

The Liver in Celiac Disease

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Celiac disease is a common (1% prevalence) chronic immune-mediated disorder of the small intestine induced by dietary wheat, barley, and rye. Several hepatic disorders have been described in association with celiac disease. Isolated hypertransaminasemia with nonspecific histologic changes in a liver biopsy is the commonest hepatic presentation of celiac disease. A gluten-free diet normalizes liver enzymes and histologic changes in most patients. Moreover, celiac disease can coexist with autoimmune liver disorders such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. Celiac disease has increasingly been reported with a variety of other liver diseases. Thus, the hepatologist needs to consider celiac disease in the differential of abnormal liver blood tests and to be aware of the clinical implications of this frequent disease in patients with liver disorders. The possible mechanisms of liver injury and those common factors that explain the association of celiac disease with liver disorders are discussed. The aims of this article are (1) to review the spectrum and pathogenesis of liver injury related to celiac disease and (2) to provide direction to those caring for patients with chronic liver diseases regarding the detection and effective treatment of celiac disease. (HEPATOLOGY 2007;46:1650-1658.)

Celiac disease (CD), also known as gluten-sensitive enteropathy or celiac sprue, is defined as a permanent intolerance to ingested gluten (the storage protein components of wheat, barley, and rye). The intolerance to gluten results in immune-mediated damage to the mucosa of the small intestine characteristically inducing villous atrophy and crypt hyperplasia that resolve with the removal of gluten from the diet.¹

Although CD is defined by the small intestine injury and resulting malabsorption, more recently it has been recognized to be a multisystem disorder that may affect other organs, such as the nervous system, bones, skin, heart, and, likely, the liver.²⁻⁴

CD, once thought to be rare, is now known to affect as much as 1% of the population.⁵ The clinical presentation of CD can vary from a classical malabsorption syndrome to more subtle atypical gastrointestinal manifestations (similar to irritable bowel syndrome) or extraintestinal presentations (for example, infertility, osteoporosis, and iron-deficiency anemia). CD can be clinically silent, often detected by serologic screening of those subjects at risk, with villous atrophy in the intestine. Finally, an individual may have a latent predisposition to CD, which is defined by a positive serology in the absence of villous atrophy on the small intestine.^{1,5}

CD itself may injure the liver but also may modify the clinical impact of chronic liver diseases when they coexist. The aims of this review are (1) to explore the spectrum and pathogenesis of liver abnormalities described in CD and (2) to summarize the association between CD and various chronic liver disorders to provide a basis for a rational diagnostic and therapeutic approach that those who care for patients with liver disease can incorporate into practice.

Material and Methods (Review Criteria)

PubMed was searched in June 2007 for full articles published in English-language journals from 1963 to June 2007 with the following keywords alone or in combination: “celiac disease,” “sprue,” “liver disorders,” “liver involvement,” “liver tests,” “hepatitis,” “cholangitis,” and “cirrhosis.” In this literature search, several points became obvious: (1) properly designed epidemiological studies are

Abbreviations: AGA, anti-gliadin antibody; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD, celiac disease; DEXA, dual energy X-ray absorptiometry; EmA, endomy-sial antibody; GFD, gluten-free diet; HFE, hemochromatosis susceptibility gene; HLA, human leukocyte antigen; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; TSH, thyroid-stimulating hormone; tTG, tissue transglu-taminase; tTGA, anti-tissue transglutaminase antibody.

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scarce; (2) the mechanisms of liver injury in CD are poorly studied (most of the available information is based on unproved hypotheses rather than experimental evidence); (3) there is a lack of large, controlled studies on the effect of a gluten-free diet (GFD) in the outcome of the liver disorder; (4) most recommendations for evaluation and treatment are based on expert opinion, not evidence-based reasoning; and (5) there are well-designed, serologically based epidemiological studies to investigate the prevalence of CD in several liver diseases. Citations were chosen on the basis of their relevance to the text.

Liver Involvement in Celiac Disease

Prevalence

Liver blood test abnormalities affect patients with classical CD or may be the sole presentation of atypical CD. CD is an important cause of hypertransaminasemia. Indeed, hypertransaminasemia has been reported in about 40% of adults and in 54% of children with a classical presentation of CD at the time of diagnosis.⁶⁻⁸ Conversely, CD is present in about 9% of patients with chronic unexplained hypertransaminasemia.^{9,10}

CD may also be associated with severe forms of liver disease.¹¹ A large general population-based study from Sweden reported that individuals with CD have a 2-fold to 6-fold increased risk of later liver disease and that prior liver disease increases the risk of later CD (4-fold to 6-fold increase).¹² Even more, CD was found to be associated with an 8-fold increased risk of death from liver cirrhosis.¹³ Thus, CD needs to be excluded before a diagnosis of cryptogenic cirrhosis is considered.¹⁴ CD should be suspected in those subjects with clinical risk factors for CD, such as a positive family history of gluten-sensitive enteropathy or dermatitis herpetiformis, and those who have the human leukocyte antigen DQ2 (HLA-DQ2) or HLA-DQ8 haplotypes, type 1 diabetes mellitus, premature osteoporosis, or osteomalacia.^{1,5}

Pathogenesis

The mechanism(s) underlying liver injury in CD are poorly understood. Serum aminotransferase elevations will normalize with the removal of gluten from the diet (as discussed later), and this suggests a causal relationship between gluten intake/intestinal damage and liver injury. Intestinal permeability is increased in CD; this is related either to the inflammation of the intestine or the induction of the secretion of zonulin, a regulator of tight junctions.¹⁵ Patients with CD and hypertransaminasemia show a significant increase in intestinal permeability in comparison with those with normal liver tests.¹⁶ The increased intestinal permeability seen in the context of CD may facilitate the entry of toxins, antigens, and inflamma-

tory substances (cytokines and/or autoantibodies) to the portal circulation, and these mediators may have a role in the liver involvement seen in patients with CD.^{6,9,17,18} Autoantibodies directed against the so-called celiac antigen [tissue transglutaminase (tTG)] are present in the liver and other extraintestinal tissues in CD, raising the possibility of a pathogenic role for the humoral-mediated immune responses in the liver injury observed in CD.¹⁹ However, the specific role of these autoantibodies and the source and biologic effects of the other proposed mediators for liver injury in CD remain to be demonstrated (Fig. 1).

