnosis. The algorithm is based on the criteria of the European Society for Paediatric Gastroenterology and Nutrition and recommendations of the National Institutes of Health Consensus Development Conference on Celiac Disease. TG2 = transglutaminase 2.

count. The criteria proposed by Marsh are often used to grade the disease (from 0 to 4) in terms of these features (51). Most symptomatic patients have partial, subtotal, or total villous atrophy, which are Marsh type 3 lesions. Positive identification of these abnormalities leads to a presumptive diagnosis of celiac disease and institution of a gluten-free diet. Clear clinical improvement while the pa-

tient is following the diet yields a definitive diagnosis. The serum antibodies generally disappear by 6 to 12 months, although they are not necessarily reliable indicators of the mucosal response (52, 53). When patients do not present with the classic clinical symptoms of celiac disease, a second biopsy that shows histologic improvement confirms the diagnosis. Gluten challenge is not considered necessary for diag-

Table 2. Common Pitfalls in Diagnosis of Celiac Disease

Problem	Effect	Possible Solution
Poor sensitivity of anti-transglutaminase 2 antibody test	False-negative result for anti-transglutaminase 2 antibody in patients with celiac disease	Test for antiendomysial antibody; proceed with biopsy in case of high clinical suspicion
Poor specificity of anti-transglutaminase 2 antibody test	False-positive result for anti-transglutaminase 2 antibody in other diseases	Use test with human transglutaminase 2 as antigen; test for antiendomysial antibody
IgA deficiency	Negative results for IgA anti-transglutaminase 2 and antiendomysial antibodies	Measure total IgA; test for the IgG isotype of anti-transglutaminase 2 (or antiendomysial) and antigliadin antibodies
Patchiness of villous atrophy	False-negative biopsy result	Obtain adequate number of biopsy samples
Equivocal biopsy result	Inconclusive diagnosis	Review results with an expert gastrointestinal pathologist; test for HLA-DQ2 and HLA-DQ8 alleles; consider gluten challenge and repeat biopsy
No initial diagnostic biopsy	Inconclusive diagnosis	Consider gluten challenge; test for HLA-DQ2 and HLA-DQ8 alleles
Patient using immunosuppressive therapy	False-negative result on serologic testing	Consider biopsy if suspicion of celiac disease is high

nosis, except in patients for whom no initial diagnostic biopsy was done or results of biopsy are unclear or uncharacteristic of celiac disease. In such cases, biopsy is repeated after clinical relapse subsequent to gluten challenge, or after 3 to 6 months if gluten challenge does not lead to symptoms (44). Patients should be told that they may have a severe reaction to the gluten challenge.

Of note, diagnosis of celiac disease based solely on serologic markers is not yet accepted, and identification of the characteristic mucosal abnormalities on intestinal biopsy is required. However, intestinal biopsy can also yield false-negative results, either because the intestinal damage is patchy or because mucosal changes are not detectable on light microscopy (2, 54). If results of biopsy are negative but serologic tests are positive and celiac disease is strongly suspected, the results of the biopsy should be reviewed with an expert gastrointestinal pathologist before additional biopsy is considered. In addition, if histologic examination yields equivocal results, it is useful to proceed with HLA typing. Although about 30% of the general population has the HLA-DQ2 or HLA-DQ8 markers, nearly all patients with celiac disease have them (55). Therefore, a negative result for both markers has an excellent negative predictive value for the disease (56). **Table 2** summarizes issues that clinicians often face in diagnosing celiac disease and ways to manage them.

The mainstay of treatment of celiac disease is strict lifelong adherence to a gluten-free diet, in which the patient avoids food products containing wheat, rye, or barley. Even though various studies have found oat to be generally well tolerated (57), some patients appear to be sensitive to it, and the presence of oat-specific intestinal T cells has been demonstrated in persons with celiac disease (58). More important, concern about contamination from the above-mentioned cereals in commercial preparations of oat has led to reluctance in recommending it (57, 59). Commonly substituted grains in the gluten-free diet include rice, corn, quinoa, and buckwheat. Although use of a gluten-free diet safely and effectively manages celiac disease, adherence is not a trivial task in an age in which wheat flour is nearly ubiquitous in foods. Patients whose disease does not respond to dietary therapy should undergo a systematic evaluation (60, 61). The 2 most important points to clarify are whether the patient actually has the disease and whether the patient is truly consuming a gluten-free diet. Evaluation requires review of the original biopsy slides and assessment by an expert dietician. Associated conditions that must be ruled out include pancreatic insufficiency, lymphocytic colitis, bacterial overgrowth, and true refractory sprue with a clonal T-cell population (62–64).

Antibodies as Diagnostic Markers

Celiac disease is associated with circulating antibodies against gliadin and endomysial tissue. These markers have proven to be highly valuable in the diagnosis and management of celiac disease. Antiendomysial antibody has higher sensitivity and specificity than does antigliadin antibody

and is regarded as a superior serologic marker for celiac disease. Although the antireticulin antibody test was widely used formerly and is still part of some antibody panels, it has inferior sensitivity and for the most part has been replaced by the antiendomysial antibody test. In 1997, the transglutaminase 2 enzyme was established to be the autoantigen for antiendomysial antibody (65). Evidence indicates that the associated antireticulin and antijejunal antibodies are also directed at the same antigen (66, 67).

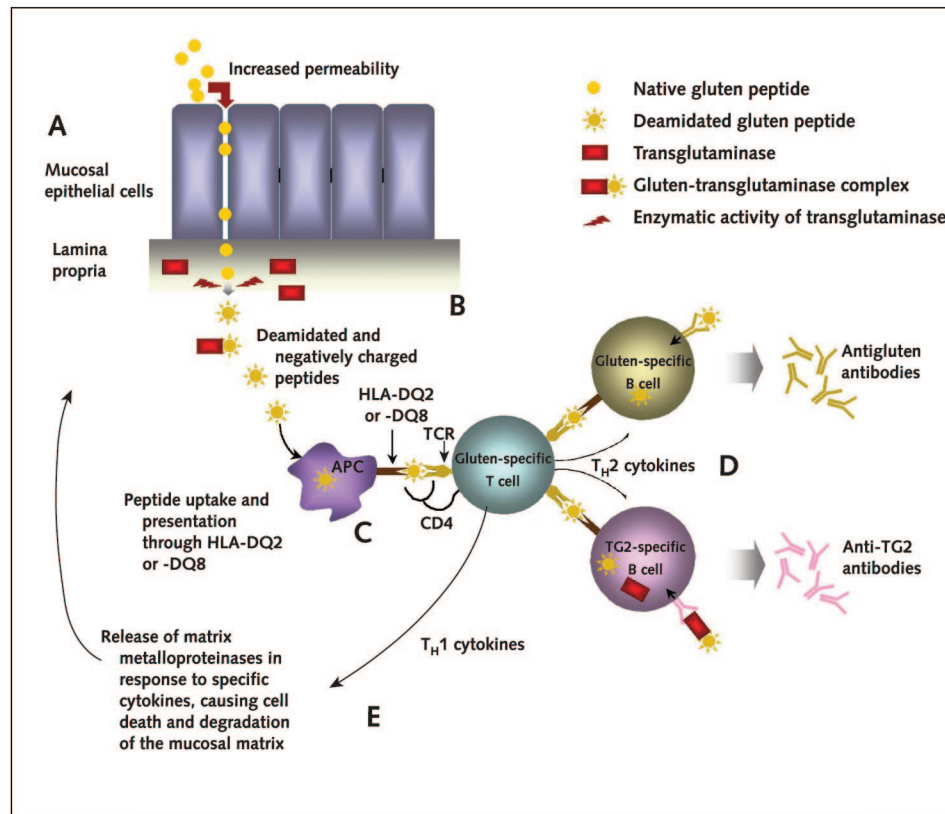
The antiendomysial antibody test is an immunofluorescence staining procedure performed by examining the binding of antibodies in patient serum to endomysial tissue from human umbilical cord or monkey esophagus. Antibodies that bind to the endomysial tissue are detected by using a microscope after they are tagged with fluorescent anti-IgA or anti-IgG antibodies. Results are qualitative or semi-quantitative.

In contrast, the anti-transglutaminase antibody test is an enzyme-linked immunosorbent assay, which is less operator-dependent and more quantitative than the immunofluorescence technique. In this method, guinea pig or human transglutaminase 2 is coated onto plastic wells, and patient serum is brought into contact with the wells. Captured serum anti-transglutaminase 2 antibodies are detected by addition of an enzyme-linked antibody against the bound IgG or IgA anti-transglutaminase 2 antibody, followed by addition of a substrate that reacts with the enzyme to produce color and measurement of the generated color by using a spectrophotometer. Use of purified or recombinant human transglutaminase 2 improves performance compared with guinea pig transglutaminase, especially with regard to specificity (68–71). Radioimmuno-precipitation assay has been reported to also perform well in the detection of anti-transglutaminase 2 antibodies (72). However, this test is less widely available than enzyme-linked immunosorbent assay.

Sensitivity and Specificity of Antibody Markers

The sensitivity and specificity of serologic markers for celiac disease vary considerably among studies because of such factors as choice of gold standard, patient selection bias, population differences, and methodologic variability. A systematic and rigorous review of the literature on the sensitivity and specificity of serologic markers celiac disease was recently published as part of an evidence report on celiac disease by the Agency for Healthcare Research and Quality (56). The investigators used strict criteria to exclude studies with methodologic flaws and specifically included only studies that used biopsy as the gold standard diagnostic test and described the biopsy criteria. Despite wide heterogeneity among the evaluated studies, results indicate that IgA anti-transglutaminase 2 antibody and IgA antiendomysial antibody have a sensitivity greater than 90% and a specificity greater than 95%. In contrast, IgA antigliadin antibody has a sensitivity of about 80% and specificity of 80% to 90%. The study also reports that IgG

Figure 2. Simplified schematic of the possible HLA-DQ2–dependent and HLA-DQ8–dependent T-cell–driven model of mucosal injury and antibody production in celiac disease.



A. Gluten peptides that are resistant to digestive enzymes reach the lamina propria after intestinal permeability increases. B. Intruding peptides are deamidated by enzymatic activity of transglutaminase 2 (*TG2*), creating epitopes with increased immunostimulatory potential. The gluten peptides may also become covalently linked to transglutaminase 2. C. Deamidated gluten peptides are presented in complex with HLA-DQ2 or HLA-DQ8 molecules of antigen-presenting cells (*APC*), such as dendritic cells, macrophages, or B cells, to $CD4^+$ T cells. D. Gluten-specific B cells receive help from gluten-specific T cells, leading to B-cell clonal expansion and release of antibodies against gluten. Transglutaminase 2–specific B cells can also receive help from gluten-specific T cells when they take up gluten–transglutaminase 2 complexes and specifically present gluten peptides to the T cells. This hypothetical mechanism of intermolecular help has been proposed to account for release of anti–transglutaminase 2 antibodies in the absence of transglutaminase 2–specific T cells. E. Expression of proinflammatory cytokines by activated T cells promotes the release of matrix metalloproteinases that cause epithelial cell damage and tissue remodeling. The resulting tissue injury leads to further release of transglutaminase 2. TCR = T-cell receptor.

class anti–transglutaminase 2 and antiendomysial antibodies have specificities greater than 95% but poor sensitivities (around 40%). The IgG anti gliadin antibody has sensitivity and specificity of around 80%. When these figures are considered, one can conclude that with the availability of tests for IgA anti–transglutaminase 2 and antiendomysial antibodies, other tests are of limited value. However, testing for IgG anti–transglutaminase 2 (or antiendomysial) and anti gliadin antibodies is useful for diagnosing celiac disease in IgA-deficient persons.

Of note, no statistically significant difference was found between the human anti–transglutaminase 2 antibody and antiendomysial antibody tests (56). Therefore, either one can be considered in the initial panel of serologic tests, but the other test may be added if results of the first test are discordant with the intestinal biopsy report. At the same time, the prevalence and serum levels of anti–transglutaminase 2 and antiendomysial antibodies correlate with the

degree of villous atrophy. Various studies indicate that the sensitivity of testing for anti–transglutaminase 2 and antiendomysial antibodies is decreased in villous atrophy of mild histologic grade (56, 73, 74). Therefore, serologic tests may not detect partial villous atrophy.