Clinical Manifestations

Clinical Features. Most patients with liver injury associated with CD have no symptoms or signs of liver disease at the time of diagnosis, although nonspecific symptoms such as malaise and fatigue are common.⁶⁻⁹ The physical examination is normal in most patients.^{8,9} Palmar erythema, jaundice, finger clubbing, spider angiomas, ascites, hepatomegaly, and splenomegaly have been described when patients with CD have cirrhosis.^{20,21} The presence of massive splenomegaly and overt portal hypertension has been reported in patients with CD and non-cirrhotic portal fibrosis.²²

Laboratory Abnormalities and Imaging Studies. Mild to moderate elevated serum levels (less than 5 times the upper limit of normal) of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) are the most common and often only laboratory manifestation of liver injury in patients with CD. In a study of 67 biopsy-confirmed CD patients with altered liver function tests, there was an increase in both ALT and AST in 47, in ALT alone in 14, and in just AST in 6.⁷ Another study showed that AST was more often abnormal than ALT.⁸ The ratio of AST to ALT is usually less than 1, whereas the bilirubin

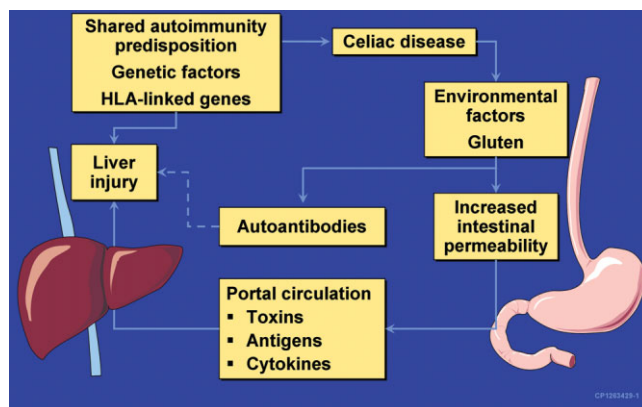


Fig. 1. Possible mechanisms of the pathogenesis of liver injury in celiac disease. HLA indicates human leukocyte antigen.

and gamma-glutamyltransferase are normal. The isolated elevation of alkaline phosphatase (ALP; 4%-20%) is less common and may reflect secondary hyperparathyroidism (bone-specific isoform).^{7,23} The presence of hypoalbuminemia, a prolonged prothrombin time, and especially hyperbilirubinemia in CD may suggest cirrhosis.^{21,22} Hypoalbuminemia and a prolonged prothrombin time, however, may be indirect markers of severe malabsorption.^{1,5}

Ultrasonographic findings vary from a normal to coarse/heterogeneous liver echo texture, depending on the degree of liver injury.^{21,22} An ultrasound examination may reveal signs of CD in the intestine, such as dilated small bowel loops with increased fluid content, free abdominal fluid, increased fasting gallbladder volume (>20 mL), enlarged mesenteric lymph nodes, increased peristalsis, intermittent invaginations of the intestine, and ab-

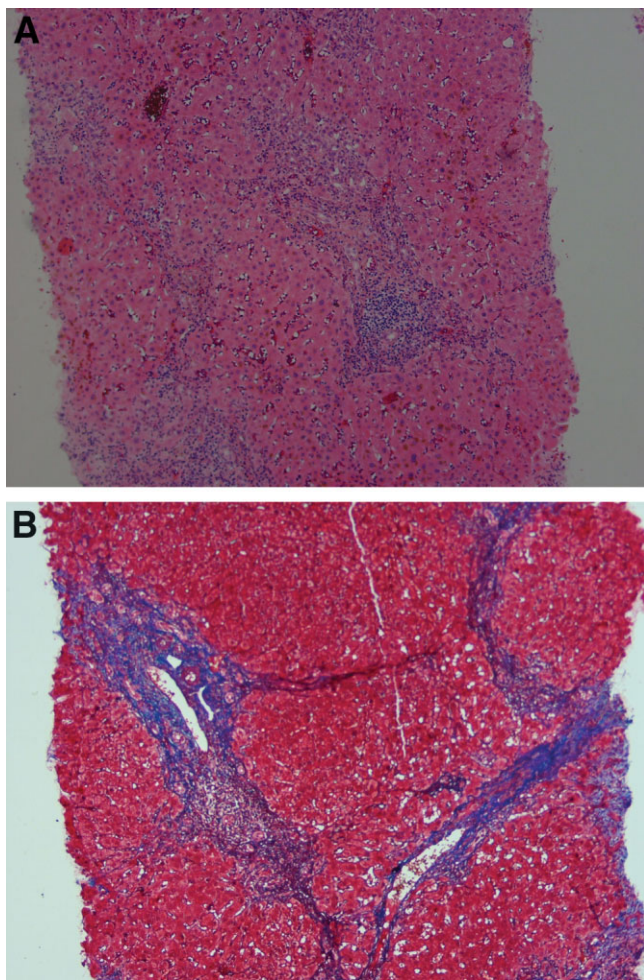


Fig. 2. Findings of liver injury associated with celiac disease on liver-biopsy specimens. (A) Nonspecific changes (mononuclear infiltration of the portal triad) in a patient with celiac disease and elevated aminotransferases (hematoxylin and eosin, $\times 200$). (B) Extensive fibrosis in a patient with celiac disease and severe liver injury (Masson's trichrome, $\times 200$).

Table 1. Histological Findings in the Livers of Patients with Celiac Disease

Nonspecific abnormalities (most common)
Periportal inflammation
Increased number of Kupffer cells
Mononuclear infiltration on the portal triad
Steatosis
Microvesicular and macrovesicular
Fibrosis
Cirrhosis

normal jejunum folds (thickening, shortening, and decrease in number).²⁴⁻²⁶ The sensitivity and specificity of each sign is variable, but a combination of signs may raise the suspicion of CD when it is not otherwise suspected.

Histologic Findings. In patients with CD and liver injury for whom a liver biopsy has been performed, histological changes are frequent (66%) but generally mild and nonspecific.^{6,8,23,27} The abnormalities include periportal inflammation, bile duct obstruction, an increased number of Kupffer cells, mononuclear infiltration in the parenchyma, steatosis, and mild fibrosis.^{6,8,23,24} Extensive fibrosis and cirrhosis have also been reported^{21,22} (Fig. 2A,B and Table 1).

Role of Liver Biopsy. A liver biopsy is of limited utility in cases of isolated hypertransaminasemia associated with CD because of the nonspecific nature of the findings and the high rate of response after gluten exclusion. However, a liver biopsy may be useful in cases with (1) lack of response of hypertransaminasemia to a GFD, (2) CD with abnormal ALP of suspected hepatic origin (after the exclusion of obstructive jaundice), and (3) a coexisting chronic liver disease in which the liver biopsy has prognostic or therapeutic significance (for example, a chronic hepatitis C infection). The decision to perform a liver biopsy, however, must be individualized to the patient age, need for prognostic information, associated comorbid conditions, and clinical significance of the liver test abnormality.¹⁴

Management

A GFD leads to normalization of serum transaminases in 75% to 95% of patients with CD, usually within a year of good adherence to the diet^{7,16,23} (Table 2). All the patients with nonspecific changes in the liver histology and a follow-up liver biopsy normalized the histological changes after adherence to a GFD.^{6,23,27} This reversible, gluten-related liver damage has been called celiac hepatitis.²⁸ An alternative etiology for liver injury should be explored in those patients with persistent hypertransaminasemia despite gluten exclusion. A response to dietary treatment with an improvement in clinical manifestations and lab-

Table 2. Abnormal Liver Chemistry Tests and Effects of a Gluten-Free Diet in Patients with Celiac Disease

Reference	Cases	Abnormal Liver Tests (%)	Responses to a Gluten-Free Diet (%)*
Hagander et al. ⁶	53	39	N/A
Bardella et al. ⁷	158	42	95
Bonamico et al. ⁸	65	57	N/A
Novacek et al. ¹⁶	176	40	96
Jacobsen et al. ²³	171	47	75

N/A indicates not available.

*The response was defined by complete normalization of the liver tests.

oratory abnormalities after a GFD has been described in adult patients and children with advanced liver disease.^{21,22} The general condition, jaundice, ascites, bilirubin, ALT, albumin, and international normalized ratio improved after 6 months of strict adherence to a GFD in three patients with advanced liver disease and CD. The reversible nature of severe histological changes in the liver of patients with CD is controversial, but the reversal of severe fibrosis in a liver biopsy after gluten exclusion has been reported.^{21,23}

Autoimmune Liver Disorders Associated with Celiac Disease

Primary Biliary Cirrhosis

Prevalence. The association of CD and primary biliary cirrhosis (PBC) was reported by Logan et al. in 1978.²⁹ Subsequently, the association between CD and PBC has been extensively investigated by screening patients with PBC for CD. The reported prevalence of CD in PBC varies widely (0%-11%; Table 3).

Two large population-based studies strongly support an association between CD and PBC. The Danish and Swedish cohort study, which included a total of 8631 patients with CD, found that the prevalence of PBC in patients with CD was increased at least 20-fold.³⁸ A study of 4732 subjects with CD and 23,620 age-matched and

sex-matched controls from England demonstrated that the prevalence of PBC was 0.17% in patients with CD versus 0.05% in controls (a 3-fold increase).³⁹ CD associated with anti-mitochondrial antibody-negative PBC has been reported.⁴⁰

Pathogenesis. There are several common pathophysiologic processes that occur in CD and PBC. These include increased intestinal permeability, which is an early abnormality in CD and has also been demonstrated in PBC.⁴¹ Abnormal intestinal permeability can result in increased exposure of gut-derived antigens (including microbial antigens) to the immune system and specifically to the liver.^{41,42} Additionally, there may be shared susceptibility (the development of two or more autoimmune diseases in one patient) to both PBC and CD through immunogenetic mechanisms.⁴³ The role of an immunological mechanism in PBC pathogenesis is supported by the fact that PBC is frequently (~53% of cases) associated with autoimmune disorders, such as scleroderma, autoimmune thyroid disease, and keratoconjunctivitis sicca.^{31,43} CD may be another immune-mediated disorder associated with PBC.

Impact of Gluten Withdrawal on Liver Disease.

Liver blood tests did not improve in patients with silent CD and PBC after 12 to 24 months on a GFD despite the disappearance of the endomysial antibody in the serum.³⁰ Information regarding the stage of PBC in these patients, however, was not provided.³⁰ Pruritus and cholestasis did not improve after 12 months of gluten withdrawal in cases with PBC and severe liver disease [stage IV on histology (Scheuer's classification), with ALP elevations 3.1-4.8 times the upper limit of normal]. These patients also were treated with ursodeoxycholic acid.³⁴ The clinical impact on the liver of a GFD in patients with CD and early PBC [stages I-II on histology (Scheuer's classification), asymptomatic, with ALP elevations < 2 times the upper limit of normal] is yet to be determined. However, the early recognition and treatment of CD are recommended, as glu-

Table 3. Case Series on Screening of Celiac Disease in Primary Biliary Cirrhosis

Author	No. Tested	Serology	Positive Cases for Serology [n (%)]	Biopsy Confirmation [n (%)]
Dickey et al. ³⁰	57	EmA	6 (11%)	4 (7%)
Kingham et al. ³¹	67	—	4 (6%)	4 (6%)
Gillett et al. ³²	378	tTGA, EmA	11 (2.6%)	5 (1.3%)
Floreani et al. ³³	87	EmA	3 (3.4%)	3 (3.4%)
Volta et al. ³⁴	173	tTGA, EmA	7 (4%)	7 (4%)
Chatzicostas et al. ³⁵	62	tTGA, EmA	6 (10%)	0*
Bardella et al. ³⁶	65	AGA, EmA	0	—
Niveloni et al. ³⁷	10	AGA, EmA	3	2†
Total	899	—	40 (4.4%)	25 (2.7%)

AGA indicates anti-gliadin antibody; EmA, endomysial antibody; and tTGA, anti-tissue transglutaminase antibody.

*An intestinal biopsy was performed in only 59% of the patients who tested positive for at least one antibody class.