The Mucosal Lesion

The key triggers in celiac disease are specific immunogenic peptides of dietary gluten proteins in wheat and similar proteins in rye and barley. These peptides, which are resistant to digestion by gastric and pancreatic enzymes, find their way into the lamina propria, presumably after changes in intercellular tight junctions and increased intestinal permeability (such as may occur after gastrointestinal infection) (2, 75). The subsequent infiltration by $CD4^+$ T cells into the lamina propria and by mainly $CD8^+$ and $CD4^- CD8^-$ T cells into the epithelium is a hallmark of active celiac disease. The function of HLA-DQ2– and

HLA-DQ8–restricted CD4⁺ T cells of the lamina propria in the immune response has been well studied. In genetically predisposed persons who express the HLA-DQ2 and HLA-DQ8 molecules, antigen-presenting cells process the intruding glutamine- and proline-rich gluten peptides and present them to gluten-specific CD4⁺ T cells. One such peptide is a 33–amino acid sequence that is resistant to digestive enzymes and is a potent activator of specific T-cell lines from patients with celiac disease (76). Recognition of HLA-bound gluten peptides by T cells leads to their activation and release of various cytokines. Some of these cytokines (released by T_H2 cells) drive the activation and clonal expansion of B cells that produce antibodies. Other cytokines (released by T_H1 cells) promote various inflammatory mechanisms, including secretion of matrix metalloproteinases by fibroblasts and inflammatory cells that can degrade the mucosal matrix and produce the intestinal lesion (77, 78). Detailed knowledge of the actual mechanism that produces the lesion is, however, limited (Figure 2).

Considerably less information is available on the activation and mode of action of intraepithelial T cells. They are known to interact with stress proteins expressed by epithelial cells and exhibit cytolytic activity that leads to destruction of the epithelium in celiac disease (79–81). Unlike the antigen-specific activation of CD4⁺ T cells that involves the adaptive immune response, activation of intraepithelial lymphocytes appears to be additionally mediated by the innate immune system (81–84). In particular, expression of the interleukin-15 cytokine after the innate immune response to intruding gluten peptides appears to play a central role in driving various processes that lead to intraepithelial lymphocyte–mediated destruction of epithelial cells and mucosal damage (81–83).

Transglutaminase 2 may play an important role in the immune response. In normal tissue, it catalyzes the cross-linking of specific glutamine residues to primary amines, leading to formation of isopeptide bonds within or between proteins (85–87). The cross-linking activity of transglutaminase 2 is involved in various functions, such as wound healing, formation of cell envelopes in apoptosis, and stabilization of the extracellular matrix (88). Its expression is therefore increased during tissue injury and is especially elevated in intestinal biopsy samples from patients with celiac disease (89, 90). In addition to having cross-linking activity, transglutaminase 2 can deamidate glutamine residues (91, 92). Glutamine-rich gluten peptides, such as the aforementioned 33–amino acid sequence, are therefore excellent substrates for transglutaminase 2 (76). The resulting deamidated and thus negatively charged peptides have much higher affinity for the HLA-DQ2 and HLA-DQ8 molecules that are involved in presenting them to T cells (93). This transglutaminase 2–driven modification is believed to be a key step in the immune response in celiac disease (944).

It is not yet clear how the ensuing immune reaction also targets the transglutaminase 2 molecule itself. Considering that transglutaminase 2 can form covalent complexes

with gliadin, a possible hypothesis is that the anti–transglutaminase 2 immune response is generated by epitope spreading through intermolecular help, where gluten acts as a carrier protein for transglutaminase 2. Accordingly, gluten-specific T cells are proposed to help transglutaminase 2–specific B cells that produce anti–transglutaminase 2 antibodies, given that transglutaminase 2–gluten complexes are formed in vivo (93) (Figure 2). This presumed gluten-specific T-cell–driven mechanism of intermolecular help would result in an anti–transglutaminase 2 immune response in the absence of transglutaminase 2–specific T lymphocytes. The strict dependence of anti–transglutaminase 2 antibodies on gluten intake in patients seems to support this mechanism (95).

The role of autoantibodies in disease pathogenesis is controversial and varies from one disease to another. Similarly, the contribution of anti–transglutaminase 2 antibodies to the observed mucosal lesion in celiac disease is not clear. Previous findings suggest that transglutaminase 2 is required for activation of transforming growth factor- β (96), which is involved in differentiation of epithelial cells (97, 98). Therefore, local production of anti–transglutaminase 2 autoantibodies that have been shown to interfere with transglutaminase 2 bioactivity (99) might have a deleterious effect on cell differentiation, contributing to the mucosal transformation observed in celiac disease. Paradoxically, if the antibodies play an inhibitory role, they might also block the proposed role of transglutaminase 2 in driving the immune response through deamidation and cross-linking. Clearly, celiac disease is a complex disorder that results from an intricate interplay among various immunologic, genetic, and environmental factors, many aspects of which remain to be elucidated.

Dermatitis Herpetiformis

Gluten sensitivity is sometimes expressed in the form of dermatitis herpetiformis, a pruritic, chronic skin disease characterized by symmetrical papulovesicular lesions and presence of granular deposits of IgA in the dermal papillae. This condition affects about 10% to 20% of patients with celiac disease (100, 101). A gluten-free diet is the treatment of choice, although it may be combined with drug therapy, usually with dapsone, to effectively and quickly resolve the itching and rash. Inflammatory small-bowel changes identical to those in celiac disease accompany the skin lesions in dermatitis herpetiformis, even in the absence of gastrointestinal symptoms. The serologic antibody profile is also similar to that for celiac disease: Antigliadin as well as anti–transglutaminase 2 antibodies are present, although at lower levels, possibly reflecting a milder enteropathy (102). One study has shown the presence of antibodies exclusively against transglutaminase 3 (also known as *epidermal transglutaminase*), a cytosolic enzyme involved in cell envelope formation during keratinocyte differentiation (88). Of note, that study also showed that transglutaminase 3, but not transglutaminase 2, is found in complex with the IgA

precipitates on the skin (103). Although these findings remain to be confirmed, they may offer clues to understanding the difference in clinical presentation between celiac disease and dermatitis herpetiformis.

DISORDERS ASSOCIATED WITH CELIAC DISEASE

Several studies have demonstrated a close association between celiac disease and other disorders (Table 1). Celiac disease is increasingly being diagnosed in patients with predominantly extraintestinal manifestations. It is therefore important that the clinician considers the possibility of celiac disease when encountering these disorders. Symptoms that are suggestive of celiac disease should be recognized and followed by serologic testing. Some of the associated disorders, including osteoporosis, anemia, short stature, and certain reproductive problems, are generally secondary to celiac disease–related malabsorption and resolve with use of a gluten-free diet. Other major groups of associated conditions include certain endocrine disorders, cancer, and neurologic problems. In these cases, the relationship between diet and disease is more complex.

Endocrine Disorders

Celiac disease is associated with some immune-mediated endocrine disorders, most commonly type 1 diabetes and thyroid disease. Each of these conditions affects 5% to 10% of patients with celiac disease (13) (Table 1). The effect of adherence to a gluten-free diet on the metabolic control of diabetes or management of thyroid disease is limited at best (13, 104), and additional studies are clearly needed to reach firm conclusions.

Cancer

The incidence of certain types of cancer is increased among patients with celiac disease (56, 105, 106). These include non-Hodgkin lymphoma at any site, enteropathy-associated T-cell lymphoma (a rare high-grade T-cell non-Hodgkin lymphoma of the small intestine), small-intestinal adenocarcinoma, and esophageal and oropharyngeal squamous carcinoma (2). Strict adherence to a gluten-free diet seems to protect against developing some cancers (56, 105).

Neurologic Disorders

Among the most common neurologic problems associated with celiac disease are peripheral neuropathy, cerebellar ataxia, epilepsy, and migraine. In a recent study of 26 patients with celiac disease, 31% had abnormalities on neurophysiologic studies, compared with 4% of controls with reflux disease (23). Nutritional factors have been suspected in the associated neurologic deficits but are rarely found (107–109). Some reports show certain neurologic symptoms to respond to gluten-free diet, but others indicate no effect (23, 24, 109–112).

Research on the underlying mechanisms for the relationship between celiac disease and other disorders is still at a preliminary stage, even though some of the associations have been known for many years. It is now evident that the

link results in part from common genetic background, most importantly the HLA region of chromosome 6 (13, 113–115). In addition to genetic predisposition, immunologic factors probably play a role. One way that this may occur is by antibody or T-cell cross-reactivity, a mechanism that is suspected of triggering the immune response in some autoimmune diseases (116–120). Alternatively, it may result from involvement of additional autoantigens through epitope spreading. Finally, the autoimmune response specific to celiac disease may be directly responsible for some of the extraintestinal manifestations. For example, considering that transglutaminase 2 plays a critical role in release of insulin from pancreatic islet cells (121, 122), an immune response against transglutaminase 2 may be involved at some point in the associated type 1 diabetes.

CONCLUSIONS

Celiac disease is a multisystem autoimmune disorder that is currently believed to affect about 1% of the general population. Although the clinical classification and diagnosis of the disease are based on gastrointestinal manifestations, patients are increasingly identified after the extraintestinal complications of the disease are detected. The clinician should therefore not only consider celiac disease in patients who are experiencing the classic gastrointestinal symptoms but also in those who have disorders whose prevalence is high among patients with celiac disease. Use of serologic markers has revolutionized the screening and diagnosis of celiac disease. Current evidence indicates that IgA anti-transglutaminase 2 and IgA antiendomysial antibodies have good sensitivity and specificity and are superior to other markers for celiac disease. Nevertheless, confirmation of characteristic mucosal damage on intestinal biopsy remains the gold standard for diagnosis.

Substantial progress in the understanding of celiac disease has been made in the past decade. Both the adaptive and innate arms of the immune system are involved in the response to gluten and the subsequent action of lamina propria and intraepithelial lymphocytes in driving the autoimmune response that eventually leads to mucosal damage. Expression of HLA-DQ2 and HLA-DQ8 molecules is an essential genetic component of the disease, being necessary for the immune reaction against gluten. Furthermore, apart from becoming a target antigen of the immune response, transglutaminase 2 enzyme appears to be involved in modifying and enhancing the immunostimulatory effect of gluten peptides. However, many important questions remain, especially with regard to additional molecular and genetic factors that drive the immune response against gluten, the mechanism of involvement of the transglutaminase 2 autoantigen in the immune response, the underlying factors that affect the association of celiac disease with other disorders, and the role of a gluten-free diet in treating the extraintestinal complications of celiac disease. A better understanding of the underlying mechanism of pathogenesis

of celiac disease and associated disorders will help in devising new strategies for diagnosis and treatment of the disease, including prevention of its long-term complications, and serve as a model for investigation of other autoimmune disorders.

From Cornell University and Columbia University, New York, New York.

Requests for Single Reprints: Armin Alaedini, PhD, Department of Neurology and Neuroscience, LC-807, Cornell University, 1300 York Avenue, New York, NY 10021; e-mail, ara2004@med.cornell.edu.

Potential Financial Conflicts of Interest: *Consultancies and Honoraria:* P.H.R. Green (Prometheus Laboratory).

Current author addresses are available at www.annals.org.