†The rectal gluten challenge test was positive in three.

ten restriction improves the symptoms attributable to CD and can also reduce the risk of complications (malabsorption, osteoporosis, and malignant neoplasms).^{44,45}

Autoimmune Hepatitis (AIH)

Prevalence. Two studies found that the prevalence of CD in patients with AIH was 4% to 6.4%. CD was found in both type 1 and type 2 AIH. Even though the diagnosis was confirmed by intestinal biopsy in most patients, few had intestinal symptoms.^{46,47}

Pathogenesis. CD and AIH are associated with specific class II HLA molecules encoded by genes of the HLA complex on chromosome 6, a region in which a large group of autoimmune diseases are linked to specific alleles or combinations of alleles (haplotypes).⁴⁸ Although CD is associated with the HLA-DQ2 or HLA-DQ8 haplotype, AIH is associated with HLA-DR3, HLA-DR4, or HLA-DR52.^{49,50} The HLA-B8DR3 region, however, is in close linkage disequilibrium with HLA-DQ2 and is a frequent extended haplotype in Caucasians.⁵¹

Impact of Gluten Withdrawal on Liver Disease. The clinical impact of a GFD on the outcome of the liver disorder in patients with AIH remains to be elucidated. Again, treatment with a GFD is necessary to improve symptoms of CD (if present) and to avoid severe chronic complications of CD.^{44,45}

Primary Sclerosing Cholangitis

Prevalence. An association between CD and primary sclerosing cholangitis (PSC) was first described in 1988.⁵² Later, new case reports of concurrent ulcerative colitis, celiac sprue, and PSC were described.⁵³ A study of 61 patients with PSC found that the prevalence of CD was 1.6%.³⁴ A large, general population-based study from Sweden suggests that the prevalence of PSC in patients with CD increased 4-fold to 8-fold in comparison with reference individuals without CD.¹² This study, although based on an analysis of a large population database, was dependent on the accuracy of the coding of the discharge diagnosis, and the criteria for the classification of PSC were unclear.¹² Because CD is a common disorder, the possibility of a chance association between CD and PSC cannot be excluded. Moreover, ulcerative colitis alone (in the absence of PSC) was found to be significantly more common in patients with CD than in the US general population (a 4-fold increase).⁵⁴ Anti-tissue transglutaminase antibodies (tTGA) antibodies have been reported to be present in patients with ulcerative colitis. Endomysial antibodies, however, are specific for CD.⁵⁵ Further studies are needed to accurately determine the strength of the association between PSC and CD.

Pathogenesis. CD and PSC are immune-mediated

diseases. Susceptibility to developing PSC is partly determined by genes in the HLA complex. A multicenter study in Europe found that the frequencies of the HLA-DRB1*03, HLA-DQA1*05, HLA-DQB1*02, HLA-DRB1*13, HLA-DQA1*0103, and HLA-DQB1*0603 haplotypes were higher in patients with PSC in comparison with ethnically-matched controls.⁵⁶ Moreover, in another study, the presence of the HLA-DR3/DQ2 heterozygous genotype was found to be associated with the rapid progression of PSC.⁵⁷ This is the same genotype that is the major genetic risk factor for the development and perhaps also severity of CD.⁴⁹ Thus, the same class II HLA molecules are important for the pathogenesis in PSC and CD, and a shared immunogenetic predisposition to autoimmunity may partially explain the association between the two diseases.

Impact of Gluten Withdrawal on Liver Disease. Severe steatorrhea responded to a GFD, whereas the clinical course of the PSC itself was not affected by dietary treatment in a small group of patients.^{52,53}

Liver Transplantation and Celiac Disease

A high prevalence of CD (4.3%) was found in a group of 185 adult patients who had undergone liver transplantation; the etiology of the end-stage liver disease leading to liver transplantation was, in most cases, autoimmune.²¹ A study of 310 patients who had undergone liver transplantation for end-stage autoimmune liver disease found that the prevalence of CD was 3%; most of the cases carried the HLA-DQ2 or HLA-DQ8 haplotype (J.A.M., unpublished data, 2007).

Miscellaneous Liver Disorders and Celiac Disease

A partial list of liver disorders reported to be associated with CD is shown in Table 4.

Table 4. Liver Diseases Associated with Celiac Disease

Isolated hypertransaminasemia with parenchymal damage reversible on a gluten-free diet (celiac hepatitis)
Cryptogenic cirrhosis
Autoimmune liver disorders
Primary biliary cirrhosis
Autoimmune hepatitis: type 1 and type 2
Autoimmune cholangitis
Primary sclerosing cholangitis
Chronic hepatitis C infection/antiviral therapy
Hemochromatosis
Nonalcoholic fatty liver disease
Acute liver failure
Regenerative nodular hyperplasia
Hepatocellular carcinoma

Viral Hepatitis

A study of 259 patients with chronic hepatitis C infection found that the prevalence of CD in patients with hepatitis C was 1.2% versus 0.4% in normal volunteers (a 3-fold increase).⁵⁸ The diagnosis of CD was confirmed with duodenal biopsy; all of those patients had mild intestinal symptoms and carried the HLA-DQ2 allele.⁵⁸ Another study showed a CD prevalence of 1.3% in a series of 534 patients affected by chronic hepatitis C.⁵⁹ A recent study of patients having both CD and chronic hepatitis C described a well-defined route of transmission in most of these subjects, raising the hypothesis that the link between these two diseases is probably biased by the route of transmission of hepatitis C infection.⁶⁰ Thus, a clear association of CD and chronic hepatitis C is lacking.

CD may present for the first time during treatment for hepatitis C.⁶¹⁻⁶⁴ Both interferon- α and ribavirin may enhance type 1 helper T cell immune responses via the signal transducers and activators of transcription-dependent pathway that subsequently induce interferon- γ gene expression.⁶⁵⁻⁶⁶ Thus, CD should be considered in the setting of unexplained diarrhea during or after interferon- α /ribavirin therapy (Table 5).

Finally, patients with CD may have a significant genetic predisposition to a hepatitis B vaccine nonresponse. Indeed, 54% and 68% of children and adults with CD, respectively, do not show a response to standard vaccination regimens for hepatitis B virus.^{67,68} This defective vaccine response seems to be linked to the HLA molecule DQ2.⁶⁷

Hemochromatosis

CD intersects with hemochromatosis in two ways: (1) case reports have shown the precipitation of iron overload and the diagnosis of hereditary hemochromatosis after the

successful treatment of CD, and (2) experimental evidence suggests an increased frequency of mutations in the hemochromatosis susceptibility gene (HFE) in British patients with CD, suggesting a protective role against iron deficiency by enhancing iron absorption.⁶⁹⁻⁷¹ However, an Italian study failed to show an increased frequency of HFE mutations in patients with CD.⁷² Thus, if the association of CD and hemochromatosis is due to chance because of the high prevalence of both diseases in the Caucasian population or if the HFE mutations provide a survival advantage in certain CD populations remains to be elucidated.