References

- Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology*. 2001;120:636-51. [PMID: 11179241]
- Green PH, Jabri B. Coeliac disease. *Lancet*. 2003;362:383-91. [PMID: 12907013]
- Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med*. 2003;163:286-92. [PMID: 12578508]
- Tommasini A, Not T, Kiren V, Baldas V, Santon D, Trevisiol C, et al. Mass screening for coeliac disease using antihuman transglutaminase antibody assay. *Arch Dis Child*. 2004;89:512-5. [PMID: 15153392]
- Bingley PJ, Williams AJ, Norcross AJ, Unsworth DJ, Lock RJ, Ness AR, et al. Undiagnosed coeliac disease at age seven: population based prospective birth cohort study. *BMJ*. 2004;328:322-3. [PMID: 14764493]
- Maki M, Mustalahti K, Kokkonen J, Kulmala P, Haapalahti M, Karttunen T, et al. Prevalence of Celiac disease among children in Finland. *N Engl J Med*. 2003;348:2517-24. [PMID: 12815137]
- Greco L, Romino R, Coto I, Di Cosmo N, Percopo S, Maglio M, et al. The first large population based twin study of coeliac disease. *Gut*. 2002;50:624-8. [PMID: 11950806]
- Howell MD, Austin RK, Kelleher D, Nepom GT, Kagnoff MF. An HLA-D region restriction fragment length polymorphism associated with celiac disease. *J Exp Med*. 1986;164:333-8. [PMID: 3014038]
- Sollid LM, Markussen G, Ek J, Gjerde H, Vartdal F, Thorsby E. Evidence for a primary association of celiac disease to a particular HLA-DQ alpha/beta heterodimer. *J Exp Med*. 1989;169:345-50. [PMID: 2909659]
- Molberg O, Solheim Flaete N, Jensen T, Lundin KE, Arentz-Hansen H, Anderson OD, et al. Intestinal T-cell responses to high-molecular-weight glutenins in celiac disease. *Gastroenterology*. 2003;125:337-44. [PMID: 12891534]
- Bao F, Yu L, Babu S, Wang T, Hoffenberg EJ, Rewers M, et al. One third of HLA DQ2 homozygous patients with type 1 diabetes express celiac disease-associated transglutaminase autoantibodies. *J Autoimmun*. 1999;13:143-8. [PMID: 10441179]
- Lampasona V, Bonfanti R, Bazzigaluppi E, Venerando A, Chiumello G, Bosi E, et al. Antibodies to tissue transglutaminase C in type I diabetes. *Diabetologia*. 1999;42:1195-8. [PMID: 10525659]
- Collin P, Kaukinen K, Valimaki M, Salmi J. Endocrinological disorders and celiac disease. *Endocr Rev*. 2002;23:464-83. [PMID: 12202461]
- Mainardi E, Montanelli A, Dotti M, Nano R, Moscato G. Thyroid-related autoantibodies and celiac disease: a role for a gluten-free diet? *J Clin Gastroenterol*. 2002;35:245-8. [PMID: 12192201]
- O'Leary C, Walsh CH, Wieneke P, O'Regan P, Buckley B, O'Halloran DJ, et al. Coeliac disease and autoimmune Addison's disease: a clinical pitfall. *QJM*. 2002;95:79-82. [PMID: 11861954]
- Rostami K, Steegers EA, Wong WY, Braat DD, Steegers-Theunissen RP. Coeliac disease and reproductive disorders: a neglected association. *Eur J Obstet Gynecol Reprod Biol*. 2001;96:146-9. [PMID: 11384797]
- Meloni GF, Dessole S, Vargiu N, Tomasi PA, Musumeci S. The prevalence of coeliac disease in infertility. *Hum Reprod*. 1999;14:2759-61. [PMID: 10548618]
- Corazza GR, Andreani ML, Ventura N, Bernardi M, Tosti A, Gasbarrini G. Celiac disease and alopecia areata: report of a new association. *Gastroenterology*. 1995;109:1333-7. [PMID: 7557104]
- Hadjivassiliou M, Grunewald RA, Davies-Jones GA. Idiopathic cerebellar ataxia associated with celiac disease: lack of distinctive neurological features [Letter]. *J Neurol Neurosurg Psychiatry*. 1999;67:257. [PMID: 10475765]
- Bushara KO, Goebel SU, Shill H, Goldfarb LG, Hallett M. Gluten sensitivity in sporadic and hereditary cerebellar ataxia. *Ann Neurol*. 2001;49:540-3. [PMID: 11310636]
- Shill HA, Alaedini A, Latov N, Hallett M. Anti-ganglioside antibodies in idiopathic and hereditary cerebellar degeneration. *Neurology*. 2003;60:1672-3. [PMID: 12771262]
- Alaedini A, Green PH, Sander HW, Hays AP, Gamboa ET, Fasano A, et al. Ganglioside reactive antibodies in the neuropathy associated with celiac disease. *J Neuroimmunol*. 2002;127:145-8. [PMID: 12044986]
- Luostarinen L, Himanen SL, Luostarinen M, Collin P, Pirttila T. Neuromuscular and sensory disturbances in patients with well treated coeliac disease. *J Neurol Neurosurg Psychiatry*. 2003;74:490-4. [PMID: 12640070]
- Chin RL, Sander HW, Brannagan TH, Green PH, Hays AP, Alaedini A, et al. Celiac neuropathy. *Neurology*. 2003;60:1581-5. [PMID: 12771245]
- Luostarinen L, Dastidar P, Collin P, Peraaho M, Maki M, Erila T, et al. Association between coeliac disease, epilepsy and brain atrophy. *Eur Neurol*. 2001;46:187-91. [PMID: 11721124]
- Gabrielli M, Cremonini F, Fiore G, Addolorato G, Padalino C, Candelli M, et al. Association between migraine and Celiac disease: results from a preliminary case-control and therapeutic study. *Am J Gastroenterol*. 2003;98:625-9. [PMID: 12650798]
- Curione M, Barbato M, De Biase L, Viola F, Lo Russo L, Cardi E. Prevalence of coeliac disease in idiopathic dilated cardiomyopathy [Letter]. *Lancet*. 1999;354:222-3. [PMID: 10421311]
- Frustaci A, Cuoco L, Chimenti C, Pieroni M, Fioravanti G, Gentiloni N, et al. Celiac disease associated with autoimmune myocarditis. *Circulation*. 2002;105:2611-8. [PMID: 12045166]
- Gillett HR, Cauch-Dudek K, Jenny E, Heathcote EJ, Freeman HJ. Prevalence of IgA antibodies to endomysium and tissue transglutaminase in primary biliary cirrhosis. *Can J Gastroenterol*. 2000;14:672-5. [PMID: 11185531]
- Sjoberg K, Lindgren S, Eriksson S. Frequent occurrence of non-specific gliadin antibodies in chronic liver disease. Endomysial but not gliadin antibodies predict coeliac disease in patients with chronic liver disease. *Scand J Gastroenterol*. 1997;32:1162-7. [PMID: 9399399]
- Volta U, De Franceschi L, Molinaro N, Cassani F, Muratori L, Lenzi M, et al. Frequency and significance of anti-gliadin and anti-endomysial antibodies in autoimmune hepatitis. *Dig Dis Sci*. 1998;43:2190-5. [PMID: 9790453]
- Davison S. Coeliac disease and liver dysfunction. *Arch Dis Child*. 2002;87:293-6. [PMID: 12243999]
- Ransford RA, Hayes M, Palmer M, Hall MJ. A controlled, prospective screening study of celiac disease presenting as iron deficiency anemia. *J Clin Gastroenterol*. 2002;35:228-33. [PMID: 12192198]
- Kempainen T, Kroger H, Janatuinen E, Arnala I, Kosma VM, Pikkarainen P, et al. Osteoporosis in adult patients with celiac disease. *Bone*. 1999;24:249-55. [PMID: 10071918]
- Cataldo F, Marino V, Ventura A, Bottaro G, Corazza GR. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study. Italian Society of Paediatric Gastroenterology and Hepatology (SIGEP) and "Club del Tenue" Working Groups on Coeliac Disease. *Gut*. 1998;42:362-5. [PMID: 9577342]
- Iltanen S, Collin P, Korpela M, Holm K, Partanen J, Polvi A, et al. Celiac disease and markers of celiac disease latency in patients with primary Sjogren's syndrome. *Am J Gastroenterol*. 1999;94:1042-6. [PMID: 10201480]
- Lepore L, Martellosi S, Pennesi M, Falcini F, Ermini ML, Ferrari R, et al. Prevalence of celiac disease in patients with juvenile chronic arthritis. *J Pediatr*. 1996;129:311-3. [PMID: 8765635]