Nonalcoholic Fatty Liver Disease

Prevalence. Nonalcoholic fatty liver disease affects 10% to 24% of the general population in various countries.⁷³ Obesity, a major risk factor for nonalcoholic liver disease, does not exclude the diagnosis of CD. The body mass index was >25 kg/m² (overweight or obese) in 27% of American patients at the time of CD diagnosis.⁴⁴ A study of 54 patients with diet-resistant nonalcoholic fatty liver disease (64% with steatohepatitis) found a prevalence of 10% and 4.3% for tTGA and EmA, respectively. The diagnosis of CD was confirmed by intestinal biopsy in 3.4% of the patients.⁷⁴ Another study of 121 patients with biopsy-proven nonalcoholic fatty liver disease found that the prevalence of CD in patients with nonalcoholic fatty liver disease was 3.3%.⁷⁵

Impact of Gluten Withdrawal on Liver Disease. The liver blood test abnormalities observed in patients with nonalcoholic fatty liver disease and CD normalized after 6 months of a GFD.^{74,75} The effect of a GFD on the reversal of histological abnormalities in nonalcoholic fatty liver disease remains to be elucidated.

Pancreaticobiliary Disorders

CD is associated with increased fasting gallbladder volume and reduced gallbladder emptying in response to meals.⁷⁶⁻⁷⁸ This is likely due to impaired meal-induced release of gut hormones (for example, cholecystokinin) secondary to the loss of enterocyte mass (villous atrophy) and increased somatostatin levels.⁷⁶⁻⁷⁸ Indeed, an impaired fat-induced gallbladder ejection fraction and cholecystokinin plasma concentration (stimulated state peak) were found in patients with untreated CD in comparison with controls.⁷⁹ Acute lithiasic cholecystitis has rarely been reported as the initial presentation of CD, but epidemiological studies supporting an association between CD and gallstone formation are lacking. Gallbladder function normalizes in CD after gluten withdrawal.^{77,78} CD was found in 7% of 169 patients with recurrent pancreatitis.⁸⁰ Papillary stenosis of the pancreatic orifice sec-

Table 5. Clues to the Diagnosis of Interferon- α -Induced Activation of Silent Celiac Disease

Clinical Manifestations*
Severe diarrhea
Pallor
Nonspecific mild abdominal pain
Marked weight loss
Fatigue
Laboratory Abnormalities
Positive celiac serology (tTGA or EmA)
Iron-deficiency anemia
Vitamin K deficiency
Hypoalbuminemia
Histology
Intestinal biopsy compatible with celiac disease

EmA indicates endomysial antibody; and tTGA, anti-tissue transglutaminase antibody.

*Time to symptom: 2 to 5 months after the onset of the interferon- α treatment.

ondary to periampullary inflammation was postulated as the mechanism of recurrent pancreatitis in these subjects.⁸⁰ Obstructive jaundice caused by neoplastic infiltration of the papilla of Vater by enteropathy-associated T-cell lymphoma has rarely been reported in patients with CD.⁸¹

Pitfalls of the Serological Diagnosis of Celiac Disease in Patients with Chronic Liver Disorders

The diagnostic accuracy of the serological tests commonly used for the diagnosis of CD may be impaired in patients with chronic liver disorders. Accordingly, the interpretation of celiac serology in patients with chronic liver disorders deserves special attention.

Anti-Gliadin Antibody

Immunoglobulin A gliadin antibody (AGA) positivity occurs with increased frequency among patients with chronic liver disease (20% in alcoholic liver cirrhosis, 16% in PBC, 24% in PSC, 19% in chronic hepatitis, and 11% in hepatitis C virus infection), but most cases are not due to CD (normal duodenal histology) and may reflect an increased permeability of the gut to food antigens that include gluten.⁸² Thus, the anti-gliadin antibody is not useful in screening for CD in patients with liver disease.

Anti-Tissue Transglutaminase Antibody and Endomysial Antibodies

The first-generation tTGA tests used tTG derived from guinea pig liver. Although they performed well in general use, there were many more false positives in patients with chronic liver disease.⁸³ This was probably due to the antigens present in the crude extract of pig liver and perhaps also to immune dysregulation (hypergammaglobulinemia) associated with the chronic liver disease itself. The specificity was improved when the tTG reagent was either derived from human red cells or generated recombinantly from human tTG sequences.⁸³⁻⁸⁵ However, occasionally false positives are seen even with the human tTG assays, especially in patients with advanced chronic liver disease. This may be due to the development of antibodies directed against tTG in the diseased liver.^{83,84} Thus, positive tTGA-based serology must be carefully interpreted in patients with cirrhosis.⁸⁵ The endomysial antibody indirect immunofluorescence assay appears to have a very high specificity for CD and may be a useful test for individuals with chronic liver disease. However, to perform the test well for this antibody requires a high level of laboratory expertise, and sensitivity varies between laboratories.⁸⁶

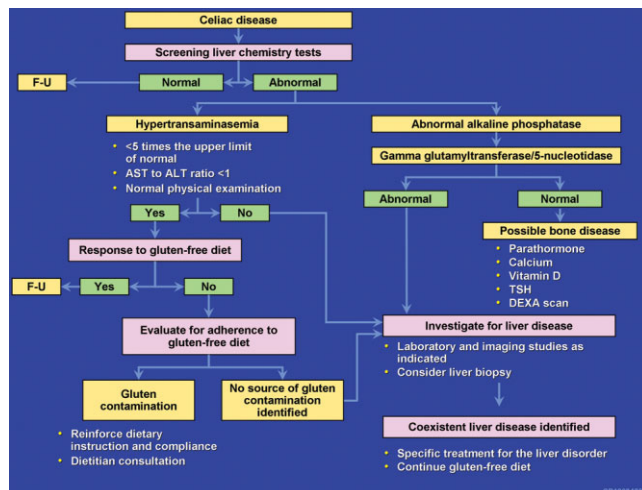


Fig. 3. Approach to the diagnosis of a liver disorder in celiac disease. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; DEXA, dual energy X-ray absorptiometry; F-U, follow-up; and TSH, thyroid-stimulating hormone.

Suggested Approach

In order to decrease the possibility of a false positive result and unnecessary and costly investigation, we recommend that a positive result based on tTGA (even with human antigen) should be confirmed with the endomysial antibody test in patients with liver disease, and if it is positive, an intestinal biopsy should be done to confirm the diagnosis of CD. The absence of CD-associated HLA haplotypes (DQ2 and DQ8) excludes the diagnosis of CD, and the investigation of the HLA molecules may be very useful in patients with contradictory results from serology or intestinal biopsy.⁸⁷ However, the presence of HLA-DQ2 or HLA-DQ8 has a low specificity for CD, with 30% of the general population carrying those haplotypes.⁸⁸

Conclusions

CD affects around 1% of the general population. Liver abnormalities are a common extraintestinal manifestation in patients with CD. The liver injury in CD has a wide spectrum ranging from mild hepatic abnormalities to severe liver disease. The mechanisms underlying liver injury in CD are poorly understood; however, a GFD is an effective medical therapy for most patients with CD and liver injury. The association of CD with other chronic liver disorders (for example, autoimmune liver disorders) is well established. The effect of a GFD on the progression of liver diseases associated with CD is less clear. Finally, although there are many gaps in our understanding of how CD and the liver interact, it is possible to suggest a rational approach to the investigation and clinical fol-

low-up of the liver abnormalities commonly associated with CD (Fig. 3).

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References

- Farrell RJ, Kelly CP. Celiac sprue—current concepts. *N Engl J Med* 2002; 346:180-188.
- Hu WT, Murray JA, Greenaway MC, Parisi JE, Josephs KA. Cognitive impairment and celiac disease. *Arch Neurol* 2006;63:1440-1446.
- Zone JJ. Skin manifestations of celiac disease. *Gastroenterology* 2005; 128(Suppl 1):S87-S89.
- Frustaci A, Cuoco L, Chimentoi C, Pieroni M, Fioravanti G, Gentiloni N, et al. Celiac disease associated with autoimmune myocarditis. *Circulation* 2002;105:2611-2618.
- Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. *Gastroenterology* 2006;131:1981-2002.
- Hagander B, Brandt L, Sjolund K, Berg NO, Norden A, Sjolund K, et al. Hepatic injury in adult celiac disease. *Lancet* 1977;2:270-272.
- Bardella MT, Franquelli M, Quatrini M, Molteni N, Bianchi P, Conte D. Prevalence of hypertransaminasemia in adult celiac patients and effect of gluten-free diet. *HEPATOLOGY* 1995;22:833-836.
- Bonamico M, Pitzalis G, Culasso F, Vania A, Monti S, Benedetti C, et al. Hepatic damage during celiac disease in childhood. *Minerva Pediatr* 1986; 38:959-963.
- Volta U, De Franceschi L, Lari F, Molinaro N, Zoli M, Bianchi F. Celiac disease hidden by cryptogenic hypertransaminasemia. *Lancet* 1998;352: 26-29.
- Bardella MT, Vecchi M, Conte D, Del Ninno E, Franquelli M, Pacchetti S, et al. Chronic unexplained hypertransaminasemia may be caused by occult celiac disease. *HEPATOLOGY* 1999;29:654-657.
- Lindgren S, Sjoberg K, Eriksson S. Unsuspected celiac disease in chronic 'cryptogenic' liver disease. *Scand J Gastroenterol* 1994;29:661-664.
- Ludvigsson JF, Elfstrom P, Broome U, Ekblom A, Montgomery SM. Celiac disease and risk of liver disease: a general population-based study. *Clin Gastroenterol Hepatol* 2007;5:63-69.
- Peters U, Askling J, Gridley G, Ekblom A, Linet M. Causes of death in patients with celiac disease in a population-based Swedish cohort. *Arch Intern Med* 2003;163:1566-1572.
- Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. *Gastroenterology* 2002;123:1367-1384.
- Clemente MG, De Virgiliis S, Kang JS, Macatagny R, Musu MP, Di Pierro MR, et al. Early effects of gliadin on enterocyte intracellular signaling involved in intestinal barrier function. *Gut* 2003;52:218-223.
- Novacek G, Miehsler W, Wrba F, Ferenci P, Penner E, Vogelsang H. Prevalence and clinical importance of hypertransaminasemia in celiac disease. *Eur J Gastroenterol Hepatol* 1999;11:283-288.
- Volta U, Granito A, De Franceschi L, Petrolini N, Bianchi FB. Anti tissue transglutaminase antibodies as predictors of silent celiac disease in patients with hypertransaminasemia of unknown origin. *Dig Liver Dis* 2001;33: 420-425.
- Pelaez-Luna M, Schmulson M, Robles-Diaz G. Intestinal involvement is not sufficient to explain hypertransaminasemia in celiac disease? *Med Hypotheses* 2005;65:937-941.