38. Bonamico M, Pasquino AM, Mariani P, Danesi HM, Culasso F, Mazzanti L, et al. Prevalence and clinical picture of celiac disease in Turner syndrome. *J Clin Endocrinol Metab.* 2002;87:5495-8. [PMID: 12466343]
39. Agardh D, Nilsson A, Carlsson A, Kockum I, Lernmark A, Ivarsson SA. Tissue transglutaminase autoantibodies and human leucocyte antigen in Down's syndrome patients with coeliac disease. *Acta Paediatr.* 2002;91:34-8. [PMID: 11883815]
40. Ventura A, Martellosi S. Dental enamel defects and coeliac disease [Letter]. *Arch Dis Child.* 1997;77:91. [PMID: 9279165]
41. Aine L, Maki M, Collin P, Keyrilainen O. Dental enamel defects in celiac disease. *J Oral Pathol Med.* 1990;19:241-5. [PMID: 2401959]
42. Lo W, Sano K, Lebwohl B, Diamond B, Green PH. Changing presentation of adult celiac disease. *Dig Dis Sci.* 2003;48:395-8. [PMID: 12643621]
43. Murray JA, Van Dyke C, Plevak MF, Dierkhising RA, Zinsmeister AR, Melton LJ 3rd. Trends in the identification and clinical features of celiac disease in a North American community, 1950-2001. *Clin Gastroenterol Hepatol.* 2003;1:19-27. [PMID: 15017513]
44. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child.* 1990;65:909-11. [PMID: 2205160]
45. NIH Consensus Development Conference Statement: Celiac Disease. 2004. Accessed at <http://consensus.nih.gov/cons/118/118celiacPDF.pdf> on 30 September 2004.
46. Hurlstone DP, Sanders DS. High-magnification immersion chromoscopic duodenoscopy permits visualization of patchy atrophy in celiac disease: an opportunity to target biopsies of abnormal mucosa [Letter]. *Gastrointest Endosc.* 2003;58:815-6. [PMID: 14997906]
47. Siegel LM, Stevens PD, Lightdale CJ, Green PH, Goodman S, Garcia-Carrasquillo RJ, et al. Combined magnification endoscopy with chromoendoscopy in the evaluation of patients with suspected malabsorption. *Gastrointest Endosc.* 1997;46:226-30. [PMID: 9378209]
48. Scott BB, Losowsky MS. Patchiness and duodenal-jejunal variation of the mucosal abnormality in coeliac disease and dermatitis herpetiformis. *Gut.* 1976;17:984-92. [PMID: 1017719]
49. Bonamico M, Mariani P, Thanasi E, Ferri M, Nenna R, Tiberti C, et al. Patchy villous atrophy of the duodenum in childhood celiac disease. *J Pediatr Gastroenterol Nutr.* 2004;38:204-7. [PMID: 14734885]
50. Dandalides SM, Carey WD, Petras R, Achkar E. Endoscopic small bowel mucosal biopsy: a controlled trial evaluating forceps size and biopsy location in the diagnosis of normal and abnormal mucosal architecture. *Gastrointest Endosc.* 1989;35:197-200. [PMID: 2668099]
51. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology.* 1992;102:330-54. [PMID: 1727768]
52. Sategna-Guidetti C, Grosso S, Bruno M, Grosso SB. Reliability of immunologic markers of celiac sprue in the assessment of mucosal recovery after gluten withdrawal. *J Clin Gastroenterol.* 1996;23:101-4. [PMID: 8877634]
53. Tursi A, Brandimarte G, Giorgetti GM. Lack of usefulness of anti-transglutaminase antibodies in assessing histologic recovery after gluten-free diet in celiac disease. *J Clin Gastroenterol.* 2003;37:387-91. [PMID: 14564185]
54. Sbarbati A, Valletta E, Bertini M, Cipolli M, Morroni M, Pinelli L, et al. Gluten sensitivity and 'normal' histology: is the intestinal mucosa really normal? *Dig Liver Dis.* 2003;35:768-73. [PMID: 14674666]
55. Dewar D, Pereira SP, Ciclitira PJ. The pathogenesis of coeliac disease. *Int J Biochem Cell Biol.* 2004;36:17-24. [PMID: 14592529]
56. Rostom A, Dube C, Cranney A, Saloojee N, Sy R, Garrity C, et al. Celiac disease. Evidence Report/Technology Assessment No. 104. Rockville, MD: Agency for Healthcare Research and Quality; 2004. AHRQ publication no. 04-E029-2.
57. Thompson T. Oats and the gluten-free diet. *J Am Diet Assoc.* 2003;103:376-9. [PMID: 12616264]
58. Arentz-Hansen H, Fleckenstein B, Molberg O, et al. The molecular basis for oat intolerance in patients with celiac disease. *Plos Med.* 2004;1:e1. [PMID: 15526039]
59. Thompson T. Gluten contamination of commercial oat products in the United States [Letter]. *N Engl J Med.* 2004;351:2021-2. [PMID: 15525734]