- Korponay-Szabo IR, Halttunen T, Szalai Z, Laurila K, Kiraly R, Kovacs JB, et al. In vivo targeting of intestinal and extraintestinal transglutaminase 2 by celiac autoantibodies. *Gut* 2004;53:641-648.
- Demir H, Yuca A, Caglar M, Kale G, Kocak N, Ozen H, et al. Cirrhosis in children with celiac disease. *J Clin Gastroenterol* 2005;39:630-633.
- Kaukinen K, Halme L, Collin P, Farkkila M, Maki M, Vehmanen P, et al. Celiac disease in patients with severe liver disease: gluten-free diet may reverse hepatic failure. *Gastroenterology* 2002;122:881-888.
- Sharma BC, Bhasin DK, Nada R. Association of celiac disease with non-cirrhotic portal fibrosis. *J Gastroenterol Hepatol* 2006;21(pt 2):332-334.
- Jacobsen MB, Fausa O, Elgjo K, Schrupf E. Hepatic lesions in adult celiac disease. *Scand J Gastroenterol* 1990;25:656-662.
- Fraquelli M, Colli A, Colucci A, Bardella MT, Trovato C, Pometta R, et al. Accuracy of ultrasonography in predicting celiac disease. *Arch Intern Med* 2004;164:169-174.
- Bartusek D, Valek V, Husty J, Uteseny J. Small bowel ultrasound in patients with celiac disease: retrospective study. *Eur J Radiol* 2007. DOI: 10.1016/j.ejrad.2007.01.28. Available at: <http://www.sciencedirect.com>.
- Rettenbacher T, Hollerweger A, Macheiner P, Huber S, Gritzmann N. Adult celiac disease: US signs. *Radiology* 1999;211:389-394.
- Pollock DJ. The liver in celiac disease. *Histopathology* 1997;1:421-430.
- Maggiore G, Caprai S. The liver in celiac disease. *J Pediatr Gastroenterol Nutr* 2003;37:117-119.
- Logan RF, Fergusson A, Finlayson ND, Weir DG. Primary biliary cirrhosis and celiac disease: an association? *Lancet* 1978;1:230-233.
- Dickey W, McMillan S, Callender M. High prevalence of celiac sprue among patients with primary biliary cirrhosis. *J Clin Gastroenterol* 1997; 25:328-329.
- Kingham JGC, Parker DR. The association between primary biliary cirrhosis and celiac disease: a study of relative prevalences. *Gut* 1998;42:120-122.
- Gillet 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;14:672-675.
- Floreani A, Betterle C, Baragiotta A, Martini S, Venturi C, Basso D, et al. *Dig Liver Dis* 2002;34:248-250.
- Volta U, Rodrigo L, Granito A, Petrolini N, Muratori P, Muratori L, et al. Celiac disease in autoimmune cholestatic liver disorders. *Am J Gastroenterol* 2002;97:2609-2613.
- Chatzicostas C, Roussomoustakaki M, Srygiannakis D, Niniraki M, Tzardi M, Koulentaki M, et al. Primary biliary cirrhosis and autoimmune cholangitis are not associated with celiac disease in Crete. *BMC Gastroenterol* 2002;2:5.
- Bardella MT, Quatrini M, Zuin M, Podda M, Cesarini L, Velio P, et al. Screening patients with celiac disease for primary biliary cirrhosis and vice versa. *Am J Gastroenterol* 1997;92:1524-1526.
- Niveloni S, Dezi R, Pedreira S, Podesta A, Cabanne A, Vazquez H, et al. Gluten sensitivity in patients with primary biliary cirrhosis. *Am J Gastroenterol* 1998;93:404-408.
- Sorensen HT, Thulstrup AM, Blomqvist P, Norgaard B, Fonager K, Ekblom A. Risk of primary biliary liver cirrhosis in patients with celiac disease: Danish and Swedish cohort study. *Gut* 1999;44:736-738.
- Lawson A, West J, Aithal GP, Logan RFA. Autoimmune cholestatic liver disease in people with celiac disease: a population-based study of their association. *Aliment Pharmacol Ther* 2005;21:401-405.
- Gogos CA, Nikolopoulou V, Zolota V, Siampi V, Vagenakis A. Autoimmune cholangitis in a patient with celiac disease: a case report and review of the literature. *J Hepatol* 1999;30:321-324.
- Feld JJ, Meddings J, Heathcote EJ. Abnormal intestinal permeability in primary biliary cirrhosis. *Dig Dis Sci* 2006;51:1607-1613.
- Selmi C, Gershwin ME. Bacterial and human autoimmunity: the case of primary biliary cirrhosis. *Curr Opin Rheumatol* 2004;16:406-410.
- Watt FE, James OF, Jones DE. Patterns of autoimmunity in primary biliary cirrhosis patients and their families: a population-based cohort study. *QJM* 2004;97:397-406.
- Murray JA, Watson T, Clearman B, Mitros F. Effect of a gluten-free diet on gastrointestinal symptoms in celiac disease. *Am J Clin Nutr* 2004;79: 669-673.
- West J, Logan RFA, Smith CJ, Hubbard RB, Card TR. Malignancy and mortality in people with celiac disease: population based cohort study. *BMJ* 2004;329:716-720.
- Volta U, DeFranceschi 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;43:2190-2195.

47. Villalta D, Girolami D, Bidoli E, Bizarro N, Tampoia M, Liguori M, et al. High prevalence of celiac disease in autoimmune hepatitis detected by anti-tissue transglutaminase autoantibodies. *J Clin Lab Anal* 2005;19:6-10.
48. Klein J, Sato A. The HLA system (first of two parts). *N Engl J Med* 2000;343:702-709.
49. Tollefsen S, Arentz-Hansen H, Fleckenstein B, Molberg O, Raki M, Kwok WW, et al. HLA-DQ2 and -DQ8 signatures of gluten T cell epitopes in celiac disease. *J Clin Invest* 2006;116:2226-2236.
50. Krawitt EL. Autoimmune hepatitis. *N Engl J Med* 2006;354:54-66.
51. Smyth C, Kelleher D, Keeling PWN. Hepatic manifestations of gastrointestinal diseases: inflammatory bowel disease, celiac disease, and Whipple's disease. *Clin Liver Dis* 2002;6:1013-1032.
52. Hay JE, Wiesner RH, Shorter RG, LaRusso NF, Baldus WP. Primary sclerosing cholangitis and celiac disease. A novel association. *Ann Intern Med* 1988;109:713-717.
53. Fracassetti O, Delvecchio G, Tambini R, Loerzi N, Gavazzeni G. Primary sclerosing cholangitis with celiac sprue: two cases. *J Clin Gastroenterol* 1996;22:71-72.
54. Yang A, Chen Y, Scherl E, Neugut AI, Bhagat G, Green PHR. Inflammatory bowel disease in patients with celiac disease. *Inflamm Bowel Dis* 2005;11:528-532.
55. Di Tola M, Sabbatella L, Anania MC, Viscido A, Caprilli R, Pica R, et al. Anti-tissue transglutaminase in inflammatory bowel disease: new evidence. *Clin Chem Lab Med* 2004;42:1092-1097.
56. Spurkland A, Saarinen S, Boberg KM, Mitchell S, Broome U, Caballeria L, et al. HLA class II haplotypes in primary sclerosing cholangitis patients from five European populations. *Tissue Antigens* 1999;53:459-469.
57. Boberg KM, Spurkland A, Rocca G, Egeland T, Saarinen S, Mitchell S, et al. The HLA-DR3,DQ2 heterozygous genotype is associated with an accelerated progression of primary sclerosing cholangitis. *Scand J Gastroenterol* 2001;8:886-890.
58. Fine KD, Ogunji F, Saloum Y, Beharry S, Crippin J, Weinstein J. Celiac sprue: another autoimmune syndrome associated with hepatitis C. *Gastroenterology* 2001;96:138-145.
59. Durante-Mangoni E, Iardino P, Resse M, Cesaro G, Sica A, Farzati B, et al. Silent celiac disease in chronic hepatitis C: impact of interferon treatment on the disease onset and clinical outcome. *J Clin Gastroenterol* 2004;38:901-905.
60. Thevenot T, Boruchowicz A, Henrion J, Nalet B, Moindrot H, and ANGH. Celiac disease is not associated with chronic hepatitis C. *Dig Dis Sci* 2007;52:1310-1312.
61. Bardella MT, Marino R, Meroni PL. Celiac disease during interferon treatment. *Ann Intern Med* 1999;131:157-158.
62. Cammarota G, Cuomo L, Cianci R, Pandolfi F, Gasbarrini G. Onset of celiac disease during treatment with interferon for chronic hepatitis C. *Lancet* 2000;356:1494-1495.
63. Narvaez I, Perez B, Alcalde M, Jimenez C, Soria A. Chronic viral hepatitis, interferon, diabetes mellitus, and celiac disease. *Am J Gastroenterol* 2003;98:2336-2337.
64. Adinolfi LE, Mangoni-Durante E, Andreana A. Interferon and ribavirin treatment of chronic hepatitis C may activate celiac disease. *Am J Gastroenterol* 2001;96:607-608.
65. Monteleone G, Pender SL, Wathen NC, MacDonald TT. Interferon- α drives T cell-mediated immunopathology in the intestine. *Eur J Immunol* 2001;31:2247-2255.
66. Tam RC, Pai B, Bard J, Lim C, Averett DR, Phan UT, et al. Ribavirin polarizes human T cell response toward a type 1 cytokine profile. *J Hepatol* 1999;30:376-382.
67. Noh KW, Poland GA, Murray JA. Hepatitis B vaccine nonresponse and celiac disease. *Am J Gastroenterol* 2003;98:2289-2292.
68. Park S-D, Markowitz J, Pettei M, Weinstein T, Sison CP, Swiss SR, et al. Failure to respond to hepatitis B vaccine in children with celiac disease. *J Pediatr Gastroenterol Nutr* 2007;44:431-435.
69. Turcu A, Leveque L, Bielefeld P, Besancenot JF, Hillon P. Adult celiac disease and hemochromatosis. *Am J Gastroenterol* 2000;95:3661-3662.
70. Heneghan MA, Feeley KM, Stevens FM, Little MPG, McCarthy CF. Precipitation of iron overload and hereditary hemochromatosis after successful treatment of celiac disease. *Am J Gastroenterol* 2000;95:298-300.
71. Butterworth JR, Cooper BT, Rosenberg WMC, Purkiss M, Jobson S, Hathaway M, et al. The role of hemochromatosis susceptibility gene mutations in protecting against iron deficiency in celiac disease. *Gastroenterology* 2002;123:444-449.
72. Barisani D, Ceroni S, Del Bianco S, Meneveri R, Bardella MT. Hemochromatosis gene mutations and iron metabolism in celiac disease. *Haematologica* 2004;89:1299-1305.
73. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002;346:1221-1231.
74. Bardella MT, Valenti L, Pagliari C, Peracchi M, Fare M, Fracanzani AL, et al. Searching for celiac disease in patients with non-alcoholic fatty liver disease. *Dig Liver Dis* 2004;36:333-336.
75. Loiacono O, Petta S, Venezia G, DiMarco V, Tarantino G, Barbaria F, et al. Anti-tissue transglutaminase antibodies in patients with abnormal liver test: is it always celiac disease? *Am J Gastroenterol* 2005;100:2472-2477.
76. Low-Beer TS, Harvey RF, Davies ER, Read AF. Abnormalities of serum cholecystokinin and gallbladder emptying in celiac disease. *N Engl J Med* 1975;292:961-963.
77. DiMagno EP, Go WLW, Summerskill WHJ. Impaired cholecystokinin-pancreozymin secretion, intraluminal dilution and maldigestion of fat in sprue. *Gastroenterology* 1972;63:25-32.
78. Maton PN, Selden AC, Fitzpatrick ML, Chadwick VS. Defective gallbladder emptying and cholecystokinin release in celiac disease. Reversal by gluten-free diet. *Gastroenterology* 1985;88:391-396.
79. Fraquelli M, Bardella MT, Peracchi M, Cesana BM, Bianchi PA, Conte D. Gallbladder emptying and somatostatin and cholecystokinin plasma levels in celiac disease. *Am J Gastroenterol* 1999;94:1866-1870.
80. Patel RS, Johlin FC, Murray JA. Celiac disease and recurrent pancreatitis. *Gastrointest Endosc* 1999;50:823-827.
81. Buess M, Steuerwald M, Wegmann W, Rothen M. Obstructive jaundice caused by enteropathy-associated T-cell lymphoma in a patient with celiac disease. *J Gastroenterol* 2004;39:1110-1113.
82. Sjoberg K, Lindgren S, Eriksson S. Frequent occurrence of non-specific gliadin antibodies in chronic liver disease. Endomysial but no gliadin antibodies predict celiac disease in patients with chronic liver disease. *Scand J Gastroenterol* 1997;32:1162-1167.
83. Carroccio A, Giannitrapani L, Soresi M, Not T, Iacono G, DiRosa C, et al. Guinea pig transglutaminase immunolinked assay does not predict celiac disease in patients with chronic liver disease. *Gut* 2001;49:506-511.
84. Vecchi M, Folli C, Donato MF, Formenti S, Arosio E, DeFranchis R. High rate of positive anti-tissue transglutaminase antibodies in chronic liver disease. Role of liver decompensation and of the antigen source. *Scand J Gastroenterol* 2003;38:50-54.
85. Villalta D, Crovatto M, Stella S, Tonutti E, Tozzoli R, Bizzaro N. False positive reactions for IgA and IgG anti-tissue transglutaminase antibodies in liver cirrhosis are common and method-dependent. *Clin Chim Acta* 2005;356:102-109.
86. Murray JA, Herlein J, Mitros F, Goeken JA. Serologic testing for celiac disease in the United States: results of a multilaboratory comparison study. *Clin Diagn Lab Immunol* 2000;7:584-587.
87. Kaukinen K, Partanen J, Maki M, Collin P. HLA-DQ typing in the diagnosis of celiac disease. *Am J Gastroenterol* 2002;97:695-699.
88. Sollid LM, Lie BA. Celiac disease genetics: current concepts and practical applications. *Clin Gastroenterol Hepatol* 2005;3:843-851.