60. Abdulkarim AS, Burgart LJ, See J, Murray JA. Etiology of nonresponsive celiac disease: results of a systematic approach. *Am J Gastroenterol.* 2002;97:2016-21.
61. Culliford AN, Green PH. Refractory sprue. *Curr Gastroenterol Rep.* 2003;5:373-8. [PMID: 12959717]
62. Fine KD, Meyer RL, Lee EL. The prevalence and causes of chronic diarrhea in patients with celiac sprue treated with a gluten-free diet. *Gastroenterology.* 1997;112:1830-8. [PMID: 9178673]
63. Cellier C, Delabesse E, Helmer C, Patey N, Matuchansky C, Jabri B, et al. Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. French Coeliac Disease Study Group. *Lancet.* 2000;356:203-8. [PMID: 10963198]
64. Gomez JC, Moran CE, Maurino EC, Bai JC. Exocrine pancreatic insufficiency in celiac disease [Letter]. *Gastroenterology.* 1998;114:621-3. [PMID: 9496962]
65. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat Med.* 1997;3:797-801. [PMID: 9212111]
66. Korponay-Szabo, Laurila K, Szondy Z, Halttunen T, Szalai Z, Dahlbom I, et al. Missing endomysial and reticulin binding of coeliac antibodies in transglutaminase 2 knockout tissues. *Gut.* 2003;52:199-204. [PMID: 12524400]
67. Korponay-Szabo, Sulkanen S, Halttunen T, Maurano F, Rossi M, Mazzarella G, et al. Tissue transglutaminase is the target in both rodent and primate tissues for celiac disease-specific autoantibodies. *J Pediatr Gastroenterol Nutr.* 2000;31:520-7. [PMID: 11144437]
68. Wong RC, Wilson RJ, Steele RH, Radford-Smith G, Adelstein S. A comparison of 13 guinea pig and human anti-tissue transglutaminase antibody ELISA kits. *J Clin Pathol.* 2002;55:488-94. [PMID: 12101191]
69. Sardy M, Odenthal U, Karpati S, Paulsson M, Smyth N. Recombinant human tissue transglutaminase ELISA for the diagnosis of gluten-sensitive enteropathy. *Clin Chem.* 1999;45:2142-9. [PMID: 10585346]
70. Clemente MG, Musu MP, Frau F, Lucia C, De Virgiliis S. Antitissue transglutaminase antibodies outside celiac disease. *J Pediatr Gastroenterol Nutr.* 2002;34:31-4. [PMID: 11753161]
71. Carroccio A, Giannitrapani L, Soresi M, Not T, Iacono G, Di Rosa C, et al. Guinea pig transglutaminase immunolinked assay does not predict coeliac disease in patients with chronic liver disease. *Gut.* 2001;49:506-11. [PMID: 11559647]
72. Bonamico M, Tiberti C, Picarelli A, Mariani P, Rossi D, Cipolletta E, et al. Radioimmunoassay to detect antitransglutaminase autoantibodies is the most sensitive and specific screening method for celiac disease. *Am J Gastroenterol.* 2001;96:1536-40. [PMID: 11374695]
73. Tursi A, Brandimarte G, Giorgetti GM. Prevalence of antitissue transglutaminase antibodies in different degrees of intestinal damage in celiac disease. *J Clin Gastroenterol.* 2003;36:219-21. [PMID: 12590232]
74. Rostami K, Kerckhaert J, Tiemessen R, von Blomberg BM, Meijer JW, Mulder CJ. Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice. *Am J Gastroenterol.* 1999;94:888-94. [PMID: 10201452]
75. Fasano A, Not T, Wang W, Uzzau S, Berti I, Tommasini A, et al. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in celiac disease [Letter]. *Lancet.* 2000;355:1518-9. [PMID: 10801176]
76. Shan L, Molberg O, Parrot I, Hausch F, Filiz F, Gray GM, et al. Structural basis for gluten intolerance in celiac sprue. *Science.* 2002;297:2275-9. [PMID: 12351792]
77. Pender SL, Tickle SP, Docherty AJ, Howie D, Wathen NC, MacDonald TT. A major role for matrix metalloproteinases in T cell injury in the gut. *J Immunol.* 1997;158:1582-90. [PMID: 9029093]
78. Daum S, Bauer U, Foss HD, Schuppan D, Stein H, Riecken EO, et al. Increased expression of mRNA for matrix metalloproteinases-1 and -3 and tissue inhibitor of metalloproteinases-1 in intestinal biopsy specimens from patients with coeliac disease. *Gut.* 1999;44:17-25. [PMID: 9862821]
79. Lundqvist C, Melgar S, Yeung MM, Hammarstrom S, Hammarstrom ML. Intraepithelial lymphocytes in human gut have lytic potential and a cytokine profile that suggest T helper 1 and cytotoxic functions. *J Immunol.* 1996;157:1926-34. [PMID: 8757311]
80. Oberhuber G, Vogelsang H, Stolte M, Muthenthaler S, Kummer AJ, Radaszkiewicz T. Evidence that intestinal intraepithelial lymphocytes are activated cytotoxic T cells in celiac disease but not in giardiasis. *Am J Pathol.* 1996;148:

- 1351-7. [PMID: 8623906]
81. Hue S, Mention JJ, Monteiro RC, Zhang S, Cellier C, Schmitz J, et al. A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease. *Immunity*. 2004;21:367-77. [PMID: 15357948]
82. Maiuri L, Ciacci C, Ricciardelli I, Vacca L, Raia V, Auricchio S, et al. Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease. *Lancet*. 2003;362:30-7. [PMID: 12853196]
83. Meresse B, Chen Z, Ciszewski C, Tretiakova M, Bhagat G, Krausz TN, et al. Coordinated induction by IL15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease. *Immunity*. 2004;21:357-66. [PMID: 15357947]
84. Gianfrani C, Troncone R, Mugione P, Cosentini E, De Pascale M, Faruolo C, et al. Celiac disease association with CD8 + T cell responses: identification of a novel gliadin-derived HLA-A2-restricted epitope. *J Immunol*. 2003;170:2719-26. [PMID: 12594302]
85. Lorand L, Conrad SM. Transglutaminases. *Mol Cell Biochem*. 1984;58:9-35. [PMID: 6143256]
86. Folk JE, Chung SI. Transglutaminases. *Methods Enzymol*. 1985;113:358-75. [PMID: 2868387]
87. Nemes Z, Steinert PM. Bricks and mortar of the epidermal barrier. *Exp Mol Med*. 1999;31:5-19. [PMID: 10231017]
88. Griffin M, Casadio R, Bergamini CM. Transglutaminases: nature's biological glues. *Biochem J*. 2002;368:377-96. [PMID: 12366374]
89. Bruce SE, Bjarnason I, Peters TJ. Human jejunal transglutaminase: demonstration of activity, enzyme kinetics and substrate specificity with special relation to gliadin and coeliac disease. *Clin Sci (Lond)*. 1985;68:573-9. [PMID: 2858282]
90. Esposito C, Paparo F, Caputo I, Porta R, Salvati VM, Mazzarella G, et al. Expression and enzymatic activity of small intestinal tissue transglutaminase in celiac disease. *Am J Gastroenterol*. 2003;98:1813-20. [PMID: 12907337]
91. Fesus L, Piacentini M. Transglutaminase 2: an enigmatic enzyme with diverse functions. *Trends Biochem Sci*. 2002;27:534-9. [PMID: 12368090]
92. Lai TS, Slaughter TF, Peoples KA, Hettasch JM, Greenberg CS. Regulation of human tissue transglutaminase function by magnesium-nucleotide complexes. Identification of distinct binding sites for Mg-GTP and Mg-ATP. *J Biol Chem*. 1998;273:1776-81. [PMID: 9430726]
93. Sollid LM. Molecular basis of celiac disease. *Annu Rev Immunol*. 2000;18:53-81. [PMID: 10837052]
94. Molberg O, McAdam SN, Sollid LM. Role of tissue transglutaminase in celiac disease. *J Pediatr Gastroenterol Nutr*. 2000;30:232-40. [PMID: 10749404]
95. Sulkanen S, Halttunen T, Laurila K, Kolho KL, et al. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. *Gastroenterology*. 1998;115:1322-8. [PMID: 9834257]
96. Nunes I, Gleizes PE, Metz CN, Rifkin DB. Latent transforming growth factor-beta binding protein domains involved in activation and transglutaminase-dependent cross-linking of latent transforming growth factor-beta. *J Cell Biol*. 1997;136:1151-63. [PMID: 9060478]
97. Halttunen T, Martinen A, Rantala I, Kainulainen H, Maki M. Fibroblasts and transforming growth factor beta induce organization and differentiation of T84 human epithelial cells. *Gastroenterology*. 1996;111:1252-62. [PMID: 8898639]
98. Dignass AU, Podolsky DK. Cytokine modulation of intestinal epithelial cell restitution: central role of transforming growth factor beta. *Gastroenterology*. 1993;105:1323-32. [PMID: 8224636]
99. Esposito C, Paparo F, Caputo I, Rossi M, Maglio M, Sblattero D, et al. Anti-tissue transglutaminase antibodies from coeliac patients inhibit transglutaminase activity both in vitro and in situ. *Gut*. 2002;51:177-81. [PMID: 12117875]
100. Reunala TL. Dermatitis herpetiformis. *Clin Dermatol*. 2001;19:728-36. [PMID: 11705682]
101. Fry L. Dermatitis herpetiformis: problems, progress and prospects. *Eur J Dermatol*. 2002;12:523-31. [PMID: 12459520]
102. Porter WM, Unsworth DJ, Lock RJ, Hardman CM, Baker BS, Fry L. Tissue transglutaminase antibodies in dermatitis herpetiformis [Letter]. *Gastroenterology*. 1999;117:749-50. [PMID: 10490368]
103. Sardy M, Karpati S, Merkl B, Paulsson M, Smyth N. Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. *J Exp Med*. 2002;195:747-57. [PMID: 11901200]
104. Kaukinen K, Salmi J, Lahtela J, Siljamaki-Ojansuu U, Koivisto AM, Oksa H, et al. No effect of gluten-free diet on the metabolic control of type 1 diabetes in patients with diabetes and celiac disease. Retrospective and controlled prospective survey [Letter]. *Diabetes Care*. 1999;22:1747-8. [PMID: 10526749]
105. Asklung J, Linet M, Gridley G, Halstensen TS, Ekstrom K, Ekbohm A. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology*. 2002;123:1428-35. [PMID: 12404215]
106. Green PH, Fleischauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI. Risk of malignancy in patients with celiac disease. *Am J Med*. 2003;115:191-5. [PMID: 12935825]
107. Muller AF, Donnelly MT, Smith CM, Grundman MJ, Holmes GK, Toghiani PJ. Neurological complications of celiac disease: a rare but continuing problem. *Am J Gastroenterol*. 1996;91:1430-5. [PMID: 8678009]
108. Chin RL, Latov N, Green PH, Brannagan TH, Alaedini A, Sander HW. Neurological complications of celiac disease. *J Clin Neuromusc Dis*. 2004;5:129-37.
109. Cicarelli G, Della Rocca G, Amboni M, Ciacci C, Mazzacca G, Filla A, et al. Clinical and neurological abnormalities in adult celiac disease. *Neurol Sci*. 2003;24:311-7. [PMID: 14716525]
110. Polizzi A, Finocchiaro M, Parano E, Pavone P, Musumeci S, Polizzi A. Recurrent peripheral neuropathy in a girl with celiac disease [Letter]. *J Neurol Neurosurg Psychiatry*. 2000;68:104-5. [PMID: 10671117]
111. Kaplan JG, Pack D, Horoupian D, DeSouza T, Brin M, Schaumburg H. Distal axonopathy associated with chronic gluten enteropathy: a treatable disorder. *Neurology*. 1988;38:642-5. [PMID: 2832786]
112. Hadjivassiliou M, Davies-Jones GA, Sanders DS, Grunewald RA. Dietary treatment of gluten ataxia. *J Neurol Neurosurg Psychiatry*. 2003;74:1221-4. [PMID: 12933922]
113. Dalton TA, Bennett JC. Autoimmune disease and the major histocompatibility complex: therapeutic implications. *Am J Med*. 1992;92:183-8. [PMID: 1543203]
114. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet*. 2001;358:221-9. [PMID: 11476858]
115. Buzzetti R, Quattrocchi CC, Nistico. Dissecting the genetics of type 1 diabetes: relevance for familial clustering and differences in incidence. *Diabetes Metab Rev*. 1998;14:111-28. [PMID: 9679666]
116. Mori M, Kuwabara S, Miyake M, Dezawa M, Adachi-Usami E, Kuroki H, et al. *Haemophilus influenzae* has a GM1 ganglioside-like structure and elicits Guillain-Barré syndrome. *Neurology*. 1999;52:1282-4. [PMID: 10214761]
117. Yuki N, Taki T, Inagaki F, Kasama T, Takahashi M, Saito K, et al. A bacterium lipopolysaccharide that elicits Guillain-Barre syndrome has a GM1 ganglioside-like structure. *J Exp Med*. 1993;178:1771-5. [PMID: 8228822]
118. Basu D, Horvath S, Matsumoto I, Fremont DH, Allen PM. Molecular basis for recognition of an arthritic peptide and a foreign epitope on distinct MHC molecules by a single TCR. *J Immunol*. 2000;164:5788-96. [PMID: 10820257]
119. Lang HL, Jacobsen H, Ikemizu S, Andersson C, Harlos K, Madsen L, et al. A functional and structural basis for TCR cross-reactivity in multiple sclerosis. *Nat Immunol*. 2002;3:940-3. [PMID: 12244309]
120. Wucherpfennig KW, Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. *Cell*. 1995;80:695-705. [PMID: 7534214]
121. Gomis R, Sener A, Malaisse-Lagae F, Malaisse WJ. Transglutaminase activity in pancreatic islets. *Biochim Biophys Acta*. 1983;760:384-8. [PMID: 6138101]
122. Driscoll HK, Adkins CD, Chertow TE, Cordle MB, Matthews KA, Chertow BS. Vitamin A stimulation of insulin secretion: effects on transglutaminase mRNA and activity using rat islets and insulin-secreting cells. *Pancreas*. 1997;15:69-77. [PMID: 9211495]